Relationship between obstructive sleep apnea-hypopnea syndrome (OSAHS) and liver fibrosis

Haifeng Kan, Long Chen, Zhiyun Yang, Shixiang Zhu

Abstract

Objective: The current study discusses the relationship between sleep apnea-hypopnea syndrome (OSAHS) and liver fibrosis by determining the level of plasma hyaluronic acid (HA), procollagen III (PIII), collagen IV (IVC), and laminin (LN) in OSAHS patients and non-OSAHS patients with obesity and normal body weight.

Methods: The patients who underwent polysomnographic (PSG) examinations in the outpatient and inpatient departments of our hospital between December 2010 and June 2013 were selected. The patients were divided into two groups based on the apnea-hypopnea index (AHI; OSAHS and non-OSAHS patients), and both groups were further divided based on obesity and normal body weight based on the body mass index (BMI). Sleep breathing indicators, including BMI, AHI, LSaO2, and MSaO2, were measured in all patients. All of the patients had their blood drawn on the morning after the day of the PSG examination, and the samples were sent to the biochemical laboratory of our hospital for determination of the levels of HA, PIII, IVC, and LN.

Results: Among the obese and normoweight patients, the levels of HA, PIII, IVC, and LN in OSAHS patients were higher than the non-OSAHS patients (P value <0.05). Amongst the OSAHS and non-OSAHS patients, the levels of HA, PIII, IVC, and LN in the obese patients were also higher than the non-obese patients (P value <0.05). The levels of HA, PIII, IVC, and LN in the obese OSAHS patients were higher than the remaining three groups (P value <0.05). The levels of HA, PIII, IVC, and LN had positive correlations with the AHI and BMI (r=0.701, 0.523, 0.639, and 0.421, respectively, P<0.05; and r=0.565, 0.441, 0.475, and 0.401, respectively, P<0.05), and negative correlations with the LSaO2 and MSaO2 in OSAHS patients (r=-0.432, -0.394, -0.403, and -0.267, respectively, P<0.05; and r=-0.591, -0.517, -0.533, and -0.484, respectively, P<0.05).

Conclusion: The levels of plasma HA, PIII, IVC, and LN in OSAHS patients were related to OSAHS. OSAHS might lead to liver fibrosis.

Keywords: Obstructive sleep apnea-hypopnea syndrome (OSAHS), Liver fibrosis, Hyaluronic acid (HA), Procollagen III (PIII), Collagen IV (IVC), Laminin (LN)

Introduction

The main symptom of obstructive sleep apnea-hypopnea syndrome (OSAHS) is recurrent upper airway collapse during sleep, which causes snoring, frequent apnea and hypopnea, recurrent nocturnal hyoxemia and hypercapnia, and disordered sleep structure. OSAHS can involve multiple systems and cause damage to multiple organs, and it constitutes an independent risk factor to cardiovascular and
cerebrovascular diseases, which has thus drawn wide attention. More and more evidence has shown that in addition to damage to the cardiocerebral vascular system, OSAHS also damages the respiratory, gastrointestinal, urogenital, endocrine, and musculoskeletal systems. The number of domestic and international studies investigating the impact of OSAHS on the liver is limited, and most of the studies have focused on changes in liver enzymeograms. We have therefore conducted a preliminary investigation involving the relationship between OSAHS and liver fibrosis as evidenced by changes in HA, PIII, IVC, and LN.

