Long-term positive airway pressure therapy is associated with reduced total cholesterol levels in patients with obstructive sleep apnea : data from the European Sleep Apnea Database (ESADA)

Longterm positive airway pressure therapy is associated with reduced total cholesterol levels in patients with obstructive sleep apnea: Data from the European Sleep Apnea Database (ESADA)

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Abstract:

Background and aim:

Obstructive sleep apnea (OSA) is an independent risk factor for dyslipidemia. The current study examined the effects of positive airway pressure (PAP) treatment on lipid status in the European Sleep Apnea Database (ESADA).

Methods:

The prospective cohort study enrolled 1564 OSA subjects (74% male, mean age 54±11y, body mass index (BMI) 32.7±6.6 kg/m^2 and apnea-hypopnea index (AHI) 40.3±24.4 n/h) undergoing PAP therapy for at least 3 months (mean 377.6 ± 419.5 days). Baseline and follow-up total cholesterol (TC) from 9 centers were analyzed. Repeated measures and logistic regression tests (adjusted for age, sex, change in weight, lipid lowering medication, PAP compliance and treatment duration) were used for comparing the changes in TC levels. Incident risk for coronary heart disease events (CHD) was calculated according to the Framingham CHD risk score (estimated from age, BMI, blood pressure, and TC).

Results:

Adjusted means of TC decreased from 194.2 mg/dl to 189.3 mg/dl during follow-up (p=0.019). A clinically significant (10%) reduction of TC at PAP follow-up was observed in 422 patients (27%). Duration of PAP therapy was identified as independent predictor for TC reduction, which implies an approximately 10% risk reduction for incident CHD events (from 26.7% to 24.1% in males, from 11.2% to 10.1% in females, p<0.001 respectively).

Conclusion:

The present study demonstrates a significant decrease in TC after long-term PAP treatment. Based on the close association of elevated TC levels with increased CV mortality, identification and treatment of OSA may have beneficial effects on overall cardiovascular risk.

Keywords: cholesterol, hypoxia, positive airway pressure, sleep apnea, cardiovascular risk

Short title: PAP effects on lipids in obstructive sleep apnea

Background

Obstructive sleep apnea (OSA) is a common sleep disorder with a prevalence of 20% in male and 10% in female adults. [1] Repetitive episodes of partial or complete upper airway obstruction during sleep with this condition may result in intermittent hypoxia which promotes oxidative stress, systemic inflammation and endothelial dysfunction. [2] OSA is recognized for its association with metabolic dysfunction and increased cardiovascular mortality.[3, 4] Treatment with positive airway pressure (PAP) was demonstrated to eliminate OSA and to provide protective effects with regard to both all-cause and cardiovascular mortality in clinical cohorts of patients with severe OSA. [5]

In previous studies of the ESADA cohort, we identified OSA as an independent predictor of dyslipidemia. In particular, measures of nocturnal hypoxia like the oxygen desaturation index (ODI) demonstrated a strong linear relationship with elevated total- and LDL-cholesterol and reduced HDL-cholesterol concentrations as well as the diagnosis of hyperlipidemia.[6, 7] However, previous studies examining the effect of PAP treatment on lipid status showed rather conflicting results. In a meta-regression analysis examining 1,958 OSA subjects from 29 observational studies, an improvement of lipid profile was reported for total-, LDL- and HDL-cholesterol. [8] In contrast, a recent review of randomized controlled PAP treatment trials in OSA reported no significant effects on lipid status. Although most controlled studies were rather small sized and of short duration, this points to the importance of control of confounding factors on top of PAP treatment.[9]

The European Sleep Apnea Database (ESADA) is a multicenter, multinational cohort including patients with suspected OSA from sleep laboratories across Europe. The aim of the current analysis was to examine the relationship between lipid concentrations and hypoxia in OSA subjects undergoing PAP therapy. As lipid status is an important parameter for the different prediction models of coronary heart disease (CHD) risk, we aimed to investigate the effect of PAP treatment on such computed CHD risk estimates. It was hypothesized that OSA treatment by PAP results in a significant reduction of serum cholesterol and triglyceride concentrations which subsequently modify the calculated incident risk for coronary heart disease (CHD).

