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Lipid profile after long term APAP in
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Lipid profile afer long term APAP in
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Lipid profile after long term APAP in OSA patients

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Sandra Rebelo e Sousa

Aos meus pais, Helena e José

Ao meu irmão, Miguel

Ao meu marido, Miguel

Às minhas filhas, Inês e Joana

A todos aqueles que me ajudaram nesta aventura

Lipid profile after long term APAP in OSA patients

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Abstract

Purpose This study aimed to explore the impact of an 8 year therapy with autoadjusting positive airway pressure (APAP) on fasting lipid level in a sample of Portuguese moderate/severe OSA patients. Besides contributing to the comprehension of the complex relationship between dyslipidemia and OSA, it provided new data regarding the effectiveness of a long term APAP treatment.

Methods Thirty-nine male patients with moderate to severe OSA were included in the study. APAP was prescribed to all patients. Fifteen patients were under lipid-lowering medication throughout the study and another fifteen patients never used lipid-lowering medication at any time during the study. Fasting morning venous blood samples were collected at three time points (baseline, 6 months and 8 years) and lipids were estimated. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 21.0 software.

Results After 8 years of APAP treatment, patients presented a similar body mass index but a significantly less severe daytime sleepiness. Patients on lipid-lowering medication exhibited a higher reduction in LDL-c, triglycerides and total cholesterol than those naïf from that medication, but the reduction was not statistically significant after adjusting for medication and APAP adherence.

Conclusions Long-term APAP treatment improves OSA but does not seem to contribute to changes in fasting lipids.

Keywords

Autoadjusting positive airway pressure, obstructive sleep apnea, cholesterol, HDL, dyslipidemia, statins

Introduction

Obstructive sleep apnea (OSA) is one of the most important medical conditions identified in the last 50 years, and it has been defined as a respiratory disorder with cardio-metabolic implications [1, 2].

Although it occurs in all age groups, it is most often found among 40-60 years old and according to a recent study [3] the prevalence rates in the middle-aged adults have risen substantially in recent decades (13% of men and 6% of women have moderate to severe sleep disordered breathing).

Besides OSA is a common disorder, it is a major cause of morbidity and significant cause of mortality [4-8] and the most common cause of daytime sleepiness [9, 10].

Patients with OSA have higher cardiovascular risk than general population [11] and cumulating evidence over the years has been shown the complex relationship between OSA and cardiovascular risk factors including obesity, hypertension, insulin resistance, impaired glucose tolerance and dyslipidemia, which together comprise the metabolic syndrome [12, 16]. OSA has also been shown to be independently associated with atherosclerotic disease [17].

OSA patients have an increased risk of proatherogenic dyslipidemia [11, 18], which is, frequently associated with reduced high-density lipoprotein cholesterol (HDL-C) and raised triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C) and total cholesterol plasma levels [19, 20]. Although a cut clean causal relationship between OSA and dyslipidemia is yet to be established, growing body of evidence and underlying mechanisms have been proposed suggesting a strong association [15].

Continuous positive airway pressure (CPAP) is the standard option for treatment of OSA [21, 22]. It eliminates upper airway narrowing, reduces daytime sleepiness, increases alertness and improves quality of life [23]. Moreover, CPAP also was shown to reduce cardiovascular morbidity through alterations of each of the components of metabolic syndrome [14, 16, 24]. Auto-adjusting positive airway pressure (APAP) devices are an alternative treatment to traditional CPAP and are able to improve symptoms [25] with the advantage of increasing long-term treatment compliance [26]. However, the impact of APAP treatment on lipid profile of OSA patients is far from being ascertained. Not only the studies are inconsistent but also they are limited in duration of follow-up [14, 16, 22, 24, 27-35].

The study here proposed aims to evaluate the long term APAP impact on lipid profile in a convenience Portuguese sample of patients with moderate/severe OSA diagnosed, treated and followed for the last 8 years.

