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► To cite this version:

Noémie Le Tallec-Estève, Chloé Rousseau, Benoît Desrues, Olivier Loréal, Ronan Thibault. Transferrin saturation is independently associated with the severity of obstructive sleep apnea syndrome and hypoxia among obese subjects. *Clinical Nutrition*, 2021, 40 (2), pp.608-614. 10.1016/j.clnu.2020.06.007 . hal-02887887

HAL Id: hal-02887887

<https://hal.science/hal-02887887>

Submitted on 8 Oct 2020

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Transferrin saturation is independently associated with the severity of obstructive sleep apnea syndrome and hypoxia among obese subjects

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ABSTRACT

Introduction and aims: Obstructive sleep apnea syndrome (OSAS) is a frequent complication of obesity. Intermittent chronic hypoxia which frequently results from OSAS could modulate the systemic control of iron metabolism and alter serum iron parameters, especially among obese patients. Aims: to evaluate whether serum parameters of iron bioavailability and storage (primary), as well as age, waist circumference, arterial hypertension and tobacco use (secondary) are associated with OSAS severity and/or hypoxia. Methods: design: a single-center retrospective study with prospective data collection; inclusion criteria: consecutive patients referred for initial assessment for obesity underwent nocturnal respiratory polygraphy and iron status serum assessment within a 3-month period. The adjusted analyzes were performed using ANOVA and reported as adjusted means and 95% confidence interval (95% CI). Results: 13 men and 56 women were included. OSAS prevalence: 72% (n=50). Ferritin (mean \pm SD, 260 \pm 276 vs. 111 \pm 89 μ g/l, p=0.01) and transferrin saturation (31 \pm 10 vs. 24 \pm 9%, p=0.002) were significantly higher in case of moderate/severe OSAS than in absent/mild OSAS, independently from gender and tobacco use. Serum iron (19.4 μ g/l [CI95%, 16.5-22.3] vs. 16.2 μ g/l ([14.1-18.2], p=0.056) and transferrin saturation (31.5 % [26.3-36.7]) vs. 25.3% [21.6-29.1], p=0.043) were higher when time under oxygen saturation <90% was >15%. Age (mean \pm SD, 51 \pm 11 vs. 41 \pm 12 yr, p=0.001), waist circumference (136 \pm 18 vs. 123 \pm 12 cm, p=0.003), arterial hypertension (59% (n=13/22) vs. 23% (n=11/47), p=0.004) and tobacco use (64% (n= 14/22) vs. 32% (n= 15/47), p=0.01) were significantly greater in moderate/severe OSAS than in absent/mild OSAS. Conclusions. Transferrin saturation was associated with OSAS severity and time under hypoxia. This suggests a relationship between OSAS-induced hypoxia and iron metabolism among obese patients.

Keywords: obesity; metabolic syndrome; iron; obesity surgery.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is defined by recurrent episodes of apnea or hypopnea during sleep that result from complete or partial upper airway collapse. It leads to chronic intermittent hypoxia (1). OSAS affects about 4% of the general population (2), but its prevalence can reach 30 to 50% among obese patients (3). Identifying and treating OSAS among obese patients is essential, because OSAS facilitates the onset of metabolic and cardiovascular diseases (4), and favors weight gain and aggravation of obesity (5–7).

Iron metabolism is finely tuned. Serum iron is mainly provided by macrophages during the erythrophagocytic process that enables iron recycling and by enterocytes in the course of digestive absorption of iron from nutrients. Serum concentration of iron and transferrin iron saturation levels are indicators of the iron that is bioavailable for cells. Hepcidin controls iron homeostasis (8,9). Hepcidin is a peptide mainly synthesized by hepatocytes and secreted into the plasma. It modulates the expression of ferroportin, the only known iron exporter from cells towards plasma. An abnormal decrease in hepcidin levels in plasma increases the serum iron concentration and transferrin saturation, exposing the patient to iron overload, which, in turn, increases serum levels of ferritin, the protein involved in the storage of excess iron (9,10). An abnormal increase in hepcidin levels decreases transferrin saturation and exposes the subject to iron deficiency (8). Hepcidin expression is increased by iron storage and inflammation (8,9). Conversely, hepcidin expression is decreased by anemia and hypoxia, through mechanisms that could involve erythropoietin, hypoxia inducible factor (11,12) and erythroferrone (13) which is synthesized by erythroblasts during erythropoiesis (14). In case of hypoxia, the down-regulation of hepcidin expression becomes a priority, irrespective of body iron levels (15); this leads to iron mobilization and an increase in transferrin saturation, in order to provide adequate amounts of iron for the erythropoiesis process, which is activated to compensate for the hypoxia.

