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ORIGINAL ARTICLES

The value of lipid profile in asthma-obstructive sleep apnea overlap

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Abstract: *The asthma obstructive sleep apnea overlap is a clinical entity relatively new and the association with a dysfunctional plasma lipid profile is not known.*

Aim. In this study, we compared the serum lipid profile in asthma-obstructive sleep apnea overlap syndrome to those in asthma and obstructive sleep apnea patients.

Methods. A cross-sectional study of 97 cases of which 26 patients had only asthma, 51 were diagnosed with OSA, and 20 were identified with A-OSA overlap. The lipid profile included the total cholesterol, HDL-cholesterol, triglycerides, the LDL-cholesterol. The Casteli indexes I and II and the atherogenic plasma index were calculated.

Results. The patients with asthma- obstructive apnea overlap were older (55.55 years vs 53,73 years in obstructive sleep apnea and 51,04 years in asthmatics), mostly obese (95%), and had a significantly higher average of BMI (38.11 vs. 35.64 and 28.8, respectively). Asthma- obstructive apnea overlap was at higher risk of cardiovascular disease than asthmatics, in respect to the lipid profile: the levels of HDL-cholesterol were lower, triglycerides were higher, and the values of Castelli index I and II were higher.

Conclusions. Based on our results, we confirm that age and BMI contribute to the risk of A-OSA overlap. The major differences in the common markers of the serum lipid profile are lower HDL-C and higher triglycerides. As a clinical implication, both Castelli indexes could provide additional value for cardiovascular risk and should be monitored in A-OSA overlap.

Keywords: *asthma, obstructive sleep apnea, HDL-cholesterol, triglycerides*

INTRODUCTION

The number of studies describing the asthma-obstructive sleep apnea overlap (A-OSA overlap), also known as "asthma-obstructive sleep apnea phenotype" is constantly increasing. The prevalence of obstructive sleep apnea (OSA) in asthmatic patients ranges from 19-60%. The prevalence is higher in older patients, with more than 10 years duration of asthma, in poorly controlled and in obese asthmatics [1, 2].

There is also a higher risk for the development of asthma in obese OSA patients. The coexistence of asthma in OSA aggravates the desaturation during the night [3].

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A pro-atherogenic serum lipoprotein profile in OSA, reported by many studies [4, 5], and broadly accepted is dyslipidemia, one of OSA's comorbidities [6, 7]. There is some clinical evidence that dyslipidemia improves after CPAP therapy [7]. The metabolic effects and, particularly, the lipid profile in asthma are less investigated. However, a systematic review showed an increased level of LDL-cholesterol in this category of patients [8].

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As more and more cases of A-OSA overlap are reported, the alterations of the lipid profile become more suggestive for additional cardiovascular comorbidity. In this respect, we developed a study to compare the serum lipid profile in patients with asthma-obstructive sleep apnea overlap syndrome compared to asthma and OSA, as a unique diagnosis.

METHODS

An observational, cross-sectional study was conducted in two Romanian centers from Bucharest and Constanta city.

From March to June 2019, patients with occupational asthma, that agreed to participate, were screened by Stop Bang and Epworth testing in the Clinic Department of Occupational Diseases in Colentina Hospital of Bucharest. Those asthmatics, with high scores, underwent a polygraphy test. OSA's diagnosis was based on apnea-hypopnea index (AHI) higher than 5/h.

The Constanta group of patients, previously diagnosed with asthma, were investigated by a similar methodology for OSA's diagnosis, in the Sleep Laboratory of Constanta Clinic Pneumophthisiology Hospital.

The study was approved by the Ethic Committee of the Constanța Clinic Pneumophthisiology Hospital.

Both research teams recorded data about demographics (age, sex), the body mass index (BMI), fasting glycemia, total cholesterol, triglycerides, high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels. BMI was calculated by dividing weight by the height squared. The current smoking habit was assessed. If the cessation of smoking was more than 1 year long, the subject was classified as a former smoker.

The blood profile of total cholesterol, triglycerides, and HDL-c cholesterol was directly measured by standardized methods, while LDL-C was calculated according to the Friedewald formula: LDL-C = TC − HDL-C − (TG/5).

