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Serum ferritin and obstructive sleep apnoea - epidemiological study

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Abstract

Purpose: Ferritin is an intracellular iron storage protein and a marker of inflammation. Studies have shown that subjects with obstructive sleep apnoea (OSA) have higher levels of circulating pro-inflammatory cytokines, but little is known about the association between ferritin and OSA. The aim of the study was to evaluate serum ferritin (S-Ferritin) levels in OSA patients compared to levels in the general population, and also examine the effect of obesity level and treatment with positive airway pressure (PAP) on S-Ferritin levels.

Methods: The OSA subjects (n=796) were part of the Icelandic Sleep Apnea Cohort. The control subjects (n=637) were randomly chosen Icelanders who participated in an epidemiological study. Propensity score methodologies were employed to minimize selection bias and strengthen causal inferences when comparing non-randomized groups. S-Ferritin levels were measured and all participants answered the same detailed questionnaire about sleep and health. Only OSA patients underwent a sleep study and were re-invited for a two-year follow-up.

Results: S-Ferritin levels were significantly higher in OSA males than controls (213.3 vs. 197.3 µg/L, p=0.007). However, after adjusting for confounders and using our PS methodology, no significant difference was found. S-Ferritin levels were not correlated with severity of OSA,

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Conflict of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent:

Informed consent was obtained from all individual participants included in the study.

obesity level or clinical symptoms. Also, no significant change in S-Ferritin levels was found with two years of PAP treatment.

Conclusions: S-Ferritin levels are comparable in OSA patients and controls and do not change consistently with obesity level or PAP treatment in our sample.

Keywords

Ferritin; OSA; inflammation; ISAC; BOLD

Introduction

Obstructive sleep apnoea (OSA) is a disease characterised by upper airway obstruction that causes breathing cessations during sleep, oxygen desaturations and arousals. Risk factors for OSA include male gender, increased age and obesity.¹ Previous studies have shown that OSA patients have a higher prevalence of hypertension¹, cardiovascular disease (CVD)² and type 2 diabetes.³ Several studies have shown that OSA patients have higher levels of circulating pro-inflammatory cytokines, chemokines and adhesion molecules compared to controls.⁴⁻⁶ We have found in our previous studies that the role of OSA on these biomarkers is much stronger in severely obese patients, than less obese patients.⁷⁻⁹ The basic mechanism of inflammation in OSA is not completely understood, but it is thought that the chronic intermittent hypoxia seen in OSA as well as the fragmented sleep play a significant role in the inflammation process.⁵

Ferritin is an intracellular storage protein that binds to iron and makes it soluble and non-toxic. Production of serum ferritin (S-Ferritin) is regulated by the concentration of free intracellular iron.¹⁰ S-Ferritin concentrations vary by age and sex. Values among men tend to peak between 30-39 years of age and then remain relatively constant. Among women, S-Ferritin values remain relatively low until menopause, when S-Ferritin concentrations start to rise.¹¹ Ferritin is, however, not only a part of the iron metabolism, but is also non-specifically elevated in a wide range of inflammatory conditions and malignancies.¹² S-Ferritin usually plays an important role in general patient care and is a part of routinely ordered blood tests in most populations. Also, S-Ferritin is a valuable tool for clinicians for evaluation of common diseases such as iron deficiency anemia and iron overload conditions such as hereditary hemochromatosis.

Previous studies have shown that S-Ferritin is increased among obese subjects. A positive correlation has been found with total body fat,¹³ body mass index (BMI),¹⁴ and waist-to-hip ratio.¹⁵ Several studies have also found a significant association between elevated S-Ferritin levels and hypertension.¹⁶⁻¹⁸ It has been hypothesised that free radicals, produced by the help of free and unbound iron, might be involved in the pathogenesis of atherosclerotic plaques by oxidative modification of low-density lipoproteins (LDL).¹⁹ In this regard, many studies have found a link between elevated iron storage and the development of atherosclerotic disease.²⁰⁻²⁴ However, other studies have not supported this hypothesis.²⁵⁻²⁸ Similarly, it has been proposed that increased iron might elevate the risk of type 2 diabetes by causing oxidative stress and tissue damage.²⁹⁻³³