OSAS has been reported to be associated with polycythemia (16) and increased hematocrit levels (17). In addition, erythropoietin plasma concentrations are higher among patients with OSAS (18). Therefore, we hypothesize that among obese patients with OSAS, an increase in iron transferrin saturation could be a marker for the severity of OSAS and hypoxia. The aims of our study were to evaluate whether serum parameters of iron bioavailability and storage (primary), and age, waist circumference, arterial hypertension and tobacco use (secondary) are associated with OSAS severity and/or hypoxia.

PATIENTS AND METHODS

Study design and population

This was a single-center retrospective study based on prospective data collection. The 69 patients were consecutively recruited from June 1st, 2016 to April 23, 2017 in the Nutrition Unit of the University Hospital of Rennes (CHU Rennes), Rennes, France. The study included all patients eligible for obesity surgery according to the French recommendations, i.e. body mass index (BMI) ≥ 40 or BMI ≥ 35 kg/m² with obesity complications (cardiovascular diseases including arterial hypertension, OSAS, type 2 diabetes, disabling osteoarticular disease, non-alcoholic steatohepatitis). They underwent a systematic nocturnal respiratory polygraphy to screen for OSAS as part of the initial assessment. The exclusion criteria were: previous diagnosis of OSAS, time between the nocturnal respiratory polygraphy and the plasma iron status assessment >3 months, history of obesity surgery (except gastric banding), ongoing iron supplementation, diseases known to be associated with iron metabolism dysregulation (genetic hemochromatosis, active chronic inflammatory disease), and pregnancy. Since this retrospective study was based on routine practice, informed consent was not required by French law.

Obesity-related diseases and therapy

Patients were considered to have type 2 diabetes in the following cases: fasting blood glucose ≥ 7.0 mmol/l, prior history of diabetes, oral antidiabetic drug use and/or insulin therapy.

Fasting hyperglycemia was defined as fasting blood glucose ≥ 5.6 mmol/l. Arterial hypertension was defined as systolic (SBP) or diastolic (DBP) blood pressures ≥ 140 or ≥ 90 mmHg, respectively, or if patients were under antihypertensive therapy. Metabolic syndrome was defined according to the International Diabetes Foundation 2005 criteria (4). History of tobacco use, respiratory diseases (chronic obstructive pulmonary disease, asthma), or chronic inflammatory diseases (systemic, rheumatic or gastrointestinal) were reported. Drugs that can interfere with iron metabolism, such as proton pump inhibitors (PPIs), nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or that affect sleep, such as psychotropes (antidepressants, benzodiazepines, hypnotics), were identified.

Anthropometric data

Weight, height, body mass index, and waist and hip circumferences were measured in all subjects the day of the nocturnal respiratory polygraphy. After one night fasting, body composition was measured at 8 am using bioimpedance analysis (Bodystat 1500, Bodystat Ltd, Isle of Man, UK). Patients were advised to restrict themselves to routine physical activity the day before. After skin swabbing with 70% ethanol, four adhesive electrodes (3M Red Dot T, 3M Health Care, Borken, Germany) were placed on the dorsal side of the left hand, left wrist, left foot, and left ankle while the patient was supine with palms facing inwards. An electrical current of 0.8 mAmp was produced at 50 KHz for five seconds by the bioimpedance analyser. The following data was collected: fat mass and fat-free mass (% of weight and kg), and total body water (%).

Nocturnal respiratory polygraphy

Nocturnal respiratory polygraphy was performed in all patients using the CID-Lx polygraph (CIDELEC, Angers, France). All graphs obtained during sleeping time were analyzed by a senior pneumologist specialized in sleep disorders (BD). Apnea was defined by a complete cessation of nasal-oral airflow for at least 10 seconds. The apnea-hypopnea index (AHI) was defined as the number of apneas or hypopneas per hour of sleep. OSAS was defined as AHI ≥ 5 /hour. The severity of OSAS was defined as mild if $5 \leq \text{AHI} \leq 15$, moderate if $15 < \text{AHI} \leq 30$, or severe if $\text{AHI} > 30$. Hypoxia was defined as the percentage of time with arterial oxygen saturation $< 90\%$ at 15% of sleeping time or more. The lowest oxygen saturation value was recorded.