The Castelli risk index I was computed by the ratio of total cholesterol/HDL-cholesterol. The risk values for primary prevention were considered (e.g. >5 for men and >4.5 for women) [9]. For the LDL-C to HDL-C ratio (Castelli risk index II), the levels associated with high were higher than 3.5 in men and 3 in women [9].

Atherogenic plasma index, as the cut-off for the cardiovascular diseases risk, was considered the logarithm of the ratio triglycerides/HDL-cholesterol higher than 0.5.10

Consolidated data were processed in a StatPLus for Mac software. Numerical data were compared by Kruskal Wallis test, while categorical ones required a Chi-square test. Regression was used to verify the relationship between variables. For the statistical significance, the threshold was set to estimate a 95% probability.

RESULTS

Among 97 cases, mean aged 53.38±6.76-year-old, mostly males (n=67), 26 patients had only asthma, 51 were diagnosed with OSA, without having a personal medical history of asthma, 20 were identified with A-OSA overlap, which made a point prevalence of asthma inside all OSA patients of 28.17%.

The main characteristics of these groups are presented in Table 1.

Table 1: Main characteristics of the patients

	All (mean ± SD)	**Asthma** (mean ± SD)	**OSA** (mean ± SD)	**Asthma-OSA overlap** (mean ± SD)
Age (years)*	53.38 ± 6.76	51.04 ± 4,87	53.73 ± 7.52	55.55 ± 6.16
Gender (F/M)*	30/67	13/13	12/39	5/15
Smoking (% active smokers/total)	17.53%	19.23%	23.53%	0%
BMI (kg/m^2)**	34.29 ± 7.06	28.8 ± 4.99	35.64 ± 6.59	38.11 ± 6.53
Total cholesterol (mg/dL)	210.78 ± 50.44	208.04 ± 28.27	207.82 ± 59.71	221.3 ± 43.66
HDL-cholesterol (mg/dL)**	50.2 ± 18,84	66.95 ± 25.76	44.42 ± 12.36	47.05 ± 13.44
LDL-cholesterol (mg/dL)	126.59 ± 42.99	116.9 ± 29.62	127.1 ± 51.22	135.5 ± 29.61
Triglycerides mg/dL)*	158.95 ± 142.03	122.45 ± 92.33	187.1±193.22	172.19 ±114.21
Castelli 1 index (TC/HDL)**	4.86 ± 2.8	3.51 ± 1.32	5.32 ± 3.27	5.14 ± 2.26
Castelli 2 (LDL/HDL)**	2.83 ± 1.4	2.04 ± 0.97	3.05 ± 1.53	3.12 ±1.18
API	0.48 ± 0.41	0.35 ± 0.31	0.6 ± 0.52	0.49 ± 0.32
Fasting glycemia (mg/dL)	118.06 ± 43.82	102.8 ± 16.5	125.65 ± 52.26	106.35 ± 18.62

*OSA = obstructive sleep apnea; F=female; M=male; BMI = body mass index; HDL cholesterol = high density lipoprotein cholesterol; LDL cholesterol = low density lipoprotein cholesterol; API= atherogenic plasma index; *statistically significant difference between all groups (p<0.05); ** high statistically significant difference*

between all groups (p<0.01)

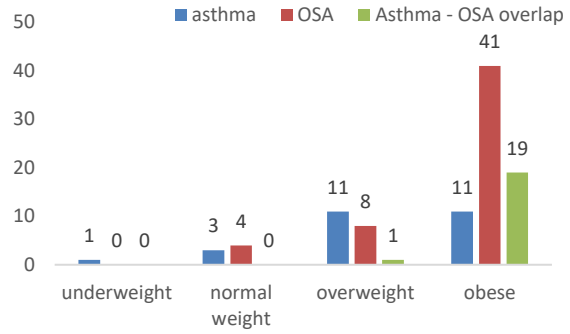
Most patients were in their 5th and 6th decade of age. The asthma-OSA association was significantly reported in the oldest patients than in the asthma group (H= 5.31, p = 0.02).