As many OSA patients are obese, have CVD, hypertension and systemic inflammation, one would expect that a marker of inflammation such as S-Ferritin would be elevated in subjects with OSA. However, little is known whether OSA has an effect on S-Ferritin levels independent of obesity. ÓBrien *et al* studied S-Ferritin levels in 80 suspected OSA patients to examine if OSA could promote lower body iron stores and thereby increase common symptoms of daytime sleepiness and periodic limb movement.³⁴ Contradictory to their hypothesis, results showed that lower minimum oxygen saturation (worse OSA), although not AHI, predicted higher S-Ferritin levels, possibly reflecting the inflammatory process in OSA.

There is a need to better understand the role of systemic inflammation in the pathophysiology and consequences of OSA, e.g., by studying markers such as S-Ferritin, a commonly measured biomarker in clinical practice. The aim of this study was to compare S-Ferritin levels in OSA patients and general population controls, taking into consideration differences in gender, age, BMI, smoking history, CVD and type 2 diabetes. Additional aims were to evaluate S-Ferritin within the OSA group with regard to OSA severity, obesity level and symptoms, as well as possible changes after 2 years of PAP treatment.

Methods

Participants

OSA patients: All patients diagnosed with OSA and referred for positive airway pressure (PAP) treatment to the Landspítali University Hospital in Reykjavik from September 2005 - December 2009 were invited to join the Icelandic Sleep Apnoea Cohort (ISAC). Over 90% of eligible and approached subjects agreed to participate in the study, resulting in 822 subjects included in the prospective cohort at baseline. Of these, 1 subject missing S-Ferritin at baseline and 25 females aged <50 years (see discussion below) were excluded from the baseline analysis set, resulting in a sample of 796 apneics at baseline. After two years of PAP treatment, the same participants were invited again to take part in a follow-up study. Follow-up information on S-Ferritin levels and PAP adherence was available on 700 (88%) of the baseline analysis set.

General population subjects: A random sample of the general population aged 40 years and over that participated in another epidemiological study on the Burden of Lung Disease (BOLD) was used as controls. Altogether 773 of the 939 eligible subjects (82.3%) responded. Of these, 27 (3.5%) missing baseline S-Ferritin levels and 109 (14.1%) women aged <50 years were excluded from the baseline analysis set, resulting in a sample of 637 controls at baseline.

The ISAC and BOLD studies were both approved by the National Bioethics Committee and the Data Protection Authority of Iceland, and the ISAC study also at the Institutional Review Board of the University of Pennsylvania.

Questionnaires and measurements

After written informed consent was obtained, subjects answered standardized questionnaires about their sleep³⁵ and previous health. Daytime sleepiness was evaluated using the Epworth

Sleepiness Scale (ESS).³⁶ Subjects were asked about whether they had hypertension (doctor diagnosis and medication use), type 2 diabetes (doctor diagnosis and medication use) or CVD (diagnosed myocardial infarction, stroke or heart failure). Smoking status was obtained by self-report. Current smokers were defined as those who smoked tobacco regularly during the month preceding the exam. Former smokers were defined as those who had denied having smoked regularly for a month prior to the exam. Those who reported no regular smoking at or prior to the exam were defined as never smokers. Blood was drawn from the antecubital vein. Samples in both groups were drawn at the similar time of the day. Specimens were collected in SST tubes (Greiner, Kremsmuenster, Austria). Tubes were allowed to stand for 20 minutes before centrifugation for 10 minutes (3,000 rpm). After separation, the serum samples were stored at -20°C until analysis. Additionally, OSA patients underwent an overnight type 3 sleep study (see details below). Height and weight were measured in the same manner for all participants. Participants were asked to remove their shoes and heavy outer garments for the measurements.