Iron serum parameters and blood analyses

Measurements of serum iron parameters were part of the systematic fasting blood analyses; the measurement methods are shown in brackets: blood cell count (impedance flow cytometry), prothrombin time (chronometry), glucose (hexokinase colorimetric assay), glycated hemoglobin (in mmol/mol hemoglobin according to the recommendations of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), and in % according to the National Glycohemoglobin Standardisation Program), albumin (bromocresol green colorimetric assay), transthyretin (immunoturbidimetry), C-reactive protein (CRP) (latex enhanced immunoturbidimetry), alanine aminotransferase (ALT), aspartate aminotransferase (ALT), γ -glutamyl-transpeptidase (γ GT) (all three by spectrophotometry according to the recommendations of the IFCC), triglycerides, total and HDL-cholesterol (colorimetry), and LDL-cholesterol (calculated from the Friedewald formula). Plasma iron parameters were assessed on heparinized plasma. Serum iron concentrations were determined by the colorimetric method (ferrozine assay), transferrin concentration, by

immunoturbidimetry, and ferritin by electrochemiluminescence (Cobas 8000 Roche). The transferrin saturation coefficient (TSC), and total transferrin binding capacity (TIBC) were calculated. The biological analyses were all performed in the Department of Biochemistry at CHU Rennes.

Study endpoints

The primary endpoint was the severity of OSAS, as defined by the AHI severity categories described above in the 'Nocturnal respiratory polygraphy' section. The secondary endpoints were the percentage of time under hypoxia, i.e. oxygen saturation <90%, and the lowest oxygen saturation value, serum iron parameters, anthropometric data, body composition, obesity-related diseases, age, tobacco use, and the metabolic syndrome parameters (waist circumference, arterial pressure, plasma glucose, triglycerides, and HDL-cholesterol). The numbers of patients in each category are shown in Tables 2, 3 & 4.

Statistical analysis

Quantitative variables are described as numbers (percentage) and means \pm standard deviation (SD). The groups were compared using Student's test (2 groups) or ANOVA tests (>2 groups) when the distribution was normal, or using Mann-Whitney or Wilcoxon (two groups) non-parametric tests otherwise. For qualitative variables, the numbers and percentage are presented for each category. The groups were compared using χ^2 parametric or Fisher non-parametric tests (theoretical number <5). The adjusted analyses were performed using ANOVA and presented as adjusted means and 95% confidence interval (95% CI). The significance threshold was 5% for all analyses. The analyses were carried out on SAS software, version 9.4.

RESULTS

Patients' enrollment and characteristics

The study flow chart is shown in **Figure 1**. Among the 69 patients included, 13 were men (19%) and 56 were women (81%). The patient characteristics are summarized in **Table 1**.

Among the eight patients with type 2 diabetes, five were treated with metformin, five with glucagon-like peptide (GLP)-1 analog, and two with insulin. Their mean glycated hemoglobin was 6.97% (range 6.30-8.40).

OSAS prevalence and severity

The overall prevalence of OSAS was 72% (n=50/69), including 40% (n=28) with mild OSAS, 13% (n=9) with moderate OSAS, and 19% (n=13) with severe OSAS (**Table 1**). The mean oxygen saturation was $91.6 \pm 3.0\%$. Twenty-seven percent (n=19) of the patients had minimum oxygen saturation $\leq 75\%$, and 32% (n=22) had oxygen saturation below 90% for more than 15% of the recording time (**Table 1**).

Relationships between iron parameters, OSAS severity, and hypoxia

Bio-clinical data according to the severity of OSAS is presented in **Table 2**. Serum iron concentration, transferrin saturation, and ferritin were significantly higher in the moderate/severe OSAS group than in the absent/mild OSAS group. After excluding the patients on PPIs, NSAIDs, aspirin, or psychotropes (n=27), the differences regarding serum iron parameters remained statistically significant (data not shown). Plasma CRP and hemoglobin were not statistically different. Transferrin saturation was associated with both the severity of OSAS (evaluated according to AHI) (**Table 3**) and with time with oxygen saturation $< 90\%$ (**Table 4**), independently from gender, tobacco use, age, arterial hypertension, waist circumference, blood glucose and triglycerides. γ GT levels were

independently associated with the severity of OSAS (**Table 3**). Iron and CRP concentrations were higher when time under oxygen saturation <90% was >15% (**Table 4**). Transaminases, prothrombin time, transferrin and albumin levels were not statistically related to OSAS severity nor to time in hypoxia (**Tables 3 and 4**).