Methods

Subjects and settings

The detailed description of the ESADA cohort has been published elsewhere.[10] In short, the ESADA gathers data from 30 sleep centers distributed across 20 countries in Europe and Israel. For the current analysis, which included only patients on PAP treatment for at least 3 months and with lipid samples at both baseline and at the PAP follow up visit. Data from 1,564 patients (aged 18 and 80 years inclusive) representing 9 different centers from South, Central and North European regions were included. The analyzed data included anthropometrics, daytime symptoms, smoking, alcohol consumption, medical history and medication. Venous blood samples were collected at each center for assessment of lipid profile at baseline and follow up. [10] Patient and physician-reported comorbidities like cardiovascular disease, metabolic disease including diabetes mellitus, hyperlipidemia and hyperuricemia were captured in detail. Daytime sleepiness was quantified by the Epworth sleepiness scale (ESS) score.[11] Lipid modifying agents were defined as those listed within the ATC code C10 ("lipid modifying agents"). Coded data were entered, reported via a web-based system and stored in a central database. The ESADA protocol has been reviewed and approved by the local research ethics committee at each participating center and written informed consent was obtained from all included patients**.** The current study consists data from ESADA database sampled between years 2007-2016.

Sleep study

A total of 854 patients (54.6%) were diagnosed with polysomnography (PSG) and the remainder with cardiorespiratory polygraphy (PG, n=710). The sleep studies were conducted in accordance with local practice at each center and manual edition of the data was applied. AASM criteria were used during the scoring of PG and PSG studies in the ESADA [12] with further details mentioned elsewhere. [13] Severity of sleep-disordered breathing (SDB) was assessed by computing the apnea-hypopnea index (AHI) and the oxygen desaturation index (ODI). AHI was presented by the mean number of apneas/hypopneas, whereas ODI was defined as the number of transient oxygen desaturations (≥4%) per hour of sleep (PSG) or per hour of analyzed time (PG).[12] Sensitivity analysis examining the potential effects of the

diagnostic methods used (PG or PSG) showed no significant effect in our previous studies about dyslipidemia in OSA. [6, 7]

Assessment of anthropometric measures

Weight and height were assessed with the patient wearing light clothing and no shoes. BMI calculated as the body mass (kilograms) divided by the square of the body height (meters) and presented in units of kg/m^2. Further calculations included the circumferences of neck, waist and hip, as well as the waist-to-hip ratio (WHR).

Calculation of Framingham 10-year Coronary Heart Disease risk score

A sex-specific point score based on categorical values of age, National Cholesterol Education Program (NCEP) [14] total cholesterol, HDL and LDL cholesterols, blood pressure, smoking, and comorbid diabetes was calculated. The scoring sheet is available in the study by Wilson et al. [15] Separate scores were calculated before and during PAP intervention for each subject.

Statistical methods

Severity of OSA was measured categorically according to AHI and ODI quartiles. In the descriptive analysis, central tendency of continuous variables was expressed as means with standard deviations and frequencies of categorical variables were calculated. The unadjusted difference in lipid concentrations between baseline and follow up was measured with the paired t-test method. In order to adjust for important confounders, repeated measures ANOVA test adjusted for age, sex, change in weight, lipid lowering medication use, PAP compliance and duration were used for comparing the changes in total-cholesterol, TG, LDL-cholesterol (Friedewald formula [16]), HDL-cholesterol concentrations and Framingham risk score.[15] The proportion of patients with a clinical meaningful decrease of cholesterol at cut off levels of ≥10% and ≥25% were identified.

All tests were two-tailed and statistical significance was defined at $p \leq 0.05$. Statistical analyses were performed using IBM SPSS Statistics 22.0 (Armonk, NY, USA: IBM Corp.).

Results

Anthropometric data

Our prospective cohort study included 1,564 OSA subjects out of 18,542 subjects registered in ESADA database. Patients had used PAP therapy for at least 3 months and information on total cholesterol data had been identified (including 866 subjects for the fasting TG, 835 subjects for the HDL-C and 828 subjects for the LDL-C analysis). Compared to ESADA patients on PAP therapy but without data on lipid status at follow up (n=1857), patients in the current analysis had similar anthropometric data (age 54 ± 11 vs. 54 ± 11 years, BMI 32.5 ± 6.8 vs. 32.7 ± 6.6 kg/m^2 and 73.5% vs. 74.4% males, all p>0.05) and a slightly more severe sleep apnea (AHI 36.1 ± 25.8 vs 40.3 ± 24.4, p<0.001). Cardiovascular comorbidities were slightly higher in the study population compared with the remaining ESADA cohort **(table 1a)**. At baseline, 25.4% OSA subjects received lipid lowering medication. During follow-up, change in lipid lowering medication treatment was reported in 3.1% subjects as lipid lowering medication was initiated in 38 patients and stopped in 11 patients. A weight reduction at follow-up was observed in 37.8% and weight gain in 44.9% of subjects. A significant weight reduction of ≥ 10% was observed in 4% of patients. Continuous positive airway pressure (CPAP) therapy was the dominant PAP modality (n=1,016, 64.8%), followed by auto-titrating positive airway pressure (n=468, 29.9%) and bilevel positive airway pressure (n=80, 5.1%) treatment. Mean treatment duration was 377.6 ± 419.5 days with a mean daily PAP use of 5.3 ± 2.0 hours. In addition, **table 1b** shows the characteristics of patients using (n= 397) and not using lipid lowering medication (n=1,167). Medication users were significantly older, had slightly more central obesity and showed higher rates of comorbidities compared with subjects not using lipid lowering medication.

