Original Article

Effect of Hypoxia on Glucose Metabolism in Nondiabetic Patients With Obstructive Sleep Apnea Syndrome

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A B S T R A C T

Aim: Obstructive sleep apnea syndrome (OSAS) may promote hyperglycemia and insulin resistance. Our aim is to investigate the effect of OSAS on the fasting plasma glucose, glycosylated hemoglobin (HbA1c), and C reactive protein (CRP) in nondiabetic patients.

Materials and methods: Blood parameters of consecutive 90 non diabetic patients whom polysomnographic evaluations were done in our sleep laboratory was evaluated. Among these 61 patients with normal fasting blood glucose were classified due to their apnea-hypopnea index (AHI) as mild (n=16, 26.2%), moderate (n=18, 29.5%) and severe (n=27, 44.2%) OSAS. The fasting plasma glucose, HbA1c, and CRP were measured.

Results: Mean age of the patients was 47.7±11.2 years, 72% male. HbA1c, fasting glucose levels show positive correlation with BMI (r=.503, P=.00; r=.258, P=.045). No relation of HbA1c to apnea index nor AHI was detected while positive correlation of fasting glucose and CRP was detected (r=.262, P=.042; r=.258, P=.045). HbA1c, fasting glucose and CRP levels show negative correlation with minimum SpO2 levels (by order of r=−.302, P=.018; r=−.368, P=.004; r=−.365, P=.004). HbA1c, fasting glucose levels and CRP levels show positive correlation with mean desaturation index (time duration in which SpO2<90% by pulse oximeter) (r=.263, P=.041; r=.311, P=.015; r=.283, P=.027).

Conclusions: Although no relation in between increased HbA1c, or glucose levels and severity of OSAS was detected in nondiabetic OSAS patients, the correlation with the night hypoxia was detected. This could also show the effect of night time hypoxia on glucose metabolism in OSAS patients.

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Efecto de la hipoxia sobre el metabolismo de la glucosa en pacientes no diabéticos con síndrome de apnea obstructiva del sueño

R E S U M E N

Objetivo: El síndrome de apnea obstructiva del sueño (SAOS) puede fomentar la hiperglycemia y la resistencia a la insulina. Nuestro objetivo es investigar el efecto del SAOS sobre la glucosa plasmática en ayunas, la hemoglobina glucosilada (HbA1c) y la proteinina C reactiva (PCR) en pacientes no diabéticos. Material y métodos: Se determinaron los parámetros de análitica hemática de 90 pacientes no diabéticos consecutivos en los que se realizaron evaluaciones polisomnográficas en nuestro laboratorio del sueño. Un total de 61 de estos pacientes con una glucemia en ayunas normal fueron clasificados según el índice de apnea-hipopnea (IAH) como casos leves (n=16, 26.2%), moderados (n=18, 29.5%) o graves (n=27, 44.2%) de SAOS. Se efectuaron determinaciones de la glucosa plasmática en ayunas, la HbA1c y la PCR. Resultados: La media de edad de los pacientes fue de 47.7±11.2 años, y el 72% eran varones. Los niveles de HbA1c, y de glucosa en ayunas presentan una correlación positiva con el IMC (r=0.503, p=0.00; r=0.258, p=0.045). No se detectó relación alguna de la HbA1c con el índice de apnea ni con el IAH, mientras que sí se observó una correlación positiva de la glucosa en ayunas con la PCR (r=0.262, p=0.042; r=0.258, p=0.045). Los niveles de HbA1c, glucosa en ayunas y PCR muestran una correlación negativa con los valores de SpO2 mínima (con valores de r=−0.302, p=0.018; r=−0.368, p=0.004; r=−0.365, p=0.004, respectivamente). Los niveles de HbA1c, glucosa en ayunas y PCR muestran una correlación positiva con el...
Introducción

El síndrome de apneas obstructivas del sueño (OSAS) y el diabetes mellitus son trastornos comunes a nivel mundial. Se estima que el 8% de los adultos de Estados Unidos tiene diabetes, y 90% de ellos tiene tipo 2 de diabetes mellitus (DM).1 Para su tratamiento, la prescripción de una dieta y ejercicio es común. Existe un mayor riesgo de desarrollar OSAS y DM en pacientes diabéticos, independientemente de la duración de la enfermedad.2,3 La asociación entre OSAS y DM es mayor en mujeres diabéticas y, en general, los pacientes diabéticos tienen una probabilidad mayor de desarrollar OSAS que los no diabéticos.4,5