Other variables associated with OSAS and its severity

As expected, patients with moderate/severe OSAS had more frequent and more marked hypoxia and more time with oxygen saturation <90% (**Table 2**). Patients with moderate/severe OSAS were significantly older, had larger waist circumference, more frequently presented arterial hypertension, and had higher fasting blood glucose and triglyceride levels. They were also more often smokers than patients with absent or mild OSAS. The group with moderate/severe OSAS was more likely to be on anti-hypertensive drugs than the absent/mild OSAS group (11 (50%) vs. 10 (21%); $p=0.016$). There was no difference in the use of anti-diabetic treatment, NSAIDs, PPIs, psychotropes, statins or fibrates between the absent/mild OSAS and moderate/severe OSAS groups.

DISCUSSION

In a group of obese patients eligible for obesity surgery, the severity of OSAS, defined by AHI and the time in hypoxia – i.e. peripheral oxygen saturation <90% - were both independently associated with an increase in transferrin iron saturation, regardless of gender, tobacco use, biological inflammation, metabolic syndrome parameters, or drug therapy. Serum iron levels were also related to time in hypoxia, whereas the serum transferrin concentration was not, suggesting that the increase in serum transferrin saturation is mostly related to an increase in serum iron.

225 The relationship between iron metabolism, metabolic syndrome, obesity and insulin resistance
226 is well known. Whether iron metabolism disturbances participate in metabolic syndrome or
227 are one of its consequence remains debated (19). Our study suggests that hypoxia secondary
228 to OSAS could have an important role in the relationship between iron metabolism, and
229 metabolic syndrome/overweight/obesity.

230 Among patients with OSAS, obesity and/or insulin resistance, sub-clinical inflammation
231 could lead to a decrease in both serum iron and transferrin saturation levels through IL6 and
232 an increase in serum hepcidin (20), the key regulator of iron metabolism. This hypothesis is
233 encouraged by the finding of increased iron storage, plasma ferritin and liver iron content
234 together with increased hepcidin levels in hemosiderosis patients (21). Among severely
235 obese patients, a lower transferrin saturation level is associated with an increase in hepcidin
236 expression in adipose tissue macrophages (22).

237 Our data show that both serum iron and transferrin saturation levels are increased alongside a
238 slight increase in CRP in moderate/severe OSAS, confirming an inflammatory context for
239 these patients. It is also possible that hypoxia could have counteracted the expected decrease
240 in transferrin saturation related to inflammation and subsequent increase in hepcidin level.

241 Indeed, hypoxia is a well-known repressor of hepatic hepcidin expression (23). Hypoxia could
242 reduce the transcription of the *Hepcidin AntiMicrobial Peptide (HAMP)* gene that encodes for
243 hepcidin by inducing Hypoxia inducible factor 2 (HIF-2) (24,25).

244 Unfortunately, because of the retrospective study design, hepcidin serum levels were not
245 measured. However, our study results could point to a hypothetical role of hepcidin in the way
246 in which hypoxia and inflammation act on iron metabolism among obese patients with OSAS.

247 A decrease in hepcidin plasma levels favored by hypoxia could in turn favor the increase in
248 transferrin saturation. The level of hepcidin expression is controlled by numerous factors,
249 especially at transcriptional level (26). Physiopathological events occurring during OSAS can

generate at least two antagonist signals that could modulate hepcidin transcription: inflammation and hypoxia. Inflammation increases hepcidin expression through the IL6/STAT3 signaling pathway, thus limiting iron release from macrophages and enterocytes and reducing transferrin saturation (26-29).

Our data shows that among patients with OSAS registering more than 15% of the time with oxygen saturation under 90%, there is a significant increase in transferrin saturation, alongside an increase in CRP. This finding supports the hypothesis that the degree of hypoxemia could counteract the effect of inflammation, favoring iron release from cells. Hypoxia could blunt the stimulating effect of inflammation on hepcidin expression (**Figure 2**). Abakay et al reported a decrease in serum iron and an increase in hepcidin level among OSAS patients compared to non-OSAS patients (30). They also showed that AHI was negatively correlated with serum iron levels and positively with hepcidin levels. Among patients with the highest hepcidin levels, two clusters in the data distribution were observed. However, the authors did not analyze the relationship between hypoxia and iron parameters/hepcidin. Among Chinese patients with and without OSAS, Liu et al reported a slight increase in hepcidin serum levels among patients with severe OSAS (31). Unfortunately Liu et al did not assess serum iron metabolism parameters or inflammatory status, so that the relationships between inflammatory parameters and AHI cannot be studied, nor can the impact of time in hypoxia and maximum hypoxemia.