Table 1a. Comparison of baseline characteristics of the analysis population (n=1564) and excluded subjects from ESADA cohort on PAP treatment with missing lipid analysis (n=1587). Despite similar anthropometric and lipid profiles between two groups; the analysis population had higher rates of cardiovascular comorbidities, more severe sleep apnea, longer use of PAP treatment.

		Analysis population (n=1564)	ESADA patients on PAP treatment without lipid analysis (n=1587)	Between group statistics
Age (year)		53.9 ± 10.7	53.9 ± 11.9	0.87
Sex (males) %		74.4	73.5	0.31
BMI (kg/m^2)		32.7 ± 6.6	32.5 ± 6.8	0.72
Waist-to-hip ratio*		0.99 ± 0.08	0.98 ± 0.08	0.001
Diabetes mellitus, % *		20.9	14.1	<0.001
Arterial hypertension, % *		48.3	44.5	0.03
Lipid lowering medication, % *		25.4	21.9	0.006
Ischemic heart disease, % *		10.6	8.6	0.02
Transient ischemic attack, %		2.9	2.9	0.92
Smokers, %		23.3	20.7	0.09
Alcohol (units) *		3.5 ± 7.1	5.1 ± 8.6	0.001
Baseline total cholesterol (mg/dl)		200.1 ± 43.8	198.2 ± 41.6	0.254
Baseline HDL cholesterol (mg/dl)		45.1 ± 13.3	46.4 ± 14.5	0.162
Baseline LDL cholesterol (mg/dl)		122.3 ± 38.7	121.0 ± 37.2	0.659
Baseline triglycerids (mg/dl)		178.9 ± 104.0	174.4 ± 106.5	0.259
ESS score *		10.1 ± 5.1	11.2 ± 5.4	<0.001
AHI (n/h) *		40.3 ± 24.4	36.1 ± 25.8	<0.001
AHI classes, % *	Mild	13.3	19.0	<0.001
	Moderate	29.2	26.2	
	Severe	57.5	54.8	
ODI (n/h)		32.6 ± 25.0	30.7 ± 25.8	0.14
Mean SaO_2, n (%)*		92.3 ± 4.0	92.7 ± 3.0	0.005
Lowest SaO_2, n (%)		77.8 ± 10.1	78.5 ± 9.4	0.14
Time spent SaO_2< 90% (min) *		50.6 ± 79.0	61.5 ± 82.4	0.013
PAP adherence (>4 h/day) n (%)*		81.6	67.5	<0.001
PAP use/day (hours) *		5.31 ± 1.98	4.39 ± 2.52	<0.001
PAP duration (days) *		377.6 ± 419.5	250.8 ± 322.5	<0.001
Change in weight during follow-up (kg)		-0.2 ± 6.1	-0.3 ± 7.9	0.93

*Parameters with p value <0.05 **Variables expressed as percentage or mean ± standard deviation

Abbreviations:

BMI: body mass index; ESS: Epworth sleepiness score; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; SaO_2: arterial oxygen saturation; CPAP: continuous positive airway pressure; PAP: positive airway pressure

Table 1b. The baseline characteristics of the study population under lipid lowering medication (n=297) compared with patients not using lipid lowering medication (n=1167). The subjects under lipid lowering medication were older, had higher rates of comorbidities, higher LDL-cholesterol CHD risk scores and lower cholesterol levels.

