

Romanian Journal of Military Medicine

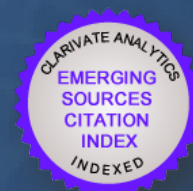
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- *Blood Pressure Variability in Patients with Hypertension and Type 2 Diabetes Mellitus: Is There More to Do?*
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- *Stackable Surgical Guides in Full-Arch Implant Rehabilitation: What They Can Deliver and Where the Evidence Still Constrains Use — A Critical Narrative Review*



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ARTICLE

A study of treatment-naïve patients with systemic lupus erythematosus: focus on the status of thyroid profile across a real-life clinical setting

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Abstract: Background: Systemic Lupus Erythematosus (SLE) is potentially associated with thyroid disturbances, which might remain underdiagnosed. The objective was to analyse the thyroid profile in adults newly diagnosed with SLE. Methods: In this observational, real-life, cross-sectional study, treatment-naïve SLE subjects were compared to (SLE-free) controls in terms of thyroid profile and clinical, hematologic, electrophoretic, immunologic, and metabolic parameters. Individuals with a prior history of autoimmune diseases, thyroidectomy, and thyroid ailments were excluded. The statistical significance cut-off was $p < 0.05$. Results: SLE patients ($N=22$) versus age- and gender-matched controls ($N=50$) had a higher prevalence of thyroid dysfunction (22.7% versus 2%, $p=0.001$), mostly subclinical hypothyroidism, with similar TSH (thyroid-stimulating hormone), free thyroxine, and anti-thyroperoxidase (TPO) antibody levels. The prevalence of autoimmune thyroiditis (as defined by positive TPO) in the SLE group (27.3%) versus controls (14%) was not statistically significant ($p=0.236$). Thyroid ultrasound findings, namely, the highest size-based nodules category rates, displayed no between-group differences. Additional parameters (25-hydroxyvitamin D and glucose status) showed a similar profile. SELENA-SLEDAI score correlated with gamma-globulins ($\rho=0.55$, $p=0.008$) and glycated haemoglobin A1c ($\rho=0.50$, $p=0.017$), but not with thyroid function or TPO. Conclusion: Commonalities in the fields of thyroid and SLE should be taken into account from SLE onset, especially thyroid function. Indirect interplay might involve the glucose profile and vitamin D status.

Keywords: thyroid, thyroiditis, antibody, ultrasound, hypothyroidism, vitamin D, glycated hemoglobin, lupus, rheumatic disorder

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a quintessential systemic autoimmune disease, characterized by a wide spectrum of clinical presentations ranging from mild forms to severe, including organ-threatening exacerbations that can lead to significant disability or mortality. The association between SLE and endocrine disorders, particularly thyroid dysfunction and autoimmunity, is well-established, with studies reporting a prevalence of hypothyroidism (of any cause) in SLE patients between 3% and 21% [1-3]. Autoimmune Hashimoto's thyroiditis was confirmed more often than it was found in the general population, mostly driven by common autoimmune pathways [2-4], but the clear underlying mechanisms are less understood so far.

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A connected genetic background was reported: a shared susceptibility conferred by polymorphisms in genes regulating immune tolerance, such as PTPN22 and CTLA-4, and by classic associations with HLA alleles like HLA-DR3 [5-7]. This genetic vulnerability is compounded by the dysregulation of common immune pathways. For instance, T helper 17 (Th17) cell axes and their associated cytokines are known to play a central role, not only in the pathogenesis of SLE, but also in the lymphocytic infiltration of the thyroid gland amid the diagnosis of autoimmune thyroiditis [8-10].

This co-diagnosis involves a larger spectrum of clinical challenges. The nonspecific symptoms of thyroid dysfunction (e.g., fatigue, weight changes, myalgia, and mood disturbances) frequently overlap with the constitutional manifestations of SLE [9-11]. This can lead to an underdiagnosis of the thyroid condition, with its symptoms being erroneously attributed solely to the lupus activity. Even subclinical hypothyroidism, which is more prevalent in patients with systemic autoimmune diseases versus the general population, might perpetuate a state of low-grade inflammation and negatively impact quality of life in addition to causing potential anomalies of the cardiometabolic status, such as those involving the glucose and lipid profile, and even a higher level of persistent oxidative stress [11-13].

An additional challenge is found in the overlapping landscape of biological markers in treatment-naïve individuals, as highlighted in those who are on specific medication against SLE or in those presenting other complications or co-ailments (e.g., cardiovascular and metabolic conditions, osteoporosis/osteoporotic fractures, vitamin D deficiency, etc.). Corticosteroids, a mainstay of SLE therapy, can independently alter glycaemic control and lipid status, while other immunomodulators might modify the inflammatory and protein profile [12-14].

Overall, there is a current gap in addressing thyroid status in SLE patients, starting with early recognition of thyroid anomalies in individuals who are newly diagnosed with the rheumatologic ailment and continuing with long-term strategies of diagnosis and therapy.

Objective

We aimed to analyse the thyroid profile (function, ultrasound, and circulating anti-thyroperoxidase antibodies) in relation to the clinical status, as well as immunological biomarkers in newly diagnosed SLE patients versus SLE-free controls.

MATERIALS AND METHODS

Study Design

This observational, cross-sectional, retrospective, real-life, single-centre study was conducted at a single department of a multidisciplinary university hospital, namely, "Dr. Carol Davila" Central Military Emergency University Hospital in Bucharest, Romania.

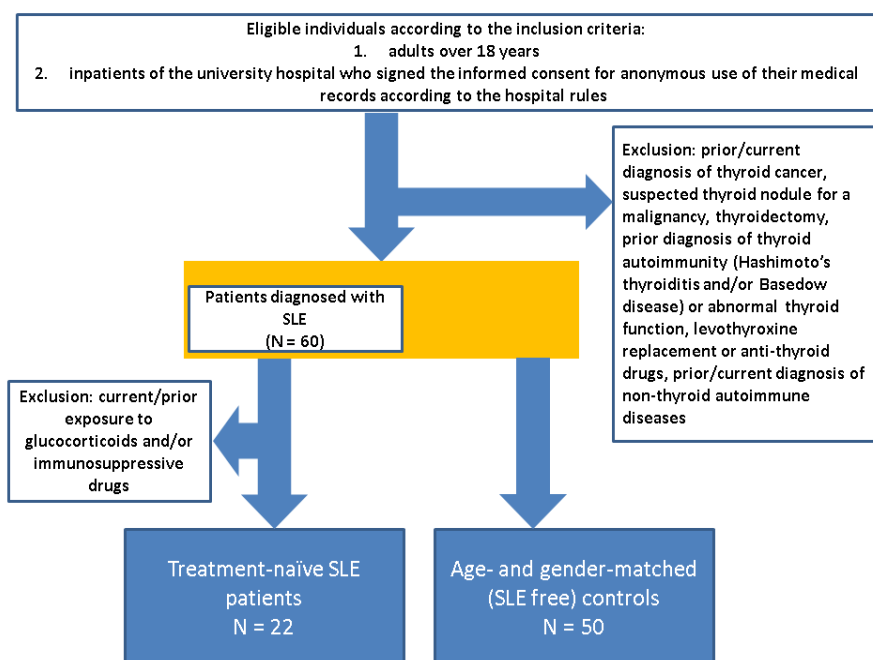
Study population

Individuals who were newly diagnosed with SLE were included according to the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria [15]. Inclusion criteria: adults over 18 years, treatment-naïve SLE subjects, inpatients of the university hospital who signed informed consent for anonymous use of their medical records according to the hospital rules/protocol.

We excluded subjects with a prior/current diagnosis of thyroid cancer, suspected thyroid nodule for a malignancy, thyroidectomy, prior diagnosis of a thyroid autoimmunity (Hashimoto's thyroiditis and/or Basedow disease), or abnormal thyroid function, levothyroxine replacement or anti-thyroid drugs, prior/current diagnosis of non-thyroid autoimmune diseases, oncologic conditions, infections, current/prior exposure to glucocorticoids and/or immunosuppressive drugs.

The control group included SLE-free individuals who were hospitalized at the same hospital/department and did not meet any criteria of suspicion/conformation for SLE and also met all the previously mentioned exclusion criteria. (Figure 1)

Figure 1: Study protocol



Study protocol

Data collection included demographic parameters (e.g., age, sex, current smoking), clinical presentation, including constitutional symptoms (e.g., fever, chills, asthenia, fatigue, recent weight loss of at least 1 kg within the last month), and systemic manifestations categorized by the organ system.

SLE disease activity was quantified using the SELENA-SLEDAI (Systemic Lupus Erythematosus Disease Activity Index), and functional disability was assessed with the Barthel index.

The lab parameters included: hematologic profile (complete blood count with differential); inflammatory markers [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and fibrinogen]; serum protein electrophoresis (albumin, alpha-1, alpha-2, beta, and gamma globulin fractions). Immunologic profile involved testing complement fractions (C3, C4), in addition to the following antibodies: ANA (antinuclear antibody), anti-dsDNA (anti-double-stranded DNA antibody), anti-Ro/SSA, anti-RNP/Sm (anti-ribonucleoprotein and Smith proteins antibodies), aCL (anti-cardiolipin antibody), and aβ2GPI (anti-β2-glycoprotein I antibody), as well as rheumatoid factor.

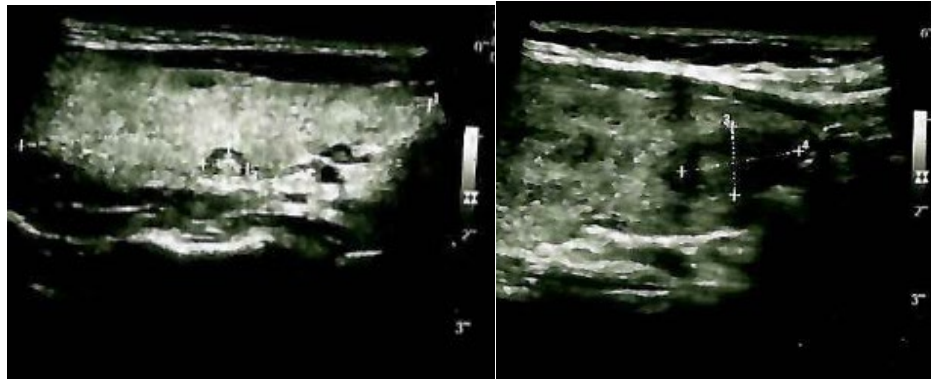
Thyroid profile included functional assessment based on thyroid-stimulating hormone (TSH), free thyroxine (FT4), and total triiodothyronine (T3), in association with an anti-thyroperoxidase (TPO) antibody assay.

We designated the following categories based on serum TSH (normal range: 0.27 - 4.2 μIU/mL) and FT4 (normal range: 0.89 - 1.76 ng/dL) levels; subclinical hypothyroidism (TSH > 4.2 μIU/mL with FT4 within the normal range); hyperthyroidism [TSH < 0.27 μIU/mL with FT4 above the normal range (> 1.76 ng/dL) and/or high T3 levels]; and low T3 syndrome [T3 below the normal range (< 0.8 ng/mL) with TSH and FT4 within normal limits under circumstances of a systemic illness]. Autoimmune thyroiditis was defined by an ATPO level above the upper normal range (> 34 UI/mL).

Additionally, 25-hydroxyvitamin D (25OHD) was measured (vitamin D deficiency was defined as a serum 25OHD level below 20 ng/mL), and glycated haemoglobin (HbA1c) was measured, with prediabetes defined based on a level between 5.7% and 6.4% and diabetes associated with a value of ≥ 6.5%. Alternatively, an abnormal glycaemic control was defined as any HbA1c value ≥ 5.7%.

An anterior neck ultrasound was performed, and data on thyroid nodules were collected, which were categorized by the maximum nodule diameter into three size groups: less than 5 mm (category I), between 5 and 10 mm (category II), and larger than 10 mm (category III). (Figure 2)

Figure 2: Anterior neck ultrasound sample according to the study assessment: thyroid nodule of 4 mm in the right thyroid lobe on a 60-year-old female with normal thyroid function and negative autoimmunity (left); 12-mm thyroid nodule in the left thyroid lobe with hypoechoic pattern on a 41-year-old woman with autoimmune thyroid disease (right)



Statistical Analysis

Statistical analysis was performed using a computational environment with Python statistical libraries (SciPy, Statsmodels). The distribution of continuous variables was assessed for normality. Non-normally distributed data were presented as median and interquartile range [IQR]. Categorical variables were presented as counts (n) and percentages (%). The following statistical tests were employed: The Mann-Whitney U test was used for the comparison of continuous variables between the two independent groups (SLE and control); Fisher's Exact Test was used for the comparison of categorical variables, which is appropriate for the sample size and distribution of the data. Correlations between continuous variables within the SLE cohort were assessed using Spearman's rank correlation coefficient (rho). A two-tailed p-value of less than 0.05 was considered statistically significant.

Ethical Aspects

All participants signed the informed consent for their anonymized medical data to be used for research purposes according to the hospital rules for inpatients. The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of "Dr. Carol Davila" Central Military Emergency University Hospital (approval number 758 from 11 March 2025).

RESULTS

The study included 72 individuals (N = 22 newly diagnosed SLE patients versus 50 SLE-free controls with the same age and gender distribution, specifically, mean age of 49.59 ± 16.24 versus 49.88 ± 15.94 years, female prevalence of 77.27% versus 76%).

SLE patients had a statistically significantly higher prevalence of constitutional symptoms, e.g., fever (27.3% versus 0%, $p < 0.001$) and weight loss (27.3% versus 4%, $p = 0.009$). The most common systemic involvements were musculoskeletal, arthralgia (72.7%), and arthritis (40.9%), being more prevalent than found in the control group ($p < 0.001$ for each). Cutaneous and mucosal manifestations, such as malar rash (36.4%) and erythema (36.4%), were exclusively present in the SLE group ($p < 0.001$). (Table 1)

Table 1: Demographic and clinical features of the study population (N = 72)

Parameter	SLE Group (N = 22)	Control Group (N = 50)	p-value
Age (years), mean $\pm$ SD	49.59 ± 16.24	49.88 ± 15.94	0.950
Female, N (%)	17 (77.27%)	38 (76.00%)	0.901
Smokers N (%)	4 (18.18%)	8 (16.00%)	0.900
Constitutional symptoms			
Fever, N (%)	6 (27.27%)	0 (0.00%)	<0.001
Chills, N (%)	1 (4.54%)	0 (0.00%)	0.232
Asthenia, N (%)	8 (36.40%)	16 (32.00%)	0.771
Fatigue, N (%)	5 (22.70%)	6 (12.00%)	0.287
Weight loss, N (%)	6 (27.30%)	2 (4.00%)	0.009

Clinical manifestations of the system			
Arthralgia, N (%)	16 (72.70%)	15 (30.00%)	<0.001
Arthritis, N (%)	9 (40.91%)	0 (0.00%)	<0.001
Myalgia, N (%)	3 (13.60%)	1 (2.00%)	0.096
Myopathy, N (%)	2 (9.10%)	0 (0.00%)	0.088
Malar rash, N (%)	8 (36.36%)	0 (0.00%)	<0.001
Erythema, N (%)	8 (36.36%)	0 (0.00%)	<0.001
Photosensitivity, N (%)	3 (13.60%)	0 (0.00%)	0.046
Oral ulcers, N (%)	3 (13.60%)	0 (0.00%)	0.046
Alopecia, N (%)	1 (4.54%)	0 (0.00%)	0.232
Purpura, N (%)	1 (4.54%)	0 (0.00%)	0.232
Pleurisy, N (%)	6 (27.30%)	0 (0.00%)	<0.001
Pulmonary hypertension, N (%)	2 (9.10%)	0 (0.00%)	0.088
Dyspnoea, N (%)	2 (9.10%)	4 (8.00%)	0.900
Pericarditis, N (%)	3 (13.60%)	0 (0.00%)	0.046
Valvular involvement, N (%)	2 (9.10%)	2 (4.00%)	0.380
Coronary vasculitis, N (%)	1 (4.54%)	0 (0.00%)	0.232
Polyneuropathy, N (%)	4 (18.18%)	0 (0.00%)	0.007
Seizures, N (%)	2 (9.10%)	0 (0.00%)	0.088
Lupus nephritis, N (%)	1 (4.54%)	0 (0.00%)	0.232
Ascites, N (%)	2 (9.10%)	0 (0.00%)	0.088
Abdominal pain, N (%)	2 (9.10%)	2 (4.00%)	0.380
Lymphadenopathy, N (%)	2 (9.10%)	1 (2.00%)	0.208
Splenomegaly, N (%)	2 (9.10%)	0 (0.00%)	0.088
Dry eye syndrome	3 (13.60%)	0 (0.00%)	0.046
Gait disturbance	1 (4.54%)	1 (2.00%)	0.536

Abbreviations: N = number of patients; SD = standard deviation

The lab findings showed lower haemoglobin, leukocytes, and lymphocytes compared to controls ($p = 0.003$, $p = 0.009$, and $p = 0.024$, respectively). The prevalence of anaemia (31.8% versus 4.0%, $p = 0.005$), leukopenia (31.8% versus 0%, $p < 0.001$), and lymphopenia (27.3% versus 2.0%, $p = 0.003$) was statistically significantly higher in the SLE group.

The median ESR was more than threefold higher (39.5 versus 11.0 mm/h, $p < 0.001$), and the median CRP was over tenfold higher (14.86 versus 1.31 mg/L, $p < 0.001$) compared to the control group. Increased fibrinogen level showed a marginal statistical significance in SLE versus SLE-free subjects ($p = 0.05$). Serum protein electrophoresis revealed a severe dysproteinaemia in the SLE cohort. SLE patients displayed a state of relative hypoalbuminemia, with statistically significantly lower albumin levels compared to controls ($p = 0.012$) in addition to higher acute-phase reactant fractions, with both alpha-1 and alpha-2 globulins being elevated ($p = 0.009$ and $p < 0.001$, respectively). Moreover, a severe hyper-gammaglobulinemia was observed in these patients, with a consequent inverted albumin-to-globulin ratio (1.21 versus 1.58, $p < 0.001$). (Table 2)

Table 2: Hematologic profile, inflammatory markers, antibody status, and serum protein electrophoresis analysis in the study population

Parameter	Normal range	Units	SLE group (N = 22)	control group (N = 50)	p-value
Haemoglobin, Median [IQR]	11.10-14.70	g/dL	11.8 [10.2-13.5]	13.3 [12.4-14.5]	0.003
Anaemia, N (%)			7 (31.82%)	2 (4.00%)	0.005
Leukocytes, Median [IQR]	4.1-10.9	$\times 10^3/\mu\text{L}$	5.5 [3.9-7.5]	7.1 [5.8-8.5]	0.009
Leukopenia, N (%)			7 (31.82%)	0 (0.00%)	<0.001
Lymphocytes, Median [IQR]	1.17-3.17	$\times 10^3/\mu\text{L}$	1.5 [0.9-2.1]	2.0 [1.6-2.4]	0.024
Lymphopenia, N (%)			6 (27.27%)	1 (2.00%)	0.003
Platelets, Median [IQR]	140-440	$\times 10^3/\mu\text{L}$	257 [185-330]	264 [215-310]	0.735
Thrombocytopenia, N (%)			4 (18.18%)	1 (2.00%)	0.027

ESR, Median [IQR]	0-30	mm/h	39.5 [20.0-58.0]	11.0 [6.0-17.0]	<0.001
CRP, Median [IQR]	0-5	mg/L	14.86 [1.32-30.96]	1.31 [0.54-4.10]	<0.001
Fibrinogen, Median [IQR]	276-471	mg/dL	489 [377-571]	395 [337-466]	0.05
Ferritin, Median [IQR]	10-120	µg/L	97.5 [29.5-356.8]	81.4 [34.0-180.5]	0.499
C3 (mg/dL), Median [IQR]	90-180	mg/dL	103.9 [75.5-130.0]	120.2 [98.0- 140.0]	0.124
Low C3 (<90 mg/dL), N (%)			9 (40.91%)	0 (0.00%)	<0.001
C4 (mg/dL), Median [IQR]	10-40	mg/dL	18.7 [8.0-28.0]	24.1 [18.0-30.0]	0.056
Low C4 (<10 mg/dL), N (%)			7 (31.82%)	0 (0.00%)	<0.001
Positive ANA (<1:80), N (%)			22 (100.00%)	0 (0.00%)	<0.001
Positive rheumatoid factor (>14 UI/mL), N (%)			6 (27.27%)	1 (2.00%)	0.003
Positive anti-dsDNA (<25 U/mL), N (%)			12 (54.55%)	0 (0.00%)	<0.001
Positive anti-Ro/SSA (<15 U/mL), N (%)			8 (36.36%)	0 (0.00%)	<0.001
Positive anti-RNP/Sm (<15 U/mL), N (%)			3 (13.64%)	0 (0.00%)	0.046
Positive aCL (<10 U/mL), N (%)			3 (13.60%)	0 (0.00%)	0.046
Positive aβ2GPI (<10 U/mL), N (%)			4 (18.18%)	0 (0.00%)	0.007
Albumin, Median [IQR]	3.5-5.2	g/dL	4.00 [3.80-4.30]	4.41 [4.14-4.63]	0.012
Alpha-1 Globulins, Median [IQR]	0.2-0.4	g/dL	0.30 [0.20-0.40]	0.30 [0.20-0.30]	0.009
Alpha-2 Globulins, Median [IQR]	0.5-0.9	g/dL	0.80 [0.60-0.90]	0.70 [0.60-0.75]	<0.001
Beta1 Globulins, Median [IQR]	0.3-0.5	g/dL	0.42 [0.40-0.50]	0.40 [0.40-0.50]	0.412
Beta2 Globulins, Median [IQR]	0.2-0.5	g/dL	0.40 [0.30-0.50]	0.40 [0.30-0.45]	0.654
Total Beta Globulins, Median [IQR]	0.7-1.2	g/dL	0.90 [0.70 - 0.90]	0.80 [0.75-0.90]	0.048
Gamma Globulins, Median [IQR]	0.8-1.4	g/dL	1.60 [1.40-1.80]	1.10 [1.00-1.25]	<0.001
Total Globulins, Median [IQR]	2.0-3.7	g/dL	3.52 [3.10-3.90]	2.90 [2.70-3.15]	<0.001
Albumin/globulin ratio	1.0-2.6		1.14 [1.02-1.34]	1.52 [1.40-1.70]	<0.001

Abbreviations: ANA = antinuclear antibody; Anti-dsDNA = anti-double-stranded DNA antibodies; Anti-RNP/Sm = anti-ribonucleoprotein and Smith proteins antibodies; aCL = anti-cardiolipin antibody; aβ2GPI = anti-β2-glycoprotein I antibody; CRP = C reactive protein; C3, C4 = complement fractions; ESR = erythrocyte sedimentation rate; IQR = interquartile range; N = number of patients

The levels of thyroid hormones (TSH, FT4, and T3) and TPO antibodies were similar between the SLE group and the SLE-free group. The prevalence of thyroid dysfunction was higher in SLE individuals versus controls (27.27% versus 2%, $p = 0.001$), with most patients presenting subclinical hypothyroidism across the mentioned thyroid function anomalies.

A higher prevalence of autoimmune thyroiditis (as defined by positive circulating TPO according to the study protocol) in the SLE group (27.3%) compared to the control group (14%) did not reach statistical significance ($p = 0.236$). Thyroid ultrasound findings in terms of the highest size-based nodules categories rates displayed no between-group differences.

Additional parameters (25OHD and glucose status) showed a similar profile. (Table 3)

Table 3: Thyroid profile according to the study protocol

Parameter	Normal range	Units	SLE group (N = 22)	Control Group (N = 50)	p-value
TSH	0.35-4.94	µUI/mL	1.77 [1.27-4.06]	1.69 [1.08-2.46]	0.901
FT4	0.70-1.48	ng/dL	0.97 [0.87-1.13]	0.97 [0.91-1.05]	0.842
T3	0.64-1.52	ng/mL	1.11 [0.80 - 1.27]	1.02 [0.90-1.16]	0.156
TPO	0.00-5.61	µUI/mL	0.65 [0.35-11.94]	0.61 [0.30-2.86]	0.634
Positive TPO, N (%)	>5.61		6 (27.27%)	7 (14.00%)	0.236
Subclinical hypothyroidism, N (%)			3 (13.64%)	1(2.00%)	0.076
Hyperthyroidism, N (%)			1(4.55%)	0 (0.00%)	0.305
Low T3 syndrome, N (%)			2 (9.09%)	0 (0.00%)	0.090
Thyroid dysfunction, N (%)			6 (27.27%)	1 (2.00%)	0.001
Category I of thyroid nodules*, N (%)			2 (9.09%)	6 (12.00%)	0.900
Category II of thyroid nodules**, N (%)			1 (4.55%)	3 (6.00%)	0.990
Category III of thyroid nodules***, N (%)			1 (4.55%)	2 (4.00%)	0.900

25-hydroxyvitamin D	>20	ng/mL	23.10 [15.50-31.40]	26.00 [16.60-34.10]	0.531
Vitamin D deficiency (<20 ng/mL), N (%)			7 (31.82%)	13 (26.00%)	0.771
HbA1c	<5.7	%	5.35 [5.03-5.70]	5.40 [5.20-5.70]	0.829
Abnormal glycaemic control, N (%)			6 (27.27%)	12 (24.00%)	0.900
Prediabetes, N (%)			5 (22.73%)	10 (20.00%)	0.990
Diabetes Mellitus, N (%)			1 (4.55)	2 (4.00%)	0.900

Abbreviations: HbA1c = glycated haemoglobin A1c; TSH = thyroid stimulating hormone; T3 = triiodothyronine; FT4 = free thyroxine; TPO = anti-thyroperoxidase antibodies; */**/***/ patients with thyroid ultrasound showing the largest diameter of the thyroid nodule/nodules of less than 5 mm, (category I)*, between 5 and 10 mm (category II)**, and larger than 10 mm (category III)***

SLE individuals presented a moderate level of disease activity, with a median/IQR SELENA-SLEDAI score of 10.5 [8.0-12.0] (ranging between 4 and 53). Functional status, as evaluated by the Barthel index, showed that most patients maintained a high level of independence, with a median score of 100. The SELENA-SLEDAI score was statistically significantly and positively correlated with gamma-globulin levels ($\rho = 0.55$, $p = 0.008$) and HbA1c ($\rho = 0.50$, $p = 0.017$), but not with TPO, TSH, or 25OHD. Barthel index was negatively correlated with SELENA-SLEDAI score ($\rho = -0.56$, $p = 0.007$) and HbA1c ($\rho = -0.54$, $p = 0.010$), but not with the thyroid profile. (Table 4)

Table 4: Correlation between the level of disease activity (SELENA-SLEDAI score) and functional status (Barthel index) in SLE patients

Parameter	Correlation with SELENA-SLEDAI	Correlation with the BARTHEL index	Title 1	Title 2
	Spearman's rho	p-value	Spearman's rho	p-value
SELENA-SLEDAI Score			-0.56	0.007
Gamma-globulins	0.55	0.008	-0.21	0.344
HbA1c (%)	0.50	0.017	-0.54	0.010
TSH (μ U/mL)	0.29	0.187	-0.16	0.478
TPO (U/mL)	-0.11	0.627	-0.01	0.963
25-hydroxyvitamin D (ng/mL)	0.16	0.468	-0.06	0.796

Abbreviations: HbA1c = glycated haemoglobin A1c; TSH = thyroid stimulating hormone; TPO = anti-thyroperoxidase antibodies

DISCUSSION

In this study, we found that disease activity, quantified by the SELENA-SLEDAI score, is positively and statistically significantly associated not only with classical markers of immune activation, such as hyper-gammaglobulinemia, but also with markers of metabolic anomalies, such as HbA1c levels, but not with thyroid function or TPO values. This should be interpreted in the context of a small-sample-size cohort with early SLE diagnosis and does not imply long-term thyroid consequences at this point. Current research comparing different autoimmune diseases has shown that essential B-cell activation with resulting hypergammaglobulinemia is also a characteristic feature of other conditions, such as Sjögren's syndrome, etc., highlighting shared pathophysiological pathways, which involve epigenetic elements, environmental factors, immune and autoimmune contributors, genetic susceptibility, co-occurrence of infections, and potential side effects of the various pharmacologic interventions [3,10].

The SLE group presented a higher rate of thyroid function anomalies, mostly subclinical hypothyroidism, versus the SLE-free group (22.7% versus 2%, $p = 0.001$). These findings are prone to actively checking the thyroid status in newly diagnosed SLE patients, as concluded by other reported data [1,16-20]. The prevalence of an abnormally elevated TPO in SLE-positive versus SLE-negative individuals was not statistically significant, which may be explained by the statistical power ($N = 22$) and by the suboptimal diagnosis of Hashimoto's thyroiditis in this study due to the fact that anti-thyroglobulin antibody testing was not available [21,22]. For instance, in a paediatric, cross-sectional study ($N = 50$, female-to-male ratio of 7), the rate of positive TPO was 2%, while we found a prevalence of 27.27%. In contrast to this study of Shamma et al. [6], which found a positive correlation between the disease duration and FT4 [6], we only included subjects with a novel SLE diagnosis in order to avoid the iatrogenic bias.

Similarly, Adapa et al. [7] found that 45% of the SLE individuals have a thyroid dysfunction of any type, with subclinical hypothyroidism being the most important contributor (22.5%, particularly in females). Of note, the rate of positive TPO was 21.25% [7]. Konte et al. [8] found in 73 childhood-onset SLE patients that 19% of them had subclinical hypothyroidism [8]. As shown in the present study, Na-Nan et al. [9] found a similar positive TPO prevalence in SLE subjects versus age- and sex-matched controls, and no correlation between SLE disease activity and thyroid function, respectively, the level of circulating antibodies against thyroid [9].

Another aspect involves the fact that thyroid function anomalies might be related not only to positive TPOs but also to incidental non-autoimmune hypothyroidism or thyroiditis with normal circulating antibodies against thyroid (e.g., atrophic thyroiditis). Currently, although the connection between SLE and thyroid disease has been reported, the multi-layered pathogenic interplay might explain the heterogeneous results observed in real-life settings [23].

Notably, we found no between-group differences with respect to the thyroid nodules, according to a size-related classification. Globally, the diagnosis of thyroid nodules represents the most common endocrine anomaly in the general population, with a higher rate in iodine-deficient areas. In this instance, no direct association with thyroid autoimmunity was established unless a hypoechoic, inhomogeneous pattern on ultrasound was co-presented [24,25].

Only a limited number of studies found a relationship between SLE and thyroid nodules, a correlation that is not unanimously recognized. For instance, Amer et al. [1] studied 80 newly diagnosed SLE patients (Egyptian population) in a single-centre cross-sectional analysis published in 2025 and found a positive correlation between SELDAI score and thyroid nodules, as well as the rate of malignancy among these nodules. The prevalence of thyroid nodules in SLE subjects with thyroid function anomalies was 43% [1], while in our group, the thyroid nodules rate was 27.27%, irrespective of thyroid function.

We found no correlation between the presence of thyroid autoimmunity and lupus disease activity, an observation that has been reported before, since the autoimmune involvement might not be synchronous at one point in life [9]. However, symptoms such as asthenia/fatigue, myalgia, cognitive difficulties, or hair loss may be exclusively attributed to lupus, while an underlying thyroid dysfunction may be missed. Even though we did not find a direct correlation between TSH/FT4 and SLE activity, a correction of thyroid dysfunction, regardless of the cause (levothyroxine replacement), is essential for the symptomatic management and for improving the patient's quality of life and, hence, allowing a clearer assessment of the symptoms that are exclusively related to the lupus disease [16,26-28].

In this study, a similar prevalence of vitamin D deficiency in SLE patients and controls was observed, noting that there is a widespread prevalence of hypovitaminosis D in the general population, influenced by the geographic and lifestyle factors [29]. 25OHD did not correlate with disease activity, while some authors suggested that it might be found in more severe forms of lupus or in the general population with an increased susceptibility to lupus [30-33].

While the overall prevalence of abnormal HbA1c was not significantly different between treatment-free SLE patients and controls, HbA1c was associated with the SELENA-SLEDAI score ($\rho = 0.5$, $p = 0.017$). This is suggestive of the concept of meta-inflammation, whereas the systemic inflammatory state of lupus itself drives an important metabolic dysregulation [34]. Moreover, HbA1c correlated with functional disability, which suggests that metabolic risk assessment should not be delayed until initiation of corticosteroid treatment, but should be part of the initial evaluation of each SLE patient. Whether glucose profile anomalies are directly or indirectly connected to the thyroid status and overall lupus outcome is still an open matter.

Limitations and further research

As limitations, we mention the cross-sectional, retrospective study design and the sample size. In this study, we excluded an essential part of the autoimmune thyroid diseases, other than Hashimoto's thyroiditis, namely, Graves' disease. Most prior data suggested a more important SLE connection with Hashimoto's thyroiditis rather than Graves's disease among the autoimmune thyroid spectrum [35], but this aspect should be added as well, in a larger analysis, and in addition to the metabolic and cardiovascular co-diagnosis (and even some malignancies) across a multidisciplinary perspective [36-43]. A longitudinal cohort might show the evolution of the thyroid anomalies in relation to the SLE outcome (including under various interventional strategies), the incidental thyroid function changes, and newly positive autoimmunity during lifelong surveillance. Other parameters may prove extremely useful, such as testing for anti-thyroglobulin antibodies and anti-TSH receptor antibodies, as well as collecting data regarding the family medical history of autoimmune conditions (e.g., autoimmune polyendocrine syndromes).

CONCLUSION

Connecting the dots with respect to the thyroid profile in therapy-naïve SLE patients, we found similar TSH, FT4, and TPO levels (versus SLE-free controls), with a higher rate of thyroid dysfunction, mostly subclinical hypothyroidism. Disease activity correlated with HbA1c, not with the thyroid spectrum, as similarly found for the Barthel index. Commonalities in the fields of thyroid and SLE should be taken into account from the onset of the rheumatologic disease. Indirect interplay might involve the glucose profile, as shown by the HbA1c levels. Follow-up of thyroid function and autoimmunity under SLE therapy and a comparison between individuals with TPO-positive versus TPO-negative profiles at baseline might help the understanding of this complex crossroads. A multidisciplinary approach, bringing together rheumatologists and endocrinologists, is mandatory for a tailored strategy and an optimum outcome.

Conflicts of interest and sources of funding

The authors declare no conflict of interest.

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Authors' contribution

Conceptualization, O.P.I., M.C., D.-M.P., and M.L.C.; methodology, O.P.I., M.C., D.-M.P., and M.L.C.; software, O.P.I.; validation, O.P.I., M.C., and M.L.C.; formal analysis, O.P.I., M.C., and M.L.C.; investigation, O.P.I., and M.L.C.; resources, O.P.I., M.C., and M.L.C.; data curation, O.P.I., M.C., D.-M.P., and M.L.C.; writing—original draft preparation, O.P.I.; writing—review and editing, M.C.; visualization, M.C.; supervision, O.P.I., M.C., D.-M.P., and M.L.C.; project administration, O.P.I., M.C., and M.L.C.; funding acquisition, M.L.C. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of “Dr. Carol Davila” Central Military Emergency University Hospital (approval number 758 from 11 March 2025).

Patient consent for publication

Patient consent was waived due to the retrospective design.

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ARTICLE

Beyond diagnostic boundaries: A multidimensional model of established and emerging eating-related psychopathology**Octavian Vasiliu^{1,2}, Andrei Gabriel Mangalagiu^{1,2*}, Bogdan Mircea Petrescu^{1,2}**¹ Neuroscience Department, Discipline of Psychiatry, Faculty of Medicine, University of Medicine and Pharmacy „Carol Davila”, Bucharest, Romania² Department of Psychiatry, University Emergency Central Military Hospital “Dr. Carol Davila”, Romania*Correspondence: AGM, andrei-gabriel.mangalagiu@umfcd

Abstract: Background: Current nosographic systems, which include chapters dedicated to eating disorders (EDs), offer clinically useful criteria but insufficiently address symptom overlap, heterogeneity within the same diagnosis, or its changes in time, and emerging or context-dependent eating-related phenotypes (ERP). Therefore, a transdiagnostic dimensional approach may be useful because it can describe, in a more nuanced manner, the psychopathological processes shared across various clinical presentations. Objectives: To develop a dimensional eating psychopathology framework as a hypothesis-generating instrument for characterizing established EDs and emerging or context-dependent ERPs. Methods: A conceptual model-development approach was applied for extending a previously proposed integrative classification of EDs and related phenomena. A set of hypothesized dimensions was selected according to their transdiagnostic applicability, dimensional nature, conceptual distinction from diagnostic labels, and potential clinical relevance. Characteristics describing the circumstances in which psychopathology is expressed were represented separately as contextual modifiers. Applying this framework, 15 ERPs were mapped theoretically across eight dimensions using a five-level ordinal scale. Results: The proposed model is composed of eight core dimensions: body-image overvaluation, restrictive dietary control, loss of control over eating, compulsivity and cognitive rigidity, reward/addiction-like eating, emotion-regulation dependence, interoceptive dysregulation, and compensatory or body-modifying behavior. Six contextual factors with modifying properties were identified, i.e., circadian/sleep, medical treatment, substance use, reproductive, athletic/performance, and health/purity-related contexts. Conclusions: The currently proposed model offers a common descriptive framework for comparing recognized EDs, emerging constructs, behavioral phenotypes, and context-dependent presentations without implying equivalent diagnostic status. In its early stages of development, the model requires formal content validation, independent expert assessment, and patient-level empirical testing before it can be used as a classification or clinical instrument.

Keywords: eating disorders; anorexia nervosa; bulimia nervosa; binge eating disorder; dimensional model; eating-related phenotypes; transdiagnostic framework; compulsivity; body-image disturbance

INTRODUCTION

The nosological field of eating disorders (EDs) has evolved slightly since one edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders or the World Health Organization's International Classification of Diseases (DSM IV TR, DSM-5, DSM-5TR, ICD-10, ICD-11) to another, being a rather conservative domain, both in terms of the number of validated diagnoses and diagnostic criteria [1-5]. A rapid comparison between the previously mentioned nosological systems, published in the last three decades, leads to the conclusion that, besides the "veterans" of this category, i.e., anorexia nervosa (AN) and bulimia nervosa (BN), a single diagnosis gained its own status, i.e., binge eating disorder (BED), while another, feeding disorder of infancy or early childhood (FDIEC) was substantially reconceptualized and expanded into avoidant/restrictive food intake disorder (ARFID) from DSM-IV TR to DSM-5 [3-5]. Of course, other aspects, such as the reorganization of the EDs chapter in the last editions of DSM and ICD by including pica and rumination disorders, or reevaluation of diagnostic criteria for AN and BN, are clinically significant, but still do not account for the complexity of the eating-related psychopathological phenotypes (ERPs), described in the medical literature over the last decades.

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A large body of literature was devoted to entities not included in the DSM or ICD, such as food addiction (FA) (or, more recently, ultra-processed food addiction, UPFA) [6-10], sleep-related eating disorder (SRED) [11-13], anorexia athletica (AA) [14-16], night eating syndrome (NES) [17-20], diabulimia [21-23], etc. Also, the level of evidence is increasing both qualitatively and quantitatively, as systematic reviews and meta-analyses on orthorexia nervosa (ON), UPFA, pregorexia, diabulimia, and muscle dysmorphia (MD) have been published, supporting the core characteristics of these ERPs [24-31]. These meta-analytic processes showed that, although clearly defined diagnostic criteria are lacking for most ERPs, they nevertheless have a substantial association with already validated EDs. For example, ON has a moderate association with ED symptoms and much weaker with obsessive-compulsive symptoms, UPFA has been reported as presenting a pooled prevalence of 20% across populations, with $\geq 50\%$ prevalence in patients with BED, while for pregorexia, body-image dissatisfaction tends to increase during pregnancy and may persist in the postpartum period; in patients diagnosed with insulin-dependent diabetes, pooled estimates showed about 25% of them present clinically significant ERP, and about 20% report insulin omission or restriction; for muscle dysmorphia, a moderate pooled association exist with ED symptomatology [24-31].

Another critique of the conservative approach to the nosology of EDs derives from high within-diagnosis heterogeneity, substantial symptom overlap between diagnoses, frequent diagnostic migration over time, and the persistence of clinically significant presentations that do not fit neatly within prototypical categories [32-33]. All these aspects have not only theoretical importance, but also may impact screening strategies, prevention policies, diagnostic instruments, and case management, by increasing the chance to identify ERPs neglected by current nosographic systems, by contributing to policies focused on early detection of such ERPs (for example, UPFA or pregorexia nervosa), by more accurately informing evidence-based strategies for pharmacological or psychotherapeutic interventions, etc.

The third line of arguments in favor of a more nuanced approach to the field of EDs stems from the significant functional impairment associated with this type of pathology, including various ERPs that are still awaiting nosological validation [34-36]. Creating adequate models of interpretation for ED and ERP would not only enhance mental health specialists' awareness of these phenomena but, again, would also enable the implementation of therapeutic interventions that may improve these patients' prognosis and overall functioning [35-36].

Therefore, searching for the conceptual foundations of a transdiagnostic approach to EDs has become increasingly attractive, not only at a theoretical level but also because of the anticipated positive impact on the case management of patients affected by this pathology. Pioneering this domain, Fairburn et al. (2003) proposed that AN, BN, and atypical eating disorders share core psychopathological processes despite differences in their clinical manifestations, and suggested that the cognitive-behavioral theory of BN may be extended to incorporate other EDs as well [37]. Fairburn also suggested the first transdiagnostic treatment for EDs that includes four stages: (1) engaging and educating the patient, creating a personalized formulation, and obtaining early behavioral change; (2) characterization of barriers to change, assessment of the contribution of maintaining mechanisms (clinical perfectionism, core low self-esteem, mood intolerance, and interpersonal difficulties), and creation of a revised and more refined intervention; (3) modification of the patient's ED psychopathology, such as the overvaluation of eating, and addressing additional processes identified in the step 2; (4) ensuring the progress is maintained after the end of the treatment [37]. A special therapy for ED, known as CBT-E (cognitive-behavioral therapy for eating disorders), has evolved from this model and is currently supported by evidence from clinical practice [38-41]. A meta-analysis ($n=15$ CBT-E studies, $N=948$ participants) showed a statistically significant effect of the active intervention across all EDs ($g=1.06$), regardless of study design [42].