There was also a male predominance in the OSA group and A-OSA.

There was no difference by gender distribution between asthmatics and patients with A-OSA overlap (chi2 = 3.59, p=0.058).

The majority of patients were obese (73%) or overweighting (21%), especially in the A-OSA overlap group (38.11±6.53), with major differences among groups according to BMI categories (42% obese, 42% overweight, 12% normal weight, and 4% underweight, among asthmatics, compare to A-OSA overlap group with 95% obese and 5% overweight). The prevalence of obesity in the OSA patients was an intermediary between the prevalence encountered in the asthmatics and A-OSA overlap group (Figure 1).

Figure 1: Distribution of cases according to diagnosis and BMI categories



OSA= obstructive sleep apnea

Concerning smoking status, the highest percentage of active smokers was in the OSA group (23.53%), followed by 19.23% in asthmatics. However, this difference was not significant (chi2 =0.18, p=0.66).There were no active smokers in A-OSA overlap.

There was a direct correlation between BMI and triglycerides blood levels (Rho = 0.48, p=0.0001) and a reverse, significant correlation with HDL-C (Rho= -0.28, p=0.007).

The serum LDL-C showed no relation with BMI. However, the differences between groups maintained their statistical significance independent of the BMI.

The lipid profile was dominated by a high level of triglycerides and a low level of HDL-C in OSA and A-OSA overlap as compared to the asthma group.

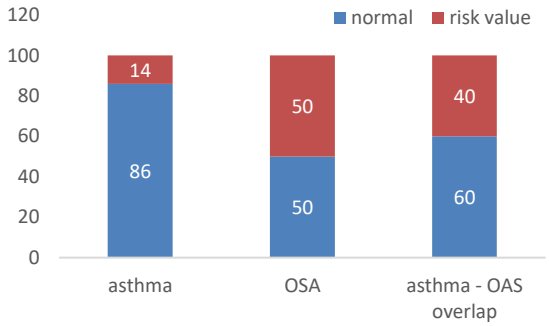
The LDL-C had the highest values in A-OSA-overlap.

The triglycerides and LDL-C were significantly higher in A-OSA overlap as compared to asthma (H=3.98, p=0.04, and H=4.52, p=0.03, respectively) while the HDL-C was significantly lower (H=8.31, p=0.003).

No significant differences were noted between the triglycerides, the LDL-C and HDL-C serum levels in OSA and A-OSA overlap (H=0.02, p=0.89; H=0.75, p=0.38, and H=0.25, p=0.62, respectively).

The average Castelli index was in the risk range values both in OSA and in A-OSA overlap groups. When measured individually, a few asthmatics had risk values than OSA patients. The highest percentage of risk values was found in the A-OSA overlap group (Figure 2).

Figure 2: Distribution of the Castelli index I among the patients with asthma, obstructive sleep apnea, and asthma-obstructive sleep apnea overlap



OSA= obstructive sleep apnea

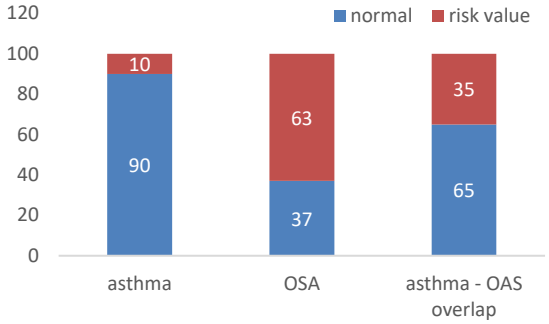
The number of patients with abnormal Castelli index in A-OSA overlap was higher than in the asthma group, but without statistical significance (chi2 =3.77, p=0.05), as the risk distribution between OSA and A-OSA overlap (chi2 = 0.21, p=0.65).

The majority (90%) of asthmatics had the ratio LDL/HDL in the normal values range.

The higher level of risk, according to this index, was among OSA patients, without significant difference compare to A-OSA overlap (chi2 = 0.02, p=0.89), as well as between asthma and A-OSA overlap (chi2 = 1.32, p=0.25) (Figure 3).