		Lipid lowering medication		P value
		Users (n=397)	Non-users (n=1167)	
Age (year) *		59.2 ± 9.3	52.2 ± 11.5	<0.001
Sex (males) %		74.7	74.2	0.78
BMI (kg/m2)		32.8 ± 6.4	32.5 ± 6.9	0.245
Waist-to-hip ratio *		1.00 ± 0.08	0.98 ± 0.08	<0.001
Diabetes mellitus, % *		33.2	12.0	<0.001
Arterial hypertension, % *		68.8	39.2	<0.001
Ischemic heart disease, % *		27.9	4.2	<0.001
Transient ischemic attack, % *		7.4	1.5	<0.001
Smokers, % *		10.8	15.7	0.004
Alcohol (units)		4.9 ± 8.3	4.4 ± 7.9	0.177
Baseline total cholesterol (mg/dl) *		177.6 ± 41.2	208.0 ± 41.9	<0.001
Baseline HDL cholesterol (mg/dl) *		43.5 ± 10.7	45.8 ± 13.2	0.011
Baseline LDL cholesterol (mg/dl) *		98.7 ± 34.8	130.7 ± 37.1	<0.001
Baseline triglycerids (mg/dl)		178.4 ± 102.5	178.2 ± 105.2	0.979
Baseline CHD risk score in males (cholesterol points)		25.7 ± 16.2	26.1 ± 16.5	0.641
Baseline CHD risk score in males (LDL-cholesterol points) *		27.8 ± 16.7	25.7 ± 16.9	0.029
Baseline CHD risk score in females (cholesterol points)		12.1 ± 8.2	11.2 ± 8.6	0.069
Baseline CHD risk score in females (LDL-cholesterol points) *		14.0 ± 9.7	12.5 ± 9.9	0.007
ESS score *		10.0 ± 5.0	11.0 ± 5.0	<0.001
AHI (n/h)		36.8 ± 24.4	38.3 ± 26.1	0.138
AHI classes	**mild**	17.7	14.9	0.092
	moderate	27.3	28.2	
	severe	55.0	56.9	
ODI (n/h)		31.6 ± 24.5	31.3 ± 26.1	0.787
Mean SaO2, n (%)		92.4 ± 3.0	92.6 ± 3.6	0.277
Lowest SaO2, n (%)		77.7 ± 9.4	78.4 ± 9.9	0.091
Time spent SaO2< 90% (min)		58.4 ± 83.9	54.5 ± 79.7	0.436
CPAP adherence (>4 h/day) n (%)		75.1%	74.5%	0.77
PAP use/day (hours)		4.9 ± 2.4	4.8 ± 2.3	0.277
PAP duration (days)		310 ± 357	303 ± 332	0.646

Change in weight during follow-up (kg)	0.2 ± 8.5	-0.4 ± 7.7	0.086

*Parameters with p-value<0.05 **Variables expressed as percentage or mean ± standard deviation

Abbreviations:

BMI: body mass index; ESS: Epworth sleepiness score; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; SaO_2: arterial oxygen saturation; CPAP: continuous positive airway pressure; PAP: positive airway pressure

Lipid status at PAP follow up

In the unadjusted analysis, a significant improvement of the lipid status with a reduction of total- and LDL-cholesterol, a reduction in triglycerides and an increase of HDL cholesterol was observed following PAP treatment **(table 2)**. In repeated measures ANOVA, after adjustment for age, sex, lipid lowering medication, change in weight, PAP compliance and duration, total cholesterol concentration significantly decreased by 4.9 mg/dl after PAP therapy (p=0.019) **(figure 1)**. In the sub-cohort analysis, adjusted LDL cholesterol and HDL concentrations tended to improve, but the changes did not reach statistical significance after adjustment for confounding factors. Triglycerides remained unchanged after PAP treatment. A ≥10% decrease in cholesterol levels (applied as a clinically relevant modification), was found in 27% of the study population. Furthermore, in 5.5% of subjects, a profound reduction of at least 25 % in total cholesterol was found. OSA patients with profound reduction in cholesterol were under either no lipid lowering medication treatment or the same initial treatment. There was no significant difference in baseline and follow up cholesterol levels between North and South European Regions. However, there was a significant difference between the change in cholesterol following PAP treatment, with patients in the North regions demonstrating a higher reduction in cholesterol compared with the South region (-6,44±33,05 vs -2,21±32,63; p=0.028).