From a nosological perspective, Wildes and Marcus advanced the concept of dimensionality in the domain of EDs, advocating more nuanced assessments of eating psychopathology and associated clinical phenomenology, and incorporating potential neurobiological characteristics alongside conventional diagnostic categories [33]. In their seminal work, they stated that ED features are observed on a continuum with normality and considered that clinical management of affected patients across the ED continuum could benefit significantly from such an approach, e.g., by guiding treatment selection, setting, intensity, etc. [33].

This dimensional approach is not in direct conflict with categorical diagnoses, but may help develop the field by incorporating the previous perspective and enabling more targeted therapeutic interventions. Categorical diagnoses may therefore be decomposed into multiple features that require dimensional evaluation, so that their existence is not denied, since they represent the end of a continuum, i.e., the more severe form such a dimension may embody. In favor of this idea, empirical evidence is starting to gather; for example, the analysis of Luo et al. (2016) directly compared categorical, dimensional, and hybrid models of eating pathology in a large population-based sample and found that dimensional models provided the best overall match for features including body dissatisfaction, binge eating, weight preoccupation, and compensatory behaviors [43]. Forbush et al. (2017) identified eating-related dimensions included within a broader internalizing psychopathology hierarchy and reported that the lower-order dimensional structure explained substantially more variance in clinical impairment than conventional DSM diagnoses [32]. A subsequent longitudinal investigation, also conducted by Forbush et al. (2018), showed that a hierarchical-dimensional model predicted 60.1% of the variance in six-month outcomes, compared with 35.8% explained collectively by DSM eating, mood, and anxiety diagnoses [44].

Other, more recent investigations have expanded this area of research. For example, a hierarchical dimensional taxonomy (HiTOP), based on results from 252 community-recruited adults with EDs, included 10 hierarchical factor dimensions [45]. Multiple lower-order dimensions were identified, including body dissatisfaction, restricting, bulimic symptoms, excessive exercise, negative attitudes toward obesity, and cognitive restraint [45]. These dimensions showed considerable utility in predicting subsequent ED behaviors and psychiatric impairment (92% and 58% of the variance in recovery outcomes at six months and one year, respectively, was predicted by the dimensions explored) [45].

Also, dimensional evidence has emerged directly from examining DSM diagnostic criteria. In a 2026 study of clinician-rated DSM-5 criteria for AN, BN, and BED, factor analysis yielded a dimensional solution for ED criteria, accounting for almost 80% of the variance: binge eating, compensatory and purging behaviors, shape/weight overvaluation, drive for thinness, and absence of bingeing and purging [46]. Considerable overlap in diagnostic criteria across conventional nosographies led the authors to conclude that a transdiagnostic model may be a superior strategy to detect important aspects of ED psychopathology [46].

Based on these arguments, the dimensionality in the domain of EDs should not be regarded as a purely conceptually interesting topic, since multiple lines of evidence show that clinically relevant features related to eating behavior may cross conventional diagnostic boundaries and that their dimensional organization may offer information not contained in the diagnostic labels alone.

However, major theoretical and practical obstacles regarding dimensionality remain to be addressed, since, for example, most empirical dimensional models have been constructed from symptoms observed within established ED diagnostic frameworks and, in some cases, their relationships with broader, related psychopathology [32-33,44-46]. Secondly, clinical practice and also clinical research increasingly recognize a wider range of ERPs whose nosological status varies considerably, with constructs such as ON and UPFA, behaviors described as emotional eating (EE), and context-dependent presentations such as AA, pregorexia, drunkorexia, and voluntary insulin restriction for weight-control purposes, benefiting from a continuing amount of attention. For now, at least, such ERPs are not assumed to represent equivalent diagnostic entities, since their validation is still far from being achieved by empirical research. Therefore, some ERPs may be considered syndromes, some represent behavioral or psychopathological constructs, and others may reflect manifestations of established EDs occurring within particular medical, behavioral, or environmental contexts.

A previous integrative model attempted to address this expanded phenomenology by organizing both recognized EDs and less well-defined eating-related conditions into four broad groups according to their predominant clinical psychopathological features: (A) self-image dysfunction, (B) impaired self-control, (C) addictive components, and (D) abnormal eating behaviors associated with another medical or psychiatric condition [47]. The respective framework was mainly conceptual and focused on increasing awareness in mental health specialists, so it did not pursue the validation of core dimensions. Also, that model highlighted at least one intrinsic limitation of distributing complex phenotypes into defined categories, i.e., a single presentation may simultaneously involve disturbance in body image, restrictive eating, loss of control, compulsivity, reward-related processes, affect regulation, altered interoception, and compensatory or behaviors targeting body modification; conversely, phenotypes assigned to different conceptual categories may share several of these mechanisms [47]. A dimensional extension of the previous model, therefore, may offer the possibility of describing patterns of psychopathology, rather than allocating each phenotype to a single predominant group.

The distinction between overall ED severity and the configuration of specific psychopathological processes is also relevant in the case of structured and validated measurement. The Eating Disorder Examination Questionnaire (EDE-Q), considered to be one of the most widely used validated instruments for EDs, was recently reconsidered by Jeon et al. (2025) [48] in a clinical sample of 2032 individuals receiving specialized treatment for various EDs. Factor-analytic and item-response analyses supported an essentially unidimensional structure reflecting overall ED symptom severity, leading to the development of a refined 13-item version. Of importance for this topic, the authors emphasized the continued need for measures that can characterize more specific cognitive, behavioral, and affective components of disordered eating [48]. Overall severity and multidimensionality in the domain of EDs may therefore provide complementary rather than competing information: while the former indicates how severe eating psychopathology is, the latter may bring clarifications about its organization.

Based on these arguments, the current study proposes the Dimensional Eating Psychopathology Model (DEPM), in which established EDs and emerging or context-dependent ERPs are characterized within a common framework rather than treated as equivalent diagnostic labels. Eight core psychopathological dimensions are considered: (D1) shape-, weight-, or body-image overvaluation; (D2) restrictive dietary control; (D3) loss of control/disinhibited eating; (D4) compulsivity and cognitive rigidity; (D5) reward/addiction-like eating; (D6) emotion-regulation dependence; (D7) interoceptive dysregulation; and (D8) compensatory and body-modifying behavior. Elements that may impact the circumstances of these dimensions' expression, including circadian/sleep involvement, medical-treatment manipulation, substance-use coupling, reproductive context, athletic/performance context, and health/purity-related motivation, are considered separately as contextual modifiers rather than psychopathological dimensions. In this formulation, dimensions describe how eating psychopathology is organized, whereas contextual modifiers describe the conditions under which it is expressed.

The primary objective of this study was to develop a hypothesis-generating, multidimensional model of eating-related presentations that could refer to both established EDs and emerging or context-dependent eating-related psychopathological configurations within a common model. More specifically, the study aimed to: (1) identify a set of core psychopathological dimensions that could be applied transdiagnostically across heterogeneous eating-related presentations; (2) distinguish these psychopathological dimensions from contextual factors that may influence the circumstances in which eating-related psychopathology emerges or become manifest; (3) construct preliminary dimensional profiles for established EDs and selected emerging or context-dependent ERPs; (4) explore, at a conceptual level, patterns of similarity and divergence between phenotypes based on their proposed dimensional configurations; and (5) extend the previously proposed categorical integrative model of EDs and ERPs into a multidimensional framework capable of account for overlapping between various phenotypes and for the simultaneous expression of several psychopathological phenomena.

The proposed framework is not focused on redefining existing diagnostic labels or criteria, nor on assigning diagnostic status to emerging constructs, but on considering diagnoses, not-yet-validated syndromes, eating-related behavioral constructs, and context-dependent presentations as phenotypes that require a dimensional characterization. The resulting DEPM should, therefore, be viewed as a theoretical and hypothesis-generating framework that would require subsequent validation through clinical and epidemiological studies.

MATERIALS AND METHODS

Study design

This study used a conceptual model-development approach to construct a multidimensional framework for established and emerging ERPs, which extends and refines a previously published integrative classification in which eating-related conditions were grouped by predominant clinical characteristics. The current method moved from assignment to a predominant category of pathological behavior to the characterization of EDs and ERPs across multiple concomitant psychopathological dimensions.

It is to be noted that during this study, no actual patient information, expert consensus data, or other primary empirical observations were gathered; therefore, the dimensional ratings presented in the DEPM should be interpreted only as hypothesized profiles.

Conceptual framework development

The starting point for model development was the observation that categorical assignment may inadequately represent phenotypes characterized by multiple overlapping psychopathological mechanisms. The previous categorical framework [47] was therefore decomposed into more specific transdiagnostic components that can vary independently across eating-related presentations.

Candidate dimensions were introduced in the model based on their capacity to fulfill the following criteria: (1) relevance across more than one ERP; (2) ability to vary in severity rather than being present or absent; (3) conceptual distinction from already confirmed diagnostic labels; (4) potential clinical relevance for differentiating phenotypes; (5) applicability to both established disorders and emerging eating-related constructs; and (6) theoretical capacity to account for overlap between otherwise distinct clinical presentations.

This process resulted in eight proposed core dimensions: (D1) Shape-, weight-, or body-image overvaluation; (D2) Restrictive dietary control; (D3) Loss of control/disinhibited eating; (D4) Compulsivity and cognitive rigidity; (D5) Reward/addiction-like eating; (D6) Emotion-regulation dependence; (D7) Interoceptive dysregulation; and (D8) Compensatory and body-modifying behavior; each dimension was conceptualized as a continuum extending from minimal or absent expression to severe or characteristic expression.

Contextual modifiers

A set of clinically important characteristics was considered inappropriate for inclusion as psychopathological dimensions, since they primarily describe the context in which eating-related behavior occurs, and not the psychopathological mechanism itself. These characteristics were represented separately and considered as "contextual modifiers". Six contextual modifiers were proposed: (C1) Circadian/sleep context; (C2) Medical-treatment context; (C3) Substance-use context; (C4) Reproductive context; (C5) Athletic/performance context; and (C6) Health/purity-related context.

Within the DEPM, dimensions are intended to characterize how eating psychopathology is organized, whereas contextual modifiers characterize where, why, or under what circumstances this may be expressed. Contextual modifiers were not assigned severity scores due to their expectedly lower impact and were not considered independent psychopathological constructs.

Selection of eating-related phenotypes

The model included both formally recognized eating disorders and selected emerging or context-dependent ERPs previously discussed in the literature and/or in the preceding integrative model [47]. The phenotypes included were: AN, restricting type; anorexia nervosa, binge-eating/purging type; BN; BED; ARFID; ON; FA/UPFA; EE; muscle dysmorphia; AA; pregorexia; eating-disorder behavior involving deliberate insulin restriction or omission for weight control; drunkorexia; NES; and SRED.

Construction of the dimensional eating phenotype matrix

Each phenotype was characterized according to the hypothesized degree of involvement in the predefined eight core dimensions, using a numerical matrix. For conceptual mapping, a Likert scale was used: 0 – absent or non-characteristic; 1 – minor or occasional; 2 – moderate or variable; 3 – prominent; 4 – defining or near-defining. When available evidence or clinical descriptions suggested substantial heterogeneity within a phenotype, dimensional involvement was expressed as a range rather than as an isolated value. The scores were assigned only as theoretical estimates intended to illustrate the structure of the proposed model, and they do not bear statistical value at this moment.

Conceptual interpretation of dimensional profiles

The dimensional profiles were examined descriptively to identify combinations of dimensions that recurred across more than one phenotype, with particular attention being given to potential constellations characterized predominantly by: restriction and compulsivity; loss of control and affect regulation; reward/addiction-related mechanisms; and body-image disturbance combined with compensatory and body-modifying behavior. These groupings were considered hypothesized dimensional configurations rather than empirically derived clusters, as no statistical clustering, factor analysis, multidimensional scaling, or other inferential analysis was performed.

Relationship with the previous integrative model

The DEPM was designed as a dimensional extension of the previously proposed categorical framework [47], rather than a replacement for it. Whereas the earlier model assigned eating-related presentations based on predominant clinical characteristics, the present framework allows each phenotype to occupy multiple positions simultaneously across eight psychopathological dimensions. The model therefore allows two complementary questions to be distinguished: (1) Which broad clinical pattern best characterizes a phenotype? (2) Which combination and relative intensity of psychopathological dimensions constitute that phenotype?. This distinction permits the explicit representation of overlap between previously separate categories and allows phenotypes with different diagnostic or contextual labels to display partially convergent dimensional profiles.

Ethical considerations

The study involved the development of a conceptual model based on previously published scientific information and did not involve human participants, identifiable personal data, biological material, or prospective data collection; therefore, institutional ethical approval and informed consent were not applicable.

RESULTS

Architecture of the Dimensional Eating Psychopathology Model

The proposed DEPM consists of two complementary levels of characterization: eight core psychopathological dimensions (D1-D8) and six contextual modifiers (C1-C6). The dimensions represent psychopathological processes hypothesized to vary continuously across eating-related presentations, whereas contextual modifiers characterize sets of circumstances that may shape the expression of these processes, but without themselves being considered as psychopathological dimensions (Table 1).

The eight dimensions were defined as: D1, shape-, weight-, or body-image overvaluation; D2, restrictive dietary control; D3, loss of control/disinhibited eating; D4, compulsivity and cognitive rigidity; D5, reward/addiction-like eating; D6, emotion-regulation dependence; D7, interoceptive dysregulation; and D8, compensatory and body-modifying behavior. Each dimension was represented using an ordinal five-level scale ranging from 0 (absent or non-characteristic) to 4 (defining or near-defining). The six contextual modifiers comprised circadian/sleep context (C1), medical-treatment context (C2), substance-use context (C3), reproductive context (C4), athletic/performance context (C5), and health/purity-related context (C6) (Table 2).

This organization generated a two-axis conceptual framework in which a phenotype may share its psychopathological architecture with other phenotypes while remaining clinically distinguishable because of the context in which that architecture is expressed.

Dimensional characterization of eating-related phenotypes

Applying the eight proposed dimensions to the selected phenotypes resulted in heterogeneous profiles rather than one-to-one relationships between individual dimensions and diagnostic categories. Established EDs generally involved multiple dimensions simultaneously, and several emerging or context-dependent phenotypes showed partial overlap with formally recognized

disorders. AN, restricting type, was hypothesized to be characterized predominantly by high body-image overvaluation, dietary restriction, and rigidity, accompanied by clinically relevant interoceptive dysregulation and variable body-modifying behavior. The binge-eating/purging subtype of AN retained this restrictive-compulsive definition but was additionally described by substantially greater loss of control and compensatory and body-modifying behavior. BN and BED shared significant loss-of-control eating and emotion-regulation dependence, but their proposed hypothesized profiles still differed in the degree of body-image overvaluation, dietary restriction, and compensatory/body-modifying behavior, which were considered substantially more prominent in BN. FA/UPFA and EE partially overlapped within the loss-of-control spectrum but were hypothesized to differ in the relative predominance of reward-related and affect-regulatory mechanisms.

Other phenotypes illustrated how similar observable behaviors may arise from different dimensional configurations. For example, restriction was prominent in AN, ARFID, orthorexia, anorexia athletica, and pregorexia, but the hypothesized contribution of body-image overvaluation, rigidity, and contextual factors differed between them. Likewise, muscle dysmorphia shared high body-image involvement, rigidity, and compensatory and body-modifying behavior with several conventional ED presentations despite its distinct emphasis on muscularity.

ARFID was a challenge for the model due to the fact that although restrictive intake may be severe in these patients, shape- and weight-related overvaluation was considered to be minimal or absent. The dimensional profile of this pathology was also characterized by relatively broad ranges for rigidity and interoceptive disturbance, reflecting the recognized heterogeneity of sensory sensitivity, low interest in eating, and fear of aversive consequences.

Table 1: Core features of the Dimensional Eating Psychopathology Model

Code	Dimension	Core question	Low end	High end
D1	Shape, weight, or body-image overvaluation (Body image)	How much is self-evaluation determined by body shape, weight, or muscularity?	Physical parameters largely irrelevant for self-worth	Physical parameters dominate self-evaluation
D2	Restrictive dietary control (Restriction)	How strongly is food intake deliberately restricted or controlled?	No significant restriction on eating	Persistent and rigid restrictive eating patterns
D3	Loss of control eating (Loss of control)	How much is eating experienced as difficult or impossible to stop?	Controlled intake	Recurrent severe loss of control
D4	Compulsivity and cognitive rigidity (Rigidity/compulsivity)	How ritualized and inflexible are eating behaviors?	Flexible	Rigid or compulsive
D5	Reward/addiction-like eating (Reward)	How much is behavior characterized by craving, salience, and continued use despite harm?	Reduced reward salience	Strong addiction-like pattern
D6	Emotion-regulation dependence (Emotion regulation)	How strongly is eating/non-eating used to regulate affect?	Low impact of eating on mood regulation	High effect of eating on mood regulation
D7	Interoceptive dysregulation (Interoception)	How disrupted is hunger/satiety/body-signal perception?	No disruption noted	Profoundly dysregulated
D8	Compensatory and body-modifying behavior (Body modification)	How strongly are exercise/purging/other compensatory actions used to modify body shape or weight?	Absent	Severe compulsive behavior

Table 2: Contextual modifiers included in the Dimensional Eating Psychopathology Model

Code	Definition	Illustrative phenotypes
C1	Circadian rhythms	Night eating syndrome, Sleep-related eating disorder
C2	Medical treatment	Diabulimia
C3	Substance use	Drunkorexia
C4	Reproductive context	Pregorexia
C5	Athletic/performance context	Anorexia athletica
C6	Health/purity-related context	Orthorexia nervosa

SRED was also challenging because although episodes of night eating may phenomenologically resemble loss-of-control eating, their occurrence during incomplete arousal from sleep and the associated alteration in awareness distinguish them from consciously experienced disinhibited eating. Accordingly, SRED was primarily linked to the circadian/sleep contextual modifier rather than being interpreted as a prototypical loss-of-control eating phenotype.

Recurring dimensional configurations

Descriptive comparison of the preliminary phenotype profiles suggested four recurring configurations. The first was a restrictive-compulsive configuration, characterized predominantly by D2 and D4, and represented most clearly by the AN restricting type, ON, AA, and pregorexia, as these phenotypes were hypothesized to differ mainly in body-image involvement and their corresponding contextual modifiers. The second was a loss-of-control/affect-regulation configuration, characterized predominantly by important scores on D3 and D6. BN, BED, and EE were found within this configuration, with substantial differentiation based on body-image overvaluation and compensatory/body-modifying behavior. The third was a reward/disinhibition configuration, characterized by the co-occurrence of D3 and D5: FA/UPFA represented its clearest expression, with partial overlap predicted for BED, BN, and some forms of EE. The fourth was a body-transformation/compulsivity configuration, characterized by D1, D4, and D8: muscle dysmorphia, AA, and some AN presentations showed the strongest hypothesized representation of this pattern.

These configurations are not intended as reciprocally exclusive clusters, since individual phenotypes may occupy more than one configuration, and the configurations themselves represent descriptive hypotheses generated from the proposed matrix rather than empirically derived latent classes.

Table 3: Interpretation of eating-related phenomena according to the Dimensional Eating Psychopathology Model

Phenotype	D1 Body image	D2 Restriction	D3 Disinhibition	D4 Rigidity	D5 Reward	D6 Emotion regulation	D7 Interoception	D8 Body change
AN restrictive type	⊕⊕⊕⊕	⊕⊕⊕⊕	⊕○○○ /○○○ ○	⊕⊕⊕⊕	⊕○○○	⊕⊕○○ / ⊕⊕⊕○	⊕⊕⊕○/ ⊕⊕⊕⊕	⊕⊕○○ / ⊕⊕⊕○
AN-binge eating/ purging type	⊕⊕⊕⊕	⊕⊕⊕⊕	⊕⊕⊕○	⊕⊕⊕⊕	⊕⊕○○	⊕⊕⊕○	⊕⊕⊕○/ ⊕⊕⊕⊕	⊕⊕⊕⊕
BN	⊕⊕⊕⊕	⊕⊕○○ / ⊕⊕⊕○	⊕⊕⊕⊕	⊕⊕○○ / ⊕⊕⊕○	⊕⊕⊕○	⊕⊕⊕⊕	⊕⊕⊕○	⊕⊕⊕⊕
BED	⊕⊕○○ / ⊕⊕⊕○	⊕○○○	⊕⊕⊕⊕	⊕○○○ / ⊕⊕○○ / ⊕⊕○○	⊕⊕⊕○/ ⊕⊕⊕⊕	⊕⊕⊕⊕	⊕⊕⊕○	○○○○ / ⊕○○○
ARFID	⊕○○○ /○○○ ○	⊕⊕⊕○/ ⊕⊕⊕⊕	○○○○	⊕⊕○○ / ⊕⊕⊕○	⊕○○○ /○○○ ○	⊕○○○ / ⊕⊕○○	⊕⊕○○/ ⊕⊕⊕○/ ⊕⊕⊕⊕	○○○○
Orthorexia	⊕○○○ / ⊕⊕○○	⊕⊕⊕○/ ⊕⊕⊕⊕	⊕○○○ /○○○ ○	⊕⊕⊕⊕	⊕○○○	⊕○○○ / ⊕⊕○○	⊕⊕○○	○○○○ / ⊕○○○

								/ ⊕⊕○○
Food addiction	⊕○○○ / ⊕⊕○○	⊕○○○ / ○○○ ○	⊕⊕⊕○/ ⊕⊕⊕	⊕○○○ / ⊕⊕○○	⊕⊕⊕⊕	⊕⊕○○ / ⊕⊕⊕	⊕⊕○○/ ⊕⊕⊕	○○○○ / ⊕○○○
Emotional eating	○○○○ / ⊕○○○ / ⊕⊕○○	⊕○○○ / ○○○ ○	⊕⊕○○ / ⊕⊕⊕	⊕○○○ / ○○○ ○	⊕⊕○○ / ⊕⊕⊕	⊕⊕○○ / ⊕⊕⊕	⊕⊕○○/ ⊕⊕⊕	○○○○
Muscle dysmorphi a	⊕⊕⊕⊕	⊕⊕○○ / ⊕⊕⊕	⊕○○○ / ○○○ ○	⊕⊕⊕⊕	⊕○○○ / ⊕⊕○○	⊕⊕○○	⊕○○○/ ⊕⊕○○	⊕⊕⊕⊕
Anorexia athletica	⊕⊕⊕○	⊕⊕⊕○/ ⊕⊕⊕	⊕○○○ / ○○○ ○	⊕⊕⊕○/ ⊕⊕⊕	⊕○○○	⊕⊕○○	⊕⊕○○	⊕⊕⊕⊕
Pregorexia	⊕⊕⊕○/ ⊕⊕⊕	⊕⊕⊕○/ ⊕⊕⊕	⊕○○○ / ○○○ ○	⊕⊕○○ / ⊕⊕⊕	⊕○○○	⊕⊕○○ / ⊕⊕⊕	⊕⊕○○/ ⊕⊕⊕	⊕⊕○○ / ⊕⊕⊕
Diabulimia	⊕⊕⊕○/ ⊕⊕⊕	⊕○○○ / ⊕⊕○○	⊕○○○ / ⊕⊕○○ / ⊕⊕⊕○	⊕⊕○○	⊕○○○ / ⊕⊕○○	⊕⊕○○ / ⊕⊕⊕	⊕⊕○○/ ⊕⊕⊕	⊕⊕⊕⊕
Drunkorexi a	⊕⊕○○ / ⊕⊕⊕	⊕⊕⊕	⊕○○○ / ⊕⊕○○ / ⊕⊕⊕○	⊕○○○ / ⊕⊕○○	⊕⊕○○ / ⊕⊕⊕	⊕⊕○○ / ⊕⊕⊕	⊕⊕○○	⊕⊕⊕
NES	○○○○ / ⊕○○○ / ⊕⊕○○	⊕○○○ / ○○○ ○	⊕⊕○○ / ⊕⊕⊕	⊕○○○	⊕⊕○○ / ⊕⊕⊕	⊕⊕⊕	⊕⊕○○/ ⊕⊕⊕	○○○○
SRED	○○○○	○○○○	⊕⊕⊕	○○○○	⊕○○○	⊕○○○ / ○○○ ○	⊕⊕⊕	○○○○

Contribution of contextual modifiers

Separating contextual modifiers from core psychopathological dimensions allowed phenotypes with potentially similar psychological mechanisms to remain distinguishable according to the circumstances surrounding their expression. Thus, eating pathology associated with deliberate insulin restriction or omission was linked to a medical-treatment context; drunkorexia to a substance-use context; pregorexia to a reproductive context; AA to an athletic/performance context; and ON to a health/purity-related context; NES and SRED were associated with circadian/sleep factors.

The contextual factors therefore prevent the model from treating pregnancy, diabetes treatment, athletic participation, alcohol consumption, sleep phenomena, or health-oriented beliefs as pathological dimensions in themselves. Instead, these circumstances are conceptualized as modifiers that shape the observable phenotype produced by a given dimensional configuration.

A hypothetical interpretation for each of the conditions described previously is provided in Table 3.

Relationship with the previous categorical model

Compared with the previous four-category integrative model [47], the DEPM allows multiple psychopathological processes to be represented simultaneously within a single phenotype. Phenotypes previously assigned to a common category may remain close at the dimensional level, but the model also predicts overlap between presentations formerly placed in different groups; consequently, the previous categories are reformulated as predominant patterns rather than reciprocally exclusive classificatory categories (Table 4).

Table 4: Relationship between Dimensional Eating Psychopathology Model and previous categorical model

Previously hypothesized cluster	Type of ED/syndrome	Dimensions affected- Intra-cluster similarities	Dimensions affected- Intra-cluster differences
A (restrictive-compulsive)	AN restrictive type	D2, D4	D1 (+Contextual modifiers)
	Orthorexia		
	Pregorexia		
	Anorexia athletica		
B (Loss of control/affect regulation)	BN	D3, D6	D1, D8
	BED		
	Emotional eating		
C (reward-driven)	Food addiction	D3, D5	
	Anorexia athletica		
	AN		
D (Body-transformation/ compulsivity)	Muscle dysmorphia	D1, D4, D8	
	Anorexia athletica		
	AN		

Table 5: Main instruments for the operationalization of the Dimensional Eating Psychopathology Model

Dimension	Preferred instruments	Observations
D1 (Body image)	EDE-Q, BSQ	EDE-Q captures core eating disorder psychopathology/shape-weight concerns
D2 (Restriction)	EDE-Q restraint items, TFEQ cognitive restraint	
D3 (Loss of control)	EDE-Q binge/LOC items + TFEQ uncontrolled eating	Can distinguish binge frequency from subjective loss of control
D4 (Rigidity/compulsivity)	OCI-R + eating-specific rigidity measure	
D5 (Reward)	YFAS 2.0	
D6 (Emotion regulation)	DERS-16/DERS + emotional-eating measure	DERS has been studied specifically in populations with eating disorders
D7 (Interoception)	MAIA-2	Gives multiple facets rather than a single “interoceptive deficit”
D8 (Body modification)	CET + EDE-Q compensatory behaviors	

BSQ= Body Shape Questionnaire; CET= Compulsive Exercise Test; DERS= Difficulties in Emotion Regulation Scale; EDE-Q= Eating Disorder Examination-Questionnaire; MAIA= Multidimensional Assessment of Interoceptive Awareness; OCI-R= Obsessive-Compulsive Inventory-Revised; TFEQ= Three-Factor Eating Questionnaire; YFAS= Yale Food Addiction Scale

Instruments for the operationalization of this model

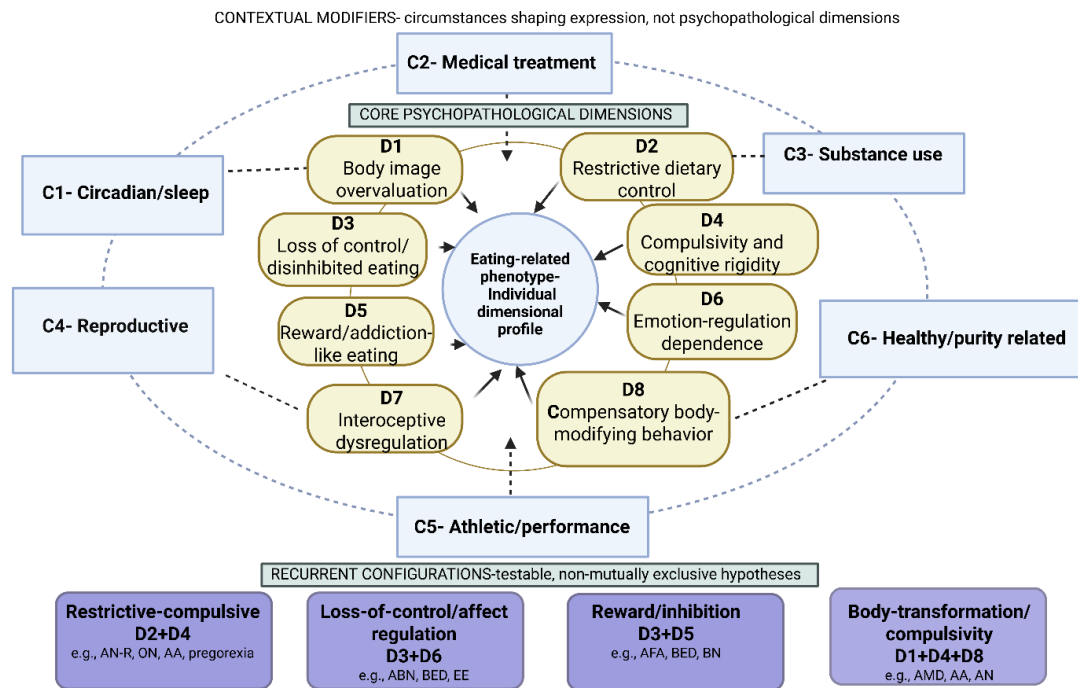
Difficulties in Emotion Regulation Scale (DERS) has been specifically evaluated in samples with eating disorders, Multidimensional Assessment of Interoceptive Awareness (MAIA) is being used to characterize multidimensional interoception rather than treating it as a single unitary function, Compulsive Exercise Test (CET) has clinical psychometric data in AN/BN populations, Three-Factor Eating Questionnaire (TFEQ), Yale Food Addiction Scale (YFAS), and EDE-Q could also be of use for specific dimensions of DEPM (Table 5).

Practical algorithm of evaluation using the suggested model

Two levels of measurement may be used in practice for patients presenting with EDs or ERPs. The first level would be considered a generic transdiagnostic dimensions assessment, consisting of all participants receiving EDE-Q-13/6.0, DERS-16, MAIA-2, YFAS 2.0, and CET

Brief compulsivity/rigidity measure. The second level would be phenotype-specific measures and would be applied only where relevant. The main instruments suggested for this stage, based on the previously mentioned model, are the TOS for orthorexia, the Night Eating Questionnaire for NES, the Muscle Dysmorphic Disorder Inventory (MDDI) for muscle dysmorphia, and the PARDI-AR-Q (Pica, ARFID, and Rumination Disorder Interview) for ARFID.

Figure 1: Conceptual architecture of the Dimensional Eating Psychopathology Model (DEPM)



Solid arrows: Psychopathological dimensions constitute the profile. Dotted arrows: context shapes clinical expression

The DEPM characterizes each eating-related phenotype through an individual profile across eight core psychopathological dimensions (D1–D8).

Contextual modifiers (C1–C6) describe circumstances that may shape the clinical expression of these dimensions but are not themselves considered psychopathological dimensions. Solid arrows indicate that the dimensions contribute to the individual phenotype profile, whereas dotted arrows indicate contextual influences on its expression. Abbreviations: AA, anorexia athletica; AN, anorexia nervosa; AN-R, anorexia nervosa, restricting type; BED, binge-eating disorder; BN, bulimia nervosa; EE, emotional eating; MD, muscle dysmorphia; ON, orthorexia nervosa. Created in BioRender. Vasiliu, O. (2026). <https://biorender.com/xs0tlci>.

DISCUSSION

The present study proposes a multidimensional extension of a previous integrative model of eating-related psychopathology (Fig.1). Its principal conceptual contribution is not the introduction of dimensionality into ED classification, an approach already supported by substantial theoretical and empirical work, but the application of a common dimensional framework to formally recognized EDs, proposed syndromes, behavioral constructs, and context-dependent eating-related presentations while explicitly preserving differences in their nosological status. A second distinctive element is the separation of core psychopathological dimensions from contextual modifiers, which permits shared psychopathological processes to be examined without equating the circumstances in which they are expressed with psychopathology itself.

The DEPM is consistent with the broader movement from exclusively categorical toward dimensional and hierarchical models of psychopathology. Existing ED research has shown that dimensional structures may explain heterogeneity and predict impairment and longitudinal outcomes more effectively than diagnostic categories alone. The hierarchical model proposed by Forbush et al., for example, identified multiple lower-order dimensions of eating psychopathology and demonstrated strong predictive utility [32,44–46]. These findings support the premise underlying the present model, i.e., psychopathological components may cross diagnostic boundaries and recombine in different proportions across phenotypes.

The DEPM nevertheless differs from these approaches in its intended level of analysis. Hierarchical systems such as HiTOP seek to derive empirically supported structures of psychopathology extending from broad spectra to increasingly specific dimensions. The

present framework is narrower and explicitly hypothesis-generating. It does not attempt to provide an alternative general psychiatric nosology or an empirically established latent structure. Instead, it asks whether a limited set of clinically interpretable dimensions may provide a common descriptive language for eating-related presentations that currently occupy markedly different positions in diagnostic systems and the scientific literature.

Restriction and compulsivity as related but non-equivalent processes

One implication of the DEPM is that restrictive eating should not automatically be equated with a single diagnostic mechanism. High D2 scores were hypothesized for AN, ARFID, orthorexia, AA, and pregorexia, yet the surrounding dimensional architecture differed substantially among these. Restriction combined with strong shape/weight overvaluation and rigidity may characterize AN, whereas severe restriction in ARFID may occur in the relative absence of shape/weight overvaluation. Orthorexic restriction may instead be particularly associated with rigid health- or purity-related rules.

This distinction is supported by emerging research on ARFID classification, which identified substantial heterogeneity within this diagnosis, particularly across sensory sensitivity, lack of interest in food or eating, and fear of aversive consequences, and current evidence remains mixed on how clearly ARFID can be distinguished from other restrictive ED presentations [49-53]. A dimensional framework may therefore be particularly useful when superficially similar restrictive behavior reflects different underlying processes.

Compulsivity and cognitive rigidity may likewise represent related phenomena rather than diagnosis-specific features. Increasing interest in dimensional models spanning obsessive-compulsive and eating psychopathology further supports examining rigidity and compulsivity independently of categorical ED diagnoses [54].

Loss of control, affect regulation, and reward processes

A second major region of overlap concerns D3, D5, and D6. BN, BED, food addiction, and emotional eating may all involve increased disinhibition or loss of control, but the proposed model distinguishes the experience of impaired control from the motivational processes accompanying it. Eating may be driven predominantly by affect regulation in one presentation and by craving/reward salience in another, while both mechanisms may coexist in individual patients, making this distinction particularly relevant to the debated construct of FA/UPFA. Existing evidence demonstrates substantial overlap between food-addiction measures and binge-spectrum EDs, and recent clinical data continue to associate food-addiction severity particularly strongly with bulimic and binge-eating symptoms [31,55-56]. At the same time, interoceptive and affective processes appear to contribute substantially to addiction-like eating across diagnostic categories. These findings argue against interpreting reward-related eating as a diagnostic category necessarily independent of other EDs and instead support examining it as a potentially transdiagnostic dimension. Thus, D5 is deliberately formulated as reward/addiction-like eating, rather than "food addiction" itself. The distinction between dimension and phenotype is important; for example, a person may demonstrate substantial reward-related or compulsive eating without satisfying any proposed threshold for FA/UPFA, and the same mechanism may contribute to more than one established ED.

Body image and body-modifying behavior

Separating D1 from D8 constitutes another potentially useful feature of the DEPM. Body-image overvaluation and behavior intended to modify the body are related but not identical. A phenotype may involve marked dissatisfaction or overvaluation without extensive compensatory behaviors, whereas another may involve highly structured exercise, dietary manipulation, purging, or treatment manipulation directed toward changing weight, shape, or muscularity.

This separation may be particularly relevant to muscle dysmorphia and anorexia athletica. Previous comparisons between muscle dysmorphia and AN have demonstrated substantial overlap in disordered eating, disturbed body image, and compulsive exercise, despite opposing desired physical outcomes [30,57-59]. Within the DEPM, such similarity does not require the two presentations to share a diagnostic category. Instead, they may occupy overlapping positions on D1, D4, and D8 while differing in the specific content and direction of body-related goals.

Interoception as a cross-cutting dimension

Interoceptive dysfunction was retained as an independent dimension because difficulties in perceiving, interpreting, or appropriately using internal bodily signals may contribute to several forms of eating pathology without being unique to any one diagnosis. Contemporary transdiagnostic work continues to implicate interoceptive abnormalities across eating, affective, and addictive psychopathology, and recent ED research suggests that interoceptive and emotional difficulties may jointly contribute to addiction-like eating [60-62].

However, D7 is also among the dimensions that will require particularly careful operationalization. Interoception is itself multidimensional and encompasses detection, attention, interpretation, trust, and regulation of bodily signals. Consequently, empirical validation may ultimately show that a single interoceptive dimension is too broad, or that its components relate differently to restrictive and disinhibited eating.

The importance of separating psychopathology from context

The proposed contextual modifiers represent an attempt to avoid a common problem when discussing emerging eating-related phenomena: treating the circumstance in which pathological eating occurs as though it were itself a new psychiatric syndrome. Pregnancy, diabetes, athletic participation, alcohol consumption, sleep, and concern with health are not pathological contexts per se. This distinction is particularly important for SRED, which is currently conceptualized as an NREM parasomnia characterized by recurrent eating following arousal from sleep, often accompanied by partial or complete amnesia [12]. Although its observable eating behavior may resemble disinhibition, equating this directly with the consciously experienced loss of control characteristic of BED or BN would obscure its sleep-related pathophysiology. Its inclusion, therefore, illustrates both the usefulness and the limits of a common dimensional framework: superficially similar behaviors should not automatically be assumed to reflect identical underlying psychopathological mechanisms.

Clinical and research implications

A categorical diagnosis could indicate which disorder is present, while the DEPM profile could describe which psychopathological processes are most prominent in that presentation. Two individuals with the same diagnosis may therefore have different dimensional profiles, whereas patients with different diagnoses may share clinically relevant targets. Such characterization may ultimately have implications for assessment and treatment formulation. Prominent D4 could suggest particular attention to rigidity and compulsive processes; D6 to emotion-regulation mechanisms; D5 to craving and reward-related mechanisms; D7 to interoceptive processes; and D8 to compulsive exercise, purging, or other body-modifying behaviors. These implications remain hypothetical, however, and the present study does not demonstrate that dimension-guided treatment improves outcomes.

The framework may also facilitate research into emerging eating-related constructs without prematurely granting them independent diagnostic status. Instead of asking first whether orthorexia, FA, pregorexia, or drunkorexia constitute independent disorders, investigators could initially determine whether these labels correspond to reproducible dimensional configurations and whether those configurations provide information beyond established ED diagnoses.

Strengths and limitations

Several strengths characterize the proposed framework: (1) it explicitly distinguishes diagnostic status from phenotypic description, thereby avoiding the treatment of all included conditions as nosologically equivalent; (2) it separates psychopathological dimensions from contextual modifiers; (3) it accommodates overlap and within-phenotype heterogeneity more readily than the previous categorical model; (4) the dimensions are formulated in clinically interpretable terms and can, in principle, be operationalized using existing or specifically developed measures.

Substantial limitations of this study exist: (1) the DEPM is currently a conceptual, hypothesis-generating model; (2) the eight dimensions may not be statistically independent: restriction and rigidity, loss of control and reward processing, or body-image overvaluation and body-modifying behavior may prove highly correlated; conversely, some dimensions—particularly interoception, compulsivity, and reward processing—may ultimately require subdivision; (3) the included phenotypes vary markedly in nosological status and evidentiary maturity; established DSM/ICD diagnoses coexist in the matrix alongside proposed syndromes, descriptive labels, behavioral constructs, and presentations that are partly context-dependent; (4) dimensional profiles may differ within a phenotype according to age, sex or gender, illness stage, severity, comorbidity, cultural context, and treatment exposure; (5) the proposed contextual modifiers should not be assumed to be exhaustive, as additional environmental, developmental, interpersonal, cultural, or biological modifiers may prove necessary as the model evolves.

Directions for future research

The next stage of research in this domain should focus on content validation rather than immediate statistical taxonomy-building. Independent experts could first evaluate whether each proposed dimension is conceptually distinct, clinically meaningful, transdiagnostically applicable, and adequately defined. This stage may lead to merging, splitting, removing, or adding dimensions before quantitative phenotype mapping is attempted. Once the dimensions are stabilized, independent expert ratings could test the reproducibility of the proposed phenotype profiles. Subsequent patient-level studies should examine whether dimensions measured with validated instruments reproduce the hypothesized architecture, independent of diagnostic labels. Patient-level validation studies should also account for medical conditions and somatic and psychiatric comorbidity that may influence eating-related symptoms and phenotypic presentation [34,63-68]. More broadly, dimensional study designs may help identify clinically relevant heterogeneity and psychopathological features that are not fully represented by categorical diagnosis alone [32-33,43-46,56,62,69-71].

CONCLUSION

The DEPM proposes that eating-related psychopathology can be conceptualized as a combination of eight transdiagnostic dimensions whose clinical expression may be further shaped by contextual modifiers. This approach does not replace established diagnostic systems, nor does it imply equivalent diagnostic status for the heterogeneous phenotypes included in the model.

Mainly, DEPM provides a common descriptive framework through which formally recognized disorders, emerging constructs, behavioral phenotypes, and context-dependent presentations can be compared without forcing them into mutually exclusive categories.

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The authors declare no conflict of interest.