Methods

Study design

This is a prospective observational study. Written informed consent was obtained from each participant. The study protocol was approved by the Hospital Ethics Committee and performed accordingly in agreement with the Helsinki Declaration of 1975, as revised in 1983.

Subjects

Thirty nine male patients, referred to our Sleep Disordered Breathing Outpatient Clinic, 8 years ago with newly diagnosed moderate/severe OSA (AHI > 15 events/h), confirmed previously [31] by domiciliary cardio-respiratory sleep study, were included in the study. Fifteen patients have been using lipid-lowering medication throughout the study (from baseline up to 8 years) and another fifteen patients never used lipid-lowering medication at any time point during the study. Seven patients were not on lipid-lowering medication at the beginning or at 6 months of the study but started the medication after. Two were on lipid-lowering medication but discontinued medication over time.

Exclusion criteria were established previously: neoplastic diseases, systemic inflammatory chronic diseases, active infectious diseases, systemic long-term corticotherapy and weight loss greater than 10%.

Body mass index (BMI) was calculated by the formula weight/height².

Study procedures

The patients here included have been on APAP therapy (REMstar™ Auto, Respiroics Inc., Murrysville, PA, USA) during the past 8 years. APAP therapy was prescribed to all patients with a pre-determined minimum and maximum pressure of 4 and 18 cmH₂O, respectively. Concerning therapy effectiveness, a periodic every six-month follow-up was conducted, with evaluation of clinical symptoms (by Epworth sleepiness scale (ESS)) and APAP compliance variables (number of hours per night, percentage of total days of APAP usage, residual Apnea Hypopnea Index (AHI) based on objective data downloaded from APAP memory cards.

Adherent patients were those using positive airway pressure therapy for ≥ 6 h per night and for ≥ 20 of the last 28 nights based on the usage data from memory cards [36].

Fasting morning venous blood samples were collected at three time points: in untreated patients at baseline, after 6 months of treatment and after 8 years of treatment. Blood samples were collected between 8 and 10 a.m. after a 12 hours period of fasting. Blood samples were immediately sent to the laboratory for estimation of lipids level (HDL-c, LDL-c, triglycerides and total cholesterol,). Indicators of “abnormal” levels were defined using the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) criteria [37] : HDL-c <40 mg/dL; LDL-c ≥ 130 mg/dL; triglycerides ≥ 150 mg/dL and total cholesterol ≥ 200 mg/dL.

Statistical analysis

Data analysis was performed using the Social Sciences (SPSS Inc., Chicago, Illinois, USA), 21.0 software version. All probabilities were two-tailed and p values <0.05 were regarded as significant.

Data were described as mean and standard deviation (SD) for quantitative variables. For comparison of quantitative variables the Student's t test and Mann-Whitney test were used. The Chi-square test or the Fisher exact test used to compare categorical variables whenever was appropriate. For comparison between median values at the three moments studied the non parametric Wilcoxon test for paired samples was used.

Associations between the use of lipid-lowering medication and number of hours per night of APAP usage were assessed using multivariate general linear regression model.

Results

Thirty-nine male voluntary patients ($n=39$) participated in the study. All of them had moderate-to-severe OSA at the beginning of the study (baseline; $n=4$ moderate OSA; $n=35$ severe OSA). Overall studied population characteristics at baseline are presented in Table 1.

After 8 years of APAP treatment the group mean age was 64.36 years (SD = 9.57 years), with ages ranging between 38 and 81 years old. Characteristics of participants considering body mass index (BMI), use of lipid-lowering medications, ESS, AHI and therapy adherence at baseline and after 8 years are shown in Table 2.

The severity of day time sleepiness (evaluated by ESS) was significantly decreased after 8 years of APAP usage (11.0 versus 2.6; $p<0.01$).