Table 2. The unadjusted pairwise comparison of lipid concentrations

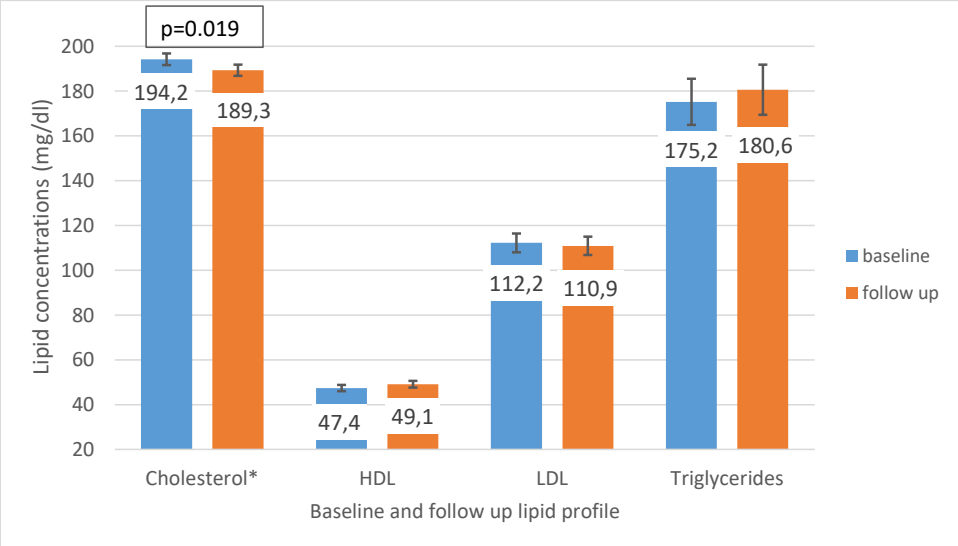
	N	Baseline Mean ± SD	Follow-up Mean ± SD	Mean Difference ± SD	95% CI	p-value
Total cholesterol *	1564	200.3 ± 43.8	195.7 ± 42.0	-4.58 ± 33.75	-6.26 ; -2.91	<0.001
HDL cholesterol *	835	45.3 ± 12.7	46.5 ± 13.7	1.30 ± 9.87	0.63 ; 1.97	<0.001
LDL cholesterol# *	828	121 (51)	120 (51)	-1.0 (30.85)	-4.35 ; -0.14	<0.001
Triglycerides	866	178.3 ± 104.5	173.7 ± 104.8	-4.28 ± 90.43	-8.78 ; 0.21	0.062

* Parameters with p value < 0.05,**All parameters expressed in mg/dl

#Median (IQR) values are expressed for LDL cholesterol

In the subsequent sensitivity analysis, the adjusted mean for total cholesterol was analyzed for subgroups defined by sex, smoking status, concomitant lipid lowering medication, comorbidities, long term PAP use and low versus high PAP compliance **(table 3)**. The decrease in cholesterol was less pronounced in patients with comorbidities like diabetes (p<0.001) and ischemic heart disease (p=0.057). However, 47.5% subjects with diabetes had lipid lowering medication use. Although subjects without lipid lowering medication demonstrated a significant reduction in cholesterol, the mean follow-up cholesterol concentrations were higher than subjects using lipid lowering medication (202.1 ± 41.3 mg/dl vs 178.5 ± 39.6 mg/dl).

Figure 1. Pairwise comparisons in lipid profile in regression model adjusted for age, sex, lipid lowering medication, change in weight, PAP compliance and duration



**Parameters with p<0.05, **all values expressed as mean ± SD (mg/dl)*

In univariate analysis, the change in total cholesterol correlated with age (r=0.065, p=0.01), PAP duration (r= -0.071, p=0.005) and partially with mean overnight oxygen saturation (r= -0.047, p=0.06) but not with measures of obesity, weight change, sleep apnea frequency or the degree of intermittent nocturnal hypoxia. A multivariate linear regression model for defining independent predictors of change in total cholesterol concentrations after PAP treatment was built and adjusted for the statistically significant parameters in univariate analysis and t-test. In the adjusted regression analysis, duration of PAP treatment was the only independent predictor for a reduced cholesterol concentration whereas comorbid diabetes and drug treated hyperlipidemia were associated with an increase in total cholesterol concentrations **(table 4)**. Furthermore, duration of PAP treatment was the only variable associated with a pronounced reduction (≥25%) of total cholesterol (p=0.003).[17] Additionally, the change in total cholesterol significantly correlated with change in LDL cholesterol (r=0.842, p<0.001).

Table 3. Independent t-test demonstrating the difference for the change in cholesterol by categorical variables. The decrease in cholesterol was less pronounced in patients with comorbidities like diabetes (p<0.001) and ischemic heart disease (p=0.057).

		n	Change in total cholesterol (mg/dl) (±SD)*	Mean difference (mg/dl) (95%CI)	P value
Sex	Male	1163	-4.46 ± 32.80	-0.48 (-4.31, 3.36)	0.81
	Female	401	-4.94 ± 36.41		
Smoking	Smokers	365	-5.46 ± 33.67	1.16 (-2.81, 5.10)	0.57
	Non-smokers	1199	-4.32 ± 33.78		
Lipid lowering medication use *	Users	397	0.47 ± 36.68	-6.77 (-10.84, -2.69)	0.001
	Non-users	1167	-6.30 ± 32.53		
PAP duration	≥365 days	590	-6.80 ± 36.70	3.56 (-0.02, 7.13)	0.051
	<365 days	974	-3.24 ± 31.77		
PAP compliance	≥ 6 hours/day	783	-4.67 ± 33.93	0.17 (-3.18, 3.52)	0.92
	<6 hours/day	781	-4.50 ± 33.59		
Arterial Hypertension (AHT)	AHT (+)	755	-3.61 ± 35.08	-1.84 (-5.21, 1.50)	0.27
	AHT (-)	804	-5.47 ± 32.50		
Ischemic heart disease (IHD)	IHD (+)	166	0.14 ± 37.84	-5.27 (-10.71, 0.16)	0.057
	IHD (-)	1393	-5.13 ± 33.23		
Transient ischemic attack (TIA)	TIA (+)	45	-0.13 ± 32.53	-4.57 (-14.59, 5.45)	0.37
	TIA (-)	1514	-4.70 ± 33.81		
Diabetes mellitus (DM) *	DM (+)	327	1.10 ± 35.94	-7.17 (-11.28, -3.07)	0.001
	DM (-)	1232	-6.07 ± 33.03		