Our hypothesis that hypoxia could explain the increase in transferrin saturation in OSAS requires confirmation. The precedence of hypoxia over other regulators of iron metabolism has been previously reported among patients with anemia secondary to chronic diseases (32) and among beta-thalassemic patients (33,34). In these extreme conditions, hypoxia takes precedence over the effect of active inflammation or the increase in iron storage, resulting in promotion rather than inhibition of iron release from macrophages and enterocytes and

275 increase in transferrin saturation. In addition, hypoxia could modulate the expression of iron
276 metabolism genes, thus contributing to an increase in transferrin saturation. In enterocytes,
277 HIF-2 can increase the transcriptional expressions of the *Duodenal Cytochrome b (DCYTb)*
278 and *Divalent Metal Transporter 1 (DMT1)* genes encoding respectively for a reductase and a
279 transporter of iron involved in non-heminic iron uptake from the digestive lumen (35,36). The
280 transcriptional expression of the *SLC40A1* gene encoding for the ferroportin protein, the iron
281 exporter from enterocytes toward plasma, is also increased by HIF-2.

282 Except for γ GT, the markers of liver diseases did not differ between absent/mild and
283 moderate/severe OSAS groups. Thus, cytolysis or hepatic insufficiency are not likely to be
284 involved in the increases in serum iron and transferrin saturation.

285 After adjustment on potential confounding factors, we found no difference in serum ferritin
286 concentrations according to the severity of OSAS or hypoxia. This is consistent with previous
287 studies (38). Despite the statistically significant relationship between transferrin saturation
288 level and severity of OSAS, serum transferrin saturation remained within the normal values.

289 However, as found in metabolic syndrome patients (39), we cannot rule out that, among
290 patients with severe OSAS, the increase in transferrin saturation could favor the appearance in
291 plasma of small amounts of non-transferrin-bound iron, an abnormal molecular form of iron
292 rapidly taken up by the liver, pancreas and heart, which could participate in the cell damage
293 related to oxidative stress (40). During OSAS it has been reported that its severity, defined by
294 AHI, was not associated with systemic oxidative stress levels, but the minimum oxygenation
295 desaturation level was associated with a decrease in antioxidant potential (41). This suggests
296 an involvement of anti-oxidant defenses in condition of hypoxia during OSAS.

297 Our study has several limitations. The most important is that, due to the retrospective design,
298 we did not measure serum levels of hepcidin, the key regulator of iron metabolism. Measuring
299 hepcidin among our obese patients with OSAS could have helped us to understand the

mechanisms of the changes observed in iron parameters in relation to hypoxia and inflammation. A prospective study is clearly needed. Also because of the retrospective design, we did not assess antioxidant potential or non-transferrin-bound iron. Our hypothesis that hypoxemia could explain the increase in transferrin saturation in OSAS needs to be confirmed. Finally, we were not able to assess whether excessive alcohol intake could have played a role in γ GT increase, as well as in the increase in serum ferritin (37). Indeed excessive alcohol intake is known to be associated with the severity of OSAS. In conclusion, our data shows that transferrin iron saturation is independently associated with OSAS severity and the time in hypoxia. More studies are needed to evaluate the mechanisms involved in transferrin iron saturation increase among obese patients with OSAS, and their role in the natural course of OSAS. In view of our findings, transferrin iron saturation in plasma merits exploration as a longitudinal marker of the severity of OSAS or hypoxia among obese patients.

Statement of authorship

All authors have made substantial contributions: NLE, OL and RT conceived, and designed the study, analysed, and interpreted the data, and drafted the article; NLE, RT, and BD collected the data; CR analysed the data; all authors have approved the final version.

Conflict of interest statement

The authors have no conflict of interest related to this article to declare.

Acknowledgements

We thank Dr Martine Ropert, Department of Biochemistry, CHU Rennes, Rennes, France, for all the biochemical analyses, including iron status.