Although the percentage of total days of APAP usage did not significantly differ between 6 months and 8 years, there was a significantly increased in the number of hours/night of APAP usage between both

groups. The mean number of hours/night of APAP usage at 6 months was 6.15 (± 1.31) with a minimum and maximum hours/night of 3.05 and 8.23, respectively. At 8 years the mean number of hours/night of APAP usage was higher amounting 7.10 (± 1.00) with a minimum and maximum hours/night of 4.55 and 9.11, respectively.

During the 8 years of APAP treatment, patients had their HDL-c levels decreased from 0.50 g/dL (SD 0.1 g/dL) at baseline to 0.46 g/dL (SD 0.1 g/dL; $p < 0.01$) after 8 years. Similarly, both triglycerides (TG) and total cholesterol levels also decreased significantly [1.70 g/dL (SD 0.7 g/dL) versus 1.40 g/dL (SD 0.8 g/dL); $p = 0.04$ and 2.00 g/dL (SD 0.5 g/dL) versus 1.69 g/dL (SD 0.3 g/dL); $p < 0.01$, respectively], although no changes were observed regarding LDL-c levels [1.08 g/dL (SD 0.4 g/dL) versus 0.99 g/dL (SD 0.3 g/dL); $p = 0.17$]. At baseline, 17 patients were under lipid-lowering medication and that number increased up to 22 patients at 8 years.

We next evaluate the variation of HDL-c, LDL-c, TG and total cholesterol levels along time using two subgroups: those since the beginning of the study were under lipid-lowering medication ($n = 15$) and those that never used any lipid-lowering medication ($n = 15$). We observed that there was a statistically significant reduction in the LDL, TG and total cholesterol levels among those who were under lipid-lowering medication that was not shown in the other group (Table 3).

In order to understand if this reduction could be explained by the use of lipid-lowering medication alone and/or by the use of APAP we performed a multivariate general linear model analysis (Table 4). After adjustments, the results suggest that those patients who did lipid-lowering medication throughout 8 years exhibited a higher reduction in total cholesterol levels than those who did not but the reduction was not statistically significant. In addition, the higher number of hours/night APAP usage indicated that there was an increase in the levels of HDL-C but again no significant association was found.

Discussion

OSA is increasingly considered as a risk factor for metabolic disturbances, such as dyslipidemia [11, 18]. Several observational and uncontrolled clinical studies allege an improvement of the metabolic variables, lipids included, through the use of positive airway pressure [24, 31, 38-40]. These investigators reported a small, but statistically significant change in the lipid profile of OSA patients, hence beneficial effects of CPAP treatment in selected patient cohorts cannot be excluded.

However, only a limited number of clinical randomised controlled trials (RCTs) have until now evaluated the effect of CPAP on lipids [22, 28, 32, 41-43]. Of these six, only one [32] found significant reductions in total cholesterol and triglycerides. Curiously, none of the others RCTs have examined lipids as a primary outcome. Phillips et al. calculated means of seven blood samples during 24 hours, whereas other authors used standard fasting lipid tests. Sharma et al. [44] conducted a randomised controlled crossover trial, showing decreases in cholesterol, but it was retracted.

The main goal of the present study was to investigate the effect of long-term APAP treatment on lipid profile of moderate-to severe OSA patients.

Although a significant reduction in triglycerides and total cholesterol levels was found among the overall sample, between baseline and 8 years, this reduction could not be directly attribute to long-term APAP usage since some of the patients were under lipid-lowering drugs. These drugs are most effective in dyslipidemia treatment and, conceivably, could mask the effect of OSA on fasting lipids, but no studies have shown whether these pharmacotherapeutic approaches are equally efficacious in patients with OSA. Indeed, when comparing two subgroups of patients, those who have been always on lipid-lowering drugs and those that never did this medication, the statistically reduction in triglycerides and total cholesterol levels is most likely accounted for by the treated subgroup. Evidently, the majority of patients not under lipid-lowering treatment do not have dyslipidemia and, in the few with abnormal lipids, we could not observe any differences in lipid changes at 8 years (data not shown). It is important to mention, that only five patients started *de novo* lipid-lowering medication during the study and the variation of dyslipidemia

did not concur with the inaugural institution of lipid-lowering medications. Also noteworthy are the additional positive airway pressure benefits related to neurocognitive and sleepiness improvements that we are not aware any lipid-lowering medication could provide. Ultimately, the best scenario would be to perform this analysis in OSA untreated dyslipidemic patients but it would be unethical to deliberately prevent these patients from its treatment.