Subjects and methods

Subjects of study

Fifty-two patients (45 males and 7 females; age range, 19–69 years; average age, 40.9±11.6 years) with OSAHS [1] were recruited from the outpatient and inpatient departments between December 2010 and June 2013. The patients were divided into 2 groups based on BMI (BMI≥28 kg/m² [n=27] and BMI<24 kg/m² [n=25]). The obesity criteria of the Guidelines for Prevention and Control of Overweight and Obesity in Chinese Adults, published by the Disease Control Department of National Ministry of Health in 2002, were followed [2]. In addition, 30 obesity patients without OSAHS (26 males and 4 females; age range, 22–64 years; average age, 39.2±9.4 years) based on PSG examinations in the outpatient and inpatient departments during the same study period were collected. Thirty patients (26 males and 4 females; age range, 24–63 years; average age, 38.5±10.3 years) were recruited for the normal control group. All of the patients were thoroughly questioned about their medical histories and biochemical testing was performed to exclude specific diseases that can cause fatty liver, such as respiratory and circulatory system diseases, metabolic diseases, viral hepatitis, drug-induced hepatitis, hepatolenticular degeneration, and autoimmune liver diseases. None of the patients had histories of alcohol consumption or the amount of alcohol consumed was <140 and <70 g/w for males and females, respectively, without a history of parenteral nutrition. In addition, all of the patients signed informed consent.

Methods

Human parametric measurements: The height (m) and weight (kg) were measured to calculate the BMI (kg/m²).

PSG: All subjects underwent PSG monitoring for at least 7 h while sleeping to record the AHI, LSaO₂, and MSaO₂.

Determination of HA, PIII, IVC, and LN: All patients had been subjected to abrosis for 12 h overnight. Three milliliters of blood was drawn from the antecubital vein while fasting between 06:15 and 07:00 the next morning, and the samples were sent to the biochemical laboratory of our hospital for determination of HA, PIII, IVC, and LN levels.

Statistical analysis

All data are expressed as the X±s. A t-test or analysis of variance was used when all measurement data were normally distributed. Enumeration data were tested by a χ² test. SPSS16.0 statistical software was used for statistical analysis. A P<0.05 indicated statistical significance.

Results

Basic information has been listed in Table 1. Among all groups tested, age had no statistical significance after one-way analysis of variance (P>0.05). Gender had no statistical significance on χ² testing (P>0.05).

Based on BMI, it was shown that among obese and normoweight patients, the levels of HA, PIII, IVC, and LN were higher than the non-OSAHS patients (P value <0.05). Based upon AHI, it was shown that the levels of HA, PIII, IVC, and LN in the obese patients were higher than the non-obese patients (P<0.05). The levels of HA, PIII, IVC, and LN were higher in the obese OSAHS patients than the other 3 groups (P<0.05).

Results of correlation analysis between the levels of HA, PIII, IVC and LN in OSAHS patients, BMI and sleep monitoring indicators are listed in Table 2. The levels of HA, PIII, IVC, and LN had a positive correlation with the AHI of OSAHS patients (r=0.701, 0.523, 0.639, and 0.421, respectively, P<0.05). The levels of HA, PIII, IVC, and LN had a positive correlation with BMI of OSAHS patients (r=0.565, 0.441, 0.475, and 0.401, respectively, P<0.05).