S-Ferritin measurements

S-Ferritin was measured with an electrochemiluminescence immunoassay on an Elecsys 2010 instrument (Roche Diagnostics, Mannheim, Germany). The analyses were carried out at the Department of Clinical Biochemistry, Landspítali University Hospital, Iceland. Two labelled monoclonal antibodies against S-Ferritin and streptavidin coated microparticles were used for the assay. The intra-assay coefficient of variation (CV%) of the S-Ferritin assay was found to be 2.9% at concentration of $30.7\text{ }\mu\text{g/L}$, 3.2% at concentration of $232\text{ }\mu\text{g/L}$ and 2.6% at the concentration of $1482\text{ }\mu\text{g/L}$. The reference values for S-Ferritin was based on normal values used in Iceland,³⁷ which is $30\text{--}400\text{ }\mu\text{g/L}$ for males older than 17 years and women older than 50 years of age. As reference values for S-Ferritin are lower for women under the age of 50 years and premenopausal women were few in the OSA group ($n=25$), all women under 50 years of age were excluded from this study.

Overnight studies in ISAC cohort

Prior to PAP treatment, all OSA patients had an overnight sleep study that has previously been described in detail.⁷ In brief, in all studies the same signals were recorded: nasal airflow by cannula, oxygen saturation, heart rate, respiratory movements by respiratory inductance plethysmography (RIP) belts, body position and activity by accelerometer. Trained sleep technologists scored all sleep studies. Scoring of a hypopnea required a 30% decrease in airflow for 10 seconds with 4% oxygen desaturation or 50% decrease in airflow for 10 seconds with a sudden increase in flow at the end of the event. Scoring of an apnea required 80% decrease in flow for 10 seconds. The apnea-hypopnea index (AHI) was calculated as the mean number of apneas and hypopneas per hour of recording (excluding upright time). The oxygen desaturation index (ODI) was calculated as the number of falls in oxygen of 4% per hour of recording. The minimum oxygen saturation (SaO_2) was defined as the lowest oxygen saturation reached during the study. Hypoxia time was defined as the percentage of time with $\text{SaO}_2 < 90\%$.

PAP use

Patients referred for PAP treatment all received care at the Department of Respiratory Medicine and Sleep, Landspítali University Hospital. At the outpatient clinic they had direct access to trained staff, which helped them find the type of device and settings they needed. All patients were treated with autoPAP or continuous PAP (CPAP) units (ResMed Corp., San Diego, California, USA) and treatment was only changed to bilevel PAP (BiPAP) or adaptive servoventilation if treatment efficacy on autoPAP or CPAP was inadequate (defined by AHI ≥ 15 using PAP and/or persistent patient complaints or based on clinical judgement). Of PAP users, 53% were on autoPAP, 43% on CPAP, 3% on BiPAP and 1% on adaptive servoventilation.

At the 2-year follow-up, adherence to PAP treatment was estimated based on downloads of usage in the previous 4 weeks from memory cards (objective data), if available, from ResMed S8 machines (ResMed Corp. San Diego, CA, USA). Also, all participants answered 3 multiple-choice questions about average PAP use (subjective data). Self reported data had 98.6% sensitivity and 45.1% specificity in distinguishing full PAP users from partial users. Full PAP users were defined as those who used PAP for ≥ 20 days and ≥ 4 hrs/day on average for the previous four weeks based on objective data or ≥ 5 nights/week for $\geq 60\%$ of the night by subjective data. PAP users that did not meet the criteria for full PAP users were classified as partial users. Those who returned their PAP device within one year of therapy initiation were defined as non-users. Of 700 patients with available S-Ferritin and PAP adherence data at follow-up, 353 (50.4%) were classified as full users, 99 (14.1%) as partial users, and 248 (35.4%) as non-users. For further details on PAP treatment in the ISAC cohort, see ³⁸.