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Authors' contribution

Conceptualization, O.V., and A.G.M.; methodology, O.V., B.M.P., A.G.M.; software, O.V., A.G.M., B.M.P.; validation, O.V., A.G.M., B.M.P.; formal analysis, O.V.; investigation, O.V.; resources, O.V.; data curation, O.V., A.G.M., B.M.P.; writing—original draft preparation, O.V.; writing—review and editing, O.V., A.G.M.; visualization, O.V., B.M.P.; supervision, O.V.; project administration, O.V. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

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ARTICLE

Blood Pressure Variability in Patients with Hypertension and Type 2 Diabetes Mellitus: Is There More to Do?

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Abstract: Fractal dimension (FD) analysis of ambulatory blood pressure monitoring (ABPM) may provide more information than conventional blood pressure variability (BPV) parameters. This study aims to assess the FDs of ABPM temporal series as a measure of BPV and its impact on optimized blood pressure (BP) control in patients(pts) with hypertension (HT) and type 2 diabetes mellitus (DM). Systolic (SBP) and diastolic (DBP) BP, dipping status, coefficient of variation (CV), and pulse pressure (PP) were analyzed on 24h-ABPM in pts with DM and HT. FDs were determined separately during daytime and nighttime for SBP, DBP, and pulse pressure (PP). 117 pts, 62.8±10.3 yo, 46% male, were divided into G1 (uncontrolled HT, 60 pts) and G2 (controlled HT, 57 pts). 61% were non-dippers or reverse-dippers, mean dipping % was 4.9 ± 8.7 in G1 and 9.6 ± 7.4 in G2 (p=0.002). 46 pts in G1 and 39 had CV > 10% (p=0.31). The mean diurnal SBP FDs were 1.229 ± 0.03 in G1 and 1.2431 ± 0.03 in G2 (p=0.02), associated with DM complications (p=0.005) and HT treatment (p<0.04). In conclusion, fractal analysis revealed a more complex, convoluted BP curve in diabetics with controlled HT, adding complementary data to conventional BPV parameters.

Keywords: fractal analysis, blood pressure variability, arterial hypertension, diabetes mellitus

INTRODUCTION

Hypertensive and diabetic patients are a large population, usually at high or very high cardiovascular risk. In the most recent ESC/EURObservational Research Program (EORP) EUROASPIRE surveys, history of hypertension (HT) was present in more than 80% of patients with known diabetes mellitus (DM) and in more than 74% of persons with newly diagnosed DM and a history of coronary heart disease [1].

Despite progress in terms of treatment options, blood pressure (BP) control remains a current and challenging problem for physicians, patients, and the healthcare system. Blood pressure variability (BPV) is a documented risk factor for cardiovascular diseases, chronic kidney disease, and cognitive decline [2,3]. However, current guidelines do not list BPV as a target in hypertension management, probably because of a lack of consistent thresholds. Based on monitoring time duration, BPV is classified into four types: very-short-term (beat-to-beat), short-term (within 24hours, using Ambulatory Blood Pressure Monitoring - ABPM), medium-term (days), and long-term (months - years). In order to improve individualized patient management, more information is needed, and it could be derived from data we already have. Fractal analysis could offer such data, as temporal series from ABPM are signals that can be analyzed using mathematical models that go beyond conventional parameters such as mean values, standard deviation (SD), or coefficient of variation (CV). Curve convolutedness is an assessment of how BP changes during day and night, and could be improved by BP control.

The aim of the study was to test fractal analysis of ABPM temporal series, beyond conventional BPV parameters, as a measure of BPV and to assess its impact on optimized BP control in patients with HT and type 2 DM.

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MATERIALS AND METHODS

We conducted a single-center cross-sectional cohort study in consecutive outpatients with HT and type 2 DM who underwent ABPM between March 1st and May 31st 2021, in the Cardiology and Internal Medicine Department of the “Prof. Dr. Th. Burghele” Clinical Hospital in Bucharest.

Study group. The inclusion and exclusion criteria are listed below:

Inclusion criteria:

- Age > 18 years
- Documented type 2 DM with target-organ damage (at least one documented micro- and/or macrovascular complication)
- Treatment with oral antidiabetic drugs/insulin therapy
- Documented HT, with or without treatment
- Patients in sinus rhythm
- Left ventricular ejection fraction >50%
- Signed informed consent

Exclusion criteria:

- Type 1 DM
- Decompensated heart failure in the last 3 months
- Sustained arrhythmias, documented in the last 3 months
- Ischemic heart disease with ongoing ischemia
- Moderate-severe valvular disease
- Decompensation of renal, hepatic, or pulmonary diseases in the last 3 months
- Moderate or severe anemia
- Liver cirrhosis, cancer, or other diseases with a life expectancy of less than 3 years
- Pregnant or breastfeeding women
- Uncooperative patients or those with predictable suboptimal compliance
- Patient refusal to participate in research.

Study variables upon inclusion were as follows:

- clinical data: age, sex, patient history, current medication list, right- and left-sided BP sitting and standing, heart rate, standard physical examination
- electrocardiogram,
- echocardiography,
- laboratory data: blood glucose, HbA1c, serum creatinine, estimated glomerular filtration rate (eGFR) by the MDRD equation;
- 24h ABPM: 24h-BP, diurnal and nocturnal SBP and DBP, dipping status, CV, pulse pressure (PP), pulse rate (PR), and fractal analysis of the recorded signals were performed.

ABPM was performed using the same device (Contec, ABPM50) in all patients, with standard sampling rates (every 15 minutes during the day, every 30 minutes during the night). A CV of 10% was used to separate low from high BPV at ABPM. BP control was defined according to European Guidelines available at the time, with all values from both the office BP and ABPM below recommended thresholds; the guidelines define hypertension for BP 140/90 mmHg for office BP, $\geq 135/85$ mmHg for diurnal BP, $\geq 120/70$ mmHg for nocturnal BP, $\geq 130/80$ mmHg for mean 24-h BP [4]. Study data were stored on password-protected computers, and data confidentiality was ensured. All research was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee.

Fractal analysis. The fractal dimensions (FDs) of the curves generated from ABPM data were calculated using the FracLac plugin for ImageJ, which is available online. FDs were determined separately for systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), and pulse rate (PR), with daytime and nighttime recordings analyzed independently to account for differences in sampling intervals. The box-counting method was utilized for each temporal series on binary images. Box counting is a sampling process used to calculate FD by systematically laying a series of grids of progressively decreasing caliber (the boxes) over an image of data (the counting) for each successive caliber. Changing the size of the boxes in a grid is the way of approximating scaling in box counting. Fractal dimension is then calculated by using the formula: $FD = \log(N) / \log(r)$, where FD=fractal dimension, N=number of self-similar pieces in the fractal, r=scaling factor (how much each piece is scaled down versus the original) [5].

Statistical analysis. Univariate analysis was applied to both categorical (expressed as percentages) and numeric variables (expressed as mean $\pm$ standard deviation). Chi-squared and Fisher's exact tests, and ANOVA or non-parametric (Kruskal-Wallis) tests were applied, respectively. Logistic regression models were used to estimate odds ratios with 95% confidence intervals ($p < 0.05$ was considered significant).

RESULTS

One hundred seventeen patients were included in the study, with a mean age of 62.8 ± 10.3 years; 46.1% were male. The participants were divided into 2 groups: G1 with uncontrolled HT (60 patients, 51.3%) and G2 with controlled HT (57 patients, 48.7%). There were no significant differences between G1 and G2 regarding age, gender, the presence of obesity, complicated diabetes mellitus (DM), the number of DM complications, or antidiabetic treatment. A statistically significant proportion of patients in G2 had controlled DM compared to G1. Treatment with ACE inhibitors, ARBs, CCBs, and beta-blockers did not differ statistically between the two groups, but a statistically significantly higher proportion of patients in G1 were treated with thiazide diuretics and other antihypertensives (centrally active drugs). The study population's main characteristics are detailed in Table 1.

Table 1: Main characteristics of the study population.

Characteristics	G1 (n=60)	G2 (n=57)	Overall (n=117)	p-value
Age, years, mean $\pm$ standard deviation	62.3 $\pm$ 10.3	63.3 $\pm$ 10.4	62.8 $\pm$ 10.3	0.61
Male sex, n (%)	32 (53.3)	22 (38.6)	54 (46.1)	0.1
Smoking (ex- or current), n (%)	18 (30)	17 (29.8)	35 (29.9)	0.98
Obesity, n (%)	36 (60)	28 (49.1)	64 (54.7)	0.23
Cardiac disease, n (%)	30 (50.8)	26 (47.3)	56 (47.8)	0.7
Complicated DM, n (%)	55 (93.2)	50 (89)	105 (89.7)	0.45
Number of DM complications, mean $\pm$ standard deviation	1.55 $\pm$ 1.1	1.4 $\pm$ 1.1	1.47 $\pm$ 1.1	0.48
Controlled DM	15 (27.2)	27 (51.9)	42 (35.9)	0.009
Drug Treatment				
Oral antidiabetics, n (%)	46 (78)	39 (70.1)	85 (72.6)	0.38
Insulin, n (%)	11 (18.6)	9 (16.3)	20 (17.1)	0.74
ACEI, n (%)	30 (50.8)	20 (36.3)	50 (42.7)	0.11
ARB, n (%)	24 (40.7)	20 (36.3)	44 (37.6)	0.63
CCB, n (%)	30 (50.8)	25 (45.4)	55 (47)	0.56
BB, n (%)	40 (67.8)	37 (67.2)	77 (67.58)	0.95
Diuretics, n (%)	49 (83)	34 (61.8)	83 (70.1)	0.01
Other antihypertensives, n (%)	12 (20.3)	2 (3.64)	14 (12)	0.01
Statin, n (%)	38 (64.4)	42 (76.4)	80 (68.4)	0.16
Antiplatelet drugs, n (%)	28 (47.5)	26 (46.3)	54 (47.3)	0.32
Office BP and Pulse rate				
Sitting SBP/DBP mmHg, mean $\pm$ standard deviation	149.5/83.6 $\pm$ 5.8/14.5	135.5/78.3 $\pm$ 8.4/8	142.7/81.1 $\pm$ 13.7/7.6	0
Standing SBP/DBP, mmHg, mean $\pm$ standard deviation	148.3/82.2 $\pm$ 11.7/7.3	133.4/76.7 $\pm$ 12.7/8	141/79.6 $\pm$ 14.3/8.1	0.005
Pulse rate, beats/min, mean $\pm$ standard deviation	74.8 $\pm$ 9.9	71.5 $\pm$ 10.3	73 $\pm$ 10	0.08
Laboratory data				
Blood glucose, mg/dL, mean $\pm$ standard deviation	145.1 $\pm$ 34.9	127.2 $\pm$ 23.1	136.4 $\pm$ 31	0.01
HbA1c, %, mean $\pm$ standard deviation	6.7 $\pm$ 1	6.2 $\pm$ 0.78	6.5 $\pm$ 0.9	0.001
eGFR by MDRD equation,	66.9 $\pm$ 28	77.5 $\pm$ 18.4	72.1 $\pm$ 24.3	0.03

mL/min/1.73 m ² , mean ± standard deviation				
Renal dysfunction (eGFR<60%), n (%)	28 (51.8)	11 (23.4)	39 (33.3)	0.003
LDL-cholesterol, mg/dL, mean ± standard deviation	102.5 ± 38	92.5 ± 37.6	96.9 ± 37.9	0.24
Electrocardiographic changes , n (%)	21 (35)	21 (36.8)	42 (35.9)	0.43
Echocardiography : LVEF %, mean ± standard deviation	58.3 ± 4.3	59.5 ± 5.1	59 ± 4.8	0.39

Abbreviations: G=group, n=number, DM=diabetes mellitus, ACEI=angiotensin-converting enzyme inhibitors, ARB=angiotensin receptor blockers, CCB= calcium channel blockers, BB=beta-blockers, BP=blood pressure, SBP=systolic blood pressure, DBP=diastolic blood pressure, HbA1c=glycated hemoglobin, eGFR=estimate glomerular filtration rate, LDL=low-density lipoprotein, LVEF=left ventricular ejection fraction.

The patients' comorbidities were respiratory diseases (13 patients, 11.1%), gastrointestinal disorders (40 patients, 34.1%), renal and genitourinary tract diseases (33 patients, 28.2%), osteoarticular changes (46 patients, 39.3%), hyperthyroidism (4 patients, 3.4%), and hypothyroidism (13 patients, 11%). No significant associations were observed between comorbidities and BP control.

Electrocardiographic changes consisted of extrasystole, ST-T changes, and bundle branch blocks. Echocardiography: the mean left ventricular EF was 58.3 ± 4.3%. 30 patients (25.6%) had left ventricular hypertrophy, and 31 patients (26.4%) had mild degenerative aortic and mitral valvular disease.

ABPM data. As controlled BP was defined based on both clinical and ABPM values, these values were expected to differ significantly between the 2 control groups (Tables 1 and 2).

Table 2: ABPM data and fractal analysis.

ABPM data	G1 (n=60)	G2 (n=57)	Overall (n=117)	p-value
Mean 24-h SBP/DBP, mmHg, mean ± standard deviation	132.4/74.8 ± 12/8.8	118.5/68.7 ± 8.2/7.1	125.7/71.8 ± 12.5/8.5	0
Mean diurnal SBP/DBP, mmHg, mean ± standard deviation	133.5/75.7 ± 11.9/8.8	120.6/70.3 ± 8.1/7.1	127.2/73.1 ± 12.1/8.4	0
Mean nocturnal SBP/DBP, mmHg, mean ± standard deviation	127/70.7 ± 16.1/11.5	109.7/60.8 ± 12/8.7	118.7/66 ± 16.6/9.4	0
Dipping, %, mean ± standard deviation	4.9 ± 8.7	9.6 ± 7.4	7.1 ± 8.4	0.002
High blood pressure variability (CV) n (%)	46 (76.7)	39 (68.4)	85 (72.6)	0.31
Fractal analysis				
FDs SBP diurnal, mean ± standard deviation	1.229 ± 0.034	1.2431 ± 0.0341	1.2358 ± 0.0347	0.02
FDs SBP nocturnal, mean ± standard deviation	1.123 ± 0.024	1.1241 ± 0.0248	1.1228 ± 0.0239	0.6
FDs DBP diurnal, mean ± standard deviation	1.2419 ± 0.0354	1.2422 ± 0.0345	1.2421 ± 0.0331	0.12
FDs DBP nocturnal, mean ± standard deviation	1.2487 ± 0.2987	1.2491 ± 0.0391	1.2489 ± 0.0395	0.09
FDs PR diurnal, mean ± standard deviation	1.2241 ± 0.0364	1.2246 ± 0.0379	1.2243 ± 0.037	0.37
FDs PR nocturnal, mean ± standard deviation	1.1219 ± 0.0345	1.1222 ± 0.0254	1.122 ± 0.0291	0.23
FDs PP diurnal, mean ± standard deviation	1.28 ± 0.04	1.3 ± 0.05	1.2962 ± 0.0466	0.03
FDs PP nocturnal, mean ± standard deviation	1.1228 ± 0.0217	1.123 ± 0.0221	1.1229 ± 0.0219	0.4

Abbreviations: ABPM=ambulatory blood pressure monitoring, G=group, n=number, FD=fractal dimension, CV=coefficient of variation, PR=pulse rate, PP=pulse pressure.

Figure 1 illustrates the distribution of nighttime blood pressure (BP) dipping patterns within the study population. 53 % of patients were non-dippers, 15% were reverse dippers, 24% were dippers, and 8% were reverse dippers. Patients in G2 had a greater decrease in nocturnal SBP (9.6% ± 7.4) than patients in G1 (4.9 ± 8.7, p < 0.002) (Figure 2).

Figure 1: Dipping status in the study population.

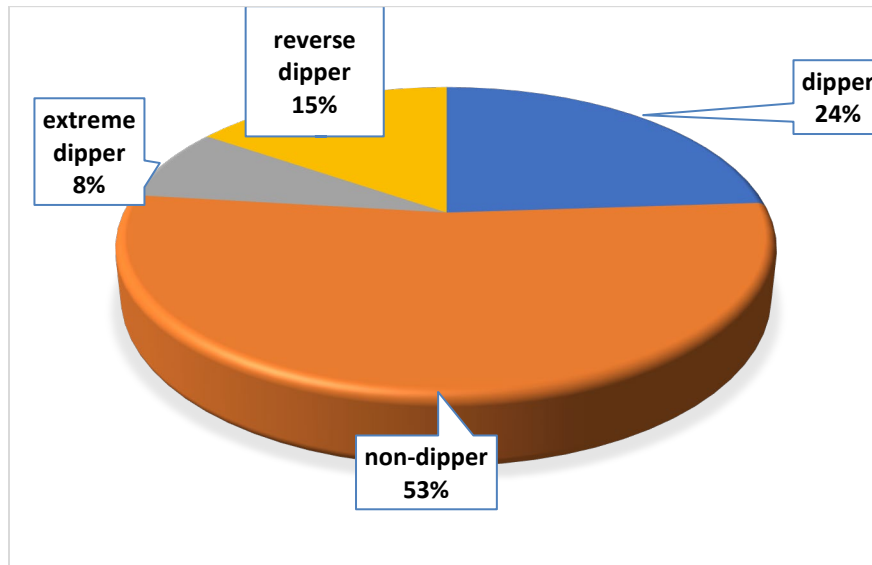
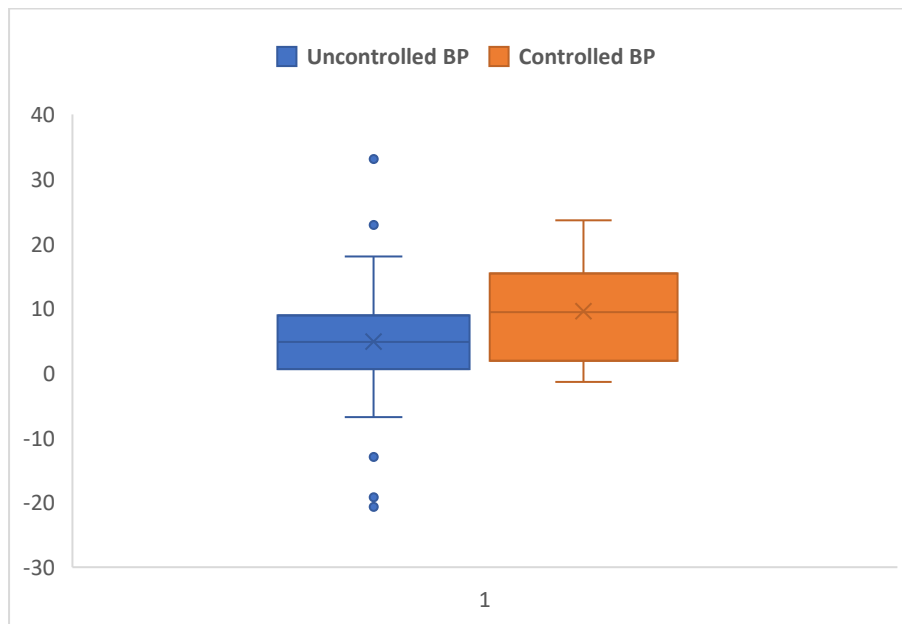
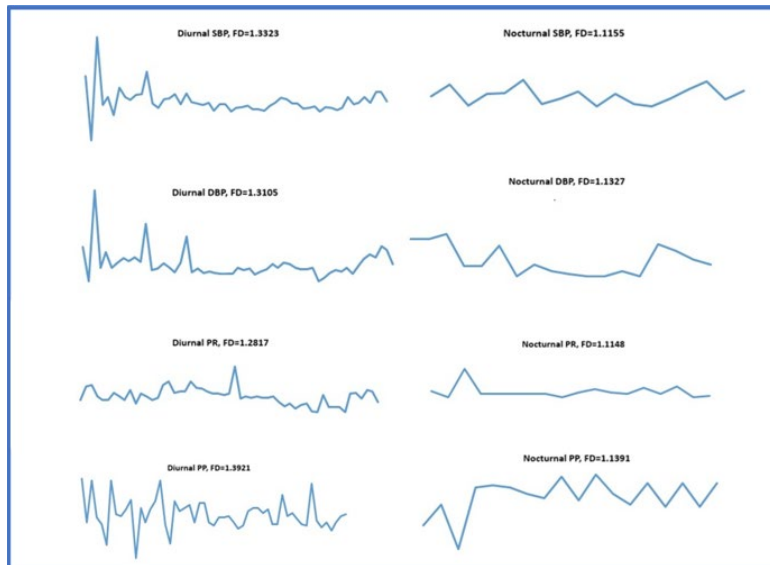


Figure 2: Dipping percentage in uncontrolled versus controlled BP for systolic BP: 4.9 ± 8.7 versus 9.6 ± 7.4 , $p = 0.002$.



Abbreviations: BP=blood pressure.

Figure 3: Example of FD estimation for daytime and nighttime time series in one study patient, based on ABPM data.



Parameters analyzed using daytime recordings (07:00–22:00; 59 valid measurements) and nighttime recordings (22:00–07:00; 18 valid measurements) were: SBP, DBP, PR and PP. The resulting 10 curves were subsequently analyzed using the box-counting method to estimate FD. Abbreviations: FD=fractal dimension, ABPM=ambulatory blood pressure monitoring, SBP=systolic blood pressure, DBP=diastolic blood pressure, PR=pulse rate, PP=pulse pressure.

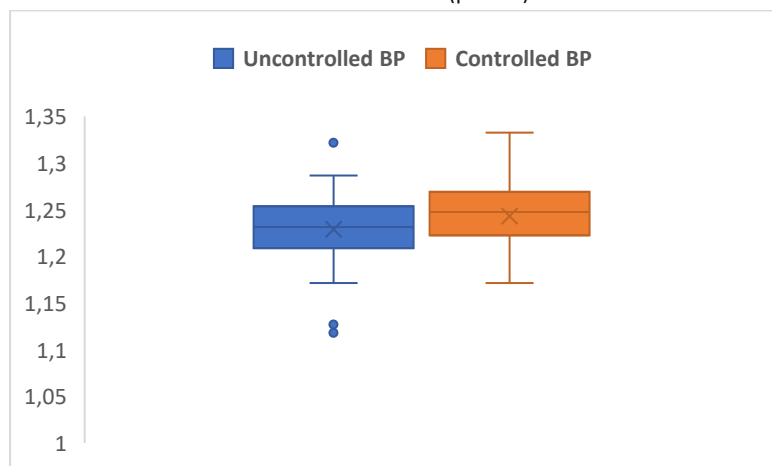
A CV >10% was observed in 85 patients (72.6%): 46 patients (76.7%) in G1 and 39 patients (68.4%) in G2, with no statistically significant difference between the groups. By univariate analysis, BP control showed significant associations with blood glucose, HbA1c, and controlled DM; with eGFR by the MDRD equation and renal dysfunction; and with treatment with diuretics and centrally acting drugs.

Fractal dimension. The FDs of the curves derived from the recorded time series reflect the complexity of the corresponding signals, providing information that complements the conventional ABPM parameters. The FD values for SBP, DBP, PR and PP during day and night in the study group and between the G1 and G2 are shown in Table 2.

Figure 3 illustrates the estimation of FD from time series recorded from ABPM in one patient. FD was calculated using the ImageJ/FracLac plugin software, applying the box-counting algorithm to the corresponding curves generated from ABPM monitoring data.

Figure 4 shows the albeit small but significant ($p=0.02$) difference in mean diurnal SBP FD values between the 2 groups: BP control (1.229 ± 0.03 in uncontrolled BP patients versus 1.2431 ± 0.03 in those with controlled BP).

Figure 4: Mean diurnal SBP FD values between groups: 1.229 ± 0.03 in uncontrolled BP patients versus 1.2431 ± 0.03 in those with controlled BP ($p=0.02$).



Abbreviations: BP=blood pressure.

Apart from BP control, FD for diurnal SBP showed significant associations with the presence of DM complications ($p=0.005$) and with the use of ACEI ($p=0.01$), diuretics ($p=0.04$), and centrally acting drugs ($p=0.04$).

All in all, logistic regression documented the use of diuretics ($p=0.04$, OR=0.19, 95% CI 0.04-0.89), FD for diurnal SBP ($p=0.03$, OR=0.03, 95% CI=0.02-0.06), night-time dipping percentage ($p=0.006$, OR=1.1, 95% CI=1.02-1.16), and the presence of renal dysfunction ($p=0.01$, OR=0.03, 95% CI 0.002-0.4) as independent predictors for BP control.

DISCUSSION

In an attempt to identify new parameters for BPV assessment—offering additional information beyond that provided by global indices—the FDs were estimated for all-time series recorded during ABPM. This approach evaluates the complexity of the resulting curves rather than merely amplitude variations. The FDs could provide data that are lost when using global indices, and FD estimation algorithms allow for the use of the limited time series characteristic of ABPM [6-8]. The differing ABPM measurement intervals—every 15 minutes during the day and every 30 minutes at night—required separate calculation of the FD for daytime and nighttime recordings. FDs were estimated consistently across all patients by converting ABPM data into curves and analyzing them using specialized software. In the future, this process could be readily automated or integrated directly into ABPM software through dedicated fractal-analysis algorithms. This method has not been systematically applied to patients with diabetes and HT, except in studies analyzing cutaneous blood flow in relation to HT and diabetic retinopathy. Its application may improve our understanding of cardiovascular dynamics in this population and enable a more comprehensive, individualized assessment using rapid analytical methods [9,10].

Although BP control was not significantly associated with BPV by ABPM CV in this study, it was independently related to the FD of the diurnal SBP, with a slightly more convoluted curve in patients with controlled BP, perhaps suggesting greater adaptability. These findings indicate that CV and FDs capture distinct, complementary characteristics of the time series. Moreover, FDs were generally substantially lower than those previously reported in normotensive individuals, suggesting that reduced signal complexity may characterize systems at risk of, or already affected by, disease, similar to the established association between reduced heart rate variability and coronary artery disease risk. [11]. This explains the association of FDs with BP control, likely due to cardiovascular mechanisms of diurnal BP autoregulation that global BPV parameters fail to capture [12]. There were no significant associations in this study between comorbidities and BP control, but acutely decompensated patients were excluded from the population in order to avoid any interference with BPV that could act as a confounding factor [13-16].

FD estimates obtained using optimized and standard algorithms may provide further insights into this alternative measure of BPV. Moreover, applying other mathematical approaches, through specialized algorithms, could enhance the informational value of BPV analysis.

The limits of the study consist of the relatively small sample size, and the results could benefit from a larger study involving repeated ABPM recordings, offering a better view on pattern reproducibility and further insight on BP control.

CONCLUSION

Optimal BP and glycemic control remain challenging in patients with HT and DM, underscoring the need for novel assessment methods alongside improved therapeutic strategies and treatment adherence. Fractal analysis may complement conventional parameters by extracting additional clinically relevant information from routinely collected data.

Conflicts of interest and sources of funding

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Authors' contribution

Conceptualization, A.M.I., and I.P.; methodology, I.P., and A.M.I.; software, B.M.P.; validation, A.M.I., A.M.B., B.M.P., C.N., and I.P.; formal analysis, I.P.; investigation, I.P. and M.G.; resources, I.P., A.M.I, C.N, and C.C.; data curation, I.P.; writing—original draft preparation, I.P., and A.M.I.; writing—review and editing, A.M.I., and I.P.; visualization, B.M.P.; supervision, A.M.I.; project administration, A.M.I., A.M.B, M.G., and I.P. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of "Prof. Dr. Th. Burghel" Clinical Hospital, 050653 Bucharest, Romania (11202/16.11.2017).

Patient consent for publication

Informed consent was obtained from all subjects involved in the study.

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REVIEW

Comparative Effectiveness of Patent Foramen Ovale Closure and Medical Therapy in Cryptogenic Stroke: A Focused Review of Current Evidence

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Abstract: Background: Patent foramen ovale (PFO) is an anatomical variant in which the normal fetal interatrial passage persists after birth. It is estimated to be present in approximately 25% of adults. Furthermore, it appears to be involved in 50% of cryptogenic strokes. A cryptogenic stroke means the etiology remains unknown despite a thorough assessment (including arterial imaging, echocardiography, rhythm monitoring, and relevant laboratory testing, such as lipid profile and hemoglobin A1c). Secondary prevention options after a PFO-associated stroke consist of antiplatelet therapy, anticoagulant therapy, or percutaneous closure of the PFO, and it is still debatable which option is better. Objective: To critically review the available evidence regarding PFO closure vs. medical therapy as the optimal therapeutic option for secondary prevention after PFO-associated cryptogenic stroke, and to discuss relevant factors for patient selection. Methods: We conducted a focused review and searched the PubMed database for relevant literature on the subject. We included records about patients with PFO and a history of stroke. We chose to include only the free full-text sources. On the other hand, studies regarding children, studies comparing different devices or techniques, and observational studies on long-term complications and recurrence predictors were excluded. Results: Eight records were included, comprising 3750 participants, all diagnosed with PFO and stroke, to compare different therapeutic strategies for preventing stroke recurrence (PFO closure versus medical therapy). Conclusions: The results indicated that closure of PFO may provide greater protection against recurrent stroke than medical therapy alone in adequately selected patients with PFO-associated cryptogenic stroke. Additionally, given the lack of recent studies, further research is warranted to improve patient selection and evaluation of medium- and long-term prognosis.

Keywords: patent foramen ovale (PFO), stroke, PFO closure, antiplatelet, anticoagulant, cryptogenic stroke

INTRODUCTION

Being an important cause of death, but also disability, ischemic stroke has an increasing incidence in young adults (1). Most patients have residual neurological deficits six months after the event (2). Data show that almost 35% of ischemic strokes could be cryptogenic, meaning the etiology remains unknown despite careful assessment (at least arterial imaging, echocardiography, rhythm monitoring, and relevant laboratory testing, such as lipid profile and hemoglobin A1c) (3). It is also important to evaluate thyroid function, as hypothyroidism seems to be an independent risk factor for neurological events (4). On the other hand, data suggest that in acute ischemic stroke, significant derangement in thyroid hormones occurs (hypothalamo-pituitary-thyroid axis damage), with some encouraging the use of low T3 levels as an indicator of poor prognosis (5). Previous studies have reported that women tend to experience stroke at an older age than men. Furthermore, obesity,

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active smoking, and the presence of the C allele of the angiotensin II type 1 receptor gene have been associated with an increased risk of stroke in women, highlighting the contribution of both genetic and environmental factors to cerebrovascular disease (6). Among cryptogenic strokes, a subset of patients with embolic stroke of undetermined source (ESUS) was described (Table 1) (7).

Table 1: Diagnostic criteria for embolic stroke of undetermined source (ESUS), adapted from Hart et al. (7)

Non-lacunar stroke on CT or MRI (Lacunar stroke being defined as a subcortical infarct ≤ 1.5 cm (≤ 2 cm on MRI diffusion images) in the distribution of the small, penetrating cerebral arteries)
Absence of extracranial or intracranial atherosclerosis causing $\geq 50\%$ luminal stenosis in arteries supplying the area of ischaemia
No major-risk cardioembolic source of embolism
• Permanent or paroxysmal atrial fibrillation
• Sustained atrial flutter
• Intracardiac thrombus
• Prosthetic cardiac valve
• Atrial myxoma or other cardiac tumours
• Mitral stenosis
• Myocardial infarction (within last 4 weeks)
• Left ventricular ejection fraction less than 30%
• Valvular vegetations
• Infective endocarditis
No other cause of stroke identified
• Arteritis
• Dissection,
• Migraine/vasospasm
• Drug misuse
• Others

Patent foramen ovale (PFO) is defined as the persistence into adulthood of a normal embryological communication between the two atria (8). About 25% of adults have PFO (9). It appears to be involved in 50% of cryptogenic strokes (10) and 10% of all strokes in young adults (18-60 years) (11).

Due to the high prevalence of both PFO and cryptogenic stroke, including ESUS, it is very hard to prove an actual link between them. It is generally accepted that PFO can lead to stroke through paradoxical embolism, and increases in right-to-left shunting (Valsalva maneuver) amplify the risk. Also, another possible mechanism is represented by in situ thrombus formation (within the PFO or atrial septal aneurysm) (9).

The reported rate of recurrent stroke after cryptogenic stroke associated with PFO appears to be higher in older patients than in younger patients, suggesting other possible causes in addition to paradoxical embolism (11).

To evaluate the likelihood of PFO being the cause of stroke, there are two risk scores clinicians use in everyday practice. The RoPE (Risk of Paradoxical Embolism) score includes clinical and paraclinical data, but also behavioral features and age (12). PFO-Associated Stroke Causal Likelihood (PASCAL) classification includes the RoPE score and anatomical features of PFO (13). A high RoPE score (≥ 7) suggests a higher probability that the detected PFO is causally related to the index stroke rather than being an incidental finding. Furthermore, by integrating the RoPE score into the PASCAL classification system, we can establish the possibility/probability of stroke being related to PFO (14). Those two scores are also used in patient selection for PFO closure, but we must mention that several limitations have been pointed out. RoPE score does not prove causality, but probability (15). It also ignores PFO anatomic features; it is derived from retrospective data; and it has limited utility in older patients, who often receive low scores due to the presence of other vascular risk factors, so the score may underestimate the role of PFO in those cases. On the other hand, PASCAL classification does not prove causality either, but classifies the likelihood of PFO-related stroke. In addition, it demands detailed ultrasonography, and the results could be altered by the technique or operator experience (16).

Secondary prevention options after a PFO-associated stroke consist of antiplatelet therapy, anticoagulant therapy, or percutaneous closure of PFO (17). It is still debatable which option is better, with some studies showing superiority of PFO closure compared to antiplatelet and anticoagulant therapy, while others claim no difference in outcome or inconclusive evidence for either of them (18).

The aim of this focused review is to critically summarize current evidence comparing PFO closure with medical therapy for secondary prevention after PFO-associated cryptogenic stroke, with particular emphasis on patient selection and medium- and long-term outcomes. Also, several studies have reported an association between elevated cardiac biomarkers and increased

stroke severity: higher CK-MB concentrations during the acute phase of ischemic stroke have been observed in patients with more severe neurological deficits, indicating that myocardial involvement may accompany extensive cerebrovascular injury (19).

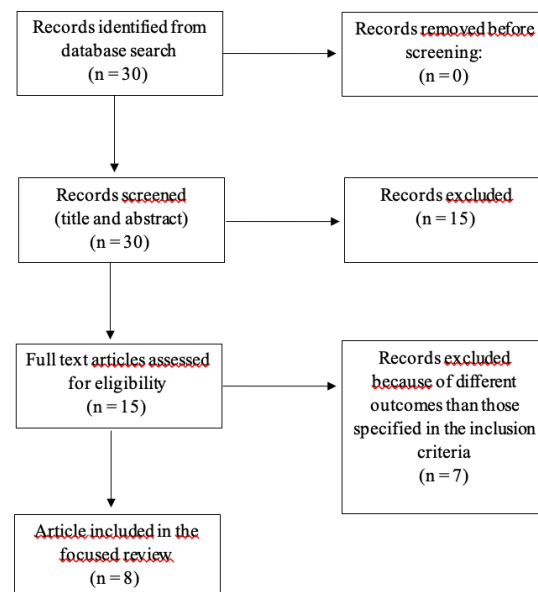
MATERIALS AND METHODS

A structured literature search was conducted in PubMed/MEDLINE for articles published between 01 January 2010 and 31 December 2025. We searched PubMed database for suitable literature data on the comparison of PFO closure with medical therapy for secondary prevention of recurrent cerebrovascular events in patients with PFO-associated cryptogenic stroke using PubMed MeSH terms, such as ("Patent Foramen Ovale"[Mesh] OR "patent foramen ovale"[tiab] OR PFO[tiab]) AND ("Stroke"[Mesh] OR "Ischemic Stroke"[Mesh] OR "ischemic stroke"[tiab] OR "cerebral infarction"[tiab] OR TIA[tiab]) AND ("Heart Septal Defects, Atrial/surgery"[Mesh] OR closure[tiab] OR occlusion[tiab] OR "device closure"[tiab] OR "transcatheter closure"[tiab]) AND ("Recurrence"[Mesh] OR recurrence[tiab] OR recurrent[tiab] OR "stroke recurrence"[tiab]). Regarding the inclusion criteria, we selected records of patients with PFO and a history of stroke, and we filtered our results by study design (clinical studies, clinical trials, multicenter studies, observational studies, randomized controlled studies) and date of publication. Also, we chose to include only free full-text sources. On the other hand, according to our exclusion criteria, studies of children, studies comparing different devices or techniques, and observational studies that focused on long-term complications and recurrence predictors were excluded from the review. The selected studies were narratively synthesized, with emphasis on study design, population characteristics, therapeutic strategies, recurrent stroke outcomes, and follow-up duration. The findings were interpreted qualitatively, with particular attention to differences in patient selection and medical treatment across trials.

RESULTS

We identified 30 records from the PubMed database search. No record was removed before screening. Half of the studies (n = 15) were excluded after screening by title and abstract. After that, a full-text article assessment led to the exclusion of another 7 studies due to outcomes that differed from those specified in the inclusion criteria. Finally, 8 records were included in the review process. The selection process is also illustrated through the following diagram (Figure 1).

Figure 1: Flow diagram of the search papers (20)



In the end, selected studies were compiled in an Excel spreadsheet, from which we extracted data on authors, study acronym, study type, year of publication, number of participants, randomization rate, primary endpoint, and comparison in the discussion and conclusions. We chose to include those studies that compared PFO closure and antiplatelet therapy to medical therapy alone (antiplatelet therapy/anticoagulation). We reviewed eight records, involving 3750 participants, all of whom were diagnosed with PFO and stroke, designed to compare different therapeutic strategies to prevent stroke recurrence (PFO closure vs medical therapy alone).

CLOSURE I (21) was a multicenter, randomized, open-label trial published in 2012 and one of the earliest reports on the subject. It included 909 patients, randomly assigned in equal proportions to two groups: one group underwent PFO closure in addition to antiplatelet therapy, and the other received medical therapy alone (warfarin, aspirin, or both). Primary endpoints were stroke recurrence, transient ischemic attack, and death. In the end, this trial found no significant difference between the two management strategies in terms of stroke recurrence. PC TRIAL (22), also a multicenter, randomized, open-label trial, published one year later, in 2013, included 414 patient, with a randomization ratio of 1:1, distributed in two arms: patients who had PFO closure as well as antiplatelet therapy (aspirin/ticlopidine/clopidogrel) and patients who recieved medical therapy only (antiplatelet therapy alone or oral anticoagulation alone - left to the discretion of the treating physician). Primary endpoints consisted of death, nonfatal strokes, transient ischemic strokes, and peripheral embolism. The results showed no significant difference between the two treatment options. The RESPECT (23) trial was a multicenter, randomized, open-label trial published in 2013, enrolling 980 patients randomized in a 1:1 ratio into two groups: those who underwent PFO closure in addition to antiplatelet therapy and those who received medical therapy exclusively (aspirin, clopidogrel, warfarin, or aspirin plus extended-release dipyridamole). It was one of the first major trials to suggest significantly lower stroke recurrence with PFO closure. Primary endpoints were stroke recurrence and death. This trial had a follow-up in 2017 (24), and the results were consistent with the initial findings. The CLOSE trial (25), another randomized, multicenter, open-label trial published in 2017, included 663 patients randomized by a 1:1:1 ratio in three groups: patients who had PFO closure besides antiplatelet therapy, patients who were given antiplatelet therapy alone (clopidogrel, aspirin, or aspirin combined with extended-release dipyridamole), and patients who received oral anticoagulation exclusively (vitamin K antagonists or direct oral anticoagulants). Its primary endpoint was stroke recurrence. The findings illustrated a significantly lower rate of stroke recurrence with PFO closure. Otherwise, the effects of oral anticoagulant therapy as compared with antiplatelet therapy on the risk of stroke recurrence could not be determined. The Gore REDUCE trial (26), also a multicenter, randomized, open-label trial published in 2017, included 664 patients randomized in two arms by a 2:1 ratio: patients with PFO closure along with antiplatelet therapy and patients who took antiplatelet therapy solely (aspirin, aspirin combined with extended-release dipyridamole, or clopidogrel). Primary endpoints included stroke recurrence, transient ischemic attack, and death. Final data illustrated significantly lower rates of stroke recurrence with PFO closure. This study had a follow-up in 2021 (27), and the results were consistent with the initial findings. The DEFENSE-PFO trial (28), a randomized, open-label, multicenter trial published in 2018, including 120 patients randomized by a 1:1 ratio in two groups, one with patients who had PFO closure plus antiplatelet therapy and one with patients who received medical therapy alone (aspirin, aspirin and clopidogrel, aspirin and cilostazol or warfarin), showed significantly lower rates of stroke recurrence with closure of the PFO in combination with medical therapy than with medical therapy alone. Its primary endpoints were stroke recurrence, death, and major bleeding (Table 2).

Table 2: Selected studies aiming to compare PFO closure and medical therapy alone (antiplatelet therapy/anticoagulation).