En los primeros estudios de asociación, se observó una relación obesidad con la resistencia a la insulina, y a menudo otras condiciones metabólicas que coexisten.6-9 En estos estudios, se asumió que las personas con OSAS tienen una mayor resistencia a la insulina, y se observó una correlación entre las concentraciones de insulina, crónicas y las desviaciones de la glucemia.10 Sin embargo, no se ha determinado si esta resistencia a la insulina es causada por la OSAS, es decir, si la OSAS es una causa o un efecto secundario de la resistencia a la insulina.11

La relación entre OSAS y DM ha sido investigada en varios estudios, y se ha demostrado que estos trastornos diferentes pueden coexistir.12 Los objetivos de este estudio eran examinar la prevalencia de OSAS y la relación entre OSAS y DM en pacientes con DM.”

Materiales y métodos

Frecuencia de desaturación media (tiempo de desaturación de la oximetría de pulso) (p = 0,263, p = 0,041; r = 0,31, p = 0,015; r = 0,283, p = 0,027).

Conclusiones: Aunque no se detectó relación alguna entre el aumento de los niveles de HbA1c y la gravedad de la OSAS en las pacientes con OSAS no diaéticos, se detectó una correlación con la hipoxia nocturna. Esto podría poner de manifiesto el efecto de la hipoxia nocturna sobre el metabolismo de la glucosa en los pacientes con OSAS.

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The BMI showed a positive correlation with the apnea index, apnea-hypopnea index and oxygen desaturation index (ODI) ($P_{=0.012}$, $r=0.321$; $P_{=0.001}$, $r=0.400$; $P_{=0.001}$, $r=0.411$, respectively), while there was a negative correlation with the minimum $SpO_2$ ($P_{=0.00}$, $r=-0.481$). The BMI also showed a positive correlation with the HbA$_{1c}$ and fasting glucose levels ($P_{=0.00}$, $r=-0.503$; $P_{=0.045}$, $r=-0.258$), but no correlation was detected with the CRP.

There were no significant differences between the mild and moderate groups, or between the mild and severe groups with respect to the HbA$_{1c}$, glucose or CRP values, but the HbA$_{1c}$ showed a significant difference between the moderate and severe groups ($P_{=0.038}$). No significant differences were observed either between the three groups in these parameters ($P_{=0.187}$, $P_{=0.646}$, $P_{=0.237}$, respectively). A correlation was observed between the HbA$_{1c}$, fasting glucose and CRP levels and the parameters related with apnea and oxygen desaturation during sleep, as shown in Table 3. All these correlations disappeared when the effect was corrected as a factor of the BMI, by partial correlation analysis ($P_{=0.05}$).

The BMI, ODI and minimum $SpO_2$ were statistically significant in comparisons between two groups, due to fasting plasma glucose levels less than 100 mg/dl (19 cases) or between 100 mg/dl and 125 mg/dl (42 cases) ($P_{=0.045}$, $P_{=0.002}$, $P_{=0.006}$).

### Discussion

This study evaluated the possible correlation of sleep-disordered breathing with glucose metabolism in non-diabetic patients with OSAS and no co-morbidities. Our results suggest that, in non-diabetic patients, hypoxia during the night is associated with an increase in fasting glucose levels and HbA$_{1c}$, but this relationship disappears when a BMI correction is introduced. It could be proposed that, apart from the disease severity and the AHI, intermittent hypoxia may play a role in, and influence glucose metabolism in patients with OSAS, but it could also cause obesity.

Glucose intolerance and an increase in DM rates have often been observed in patients with OSAS, and could be related to obesity, as has also been documented in the study by Tasali et al. in their patient group. However, some studies suggest that OSAS could be a risk factor for DM, regardless of the concomitant presence of obesity. The hypothesis is that nocturnal respiratory disorders include glucose metabolism either due to repeated oxygen desaturation or due to a sleep disturbance. As in previous studies, the relationship between the mean desaturation index and the length of time during which the patient remains below 90% $SpO_2$, and the HbA$_{1c}$ and glucose levels disappeared after we introduced a correction for obesity. This may be related to the fact that we included all consecutive non-diabetic patients with a diagnosis of OSAS in our sleep laboratory, and because most of our patients were obese (median BMI of 31.2). This could be explained because OSAS was also a component of metabolic syndrome.