Statistical analyses

All statistics were calculated using STATA software, Version 13.0 (Stata Corporation, College Station, Texas) or SAS Version 9.4 (SAS Institute, Cary, NC). Differences in categorical and continuous variables between the groups of subjects with and without OSA were first compared using the chi-squared test and unpaired t-test, respectively. The relationships of S-Ferritin levels and presence or absence of disease (i.e., OSA, CVD, type 2 diabetes) were explored using linear regression. Multiple linear regression was then used to calculate adjusted p-values for associations between S-Ferritin values and OSA status, controlling for age, sex, BMI, smoking history, CVD, hypertension and type 2 diabetes; models examining robust differences in the propensity score derived subsample (see below and online supplement) were controlled for propensity score quintile. Associations between baseline OSA severity measures (AHI, ODI, minimum SaO₂, hypoxia time, ESS) and S-Ferritin levels were assessed using linear regression within OSA patients only. Changes in S-Ferritin values from baseline to follow-up in OSA patients were calculated within subject as follow-up minus baseline and compared between full and non-users using similar methods to those comparing OSA vs. controls. In addition to analyses in the overall sample, we also examined associations in strata defined by BMI (<30 , $30-35$, and ≥ 35 kg/m²). A p-value < 0.05 was defined as being statistically significant. S-Ferritin levels were not normally distributed and were natural log transformed for all analyses.

Propensity score sub-classification analyses

In order to obtain a comparable sample of OSA patients from ISAC and controls from the BOLD cohort for assessment of the relationship between S-Ferritin levels and OSA, we used sub-classification by propensity score quintiles, following an established sequential heuristic described in detail by Maislin & Rubin.³⁹ The same method was used to compare full PAP users and non-users. Propensity score methodologies allow for the purposeful ‘design’ of the non-randomized group comparisons inherent in observational data. The resulting sample is designed to have within subclass covariate balance between cases and controls, which is shown to be at least as good as that expected if patients had been randomized.^{39, 40}

Using the propensity score subclassification heuristic, OSA and control patients were balanced with respect to baseline age, gender, BMI, current and previous smoking status, hypertension, CVD and type 2 diabetes. The resulting sample included 510 OSA cases and 355 general population controls and is referred to as the ‘*OSA-general population PS Sample*’. The propensity score sub-classification for full and non-users was determined with respect to the following potential confounders at baseline: age, gender, BMI, OSA severity measures (AHI, ODI, minimum SaO₂ and hypoxia time [percent time with SaO₂<90%]), Epworth Sleepiness Scale (ESS), smoking status, hypertension, type 2 diabetes and CVD. Baseline levels of S-Ferritin (natural log transformed) were also included to control for any potential regression to the mean when examining change scores. The final sample included 304 full users and 240 non-users. For further details on propensity score methods, including comparisons of patients included and excluded from the PS sample, see Tables S1 and S2 in the online supplement.

Results

Participation and characteristics in the overall sample

The demographics and clinical characteristics of both study groups are shown in Table 1 for the original observational sample. There were more men in the OSA group (83.7% vs. 61.9%) and OSA patients were 3 years younger on average than participants in the control group. Furthermore, the OSA patients had a higher BMI, were more likely to have a history of smoking and had a higher prevalence of hypertension and type 2 diabetes. Also, OSA patients reported more sleepiness than controls.

S-Ferritin levels, age, gender, obesity, smoking and comorbidities of OSA

Most participants had S-Ferritin levels within the normal range from 30-400 µg/L (Table 1). The independent associations of OSA, gender, age, BMI, smoking, hypertension, CVD and type 2 diabetes with S-Ferritin concentrations was analysed with multiple linear regression analysis. As seen in Table 2, gender had the most profound effect on S-Ferritin levels, where females had significantly lower S-Ferritin than males ($p<0.0001$). Also, S-Ferritin was positively correlated with BMI ($p=0.001$). Current smokers had lower S-Ferritin compared with those who had never smoked ($p=0.001$), but no difference was found between past and never smokers. S-Ferritin was found to be significantly lower in those with CVD ($p<0.0001$), but higher in those who had hypertension ($P=0.015$). Type 2 diabetes and age did not have a significant effect on S-Ferritin levels. When looking at men and women

separately, S-Ferritin levels showed the similar correlation among men but the differences were not significant among women (Table S3 in supplement). Associations were generally similar when the subjects were divided into BMI groups (<30, 30-35, and ≥ 35 kg/m², Table S4 in supplement).