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Table 1 – Clinical and demographic characteristics of obese patients with obstructive sleep apnea syndrome (n=69).

Variables	
Women / Men – n (%)	56 (81) / 13 (19)
Age (yr)	44.3 ± 12.6
Gastric banding history - n (%)	4 (6)
Tobacco use - n (%)	29 (42)
Smoking cessation (N= 28)* - n (%)	13 (46)
OSAS - n (%)	50 (72)
Mild	28 (40)
Moderate	9 (13)
Severe	13 (19)
Minimum oxygen saturation ≤ 75%	19 (27)
Time with oxygen saturation < 90% > 15%	22 (32)
Anthropometric data	
Body mass index	42.8 ± 6.3
Body composition	
Fat-free mass (%)	52.6 ± 6.5
Fat mass (%)	47.4 ± 6.5
Total body water (%)	39.5 ± 4.7
Fat mass index (kg/m ²)	20.4 ± 5.3
Waist circumference (cm)	126.8 ± 15.2
Waist/Hip ratio	1.0 ± 0.1
Comorbidities – n (%)	
Type 2 diabetes	8 (12)
Arterial hypertension	24 (35)

Metabolic syndrome	44 (64)
Asthma	13 (19)
COPD	2 (3)
Chronic inflammatory diseases	4 (6)

430 COPD, chronic obstructive pulmonary disease.

431 **Table 2 – Univariate analysis of factors associated with obstructive sleep apnea**
432 **syndrome and its severity (n=69).**
433

Variables	Absent/mild OSAS N=47	Moderate/severe N=22	P
Women / Men - n (%)	41 (87) / 6 (13)	15 (68) / 7 (32)	0.096
Age (yr) – mean±SD	41.0 ± 12.0	51.5 ± 11.1	0.001
Tobacco use - n (%)	15 (32)	14 (64)	0.013
Smoking cessation (N= 28)-n(%) (%)	4 (27)	9 (69)	0.024
Nocturnal polygraphy – mean±SD			
Minimum oxygen saturation (%)	83.5 ± 9.1	71.0 ± 10.5	<0.0001
% time oxygen saturation <90%	11.6 ± 25.6	38.3 ± 30.4	<0.0001
Oxygen saturation decrease (%)	4.1 ± 1.1	7.9 ± 2.7	<0.0001
Oxygen saturation <90% / hour (n)	9.5 ± 5.5	51.2 ± 27.3	<0.0001
Anthropometric data – mean±SD			
Body mass index (kg/m ²)	41.6 ± 4.6	45.6 ± 8.3	0.044
Waist circumference (cm)	122.6 ± 11.6	135.6 ± 18.3	0.003
Total body water (%)	39.0 ± 3.6	40.5 ± 6.3	0.297
Fat free mass (kg)	59.3 ± 10.3	65.7 ± 13.0	0.031
Fat free mass (%)	52.8 ± 5.4	52.1 ± 8.6	0.749
Fat mass (kg)	54.0 ± 9.9	62.1 ± 20.6	0.089
Fat mass (%)	47.2 ± 5.4	47.9 ± 8.6	0.642
Fat mass index (kg/m ²)	19.6 ± 3.6	22.3 ± 7.5	0.335
Comorbidities – n (%)			
Type 2 diabetes	4 (8.5)	4 (18)	0.255
Arterial hypertension	11 (23)	13 (59)	0.004
Metabolic syndrome	28 (60)	16 (73)	0.289
Asthma	8 (17)	5 (23)	0.742
COPD	1 (2)	1 (4.5)	0.539
Blood parameters – mean±SD			
Iron (µmol/l)	15.2 ± 4.8	18.7 ± 5.6	0.021
Transferrin (g/l)	2.6 ± 0.4	2.4 ± 0.4	0.211
Transferrine saturation (%)	24.2 ± 8.8	31.5 ± 9.6	0.002
Ferritin (µg/l)	111.5 ± 88.9	260.5 ± 276.3	0.011
Hemoglobin (g/dl)	13.4 ± 1.2	13.5 ± 1.0	0.593
Hematocrit (%)	40.6 ± 3.2	40.8 ± 3.0	0.787
CRP (mg/l)	8.3 ± 5.6	9.5 ± 7.5	0.728
ALAT (IU/l)	28.8 ± 14.1	38.9 ± 20.5	0.029
ASAT (IU/l)	24.5 ± 8.6	28.1 ± 11.8	0.233
γGT (IU/l)	31.6 ± 14.1	74.8 ± 101.7	0.030
Prothrombin time (%)	99.4 ± 12.8	98.8 ± 11.7	0.342
Albumin (g/l)	41.9 ± 2.7	42.5 ± 3.3	0.412
Glucose (mmol/l)	5.5 ± 1.0	5.9 ± 1.0	0.016
Triglycerides (mmol/l)	1.3 ± 0.5	1.7 ± 0.8	0.007
Total cholesterol (mmol/l)	4.8 ± 0.8	5.3 ± 1.5	0.127
HDL cholesterol (mmol/l)	1.2 ± 0.3	1.1 ± 0.3	0.430
LDL cholesterol (mmol/l)	3.0 ± 0.7	3.2 ± 1.4	0.501