The percentage of patients with atherogenic plasma index (API) >0.5 was almost equally distributed among groups; 33% in asthma, 37% in OSA, and 38% in A-OSA overlap (chi2 =0.88, p=0.64). However, there is a significant difference between the API values in asthma as compared to the OSA group (H=3.89, p=0.04).

Figure 3: Distribution of the Castelli index II among the patients with asthma, obstructive sleep apnea and asthma-obstructive sleep apnea overlap



OSA= obstructive sleep apnea

DISCUSSION

In this study, we report differences in the serum lipid profile between asthma, OSA, and the co-existence of these two clinical entities referred to as asthma-obstructive sleep apnea overlap. The main findings are higher risk values for the Castelli index I and II in patients with A-OSA overlap compare to asthma patients.

Patients with A-OSA overlap were older, mostly obese (95%), with a significantly higher average BMI. These findings are from previous literature data [1, 2, 11]. The progression to A-OSA overlap requires a longer duration of time [12], considering the convergent effect of prolonged persistent chronic airways inflammation and aging.

Obesity contributes as well to the inflammatory status and increases the collapsibility of the upper airways and it is commonly accepted as a major risk factor for OSA [13]. In what concerns asthma, obese patients are reporting more severe symptoms, have a greater prevalence of co-morbidities [14], and a higher number of hospitalizations due to exacerbations [15]. The risk for A-OSA overlap might increase by higher corticoid doses that contribute to the deposition of fat in the neck region [1], another cause of upper airways resistance. OSA could be an explanation, as CPAP therapy in these patients reduces asthma reported symptoms [16].

Between the three groups, and between asthma and A-OSA overlap, the most significant difference in the serum lipid profile concerns the HDL-C. The presence of OSA seems to be the most important factor, as patients in this group had a lower blood level of HDL-C. Several studies have found the same reduction in HDL-C levels in OSA [4]. In asthma, a meta-analysis revealed no association between asthma and HDL-C levels in adults, but an increase in the LDL-C [17]. These studies support our hypothesis that the reduction in HDL-C levels in A-OSA overlap is mainly a consequence of the intermittent hypoxia related to chronic nocturnal repeated desaturation. As the A-OSA overlap is a relatively newly described entity, we could not directly compare our results with other studies. To the best of our knowledge, neither Medline nor Scopus databases give any result of a study specifically looking to this relation.

Despite the reproducible association in large cohorts of the increased cardiovascular risk related to low HDL-C level, the current clinical guidelines did not found enough evidence that raising HDL-C in serum would be of any benefit for these patients [18].

The latest evidence shows that not only the quantity but also the type of HDL particulate matters. The HDL particles are very heterogeneous and carry more functions than reverse cholesterol transport. Apolipoprotein A I and A-II are the major protein components in HDL. The HDL particle also contains a variety of lipids (phospholipids, cholesterol, in not esterified or esterified forms, and triglycerides) according to the maturation stage. It is a plasma vehicle for many other biologically active molecules, such as fat-soluble vitamins, steroid hormones, bile acids, bioactive lipids, haptoglobin, α-1 antitrypsin, transferrin, micro RNA) [19] and enzymes with antioxidant properties that would protect for reactive oxygen species and reactive nitrogen species damaging the endothelium [20]. To assure the esterification of the cholesterol, HDL contains lecithin cholesterol acyltransferase (LCAT) and to exchange esterified cholesterol and triglycerides with other lipoproteins, cholesteryl ester transfer protein (CEPT) [21].

The nomenclature of the HDL-C varies according to the method utilized for detection, and the degree of correspondence is far from perfect [22], leading to some confusion in the interpretation of results coming from different studies. Briefly, HDL is synthesized in the liver and the small intestines [23] as lipid poor preβ-HDL (the nascent HDL). In peripheral tissues, including macrophages foam cells, this particle interacts with ATP-binding cassette transporter A1 (ABCA1) to initiate the reverse transport of cholesterol to the liver and transforms to small HDL. Esterification of cholesterol inside the small HDL by LCAT and the exchange of esterified cholesterol with triglycerides from VLDL, IDL, and LDL-C, via the CEPT, end up in the formation of the mature HDL-C particle (the large HDL). Finally, HDL binds to the HDL receptor in the liver, and, through endocytosis, it is removed from circulation [24]. The triglyceride content of HDL promotes its clearance [23]. This permanent exchange, between the lipoproteins, in the bloodstream, influences the types of HDL particles in circulation.