S-Ferritin levels and OSA

As shown in Table 1, OSA males had significantly higher S-Ferritin than controls in unadjusted analyses (213.3 μ g/L vs. 197.3 μ g/L, $p=0.007$). In females, S-Ferritin levels showed a trend in the same direction as for men but results did not reach significance ($p=0.115$). When adjusting for age, BMI, smoking history, hypertension, CVD and type 2 diabetes this difference in S-ferritin levels by OSA was no longer found (Table 2). Similarly, no significant effect of OSA was observed in adjusted models stratified by gender (Table S3 in supplement) or BMI group (Table S4 in supplement).

S-Ferritin and OSA severity

No significant associations were observed between S-Ferritin values and severity of OSA (estimated by AHI, ODI, minimum SaO₂ or hypoxia time) among OSA patients, both unadjusted and after adjusting for relevant confounders (Table 3). Also, S-Ferritin values did not show significant correlation with sleepiness, estimated by the ESS score (Table 3).

S-Ferritin and OSA: results in the PS sample

Before applying our PS methodology, there were significant differences between the OSA patients and controls for a number of covariates, including BMI ($p<0.0001$), gender ($p<0.0001$), past smoking status ($p=0.002$), never smoker status ($p<0.0001$), hypertension ($p<0.0001$), and type 2 diabetes ($p=0.0001$). However, after sub-classification and controlling for propensity score subclass, there were no differences between cases and controls (all $p>0.76$; Fig. S1 in supplement).

As shown in Fig. 1, there was no significant difference in S-Ferritin levels between OSA and general population PS sample (191.1 vs. 172.6 respectively, $p=0.64$). Similarly, when assessed within different obesity levels, no significant difference was found in S-Ferritin levels between OSA patients and controls in any BMI group (Table S5 in supplement).

S-Ferritin and PAP use

As seen in Table 4, subjects were more likely to be adherent to PAP treatment if they were more obese and had hypertension. Also, patients with more severe OSA (higher AHI) were more likely to use the PAP device ($p<0.0001$).

After two years of PAP use, there was no significant change in S-Ferritin, in either full or non-users, and no difference in the magnitude of changes between the two treatment adherence groups (Figure 2). Similarly, no significant effect of PAP was observed within BMI strata (Table S6 in supplement). Sensitivity analysis excluding patients reporting alternative therapy to PAP and those reporting $>5\%$ weight loss again showed the same results (Table S7 in supplement).

Full PAP users versus non-users: results in the PAP treatment PS sample

Prior to implementing the PS heuristic, there were significant differences between full and non-users for a number of covariates, including BMI ($p<0.0001$), OSA severity measures (all $p<0.0001$), and hypertension ($p<0.0001$). After sub-classification and controlling for propensity score subclass, there were no differences between full and non-users for any covariates included in the heuristic (all $p>0.724$; Fig. S2 in supplement).

Overall, we observed no significant differences in the magnitude of change in S-Ferritin between full PAP users and non-users over the 2-year follow-up (Figure 2). When assessed within BMI strata, again no difference in changes in S-Ferritin levels with PAP treatment was found (Table S6 in supplement). Similarly, there was no effect in sensitivity analyses (Table S7 in supplement).

Discussion

This present study shows that OSA does not have an independent effect on S-Ferritin levels. No differences were found in S-Ferritin levels in a well-defined cohort of moderate to severe OSA patients compared to the general population. Also, no effect of OSA severity was found on S-Ferritin levels and after 2 years of PAP treatment. This lack of effect was consistent across BMI group and therefore independent of obesity level. There was not a significant change in S-Ferritin levels and no differences between full PAP users and non-users.