ALAT, alanine amino transferase; ASAT, aspartate amino transferase; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; γ GT, gamma-glutamyl-transpeptidase.

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Table 3 - Serum iron parameters independently associated with the severity of OSAS (n=69).

Variables	Absent OSAS (n=19)		Mild (n=28)		Moderate (n=9)		Severe (n=13)		P value
Transferrin saturation (%)	26.3	[21.1-31.6]	23.7	[19.4-28.1]	29.3	[22.3-36.2]	34.5	[27.7-41.3]	0.048
Ferritin (µg/l)	167.7	[113.4-247.9]	128.0	[90.2-178.7]	248.5	[143.6-430.0]	214.8	[131.3-351.3]	0.107
Iron (µmol/l)	17.5	[14.6-20.5]	15.2	[12.8-17.7]	17.8	[13.9-21.7]	20.2	[16.4-24.0]	0.097
Transferrin (g/l)	2.7	[2.5-2.9]	2.6	[2.4-2.8]	2.5	[2.2-2.8]	2.4	[2.1-2.6]	0.362
CRP (mg/m)	6.2	[4.5-8.5]	5.9	[4.4-7.9]	6.8	[4.4-10.6]	10.8	[7.2-16.2]	0.100
ASAT (IU/l)	25.7	[21.8-30.4]	26.6	[23.1-30.6]	29.9	[23.7-37.7]	29.3	[23.9-36.1]	0.640
ALAT (IU/l)	32.9	[26.5-40.9]	31.8	[26.3-38.5]	42.1	[31.0-57.3]	41.2	[31.5-54.1]	0.218
γGT (IU/l)	38.6	[29.4-50.8]	44.8	[35.5-56.6]	55.1	[37.8-80.5]	80.9	[58.6-111.8]	0.013
Prothrombin time (%)	100.3	[93.1-107.6]	96.8	[90.6-103.1]	102.1	[92.2-111.9]	97.9	[88.9-106.9]	0.713
Albumin (g/l)	43.2	[41.7-44.6]	42.3	[41.0-43.5]	42.9	[40.9-44.9]	44.6	[42.8-46.4]	0.169

Comparisons of different parameters per AHI group adjusted for gender, tobacco use, age, arterial hypertension, waist circumference, blood glucose and triglycerides. Adjusted mean (95% confidence interval); ANOVA test. ALAT, alanine amino transferase; ASAT, aspartate amino transferase; CRP, C-reactive protein; γGT, gamma-glutamyl-transpeptidase.

Table 4 - Serum iron parameters independently associated with the percentage of time with oxygen saturation under 90% (n=69).

Variables	Oxygen saturation<90% ≤ 15% of time (n=47)		Oxygen saturation<90% > 15 % of time (n=22)		P value
Transferrin saturation (%)	25.3	[21.6-29.1]	31.5	[26.3-36.7]	0.043
Ferritin (µg/l)	165.2	[126.8-215.3]	202.0	[129.5-315.3]	0.407
Iron (µmol/l)	16.2	[14.1-18.2]	19.4	[16.5-22.3]	0.056
Transferrin (g/l)	2.58	[2.4-2.7]	2.6	[2.4-2.8]	0.861
CRP (mg/m)	6.1	[4.8-7.7]	9.0	[6.6-12.4]	0.044
ASAT (IU/l)	26.1	[23.2-29.3]	29.8	[25.3-35.0]	0.179
ALAT (IU/l)	34.5	[29.4-40.5]	37.3	[29.6-46.9]	0.574
γGT (IU/l)	51.2	[41.2-63.8]	55.0	[41.8-72.5]	0.689
Prothrombin time (%)	99.4	[94.4-104.5]	97.9	[91.0-104.7]	0.713
Albumin (g/l)	42.9	[41.9-44.0]	43.5	[42.1-44.9]	0.529

Comparisons of biological parameters by percentage of time under hypoxia (oxygen saturation <90%) adjusted for gender, tobacco use, age, arterial hypertension, waist circumference, blood glucose and triglycerides. Adjusted mean (95% confidence interval); ANOVA test. ALAT, alanine amino transferase; ASAT, aspartate amino transferase; CRP, C-reactive protein; DBP, diastolic blood pressure; γGT, gamma-glutamyl-transpeptidase.