Nonetheless, after adjustments for all relevant covariates (lipid-lowering drugs and APAP adherence), we were not able to discriminate a statistically significance that could explain the reduction in triglycerides and total cholesterol in the patients under lipid-lowering medication. In fact, it seems that lipid-lowering drugs could not per se explain the changes observed on triglycerides and total cholesterol. We have to consider the size of our sample and other covariates not taken in account that may justify this outcome. This is also valid for the adjustment using number of hours/night of APAP. Although it was observed that lipid-lowering medicated patients used more hours/night of APAP we can always speculate that these are more aware of their disease and thus more adherent to treatment. APAP better usage could not also explain the lipid effect.

Several studies have associated OSA with a decrease in HDL-c [30, 45, 46]. HDL is anti-atherogenic and has anti-oxidant, anti-inflammatory and anti-coagulant properties [47] but may become pro-oxidant and pro-inflammatory under special circumstances [48, 49]. Tan et al. [50] have shown that the increase in oxidative stress in subjects with OSA is associated not only with increased lipid peroxidation but is also associated with HDL dysfunction, which may in part contribute to the increased cardiovascular risk of these subjects. We found out that there is a significant decrease on HDL-c levels despite the use of lipid-lowering drugs after long-term APAP, although after multivariate analysis it seems to have a trend of increase in the most adherent patients.

Since our population is heterogeneous regarding age, marital status, socioeconomic status and psychological factors it does not seem possible that these variables can interfere in the results obtained.

It is known that the pattern of adherence to positive airway pressure therapy is established as early as 3 days following CPAP initiation and predicts long-term use [51]. In addition, it is possible that the compliance here observed might be related to the symptomatic severity expressed initially, which is known to be a stronger support to influence adherence [52, 53]. Moreover, this outcome does not seem to be related to weight since we could not observe any effect of long-term APAP in BMI. Contrary to other recent studies [35, 54], where adherent patients had an average increase in BMI of 1 kg.m^{-2} over follow-up, we could not observe an increase in our patients BMI. It has been suggested that OSA patients have an increase in their energy expenditure and that positive airway pressure reduces this expenditure, by an unclear mechanism [54, 55]. Not only did they not increase in weight but also the reduction of OSA severity does not seem to be related to weight loss, as observed by Teramoto et al. [56].

Our study has strengths and some limitations. To the best of our knowledge this is the longest study to date exploring the relationship between APAP long-term therapy and fasting lipids in a moderate-to-severe OSA population. The moderate-to-severe OSA Portuguese patients here used were a male Caucasian heterogeneous population that we would expect to be similar to others of similar ethnicity throughout the world. We could not exclude the possibility that results may be different depending on the ethnicity. Moreover, results only reflect a male moderate-to-severe OSA population. It is known that the influence of sex is particularly important given the higher cardiovascular risk associated with lipidemia in females and it would be interesting to study the potential of sex to modify the effect. The here used sample is small and we recognise the potential for presently unknown or unmeasured confounders to influence the results. Although the blood samples were collected after a 12 hours fasting period we could not control the effect of meal composition the day before the blood samples were collected. It is also arguable to use only one time period to perform the blood collections, a calculated means of several blood samples would be better but would be time consuming and not appreciated by the patients. A possible limitation is that it was not a randomized controlled trial, but such a study is not easy to perform since it would be unethical to leave patients with confirmed OSA and dyslipidemia untreated.