In recent studies, it was observed that the relationship of HbA$_{1c}$ and hypoxia in euglycemic patients with OSAS was significant. In one study, the hypoxemia severity in non-diabetic patients with sleep apnea showed a relationship with HbA$_{1c}$ levels, and CPAP therapy for 3–5 months reduced HbA$_{1c}$ levels in patients with severe sleep apnea. As in another study conducted in 56 euglycemic patients newly diagnosed with OSAS, it was observed that nocturnal hypoxia may affect fasting insulin levels. Good adherence to more than 6 months of CPAP therapy can significantly reduce HbA$_{1c}$ levels, but has no effect on insulin resistance markers. In a recent meta-analysis, it was observed that OSAS was associated with potentiation of sympathetic activation and a decrease in glucose tolerance, and that both conditions remitted after CPAP treatment. However, these studies were of short duration, and the issue has still not been addressed in long-term randomized, controlled trials.

Our study supported this hypothesis, and showed that nocturnal hypoxia is related with glucose and HbA$_{1c}$ levels in non-diabetic euglycemic patients with OSAS. The intermittent hypoxia parameters were also correlated with the CRP. Intermittent hypoxia affects glucose metabolism by inducing systemic activation, increasing systemic inflammation, increasing counter-regulatory hormones and fatty acids, and causing pancreatic beta cell dysfunction.

However, in the present study, we did not observe a significant relationship between the CRP values and the HbA$_{1c}$ and glucose levels, which could be because we did not use high sensitivity CRP, which is a more sensitive measure of inflammation.

A harmful effect of severe OSAS on blood glucose levels has been observed in elderly hypertensive patients, and a significant increase in fasting glucose and HbA$_{1c}$ levels has been found in these patients. We did not observe any relationship between fasting glucose and the apnea-hypopnea index, or with OSAS severity. However, we did observe that the oxygen desaturation index and minimum desaturation index were significantly higher in patients with fasting glucose values between 100 mg/dl and 125 mg/dl (which is a marker of impaired fasting blood glucose) compared with those who had fasting glucose values less than 100 mg/dl. Patients with fasting glucose values between 100 mg/dl and 125 mg/dl were referred for further assessment of possible diabetes. The reason for the abnormal fasting glucose values could be an effect of the intermittent hypoxia. The effect of hypoxia and re-oxygenation cycles cause impaired glucose metabolism, as it causes endothelial dysfunction, which would trigger the formation of inflammatory cytokines, an increase in the release of vasoactive hormones and development of oxidative stress. Another factor that causes impaired fasting glucose could be an effect of activation of the sympathetic system on glucose homeostasis, by increasing the degradation of muscle glycogen.

### Table 1

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean±SD (min–max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recording time, min</td>
<td>462.40±13.91 (429–494)</td>
</tr>
<tr>
<td>Total sleep time, min</td>
<td>355.68±73.34 (122–467)</td>
</tr>
<tr>
<td>Sleep efficiency, STST</td>
<td>77.02±15.54 (25.90–97.30)</td>
</tr>
<tr>
<td>Sleep latency, min</td>
<td>17.30 (IQR: 8.25–34.75)</td>
</tr>
<tr>
<td>AI, events/h</td>
<td>11.2 (IQR: 3.5–29.8)</td>
</tr>
<tr>
<td>AHI, events/h</td>
<td>26.8 (IQR: 10.45–45.15)</td>
</tr>
<tr>
<td>Mean $SpO_2$, %</td>
<td>94.57±3.59 (77–99)</td>
</tr>
<tr>
<td>Minimum $SpO_2$, %</td>
<td>80.50±8.78 (53–93)</td>
</tr>
<tr>
<td>Oxygen desaturation index</td>
<td>29.87 (IQR: 1–105)</td>
</tr>
<tr>
<td>Time with $SpO_2$&lt;90%, min</td>
<td>34.64 (IQR: 0–271.7)</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>61.51±12.09 (40–91)</td>
</tr>
</tbody>
</table>

TST, total sleep time; AI, apnea index; AHI, apnea-hypopnea index; $SpO_2$, hemoglobin oxygen saturation measured with pulse oximetry.

### Table 2

<table>
<thead>
<tr>
<th>Severity</th>
<th>Number, %</th>
<th>Males/females</th>
<th>Age</th>
<th>BMI</th>
<th>AHI</th>
<th>Glucose, mean</th>
<th>HbA$_{1c}$, mean</th>
<th>CRP, mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>16 (26.2%)</td>
<td>7/9</td>
<td>45.62±10.61</td>
<td>29.98±4.17</td>
<td>5–15</td>
<td>105.12±13.20</td>
<td>5.81±0.54</td>
<td>0.18 (IQR: 0–0.2)</td>
</tr>
<tr>
<td>Moderate</td>
<td>18 (29.5%)</td>
<td>14/4</td>
<td>48.83±12.38</td>
<td>28.93±3.83</td>
<td>15–30</td>
<td>103.44±8.68</td>
<td>5.55±0.55</td>
<td>0.15 (IQR: 0.1–0.4)</td>
</tr>
<tr>
<td>Severe</td>
<td>27 (42.4%)</td>
<td>23/4</td>
<td>48.18±19.96</td>
<td>34.37±8.72</td>
<td>&gt;30</td>
<td>108.7±11.35</td>
<td>5.99±0.72</td>
<td>0.5 (IQR: 0–0.9)</td>
</tr>
</tbody>
</table>