No.	Study	Type of study	Year	Number of participants	Primary endpoint	Comparison in study	Conclusions
1	CLOSURE I	Multicenter, randomized, open-label trial	2012	909 (1:1)	Stroke , death	PFO closure (as soon as possible, preferably 7days) plus antiplatelet therapy vs medical therapy alone (warfarin, aspirin or both)	No significant difference
2	PC Trial	Multicenter, randomized, open-label clinical trial	2013	414 (1:1)	Death, nonfatal stroke, transient ischemic attack, peripheral embolism	PFO closure (as soon as possible) plus antiplatelet therapy (aspirin/ticlopidine/clopidogrel) vs medical therapy alone (antiplatelet therapy alone or oral anticoagulation alone - left to the discretion of the treating physician)	No significant difference
3	RESPECT	Multicenter, randomized, open-label trial	2013	980 (1:1)	Stroke, death	PFO closure (within 21 days) plus antiplatelet therapy vs medical therapy alone (aspirin, warfarin, clopidogrel or aspirin combined with extended-release dipyridamole)	Recurrent ischemic stroke was significantly lower with PFO closure plus antiplatelet therapy than with antiplatelet therapy alone.
4	RESPECT follow up		2017				
5	CLOSE	Multicenter, randomized, open-label trial	2017	663 (1:1:1)	Stroke	PFO closure (within 21 days) plus antiplatelet therapy vs antiplatelet therapy alone (aspirin, clopidogrel, or aspirin combined with extended-release dipyridamole) vs oral anticoagulation alone (vitamin K antagonists or direct oral anticoagulants)	Recurrent ischemic stroke was significantly lower with PFO closure plus antiplatelet therapy than with antiplatelet therapy alone. The effects of oral anticoagulant therapy as compared with antiplatelet therapy on the risk of stroke recurrence could not be determined.
6	Gore REDUCE	Multicenter, randomize, open-label trial	2017	664 (2:1)	Stroke, transient ischemic attack, death	PFO closure (within 90 days - median of 28 days) plus antiplatelet therapy vs antiplatelet therapy alone (aspirin, aspirin combined with extended-release dipyridamole or clopidogrel)	Recurrent ischemic stroke was significantly lower with PFO closure plus antiplatelet therapy than with antiplatelet therapy alone.
7	Gore REDUCE follow up		2021				
8	DEFENSE-PFO	Multicenter, randomized, open-label trial	2018	120 (1:1)	Stroke, death, major bleeding	PFO closure (as soon as possible) plus antiplatelet therapy vs medical therapy alone (aspirin, aspirin combined with clopidogrel, aspirin combined with cilostazol or warfarin)	Recurrent ischemic stroke was significantly lower with closure of the PFO in combination with medical therapy than with medical therapy alone

DISCUSSION

We reviewed eight records, six of them being multicenter randomized open-label trials and two of them being follow-ups. The findings demonstrated a relative benefit from PFO closure in terms of stroke recurrence. Two out of eight records (25%) indicated no significant difference when comparing PFO closure and antiplatelet therapy to medical therapy alone (antiplatelet therapy/anticoagulation), while the rest of them (six out of eight, 75%) indicated superiority of PFO closure and antiplatelet therapy in stroke recurrence. We also noticed that the two studies demonstrating similar therapeutic efficacy were among the earliest large trials on this topic, while more recent studies suggest a definite benefit of PFO closure on stroke recurrence. Future research could focus on better scores to determine the causality of PFO in cryptogenic stroke, optimal therapeutic options, optimal medical therapy alone, and best imaging techniques (contrast-enhanced transthoracic echocardiogram, contrast-enhanced transoesophageal echocardiogram, contrast-enhanced transcranial Doppler).

An additional challenge in interpreting the available trials is the heterogeneity of medical therapy used in the control groups. “Medical therapy” encompassed antiplatelet agents, oral anticoagulation, or combinations of different agents, and treatment allocation was sometimes left to the discretion of the treating physician. Consequently, the available evidence more robustly addresses the question of PFO closure versus heterogeneous medical management than the specific comparative efficacy of closure versus antiplatelet therapy or anticoagulation individually. The optimal medical strategy for patients who do not undergo closure therefore remains less clearly defined.

Taken together, current evidence suggests that the clinical question has shifted from whether PFO closure is generally effective to identifying which patients are most likely to derive a net benefit from the procedure. The available randomized evidence supports closure in appropriately selected patients with PFO-associated cryptogenic stroke, particularly when alternative stroke mechanisms have been carefully excluded and clinical and anatomical features increase the likelihood of PFO causality.

Limitations

This focused review had several limitations. First, the available randomized evidence is based on a relatively small number of trials, with few recent large-scale randomized studies, none of which have been published. There were only two follow-up studies, so it is difficult to appreciate accurate long-term efficacy and prognosis. Furthermore, in PFO closure groups, different devices were used, and at the same time, in medication-alone groups, the choice between antiplatelet therapy and anticoagulation, as well as which specific drug was used, varied between trials, making it hard to draw a reliable conclusion.

Future directions

Age represents another unresolved issue in the explored domain. Most randomized trials supporting PFO closure predominantly enrolled younger patients, whereas evidence in individuals older than 60 years remains substantially more limited. In older patients, competing mechanisms of stroke—including occult atrial fibrillation and atherosclerotic disease—become increasingly prevalent, while the RoPE score tends to assign a lower probability of PFO causality because of age and accompanying vascular risk factors. Whether carefully selected older patients with high-risk PFO anatomy may nevertheless benefit from closure remains an important area for future investigation.

CONCLUSION

This focused review aimed to compare different therapeutic strategies to prevent stroke recurrence (PFO closure vs medical therapy alone). Current evidence supports PFO closure as an effective strategy for reducing recurrent stroke in appropriately selected patients with PFO-associated cryptogenic stroke. However, treatment decisions should incorporate clinical characteristics, PFO anatomy, the likelihood of a causal relationship between the PFO and the index event, competing stroke mechanisms, and the risks associated with both interventional and medical strategies. Also, we would like to point out the need for further research, considering that the latest large-scale study on this subject was published in 2018 and that access to diagnostic investigations and closure procedures has improved in recent years. It is expected that more data on this topic would optimize patient selection and evaluation of medium- and long-term prognosis.

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Authors' contribution

Conceptualization, I.G., A.B., F.A.A., and C.A.S.; methodology, I.G., A.B., F.A.A., and A.A.B.; software, A.A.B.; validation, A.A.B. and C.A.S.; formal analysis, I.G., F.C.P., and A.A.B.; investigation, I.G. and A.B.; resources, C.A.S., and F.C.P.; data curation, I.G. and A.B.; writing—original draft preparation, I.G. and A.B.; writing—review and editing, A.A.B. and C.A.S.; visualization, I.G. and A.A.B.; supervision, C.A.S., and F.C.P.; project administration, A.A.B., F.A.A., and C.A.S. All authors have read and agreed to the published version of the manuscript.

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Not applicable.

Patient consent for publication

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REVIEW

Dental Implants in Postmenopausal Women: Biological Considerations, Clinical Outcomes, and Treatment Guidelines

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Abstract: Dental implants have risen as the gold standard for oral rehabilitation, offering predictable outcomes and improved quality of life for patients with missing teeth. However, postmenopausal women constitute a distinct patient population due to the systemic effects of estrogen deficiency, particularly on bone metabolism. The decline in estrogen levels following menopause can negatively impact bone remodeling, potentially influencing osseointegration and the long-term success of dental implants. This review aims to evaluate the current evidence regarding implant outcomes in postmenopausal women, examine the biological implications of hormonal changes on bone physiology, quality, and quantity, and provide evidence-based clinical recommendations to enhance treatment planning and optimize outcomes in this demographic segment.

Keywords: dental implants, postmenopausal women, osteoporosis, estrogen deficiency, osseointegration, bone density

INTRODUCTION

Dental implants have become the gold standard in everyday oral rehabilitation, offering predictable clinical outcomes and improving the quality of life for individuals with missing teeth [1]. By restoring function, aesthetics, and overall oral health more effectively than traditional prosthetic solutions, they have become the preferred choice in modern dental practice [2-4].

Tooth loss is a common concern among postmenopausal women, due to a combination of age-related changes, systemic health conditions, and the cumulative effects of periodontal disease [5,6]. While dental implants are a valid and effective modality for restoring oral function and aesthetics [7], postmenopausal women present distinct biological and clinical challenges. Estrogen deficiency after menopause is linked to decreased bone mineral density, altered bone remodeling, and a heightened risk of osteoporosis—all factors that may affect osseointegration and long-term implant stability [8-10]. Furthermore, the higher prevalence of comorbidities, polypharmacy, and immune function changes in this population requires an individualized and comprehensive approach to treatment planning [11-13].

A growing body of literature has investigated implant survival rates, peri-implant bone loss, and complication profiles in postmenopausal women, mainly in subjects with osteoporosis [14-17]. Despite these advances, inconsistencies remain regarding the extent to which hormonal changes and altered bone metabolism influence clinical outcomes. A clearer understanding of these biological factors is essential for refining surgical protocols, selecting implant designs optimized for compromised bone quality, and implementing adjunctive strategies such as hormone replacement therapy or bone augmentation procedures.

Given the high prevalence of osteoporosis and the increasing demand for implant-based rehabilitation in this population segment, the relationship between osteoporosis treatments, bone metabolism, and implant placement is the focal point in current research.

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This review synthesizes current evidence on the biological mechanisms that might influence implant therapy in postmenopausal women. It evaluates reported clinical outcomes in postmenopausal women and proposes practical treatment guidelines to improve prognosis. By integrating insights from basic science with clinical data, this study aims to provide a comprehensive, evidence-based framework for clinicians involved in the implant rehabilitation of postmenopausal women.

MENOPAUSE AND BONE HEALTH

Hormonal Changes

Menopause is characterized by a significant decline in circulating estrogen, a hormone that plays a central role in maintaining skeletal homeostasis [18-20]. Estrogen exerts anti-resorptive effects by downregulating osteoclast differentiation through inhibition of the receptor activator of nuclear factor kappa-B ligand (RANKL) pathway and by promoting osteoprotegerin production, thereby reducing osteoclastic bone resorption [21,22]. It also enhances osteoblastic activity and facilitates calcium absorption via modulation of vitamin D metabolism [23,24].

In the context of estrogen deficiency, this tightly regulated balance is disrupted. Osteoclast lifespan is prolonged, osteoblast activity declines, and calcium absorption efficiency is reduced due to the decrease in estradiol levels, collectively resulting in a negative bone balance [25,26]. These systemic alterations lead not only to generalized skeletal demineralization, manifesting as postmenopausal osteoporosis, but also to localized effects within the oral cavity. The alveolar bone mirrors the skeletal bone, but given its high turnover rate, it is particularly vulnerable to accelerated resorption [23]. This localized bone loss contributes to periodontal breakdown, decreased tooth support, and impaired healing capacity, which can compromise the stability and longevity of dental implants and other rehabilitative interventions [27,28]. Thus, estrogen deficiency represents a shared mechanistic link between systemic osteoporosis and oral bone loss, highlighting the importance of considering hormonal status in both medical and dental management of postmenopausal women.

Osteoporosis and Oral Bone Loss

Osteoporosis is prevalent in postmenopausal women and is defined by reduced bone mineral density (BMD) and microarchitectural deterioration, leading to increased fracture susceptibility [29]. Several studies have reported that systemic osteoporosis is associated with decreased mandibular bone cortical width and trabecular density, potentially influencing implant site quality and the predictability of osseointegration [30,31]. However, the relationship between systemic BMD and alveolar bone support is still debated. Evidence regarding the relationship between systemic osteoporosis and oral bone loss remains inconsistent. Wang and McCauley reported that osteoporosis and periodontal disease may share common inflammatory and bone remodeling pathways, suggesting a biological association between systemic and oral skeletal deterioration [32]. Similarly, Erdem et al. demonstrated a positive association between reduced bone mineral density and compromised oral health parameters in postmenopausal women [33].

Conversely, Albandar et al. emphasized that local factors—including periodontal inflammation, mechanical loading, oral hygiene status, and microbiological composition—may independently influence alveolar bone loss regardless of systemic skeletal status [34]. Additional studies have similarly suggested that oral bone remodeling is multifactorial and may not directly reflect systemic bone mineral density [35–39].

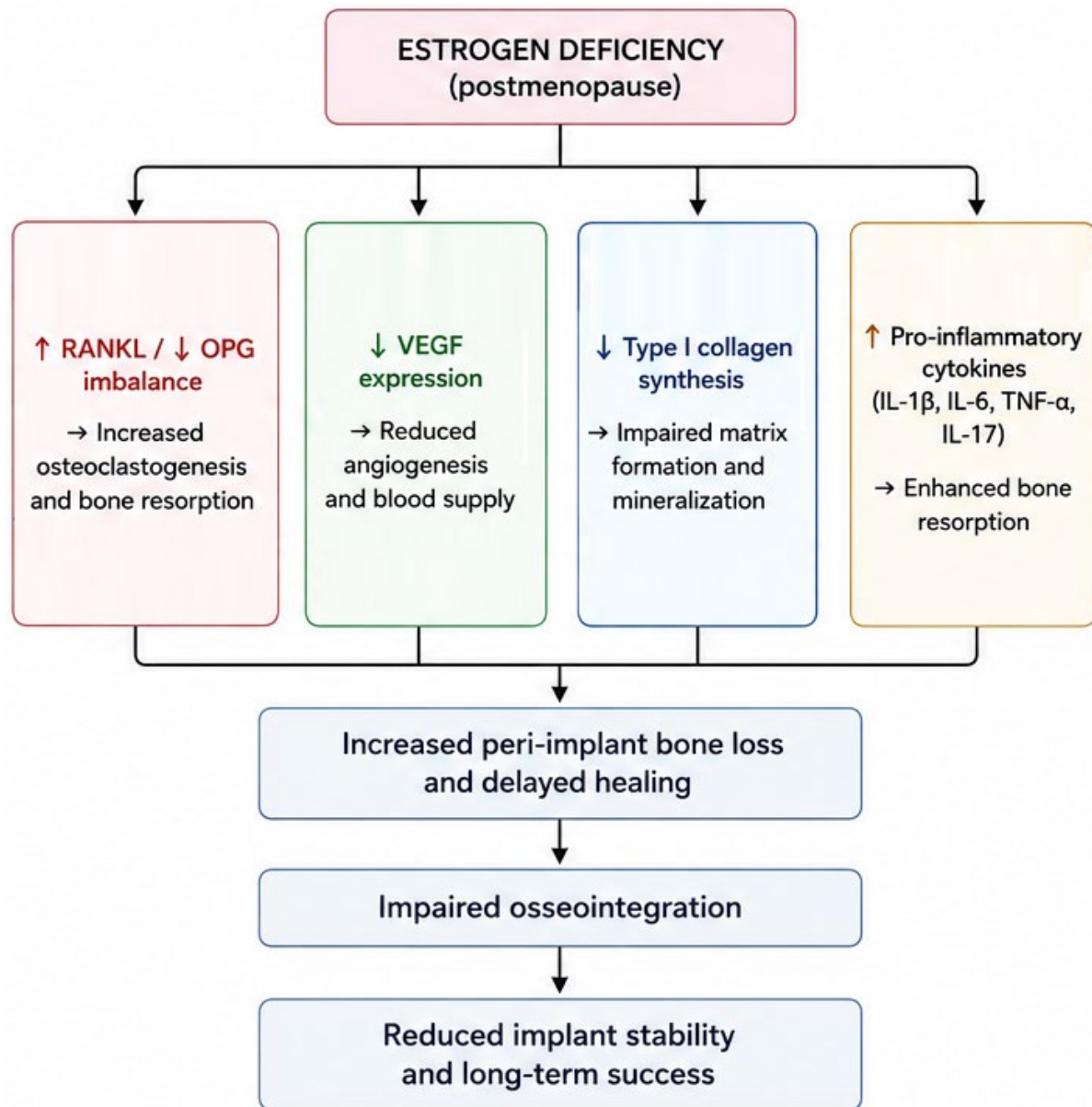
In summary, menopause-induced estrogen deficiency disturbs the finely balanced process of bone remodeling, and these systemic alterations are reflected in the alveolar bone (Figure 1). Therefore, estrogen deficiency is a central driver of both systemic and oral bone deterioration, underscoring the need for integrated medical and dental strategies in the management of postmenopausal women.

Genetic Considerations

In postmenopausal women, where estrogen deficiency already compromises bone remodeling and increases the risk of osteoporosis, host genetic variability may further amplify susceptibility to peri-implant bone loss [8,9]. Genetic determinants, therefore, help account for the heterogeneity of implant outcomes observed within this patient population [40,41]. Genetic factors shape inflammatory signaling and bone turnover and exert a direct influence on osseointegration, which is already challenged by the systemic hormonal environment of menopause [42].

Recent studies have highlighted the role of matrix metalloproteinase-8 (MMP-8) gene variants in peri-implant disease susceptibility [43,44]. A 2025 cross-sectional investigation demonstrated that the –799 C/T promoter polymorphism in MMP-8 was significantly associated with peri-implantitis, with carriers of the T allele exhibiting nearly a three-fold higher risk (OR = 3.04; 95% CI: 1.31–7.10; $p = 0.010$) compared with C allele carriers [42]. These findings are consistent with the established collagenolytic activity of MMP-8 in connective tissue degradation [42,43]. Notably, in the postmenopausal setting—where collagen metabolism and wound healing are already impaired—such polymorphisms may further compromise peri-implant tissue stability and long-term osseointegration [44].

Figure 1: Molecular mechanisms linking estrogen deficiency with impaired osseointegration in postmenopausal women



Legend: Estrogen deficiency initiates multiple biological mechanisms that negatively affect peri-implant bone healing and osseointegration. Reduced estrogen levels increase receptor activator of nuclear factor of kappa-light-chain-enhancer of activated B cells (RANKL) expression and decrease osteoprotegerin (OPG) production, thereby promoting osteoclast differentiation and bone resorption. Simultaneously, estrogen deficiency reduces vascular endothelial growth factor (VEGF) expression, impairing angiogenesis and early healing. Decreased type I collagen synthesis and altered extracellular matrix mineralization further compromise bone quality. Elevated levels of pro-inflammatory cytokines, including interleukin (IL)-1β, IL-6, tumor necrosis factor-α (TNF-α), and IL-17, further stimulate osteoclastogenesis and peri-implant bone loss, collectively resulting in impaired osseointegration and reduced implant stability.

Complementary evidence concerns interleukin-17A (IL-17A), a cytokine with well-documented pro-inflammatory and bone-resorptive properties [45]. A 2024 case-control study reported that individuals carrying the AA genotype of the rs2275913 SNP had a 6.9-fold increased risk of peri-implantitis compared with healthy controls and implant-success patients (OR = 6.9; 95% CI: 1.71–27.46; $p = 0.0065$) [46]. A recent systematic review of the IL-17/IL-23 axis confirmed these findings, with approximately one-third of included studies confirming an association between rs2275913 and peri-implant inflammatory conditions [47]. In postmenopausal women, where estrogen deficiency promotes osteoclastogenesis and inflammatory bone loss, IL-17A polymorphisms may act concomitantly to accelerate peri-implant bone resorption, thereby impairing osseointegration [48].

Moreover, genetic variants in the interleukin-1 gene cluster—including IL-1A, IL-1B, and the IL-1 receptor antagonist (IL-1RN) gene—represent central regulators of peri-implant inflammatory responses [49]. Though recent data showed no significant difference in IL-1A, IL-1B, or IL-1RN polymorphism frequencies in peri-implantitis patients versus controls [50], earlier evidence remains highly relevant: a classic study revealed that carriers of the IL-1RN allele 2 (VNTR in intron 2) had a significantly higher risk of peri-implantitis (OR $\approx$ 3.0; 95% CI: 1.2–7.6; p = 0.02) [51]. In postmenopausal women—already predisposed to inflammatory bone loss—the absence or impaired function of IL-1RN may amplify the effects of IL-1A and IL-1B, acting in concert to accelerate bone resorption and disrupt osseointegration.

Together, all these findings underscore the genetic support of peri-implant disease in postmenopausal women and reinforce the rationale for incorporating host genomics into the framework of personalized implant therapy [52].

Despite emerging evidence supporting the role of genetic polymorphisms in peri-implant inflammation and bone remodeling, current findings remain insufficient for routine clinical implementation. Larger prospective studies are needed before genomic biomarkers can be integrated into personalized implant treatment protocols.

DENTAL IMPLANTS AND OSSEOINTEGRATION IN POSTMENOPAUSAL WOMEN

Biological Considerations

Osseointegration is defined by the Glossary of Prosthodontic Terms – 9th edition (GPT-9) as the apparent direct attachment or connection of osseous tissue to an inert, alloplastic material without the interposition of fibrous connective tissue [53]. This process requires adequate bone volume and quality for primary stability, as well as a favorable local environment to achieve long-term stability.

Estrogen deficiency poses significant challenges to osseointegration through several interconnected biological mechanisms. At the vascular level, reduced estrogen impairs the expression of vascular endothelial growth factor (VEGF), compromising neovascularization at the implant site and diminishing the oxygen and nutrient supply essential for early bone healing [54]. At the matrix level, decreased estrogen leads to reduced synthesis of type I collagen and impaired mineralization of the osteoid matrix, resulting in a less competent bone substrate for implant anchorage [55]. Furthermore, the disrupted RANKL/OPG ratio characteristic of estrogen deficiency accelerates osteoclastic resorption at the peri-implant interface, directly undermining the remodeling process necessary for long-term osseointegration [21,22].

Evidence from animal models supports these observations. Ovariectomized rat and rabbit models consistently demonstrate a significant reduction in bone-to-implant contact (BIC), decreased peri-implant bone volume fraction, and delayed cortical healing compared with intact controls [56–58]. Du et al. demonstrated that estrogen deficiency not only reduced BIC values but also altered the transcriptional profile of peri-implant tissue by downregulating genes associated with osteoblast differentiation and extracellular matrix organization [56]. Latimer et al. further confirmed impaired extraction socket healing and reduced implant stability in aged ovariectomized models, suggesting a cumulative effect of aging and hormonal deficiency [58].

Collectively, these findings suggest that estrogen deficiency negatively influences peri-implant healing through impaired angiogenesis, altered matrix formation, and enhanced bone resorption, potentially reducing the biological predictability of osseointegration in postmenopausal women.

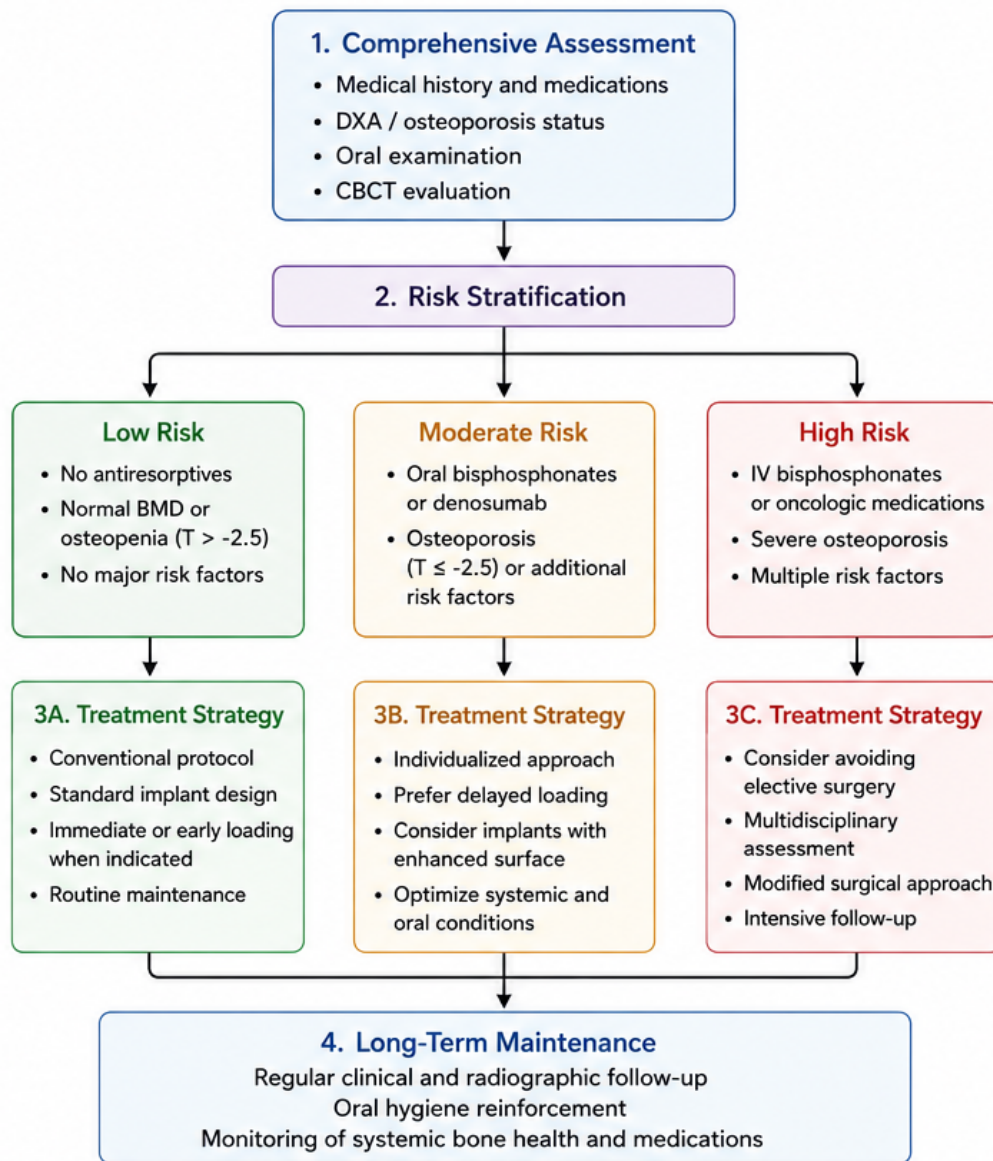
Table 1: Summary of clinical studies evaluating implant outcomes in postmenopausal women

Study	Study design	Population	Follow-up	Implant survival	Main findings	References
Toy and Uslu (2020)	Retrospective	Postmenopausal women	5 years	94.7%	No significant reduction in implant success	[15]
Liapaki et al. (2022)	Retrospective pilot	Osteopenia/osteoporosis	3 years	95%	Slightly increased marginal bone loss	[16]
Alsaadi et al. (2021)	Retrospective	Osteoporotic PM women	Variable	Similar to controls	Menopause alone not associated with failure	[60]
Lemos et al. (2023)	Systematic review/meta-analysis	Osteoporosis patients	Multiple studies	Comparable overall survival	Greater marginal bone loss observed	[61]
Shibli et al. (2025)	Systematic review	Osteoporosis patients	Multiple studies	Comparable survival	Osteoporosis should not be considered an absolute contraindication	[17]

Clinical Outcomes

While biological concerns regarding osseointegration in estrogen-deficient states are well founded, clinical evidence presents a more nuanced picture. Several retrospective studies and systematic reviews have reported implant survival rates in postmenopausal women comparable to those observed in the general population, suggesting that menopause itself should not be considered a contraindication for implant therapy [59–61]. The main clinical studies evaluating implant survival and peri-implant outcomes in postmenopausal women are summarized in Table 1.

Figure 2: Evidence-based clinical decision algorithm for implant therapy in postmenopausal women



Legend: Proposed evidence-based clinical algorithm for treatment planning in postmenopausal women undergoing implant rehabilitation. The process integrates skeletal evaluation, medication history, risk stratification, and individualized implant strategies in order to maximize implant success and minimize complications such as peri-implant bone loss and medication-related osteonecrosis of the jaw (MRONJ). DXA, dual-energy X-ray absorptiometry; CBCT, cone-beam computed tomography; BMD, bone mineral density; IV, intravenous.

Analysis of currently available studies suggests that menopause alone does not significantly impair implant survival; however, osteoporosis and associated systemic conditions may influence marginal bone remodelling and long-term peri-implant stability [62]. Lemos et al. demonstrated that although implant survival rates were similar between osteoporotic and healthy patients,

osteoporotic individuals exhibited greater marginal bone loss [61]. Furthermore, Sachelarie et al. reported that the coexistence of osteoporosis and diabetes adversely affected implant stability, suggesting a cumulative effect of systemic conditions [63].

Variability among studies may be explained by differences in patient selection, medication exposure, osteoporosis severity, implant protocols, and duration of follow-up. Collectively, these findings indicate that individualized risk assessment remains essential before treatment planning. A proposed clinical algorithm for risk assessment and treatment planning in postmenopausal women undergoing implant rehabilitation is illustrated in Figure 2.

Overall, the currently available evidence suggests that implant survival in postmenopausal women is influenced less by menopause itself and more by associated biological and systemic factors, including osteoporosis severity, medication exposure, and comorbidities. Therefore, successful implant therapy requires integration of biological understanding with individualized clinical risk assessment.

IMPACT OF OSTEOPOROSIS MEDICATIONS

Bisphosphonates

Bisphosphonates, administered either orally or intravenously, remain the primary therapy for osteoporosis due to their proven efficacy in reducing fracture risk [64,65]. However, their use has been linked to the development of medication-related osteonecrosis of the jaw (MRONJ), previously known as bisphosphonate-related osteonecrosis of the jaw (BRONJ), a rare but serious complication most frequently triggered by surgical dental procedures such as extractions or implant placement [66–68].

Ruggiero et al., in the updated AAOMS position paper, identified medication dosage, treatment duration, route of administration, and concomitant systemic risk factors as major determinants of MRONJ development [67]. Coropciuc et al. demonstrated that the risk of MRONJ significantly increased following invasive dental procedures in patients receiving antiresorptive therapy [69]. Furthermore, Migliorati et al. emphasized that high-dose intravenous bisphosphonate regimens prescribed for oncologic indications represent the highest-risk category for osteonecrosis development [70].

Denosumab and Other Therapies

Antiresorptive and Anabolic Agents in Osteoporosis: Implant Considerations and MRONJ Risk

Among antiresorptive agents used specifically for osteoporosis management, denosumab—a fully human monoclonal antibody targeting RANKL—represents a widely prescribed alternative to bisphosphonates, with demonstrated efficacy in reducing vertebral, non-vertebral, and hip fractures in postmenopausal women [71,72]. However, similar to bisphosphonates, denosumab has been associated with MRONJ, particularly following invasive dental procedures such as extractions or implant placement [73,74].

The reported incidence of denosumab-associated MRONJ in osteoporosis patients remains low (approximately 0.04–0.3%), but risk increases with treatment duration and previous exposure to bisphosphonates [73]. A unique clinical consideration with denosumab is the risk of rebound bone resorption after discontinuation, leading to rapid bone mineral density loss and increased fracture risk. Therefore, current recommendations suggest scheduling elective implant surgery approximately six months after the last denosumab administration and delaying the next dose by at least three months following surgery, always in consultation with the prescribing physician [74,75].

Regarding implant survival, current evidence remains limited. Salabert et al. described successful implant-based rehabilitation after resolution of denosumab-associated MRONJ, indicating that implant placement may remain feasible in selected cases after complete healing and multidisciplinary assessment [74].

Anabolic agents present a contrasting therapeutic profile. Teriparatide (PTH 1–34), a recombinant parathyroid hormone analogue, stimulates osteoblast activity and promotes new bone formation [76]. Studies suggest beneficial effects on peri-implant bone healing and graft maturation, with successful use reported even in patients with MRONJ [77,78]. However, its routine use in implant dentistry remains insufficiently validated [79,80].

Abaloparatide, a synthetic PTHrP analogue, has demonstrated enhanced peri-implant bone formation in preclinical studies; however, evidence from human implant studies remains insufficient for routine clinical recommendation [81].

Oncologic Medications and MRONJ: A Distinct Clinical Population

It is important to distinguish postmenopausal patients treated for osteoporosis from oncologic patients receiving bone-modifying agents, as the clinical context, medication dosage, and MRONJ risk profile differ substantially. Several medications used in oncology have been associated with MRONJ, including tyrosine kinase inhibitors such as sunitinib, anti-angiogenic monoclonal antibodies such as bevacizumab, fusion proteins such as aflibercept, mTOR inhibitors such as everolimus, and radiopharmaceutical agents such as radium-223 [82–87].

Unlike antiresorptive-associated osteonecrosis, the pathophysiology in these patients frequently involves impaired angiogenesis and reduced vascular supply in addition to altered bone remodeling. Consequently, implant placement in oncologic patients receiving these medications requires extensive multidisciplinary consultation and should generally be avoided during active treatment. The main osteoporosis-related and oncologic medications, their mechanisms of action, associated MRONJ risk, and implant-related considerations are summarized in Table 2.

Table 2: Osteoporosis-Related and Oncologic Medications: Mechanisms, MRONJ Risk and Implant Considerations

Drug class	Examples	Mechanism	MRONJ risk	Implant considerations	References
Bisphosphonates	Alendronate, zoledronate	Inhibit osteoclast-mediated bone resorption	Low in osteoporosis doses; higher with IV use, oncologic doses, treatment >2–4 years	Assess duration, route, dose, systemic risk factors; medical consultation recommended; consider drug holiday only in selected high-risk cases	[64–70]
Denosumab	Denosumab	RANKL inhibition, suppression of osteoclast activation	Low to moderate in osteoporosis patients; increases with duration and prior bisphosphonate exposure	Plan elective surgery near the end of the 6-month dosing interval; delay next dose until mucosal and bone healing, in consultation with physician	[71–75]
Teriparatide	Teriparatide, PTH 1–34	Stimulates osteoblast activity and bone formation	Low; may support bone healing	Potential adjunct for bone regeneration and MRONJ healing; not validated for routine implant use; limited treatment duration	[76–80]
Abaloparatide	Abaloparatide	PTHrP analogue; stimulates osteogenesis	Low; evidence mainly preclinical	May enhance peri-implant bone formation in experimental models; insufficient human clinical evidence	[81]
SERMs	Raloxifene	Modulate estrogen receptors and reduce bone resorption	Low; isolated cases reported	Careful assessment, especially if combined with antiresorptives	[88,89]
Immunosuppressive agents	Corticosteroids, methotrexate	Impair immune response, wound healing, and bone turnover	Contributing risk factor	Optimize systemic condition before surgery; increased caution for healing and infection risk	[90,91]
Tyrosine kinase inhibitors	Sunitinib	Inhibit angiogenesis and tumor signaling pathways	Moderate; mainly oncologic population	Oncologic consultation mandatory; elective implant placement generally deferred during active therapy	[83,84]
Anti-angiogenic monoclonal antibodies	Bevacizumab	VEGF inhibition and impaired angiogenesis	Moderate; oncologic population	High caution; impaired vascularization may compromise healing; avoid elective surgery during active treatment	[82,85–87]
Fusion proteins	Aflibercept	VEGF ligand binding and angiogenesis inhibition	Moderate; oncologic population	Caution required; possible impairment of bone and soft tissue healing	[83]
mTOR inhibitors	Everolimus	mTOR inhibition; impaired bone remodeling and immune response	Moderate; reported mainly in oncology	Avoid elective implant placement during active oncologic therapy; multidisciplinary decision required	[82]
Radiopharmaceuticals	Radium-223	Cytotoxic effect on bone cells	Moderate, especially when combined with antiresorptives	Oncologic consultation required; risk increases with combined bone-modifying therapy	[82,85–87]

Taken together, available evidence highlights the importance of differentiating osteoporosis-related therapies from oncologic medications when assessing implant candidacy and MRONJ risk. Implant planning in postmenopausal women requires comprehensive medication history-taking, individualized risk stratification, and close collaboration with physicians to balance treatment benefits against possible complications.

DIAGNOSTIC AND TREATMENT CONSIDERATIONS

Preoperative Assessment

Preoperative assessment in postmenopausal women planned for dental implant therapy must extend beyond the standard evaluation protocol applicable to the general population, incorporating a systematic appraisal of hormonal status, skeletal health, and pharmacological history.

A comprehensive medical history should document menopausal onset, duration of estrogen deficiency, current or previous hormone replacement therapy (HRT), and any diagnosis of osteopenia or osteoporosis confirmed by dual-energy X-ray absorptiometry (DXA) [92]. T-score values should be reviewed carefully, as osteopenia (–1 to –2.5) and osteoporosis (<–2.5) may influence surgical planning, implant design selection, and loading protocols [29,30].

Pharmacological history requires particular attention, with systematic identification of antiresorptive or anabolic therapies, including bisphosphonates, denosumab, SERMs, and teriparatide. Current AAOMS recommendations indicate that patients receiving oral bisphosphonates for less than four years and without additional risk factors generally do not require modification of therapy prior to implant placement. However, prolonged treatment duration or concomitant corticosteroid use requires individualized evaluation [67].

Oral examination should identify and eliminate active periodontal disease, residual infection foci, dental caries, and mucosal pathology before implant surgery. Menopause-associated changes such as reduced salivary flow, mucosal atrophy, altered microbiota, and impaired healing capacity may negatively influence peri-implant tissue stability [13,37,38].

Cone-beam computed tomography (CBCT) should be considered mandatory for evaluating bone volume, cortical thickness, bone density, and anatomical limitations. Patients with low-density bone may require modifications of surgical and prosthetic planning.

Patient counseling should include discussion of expected outcomes, possible complications, treatment limitations, and the importance of long-term maintenance.

Surgical Protocol

The primary objective of surgical management in postmenopausal women is to maximize implant primary stability while minimizing tissue trauma and preserving vascular supply.

Implant selection should consider reduced bone density and altered trabecular architecture frequently associated with postmenopausal osteoporosis [93]. Evidence suggests that moderately rough implant surfaces (SLA or SLActive) improve bone-to-implant contact and accelerate osseointegration compared with machined surfaces [56,94].

Implant dimensions should also be adapted according to bone availability and density. Wider-diameter implants may improve stress distribution and primary stability in low-density bone; however, anatomical limitations should be carefully considered [93]. Similarly, short implants have demonstrated favorable clinical outcomes in severely resorbed ridges and may reduce the need for extensive bone augmentation procedures [95,96].

Loading strategies should be individualized according to primary stability. Conventional loading remains preferable in patients presenting with osteoporosis or reduced insertion torque values, whereas immediate loading protocols should be reserved for cases achieving adequate primary stability.

In patients presenting with low-density bone (type III–IV), under-preparation of the osteotomy site may improve primary stability without inducing excessive compression. A minimum insertion torque of 20–35 Ncm should be targeted for conventional loading protocols.

When severe ridge resorption is present, alternative approaches including short implants, tilted implants, zygomatic implants, or pterygoid implants may reduce the need for extensive bone augmentation procedures [95–97].

Collectively, individualized implant selection and minimally invasive surgical techniques may improve predictability and reduce complications in postmenopausal women.

Current evidence therefore suggests that implant success in postmenopausal women depends not only on systemic bone status but also on optimization of surgical variables, including implant macrodesign, surface characteristics, primary stability, and loading protocol selection.

Postoperative Care and Long-Term Maintenance

Postoperative management should account for the possibility of delayed osseointegration and progressive systemic bone loss.

Conventional loading protocols following healing periods of three to six months are generally preferred over immediate loading in patients presenting with osteoporosis or compromised bone quality.

Final prosthetic design should ensure uniform distribution of occlusal forces and minimize cantilever loading to reduce peri-implant stress and marginal bone loss [98-100].

Clinical and radiographic follow-up should be performed at three, six, and twelve months after implant loading and annually thereafter. Evaluation should include peri-implant probing depth, bleeding on probing, implant mobility, and radiographic assessment of marginal bone loss.

According to implant success criteria proposed by Albrektsson et al., acceptable marginal bone loss should remain below 1.5 mm during the first year and below 0.2 mm annually thereafter [101].

Long-term maintenance remains essential because systemic bone changes may continue throughout the postmenopausal period.

CONCLUSION

Although estrogen deficiency introduces biological challenges to osseointegration through alterations in bone remodeling, angiogenesis, and inflammatory regulation, menopause itself should not be considered a contraindication to dental implant therapy.

Based on currently available evidence, successful implant rehabilitation in postmenopausal women should follow a structured clinical approach:

- (1) comprehensive evaluation of skeletal status, including osteoporosis screening and medication history;
- (2) identification of antiresorptive or other medications associated with medication-related osteonecrosis of the jaw (MRONJ);
- (3) individualized risk stratification according to systemic conditions and bone quality;
- (4) selection of implant designs and surgical protocols adapted for compromised bone conditions, including optimization of primary stability and loading strategies;
- (5) implementation of long-term supportive care through regular clinical and radiographic follow-up.

Collectively, current evidence suggests that implant prognosis in postmenopausal women depends primarily on individualized treatment planning rather than menopause itself. Integration of systemic assessment, evidence-based surgical strategies, and individualized long-term maintenance protocols may improve treatment predictability and minimize complications.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. No generative AI-produced text was inserted in this manuscript, and no image was previously published in another journal or is under consideration for publication elsewhere. This research received no external funding.

Authors' contribution

Conceptualization, V.T., and D.A.S.; methodology, C.V.P.; software, D.A.S.; validation, V.T., C.V.P., and C.R.C.; formal analysis, V.T.; investigation, C.R.C.; resources, V.T.; data curation, D.A.S.; writing—original draft preparation, C.V.P.; writing—review and editing, C.R.C.; visualization, D.A.S.; supervision, V.T.; project administration, V.T.; funding acquisition, C.V.P. All authors have read and agreed to the published version of the manuscript.

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REVIEW

Effects of intermittent pneumatic compression method on muscle pain, soreness, and recovery after exercise: a systematic review with meta-analysis

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Abstract: Introduction: Athletes generally seek alternatives for muscle recovery after exercise in order to alleviate the resulting pain and accelerate muscle recovery. One of the commonly used procedures is the intermittent pneumatic compression (IPC) method. Objective: Analyze the effects of IPC on muscle pain and physical recovery after fatigue. Methods: A systematic review with meta-analysis registered in the PROSPERO platform (CRD42024530298) was conducted, following the PRISMA guidelines, using the PICOS approach. Eligible studies focused on individuals who used IPC as an intervention method and its effects on the components of physical conditioning and recovery. Quality, certainty of evidence, and completeness of descriptions were assessed using different tools. Results: 10 articles met the eligibility criteria. Meta-analysis data showed that interventions through IPC had a significant effect in favor of the experimental group in the outcome flexibility (SMD = -0.30; CI = 95%; -0.56 to -0.05), subjective perception of recovery (SMD = -0.22; CI = 95%; -0.40 to -0.05) and delayed onset muscle soreness (SMD = -0.34; CI = 95%; -0.51 to -0.17). Conclusion: IPC can become a superior option to passive recovery. In turn, the meta-analysis suggested a beneficial effect of IPC on flexibility, PSR, and DOMS after intervention.

Keywords: athlete; muscle recovery; intermittent pneumatic compression; myalgia.

INTRODUCTION

Across the world, sportspeople and recreational athletes are exposed to demanding conditions through work demands and intense physical activity in their daily activities(1). These daily activities place significant demands on these athletes' physical fitness and performance, exposing them to a high risk of musculoskeletal injuries(2).

Some of these injuries, while undesirable, are likely unpreventable due to the unfavorable conditions of the service in which they are performed(3). However, it is important to recognize that a substantial proportion of these injuries can be attributed to controllable factors, such as training, fitness components, equipment, and preventative factors(4). It is within this preventative context that the intermittent pneumatic compression (IPC) method fits.