* Parameters with p value < 0.05, **Change in total cholesterol was calculated as follow-up cholesterol-baseline cholesterol concentrations

Abbreviations: PAP: positive airway pressure; AHT: arterial hypertension; IHD: ischemic heart disease; TIA: transient ischemic attack; DM: diabetes mellitus

Table 4. Multivariate linear regression model with independent predictors of change in total cholesterol concentrations after PAP treatment (n=1559) adjusted for age, lipid lowering medication, PAP duration and diabetes

Predictors	β	Std. Error	CI (95%)	P value
Lipid lowering medication use (yes/no) *	4.82	2.08	0.74, 8.90	0.021
Diabetes mellitus (yes/no) *	4.67	2.20	0.36, 8.98	0.034
Duration of PAP (months) *	-0.16	0.06	-0.28,- 0.04	0.011

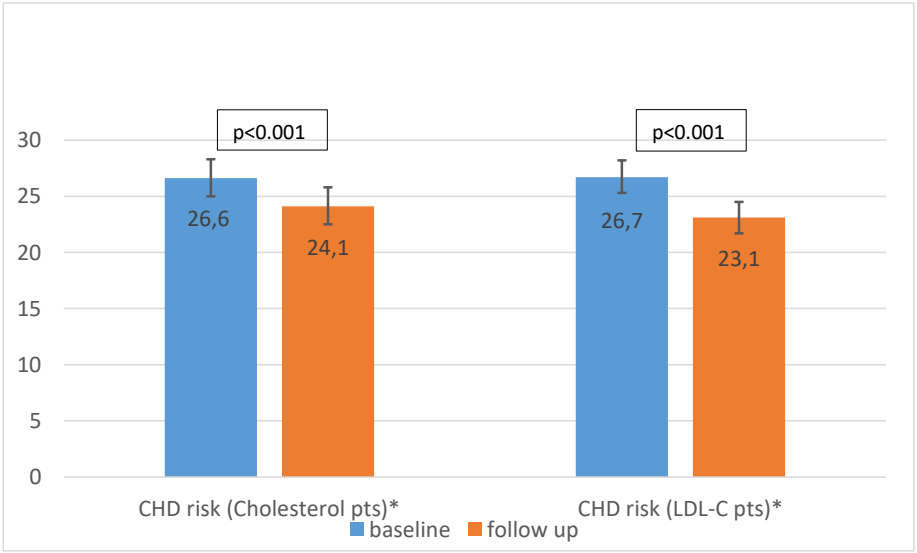
*Parameters with p value < 0.05 ** β value indicates the change in cholesterol in mg/dl for each predictor. The effect of age is calculated in terms of years and duration of PAP is calculated in terms of months.

Framingham risk score for coronary heart disease

Framingham risk score for incident CHD based on total cholesterol and LDL cholesterol decreased significantly following PAP in both sexes in the regression analysis for repeated measures after adjustment for PAP duration, use of lipid lowering medication and change in weight **(figure 2 a, b)**. Duration of PAP was significantly associated with CHD risk reduction in both sexes (p<0.001).

Figure 2 a,b. Comparison of baseline and follow up CHD risk scores** in male (2a) and female (2b) patients adjusted for PAP duration, lipid lowering medication and change in weight.

Figure 2a.