Though a direct cause and effect relationship between OSA and dyslipidemia is yet to be established, there is a significant and growing body of evidence that a strong association exists [15] (Adedayo et al., 2012). Simultaneously, our data is in keeping with a very recently published study [35] (Keenan et al., 2014) where it was shown that positive airway pressure does not significantly affects fasting lipid levels after 2 years APAP treatment. To clarify the actual impact of positive airway pressure on total cholesterol and other lipids, large RCTs with carefully selected patients are warranted.

In summary, long-term APAP treatment improves OSA but does not seem to contribute to changes in fasting lipids.

Conflict of interests: there is no financial or personal relationship with other people or organisation that could inappropriately influence this work.

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Table 1: Sample characteristics at baseline

VARIABLE*	BASELINE	<i>n=39</i>
AGE (years)	56.4 (9.57)	
BMI (kg/m ²)	33.6 (5.20)	
ESS	10.6 (6.00)	
AHI (events/h)	51.9 (19.6)	
SMOKING HABITS <i>n</i> (%)		
NON-SMOKERS	18 (46.2)	
FORMER SMOKERS	18 (46.2)	
SMOKERS	3 (7.70)	

BMI body mass index, *ESS* Epworth sleepiness scale, *AHI* apnea/hypopnea index

* Quantitative variables are expressed as mean and standard deviation (SD)

Table 2: Sample characteristics at the three evaluated stages: baseline, 6 months and 8 years

VARIABLE*	BASELINE	6 MONTHS	8 YEARS	<i>p</i> value	n=39
BMI (kg/m ²)	33.6(5.2)	--	33.0(4.6)	0.36	
ESS	11.0(6.0)	--	4.6(3.2)	0.00**	
AHI (events/h)	52.6(19.4)	--	2.6(1.3)	0.00**	
TOTAL DAYS APAP USAGE (%)	--	94.9(12.1)	98.3(3.1)	0.11	
APAP HOURS PER NIGHT	--	6.23(1.23)	7.09(1.0)	0.00**	
HDL-C	0.50(0.1)	--	0.46(0.1)	0.01**	
LDL-C	1.08(0.4)	--	0.99(0.3)	0.17	
TOTAL CHOLESTEROL	2.00(0.5)	--	1.69(0.3)	0.00**	
TG	1.70(0.7)	--	1.40(0.8)	0.04*	

BMI body mass index, *ESS* Epworth sleepiness scale, *AHI* apnea/hypopnea index, *APAP* autoadjusting positive airway pressure, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglycerides * Quantitative variables are expressed as mean and standard deviation (SD) **p < 0.01 *p < 0.05

Table 3: Baseline and 8 years characteristics of patients under lipid-lowering drugs and patients without lipid-lowering drugs treatment within the sample

VARIABLE*	LIPID-LOWERING DRUGS			NO LIPID-LOWERING DRUGS		
	n=15			n=15		
	MEAN(SD) BASELINE	MEAN(SD) 8 YEARS	<i>p value</i>	MEAN(SD) BASELINE	MEAN(SD) 8 YEARS	<i>p value</i>
HDL-C	0.53(0.19)	0.47(0.13)	0.039*	0.45(0.67)	0.43(0.77)	0.049*
LDL-C	0.93(0.32)	0.84(0.29)	0.397	1.23(0.31)	1.10(0.30)	0.222
TOTAL CHOLESTEROL	1.86(0.44)	1.57(0.28)	0.008**	2.02(0.40)	1.77(0.32)	0.031*
TG	1.75(0.82)	1.48(0.99)	0.191	1.67(0.69)	1.39(0.85)	0.125
BMI (kg/m ²)	33.3(4.02)	31.9(3.54)	0.038*	34.0(6.20)	33.2(4.67)	0.334
AHI (events/h)	42.4(16.0)	2.66(1.49)	0.001**	58.4(21.9)	2.36(1.19)	0.001**

Wilcoxon Signed Ranks Test (non-parametric test) *BMI* body mass index, *ESS* Epworth sleepiness scale, *AHI* apnea/hypopnea index, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, TG triglycerides * Quantitative variables are expressed as mean and standard deviation (SD) **p < 0.01 *p < 0.05