IPC has been used as an innovative method, as it aims to reduce edema, increase lymphatic return, increase blood flow, and consequently reduce local pain, which in theory could bring greater benefits to the recovery of individuals after physical stress(5). Furthermore, compression boots are a low-cost, non-invasive, fast, and safe method, free of radiation, highly reproducible, and can be easily included in any activity routine, so that these do not affect and/or have their prevalence reduced(6).

The effects of IPC on muscle recovery during training and sports performance still lack consensus in the scientific literature(7). There is a progressive increase in the number of athletes and professionals using this strategy as a post-exercise recovery tool, but available data are still limited and sometimes contradictory regarding its effectiveness(5).

Studies have investigated the physiological effects of IPC, such as the reduction of inflammatory markers, the perception of muscle soreness, and improved metabolite clearance. However, results vary depending on the protocol used, the intensity of

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the exercise, and the characteristics of the population studied. Despite the growing popularity of IPC as a recovery strategy, there are still no systematic reviews or robust meta-analyses that comprehensively investigate its effects on parameters such as delayed onset muscle soreness (DOMS) and functional recovery in athletes and physically trained individuals(6, 8, 9).

Furthermore, recovery responses may differ between high-level athletes and recreational athletes due to training-specific neuromuscular, cardiovascular, and metabolic adaptations. This reinforces the need for controlled studies with methodological rigor that stratify participants according to training level and comprehensively assess both objective and subjective markers of physical recovery(10).

Therefore, the objective of this study was to analyze the effects of intermittent pneumatic compression (IPC) using boots on muscle soreness and physical recovery in trained individuals after acute interventions involving aerobic and anaerobic exercise, performed alone or in combination, including training sessions, physical tests, games, and sports competitions.

MATERIALS AND METHODS

A systematic literature review was carried out considering the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) methodological guidelines (11) for data reporting, registered in the Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42024530298) and following the PICOS eligibility criteria (population, intervention, comparison, outcome of interest, and type of study)(12).

The search was conducted in January 2025 in the Cochrane Library, Scopus, Web of Science, and MEDLINE/PubMed databases, using a group of two relevant vocabulary terms in Portuguese and their English counterparts from the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH): ("intermittent pneumatic compression devices" or "compression boot" or "external pneumatic compression") and ("myalgia" or "muscle pain" or "muscle soreness" or "muscle sorenesses" or "muscle tenderness") (a detailed description of the full search strategy is available in Appendix A).

No filtering was used for this search. This led to the identification of 106 potential studies for inclusion in the analysis, and all studies found in this search were entered into the Rayyan platform (available at <https://www.rayyan.ai/>).

Studies were considered eligible and included in this review if they met the PICOS criteria: Population (P): Healthy adult individuals; Intervention (I): Use of intermittent pneumatic compression (IPC) method; Comparison (C): Comparison group with any other preventive method, with/without control group; Outcome (O): Flexibility, perceived exertion, biochemical markers, performance, pain intensity; and Study (S): Randomized clinical trials.

Additionally, a manual search of the bibliographic references of the previously included studies was conducted to identify potentially relevant publications that had not been retrieved in the initial stages of the systematic search. However, no new eligible studies were found that were not already included in the selection results based on the established inclusion and exclusion criteria. Additionally, the titles of the eight initially selected studies were entered into the Connected Papers platform (<https://www.connectedpapers.com/>) to identify related, potentially relevant articles that might have been omitted by the databases used. This strategy resulted in the identification of two additional studies, which were subsequently manually included for analysis of their respective abstracts.

The inclusion criteria for studies are described below: a) level of evidence 2 or higher; b) use of pneumatic compression boots; c) studies investigating intermittent pneumatic compression as a recovery strategy in trained individuals or recreational, amateur, or professional athletes; d) studies that included aerobic and anaerobic exercises, performed alone or in combination, including training sessions, physical tests, games, and sports competitions; athletes; e) studies that described at least one clinical outcome, such as: 1) muscle soreness intensity; 2) perception of fatigue; 3) blood markers of muscle damage/fatigue; 4) aerobic, power, and/or strength physical tests; and 5) range of motion (ROM) and/or flexibility.

Randomized controlled clinical trials published in English, Portuguese, and Spanish, regardless of the year of publication, whose objective was to evaluate the applicability of the intermittent pneumatic compression method, were included.

Studies that: a) investigated the upper limbs, b) did not include intermittent pneumatic compression as an intervention, and c) were systematic reviews, cohort studies, pilot studies, abstracts, or unpublished studies were excluded from the sample.

The methodological quality of the included studies was assessed using the Quality Assessment Tool (TESTEX) for exercise science studies. This 12-item, 15-point scale is divided into two sections: 5 points for methodological study quality and 10 points for reporting quality. Some of these criteria include intention-to-treat analysis, monitoring of activities in the control group(s), keeping relative exercise intensity constant, exercise volume characteristics, and energy expenditure(13). Two reviewers independently scored the studies and compared any discrepancies to reach a consensus on the final score. In case of discrepancies, a third reviewer was consulted.

Risk of bias was assessed by two independent reviewers using the Cochrane Risk-of-Bias Tool for Randomized Trials (Cochrane ROB 2)(14), in which seven domains were assessed: randomization process, deviations from intended interventions, missing

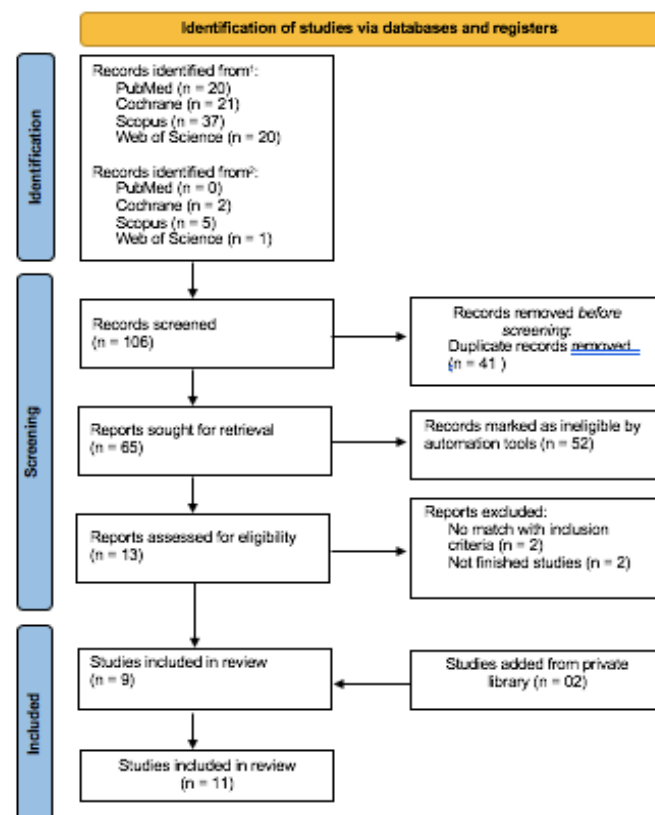
outcome data, outcome measurement, incomplete outcome data, outcome selection, and other biases. Each domain was assessed for risk of bias. Studies were classified as (i) “low risk of bias” when a low risk of bias was determined for all domains; (ii) “unclear” if at least one domain was assessed as raising some concerns, but without a high risk of bias for any single domain; or (iii) “high risk of bias” when a high risk of bias was reached for at least one domain or the trial studied included some concerns across multiple domains⁽¹⁵⁾. A third available reviewer was consulted in case of disagreement.

Two independent reviewers extracted relevant data (study participant characteristics, number and age of participants, intermittent compression methods used, weekly frequency, functional capacity assessed (e.g., strength, power), muscle damage markers (e.g., creatine kinase (CK) levels), subjective perception of recovery, flexibility, performance, and pain intensity). The same method was applied to review the full-text articles. In case of discrepancies, a third reviewer was consulted for the final determination on the articles.

The complete descriptions of the treatments in the included studies were extracted using the “Template for Intervention Description and Replication” (TIDieR), a checklist composed of 12 items, designed with the aim of identifying and encouraging improvements in the description of interventions in randomized clinical trials, with sufficient details to allow their replication^(16, 17).

Treatment effects were quantified using standardized mean differences (SMD) with 95% confidence intervals (95% CI), as the included studies assessed similar outcomes using different measurement scales. A negative SMD value indicates a favorable effect of the intervention (intermittent pneumatic compression) compared to the control group.

Figure 1: PRISMA search diagram



¹Termos de busca= (intermittent pneumatic compression) AND (muscle pain)

²Termos de busca= (compression boot) AND (muscle pain)

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;[372](#):e71. doi: 10.1136/bmj.n71

A fixed-effects model was adopted for flexibility, subjective perception of recovery, and delayed onset perception of recovery outcomes, considering the expected clinical and methodological heterogeneity among studies (e.g., differences in exercise

protocols, populations, and IPC application parameters). Only for the biochemical marker outcome was a random-effects model adopted.

Heterogeneity was assessed using the I^2 statistic and Chi-square test, with I^2 values interpreted as low (<25%), moderate (25–50%), or high (>50%). All analyses were conducted using Review Manager (RevMan, version 5.4). In studies that presented only graphs as results, the “WebPlotDigitizer” software (<https://automeris.io>) was used for correct data extraction and subsequent use in the “Review Manager 5” software(16, 18-20).

The certainty of evidence was assessed by two independent and experienced reviewers using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool through the GRADE PRO website (available at <https://grade.pro.org>) and could be classified as high, moderate, low, or very low(21). Evidence from clinical trial reviews begins with low certainty. At the same time, five aspects reduce the certainty of evidence: risk of bias; imprecision; inconsistency of results; indirect evidence; and publication bias. On the other hand, three aspects increase the certainty of evidence: the dose-response gradient of effect and confounding factors. For each aspect that met the criterion, the certainty increases by one level; if the criterion was not met, the certainty decreases by one level.

RESULTS

Initially, a total of 106 database abstracts were found from the initial search. The next step was to remove 41 duplicates. Further screening of the abstracts and titles led to the exclusion of another 52 articles, resulting in 13 articles being selected for abstract analysis, meeting the inclusion criteria, and being included in this step. Subsequently, five studies were eliminated: two for not being finalized, one for having the same content as another with a different title, one for being a systematic review(9), and one for being a cohort study(22). After this selection, eight studies were added. After listing each of these eight titles found on the Connected Papers platform (available at <https://www.connectedpapers.com/>), two additional studies were found(23, 24), resulting in a total of 10 articles that are part of the current systematic review. The detailed screening process is described in Figure 1.

1. Characteristics of intervention protocols, therapies, and samples

The quality score of the 10 studies included in this review, based on the Quality Assessment Tool for the Assessment of Study Quality and Reporting in Exercise (TESTEX) scale for studies in the area of exercise science, was between 10 (8, 16, 19) and 15 (25) (Table 1), contributing to a risk of bias considered low (Table 2).

Table 1: Quality Assessment Tool for the Assessment of Study Quality and Reporting in Exercise (TESTEX)

Trials	Criteria												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
(8)	1	1	1	0	0	2	1	2	1	0	1	0	10
(23)	1	1	0	1	0	3	1	2	1	0	1	1	12
(19)	0	1	1	0	0	3	1	2	1	0	0	1	10
(16)	1	1	0	0	0	3	1	2	1	0	0	1	10
(20)	0	1	1	1	0	3	1	2	1	1	1	0	12
(18)	1	1	0	1	0	3	1	2	1	0	1	1	12
(24)	0	1	1	0	0	3	1	2	1	0	1	1	11
(25)	1	1	1	1	1	3	1	2	1	1	1	1	15
(26)	1	1	1	0	0	3	1	2	1	1	0	1	12
(27)	0	1	1	1	0	3	1	2	1	1	0	0	11

Quality Assessment Tool for the Assessment of Study Quality and Reporting in Exercise (TESTEX) scale. 1 – Eligibility criteria specified; 2 – Randomization specified; 3 – Allocation concealment; 4 – Similarity of groups at baseline; 5 – Blinding of assessor; 6 – Outcome measures in 85% of participants, adverse events reported and attendance reported; 7 – Intention-to-treat analysis; 8 – Statistical comparisons between groups; 9 – Point measures and measures of variability for all outcome measures reported; 10 – Activity monitoring in control groups; 11 – Relative exercise intensity kept constant; 12 – Volume characteristics.

Table 2 presents the risk of bias analysis based on the Cochrane Risk-of-Bias Tool for Randomized Trials (Cochrane ROB 2)(28). Nine included studies (90%) had a low risk of bias, evidencing good control in the randomization process, blinding, control, and description of results(8, 16, 18-20, 24-27). Only one study (10%) (23) had a high risk of bias (detection bias).

Table 2: Risk of bias of included studies

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Wiecha et al, 2021	+	+	+	+	+	+	+
Draper et al, 2020	+	+	+	+	+	+	+
Haun et al, 2017-a	+	+	+	-	+	+	+
Haun et al, 2017-b	+	+	+	+	+	+	+
Heapy et al, 2016	+	+	+	+	+	+	+
Northey et al, 2016	+	+	+	+	+	+	+
Hoffman et al, 2015	+	+	+	+	+	+	+
Sands et al, 2015	+	+	+	+	+	+	+
Martin et al, 2015	+	+	+	+	+	+	+
Kim et al, 2001	+	+	+	+	+	+	+

Risk of bias of the included studies. 1 – Bias resulting from the randomization process; 2 – Bias due to deviations from planned interventions; 3 – Bias due to lack of outcome data; 4 – Bias in outcome measurement; 5 – Incomplete outcome data; 6 – Bias in selection of the reported outcome; and 7 – Other biases. Low risk (green), Uncertain (yellow), high risk (red).

Table 3 presents the full descriptions of the treatments used in the included studies, using the “Template for Intervention Description and Replication” (TIDieR) tool. This analysis showed that all studies found can be replicated, as they adequately included the items in this tool, such as the name, a logical basis, description of the materials used, procedures and clearly stated the application sites.

The characteristics of the studies included in the systematic review are described in Table 4. Among the 10 studies analyzed, six are Randomized Clinical Trials(16, 18-20, 26, 27), one double-blind (26) and three crossover randomized clinical trials(8, 23, 24). Overall, the studies included patients from four countries: USA (n=191), Australia (n=12), Poland (n=45), and New Zealand (n=56). The total population of the selected studies consisted of 304 healthy volunteers, with unequal gender distribution (male: n=267; female: n=37). Across all studies, the average sample size ranged from 10 to 72 volunteers.

The mean sample size for the intervention group was 20.27 individuals, and for the control group, 11.45 individuals. The mean age of the study population was 28.4 years. Only one study investigated participants with a mean age over 40 years(19), and one of them did not report the mean age of the participants(16).

Table 3: Completeness of the description of interventions

Legend: E = Experimental Group; C = Control Group; S = Yes; N = No.

Studies	Brief name		Logical basis		Materials		Procedures		Supplier		How		Where		When and how much		Customization		Modified		How well planned		How current	
	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C
(8)	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	N	N	N	N	S	S	S	S
(23)	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	N	N	S	S	S	S
(19)	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	N	N	N	N	S	S	S	S
(16)	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	N	N	N	N	S	S	S	S
(20)	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	N	N	S	S	S	S
(18)	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	N	N	S	S	S	S
(24)	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	N	N	S	S	S	S
(25)	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	N	N	N	N	S	S	S	S
(26)	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	N	N	N	N	S	S	S	S
(27)	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	N	N	N	N	S	S	S	S

Four studies involved well-trained volunteers (8, 16, 19, 26). Three studies included runners (16, 19) and (8). Two studies included strength-trained men (20) and (18). Two studies included physically active volunteers (27) and (25), and one study included professional athletes (26). Two other studies chose healthy participants (24) and (23). Detailed information on training status is presented in Table 4.

All studies used pneumatic compression boots, and the comparators were: massage (16, 19), control (rest with extended legs)(19, 20), control (no treatment)(8), control (electrodes off)(25), control (boots off)(18, 23, 24, 26), local warming with hot water (27) and intermittent negative pressure (25).

Considerable variation was observed in the therapeutic parameters used in the studies found. IPC was used with different therapy times. The average boot application time was 39.3 minutes, ranging from 15 (26) to 120 (8, 18, 23, 27) minutes. Regarding compression pressures, four studies used 70 mm Hg (18, 23, 24, 27), four authors used 80 mm Hg(16, 19, 25, 26), one study used 220 mm Hg(20), two studies used a system that varied the pressure from 90 mm Hg to 100 mm Hg (8) and from 70 mm Hg to 80 mm Hg(26).

The reviewed studies showed considerable variations in IPC application protocols. Most investigations adopted a single IPC application immediately after the fatigue protocol (16, 19, 22, 24, 27). Only one study employed IPC continuously, for five consecutive days, for therapeutic purposes(8), while another study conducted three sessions on a single day(26). Furthermore, three studies applied IPC at different time points after induced fatigue, specifically 1 hour, 24 hours, and 48 hours post-exercise (18, 23, 25). Notably, only one study adopted two IPC sessions at different time points, immediately after fatigue and again 24 hours later(20).

In order to induce muscle damage, five studies used running for this purpose (8, 16, 19, 23, 24, 27). Among running as an intervention method, two of them adopted short runs: High-Intensity Interval Training (23) and Loughborough Intermittent Shuttle Test (27). Two other studies addressed ultramarathons (16, 19), and one study only used intermediate-volume running (8) as an intervention protocol. Two studies used the squat exercise: 10 sets of 5 repetitions at 80% 1RM (18) and 10 sets of 10 repetitions at 70% 1RM(20). Another way to induce muscle fatigue was the Wingate anaerobic test, with 7.5% of the individual's body weight as resistance (24). One study used plyometric exercises for this purpose(25). Because they included professional athletes among the participants, another study did not intervene in their routines, using only routine morning training (26). It is worth noting that Sands et al. (2015) used a sample of 24 highly trained individuals from the US Olympic Center to apply pneumatic compression boots after a training session, whose sports were wrestling, Greco-Roman wrestling, triathlon, track cycling, weightlifting, modern pentathlon, and shooting.

The most common compression method used was a cycle of 30 seconds of inflation and 30 seconds of deflation (8, 18, 23, 26). Three studies used a cycle of 30/40 seconds of inflation and 15 seconds of deflation (16, 19, 20). Two studies did not specify the type of cycle used in their intervention(25, 27), and one study used a cycle of 60 seconds of inflation and 30 seconds of deflation(24).

The most commonly measured outcome parameters were those related to creatine kinase (CK) concentration (16, 18, 19, 23, 25). Perceived recovery rate (PSR)(19); pressure pain threshold (18, 23, 26); performance in the 400-meter test (16); average power, fatigue index, peak power, and blood lactate concentration(24); Reactive Protein (CRP)(8); subjective perception of recovery and muscle soreness through the Visual Analog Scale (VAS)(8, 16, 25, 27); flexibility (18, 23); muscle glycogen (27), and Lactate Dehydrogenase (LDH)(25). Isokinetic quadriceps torque, squat jump test, and countermovement jump test were also analyzed in one study (20).

2. Meta-analysis results

The following outcomes were meta-analyzed in the present study: flexibility, perceived recovery (PSR), biochemical marker (CK), and delayed-onset muscle soreness. The effect size was calculated by Standardized Mean Difference (SMD) with a 95% confidence interval (CI). When calculating the effect size, the negative sign means larger effects for the Experimental Group (EG) when compared to the Control Group (CG). The diamond represents the average effect size of the studies included in each outcome and should be interpreted equally.

2.1. Outcome: flexibility

Figure 2 presents a meta-analysis of the outcomes related to flexibility investigated after 24, 48, 72, 96, and 120 hours. Three studies and 12 analyses were included, and the pooled effect size, calculated using a fixed-effects model, showed a significant effect in favor of the experimental group (SMD = -0.30; 95% CI: -0.56 to -0.05), and significant differences were found in favor of the experimental group ($z = 2.35$, $p = 0.02$). The Q test showed low heterogeneity ($p = 0.30$, $I^2 = 15\%$). There was no effect ($p = 1.00$, $I^2 = 0\%$) in the test for subgroup difference.

Table 4: Characteristics of the studies included in the review (n=10)

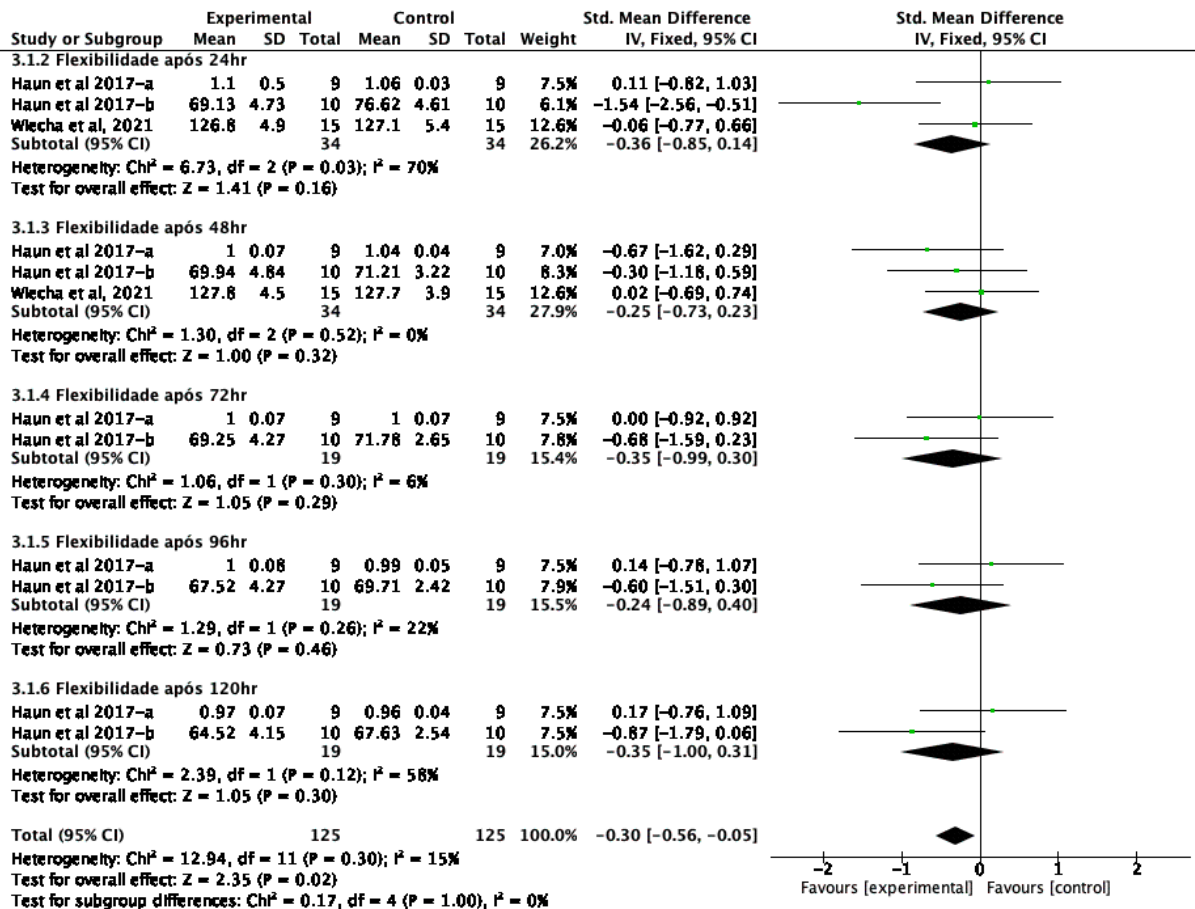
Author	Type of study/year	Participants	Intervention	Intervention vs. Control Group	Study Variables	Outcomes
(8)	ERC/ 2020	10 US endurance athletes (marathoners, ironman triathletes) 5 men 5 women 18-55 years old	2 x 20 mile runs at 70% VO2 max over a 3-4 week period	IPC group used 60 min (NormaTec from 90mm Hg to 100mm Hg) 1hr, 24hr, 48hr, 72hr, 96hr, 120hr post IPC Vs. Control Group (CG) received no intervention 1hr, 24hr, 48hr, 72hr, 96hr, 120hr post Placebo	CRP VAS	IPC x CG CRP (24hr↑*, 48hr↑, 72hr↑, 96hr↔→120hr) VAS (24hr↑*, 48hr↑*, 72hr↑, 96hr↑, 120hr↔→)
(18)	ECR/ 2017-b	20 well-trained US males 19-24 years old, BM (kg) = 78.9±3.2, Height (cm) = 177±3.9, BMI (kg/m2) = 25.6±1.6	10 sets of 5 reps of squats at 80% 1RM for 3 days in a row	IPC Group (n=10) (NormaTec™, 70mm Hg for 60min, Cycle 30sec/30sec) vs. Control Group (n=10) (boots not inflated for 60 min)	Vastus Lateralis Biopsy LDP Oxidative Stress CK Flexibility	IPC x CG CK (72-120hr↑*, 144-168hr↑) Flexibility (72hr↑*, 96hr↑, 120hr↑*, 144hr↑, 168hr↓) CRP (48-168hr↑) LDP (72hr↓*, 96hr↓, 120hr↓*, 144hr↓, 168hr↔→)
(19)	ECR/ 2016	56 New Zealand male ultramarathon runners (Tarawera race) 34-52 years old, BMI (kg/m2) = 24.3±2.3	One of three races: 62.7km or 87.4km or 102.8km	IPC Group (n=18) used Recovery Pump LLC for 20 minutes at 80mm Hg 3 days of treatment Vs. Massage Group (MG) (n=19) received 20 min of lower limb massage, 3 days of treatment Cycle 30-40sec/15sec Vs. Control Group (CG), passive recovery for 20 min (n=19) 3 days of observation	DOMS LL Fatigue (PSR) VAS Plasma CK 400m time	IPC x CG 400m time (pre↔→, 72↔→120hr) VAS (pre↑*, post↑*, 24hr↑*, 48-120hr↑, 144-336hr↔→) Fatigue (pre-post↑*, 24-72hr↑*, 96-120hr↑, 144-336hr↔→)
(16)	ECR/ 2015	72 US ultramarathoners (WSER 2015) men, Age (years) = 43±8	Ultramarathon 161km Western States Endurance Run 2015	IPC Group (n=24) used Recovery Pump LLC for 20 minutes at 80mm Hg (Cycle 30-40sec/15 sec) Vs. Massage Group (MG) (n=25) performed lower limb massage for 20 minutes Vs. Control Group (CG) (n=23) rested for 20 minutes with legs extended	DOMS LL Fatigue (PSR) Plasma CK 400 m time	IPC x CG 400 m. tempo (72hr↑, 120hr↓) DMIT (pre↔→, post↑*, 24-96hr↑*) Fatigue (pre↔→, post↑, 24-68hr↑) CK (pre↔→, post↑*, 24-96hr↑)

(20)	ERC/ 2016	12 healthy males Resistance training 3x weekly Australia 20-35 years old, Height (cm) = 180.4±9.7, BM (kg) = 84.8±9.6	10 sets of 10 squats at 70% 1RM	OV Group (FRBPC with 220mm Hg, 45 minutes, 4x3 minutes alternating limbs) Vs. IPC Group (RecoveryPump with 80mm Hg for 45 min) Vs. Control Group (CG) (lying down for 45 min)	DMIT MMII VAS S.J. CMJ Measure 1h and 24h	IPC x OV VAS (pre-post↑*, 1hr↑*, 24hr↑*) CMJ (pre-post↓*, 1hr↓*, 24hr↓*) SJ (pre-post↓*, 1-24hr↓*) Control (pre-post↓*, 1hr↓*, 24hr↔)
(23)	ECR/ 2017-a	18 male recreational athletes from the USA 19-24 years old, MC (kg) = 80.1±2.2, Height (cm) = 179±3, BMI (kg/m2) = 24.9±0.7	HIIT 3 days in a row (15 sets of 45 seconds running + 45 seconds walking)	IPC Group (n=9) (NormaTec™, 70mm Hg for 60 min) Vs. Control Group (n=9) (boots not inflated for 60 min) 03 days of methods (PRE, POST1, POST2) Cycle 30sec/ 30 sec	CK Flexibility 6km performance Vastus Lateralis Biopsy	IPC x CG 6km performance (PRE, POST1↔, POST2↔) CK (PRE, POST1↑*, POST2↑*) Flexibility (PRE, POST1↔, POST2↔)
(24)	ERC/ 2015	14 apparently healthy US subjects (7 males, 7 females) Age 19.3-32.2 years BM (kg) = 72.6±11.1; Height (cm) = 174.6 ±9.5; BF (%) = 12.7±1.3	Wingate Anaerobic Test 30sec with 7.5% body weight	IPC Group (NormaTec™, 70mm Hg for 30 min) vs. Control Group (CG) (boots not inflated for 30 min)	Peak Power (PP) Average Power (PM) Fatigue Index (PSR) CLac (pre, post, 5min, 15min, 25min, 35min)	IPC x CG PP↔, PM↔, PSR↔ CLac (pré, pós↑*, 5min↓, 15min↓*, 25min↓*)
(25)	ECRDC/ 2021	45 healthy adult Polish men 18-26 years 3-5 hours recreational activities/week	5 sets of 20 drop jumps	30 minutes in each group IPC Group (n=15) (BOA-Max 2 boot, 80mm Hg) Vs. PIN Group (n=15) (vacuum 24.7-36.7mm Hg) Vs.	CK LDH Isokinetic strength VAS ROM QPT 1hr, 24hr and 48hr	IPC x PIN CK (pré, 1hr↔, 24-48hr↑*) LDH (pré, 1hr-48↓*) VAS (pré, 1hr↔, 24-48hr↑*) ROM (pré, 1-48hr↓*) QPT (pré, 1hr↓, 24-48hr↓*)

FTM Group (n=15) (electrodes off)					
(26)	ECR/ 2015	24 highly trained individuals (USA Olympic Center) 12 men (ages 23-40) 12 women (ages 18-36)	Training session	IPC Group (70 to 80 mmHg for 15 min) N = 12 Vs. Control Group (CG) (boots not inflated for 15 min) N = 12 3 interventions on the same day (pre (pre1), immediate post (post1) and delayed post (post2))	LDP in various parts of the MMII and PSR IPC x CG Pre (Lateral gastrocnemius, biceps femoris, vastus lateralis) Post1 (Lateral gastrocnemius↓*, biceps femoris*, vastus lateralis*) Post2 (Lateral gastrocnemius↔, biceps femoris↔, vastus lateralis↔)
(27)	ECR/ 2001	26 trained US subjects (13 men and 13 women) 18-35 years Active 5x week for 60 min	90 min LIST	IPC Group (70mm Hg) 60 min single leg intervention Other leg was control 1hr and 24hr Vs. Local Warming Group (GA) (water at 48-52°C) 60 min single leg intervention Other leg was control	Muscle Glycogen GM Muscle Function FM VAS 1hr and 24hr IPC x GA GM (24hr↑*) VAS (1hr-24hr↔) FM (1hr-24hr↓)

Abbreviations: RCT (Randomized Controlled Trial), ERC (Randomized Cross-over Trial), RCTDC (Double Blind Randomized Clinical Trial), IPC (Intermittent Pneumatic Compression), RPE (Perceived Exertion), CRP (Reactive Protein), SJ (Squat Jump), CMJ (Countermovement Jump), OV (Vascular Occlusion), PIN (Intermittent Negative Pressure), FTM (Fake Microcurrent Therapy), CK (Creatine Kinase), LDH (Lactate Dehydrogenase), IAG (Ice Water Immersion), LDP (Pressure Pain Threshold), HIIT (High Intensity Interval Training), CLac (Lactate Concentration), FRBPC (Flexiport Reusable Blood Pressure Cuff), LIST (Loughborough Intermittent Shuttle Test), VAS (Visual Analog Scale), DMIT (Delayed Muscular Onset Soreness), AL (Local Warming), GM (Muscle Glycogen), FM (Muscle Function), ROM (Range Of Motion), QPT (Quadriceps Peak Torque), NH (Hydration Level), QS (Sleep Quality), MC (Body Mass), Est (Height), BF (Body Fat), BMI (Body Mass Index).

Figure 2: Perception of Flexibility in IPC x placebo



2.2. Outcome: subjective perception of recovery

Figure 3 presents a meta-analysis of the outcomes related to PSR studied after 24, 48, 72, 96 and 120 hours after IPC. Two studies and 12 analyses were included, and the pooled effect size calculated using a fixed-effects model showed a significant effect in favor of the experimental group (SMD = -0.22; (95% CI: -0.40 to -0.05)), and significant differences were found ($z = 2.48$, $p = 0.01$) in favor of the experimental group. The Q test showed moderate heterogeneity ($p = 0.06$, $I^2 = 42\%$). There was no effect ($p = 0.98$, $I^2 = 0\%$) in the test for subgroup difference.

2.3. Outcome: Biochemical marker (CK) in IPC x placebo

Figure 4 presents a meta-analysis of the outcomes related to CK concentrations 24, 48, 72, 96 and 120 hours after the use of IPC. Three studies and 12 analyses were included, and the pooled effect size calculated using a random-effects model showed a significant effect in favor of the experimental group (SMD = -0.38 (95% CI: -1.19 to 0.43)), and no significant differences were found ($z = 0.92$, $p = 0.36$). The Q test showed high and true heterogeneity ($p < 0.001$, $I^2 = 87\%$). There was no effect ($p = 0.89$, $I^2 = 0\%$) in the test for subgroup difference.

2.4. Outcome: Delayed Onset Muscle Soreness (DOMS)

Figure 5 shows a meta-analysis of outcomes related to DOMS immediately, 1, 24, 48, 72 and 96 hours after IPC. Four studies and 16 analyses were included, and the pooled effect size calculated using a fixed-effects model showed a significant effect in favor of the experimental group (SMD = -0.34 (95% CI: -0.51 to -0.17)), showing significant differences in favor of the experimental group ($z = 3.88$, $p = 0.0001$). The Q test showed low heterogeneity ($p = 0.69$, $I^2 = 0\%$). There was no effect ($p = 0.41$, $I^2 = 1.7\%$) in the test for subgroup differences.

Figure 3: Subjective Perception of Recovery in IPC x placebo

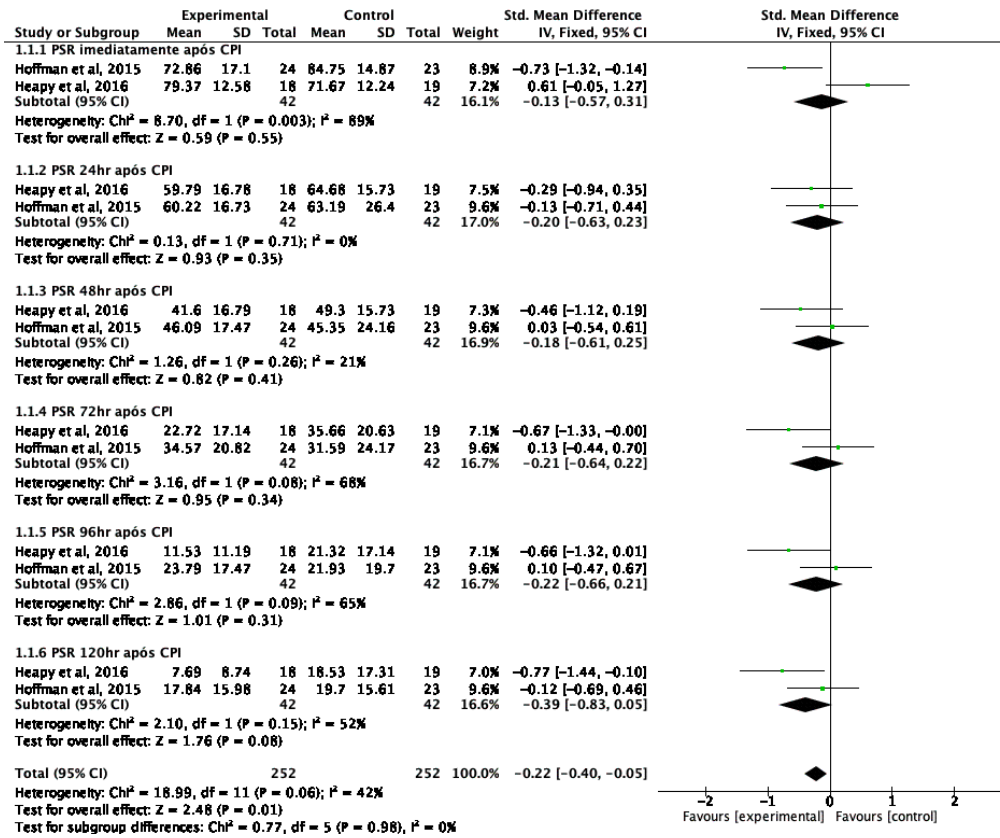


Figure 4: Biochemical marker (CK) in IPC x placebo

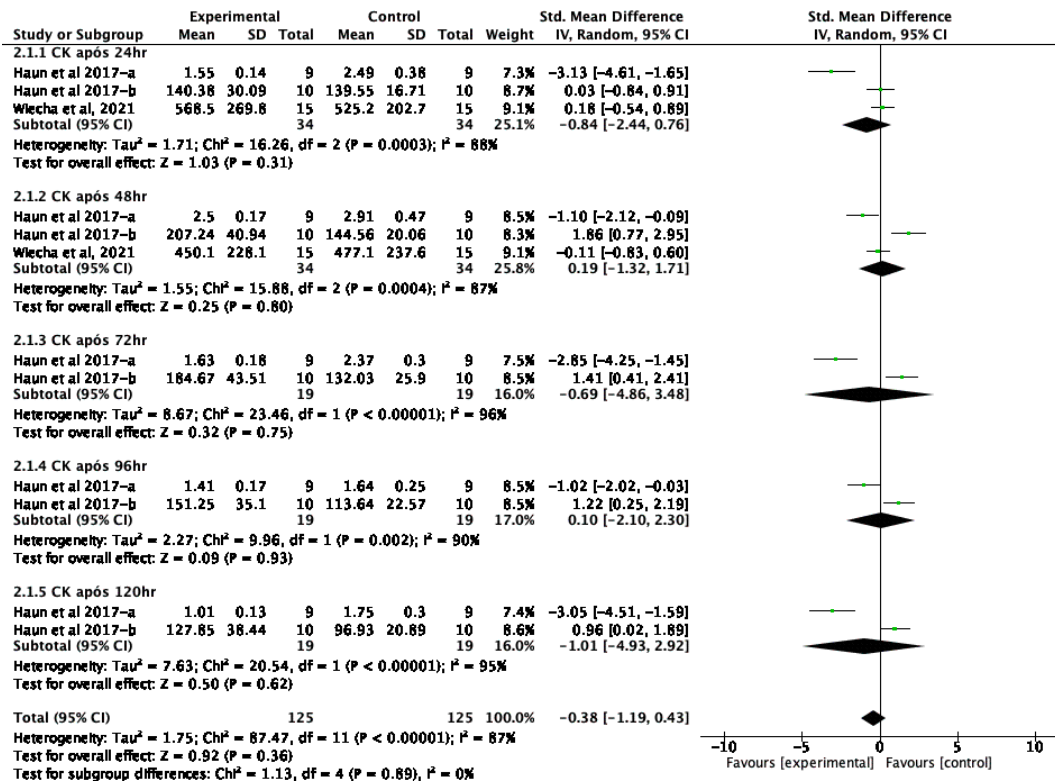


Figure 5: Delayed Onset Muscle Soreness in IPC x placebo

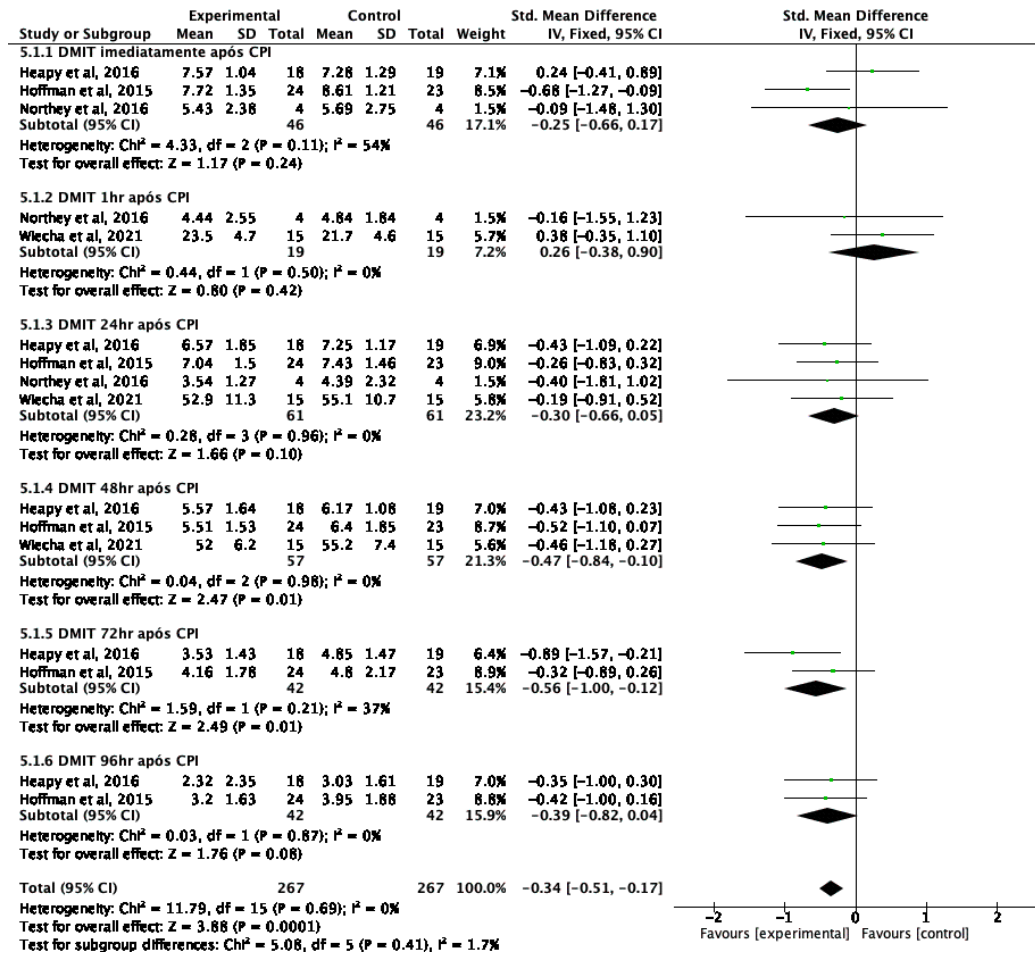


Table 5 shows the level of evidence of the studies included in the meta-analysis, which was considered high according to the GRADE tool, meaning there is high confidence in the estimated effect found. The downgraded aspect was the risk of bias (18) and the inconsistency found in the PSR based on the overlap of confidence intervals and heterogeneity testing. Furthermore, none of the other aspects (effect size, dose-response gradient, or confounding factors) increased the certainty of the evidence.