Our previous studies based on the ISAC cohort have shown that other inflammatory markers (e.g. IL-6 and CRP) are affected by OSA severity, but mainly in severely obese OSA patients (BMI ≥ 35 kg/m²), not in nonobese subjects and that the contribution of OSA severity on these inflammatory biomarkers is of much less degree than the effects of obesity.⁷ Also, severely obese OSA subjects who were non-compliant with PAP treatment demonstrated a significant increase in IL-6 levels over 2 years, whereas those who were compliant with PAP treatment maintained their IL-6 levels.⁹ Similar beneficial effects of PAP were found on adhesion molecules (intercellular adhesion molecule 1 [ICAM-1] and vascular cell adhesion molecule 1 [VCAM-1]), with the largest effects in severely obese subjects for ICAM-1.⁸ Similar calculations were done in this present study for S-Ferritin levels, but no differences were found based on obesity level, OSA severity or changes with PAP treatment. This is in agreement with our previous findings in the ISAC cohort, showing no relationship between OSA and fasting lipids.⁴¹

Our results are contradictory to what was described by O'Brien *et al.* among 80 OSA patients, where a significant association between higher S-Ferritin and OSA was found.³⁴ In that study, adjustments were done for age, sex, BMI and restless leg syndrome, but not hypertension, CVD, type 2 diabetes, or smoking status, which could have affected the results. We note that we did observe a strong association between S-Ferritin and OSA in unadjusted analyses. Another small study of 44 OSA subjects and 46 controls found no significant correlation between S-Ferritin and OSA in unadjusted analysis, further supporting that S-Ferritin levels do not correlate with OSA.⁴²

S-Ferritin was found to be significantly higher among men than women. This difference between genders is likely because of the high mean age in this study; S-Ferritin concentrations tend to peak later in life among women.¹¹ Obesity is a major risk factor for OSA and in this study, OSA patients had significantly higher BMIs on average than controls. We also found that S-Ferritin had a positive correlation with BMI in men and this association was still significant after adjusting for confounding factors such as age, smoking status, hypertension, CVD and type 2 diabetes. Our results therefore support previous studies that have found higher S-Ferritin levels in obese subjects compared to the normal population.¹³⁻¹⁵

In our study, we found that OSA patients were more likely to have a history of smoking, both among men and women. It has been shown that several systemic markers of inflammation are elevated in current smokers,⁴³ but little is known about S-Ferritin levels in smokers compared to non-smokers. In this present study, we found an independent effect of current smoking to lower S-Ferritin levels after adjustment for confounders. Accordingly, S-Ferritin does not appear to act as a systematic inflammatory marker in cigarette smokers.

Previous studies have found contradictory findings regarding S-Ferritin levels and CVD.¹⁹⁻²⁸ In this present study, S-Ferritin was found to be lower in those reporting CVD and therefore does not support the hypothesis that high S-Ferritin could reflect elevated stores of iron that could work as free radicals and be involved in oxidative modification of LDL.

Finally, studies have shown that subjects with type 2 diabetes have higher S-Ferritin levels than non-diabetic individuals (for review see ³³). However, our results did not show any significant association between S-Ferritin and type 2 diabetes.

This study has several advantages. Firstly, the study involves a large number of participants and the participation rate was high both among OSA patients and the general population. Secondly, the 2-year follow-up in this study also had a high participation rate. Importantly, our cohort is a clinical cohort, with no exclusion of the relevant comorbidities with OSA such as hypertension and CVD and a large range of obesity level. The control group used in this study also has several advantages that deserve mention. Approximately the same number of men and women participated and there was a good distribution among age groups. Also, there was no difference between responders and non-responders. Our study was an observational study, not a randomized controlled trial (RCT), which may be considered a limitation. However, an RCT study would be difficult to perform in such a long-term follow-up of untreated symptomatic OSA patients. We utilized propensity score methodologies to reduce bias and create covariate balance between non-randomized groups from our observational study that is similar to that expected in a randomized trial, allowing for improved causal interpretations. Another limitation is the lack of data regarding conditions that may influence S-Ferritin levels among subjects presenting themselves as healthy, such as subclinical anemia, iron deficiency, malignancies, alcoholism, gastrointestinal malabsorption, hemochromatosis and dysthyroidism. Other weaknesses include the relative lack of females in the OSA group, a consequence of the low number of currently diagnosed women with OSA in Iceland. Therefore, the power to analyze S-Ferritin levels in women is lower than among men. Another potential limitation is the lack of