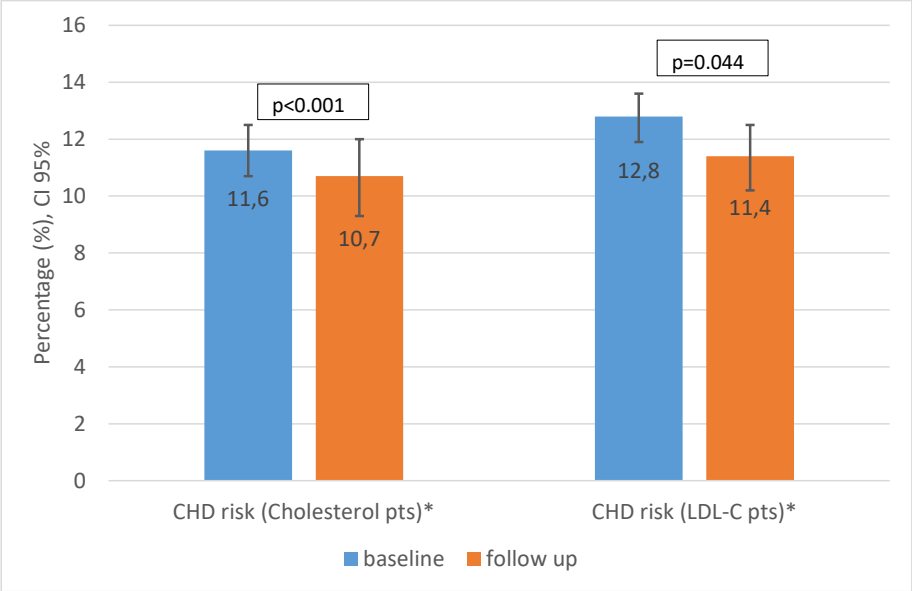


Baseline and follow up coronary heart disease risk scores in males

*Parameters with p value<0.05

**Framingham coronary heart disease risk has been calculated in terms of total cholesterol and LDL-C points

Figure 2b.



Baseline and follow up coronary heart disease risk scores in females

*Parameters with p value <0.05

**Framingham coronary heart disease risk has been calculated in terms of total cholesterol and LDL-C points

Discussion

In this prospective study comprising a large multinational cohort, we observed a significant effect of PAP therapy on lipid profile. The reduction in total cholesterol following PAP persisted after adjustment for important confounding factors and the change was predicted by the duration of PAP treatment. The reduction in cholesterol and LDL-cholesterol concentrations may translate into a 10% reduction of predicted risk for incident coronary heart disease.

OSA causes repetitive episodes of upper airway obstruction and results in intermittent hypoxia, increased sympathetic activity, inflammation, oxidative stress, endothelial and metabolic dysfunction. These pathophysiologic mechanisms may cause the increased risk of cardiovascular disease in patients with OSA.[18] Although there is extensive literature regarding the role of hypoxia induced factor (HIF) on the regulation of carbohydrate metabolism, the effects of hypoxia and HIF on lipid metabolism have recently become the focus of closer examination. Thus, the role of hypoxia in triggering complex intracellular molecular pathways and resulting in enhanced lipogenesis by HIF-dependent induction of genes involved in fatty acid uptake, synthesis and storage has been proven. [19] In a recent study with 15 OSA subjects without comorbid diseases, Drager et al. [20] have reported that severe OSA and nocturnal hypoxemia decreases lipolysis of triglyceride-rich lipoproteins and delays removal of remnants. Interestingly, our previous studies from the ESADA cohort suggested an independent association between intermittent nocturnal hypoxia and lipid concentrations as well as a diagnosis of hyperlipidemia. [6, 7] Furthermore, there are studies indicating that PAP treatment reduces systemic oxidative stress which is a consequence of CIH in OSA. [21, 22]

The direction and size of PAP treatment effects on cardio-metabolic health in OSA patients has been studied extensively over the past decades. However, many of these studies have limited sample size and treatment duration was generally short. In a meta-regression analysis examining lipid profile in 1,958 OSA subjects from 29 studies, total cholesterol was the only parameter demonstrating a statistically significant reduction [8]. Treatment duration ranged from 2 days to 6 months and only one study reached 1 year. The calculated mean reduction of cholesterol was -5.7 mg/dl in the unadjusted meta-regression analysis which compares well with -4.9 mg/dl in our study. However, adjustments for duration of PAP treatment were not performed in the meta-regression. Nevertheless, a recent longitudinal pilot study following 31 OSA subjects for 5 years has reported positive effect of PAP on total cholesterol and LDL-cholesterol levels which supports our findings on positive effects of long-term PAP treatment on total cholesterol levels.[23] In contrast to these analyses, a review of randomized controlled trials found no consistent reduction of lipid levels when sham-CPAP was applied as

a control condition.[9] In the study of Drager et al. [20], although there was no significant change in the lipid levels following 3 months of PAP treatment; CPAP treatment in was still associated with improvement in lipolysis process estimated by the ^{3}H-triglyceride clearance and was considered as effective in order to restore the lipolysis rates. It is also possible that factors like weight reduction, life style and physical activity may have influence on the application of the PAP treatment.

The current analysis applied several steps to better understand the effects of PAP treatment on lipid status and to account, at least in part, for the observational, non-randomized study design. The unadjusted analysis showed highly significant changes in all lipid parameters, and adjustment for important confounders like change in weight or age reinforced the significant overall reduction of total cholesterol by PAP. We also addressed treatment duration which appeared to be dose dependently related to reduction of cholesterol level reduction.