Table 5: Certainty assessment

Certainty Assessment					No of participants				Certainty	Importance
No of Studies	Study Design	Risk of Bias	Inconsistency	Indirect Evidence	No of Studies	Study Design	Risk of Bias	Inconsistency	Study Design	Risk of Bias
4	Randomized clinical trials	Not serious	serious ^a	Not serious	Not serious	None	103/206 (50.0%)	103/206 (50.0%)	⊕⊕⊕○ Moderate ^a	IMPORTANT
5	Randomized clinical trials	Not serious	Not serious	Not serious	Not serious	None	83/156 (53.2%)	73/156 (46.8%)	⊕⊕⊕⊕ High	IMPORTANT
3	Randomized clinical trials	serious ^b	Not serious	Not serious	Not serious	None	19/38 (50.0%)	19/38 (50.0%)	⊕⊕⊕○ Moderate ^b	NOT IMPORTANT
6	Randomized clinical trials	Not serious	Not serious	Not serious	Not serious	None	76/152 (50.0%)	76/152 (50.0%)	⊕⊕⊕⊕ High	IMPORTANT

DISCUSSION

This study aimed to analyze the effects of the intermittent pneumatic compression (IPC) method on muscle pain and physical recovery of individuals after acute interventions involving aerobic and anaerobic exercises, performed in isolation or combined, including training sessions, physical tests, games, and sports competitions.

The relationship between the IPC method, muscle soreness, and post-exercise recovery is complex. Evidence suggests that the effectiveness of IPC may be related to the immediate preventive nature of the method (19, 25, 26). The present study did not find sufficient evidence to conclude on the effectiveness of IPC when administered for 48 hours (19), 96 hours, or 120 hours (8). The long-term nature of this method (48 hours or more) still appears to be contradictory. The effectiveness of IPC also appears to be similar when assessed in other physical components, such as lactate concentration, CK, DOMS, muscle glycogen concentration, and flexibility. In this sense, flexibility showed a heterogeneous direction in the results. One study observed a decrease in range of motion (ROM) 48 hours after exercise (25), while another observed the maintenance of flexibility in two assessments, 24 hours and 48 hours after the execution of High Intensity Interval Training (23). Other studies also reported an increase in flexibility after 72 hours, 96 hours, 120 hours and 144 hours of neuromuscular training using IPC (18). Regarding delayed onset muscle soreness (DOMS), positive effects of IPC were found when analyzed immediately, 24 hours and up to 96 hours after physical stress (16, 19), corroborating narrative review studies (29) and meta-analyses found in the literature (30, 31).

In response to prior exercise, one study found high-quality evidence that IPC was superior to placebo in reducing CK concentrations in trained young individuals (16). Regarding oxidative stress and proteolysis markers, IPC was effective in reducing pressure pain thresholds compared to placebo after 3 and 6 days of intervention, as well as in reducing muscle proteolysis and oxidative stress in trained men after neuromuscular intervention (18), and also after High Intensity Interval Training (23). However, one study did not observe improvements in CK concentration (19) in athletes undergoing ultramarathon running, and in three more invasive studies lasting 3 days, IPC was effective in reducing proteolysis when compared to the control group (16, 18, 23).

Regarding the perception of muscle fatigue, measured through the subjective perception of recovery (PSR), IPC was able to induce benefits related to PSR (16). The beneficial effect of IPC on perceived fatigue can be explained by a possible reduction in the space available for swelling and edema due to the compression applied to the limb, and smaller changes in osmotic pressure that ultimately provide better venous return (32). Haun et al. (18) and Haun et al. (23) reported that the use of the IPC method was able to decrease muscle discomfort when compared to a placebo group, although for unknown reasons. However, Wiecha et al. (25) found no reduction in CK markers immediately and up to 48 hours after intervention. These discrepancies in the findings can be explained by the different durations of the recovery period (8), the duration of compression applied (32), the amount of pressure applied (22), and the location where the compression was applied (31, 33). In addition to these extrinsic factors, some intrinsic factors, such as individual variability in sensitivity to blood flow changes and body composition, especially in the lower limbs, can also be considered (34).

Three studies analyzed the use of IPC and its effects on sports performance (16, 19, 23). The use of pneumatic compression boots was not superior in improving performance in successive 400-meter anaerobic tests after 72 and 120 hours. These findings corroborate those found by Haun et al. (23). Although positive effects were found in the use of compression boots in reducing CK and skeletal muscle proteolysis markers, no beneficial effect was found regarding sports performance. It may be possible that IPC is more effective in studies that have a neuromuscular test as an intervention, given the findings of Haun et al. (18).

Of the 10 studies included in this systematic review, six were meta-analyzed. Regarding flexibility, the Flexibility after 48 hours subgroup showed low heterogeneity. However, the variables analyzed among the three included studies showed no similarities. The study by Wiecha et al. (25) had greater weight in the meta-analysis. This was a double-blind clinical study with an intervention protocol of IPC for 30 minutes at a pressure of 80 mm Hg, after plyometric drop jump exercises, during a 2-day intervention. However, its results should be interpreted with caution, as they were influenced by the larger number of participants and lower variation between the results. Haun et al. (18) and Haun et al. (23) presented different interventions. Haun et al., (18) used neuromuscular exercises (10 sets of 5 repetitions of squats at 80% 1RM for 3 consecutive days) as an intervention, while Haun et al. (23) used a HIIT protocol for 3 consecutive days consisting of 15 sets with 45 seconds of running interspersed with 45 seconds of walking. However, one study showed an increase in the variable (18) and the other did not (23).

The outcome of PSR in IPC showed differences in favor of the experimental group, with PSR improving only when assessed immediately after IPC, despite its moderate degree of heterogeneity ($I^2 = 42\%$). The small number of studies ($n = 2$) and the different findings can be attributed to this high heterogeneity. The results favored the experimental group, i.e., greater muscle recovery values were found in the group that received IPC as the intervention method.

As shown in Figure 4, IPC and its relationship with the attenuation of CK levels were somewhat different. The intervention methods evaluated were neuromuscular and cardiovascular exercises, but no differences ($p < 0.05$) were found in the analyzed outcomes (CK after 24, 48, 72, 96, and 120 hours).

Through the analysis of the outcome related to DOMS, a difference ($p < 0.05$) was found for this variable. Hoffman et al. (16) and Heapy et al. (19) subjected their sample to an ultramarathon, while Northey et al. (20) analyzed DOMS in men who underwent 10 sets of 10 squats at 70% 1RM. No heterogeneity was found ($I^2 = 0\%$) when comparing the groups evaluated, although some heterogeneity arises due to the different sample types.

Quality of evidence and limitations

The lack of control over some parameters during the intervention, as well as dietary and functional control after the intervention, may have influenced subsequent tests and assessments and, consequently, the outcomes and results of the physical components assessed. In addition to these factors, the different protocols and distinct modalities in which the IPC can be employed can generate varied outcomes. Although one double-blind study was analyzed in this study (25), most studies presented good methodological quality, with moderate/high certainty of evidence, with some being downgraded only after analyzing the overlapping confidence intervals and testing for heterogeneity (8, 26). Regarding the subjective criterion, when analyzed on the subjective PSR and VAS scales, the IPC proved to be quite positive. Although general well-being is recognized as important for athletic performance (35), these measures are more susceptible to bias, relying on the participant's belief in the recovery technique (36), familiarity with the assessment scales (37), among others (6).

It's uncommon to find IPC studies that analyze multiple sports using such a heterogeneous sample. Due to the numerous protocol possibilities and characteristics, IPC offers a wide range of possibilities to a broad audience, making this study one of the first to investigate the IPC's response to different outcomes, even meta-analyzing them.

CONCLUSION

Based on the available evidence, the studies included in the review showed improvements in the subjective perception of recovery and a decrease in CK concentration, although no beneficial effects were found with the use of intermittent pneumatic compression as a recovery strategy regarding sports performance. In turn, the meta-analysis indicated improvements in flexibility, subjective perception of recovery and attenuation of delayed onset muscle soreness after intervention using IPC. Recreational, amateur and professional athletes, practicing a variety of sports, were analyzed, thus covering a broad audience that can benefit from the use of IPC. In this sense, IPC has proven to be a valid tool as a form of recovery for individuals after fatigue induced by physical stress. Its provision may become a viable alternative and a superior option to passive recovery when another type of recovery is not indicated or cannot be provided. Future research is recommended to investigate IPC and its benefits on the performance of a variety of sports.

Conflicts of interest and sources of funding

AI tools were used only for language editing. Authors are responsible for content.

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Authors' contribution

Conceptualization, Castro Douglas (CD), Rodrigo Vale (RV), Gama Diego (GD) and Daniell Mello (DM); methodology, CD, RV, DG, DM; software, CD; validation, CD, RV, DG, DM; formal analysis, CD, RV, DG, DM; investigation, CD; resources, CD; data curation, CD, DM; writing—original draft preparation, CD, RV, DG, DM; writing—review and editing, CD, RV, DG, DM; visualization, CD; supervision, MD; project administration, MD; funding acquisition, MD. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable

Patient consent for publication

Not applicable.

APPENDIX

Group of descriptors and synonyms used for searches in databases

Database	Search
Pubmed	("compression boot"(All Fields) AND ("muscle pain"(All Fields)) OR ("compression boot"(All Fields) AND ("myalgia"(All Fields)) OR ("compression boot"(All Fields) AND ("muscle soreness"(All Fields)) OR ("compression boot"(All Fields) AND ("muscle tenderness"(All Fields)) OR ("intermittent pneumatic compression devices"(All Fields) AND ("muscle pain"(All Fields)) OR ("intermittent pneumatic compression devices"(All Fields) AND ("myalgia"(All Fields)) OR ("intermittent pneumatic compression devices"(All Fields) AND ("muscle soreness"(All Fields)) OR ("intermittent pneumatic compression devices"(All Fields) AND ("muscle tenderness"(All Fields)) OR ("external pneumatic compression"(All Fields) AND ("muscle pain"(All Fields)) OR ("external pneumatic compression"(All Fields) AND ("myalgia"(All Fields)) OR ("external pneumatic compression"(All Fields) AND ("muscle soreness"(All Fields)) OR ("external pneumatic compression"(All Fields) AND ("muscle tenderness"(All Fields))
Scopus	(TITLE- ABS- KEY (compression boot AND muscle pain) OR TITLE- ABS- KEY (compression boot AND myalgia) OR TITLE- ABS- KEY (compression boot AND muscle soreness) OR TITLE- ABS- KEY (compression boot AND muscle sorenesses) OR TITLE- ABS- KEY (compression boot AND muscle tenderness) OR TITLE- ABS- KEY (intermittent pneumatic compression devices AND muscle pain) OR TITLE- ABS- KEY (intermittent pneumatic compression devices AND myalgia) OR TITLE- ABS- KEY (intermittent pneumatic compression devices AND muscle soreness) OR TITLE- ABS- KEY (intermittent pneumatic compression devices AND muscle sorenesses) OR TITLE- ABS- KEY (intermittent pneumatic compression devices AND muscle tenderness)
Web of Science	compression boot (all fields) OR intermittent pneumatic compression devices (all fields) OR external pneumatic compression (all fields) AND muscle pain (all fields) OR myalgia (all fields) OR muscle soreness (all fields) OR muscle sorenesses (all fields) OR muscle tenderness (all fields)
Science Direct	Title, abstract, keywords: "compression boot" OR "intermittent pneumatic compression devices" OR "external pneumatic compression" AND "muscle pain" AND "myalgia" AND "muscle soreness" AND "muscle sorenesses" AND "muscle tenderness"

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REVIEW

Health Literacy and Its Social Impact in Eastern Europe: Challenges and Policy Implications

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Abstract: Health literacy, representing the ability to understand and apply health information, is a key determinant of public health. In Eastern Europe, decades of underinvestment in health education, socioeconomic disparities, and institutional mistrust have contributed to persistently low levels of health literacy. Objective: This review synthesizes evidence on the social consequences of inadequate health literacy in Eastern Europe, focusing on behavioral, structural, and policy-related outcomes. Methods: A narrative literature review was conducted using PubMed, Scopus, Web of Science, Google Scholar and institutional reports. Studies were included if they examined health literacy, public medical education, and social outcomes in Eastern European populations. Results: The synthesis of evidence identified four major thematic domains through which inadequate health literacy is associated with negative outcomes in Eastern European populations. Low health literacy is consistently associated with preventable disease, poor health behaviors, limited uptake of preventive services, and reduced adherence to medical advice. Vulnerable groups bear a disproportionate burden. Inadequate health knowledge is also associated with increased and inappropriate healthcare utilization, delayed care-seeking, and higher rates of avoidable mortality. Furthermore, low health literacy is plausibly linked to the proliferation of health misinformation, erosion of trust in healthcare systems, and has contributed to excess mortality during public health crises such as the COVID-19 pandemic. Discussion: The observed patterns are shaped by historical and structural factors, including the post-communist legacy of under-resourced health systems and the persistent under-prioritization of preventive care. Eastern Europe is a heterogeneous region, and the availability of health literacy data varies considerably across countries, limiting the generalizability of findings. At the clinical level, healthcare providers play a key role in identifying low health literacy, adapting communication strategies, and addressing vaccine hesitancy and misinformation. Addressing these challenges requires coordinated strategies, investment in education, culturally tailored communication, and cross-sectoral collaboration. Improving public health literacy can enhance health outcomes, reduce system costs, and strengthen societal resilience. Conclusions: This review underscores the challenges associated with health literacy in Eastern Europe, illustrating how insufficient health literacy contributes to detrimental behaviors, undermines trust in healthcare systems, exacerbates misinformation, and ultimately imposes a significant societal and systemic burden on public health.

Keywords: health literacy, public medical education, Eastern Europe, social impact, health inequalities, health behavior

INTRODUCTION

Health literacy, the ability of individuals to access, comprehend, and apply basic health information, is a fundamental determinant of public health outcomes. Individuals with adequate medical knowledge are more likely to engage in preventive behaviors, adhere to treatment regimens, and navigate healthcare systems effectively. However, in many Eastern European countries, the general population continues to face substantial deficits in health-related education, with far-reaching social implications [1].

For the purposes of this review, health literacy is adopted as the central organizing construct, defined in accordance with the WHO (World Health Organization) and HLS-EU (European Health Literacy Survey) framework as the ability of individuals to understand health information in order to make informed decisions regarding their health. This encompasses what may be known as public medical education and

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health knowledge itself. Public medical education is the formal and informal processes through which health knowledge is disseminated to the general population. Health knowledge refers to the factual understanding of disease, risk factors, and healthcare practices. While these terms are related and often used interchangeably in the broader literature, this review treats health literacy as the overarching concept, recognizing that public medical education and health knowledge are key determinants of an individual's overall health literacy level.

According to the HLS-EU, more than 50% of adults in Bulgaria demonstrate inadequate or problematic levels of health literacy, among the worst scores in Europe (EU). Eastern countries also report some of the lowest rates of health-promoting behaviors, such as vaccination uptake, cancer screening participation, and physical activity. Even though vaccination rates remain low, the influenza mortality rates in Romania, Hungary, and Poland are under 0.5/100000. The influenza vaccination rates are over 70% in the Netherlands and 75% in Ireland and Denmark [2-4].

Poor health literacy is associated with a higher prevalence of preventable conditions, such as cardiovascular disease and type 2 diabetes, which are significantly more common and poorly controlled in Eastern Europe. In Romania, for example, approximately 45% of adults are hypertensive, yet over 40% are unaware of their diagnosis [5]. Similarly, avoidable mortality, defined as deaths that could be prevented through effective public health and medical interventions, remains disproportionately high in Eastern Europe. In 2020, Eurostat reported that Romania and Hungary ranked among the top three EU countries in terms of avoidable mortality rates [6,7].

Beyond individual health outcomes, poor medical education in the general population may contribute to increased pressure on healthcare services due to unnecessary emergency room visits, late presentation of chronic conditions, and reduced adherence to public health guidelines. During the COVID-19 pandemic, misinformation and low trust in medical authorities were associated with alarmingly low vaccination coverage in some Eastern European countries, with less than 20-40% of the adult population fully vaccinated by mid-2022 in Romania and Bulgaria, contributing to higher excess mortality compared to Western Europe [8,9].

This literature review aims to explore the social impact of inadequate medical education among the general population in Eastern Europe. Through a comprehensive synthesis of data and published research, we seek to highlight the structural, cultural, and policy-related factors that contribute to low health literacy in the region and outline potential pathways for intervention and reform.

MATERIALS AND METHODS

This narrative literature review was conducted to explore and synthesize current knowledge on the social impact of inadequate public medical education in Eastern European countries. Given the interdisciplinary nature of the topic, including public health, education, sociology, and policy studies, a broad and flexible methodological approach was adopted.

Search Strategy

A comprehensive search of the scientific literature was performed in September-October 2025 in the following electronic databases: PubMed, Scopus, Web of Science, and Google Scholar. Boolean search strings were adapted to the syntax and indexing conventions of each database, using the following keywords in various combinations: ("health literacy" OR "medical education" OR "public health education") AND ("social impact" OR "health outcomes" OR "health inequalities") AND ("Eastern Europe" OR "Romania" OR "Bulgaria" OR "Ukraine" OR "Moldova" OR "Serbia" OR "Poland").

In addition, grey literature was searched using institutional websites (e.g., WHO Europe, the Organization for Economic Cooperation and Development (OECD), Eurostat, World Bank), and relevant government or NGO reports were included when peer-reviewed data were unavailable or limited.

Inclusion and Exclusion Criteria

Studies and reports were included in this review if they concentrated on health literacy, health knowledge, or health education within adult or general populations, and specifically addressed at least one Eastern European country. Articles examining social, behavioral, or health system outcomes related to low health literacy or inadequate medical education were also considered. Only articles written in English were included. No formal date restriction was applied. The majority of included sources were published within the last ten years; older studies were retained when considered particularly relevant to the topic.

Excluded from this review were articles focusing solely on professional medical training, studies lacking relevance to the general population or public health outcomes and opinion pieces or editorials without supporting data.

Screening and Selection Process

The screening and selection process was conducted independently by two authors. Following the database searches, titles and abstracts of all retrieved records were initially screened for relevance against the inclusion and exclusion criteria. Records that

could not be excluded based on title and abstract alone were retrieved in full text and assessed for eligibility. Final inclusion decisions were made by consensus between the two reviewers. Discrepancies were resolved through discussion.

Data Extraction and Synthesis

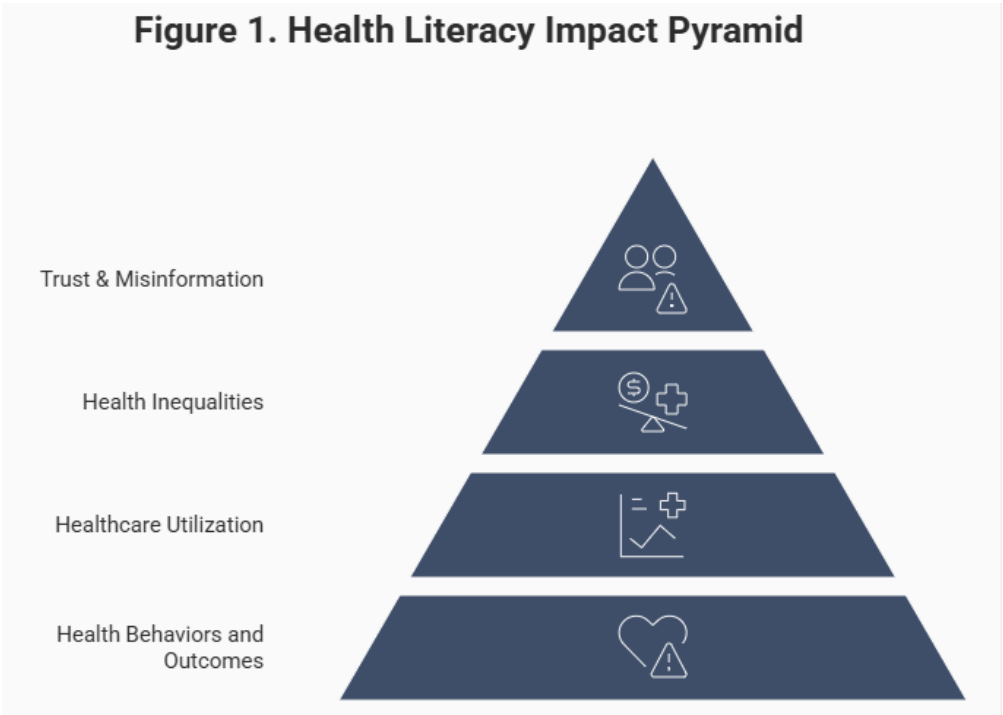
Relevant information was extracted from each included source, including study design, country, sample population, key findings related to health literacy or public education and reported social impacts. Given the heterogeneity of study types and outcomes, a meta-analysis was not performed. Instead, findings were synthesized narratively to provide a contextual and comprehensive overview of the issue across Eastern Europe. As this is a narrative review, no formal quality appraisal tool was applied; however, methodological rigor and relevance to the research question were considered during the selection process.

Following the screening and selection process, the included sources encompass peer-reviewed studies, public health reports, and grey literature from Eastern European countries, reflecting a range of study designs, national contexts, and outcome measures relevant to the research question.

RESULTS

The synthesis of included sources identified four major thematic domains through which inadequate health literacy is associated with negative outcomes in Eastern European populations (Figure 1). The following subsections present the key findings identified across these domains.

Figure 1: Health Literacy Impact Pyramid



1. Health Behaviors and Health Outcomes

Low levels of health literacy in Eastern Europe are consistently associated with adverse health behaviors and outcomes. Multiple studies indicate that individuals with inadequate understanding of basic health principles are less likely to engage in preventive behaviors such as regular physical activity, healthy diet, smoking cessation, or routine medical screening [10–12]. In terms of outcomes, countries with lower health literacy scores tend to report higher rates of obesity [13,14], undiagnosed or poorly controlled diabetes [15,16], or avoidable mortality, particularly from cardiovascular diseases and certain cancers [17–19]. These findings are supported by a systematic review of observational studies conducted between 1980 and 2003 that concluded the significant correlation between low literacy and poorer health behaviors and outcomes [20].

In relation to diet, health literacy has been shown to have a substantial impact. The study by Stefler et al. analyzed dietary intake within the Health, Alcohol and Psychosocial Factors in Eastern Europe (HAPIEE) cohort study, concluding that decreased literacy

in nutrition and awareness contributes to widespread unhealthy eating behaviors, which are strongly associated with higher all-cause and cardiovascular mortality [21]. Furthermore, the issue of diet-related health literacy is also expanding within families, where children's habitual systems are significantly related to parental health literacy [22].

Another health outcome associated with health literacy is regular physical activity. In European countries, health literacy is linked to reduced physical activity, as demonstrated in the study by Mrazek et al. By comparing a country from Western Europe (Germany) with one from the East (Russia), they concluded that Western Europeans are more health- and body-conscious, internally motivated, and actively engage in sports and physical activity. In contrast, Eastern Europeans are less health-conscious, more externally motivated and engage less in physical activity [23]. These findings are further supported by a study conducted on the Bulgarian population, in which only 38% of adults reported engaging in regular physical activity, well below the EU average [24].

2. Healthcare Utilization

Low health literacy is associated with delayed presentation to medical services, reliance on emergency care, and inappropriate use of health resources. The study by Rasu et al., involving 22,599 participants, concluded that decreased health literacy is associated with increased healthcare utilization and expenditure, with a significant portion of the costs attributed to prescriptions [25]. Another study focused on this topic, establishing a correlation between health literacy and a higher likelihood of utilizing emergency departments for non-urgent conditions [26]. In terms of financial resources, health literacy is correlated with inappropriate healthcare utilization and inadequate patient follow-up, which may be associated with deteriorating health outcomes and ultimately, increased healthcare costs [27].

Furthermore, the uptake of preventive services remains critically low in many Eastern European countries. Regarding cervical cancer screening, research indicates reduced engagement in Eastern European countries, where health literacy is lower. A study conducted in Serbia reported that screening coverage varies between 35% and 68% across different regions [28]. Similarly, in Romania, a national colorectal cancer screening program remains absent, with only EU-funded regional pilot programs initiated since 2019 covering a limited proportion of the population, despite high incidence rates [29,30].

The research conducted by Andreeva et al. on Eastern European immigrant women underscores that a primary challenge in preventive medicine and cancer screening is health literacy, specifically the inadequate knowledge regarding early disease detection, regardless of the host country [31].

3. Health Inequities and Vulnerable Populations

The burden of low medical education is unevenly distributed, disproportionately affecting rural populations, ethnic minorities, older adults, and those with lower socioeconomic status [32]. In Moldova and Ukraine, rural residents were found to have significantly lower awareness of chronic disease risk factors and lower participation in vaccination or screening programs [33,34]. On the other hand, Roma populations in several countries remain especially vulnerable: studies from Slovakia and Romania report significantly higher rates of communicable diseases and lower vaccination coverage among Roma children—often due to a combination of poor education, marginalization, and distrust in institutions [35–38].

Vulnerable populations—particularly rural residents, ethnic minorities, and low-income groups—bear a disproportionate burden of inadequate medical education. While some nations have implemented targeted health promotion initiatives, these efforts often lack sustainability, funding, and evaluation. In countries such as Romania and Bulgaria, public health campaigns remain fragmented and reactive rather than strategic and evidence-based [35,39].

4. Trust, Misinformation and Public Health Crises

Perhaps one of the most socially disruptive consequences of low public health literacy is the proliferation of health misinformation and the erosion of trust in medical authorities. During the COVID-19 pandemic, misinformation about vaccines, treatments, and the virus itself spread rapidly, with Eastern European countries being among the hardest hit.

By mid-2022, vaccination rates remained below 50% in Bulgaria and Romania, and excess mortality rates were among the highest in the EU [8]. In a study from 2024 that analyzed 2020–2022 Standard Eurobarometer datasets, only 52% to 66% of citizens in Eastern European countries expressed trust in their national health institutions, compared to 78% to 97% in Central and Western Europe. This placed countries such as Romania, Hungary, Greece, and Bulgaria among the lowest in the EU in terms of public trust in healthcare systems [38].

Low trust in health authorities is associated with refusal of vaccines, preference for alternative or unproven treatments, and resistance to public health regulations. A key theme emerging from the literature is the interplay between low health literacy and distrust in healthcare systems. This dynamic creates a vicious cycle: populations with a poor understanding of health information are more vulnerable to misinformation, less likely to follow medical advice and more prone to avoid preventive care. In turn, low engagement with the healthcare system is plausibly linked to poorer health outcomes, further eroding trust and increasing

skepticism. This was particularly evident during the COVID-19 pandemic, which served as a real-time stress test for public health communication and education infrastructures [4,8].

DISCUSSION

The findings synthesized in this review point to a consistent and multifaceted association between inadequate health literacy and adverse social, behavioral, and systemic outcomes across Eastern Europe. The following sections contextualize these findings within the broader structural and historical landscape of the region, identify key research gaps, outline practical implications for clinical practice, and acknowledge the limitations of the present review.

1. Historical and Structural Determinants of Health Literacy

The findings of this review clearly demonstrate that inadequate health literacy in Eastern Europe is associated with a wide range of negative social and health outcomes. From preventable morbidity and mortality to systemic inefficiencies and widening health inequalities, the impact of poor health literacy is both multifaceted and profound. Importantly, one of the causes of this outcome is the legacy of the post-communist transition that still casts a long shadow. Many Eastern European states inherited under-resourced health systems, limited public health expertise, and low institutional transparency. As a result, public health education has historically been under-prioritized in policy agendas, with greater focus placed on curative rather than preventive care. Despite EU membership and access to structural funds, progress remains uneven and hampered by bureaucratic and political instability [39,40].

It should also be acknowledged that Eastern Europe is not a homogeneous region. Countries vary considerably in terms of economic development, healthcare system structure, cultural context, EU membership status, and the availability of health literacy data. Well-documented cases such as Romania, Bulgaria, and Poland contrast with countries such as Moldova, Ukraine, or Albania, for which peer-reviewed evidence on health literacy remains scarce.

Table 1: Practical implications of low health literacy for clinical practice in Eastern European settings

Domain	Clinical Implication	Recommended Action	Relevance for Eastern Europe
Patient Assessment	Low health literacy is frequently undetected in routine clinical encounters	Implement routine health literacy screening using validated tools (e.g., SILS, BHLS) in primary care settings	Brief patient-provider interactions and acute-focused consultations make systematic screening particularly important
Clinical Communication	Patients with low health literacy may not understand diagnoses, treatment plans, or medication instructions	Adopt plain language communication; use the teach-back method; provide written materials at an accessible reading level	Cultural norms of deference toward medical authority may prevent patients from asking clarifying questions
Vaccine Hesitancy and Misinformation	Low health literacy increases vulnerability to misinformation and vaccine refusal	Engage patients in non-judgmental, motivational conversations about vaccination, preventive care, and cancer screening	Documented erosion of institutional trust in the region makes clinician-patient dialogue a critical point of intervention
Culturally Adapted Patient Education	Standard health education materials may be inappropriate for ethnic minority or low-literacy populations	Develop locally adapted materials; involve community health mediators, particularly for Roma and other marginalized groups	Significant ethnic minority populations in Romania, Slovakia, Bulgaria, and other countries require targeted, culturally sensitive approaches
Healthcare Provider Training	Health literacy is only partially integrated into medical and nursing curricula in Eastern Europe	Incorporate health literacy competencies into undergraduate medical education and continuing professional development programs	Systematic training is needed to prepare clinicians for the communicative demands of health-literate care across the region

SILS= Single Item Literacy Screener, BHLS= Brief Health Literacy Screen

2. Research Gaps and Methodological Challenges

The literature also points to a lack of coordinated, region-specific research. While several cross-sectional studies highlight the magnitude of the problem, there is a notable scarcity of longitudinal or intervention-based research evaluating the effectiveness of public education programs. Moreover, national health literacy assessments are rarely standardized, making comparisons and benchmarking difficult [32,41].

3. Practical implications for clinical practice

The findings of this review carry important practical implications for healthcare professionals working in Eastern European settings. Clinicians occupy a frontline position in identifying and responding to low health literacy, and their role extends well beyond diagnosis and treatment. Table 1 summarizes the key domains of clinical relevance, together with recommended actions and their specific applicability to the Eastern European context.

4. Future directions

Despite the major challenges that health literacy implies in Eastern European countries, there are emerging opportunities for improvement. International collaborations (e.g., WHO Europe, EU4Health), digital health tools, and school-based health education programs have shown promise in increasing health awareness and shaping healthy behaviors. Slovenia has developed a nationally scaled community-based health promotion model, establishing Health Promotion Centers across the country to increase health literacy at the primary care and community level. Poland has recently introduced structured health education as a dedicated school subject, signaling a policy shift towards embedding health literacy in formal education. While these represent promising examples, their long-term effectiveness and potential for regional adaptation remain to be fully evaluated. [42,43].

Overall, there is an urgent need for strategic, long-term investment in public medical education as a cornerstone of health system resilience and social cohesion. Addressing this issue requires a multi-sectoral approach involving healthcare providers, educators, policy-makers, media, and civil society. These include: investing in comprehensive, evidence-based health literacy programs, starting from school and continuing throughout adulthood; improving communication strategies by using accessible, culturally appropriate messaging across traditional and digital platforms; training healthcare providers to recognize and respond to low health literacy in clinical settings, and supporting research and evaluation to monitor the effectiveness of public education initiatives [44–46].

Crucially, these efforts must be tailored to the specific cultural, economic, and historical contexts of Eastern European societies. A one-size-fits-all approach is unlikely to succeed; instead, collaborative, interdisciplinary strategies grounded in local realities are essential.

Improving public health education is not merely a health sector responsibility—it is a cross-cutting issue that affects education, labor, social welfare, and democratic participation. Addressing it meaningfully has the potential to transform not only healthcare outcomes, but the overall well-being and resilience of societies across Eastern Europe.

Digital transformation in healthcare presents a unique opportunity to strengthen health literacy across Europe. Through mobile health applications, telemedicine platforms, and patient portals, individuals can access personalized health information, monitor key parameters, receive alerts, and communicate directly with healthcare providers. Research on digital health literacy—defined as the ability to seek, find, understand, and apply health information in digital environments—shows that it is now a critical determinant of whether technology translates into better health outcomes [47].

Expanding these tools in Eastern European populations could empower citizens to take a more active role in disease prevention and self-management, helping to close long-standing information and access gaps.

At the policy level, the European Union has positioned digitalization as a key pillar of public health reform. The EU4Health Program (2021–2027) aims to enhance health system resilience, improve digital infrastructure, and promote e-health and health literacy initiatives across Member States [48]. Complementing this, the European Health Data Space (EHDS) establishes a unified framework for citizens' access to their health data and secure data sharing between Member States [49]. Together, these initiatives lay the groundwork for a digital ecosystem where informed citizens, interoperable data systems, and evidence-based policymaking can mutually reinforce one another, reducing inequities in health information and outcomes.

Nevertheless, the success of digital transformation depends on ensuring equitable access and adequate digital competencies among all population groups. Without deliberate efforts to improve digital and health literacy, technological advances risk widening existing inequalities. Studies emphasize the importance of user-friendly design, plain language communication, and inclusive training for patients and healthcare workers to prevent digital exclusion [50]. Therefore, digital transformation must be accompanied by education, outreach, and accessibility measures tailored to local contexts.

5. Limitations

Several limitations of this review should be acknowledged. First, the search was restricted to English-language publications, which may have led to the exclusion of relevant studies published in Eastern European languages. This can potentially introduce a language bias and underrepresent locally conducted research. Second, the evidence base combines peer-reviewed studies with grey literature, including institutional reports and policy documents from organizations such as WHO Europe, Eurostat, and the OECD. While this approach was adopted deliberately to capture the full scope of available evidence in a field where peer-reviewed data are sometimes limited, grey literature sources are subject to less rigorous methodological scrutiny than peer-reviewed publications. Third, no formal quality appraisal tool was applied to the included sources, as is consistent with the narrative review methodology. However, this means that studies of varying methodological quality may have been weighted similarly in the synthesis. Fourth, the heterogeneity of study designs, populations, and outcome measures across the included sources precluded quantitative synthesis and limits the comparability of findings across countries and contexts. These limitations should be considered when interpreting the conclusions of this review, and future research would benefit from more standardized, longitudinal approaches to assessing health literacy and the effectiveness of public medical education interventions across Eastern Europe.

CONCLUSION

This review highlights the substantial social burden posed by inadequate health literacy among the general population in Eastern European countries. Low levels of health literacy are consistently associated with poor health behaviors, underutilization of preventive services, delayed care-seeking, and a higher prevalence of preventable diseases. These challenges are further amplified by systemic distrust in health institutions and the rapid spread of health misinformation, especially during public health crises.

In many countries across the region, the consequences of poor health education are not merely individual- they are societal. The cumulative effect of millions of people misunderstanding, ignoring, or distrusting medical advice may place unsustainable pressure on healthcare systems, widen existing health inequalities, and undermine national efforts to improve public health outcomes.

Conflicts of interest and sources of funding

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Authors' contributions

Conceptualization, D.N.P. and A.C.P.; methodology, O.A.; validation, D.N.P., A.C.P., and O.A.; formal analysis, A.D.; investigation, A.C.P and A.D.; data curation, A.P.; writing—original draft preparation, A.C.P. and A.D.; writing—review and editing, O.A. and A.P.; visualization, D.N.P.; supervision, O.A.; project administration, D.N.P.; All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable

Patient consent for publication

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REVIEW

Health promotion through lifestyle medicine. Conceptual convergences between general medicine and dentistry in public health and integrated medical practice

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Abstract: Background: Health promotion and prevention are becoming increasingly important in the context of the growing prevalence of chronic diseases, population aging, and the shift towards patient-centered care. Objective: This review examines the relationship between health promotion, lifestyle medicine, and medical prevention, with particular emphasis on the convergence between general medicine and dentistry and on the positioning of the conceptual framework of Individual Health–General Health–Primordial Health–Total Health. Methods: A narrative review with a conceptual component was conducted. Relevant literature was identified through thematic searches in PubMed and Google Scholar. Sources were selected according to their relevance to the objectives of the review. The quality and applicability of the evidence were considered in relation to the type and authority of the source, its relevance, and its consistency with the literature and reference frameworks used. Results: The literature identifies several risk factors shared by oral and systemic health, including diet, smoking, obesity, chronic inflammation, and stress. These interrelationships support the integration of prevention, health education, and interventions targeting modifiable behaviors into both medical and dental practice. Conclusions: Closer collaboration between general medicine, dentistry, and public health may facilitate a more coherent framework for preventive care. The proposed conceptual model may provide a starting point for future research.

Keywords: health promotion; preventive medicine; public health; lifestyle medicine; oral health; dentistry; integrated care; screening.

INTRODUCTION

Constitution, "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition. The health of all peoples is fundamental to the attainment of peace and security and is dependent upon the fullest co-operation of individuals and States" [1].

In 2025, Daniela Mănuc proposed a conceptual framework that approaches health through four interrelated dimensions. Rather than treating health solely as a clinical or biological state, the framework brings together individual, population-level, and theoretical dimensions of health. According to the author, it comprises four main components:

"1. Individual Health (IH) refers to everything that is individual, variable, contingent, and accidental, and falls within the scope of sciences concerned with the personal dimension.

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2. General Health (GH) / Unified Health addresses the community, the environment, and related aspects from a public health perspective, with an emphasis on the social dimensions of health.

3. Primordial Health (PH) has a universal character in a metaphysical sense and refers to the capacity for regeneration, both at the individual and species level, as well as to the realization of the Universal Human Being. The meaning of Primordial Health is reflected in the term itself, referring to what lies ‘beyond the physical’ (with ‘physics’ understood broadly as encompassing the natural sciences as a whole, rather than only the particular discipline known today as physics).

4. Total Health (TH) represents the contextual manifestation of Primordial Health (PH). It refers to the highest potential level of ‘Health’ that Individual Health and General Health may attain, depending on both the general genetic determinants of the species, which are relatively difficult to modify, and external determinants, which are more amenable to change and characteristic of the current stage of human development. Total Health therefore refers to the attainment of the highest possible level of individual or general ‘Health’, taking into account the internal and external determinants operating at a given time” [2].

A clear understanding of this health model and its constituent dimensions (Table 1) may help support the development of more integrated standards of care and reduce fragmented approaches to clinical practice.

According to the Ottawa Charter, “Health promotion is the process of enabling people to increase control over, and to improve, their health. To reach a state of complete physical, mental and social well-being, an individual or group must be able to identify and to realize aspirations, to satisfy needs, and to change or cope with the environment. Health is, therefore, seen as a resource for everyday life, not the objective of living. Health is a positive concept emphasizing social and personal resources, as well as physical capacities. Therefore, health promotion is not just the responsibility of the health sector, but goes beyond healthy lifestyles to well-being” [3].

Table 1: Components of the proposed conceptual framework: Individual Health–General Health–Primordial Health–Total Health

Concept	Brief definition	Level of application	Main focus	Clinical / public health implications	Position within the proposed framework
Individual Health (IH)	The dimension of health related to the characteristics and variability specific to each individual.	Individual	Individual characteristics and personal determinants of health	Supports individualized health assessment and the adaptation of preventive and clinical interventions to the person's profile.	Represents the individual component of the conceptual framework.
General Health (GH) / Unified Health	The dimension of health related to the community, the environment, and social determinants, considered in relation to public health.	Population / community / environment	Social, collective, and environmental determinants of health	Supports prevention, health promotion, and risk-reduction interventions at the population level.	Represents the population and public health component of the conceptual framework.
Primordial Health (PH)	A theoretical component of the model, defined in the original source as a potential and universal state of health that precedes its individual or collective expression.	Conceptual level	Theoretical potential of health	Provides a conceptual basis for organizing the relationship between health potential and its expression.	Represents the theoretical component of the proposed conceptual framework and is distinct from established biomedical models.
Total Health (TH)	An integrative concept describing the highest potential level of health that may be attained at the individual and population levels, depending on existing internal and external determinants.	Individual and population	Integration of individual, social, and environmental determinants of health	May conceptually guide interventions towards optimizing modifiable factors and integrating prevention, clinical care, and public health.	Represents the integrative outcome of the proposed conceptual framework.

The Ottawa Charter for Health Promotion presents health as a resource for everyday life rather than as an end in itself. From this perspective, health is understood as a positive concept that encompasses not only the biological dimension, but also personal and social resources, together with individual physical capacities [3].

Consistent with the recognition of health as a fundamental human right, the Ottawa Charter also identifies several prerequisites for achieving and maintaining health. These include peace, adequate economic resources, access to food and housing, education, social equity, a stable ecosystem, and the sustainable use of natural resources. Improvements in health depend on a sound foundation built on these basic conditions [3].

These prerequisites highlight the close interrelationships between social and economic determinants, the physical and social environment, individual health-related behaviors, personal skills, and overall health status [4].

Taken together, these relationships support a holistic understanding of health, which is central to contemporary approaches to health promotion. An integrative perspective therefore requires the systems and structures that shape health determinants to consider how their activities may affect health and well-being at both individual and population levels [4].

Health promotion can be understood as a complex social and political process that extends beyond the development of individual skills. It includes a range of strategies aimed at addressing structural determinants of health, including social, environmental, and economic factors, with the goal of improving both individual and population well-being. In practical terms, health promotion seeks to strengthen the ability of individuals and communities to gain greater control over the factors that influence their health [4].