subjects with mild OSA; we cannot exclude a potential effect of OSA severity on S-Ferritin levels from mild to moderate disease, with a plateau among moderate to severe apneics. However, given the lack of difference in S-Ferritin levels between the general population cohort and moderate-to-severe OSA patients, we find this highly unlikely. Another possible limitation is the use of portable type III monitor for the sleep apnea recording, which lacks EEG recording and assessment of arousals. This lack of EEG can thus lead to overestimation of sleep time that can lead to decrease in the AHI and ODI assessed. Also, since a sleep study was not performed in the general population cohort, we do not know how many subjects had treated or untreated OSA; the presence of unrecognized OSA among the control population would make it more difficult to observe an effect of OSA on S-Ferritin levels. Finally, the blood sample collection was performed at different times of the day. However, S-Ferritin levels do not have a consistent diurnal variation so this should not affect our findings.⁴⁴

Conclusions

Our results show that OSA does not have an independent effect on S-Ferritin levels. Supporting this observation, no significant effect of PAP treatment or change in S-Ferritin levels was found after 2 years of treatment. Also, no differential effects were found depending on gender or obesity level after adjustment for other confounders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Statement of Significance

There is a need to better understand the characteristics of systemic inflammation in the pathophysiology of OSA so that we can better assess and treat OSA patients and comorbid conditions. S-Ferritin, a marker of systemic inflammation, is a commonly measured biomarker in clinical practice. Previous studies have shown that subjects with OSA have higher levels of circulating pro-inflammatory cytokines, especially in severely obese patients but little is known about the association between S-Ferritin and OSA.

Mean S-Ferritin levels in OSA patients and controls, results from the observational and PS matched samples

Figure 1:

Adjusted associations with OSA status and S-Ferritin levels in PS matched and original observational samples. [†]Model adjusted for PS quintile; [‡]Adjusted for variables included in the PS matching heuristic.

Mean S-Ferritin levels in full PAP users and non-users; results from the observational and PS matched samples

Figure 2:

Adjusted associations between PAP adherence and change in s-Ferritin levels in PS matched and original observational samples. [†]Model adjusted for PS quintile; [‡]Adjusted for baseline s-Ferritin and all other baseline variables included in the PS matching heuristic.

Table 1:

Demographics and S-Ferritin Levels in Study Population by Gender

Variable	Males			Females		
	ISAC (N=666)	BOLD (N=394)	P [†]	ISAC (N=130)	BOLD (N=243)	P [†]
Age, years	53.6 ± 10.7	56.6 ± 11.6	<0.0001	60.8 ± 7.3	63.4 ± 10.2	0.005
BMI, kg/m ²	33.4 ± 5.6	28.3 ± 4.4	<0.0001	33.4 ± 5.9	27.9 ± 5.5	<0.0001
Smoking History, %			<0.001			0.039
Never	26.9	39.0		27.7	39.1	
Past	51.6	45.4		53.9	40.7	
Current	21.6	15.6		18.5	20.2	
Hypertension, %	44.5	22.5	<0.0001	50.8	37.7	0.016
CVD, %	20.0	15.5	0.067	11.6	21.4	0.020
Type 2 diabetes, %	8.7	2.8	<0.001	8.5	3.3	0.030
Epworth Sleepiness Scale	11.8 ± 5.0	6.4 ± 3.9	<0.0001	10.8 ± 5.1	5.3 ± 4.0	<0.0001
S-Ferritin, µg/L [‡]	213.3 ± 165.3	197.3 ± 225.4	0.007	112.8 ± 79.8	98.5 ± 73.3	0.115
S-Ferritin Groupings, %			0.569			0.377
0 – 30 µg/L	4.1	4.8		10.8	13.2	
30 – 400 µg/L	85.6	86.6		88.5	86.8	
> 400 µg/L	10.4	8.6		0.8	0.0	

[†]p-value from T-test (continuous) and Chi-squared or Fisher's Exact tests (categorical)

[‡]p-value is for natural log transformed data.