Table 4: Differences in 8-year fasting lipid changes after adjustment for lipid-lowering medication and number of hours/night of APAP. Data collected after a multivariate general linear model analysis

VARIABLE	LIPID LOWERING DRUGS						APAP					
	NON-ADJUSTED			ADJUSTED			NON-ADJUSTED			ADJUSTED		
	MEAN DIFFERENCE	95% CI	<i>p</i> <i>value</i>	MEAN DIFFERENCE	95% CI	<i>p</i> <i>value</i>	MEAN DIFFERENCE	95% CI	<i>p</i> <i>value</i>	MEAN DIFFERENCE	95% CI	<i>p</i> <i>value</i>
HDL-C	0.03	-0.33 0.10	0.30	0.03	-0.02 0.12	0.37	-0.04	-0.17 0.09	0.51	-0.04	-0.16 0.13	0.57
LDL-C	0.04	-0.25 0.32	0.79	-0.01	-0.29 0.28	0.94	-0.24	-0.73 0.26	0.35	-0.23	-0.75 0.27	0.35
TC	0.09	-0.47 0.66	0.73	0.11	-0.45 0.68	0.69	-0.69	-1.80 0.33	0.18	-0.68	-1.71 0.36	0.19
TG	0.23	-0.66 0.52	0.12	0.19	-0.10 0.50	0.19	-0.29	-0.84 0.26	0.29	-0.26	-0.80 0.29	0.34

HDL-C high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TC* total cholesterol, *TG* triglycerides, *95%CI* confidence interval at 95%; mean difference negative values indicate an increase

Agradecimentos

Esta tese é o corolário de uma aventura que começou há 6 anos atrás e jamais teria visto a luz do dia se não fosse a teimosia e persistência da minha amiga Joana Gomes. Foi a Joana que insistiu para que concorresse a Medicina. A ideia só não me pareceu péssima porque coincidiu com uma fase de algum desalento na minha vida profissional. Sempre desejei ser cientista mas naquele Agosto de 2008 a ciência não me retribuía como até então e encontrava-me desanimada. Na realidade, a medicina não fazia parte do meu pensamento, não era um sonho por realizar, não era uma ambição de futuro, mas concorri!

É claro que se não fosse o entusiasmo da Dr^a Eugénia Mota da Divisão Académica da FMUP não teria conseguido ter os documentos que precisava para concorrer. Se não fosse a D^a Leonor da Direcção da FMUP a avisar-me que a entrevista, que fazia parte do concurso, iria ter lugar dali a 5 minutos, jamais me lembraria e teria continuado a dissecar embriões nessa tarde. A medicina continuava tão distante que o resultado do concurso saiu e nem fui ver. O destino trouxe-me a novidade pela mão da Joana, já as aulas tinham começado, tinha de ser!

Pensei fazer duas unidades curriculares por ano mas fiquei contaminada com a alegria, boa disposição, garra e amizade dos garotos do meu curso, pelo que tratei de correr a maratona com eles e foi um prazer. Agradeço especialmente à amizade genuína do João Barreto, da Joana Queiroz Machado, Sofia Novo e, daquele com quem fazia revisões nas horas que antecediavam cada exame, o Rui Loureiro. Um obrigada grande aos meus companheiros de gabinete que sempre me proporcionaram um ambiente agradável, aos regentes das unidades curriculares que leccionei nestes 6 anos, à minha ex-directora de serviço Professora Deolinda Lima por acreditar que conseguiria conciliar a vida profissional com a de estudante. À Ana Tavares por estar sempre presente quando mais precisava.

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Tenho que agradecer imenso à minha família por todo o apoio e ajuda que me deram. Foram sem dúvidas os maiores sacrificados desta minha loucura. Sem vocês, a vida não seria o doce que é, eu não seria quem sou! Adoro-vos!

Anexo - Normas de Publicação da Revista Sleep and Breathing

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