Within this perspective, closer integration between general medicine and dentistry may help reduce the traditional separation between medical specialties and support a more comprehensive view of the patient. A holistic and integrative approach considers the individual as a whole rather than focusing exclusively on a specific organ system or clinical condition (Table 2). Drawing on the conceptual framework proposed by D. Mănuc, this review explores how integrated medical practice may connect Individual Health with the broader orientation towards Total Health.

The transition from reactive care to preventive and integrated care involves an approach that takes into account the biological, functional, and psychosocial dimensions of health, together with modifiable factors that may influence quality of life.

In this context, collaboration between general medicine and dentistry may support the integration of prevention and patient-centered care.

Table 2: Conceptual distinctions between holistic, integrative, integrated, and biopsychosocial approaches

Concept	Brief definition	Level of application	Main focus	Clinical / public health implications
Holistic	Views the person as a whole, including mind, body, and emotions, rather than focusing only on the disease or affected organ.	Individual / clinical practice	The full range of dimensions that shape a person's health	Encourages multidimensional assessment of the patient and consideration of the individual's personal context.
Integrative	Brings together different perspectives or interventions within a coordinated approach to health, for example conventional medicine alongside lifestyle medicine.	Individual / clinical practice	Combining different approaches within a coordinated model	May support complex preventive and therapeutic interventions tailored to the patient's needs.
Integrated	Refers to a model of care in which professionals and services from different fields collaborate in a structured manner to provide coherent care.	Individual / interdisciplinary clinical practice	Collaboration across specialties for prevention, diagnosis, and treatment	Supports continuity and coordination of care, including collaboration between general medicine and dentistry.
Biopsychosocial	Explains health and disease through the interaction of biological, psychological, and social factors.	Individual / clinical practice	Biological, psychological, and social determinants	Supports the assessment of multiple factors that influence health and the use of multidisciplinary interventions.

METHODS

This study was conducted as a narrative review aimed at synthesizing the literature on health promotion, lifestyle medicine, preventive medicine, and the relationship between oral and systemic health, with particular emphasis on the convergence between general medicine and dentistry. Relevant literature was identified through a narrative search of PubMed and Google Scholar guided by the main themes of the review. The conceptual component also examined the positioning of the proposed Individual Health–General Health–Primordial Health–Total Health framework in relation to contemporary approaches in medicine and public health.

Several types of sources were considered, depending on the nature of the information being examined. These included articles published in peer-reviewed scientific journals, including review and perspective articles; official World Health Organization documents and reports; public health policy and strategy documents; scientific opinions issued by European bodies;

recommendations from professional organizations; consensus reports; academic books and monographs; and relevant institutional publications.

Sources were selected according to their relevance to the objectives of the review, their suitability for the topic under consideration, and their contribution to the concepts and relationships discussed. The quality and applicability of the evidence were assessed by considering the type and authority of the source, its relevance, and its consistency with the literature and reference frameworks used. The selected evidence was organized thematically and synthesized narratively, bringing together clinical, preventive, and public health perspectives. The synthesis was used both to examine the convergence between oral and systemic health and to discuss the position of the proposed conceptual framework within contemporary approaches to health promotion and integrated medicine.

RESULTS – NARRATIVE SYNTHESIS OF THE LITERATURE

HEALTH PROMOTION – CONCEPTUAL CONVERGENCES BETWEEN GENERAL MEDICINE AND DENTISTRY IN THE CONTEXT OF INTEGRATED PRACTICE

Health promotion is a core component of contemporary medicine and is closely linked to a holistic view of the individual and to greater integration across medical disciplines. Within this framework, the relationship between general medicine and dentistry has become increasingly relevant, reflecting the close links between oral health and overall health. Integrated medical practice relies on interdisciplinary collaboration, with an emphasis on prevention, early detection, and coordinated clinical management. A growing body of evidence has shown associations between oral conditions, particularly periodontal disease, and systemic disorders such as cardiovascular disease and diabetes mellitus. General medicine and dentistry therefore share important goals in promoting healthier behaviors through lifestyle medicine and in addressing modifiable risk factors.

Health education, early screening, and patient counseling are central to this integrated approach. Patient-centered care also requires recognition of the oral cavity as part of the whole organism rather than as an isolated area of clinical practice. Closer collaboration between general practitioners and dental professionals may support more coordinated and sustainable preventive strategies, with potential benefits for clinical outcomes and quality of life. From this perspective, health promotion is inherently interdisciplinary and depends on the complementary roles of different areas of medical practice.

The conceptual overlap between health promotion and prevention is particularly evident in interventions aimed at reducing risk factors and encouraging healthier behaviors. Many educational initiatives and public health strategies serve both purposes at the same time. Oral hygiene education, nutritional counseling, and smoking cessation programs are relevant examples, as they can contribute both to better overall health and to a lower burden of specific oral diseases.

From this perspective, prevention may be regarded as an essential dimension of health promotion, embedded within a broader set of actions designed to maintain and improve quality of life through health education and the promotion of health-enhancing factors [5].

The complementarity between these two concepts reflects the broader shift in contemporary medicine towards a more proactive approach, concerned not only with treating disease but also with protecting and strengthening health at both individual and community levels.

Following the adoption of the World Health Assembly Resolution on Oral Health in 2021 and the subsequent development of the Global Strategy and Action Plan for 2023–2030, oral health has gained a more prominent place on the global public health agenda [6]. These strategic frameworks move beyond a narrowly biomedical model focused mainly on disease and curative care, and place greater emphasis on the broader determinants of health. Psychological, environmental, and social factors are therefore considered alongside clinical aspects of oral health. In this regard, the second WHO strategic objective focuses on improving access to high-quality oral health care while also addressing the social and commercial determinants that contribute to the risk of oral diseases [6].

WHO defines oral health as “the state of the mouth, teeth and orofacial structures that enables individuals to perform essential functions such as eating, breathing and speaking, and encompasses psychosocial dimensions such as self-confidence, well-being and the ability to socialize and work without pain, discomfort and embarrassment. Oral health varies over the life course, from early life to old age, is integral to general health and supports individuals in participating in society and achieving their potential” [7].

Oral health is therefore part of the fundamental human right to health and an important component of sustainable human development, both of which are central to a rights-based global health approach. Promoting oral health can contribute to broader societal well-being by reducing the burden of oral diseases and their associated economic and social consequences [8].

Health promotion also requires a holistic view of the patient in which oral health is recognized as an integral part of overall health. From an integrative perspective, general medicine and dentistry share common goals in disease prevention, early identification

of risk factors, and maintenance of well-being. This approach reflects the close relationship between oral and systemic conditions and supports stronger interdisciplinary collaboration among healthcare professionals. Integrated practice can therefore facilitate coordinated interventions that combine treatment, prevention, and health education.

MEDICAL PREVENTION – A CENTRAL ELEMENT IN HEALTH PROMOTION

Preventive medicine is a key component of modern health promotion policies and plays an important role in shifting healthcare systems towards maintaining and improving population health. Contemporary preventive medicine is often described through the 4Ps: prediction, prevention, personalization, and participation. Unlike approaches focused primarily on curative care, prevention aims to identify and address risk factors before disease develops, thereby helping to reduce disease incidence and prevalence [5]. In this review, prevention is discussed across the primordial, primary, secondary, tertiary, and quaternary levels commonly used in the preventive medicine literature.

Primordial prevention focuses on reducing the emergence of risk factors across the population by addressing the social and environmental conditions in which they develop. This may involve sustainable socioeconomic and cultural policies intended to reduce the conditions that contribute to the development of chronic diseases [2].

Primary prevention aims to reduce the risk of disease before it occurs by identifying and addressing modifiable risk factors in individuals who are clinically healthy. Examples include maintaining a healthy oral microbiome through appropriate oral hygiene and a low-sugar diet, smoking cessation counseling, and nutritional education aimed at supporting metabolic health and maintaining a healthy body weight [3].

Secondary prevention focuses on detecting disease at an early stage, primarily through screening, followed by timely diagnosis and treatment. Examples include cervical cytology and HPV testing for cervical cancer, mammography for breast cancer, fecal occult blood testing, low-dose computed tomography for lung cancer screening in high-risk populations, and periodontal probing and bleeding indices to identify early signs of periodontitis [9,10,11].

Tertiary prevention aims to limit the long-term consequences of established disease by reducing complications, preventing disability, and improving quality of life [5].

Quaternary prevention seeks to identify and limit unnecessary, unjustified, or insufficiently evidence-based medical interventions in order to protect patients from overdiagnosis, overtreatment, adverse effects, and other potential harms associated with medical care [12].

Health promotion is closely linked to the principles of preventive medicine, which extend beyond preventing the onset of disease to supporting healthy behaviors and environments that are conducive to health. Preventive interventions can therefore operate at the individual, community, and societal levels, combining health education, regulatory policies, and population-protection measures. Through these strategies, prevention can help foster a culture in which responsibility for maintaining and improving health is shared by both individuals and society.

Contemporary public health policies place considerable emphasis on preventive strategies because of their potential to reduce the burden of disease and improve quality of life.

Integrating preventive medicine into health promotion policies also reflects a broader shift in the way healthcare systems are organized, with increasing emphasis on proactive and interdisciplinary approaches. Within this framework, collaboration across medical specialties, including between general medicine and dentistry, is important for delivering coordinated and effective care. Preventive medicine should therefore be viewed not only as part of clinical practice, but also as a guiding principle of public health policy, contributing to the development of sustainable health systems that are more responsive to population needs.

The effectiveness of health promotion policies also depends on the ability of governments to address socioeconomic determinants through coordinated action across different sectors. Such initiatives can support the transition from reactive to more proactive models of care, improve access to early diagnosis, including during asymptomatic stages, and contribute to reducing avoidable mortality at the population level.

A relevant example is the implementation of the Health in All Policies (HiAP) approach in emerging socioeconomic settings. This approach extends action beyond the healthcare sector by promoting multisectoral policies that address the social determinants of health. From this perspective, key components of sustainable development include:

- Strengthening basic infrastructure by ensuring access to essential resources such as safe drinking water, sanitation, and adequate housing, thereby helping to reduce epidemiological risks.
- Building economic resilience by supporting productivity and equitable income, with the aim of reducing household vulnerability to the financial consequences of illness. Investment in human capital through coordinated development of education and healthcare services can further strengthen individual capabilities and collective well-being.

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- Promoting gender equity and social support by redistributing and sharing caregiving responsibilities for vulnerable members of society, including children, older adults, and people with chronic illnesses [13].

LIFESTYLE MEDICINE AS A PRIMARY INSTRUMENT IN HEALTH PROMOTION

Lifestyle medicine is a relatively recent approach within contemporary medicine that shifts part of the focus from symptom-oriented, curative care towards prevention and the identification and management of modifiable determinants of chronic non-communicable diseases, while also serving as an adjunct to conventional treatment [14].

This approach goes beyond general behavioral advice and incorporates evidence-based interventions aimed at improving nutrition, promoting appropriate levels of physical activity, supporting healthy sleep patterns, and reducing chronic stress. Together, these measures may contribute to better physiological resilience and long-term health.

By addressing these core areas, lifestyle medicine can play an important role in health promotion and may help patients take a more active role in managing their own health.

When incorporated into routine clinical practice and supported by coherent public health policies, lifestyle interventions can become a practical and measurable component of care rather than remaining a broad or abstract concept. Within the framework discussed in this review, such interventions may also contribute to the broader goals associated with Total Health.

Principles of nutrition through the bidirectional integration of oral and systemic health

The relationship between diet, nutrition, systemic health, and oral health is bidirectional, with each component influencing the others. This interdependence supports a holistic approach, as oral health can affect the nutritional management of chronic disease, while systemic conditions may in turn influence oral health status [15]. Diets high in refined carbohydrates and free sugars, particularly when combined with frequent consumption of acidic foods, represent shared risk factors for both obesity and dental caries. This relationship also highlights the broader role of oral health in chronic disease management. Maintaining adequate oral function can support nutritional intake and overall disease management, while changes in oral health may sometimes reflect underlying systemic conditions. Poorly controlled diabetes mellitus provides a relevant example, as affected individuals have a substantially higher risk of periodontal disease than those with normal glycaemic control [15]. These associations support a more integrated approach to the monitoring and care of patients with chronic disease.

Stress – a metabolic and affective risk factor

Stress is difficult to assess clinically because of its diffuse and multifaceted nature, yet its impact on mental health is well established. Depression, in particular, is among the leading causes of disability worldwide. Psychological resilience is closely connected with broader aspects of health, and the relationship between depression and obesity is one of the most consistently reported associations in the literature. Large meta-analyses have described a bidirectional relationship between metabolic dysfunction, particularly obesity, and affective disorders such as depression, reinforcing the close links between mental and systemic health [16]. Prolonged exposure to chronic stress has also been associated with accelerated cellular aging, including greater telomere shortening, a process linked to biological aging and cumulative physiological stress [17]. In addition, several studies have reported associations between gut microbiome composition and symptoms of anxiety and depression. Within this broader context, lifestyle interventions, particularly improvements in diet and regular physical activity, may support psychological well-being and contribute to better metabolic, cardiovascular, and overall health outcomes [16].

Inflammation – A major risk factor in chronic non-communicable diseases

Chronic inflammation is increasingly recognized as an important pathophysiological factor in many non-communicable diseases. From an evolutionary perspective, the inflammatory response developed as a crucial adaptive mechanism that supported survival in environments with a high infectious burden, before the widespread availability of modern hygiene and sanitation measures. In contemporary settings, however, persistent or inappropriate activation of these defense mechanisms may contribute to chronic low-grade systemic inflammation. This is particularly relevant in the context of longer life expectancy and prolonged exposure to lifestyle-related pro-inflammatory factors. Western lifestyle patterns may therefore contribute to sustained low-grade inflammation, which can disrupt physiological homeostasis and promote the development and progression of chronic degenerative conditions [16].

Obesity – A carcinogenic risk factor and an unfavorable vector in neoplastic therapies

“Obesity results from a disruption of energy homeostasis, namely an imbalance between energy intake and expenditure that leads to a positive energy balance and excessive energy storage. Its etiology is multifactorial and involves genetic, neurohormonal, environmental, and behavioral factors. From an epigenetic perspective, obesity cannot be explained solely by genetic or environmental factors, but rather by their interaction, to which lifestyle also contributes. Some of these influences may be modifiable through appropriate behavioral changes. People with obesity are at increased risk of premature death as a result of

associated conditions such as diabetes mellitus, coronary heart disease, and cerebrovascular disease” [18]. In addition, systemic inflammation related to adipose tissue may also have implications for oral health [16].

“Studies have shown that obesity is associated with an increased incidence of several malignancies, including breast, colorectal, uterine, ovarian, thyroid, renal, pancreatic, liver, and gallbladder cancers, as well as multiple myeloma, meningioma, gastric cardia cancer, and oesophageal adenocarcinoma. Obesity may also be associated with a poorer prognosis in patients with cancer, while excess body weight may influence treatment outcomes and has been linked to a higher risk of recurrence and mortality. Management therefore requires medical, nutritional, and psychological counseling aimed at lifestyle modification, including dietary optimization through reduced caloric intake and behavioral changes that support healthier habits. Pharmacological treatment may be considered as an adjunct to dietary measures, while bariatric surgery may be an option when previous interventions do not achieve the desired results” [18].

LIFESTYLE FACTORS INFLUENCING HEALTHY AGEING AND HEALTHSPAN

This section examines lifestyle medicine as an important component of health promotion, bringing together balanced nutrition, physical activity, stress management, sleep quality, and the development of health-promoting behaviors. These elements are considered alongside the principles of prevention and healthy aging. When combined with a structured preventive approach, they provide a broader framework for supporting health and maintaining function later in life.

The main objective is to promote a sustainable biopsychosocial balance that may help preserve autonomy, functional capacity, and well-being throughout the aging process.

The growing gap between longer life expectancy and the number of years lived in good health has important implications for public health policy. Addressing this gap requires multidimensional strategies that combine lifestyle-related factors with advances in geroscience. As populations live longer, the prevalence of chronic disease and disability also increases, making the preservation of functional health increasingly important. Personalized approaches, supported by medical innovation and appropriately targeted interventions, may therefore contribute to reducing the burden of chronic disease and to maintaining vitality and independence in later life [19].

Active longevity depends on extending healthspan, with the aim of preserving physiological well-being as chronological age advances. This involves, among other factors, reducing allostatic load—the cumulative biological burden resulting from chronic activation of stress-response systems—and limiting systemic inflammation [20].

Aging can therefore be approached as a stage of life in which functional reserves may be preserved through evidence-based measures such as appropriate nutrition, regular physical activity, stress management, and sustained social engagement.

Adopting this perspective requires a shift from predominantly reactive care towards a more proactive model, in which clinicians play an active role in preventing functional decline and supporting biological resilience. Evidence-based strategies, including appropriate caloric restriction and optimization of sleep quality, may help preserve physical and cognitive function over time.

From this perspective, healthcare is viewed as an integrated process that addresses physical, psychological, and broader dimensions of well-being. Within the conceptual framework discussed in this review, such an approach contributes to the idea of Total Health, understood as an aspiration towards healthy living and longevity supported by balanced everyday choices.

DISCUSSION

The literature synthesis indicates that health promotion, preventive medicine, and lifestyle medicine should not be viewed as separate fields, but rather as complementary components of an integrated approach to health. From a preventive perspective, the traditional separation between general medicine and dentistry is becoming increasingly difficult to justify, given the presence of shared determinants and risk factors such as diet, smoking, obesity, chronic inflammation, stress, and individual health-related behaviors. The bidirectional relationship between oral and systemic health therefore supports a patient-centered approach and closer interdisciplinary collaboration [6,15,16].

At the population level, the implications extend beyond the direct clinician–patient relationship. The principles of the Ottawa Charter and contemporary public health approaches emphasize the role of social, economic, and environmental determinants in shaping health [3]. Integrating oral health into broader health policies, in line with WHO guidance, supports the development of interventions that combine prevention, access to care, health education, and efforts to reduce health inequalities [6].

Within this context, the Individual Health–General Health–Primordial Health–Total Health framework may serve as a conceptual tool for bringing together the different levels at which health is shaped. Its value lies in linking the individual dimension of health with population-level determinants and with efforts to improve health potential through interventions targeting modifiable factors. This perspective is consistent with current trends in medicine towards personalization, prevention, patient involvement in clinical decision-making, and interdisciplinary coordination of care.

The relevance of this approach is further reinforced by population aging and the rising prevalence of chronic diseases. Extending healthspan requires not only the treatment of established disease, but also earlier intervention on behavioral, metabolic, and psychosocial factors that influence health across the life course [19,20].

Looking ahead, translating these principles into practice will require the development of interdisciplinary models that can be applied in both clinical care and public health. The proposed conceptual framework may therefore provide a starting point for future research on integrating prevention and health promotion across general medicine, dentistry, and other components of the healthcare system.

CONCLUSION

Within health promotion as a broader systemic approach, preventive medicine and lifestyle medicine provide a common framework for integrating preventive interventions and addressing risk factors that affect both general and oral health. Closer collaboration between general medicine and dentistry may therefore help reduce fragmentation of care and strengthen an interdisciplinary, patient-centered approach.

The Individual Health–General Health–Primordial Health–Total Health framework is presented in this review as a proposed conceptual model rather than a validated biomedical construct. It offers an integrative perspective on the relationship between individual, social, and environmental determinants of health. Translating this perspective into clinical practice and public health policy may support a gradual shift from predominantly reactive care towards a more proactive and preventive model focused on maintaining health and quality of life across the life course.

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Authors' contribution

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Ethics approval and consent to participate

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REVIEW

Operational Cardiology in the Military Population: Cardiovascular Risk Assessment and Implications for Mission Fitness

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Abstract: Introduction: Operational cardiology is an emerging field of military medicine focused on cardiovascular risk assessment and maintaining mission fitness. Military activities involve intense physical exertion, operational stress, sleep deprivation, and occupational exposures that can trigger acute cardiovascular events, including in apparently healthy individuals. The aim of this review is to synthesize data on cardiovascular risk in the military population and its implications for determining mission fitness. Materials and Methods: This review included 52 studies published between 2000 and 2026, identified in PubMed/MEDLINE, Web of Science, and Scopus. The papers were analyzed thematically: cardiovascular epidemiology, sudden cardiac death, specific risk factors, impact of exertion and operational stress, cardiovascular screening, and physiological monitoring. Results: Cardiovascular events occur predominantly during intense exertion and are frequently associated with previously undiagnosed pathology. Traditional risk factors coexist with operational stressors, increasing cardiovascular load. Cardiovascular screening and cardiorespiratory fitness assessment allow risk stratification and identification of overload. Conclusions: Integration of cardiovascular screening, fitness assessment, and physiological monitoring may reduce the risk of cardiovascular events and optimize operational safety. Standardized protocols adapted to the military environment are needed.

Keywords: operational cardiology; military personnel; cardiovascular risk; mission fitness; sudden cardiac death; cardiovascular screening; military physical exertion; operational stress; heart rate variability; cardiorespiratory fitness; physiological monitoring; military medicine.

INTRODUCTION

Operational cardiology represents an emerging field at the intersection of cardiovascular, occupational, and military medicine, with the primary objective of maintaining the operational capability of military personnel through the prevention, identification, and management of cardiovascular risk [1]. Unlike classical cardiology, which is predominantly oriented toward long-term prevention, operational cardiology focuses on the immediate risk of acute incapacitating events that may compromise individual safety and mission success.

The specific characteristics of military activities involve exposure to intense physical exertion, extreme environmental conditions, hypoxia, acute and chronic psychological stress, as well as sleep deprivation—factors that may exacerbate underlying cardiovascular pathology or trigger acute events even in apparently healthy individuals [6,7]. In this context, cardiovascular risk assessment in the military population becomes strategically important, extending beyond preventive medicine and integrating into the concept of “fitness for duty.”

Epidemiological data indicate that although the military population is generally considered healthier than the general population, the prevalence of cardiovascular

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risk factors—including hypertension, dyslipidemia, obesity, and smoking—remains significant and is increasing [2,3]. In addition, demographic changes, such as the rising average age of active personnel, contribute to the growing burden of cardiovascular disease in this group.

Acute cardiovascular events, particularly sudden cardiac death and myocardial infarction, represent important causes of morbidity and mortality among military personnel and are frequently associated with intense physical exertion or demanding operational conditions [4,5]. These events have major implications not only for individual health but also for operational effectiveness, potentially leading to mission interruption, medical evacuation, and additional risks for the team.

In this context, cardiovascular screening and functional assessment strategies have evolved considerably, including modern imaging methods, exercise testing, and monitoring under simulated operational stress conditions [6]. Current guidelines also emphasize the need for an individualized approach, adapted to the specific requirements of different military roles and the acceptable level of risk depending on mission type [7].

An essential aspect of operational cardiology is determining mission fitness (“deployability”), which involves assessing the probability of an incapacitating cardiovascular event under operational conditions and its impact on task performance [8]. This assessment requires integration of clinical, functional, and occupational data into a complex decision-making model.

Therefore, operational cardiology is becoming a central element of modern military medicine, aiming to balance the need to maintain operational capability with the imperative to protect personnel health. This review aims to analyze current methods for cardiovascular risk assessment in the military population and their implications for determining mission fitness.

MATERIALS AND METHODS

The present study was conducted as a review, aiming to synthesize the available data on operational cardiology in the military population, with a focus on cardiovascular risk assessment and determination of fitness for duty. A systematic literature search was performed in the PubMed/MEDLINE, Web of Science, and Scopus databases. A total of 52 articles published between 2000 and 2026 were included, with emphasis on recent studies.

The search strategy used combinations of MeSH terms and keywords, together with Boolean operators:

("operational cardiology" OR "military cardiology" OR "military personnel") AND ("cardiovascular risk" OR "cardiovascular disease" OR "sudden cardiac death") AND ("military training" OR "operational stress" OR "physical exertion") AND ("cardiovascular screening" OR "fitness for duty" OR "pre-participation screening") AND ("physiological monitoring" OR "heart rate variability" OR "cardiorespiratory fitness"). Additional relevant articles were identified through manual screening of the reference lists of the included studies.

Eligibility criteria. Studies were included if they met the following criteria: they analyzed active military populations or tactical personnel; evaluated cardiovascular risk factors or cardiovascular diseases; examined sudden cardiac death in military personnel; assessed the impact of military physical exertion on the cardiovascular system; analyzed operational stress and autonomic regulation; evaluated cardiovascular screening methods; examined physiological monitoring in an operational context; and were published in scientific journals. Exclusion criteria were: studies not involving military populations; studies without relevant cardiovascular outcomes; conference abstracts without full text; editorials without original data; and articles lacking access to relevant scientific data.

Study selection. All identified records were initially screened based on title and abstract. Subsequently, potentially eligible articles were assessed in full text. Studies meeting the inclusion criteria were selected for qualitative synthesis. Duplicate records were removed prior to the selection process.

Data extraction. The following information was extracted from the included studies: study type; population characteristics; military category (active duty personnel, recruits, special forces, pilots); cardiovascular events evaluated; analyzed risk factors; cardiovascular screening methods; physiological monitoring techniques; operational stress parameters; and main findings.

Data synthesis. The extracted data were synthesized and organized into the following thematic domains: epidemiology of cardiovascular diseases in the military population; sudden cardiac death and acute cardiovascular events in military personnel; cardiovascular risk factors specific to the military environment; impact of military physical exertion on the cardiovascular system; operational stress, autonomic regulation, and physiological monitoring; cardiovascular screening and fitness-for-duty assessment; and operational cardiology in the theater of operations.

RESULTS

1. Epidemiology of Cardiovascular Diseases in the Military Population

Cardiovascular diseases represent an important cause of non-traumatic morbidity among military personnel, despite rigorous medical selection. Epidemiological studies have identified the prevalence of traditional cardiovascular risk factors, including hypertension, dyslipidemia, obesity, and smoking — at varying proportions among active-duty service members. These findings have been reported both in descriptive studies and in comparative analyses between personnel with and without acute coronary events [2,9–11]. Recent research has confirmed the relationships between physical activity level, cardiometabolic profile, and cardiovascular risk among active military personnel, highlighting the role of health behaviors and operational physical fitness [12–14].

Comparative analyses between military and civilian populations have shown that, although military personnel often present a more favorable health profile, cardiovascular risk is not absent [15,16]. In addition, the assessment of cardiometabolic biomarkers has proven useful for cardiovascular risk stratification in military personnel [17]. (Table 1).

Table 1: Scientific articles presenting studies on the epidemiology of cardiovascular diseases in the military population

Focus / Application	Year	Author	Conclusions
Review of cardiovascular risk factors in military	2008	McGraw L.K., [2]	Significant prevalence of hypertension, dyslipidemia, and smoking
Risk factors in service members with ACS	2011	McGraw L.K., [9]	Risk profile comparable to civilians, with operational impact
Coronary artery disease risk factors	2019	Mirzaeipour F., [10]	High prevalence of obesity and dyslipidemia
Prevalence of risk factors in soldiers	2020	Gielerak G., [11]	Multiple risk factors present even in active personnel
Physical activity and cardiovascular risk	2025	Dawood J., [12]	Physical activity is inversely associated with cardiometabolic risk
Military vs civilian populations	2025	Zawadzka M., [13]	Moderate differences, but persistent cardiovascular risk
POL-SCORE assessment in soldiers	2025	Zawadzka M., [14]	Effective identification of high-risk individuals
Racial differences and military service	2019	Walker L.E., [15]	Variability in cardiovascular risk across subgroups
Epidemiology in UK Armed Forces	2015	Cox A.T., [16]	CVD is a major non-traumatic cause of morbidity
Cardiometabolic biomarkers	2025	Pabin A., [17]	Biomarkers improve cardiovascular risk stratification

2. Sudden Cardiac Death and Acute Cardiovascular Events in Military Personnel

Sudden cardiac death represents one of the leading causes of non-traumatic death among military personnel. Autopsy studies conducted on military recruits have identified cardiomyopathies, congenital coronary anomalies, and cardiac electrical disorders as the main causes [4,18,19].

Similar findings have been reported in analyses of British military personnel and air force recruits [20]. Most events occur in the context of intense physical exertion or demanding training, even in individuals previously considered healthy [5,21]. Recent meta-analyses indicate a relatively low incidence of cardiac arrest among military personnel and tactical athletes, but with significant operational impact [22,23].

Additionally, case reports have highlighted the role of rare conditions, such as congenital long QT syndrome or mitral annular disjunction, in the occurrence of cardiac arrest in the military setting [24,25]. Comparative data from populations of young athletes support these observations regarding mechanisms of sudden death in apparently healthy individuals subjected to intense exertion [26]. (Table 2).

Table 2: Scientific articles on sudden cardiac death and acute cardiovascular events in military personnel

Focus / Application	Year	Author	Conclusions
Autopsy study in recruits	2004	Eckart R.E., [4]	Cardiomyopathies and coronary anomalies are the main causes
Sudden death in female recruits	2006	Eckart R.E., [18]	Similar causes as in males
DoD sudden death registry	2011	Eckart R.E., [19]	Low incidence but high operational impact
Sudden death in UK military	2011	Vanezis A.P., [20]	Events often associated with exertion
Exertion-related sudden death	2016	Smallman D.P., [5]	Most events occur during training
Case series in healthy soldiers	2023	McLeod E.V., [21]	Events occur in apparently healthy individuals
Meta-analysis of cardiac arrest	2022	Lear A., [22]	Low incidence but operationally relevant
Incidence and survival	2025	Franzos M.A., [23]	Survival improved with rapid response
Long QT syndrome	2023	Chung T.F., [24]	Congenital causes of cardiac arrest
Mitral annular disjunction	2025	Dean J.L., [25]	Arrhythmic risk in military aviators
Athlete comparison data	2015	Harmon K.G., [26]	Similar mechanisms to young athletes

3. Cardiovascular Risk Factors Specific to the Military Environment

In addition to traditional risk factors, military personnel are exposed to occupation-specific determinants.

Autopsy studies have demonstrated the presence of subclinical atherosclerosis even among special forces members considered physically fit [27]. Analyses of occupational factors have identified operational stress, exposure to extreme temperatures, hypoxia, vibrations, and specific environmental conditions as additional determinants of cardiovascular risk [28,29]. The literature also shows an association between combat experience and increased cardiovascular risk [8].

Other relevant occupational factors include night shift duties, which are associated with cardiometabolic changes, and exposure to pollutants from burn pits, correlated with increased cardiovascular and respiratory risk [30,31]. The impact of cardiovascular diseases on operational capability is significant, being associated with reduced productivity and limitations in mission readiness [32] (Table 3).

Table 3: Scientific articles presenting studies on cardiovascular risk factors specific to the military environment

Focus / Application	Year	Author	Conclusions
Subclinical atherosclerosis in elite forces	2021	Kotwal R.S., [27]	Atherosclerosis present even in elite personnel
Endogenous risk in military pilots	2022	Maculewicz E., [28]	Metabolic and autonomic factors relevant
Occupational and environmental risks	2023	Maculewicz E., [29]	Heat, hypoxia, and stress increase risk
Combat exposure and cardiovascular risk	2019	Boos C.J., [8]	Combat associated with increased risk
Night duty impact	2025	Byeon H., [30]	Associated with cardiometabolic disturbances
Burn pit exposure	2024	Savitz D.A., [31]	Increased cardiovascular and respiratory risk
Productivity impact	2018	Gharasi-Manshadi M., [32]	CVD reduces operational capacity

4. Impact of Military Physical Effort on the Cardiovascular System

Intense physical exertion characteristic of military activities can precipitate acute cardiovascular events. Studies on myocardial infarction during military training have shown that intense physical demands may trigger acute events in apparently healthy service members [33]. Scientific statements on physical exercise confirm the existence of a transient increase in cardiovascular risk during vigorous exertion, particularly in individuals with subclinical risk factors [34].

Recent analyses have highlighted differences in cardiopulmonary function between special forces and conventional infantry, suggesting distinct physiological adaptations depending on the type of operational demand [35]. (Table 4).

Table 4: Scientific articles presenting studies on the impact of military physical effort on the cardiovascular system in military settings

Focus / Application	Year	Author	Conclusions
STEMI during military training	2021	Singh N., [33]	Intense exertion can trigger myocardial infarction
Exercise and acute events	2007	Thompson P.D., [34]	Transient increase in cardiovascular risk during exertion
Cardiopulmonary function comparison	2025	Rasmussen R.S., [35]	Different physiological adaptations between units

5. Operational Stress, Autonomic Regulation, and Physiological Monitoring

Operational stress induces changes in the autonomic nervous system and cardiovascular function. Systematic analyses have shown that psychological and physical stress produce sympathetic activation and a reduction in heart rate variability (HRV), an indicator of physiological load [36]. The relationships between HRV, occupational performance, and fitness level have been confirmed in studies conducted on tactical personnel [37]. Continuous monitoring of autonomic parameters has demonstrated the usefulness of HRV for evaluating operational strain and physiological recovery in military personnel [38,39].

Additional studies have highlighted changes in heart rate complexity during pre-deployment training and during patrol operations [40,41]. The use of portable ECG devices has enabled the assessment of the physiological cost of military activities in real-world field conditions [42]. (Table 5).

Table 5: Scientific articles presenting studies on operational stress, autonomic regulation, and physiological monitoring in operational settings

Focus / Application	Year	Author	Conclusions
Stress and autonomic system	2020	Bustamante-Sánchez A., [36]	Sympathetic activation and reduced HRV
HRV and tactical performance	2020	Tomes C., [37]	HRV correlates with operational performance
Heart rate complexity	2020	Mulder M.B., [40]	HRV reflects operational strain
HRV monitoring in soldiers	2025	Chapman C.L., [38]	HRV useful for daily monitoring
HRV in simulated operations	2025	Lowe A.C., [39]	Autonomic changes during missions
Patrol operations and HRV	2015	Duarte A.F., [41]	Field-induced autonomic modulation
Wearable ECG monitoring	2023	Bocharov M., [42]	Real-time physiological assessment

6. Cardiovascular Screening and Mission Fitness Evaluation

Cardiovascular screening represents an essential component of preventing acute events in the military environment. The introduction of electrocardiography in the evaluation of recruits has been proposed to detect silent cardiac pathology and reduce the risk of sudden death [43,45].

Clinical studies have demonstrated the usefulness of evaluating service members with post-exercise palpitations to identify clinically relevant arrhythmias [46]. Cardiopulmonary exercise testing has been proposed as a method for assessing operational capacity and mission fitness [44]. Longitudinal cardiorespiratory fitness monitoring programs have demonstrated the predictive value of functional parameters for cardiovascular events and hospitalizations in the military population [47]. (Table 6).

Table 6: Scientific articles presenting studies on cardiovascular screening and mission fitness evaluation in operational settings

Focus / Application	Year	Author	Conclusions
ECG screening in recruits	2011	Boos C.J., [43]	ECG may detect silent cardiac disease
Military cardiovascular screening	2020	Magee C., [45]	Need to reconsider ECG implementation
Palpitations post-training	2022	Günlü S., [46]	Useful in identifying arrhythmias
Cardiopulmonary exercise testing	2026	Holland J.L., [44]	CPET is valuable for mission fitness assessment
Cardiorespiratory fitness study	2016	Lin G.M., [47]	Fitness predicts cardiovascular outcomes

7. Operational Cardiology in the Theater of Operations

The management of cardiovascular pathology in the operational environment requires adapting evaluation and treatment to field conditions. Studies have described the need for rapid decision-making regarding mission fitness within advanced medical facilities [48].

Cardiology telemedicine has been proposed as a decision-support tool for remote consultations in theaters of operations [49]. The aeronautical cardiology literature highlights the specific aspects of evaluating military aviation personnel [50]. Reports from advanced military hospitals have identified the most common types of cardiovascular conditions encountered during military operations [51,52] (Table 7).

Table 7: Scientific articles presenting studies on operational cardiology in the theater of operations setting

Focus / Application	Year	Author	Conclusions
Field cardiology practice	2007	Nayak G., [48]	Need for rapid decision-making in deployment
Telecardiology	2009	Rand E.R., [49]	Remote consultation improves decision support
Aviation cardiology	2019	Nicol E.D., [50]	Specific considerations for aircrew
CVD in deployed hospital	2008	Sullenberger L., [51]	Cardiovascular cases frequent in operations
Cardiovascular complaints in deployment	2016	Watts J.A., [52]	Common cardiovascular presentations in theater

DISCUSSION

Data from the scientific literature highlight that the epidemiology of cardiovascular diseases in the military population presents distinct characteristics compared with the general population. Although initial medical selection results in a more favorable health profile, studies show that traditional risk factors—arterial hypertension, dyslipidemia, obesity, and smoking—remain frequently encountered among active military personnel [2,9–11]. Compared with the civilian population, the prevalence of these factors is often lower; however, cardiovascular risk is not absent, supporting the need for continuous monitoring and periodic evaluation of the cardiometabolic profile [15,16].

Regarding non-traumatic mortality, sudden cardiac death represents one of the leading causes of death among military personnel. Unlike the general population, where events are frequently associated with advanced coronary artery disease, in the military environment, these events often occur in apparently healthy individuals during intense physical exertion. Autopsy studies have identified cardiomyopathies, congenital coronary anomalies, and cardiac electrical disorders as the main causes [4,18,19].

Although incidence is relatively low, the operational impact is significant, and most events are reported during demanding physical activities [22,23].

An important aspect is the influence of occupational factors specific to the military environment. Unlike the civilian population, military personnel are exposed to operational stress, extreme conditions, and combat experiences, factors associated with increased cardiovascular risk and long-term cardiometabolic changes [8,28,29]. The presence of subclinical atherosclerosis even in highly fit military personnel suggests the cumulative impact of these exposures on the cardiovascular system [27].

The intense physical effort characteristic of military activities highlights a dual relationship compared with physical activity in the general population. On the one hand, it produces favorable physiological adaptations; on the other, it may trigger acute cardiovascular events in apparently healthy individuals. Studies of myocardial infarction during military training show that maximal exertion may act as a precipitating factor for acute events [33]. In addition, differences between types of military units suggest that the nature of operational demands influences the cardiovascular response to exertion [35].

Operational stress produces more pronounced changes in autonomic regulation than those observed in the civilian population, characterized by sympathetic activation and reduced heart rate variability. Systematic analyses have demonstrated the usefulness of HRV as an indicator of physiological load and recovery in tactical personnel [36,37]. Continuous monitoring using wearable devices allows assessment of physiological strain in real operational conditions and optimization of performance [38,39].

Cardiovascular screening remains essential for preventing acute events in the military population. The introduction of electrocardiography in recruit evaluation has been proposed to detect silent cardiac pathology and reduce the risk of sudden death [43,45]. Cardiopulmonary exercise testing provides objective information regarding functional capacity and may contribute to mission-fitness assessment [44].

Management of cardiovascular disease in the operational environment differs from the civilian approach due to the need for rapid decisions regarding mission fitness and the logistical limitations of operational theaters. Studies have highlighted the role of advanced medical facilities and the need to adapt evaluation and treatment strategies to field conditions [48]. In this context, cardiology telemedicine has been proposed as a decision-support tool for remote consultations and optimization of cardiovascular case management in operational theaters [49].

Overall, although military personnel present a more favorable initial health profile, exposures specific to the operational environment and intense physical demands generate distinct cardiovascular risks. These particularities justify the implementation of dedicated screening, monitoring, and management strategies tailored to the military population [15,27,36,44].

CONCLUSION

Cardiovascular disease represents a significant cause of non-traumatic morbidity in military populations and has direct implications for operational capability. Despite a generally favorable baseline health profile, military personnel remain exposed to both traditional cardiovascular risk factors and occupation-specific stressors that contribute to disease development.

Sudden cardiac death, although uncommon, constitutes a critical operational concern and frequently occurs during intense physical exertion in apparently healthy individuals, underscoring the limitations of conventional screening strategies. Operational stress, extreme environmental conditions, and high physical demands further increase cardiovascular load and may precipitate acute events.

Comprehensive cardiovascular screening, physiological monitoring, and periodic assessment of fitness for duty are therefore essential components of risk mitigation. An integrated operational cardiology approach, tailored to the unique demands of the military environment, is required to reduce cardiovascular risk and maintain operational readiness.

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Authors' contribution

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REVIEW

Stackable Surgical Guides in Full-Arch Implant Rehabilitation: What They Can Deliver and Where the Evidence Still Constrains Use — A Critical Narrative Review

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Abstract: Objectives: This review examines the current role of stackable surgical guides in full-arch implant rehabilitation, with particular attention to what these systems can reliably achieve in clinical practice and where the available evidence remains insufficient to support broader claims. Materials and methods: A critical narrative review of PubMed/MEDLINE and Scopus was conducted and updated through August 2026. The search combined the terms "stackable," "sequential," and "modular" surgical guides with "dental implant," "full arch," "bone reduction," "accuracy," and "immediate loading." Clinical studies, evidence syntheses, and relevant laboratory investigations were assessed individually. Because of the heterogeneity of the available literature and the narrative design of the review, no meta-analysis or formal risk-of-bias assessment was performed. Results: Stackable systems use a stable base with interchangeable components to maintain the planned reference throughout bone management, implant placement, and prosthetic transfer. The available clinical evidence remains limited. A 2024 scoping review identified only 12 case reports or case series, including 25 patients, 27 arches, and 173 implants, and accuracy was quantified in only four of these reports. More recent clinical studies provide additional information, although their findings remain specific to the protocols investigated. In one retrospective series involving 60 implants placed with a rigid, bone-fixed base, mean angular, neck, and apical deviations were 1.25°, 0.96 mm, and 1.07 mm, respectively. The first in vivo comparison with other forms of static guide support found no overall accuracy advantage for stackable guides and reported the greatest vertical discrepancy in the stackable group (0.26 mm; $P < .001$). In the 43-arch STAGE cohort, approximately 93% of arches were loaded on the day of surgery, while 274 of 284 implants had osseointegrated at four months. Implant replacements and provisional fractures were nevertheless reported. Conclusions: Current evidence supports stackable guides primarily as a method for maintaining a common planned reference throughout successive surgical and restorative steps. In appropriately selected cases, they can facilitate prosthetically driven implant placement, guided or selective bone reduction, and immediate provisionalization. Available studies, however, do not establish superiority over conventional guidance, identify one stackable design as preferable to another, provide validated criteria for bone reduction, or demonstrate advantages in patient-reported outcomes or cost-effectiveness.