Figure legends

Figure 1 – Study flow chart.

Figure 2 – Diagram representing the potential mechanisms that could modulate systemic iron metabolism and parameters among obese patients with severe OSAS.

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Figure 1

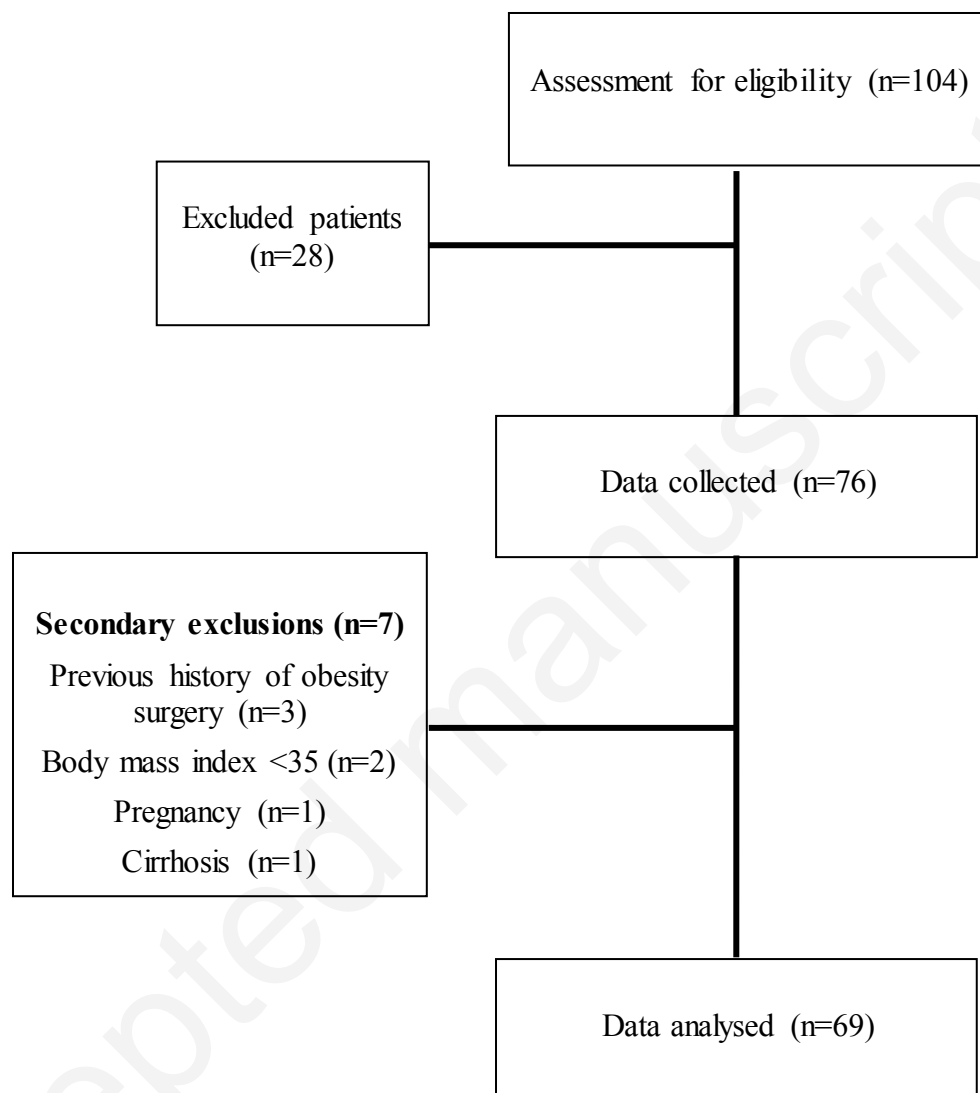


Figure 2