Table 2:

Multivariate Regression Model Examining Association with ln(S-Ferritin)

Variable	β (95% CI) [†]	p [‡]
OSA	0.06 (−0.04, 0.16)	0.256
Male Gender	0.64 (0.53, 0.74)	<0.0001
Age	−0.01 (−0.06, 0.04)	0.697
BMI	0.08 (0.03, 0.13)	0.001
Smoking History	<i>Overall</i>	0.002
Current vs. Never	−0.21 (−0.99, −0.08)	0.001
Past vs. Never	0.00 (−0.10, 0.09)	0.929
Hypertension	0.12 (0.02, 0.22)	0.015
CVD	−0.24 (−0.37, −0.12)	<0.0001
Type 2 diabetes	−0.14 (−0.33, 0.04)	0.130

[†] Coefficient from linear regression representing the expected change in ln(S-Ferritin) for a one standard deviation increase in continuous variables or the presence of dichotomous traits

[‡] p-value from linear regression model.

Table 3:

Associations between S-Ferritin Levels and markers of OSA severity

Variable	Unadjusted		Adjusted [*]	
	β (95% CI) [†]	p [‡]	β (95% CI) [†]	p [‡]
Apnea-Hypopnea Index	−0.03 (−0.08, 0.03)	0.404	−0.06 (−0.11, 0.003)	0.065
Oxygen Desaturation Index	−0.01 (−0.07, 0.05)	0.657	−0.06 (−0.12, 0.004)	0.067
Hypoxia Time	−0.04 (−0.10, 0.02)	0.206	−0.05 (−0.11, 0.01)	0.119
Minimum SaO ₂	0.01 (−0.05, 0.07)	0.723	0.02 (−0.04, 0.08)	0.465
Epworth Sleepiness Scale	0.05 (−0.01, 0.11)	0.129	0.01 (−0.05, 0.07)	0.649

^{*} Model adjusted for gender, age, BMI, smoking status, hypertension, CVD and type 2 diabetes

[†] Coefficient from linear regression representing the expected change in ln(S-Ferritin) for a one standard deviation increase in indicated OSA severity measure

[‡] p-value from linear regression model.

Table 4:

Demographics and S-Ferritin Levels in PAP Adherent and Non-users at Baseline and Follow-up

Variable	Baseline			Follow-up		
	Adherent (N=353)	Non-user (N=248)	P [†]	Adherent (N=353)	Non-user (N=248)	P [†]
Age, years	55.3 ± 10.7	54.5 ± 10.1	0.377	57.4 ± 10.7	56.6 ± 10.1	0.379
Male, %	85.0	80.2	0.127	–	–	–
BMI, kg/m ²	34.1 ± 5.7	32.3 ± 5.5	<0.0001	35.0 ± 5.7	32.4 ± 5.5	<0.0001
Smoking History			0.430			0.010
Never, %	27.1	26.2		28.2	26.6	
Past, %	54.6	51.2		55.6	47.2	
Current, %	18.3	22.6		16.2	26.2	
Hypertension, %	52.1	34.7	<0.0001	51.3	38.3	0.002
CVD, %	18.8	19.8	0.757	19.6	20.2	0.847
Type 2 diabetes, %	9.7	6.9	0.231	12.0	8.6	0.177
Epworth Sleepiness Scale	11.9 ± 5.1	11.2 ± 5.0	0.081	7.5 ± 4.5	9.3 ± 4.6	<0.0001
AHI, events/hour	49.8 ± 21.0	38.0 ± 17.8	<0.0001	–	–	–
S-Ferritin, µg/L [‡]	207.5 ± 163.3	186.5 ± 161.6	0.160	197.9 ± 148.6	192.5 ± 178.0	0.324
S-Ferritin Groupings, %			0.861			0.399
0 – 30 µg/L	4.8	4.8		3.7	6.1	
30 – 400 µg/L	85.8	87.1		87.3	85.1	
> 400 µg/L	9.4	8.1		9.1	8.9	

[†]p-value from T-test (continuous) and Chi-squared or Fisher's Exact tests (categorical)

[‡]p-value is for natural log transformed data