In theory, both small and large particles might point towards a certain risk: the predominance of the small ones could show an ineffective/diminished potential for reverse cholesterol transport, while the predominance of the large ones could indicate a high burden of cholesterol in blood circulation. In epidemiological studies, a high level of large HDL seems to be protective for atherosclerosis [25], while, in already confirmed cardiovascular disease, high levels of small HDL are found [26] with a certain positive prognosis potential [27].

The techniques used to define the types of HDL particles are currently available mainly for research purposes, although their clinical value in assessing the risk and adapting therapy is of major value. Without this availability, different ratios of the commonly determined plasma lipoproteins and lipids were proposed to better characterize the atherogenic risk.

The estimation of the particle size is partially fulfilled by the API and the 2 Castelli indexes.

API was initially described to assess the atherogenic risk. Indeed, high levels were found in apparently healthy individuals in correlation with other biochemical markers of subclinical vascular diseases [28-29] and it was increased in subjects with cardiovascular disease compared to healthy controls [30, 31]. However, this marker was not confirmed as a predictable tool for stroke prediction [32]. In our study, the API did not have a discriminative value between the 3 groups. As there is no other study to compare with, this result should be cautiously interpreted and further investigated.

The Castelli risk I was a better estimation of the cardiovascular risk than individual lipoprotein particles measurement in the initial large cohort studies, as the Framingham study or the LRCP one [9], reflecting mostly the particles are responsible for the peripheral transport of cholesterol (the LDL and VLDL). It was, later, related to insulin resistance [33]. Even in normal weighted subjects, this marker had significant prognostic value for cardiovascular disease [34]. Castelli risk I show a direct relationship with the large HDL particles and indirect relation with the HDL 2b (small particles) and the small LDL [35].

Castelli index II describes the ratio between the HDL and LDL particles and is generally well associated with the Castelli index I and non-HDL cholesterol. It has been also used to differentiate the risk of atherosclerosis in chronic renal disease [36] or metabolic syndrome [37].

It is important to notice a high negative correlation between BMI and HDL with HDL-C in our study population. This finding is important, because, in certain circumstances, as in a chronic, persistent, inflammatory milieu that characterizes obesity, HDL particles become dysfunctional, losing their capacity for cholesterol efflux, and their anti-inflammatory and antithrombotic potential [38]

The low HDL-C and the high-risk Casteli index were not influenced by smoking, as all the A-OSA overlap patients were non-active smokers. It is assumed that, after smoking cessation, an improvement of the serum lipid profile manifests, mainly, on the elevation of HDL-C [39]. Even if the smoking effects would have been present, it was probably opposed by other pathogenic mechanisms. The groups of asthma and OSA had similar numbers of active smokers. Therefore, even if a certain influence of smoking on the lipid profile cannot be excluded, the significant difference in HDL-C noted between the groups should have another explanation.

We are aware of certain limitations of this study. Respiratory nocturnal polygraphy might underestimate the number of OSA patients inside the asthma population, because the majority of respiratory events are hypopneas, with arousals, that are more accurately counted only by polysomnography study [11]. Even so, the asthma patients were actively interviewed for OSA –related symptoms and none of them would clinically qualify for the diagnosis.

Another limitation of our study consists in the moderate number of patients, but from the perspective of no existing studies, we do consider that these results should be shared with the research community to promote further investigation in this domain. Despite these limitations, the results presented from this study add valuable information for the domain and substantiate the need for larger studies.

CONCLUSION

Based on our results, we confirm that age and BMI contribute to the risk of A-OSA overlap.

The major differences in the common markers of the serum lipid profile are lower HDL-C and higher triglycerides. As a clinical implication, both Castelli indexes could provide additional value for cardiovascular risk and should be monitored in A-OSA overlap.

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