Keywords: Dental Implants; Surgery, Computer-Assisted; Immediate Dental Implant Loading; Dental Prosthesis, Implant-Supported; Dental Arch

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1. Introduction

Immediate fixed rehabilitation of a terminal dentition or a completely edentulous arch requires several clinical and digital steps to remain coordinated. The intended tooth position must first be related to the facial and occlusal plan and subsequently transferred to the available bone, the required restorative space, the planned implant positions, and finally the provisional restoration. Maintaining this

relationship during surgery can be difficult. Extractions, flap elevation, and alveolar reduction may modify or remove anatomical landmarks that were initially used to position a conventional surgical guide. Consequently, a guide that seats accurately at the beginning of the procedure may become less reliable after the surgical anatomy has changed.

Static computer-assisted implant surgery improves the reproducibility of implant positioning, but discrepancies between planned and actual implant positions remain clinically relevant. A systematic review including 20 clinical studies reported mean deviations of 1.2 mm at the entry point, 1.4 mm at the apex, and 3.5° in angulation. The authors also emphasized the heterogeneity of the available data and the need to maintain an appropriate safety margin around critical anatomical structures [1]. Subsequent evidence has similarly shown that guide support, fixation, sleeve design, and manufacturing procedures can influence accuracy, while methods used to measure deviations remain insufficiently standardized [2,3]. These findings provide useful background for static guided implant surgery in general, but they should not be interpreted as direct evidence of the accuracy of stackable systems.

Stackable surgical guides were developed to address a related but distinct clinical challenge: maintaining a consistent reference throughout successive surgical and restorative procedures. In these systems, a stabilized base remains in position while different components are connected sequentially for bone reduction, osteotomy preparation, implant placement, and prosthetic indexing [4–6]. This arrangement may help preserve the relationship between the prosthetically driven plan and the surgical field even when the local anatomy changes during treatment. Its effectiveness, however, still depends on accurate initial positioning and stable fixation of the reference base. Incomplete seating after flap elevation or interference from residual teeth or soft tissues may compromise the position of the base. Any discrepancy introduced at this stage may subsequently affect every component connected to it.

Previous reviews have mainly described the available techniques and their reported outcomes. A systematic review from our group summarized the techniques, workflows, and short-term outcomes reported for stackable surgical guides over a ten-year period [7]. A separate scoping review of stackable metallic and magnetic guides used in immediate-loading protocols evaluated eight studies involving 351 implants and reported considerable heterogeneity, together with a substantial lack of validated patient-reported data [8]. The purpose of the present review is therefore different from simply determining whether stackable guides can be used successfully. We critically examine the clinical tasks for which these systems currently have supporting evidence, the points at which transfer errors may occur during the sequential workflow (Figure 1), and the practical decisions that determine whether the planned sequence can be safely continued (Figure 2). Given the heterogeneity of the available evidence, non-comparable outcomes are not pooled and individual design variants are not ranked beyond what the existing data support.

2. Materials and Methods

This critical narrative review was based on targeted searches of PubMed/MEDLINE and Scopus, with the final search updated on 26 August 2026. Search terms included “stackable guide,” “stackable surgical template,” “sequential template,” “modular guide,” and “full-arch implant,” combined with “bone reduction,” “osteotomy,” “accuracy,” “immediate loading,” “provisional,” and “patient-reported outcome.” Reference lists from recent systematic and scoping reviews, as well as from the primary studies included in the review, were also examined to identify additional relevant publications.

English-language, full-text articles were considered when they described the use of a stackable or sequential guide for full-arch implant rehabilitation, assessed implant-placement or bone-reduction accuracy, reported clinical or prosthetic outcomes, or investigated design and manufacturing factors with a potential influence on transfer accuracy. Studies addressing static guided implant surgery more broadly were considered only when they provided relevant information regarding measurement, safety, or manufacturing. As this was a critical narrative review rather than a systematic review, no PRISMA flow diagram, formal risk-of-bias assessment, or meta-analysis was performed. Numerical findings reported in the review were attributed to their original studies, with study design, sample characteristics, endpoints, and relevant limitations considered when interpreting the results.

The methodology also has limitations inherent to the narrative-review design. The literature search was restricted to PubMed/MEDLINE and Scopus and to publications available in English. Study selection and appraisal were not performed independently by two reviewers, and no formal risk-of-bias instrument was applied. In addition, the available evidence is limited and heterogeneous, which increases the possibility of selection bias. The findings should therefore be interpreted as a structured clinical assessment of the available literature rather than as a quantitative estimate of treatment effect.

3. The Stackable Concept: One Planned Reference Across Multiple Phases

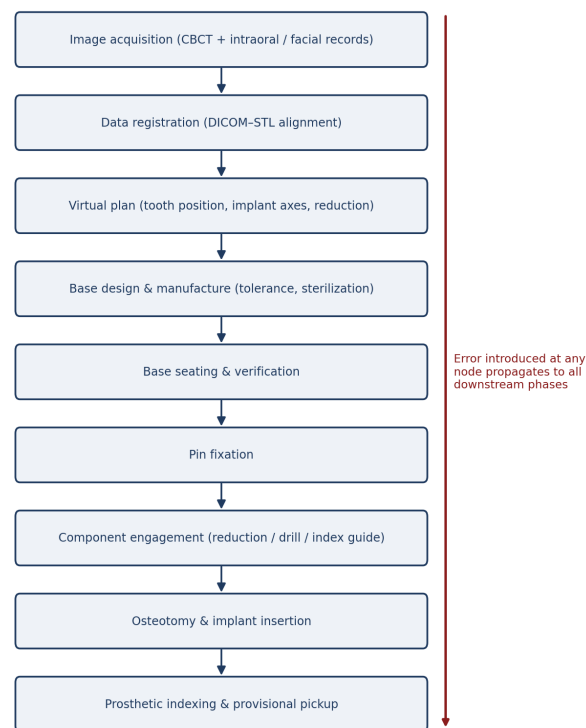
A stackable system generally consists of a reference base and two or more removable components. Initial positioning of the base may rely on the remaining teeth, mucosa, a duplicate denture, an external index, or a dedicated positioning guide, after which the base is usually secured with lateral fixation pins. Once fixed, it provides a common support for the components used during bone reduction, osteotomy preparation, or implant placement, and prosthetic transfer. Different systems use screws, pins,

geometric keys, ball attachments, cones, or magnets to connect these components. The guides themselves may be produced by resin printing, milling, or additive manufacturing in metal [4,5].

The main purpose of this arrangement is to maintain the same spatial reference throughout the different stages of treatment. Provided that the base remains accurately positioned and stable, each successive component can reproduce the planned relationship even after teeth have been extracted or the alveolar ridge has been modified. This is particularly relevant when the provisional restoration is fabricated before surgery, since its transfer depends on reproducing the planned relationship between implant positions and the restorative components.

The accuracy of the workflow therefore depends on more than the number or design of the individual components. Errors may occur during image acquisition, data registration, base positioning, pin fixation, guide fabrication, component seating, drilling, implant insertion, or prosthetic transfer. When these stages depend on the same reference base, an error introduced early in the workflow may also influence subsequent stages (Figure 1). Reducing the need to reposition separate guides may simplify the sequence, but it does not compensate for inaccurate initial positioning. For this reason, the position and stability of the reference base should be verified throughout the procedure. The base, then, is best treated as a clinical reference to be checked and rechecked — not as proof that the virtual plan has actually been transferred.

Figure 1: Propagation of reference errors through a stackable workflow. AI assistance was used to create the illustration (Claude Opus 4.8, Anthropic). The authors reviewed and verified the final diagram and take full responsibility for its accuracy and content.



4. Current Applications and Reported Outcomes

4.1. Integrated prosthetic planning and bone management

Stackable systems allow implant placement and, when indicated, alveolar reduction to be planned in relation to the intended definitive restoration. In full-arch rehabilitation, bone reduction may be required to correct an irregular or knife-edge ridge, provide adequate width for implant placement, create sufficient restorative space, reposition the prosthetic transition zone, or coordinate the occlusal plane and smile line [9]. The decision to perform alveolar reduction, as well as the amount of bone to be

removed, should therefore be based on the planned restoration and the residual anatomy rather than on the availability of a reduction guide.

Several clinical reports have incorporated facial information, planned tooth position, osteotomy, and implant placement within the same digital workflow. Fu et al. described an esthetically driven approach in which the planned lip and tooth positions were used to coordinate maxillary osteotomy and immediate rehabilitation with six implants [10]. A scalloped-guide proof-of-concept technique used selective bone reduction to preserve interproximal bone and facilitate a pink-free FP1 restoration in an appropriately selected case [11]. These reports demonstrate the clinical feasibility of incorporating bone management into a prosthetically driven digital workflow, although they do not provide evidence that a particular reduction design is generally superior.

Alveolar reduction is not required in every stackable protocol. Cristache et al. reported four maxillary cases treated with low-profile restorative components without planned alveolar reduction. A tissue- or mixed-supported pinned base was used, followed by delivery of immediate long-term provisional restorations [12]. These cases demonstrate that the sequential transfer provided by a stackable system can also be used when bone reduction is not indicated. The indication and extent of alveolar reduction should therefore remain independent biological and prosthetic decisions.

4.2. Study-specific implant-placement accuracy

Clinical studies evaluating implant-placement accuracy have provided additional information beyond the earlier technique reports. In a retrospective study of 15 completely edentulous patients receiving 60 implants, Bjelica et al. evaluated a bone-supported, pin-fixed, magnetically connected resin system after flap elevation and alveolar reduction. Mean angular deviation was $1.25 \pm 0.80^\circ$, while mean three-dimensional deviations were 0.96 ± 0.57 mm at the implant neck and 1.07 ± 0.56 mm at the apex. Mean depth discrepancy was 0.37 ± 0.58 mm [13]. These results describe the performance of a specific workflow used by an experienced operator. The retrospective design, absence of a comparator, CBCT-based registration, and inclusion of multiple implants within individual patients limit conclusions regarding superiority or generalizability.

The first in vivo study directly comparing stackable guides with other types of static guide support was reported by Eldabe et al. The study included 86 implants placed using bilateral tooth-supported, unilateral tooth-supported, mucosa-supported, and stackable bone-supported guides. No statistically significant differences were identified between groups for angular, coronal, or apical global deviations. A significant difference was found for vertical discrepancy, with the stackable group showing the highest value (0.26 ± 0.06 mm; $P < .001$), together with a mean angular deviation of $5.42 \pm 1.16^\circ$ [14]. Interpretation is limited by the small, non-randomized, stackable subgroup of 3 patients and 19 implants, the absence of blinding, and the use of a single magnetic connection system. Bjelica et al. also evaluated a magnetically connected system but reported substantially lower deviations with a rigidly bone-fixed base [13]. The different results obtained with systems sharing a magnetic connection indicate that connector type cannot be considered independently from base support, fixation, component seating, and the overall stability of the reference system.

Cristache et al. evaluated another clinical configuration in four patients receiving 25 maxillary implants. Mean coronal, apical, and angular discrepancies were 0.87 ± 0.50 mm, 2.04 ± 0.69 mm, and $2.67 \pm 1.25^\circ$, respectively [12]. The greater apical than coronal deviation is compatible with the effect of angular error over the length of an implant. However, the small case-series design does not allow these values to be considered representative of expected performance. The study does show that successful clinical treatment and one-year implant survival may occur despite measurable transfer discrepancies.

Evidence from guided implant surgery more broadly also illustrates the limitations of interpreting mean deviation values in isolation. In a prospective study of mucosa-supported guides involving 13 edentulous maxillae, D'haese et al. reported a mean angular deviation of 2.60° , while the maximum deviation reached 8.86° [15,16]. Although this study did not evaluate a stackable workflow and should not be interpreted as a direct comparator, it demonstrates the potential difference between mean values and individual deviations. Anatomical safety margins and intraoperative verification therefore remain necessary regardless of the reported average accuracy.

The limited comparative evidence available for stackable systems remains specific to individual designs and manufacturing protocols. Hameed and Hebeshi placed 24 implants using stackable guides manufactured either from selective-laser-melted cobalt–chromium or digital-light-processed resin and reported lower coronal, apical, and angular deviations with the metal configuration [17]. However, the material and manufacturing method differed simultaneously, the sample was small, and the study involved terminal maxillary dentitions. The findings therefore cannot establish a general advantage of metal over resin stackable guides.

In a 12-model in-vitro study, Tallarico et al. found that modular guidance produced accuracy broadly comparable with conventional fully guided implant placement, although screw fixation and operator experience influenced some deviations, particularly following simulated bone reduction [18]. Laboratory studies of conventional surgical guides have similarly shown that sleeve design, fabrication by printing or milling, resin type, printer, and sterilization procedures can affect accuracy, with results varying according to the specific configuration [19–21]. These findings emphasize the importance of controlling the complete

guide, instrumentation, manufacturing, and operator workflow rather than attributing accuracy to a single material or design feature.

Beretta et al. described a different approach for assessing transfer accuracy using a dedicated “number guide” screwed onto the fixed base to improve intraoperative registration of scan bodies. The technique was applied in 10 patients receiving 47 one-piece implants with immediate provisionalization, with greater placement precision reported in the mandible than in the maxilla [22]. As a single-arm case series without a comparator, the study provides preliminary evidence for a standardized method of intraoperative accuracy assessment rather than an estimate of comparative effectiveness.

4.3. Prosthetic indexing and immediate provisionalization

Transfer of a prefabricated provisional restoration is an important application of the stackable workflow. Prosthetic components can be indexed to the same reference base used during implant guidance, helping to maintain the planned vertical dimension, midline, occlusal plane, and restorative position after the surgical phase. Clinical techniques and cohort studies have used magnetically retained components, while mechanical keys, pins, screws, and ball attachments represent alternative methods of indexing [4,23]. These different connection methods have demonstrated clinical feasibility, but the available evidence does not establish their equivalence or the superiority of one approach.

The 2024 scoping review by Lan et al. identified 12 case reports or case series involving 25 patients, 27 arches, and 173 implants. Immediate loading was reported in 11 of the included studies, while implant-placement accuracy was quantified in only four. No prospective comparative study was identified [4]. The available literature at that time therefore primarily supported technical feasibility, with insufficient evidence for comparative effectiveness.

A larger clinical dataset was subsequently provided by the STAGE study. Thirty-five patients with 43 treated arches, including 15 arches in native bone and 28 following grafting, received 284 implants using a stackable workflow. Approximately 93% of arches (40 of 43) were loaded on the day of surgery. At the four-month reverse-torque assessment, 10 implants (3.5%) had failed to osseointegrate and were replaced, corresponding to an early osseointegration success of 96.5%. Because the failed implants were replaced and treatment continued, this value represents early osseointegration rather than final implant survival. All 35 patients subsequently received definitive fixed rehabilitation, with 100% prosthetic success reported at one year. Five provisional prostheses fractured, and complications occurred in a limited number of patients. Bruxism was significantly associated with implant loss (Fisher exact $P = .0002$) [24]. This association is consistent with broader evidence concerning immediate full-arch loading and bruxism as a risk factor for implant loss [25–28]. The STAGE study supports the feasibility of the workflow in a heterogeneous clinical population, including reconstructed arches, but its retrospective, single-arm design does not allow implant survival or complications to be attributed specifically to the stackable guide.

In the four-patient series reported by Cristache et al., all 25 implants survived to one year, and one patient required two unscheduled occlusal adjustments [12]. Although these outcomes are favorable, the small uncontrolled sample does not provide a reliable estimate of complication rates. Taken together, the available studies indicate that immediate provisionalization can be achieved with stackable workflows when appropriate clinical conditions are present. The decision to proceed with immediate loading remains dependent on primary stability, implant distribution, restorative design, occlusion, patient-related risk factors, and clinical judgment.

4.4. Emerging patient-reported outcomes

Patient-reported outcomes have received limited attention in the literature on stackable workflows. De Araújo Nobre et al. prospectively followed 16 patients who received 20 immediately loaded full-arch interim prostheses. Ten rehabilitations were performed using a bone-fixed stackable workflow and ten using freehand surgery followed by photogrammetry [29,30]. OHIP-14 was recorded at 10 days and at two, four, and six months, together with study-specific assessments of comfort and chewing. At six months, the overall mean OHIP-14 score was low, while comfort and chewing received high ratings [29,31].

Interpretation of these findings is limited by the absence of a pretreatment OHIP-14 baseline, incomplete description of allocation between workflows, inclusion of patients treated in both arches, and the descriptive rather than inferential analysis. Two prostheses failed, two implants were lost, and mechanical complications were reported in half of the patients. The study demonstrates that validated patient-reported outcome measures can be incorporated into the assessment of these workflows, but the available data are insufficient to determine whether stackable guidance provides an advantage in oral health-related quality of life.

5. Evidential and Methodological Constraints

5.1. The evidence base remains heterogeneous

The main limitation of the available literature is its methodological and clinical heterogeneity. The 2024 scoping review identified only case reports and case series [4]. More recent studies have added clinical accuracy and outcome data, but most remain small,

retrospective, or uncontrolled [12,13,24,29]. Considerable variation also exists between studies in patient characteristics, treated arch, grafting procedures, guide support and fixation, number of components, guide material, drilling protocol, implant design, loading criteria, operator experience, and outcome assessment. Because many of these variables differ simultaneously, their individual contribution to the reported outcomes cannot be determined with confidence.

Table 1: . Overview of evidence relevant to current stackable-guide practice. For each study, the table presents the comparator, sample size and relevant denominators, follow-up period, accuracy results and reported outliers, measurement method, clustering, and a note on the certainty of interpretation. AI assistance (Claude, Anthropic) was used to format and organize the table. All data were extracted from the cited primary sources and verified by the authors, who take full responsibility for their accuracy.

Study & design	Sample & protocol	Comparator	Follow-up	Accuracy: mean (max / outlier)	Measurement & clustering	Principal limitation & interpretive weight
Lan et al., 2024 [4]; Scoping review	12 case reports/series; 25 patients, 27 arches, 173 implants	None	NA	Accuracy quantified in only 4/12 reports	Descriptive charting	Maps feasibility & design diversity; no prospective comparison — very limited
Cristache et al., 2024 [12]; Case series	4 patients, 25 maxillary implants; pinned tissue/mixed base; no reduction	None	1 yr	0.87 coronal / 2.04 apical / 2.67° (max NR)	Postop CBCT; implant-level	Immediate rehab without reduction feasible; very small, uncontrolled — very limited
Bjelica et al., 2026 [13]; Retrospective	15 patients, 60 implants; bone-supported, pinned, magnetic; with reduction	None	(accuracy endpoint)	1.25° / 0.96 neck / 1.07 apex / 0.37 depth (apex max 2.17)	Postop CBCT superimposition; patient- & arch-level reported	Rigidly bone-fixed protocol; no comparator, single operator, no PROM — limited
Eldabe et al., 2026 [14]; Comparative in vivo (nonrandom, unblinded)	31 patients, 86 implants; stackable subgroup 3 pt / 19 impl; magnetic	3 other static supports	12 mo	Stackable 5.42° / 1.70 coronal / 1.72 apical / 0.26 vertical (highest, P<.001); no group difference in angular/coronal/apical	Digital registration; patient-level averaging (clustering handled)	Tiny stackable subgroup, unblinded, single system — limited, but the only direct comparison
Beretta et al., 2026 [22]; Case series	10 patients, 47 one-piece implants; 'number-guide' registration; immediate loading	None	NR	Deviation magnitudes NR in abstract; greater precision in mandible than maxilla	Number-guide scan-body registration	No comparator; numeric data pending — very limited; proof of concept for accuracy capture
Hameed & Hebeshi, 2023 [17]; Clinical comparison	24 implants; SLM Co–Cr vs DLP resin stackable guides	Metal vs resin (bundled)	NR	Lower coronal/apical/angular with metal	Postop deviation	Small; material & manufacturing method confounded — limited
Tallarico et al., 2024 [18]; in vitro	12 mandibular models; conventional / modular / modular-after-reduction	Conventional guidance	NA	Modular ≈ conventional; fixation & experience affected some deviations	Model-based	Not a clinical outcome study — indirect evidence
Levy-Bohbot et al., 2025 (STAGE) [24]; Retrospective cohort	35 patients, 43 arches, 284 implants; native + grafted bone	None	4 mo (12 mo prosthetic)	40/43 arches same-day loaded; 274/284 osseointegrated (96.5%); 5 provisional fractures	Clinical / reverse-torque; arch-level	Single-arm, heterogeneous cohort — limited
de Araújo Nobre et al., 2025 [29]; Prospective mixed-workflow	16 patients, 20 arches, 80 implants; 10 stackable / 10 freehand + photogrammetry	Freehand + photogrammetry (not inferential)	6 mo	OHIP-14 low at 6 mo; comfort/chewing high; 2 prosthesis & 2 implant failures	OHIP-14; descriptive	No pretreatment baseline, no inferential comparison — limited

Abbreviations: Co–Cr, cobalt–chromium; DLP, digital light processing; NA, not applicable; NR, not reported; OHIP-14, 14-item Oral Health Impact Profile; PROM, patient-reported outcome measure; SLM, selective laser melting.

Direct comparisons with conventional static guidance, dynamic navigation, or freehand implant placement remain limited. Even studies comparing different stackable configurations frequently involve changes in several design variables at the same time [17,32]. This is also evident in the two relevant datasets published in 2026. One study using a rigidly bone-fixed system with magnetic connections reported relatively low placement deviations [13], whereas another study evaluating a magnetically connected stackable system against other guide-support configurations found the highest vertical discrepancy in the stackable subgroup [14]. Although both systems used magnetic connections, their accuracy differed considerably. These findings suggest that connector type alone is unlikely to determine clinical accuracy. At present, the evidence is insufficient to establish the general superiority of bone-, mucosa-, or tooth-supported bases, magnetic or mechanical indexing, printed resin or metallic components, or sleeved versus sleeveless guidance.

5.2. Accuracy measures are not interchangeable with clinical success

Coronal, apical, angular, and depth deviations represent different aspects of implant-placement accuracy. Their reported values may also be influenced by the registration method, imaging resolution, implant length, measurement software, and the method used for postoperative assessment, including CBCT, scan bodies, or surface scans. For static computer-assisted implant surgery in general, a safety margin of at least 2 mm from critical anatomical structures has been recommended [1,33], while individual stackable studies have also applied linear and angular acceptance thresholds based on ITI Consensus recommendations [13]. However, stackable-specific reporting standards and clinically validated acceptance thresholds have not yet been established [4].

For this reason, mean placement deviation alone should not be considered a surrogate for clinical success. Mean values may conceal individual outliers and do not directly establish anatomical safety, passive prosthetic fit, or long-term biological outcomes.

The statistical unit used for analysis is another relevant consideration. Multiple implants placed within the same patient or arch are not independent observations. Analyses that treat each implant independently may therefore overestimate statistical precision. Future studies should include patient- and arch-level reporting, account for clustering, define clinically relevant margins prospectively, and document the sequence of potential errors from data acquisition to definitive prosthetic connection.

5.3. Bone-reduction accuracy and indications remain underdeveloped

Bone reduction is an important component of many stackable protocols, but its accuracy has received considerably less investigation than implant-placement accuracy. Most available reports describe the indication for alveolar reduction or the method used to guide it, while relatively few compare the planned reduction surface with the postoperative ridge [4,9,34]. Guided instrumentation may improve control of bur or saw position, but it does not eliminate the possibility of under-reduction, over-reduction, irregular contouring, thermal injury, or extension beyond the planned reduction.

Criteria for determining the required amount of bone reduction are also not standardized. Several factors may influence this decision, including restorative space, soft-tissue thickness, smile line, prosthetic transition-zone position, available bone width, implant trajectory, restorative material, and access for hygiene. At present, prospective evidence linking specific amounts of planned bone reduction with improved patient outcomes is lacking. Bone-reduction guides should therefore be regarded as instruments for transferring a previously established surgical and prosthetic plan rather than as a means of determining how much bone should be removed.

5.4. Cumulative error and intraoperative verification

Transfer errors may arise at multiple stages of the workflow, including acquisition of facial and intraoral records, CBCT imaging, DICOM–STL registration, virtual tooth arrangement, base design, manufacturing, sterilization, guide seating and fixation, component connection, drill–sleeve interaction, osteotomy preparation, implant insertion, abutment seating, and prosthetic indexing. When a common reference base is used throughout the procedure, an error introduced early in the sequence may also affect subsequent components (Figure 1).

Clinical verification is therefore required throughout the procedure. Full seating and stability of the base should be confirmed before fixation and reassessed after extraction and flap elevation. Each subsequent component should engage passively, and the connection interface should remain free of interference. Irrigation and drill access must also be maintained. If the clinical anatomy prevents reliable execution of the planned sequence, modification or discontinuation of the guided protocol may be necessary. Limited mouth opening, increased posterior guide height, bulky components, mobile mucosa, thin or irregular bone, and restricted access for fixation pins may all interfere with execution [4,5,35,36]. Alternative fixation, freehand correction, dynamic navigation, or delayed prosthetic conversion should therefore be considered during preoperative planning as possible rescue options (Figure 2).

5.5. Learning curve, resources, and patient-centered value

Stackable workflows require substantial preparation before surgery. Accurate records, coordinated surgical and prosthetic planning, appropriate design, validated manufacturing procedures, trial assembly, and communication between the clinician and dental laboratory are all required. Operator experience may also influence accuracy in modular guided procedures [18,37].

Additional guide components and fixation devices may increase planning requirements, material use, sterilization procedures, and overall cost. Although reduced chair time and lower treatment costs have been proposed as potential advantages, these claims are currently supported mainly by qualitative observations, as formal time-and-motion and cost-effectiveness comparisons are lacking [4,24,29].

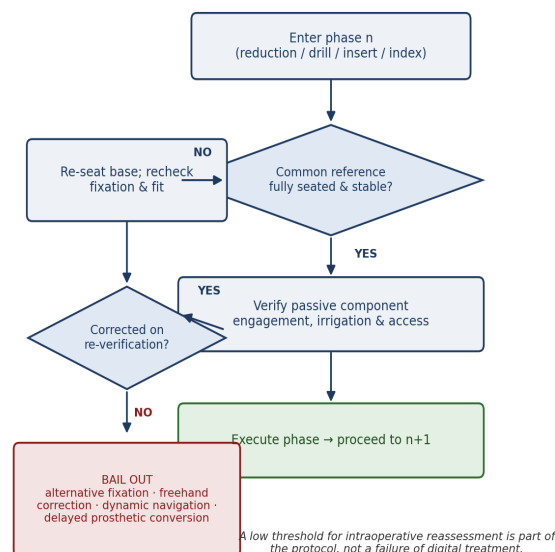
Evidence regarding long-term outcomes is similarly limited. Most published studies focus on implant-placement accuracy, immediate provisionalization, or short-term implant survival. Comparative information regarding definitive prosthesis fit, maintenance requirements, marginal bone changes, peri-implant disease [38], hygiene, speech, esthetic outcomes, complications, and the need for revision remains scarce. Future studies evaluating patient-reported outcomes should include pretreatment baseline measurements, validated instruments, predefined follow-up intervals, and statistical methods that account for repeated measurements and treatment of both arches. Until such evidence becomes available, technical feasibility alone cannot establish a patient-centered advantage.

6. Where This Leaves the Clinician

Based on the available evidence, stackable guides should primarily be considered a method for maintaining a controlled spatial reference throughout full-arch treatment rather than an independent guarantee of placement accuracy. Their clinical value may be greatest when surgical procedures alter the anatomy during treatment and the original prosthetic plan must remain related to bone management, implant positioning, and delivery of a prefabricated provisional restoration. In these situations, maintaining the same reference throughout the procedure may reduce the need for repeated guide repositioning, additional intraoperative records, or extensive modification of the provisional restoration.

Planning should begin with the intended definitive restoration and an independent assessment of whether alveolar reduction is required. The reference base should have a reproducible seating position and adequate fixation while allowing direct clinical verification whenever possible. Component height and insertion paths should be evaluated during digital planning and, when appropriate, verified on a printed model. This is particularly relevant in posterior regions and in patients with limited mouth opening. Manufacturing and sterilization procedures should be validated for the material being used, and the complete assembly should be checked before surgery.

Figure 2: Go/no-go decision and bailout algorithm for each phase of the stackable workflow. AI assistance was used to create the illustration (Claude Opus 4.8, Anthropic). The authors designed, reviewed, and verified the algorithm and take full responsibility for its accuracy and content.



During treatment, progression from one component to the next should depend on confirmation that the common reference remains fully seated and stable (Figure 2). If stability and seating are maintained, the sequential components can transfer the planned relationship from the virtual design through implant placement and provisionalization. If the reference position becomes uncertain, continuing with subsequent components may transfer the discrepancy to later stages of treatment. The reference should therefore be reassessed whenever seating or stability is questionable, and the guided sequence should be modified or discontinued when reliable transfer can no longer be confirmed.

Patients should also be informed about the clinical limitations of the workflow. Stackable guidance may facilitate same-day fixed rehabilitation, but it does not ensure that immediate loading will always be possible or eliminate the risks of implant failure, prosthetic complications, or subsequent maintenance. The decision to proceed with immediate loading remains dependent on primary stability, implant distribution, bone conditions, occlusal risk, and clinical judgment. Based on current evidence, selection of guide support, connection design, and material should be individualized according to the anatomy of the case, verified guide fit, surgical access, instrument compatibility, manufacturing quality, and operator experience. There is currently insufficient evidence to support the universal superiority of any specific configuration.

7. Conclusion

Stackable surgical guides extend static computer-assisted implant surgery by maintaining a common prosthetically planned reference throughout successive stages of full-arch rehabilitation, including bone management, implant placement, and provisional restoration. Clinical studies have reported placement deviations within ranges previously described for static computer-assisted implant surgery. However, the available studies are heterogeneous, generally involve small samples, and provide very limited direct comparative evidence. Consequently, the current data do not demonstrate that stackable systems provide greater placement accuracy than conventional static guidance. In the available controlled comparison, stackable guides did not show superior overall accuracy compared with other static guide supports and presented the greatest vertical discrepancy among the evaluated groups [14].

Current clinical evidence nevertheless indicates that stackable workflows can be used successfully for immediate full-arch provisionalization, including in selected grafted or anatomically complex cases. Published selective-reduction and no-reduction protocols further demonstrate that alveolar reduction is not an inherent requirement of the stackable approach. The primary function of these systems is to maintain and transfer the planned spatial relationship between successive surgical and restorative stages.

The evidence supporting these workflows remains limited by small and heterogeneous clinical studies, infrequent assessment of bone-reduction accuracy, limited comparisons between different system designs, and insufficient information on long-term outcomes, patient-reported measures, treatment time, and cost. Reliable clinical use therefore depends on stable positioning of the reference base and verification of its seating throughout the procedure. Further prospective comparative studies are required to evaluate arch-level placement accuracy, bone-reduction accuracy, definitive prosthetic outcomes, validated patient-reported measures, and workflow costs before the relative advantages of stackable systems or specific design configurations can be established.

Conflicts of interest and sources of funding

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Authors' contribution

Conceptualization, E.A.R. and I.S.; methodology, A.M.C. and E.A.R.; literature search and screening, A.M.C., F.M.T. and A.T.; data curation, F.M.T., A.T. and L.R.; formal analysis, E.A.R., I.S. and E.B.; visualization, A.M.C. and F.M.T.; writing—original draft preparation, E.A.R. and A.M.C.; writing—review and editing, I.S., E.B., L.R., V.D.S., F.M.T. and A.T.; supervision, I.S., V.D.S. and E.B.; project administration, A.M.C. and E.A.R. All authors have read and agreed to the published version of the manuscript.

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Ethics approval and consent to participate

Not applicable

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ADMINISTRATIVE ISSUES

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We strongly recommend, as a condition of consideration for publication, registration in a public trials registry. Trials register at or before the onset of

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- Accessible to the public at no charge;
- Searchable by standard, electronic (Internet-based) methods;
- Open to all prospective registrants free of charge or at minimal cost;
- Validates registered information;
- Identifies trials with a unique number; and
- Includes information on the investigator(s), research question or hypothesis, methodology, intervention and comparisons, eligibility criteria, primary and secondary outcomes measured, date of registration, anticipated or actual start date, anticipated or actual date of the last follow-up, a target number of subjects, status (anticipated, ongoing or closed) and funding source(s).

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All figures, images, and tables should be original and acknowledged as such by the authors. However, if figures, images, or tables from other sources are included, the copyright must be obtained from the authors of the original article, and proof of the copyright waiver must be provided to the Editors of RJMM. In case of any uncertainty regarding the copyright, the Editors may request the authors to remove from the article certain figures/tables/images.

Generative AI use

The journal requires a statement from the authors confirming that no generative AI tools were used to produce the articles. Still, if AI tools have been used to generate the main text, then this aspect should be clearly disclosed in the acknowledgments, specifying the purpose, specific areas of use, and acknowledging that the final responsibility for the text remains with the authors.

Committee on Publication Ethics

The Journal subscribes to the principles of the Committee on Publication Ethics (COPE).

MANUSCRIPT CATEGORIES AND SPECIFICATIONS

All articles, except for Editorials, must contain an abstract of no more than 200 words. Abstracts for original articles should be formatted as detailed in the Word form. Titles must not be longer than 120 characters (including spaces). In every article, there must be three to ten pertinent keywords specific to the article yet reasonably common within the subject discipline.

Editorials

These are invited by the Editor-in-Chief or their delegated editor and should be a brief review of the subject concerned, with reference to and commentary about one or more articles published in the same issue of RJMM. Editorials are generally 1200–1500 words, may contain one table or figure, and cite up to 15 references, including the source article. This should be cited as Rom. J. Mil. Med. (year); (vol): [issue].

Review Articles

RJMM welcomes reviews of important topics across the scientific basis of medicine and advances in clinical practice. Most published reviews are in response to the editorial invitation, including thematically related “miniseries” of reviews. Authors considering submitting a review for RJMM are advised to canvas their possible review with the Editor-in-Chief or a colleague editor; this avoids early rejection if the subject matter is not deemed a high priority for the Journal at the time of submission. Reviews are suggested to limit to 3500–5000 words, with an abstract of up to 200 words and up to 100 references and figures or tables.

Meta-Analyses or Systematic Reviews

RJMM particularly welcomes the submission of Meta-Analyses and Systematic Reviews, which underpin evidence-based medicine. Guidelines for the preparation of meta-analyses and Systematic Reviews are similar to other reviews, and articles are subject to the usual peer review process. Meta-analyses and Systematic Reviews are suggested to be limited to 3500–5000 words, with an abstract of up to 200 words and up to 100 references and figures or tables.

Original Articles (including clinical trials)

RJMM welcomes original articles concerned with clinical practice and research in the fields of medicine. Papers can cover the medical, surgical, radiological, pathological, biochemical, physiological, ethical, and/or historical subject areas. Clinical trials are afforded expedited publication if deemed suitable. RJMM also deals with the basic sciences and experimental work, particularly that with clear relevance to disease mechanisms and new therapies. Original articles are suggested to be limited to 3000 words, with an abstract of up to 200 words and up to 100 references and figures or tables.

Education and Imaging

The Editors welcome contributions to the Education and Imaging section. The purpose is to present imaging for the evaluation of unusual features of common conditions or the diagnosis of unusual cases. Contributions will be reviewed by the Executive Editors. The format of the Images pages involves two parts, each of which will occupy up to one journal page. In Part 1, a case will be described briefly, including a summary of the presentation, clinical features, and key laboratory results. One to two key images will then be presented. It is helpful to the reader if the author responds to questions that follow from the images of the case, such as ‘What is your diagnosis? What are the features indicated on the CT scan? What is the differential diagnosis?’ Part 2 will briefly describe the imaging features, particularly those that lead to a diagnosis or are critical for management. Differential diagnosis should be mentioned. It will be useful to include either further images or pathological details that validate the imaging diagnosis. Occasionally, the presentation of analogous cases or related images from a similar case might be appropriate.

Please include between one and three references to definitive studies and appropriate reviews of the subject. The format of the Images page involves a brief background and description of the disorder of interest, together with two figures of high quality. Colored photographs are encouraged. The submission may take the form of a case report or may illustrate particular features from more than one patient.

MANUSCRIPT PREPARATION

Style

Manuscripts should follow the style of the Vancouver agreement detailed in the International Committee of Medical Journal Editors’ revised ‘Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, as presented at <http://www.ICMJE.org/>.

Spelling

The journal uses US spelling and authors should, therefore, follow the latest edition of Merriam-Webster’s Collegiate Dictionary.

Units

All measurements must be given in SI units as outlined in the latest edition of Units, Symbols, and Abbreviations: A Guide for Biological and Medical Editors and Authors (Royal Society of Medicine Press, London).

Abbreviations

Abbreviations should be used sparingly and only where they ease the reader’s task by reducing the repetition of long technical terms. Initially, use the word in full, followed by the abbreviation in parentheses. Thereafter, use the abbreviation.

Trade names

Trade names should not be used. Drugs should be referred to by their generic names, rather than brand names.

Parts of the Manuscript

The manuscript should be submitted in separate files: the title page and the main text file according to the Word model.

Title page

The title page should contain (i) a short informative title that contains the major keywords. The title should not contain abbreviations; (ii) the full names of the authors (if possible, not more than 5 authors per title); (iii) the author’s institutional affiliations at which the work was carried out; (iv) the full postal and email address, plus telephone number, of the author to whom correspondence about the manuscript should be sent; (v) disclosure statement; and (vi) acknowledgments. The present address of any author, if different from that where the work was carried out, should be supplied in a footnote.

Disclosure statement

The source of financial grants and other funding should be acknowledged, including a frank declaration of the authors’ industrial links and affiliations. In the case of clinical trials or an article describing the use of a commercial device, therapeutic substance, or food must state whether there are any potential conflicts of interest for each of the authors: failure to make such a statement may jeopardize the article being sent out for peer review.

Acknowledgments

The contribution of colleagues or institutions should also be acknowledged. Thanks to anonymous reviewers are not allowed.

Main text

As papers are double-blind peer-reviewed, the main text file should not include any information that might identify the authors. The main text of the manuscript should be presented according to the word model. Figures and supporting information should be submitted as separate files. Footnotes to the text are not allowed, and any such material should be incorporated into the text as parenthetical matter.

Abstract and keywords

Original articles must have a structured abstract that states in 200 words or fewer the purpose, basic procedures, main findings, and principal conclusions of the study. If appropriate, divide the abstract with the headings: Background and Aim, Methods, Results, and Conclusions. The abstracts of reviews need not be structured. The abstract should not contain abbreviations or references. Three to ten keywords should be supplied below the abstract and should be taken from those recommended by the US National Library of Medicine’s Medical Subject Headings (MeSH) browser – <http://www.nlm.nih.gov/mesh/meshhome.html>.

Text

Authors should use the word form when editing the submitted material.

References

The Vancouver system of referencing should be used. In the text, references should be cited using Arabic numerals in square parentheses in the order in which they appear. If cited only in tables or figure legends, number them according to the first identification of the table or figure in the text. In the reference list, the references should be numbered and listed in order of appearance in the text. Cite the names of all authors when there are six or fewer; when seven or more, list the first three followed by et al. Names of journals should be abbreviated in the style used in MEDLINE. References to unpublished data and personal communications should appear in the text only.

Use Index Medicus as the style guide for references and other journal abbreviations.

Always insert the DOI of the article, if available.

Tables

Tables should be self-contained and complement, but not duplicate, the information contained in the text. Number tables consecutively in the text in

Arabic numerals. Type tables on a separate page with the legend above. Legends should be concise but comprehensive – the table and legend must be understandable without reference to the text. Column headings should be brief, with units of measurement in parentheses; all abbreviations must be defined in footnotes. Footnote symbols: †, ‡, •, * should be used (in that order) and *, **, *** should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings.

Figure legends

Type figure legends on a separate page. Legends should be concise but comprehensive – the figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement. Indicate the stains used in histopathology. Identify statistical measures of variation, such as standard deviation and standard error of the mean.

Figures

All illustrations (line drawings and photographs) are classified as figures. Figures should be numbered using Arabic numerals and cited in consecutive order in the text. Each figure should be supplied as a separate file, with the figure number incorporated in the file name.

Preparation of Electronic Figures for Publication:

Although low-quality images are adequate for review purposes, publication requires high-quality images to prevent the final product from being blurred or fuzzy.

SUBMISSION REQUIREMENTS

Manuscripts should be submitted online at office@rjmm.ro. A cover letter containing an authorship statement should be included. The cover letter should include a statement covering each of the following areas:

- Confirmation that all authors have contributed to and agreed on the content of the manuscript, and the respective roles of each author. It is not accepted that the idea of equal contribution.
- Confirmation that the manuscript has not been published previously, in any language, in whole or in part, and is not currently under consideration elsewhere.

- A statement outlining how ethical clearance has been obtained for the research, particularly concerning studies involving human subjects and animal experimentation.

The institutional ethics committees approving this research must comply with acceptable international standards (such as the Declaration of Helsinki), and this must be stated.

- For research involving pharmacological agents, devices, or medical technology, a clear Conflict of Interest statement about any funding from or pecuniary interests in companies that could be perceived as a potential conflict of interest in the outcome of the research.

- For clinical trials, these have been registered in a publicly accessible database (see more under 'ETHICAL CONSIDERATIONS (Further Information)' later in these guidelines).

If the above items are not included in the cover letter, manuscripts cannot be sent for review. Please also note that the cover letter does not require a detailed or lengthy description of the content or structure of the manuscript itself.

Two Word files need to be included upon submission: A title page file and the main text file that includes all parts of the text in the sequence indicated in the section 'Parts of the manuscript', including tables and figure legends but excluding figures, which should be supplied separately.

The main text file should be prepared using the Word model that is to be found on the web page (<https://revistamedicinamilitara.ro/author-submission/>).

Each figure should be supplied as a separate file, with the figure number incorporated in the file name. For submission, high-resolution figures (at least 300 d.p.i.) saved as .eps, .jpg, or .tif files are required.

PUBLICATION PROCESS AFTER ACCEPTANCE

Accepted Articles

Accepted Articles are published online after final acceptance, and appear in PDF format only.

Proofs

Once the paper has been typeset, the corresponding author will receive an email alert containing the proof of acceptance. It is therefore essential that a working e-mail address is provided for the corresponding author.

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