The levels of HA, PIII, IVC, and LN had a negative correlation with the LSaO₂ of OSAHS patients (r=−0.432, −0.394, −0.403, and −0.267, respectively, P<0.05).
Table 1. Basic information of patients in all groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Gender (male/female)</th>
<th>BMI (kg/m²)</th>
<th>AHI (times/h)</th>
<th>L SaO² (%)</th>
<th>M SaO² (%)</th>
<th>HA (ng/mL)</th>
<th>PIIP (ng/mL)</th>
<th>IVC (ng/mL)</th>
<th>LN (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese OSAHS patients</td>
<td>42.0±7.7</td>
<td>23/4</td>
<td>30.2±1.4</td>
<td>39.3±15.7</td>
<td>74.8±7.5</td>
<td>86.1±6.1</td>
<td>91.7±19.0</td>
<td>10.1±3.6</td>
<td>88.5±12.7</td>
<td>98.2±16.9</td>
</tr>
<tr>
<td>Normoweight OSAHS patients</td>
<td>40.1±8.4</td>
<td>22/3</td>
<td>30.2±1.3</td>
<td>3.6±1.0</td>
<td>96.5±1.3</td>
<td>98.2±1.0</td>
<td>46.7±10.4</td>
<td>5.7±2.5</td>
<td>39.2±11.7</td>
<td>55.7±9.3</td>
</tr>
<tr>
<td>Obese non-OSAHS patients</td>
<td>39.2±9.4</td>
<td>26/4</td>
<td>30.2±1.9</td>
<td>3.4±1.0</td>
<td>96.2±1.0</td>
<td>98.6±0.8</td>
<td>22.6±10.8</td>
<td>2.8±0.9</td>
<td>22.8±8.3</td>
<td>29.1±8.6</td>
</tr>
<tr>
<td>Normoweight non-OSAHS patients</td>
<td>38.5±10.3</td>
<td>26/4</td>
<td>20.9±1.5</td>
<td>3.6±1.0</td>
<td>96.7±1.3</td>
<td>98.6±0.8</td>
<td>22.6±10.8</td>
<td>2.8±0.9</td>
<td>22.8±8.3</td>
<td>29.1±8.6</td>
</tr>
</tbody>
</table>

Note: *The OSAHS group was compared with the non-OSAHS group (matched BMI), P<0.05; †The obese patients were compared with the non-obese patients, P<0.05; ‡The obese OSAHS patients were compared with the other three groups, P<0.05.

Table 2. Correlation analysis (correlation coefficient) between serum fibrosis markers of OSAHS patients and BMI and sleep monitoring indicators

<table>
<thead>
<tr>
<th>Serum fibrosis marker</th>
<th>AHI (times/h)</th>
<th>BMI (kg/m²)</th>
<th>SaO² (%)</th>
<th>M SaO² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HA (ng/mL)</td>
<td>0.701*</td>
<td>0.565*</td>
<td>-0.432*</td>
<td>-0.591*</td>
</tr>
<tr>
<td>PIIP (ng/mL)</td>
<td>0.523*</td>
<td>0.441*</td>
<td>-0.394*</td>
<td>-0.517*</td>
</tr>
<tr>
<td>IVC (ng/mL)</td>
<td>0.639*</td>
<td>0.475*</td>
<td>-0.403*</td>
<td>-0.533*</td>
</tr>
<tr>
<td>LN (ng/L)</td>
<td>0.421*</td>
<td>0.401*</td>
<td>-0.267*</td>
<td>-0.484*</td>
</tr>
</tbody>
</table>

*P<0.05.

The levels of HA, PIIP, IVC, and LN had a negative correlation with the MSaO² of OSAHS patients (r=-0.591, -0.517, -0.533, and -0.484, respectively, P<0.05).

**Discussion**

OSAHS is closely associated with metabolic syndrome (MS). Intermittent hypoxia, hypercapnia, sleep deprivation, and awakening play a vital role in the occurrence and development of MS. Insulin resistance, dyslipidemia, and obesity exacerbate OSAHS, thus creating a vicious circle. Due to such a close association between the OSAHS and MS, the co-existence of OSAHS and MS z-syndrome has been suggested [3].

The liver is the most important organ involved in patients with glucose and lipid metabolic disorders. Insulin resistance and lipid metabolic disorders can lead to hepatic cell lipodosis and form simple fatty liver, which further causes non-alcoholic steatohepatitis (NASH) under the influence of oxidative stress and lipid peroxidation-associated damage. In the event of persistent NASH, the patient will develop inflammation and necrosis, which is converted to fatty liver fibrosis [4, 5]. The occurrence of liver fibrosis relies on excitation of hepatic stellate cells. Hyperglycemia can promote proliferation of hepatic stellate cells and collagen synthesis. Insulin resistance can stimulate the amount of free fatty acids (FFA) that flow into the liver. An abundance of FFA peroxisome proliferator-activated receptor a (PPAR-a) increases the concentration of peroxide, gives rise to the generation of oxygen radicals, and induces the release of inflammatory mediators. Various inflammatory mediators activate the hepatic stellate cells, which further proliferate and are activated to develop into muscle fiber cells. Many muscle fiber cells can synthesize extracellular matrix (ECM) protein, and the substantial deposition of ECM eventually leads to the formation of liver fibrosis.