BMI, body mass index; AHI, apnea-hypopnea index; HbA$_{1c}$, glycosylated hemoglobin; CRP, C-reactive protein.
stores, glucose production and release of fatty acids via stimulation of lipolysis, as shown in the study by Iiyori et al.\textsuperscript{27}

Studies have not only been conducted that show an inverse relationship between OSAS severity and HbA\(_{1c}\) levels in patients with type 2 diabetes, but there are also studies that show the same relationship in non-diabetic patients with OSAS.\textsuperscript{12,28} A significant correlation was observed between HbA\(_{1c}\) and the apnea-hypopnea index, arousal index and severity of nocturnal hypoxemia in the study carried out by Papanas et al., but these authors did not observe any relationship between the BMI and HbA\(_{1c}\) and fasting glucose levels.\textsuperscript{12} In our study, the BMI showed a correlation with the hypoxia severity and the AHI. A positive relationship was also identified between the BMI and HbA\(_{1c}\), and fasting glucose levels, unlike that observed in the study by Papanas et al. It is likely that OSAS severity increases as the BMI increases. In a study carried out on morbidly obese patients, it was observed that as the severity of the AHI increased, there was progressive worsening of the metabolic parameters.\textsuperscript{29} This suggests a metabolic syndrome, which is known to accelerate atherosclerosis, diabetes and dyslipidemia, as does OSAS.\textsuperscript{30}

In the medical literature, it has been indicated that patients with OSAS have a higher probability of having glucose intolerance compared to healthy controls.\textsuperscript{14} Compared to controls, the mean HbA\(_{1c}\) increased in patients with OSAS, and the percentage of values above the reference range for both HbA\(_{1c}\) and fasting plasma glucose indicated an increased risk of diabetes in patients with OSAS (20-fold), respectively.\textsuperscript{10} There was no control group in this study, but we observed a significant difference between the moderate and severe OSAS groups with respect to the mean HbA\(_{1c}\) values. However, since our sample size was small, it is difficult to draw definitive conclusions about our results.

OSAS and metabolic syndrome have common etiological risk factors, such as central obesity and age. The increased beta cell function caused by the hypoxia will exert an effect on endothelial dysfunction in both conditions. As has been defined in previous studies, nocturnal hypoxia may influence fasting glucose levels, but CPAP treatment reduces HbA\(_{1c}\), only.\textsuperscript{17} As in our study, these authors did not observe a relationship between the AHI and HbA\(_{1c}\), and, similarly, this effect can be explained by the correction of the hypoxia brought about by the CPAP.

Few studies have evaluated the relationship between sleep apnea and HbA\(_{1c}\), an issue which is becoming increasingly important. In contrast to the study by Steiropoulos et al., we observed a relationship between HbA\(_{1c}\) and sleep characteristics.\textsuperscript{18} Unlike that observed in the \textit{Sleep Heart Health Study}, in which patients with moderate or severe sleep-disordered breathing had higher HOMA index values, regardless of age, BMI, gender, or smoking, we used HbA\(_{1c}\) to evaluate the insulin metabolism, which is simpler and cheaper to measure in clinical practice.\textsuperscript{8}

In conclusion, this study examined the possible correlation of sleep-disordered breathing with glucose metabolism in non-diabetic patients with OSAS. Our results suggest that, in non-diabetic patients with OSAS and no comorbidities, nocturnal hypoxia is associated with an increase in fasting glucose, HbA\(_{1c}\) and CRP levels, although there is no relationship with the apnea-hypopnea index. It could be proposed that, apart from the severity of the disease, intermittent hypoxia plays a role in sympathetic hyperactivity, impaired endothelial function and the influence of glucose metabolism in patients with OSAS. However, since many of our patients were obese, and taking into account that the relationship disappeared after introducing a correction for the BMI, it is not clear whether hypoxia is the primary and principal cause of glucose intolerance in patients with OSAS. Our data suggest that a more detailed study assessing diabetes in obese patients with intermittent hypoxia during the night may be recommended.

**Conflict of Interests**

The authors have not declared any conflict of interests.

**References**