Interestingly, we identified the largest effects on cholesterol in patients without comorbidities like ischemic heart disease, diabetes mellitus, and hyperlipidemia as well as in patients without prior lipid lowering medication. It is speculated that patients with ischemic heart disease and diabetes were more likely to be aware of the health burden of hyperlipidemia and this might lead to better adherence to international guidelines for prevention and therapy. Furthermore, a considerable number of subjects with comorbidities like diabetes mellitus and ischemic heart disease were under lipid lowering treatment. Additionaly, there are also meta-analysis suggesting that statin therapy is associated with approximately a 10% to 20% proportional increase in the risk for developing diabetes. [24, 25] In a meta-analysis with 21,303 randomized subjects, lipid lowering medication have been defined for having an effect of 1.2-1.7 mmol/L (19.5-22.0%) reduction in total cholesterol following lipid lowering medication. [26] Use of high intensity statin therapy is also expected to reduce LDL cholesterol levels by at least 1-2 mmol/L depending on the pre-treatment lipid levels. [27] Indeed, our data demonstrate that PAP treatment has a weaker effect on lipids compared with lipid lowering medication.

LDL cholesterol is a primary target for lipid lowering treatment and total cholesterol is suggested as an alternative target. The Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice proposes that a reduction of 25% in total cholesterol in patients with high risk for CV disease may be a target for a clinically meaningful change by

treatment.[17] In our study, 5.5% subjects demonstrated a reduction of 25% in cholesterol. According to Rossouw [28], a cholesterol reduction by 10% may decrease clinical event rate by approximately 20%. In our study 27% subjects had a reduction of 10% in cholesterol which underlines the clinical impact of modest changes in cholesterol concentration. The statistically significant decrease in the Framingham risk score also emphasized this clinical impact.

In our previous studies from our ESADA cohort, significant differences in lipid levels across European regions were demonstrated and the influence of geographical regions were emphasized. The influence of European regions on lipid profiles following PAP treatment was also observed in the present study as OSA subjects in North European regions demonstrated a higher reduction in total cholesterol following PAP treatment compared with subjects from South European regions. These findings emphasize the importance of regional differences in regards to dietary factors, physical activity, health care systems as well as patients' attitude and compliance during morbidities.

A number of methodological strengths and limitations of the study need to be considered. This is a prospective cohort study based on a large sample size and a multicenter study design. Our findings add evidence to a literature characterized by conflicting data. Important potential confounders like measures of obesity, weight change over time, long and short term of treatment duration, intake of lipid lowering drugs and anthropometric factors were accounted for. On the other hand, a clinical referral bias cannot be excluded in our study since the majority of ESADA centers represent academic tertiary health institutions and this may have resulted in an enrichment of patients with multiple important comorbidities. Since the ESADA reflects clinical practice, the influence of patients' comorbidities on physicians' repeated lipid analysis registries can not be ruled out. However, the association of the diabetes with an increase in total cholesterol levels following PAP treatment suggest that a potential selection bias was rather in favor for an underestimation of the overall effect of PAP treatment on the changes in lipid levels. Another limitation is that PAP follow-up data and a second lipid sample was obtained only in a subgroup of the ESADA population. However, anthropometric data and sleep apnea severity did not differ in a clinically meaningful manner between the analysis population and the remaining ESADA on PAP treatment. Data on cholesterol was available in more than 1,500 subjects whereas the statistical power for the analysis of LDL and HDL cholesterol and fasting triglycerides was substantially lower. This may at least explain the lack of significant findings for these three parameters of lipid metabolism. Although changes in

lipid lowering medication was not associated with a relevant change in lipid levels, we were not able to adjust for the exact dosage of each concomitant medication in the entire ESADA dataset as this information is of high uncertainty. Another limitation was the decentralized analysis of lipids which may have generated differences between centers. Similarly, sleep study methodologies differ between ESADA centers but a sensitivity analysis confirmed that there was no systematic influence of the type of different sleep study recording equipment used on the PAP treatment effect. Although we controlled for several factors that may confound the change in cholesterol following PAP treatment, we did not monitor potential confounders such as dietary modifications and changes in physical activity over the treatment period.

In conclusion, the present study reports a significant reduction in total cholesterol as well as in coronary heart disease risk score after PAP treatment. Considering the close association between hypercholesterolemia and increased cardiovascular mortality, identification and treatment of OSA patients with dyslipidemia may be relevant. In fact, a multimodal treatment approach with traditional risk factor management including implementation of a healthier lifestyle is warranted in individualized OSA patient care.

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