The laboratory diagnoses of liver fibrosis proposed in the *Diagnosis and Treatment Guidelines for Combination of Chinese Traditional and Western Medicine of Liver Fibrosis* [6] and *Consensus of Liver Fibrosis Diagnosis and Therapeutic
Effect Evaluation [7] include histopathologic, imaging, and serum fibrosis marker examinations. Histopathologic examinations provide the most important information with which to support a diagnosis, measure the extent of inflammation and fibrosis, and ascertain the drug therapeutic effect; however, a liver biopsy requires a thick needle penetration, which falls into the category of a traumatic and invasive procedure. Such experiments cannot be conducted for ethical reasons, therefore we selected non-traumatic examination indicators. Non-traumatic examinations consist of imaging and serum fibrosis marker examinations. The serum fibrosis marker examination reflects liver inflammation and fibrosis.

Plasma HA, PIII, IVC, and IN are all markers of serum fibrosis. Joint detection of the serum fibrosis indicators is of importance in establishing a diagnosis [6, 7].

The levels of serum HA, PIII, IVC, and LN in the obese patients were higher than the non-obese patients amongst OSAHS and non-OSAHS patients (P value <0.05), and the levels of serum HA, PIII, IVC, and LN had a positive correlation with BMI.

Whether obese or normoweight, the levels of serum HA, PIII, IVC, and LN in OSAHS patients were higher than non-OSAHS patients, and the levels of serum HA, PIII, IVC, and LN in OSAHS patients had a positive correlation with AHI and a negative correlation with the lowest blood oxygen saturation and the average blood oxygen saturation, which indicated that OSAHS might cause liver fibrosis. Based on a histologic analysis, Kallwitz et al. [8] reported that obese OSAHS patients were more likely to develop fatty liver hepatitis and liver fibrosis when compared with obese patients. Among patients with obesity, more severe OSAHS was associated with more severe fatty liver hepatitis and liver fibrosis [9]. Tatsumi et al. [10] reported in a non-obese OSAHS patients-focused study, that in spite of a similar incidence of simple fatty liver between the OSAHS and non-OSAHS patients, the level of PIIIP, which reflects fibrosis, was associated with the average blood oxygen saturation. Tatsumi et al. [10] believes that the average blood oxygen saturation is a risk factor for fatty liver hepatitis, and OSAHS is one of the mechanisms underlying liver fibrosis. Our research results showed that the lowest blood oxygen saturation and the average blood oxygen saturation were closely associated with liver fibrosis. Animal experiments have confirmed that chronic intermittent hypoxia is a risk factor [11, 12] for changing simple fatty liver into fatty liver hepatitis. In addition, the “two-hit hypothesis” suggests that intermittent hypoxemia in OSAHS patients can further prompt transformation from fatty liver to fatty liver hepatitis, which develops into liver fibrosis [13, 14].

In summary, OSAHS patients might develop liver damage or even liver fibrosis due to insulin resistance [15], nocturnal intermittent hypoxia, and oxidative stress. The explicit mechanism for liver fibrosis caused by OSAHS is not clear. In obese and non-obese patients with OSAHS, determination of the levels of serum HA, PIII, IVC, and LN can help identify damage early to facilitate the timely treatment of primary diseases and to reduce the incidence of liver fibrosis and to improve the prognosis of OSAHS patients. In addition, we plan to conduct experiments with color Doppler ultrasound and CT to further prove the relationship between OSAHS and liver fibrosis.

Conflict of interest

The authors declare no conflict of interest.

References

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