

Obstructive Sleep Apnoea: Another Burden on Cirrhotic Liver

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Abstract: Obstructive sleep apnea syndrome (OSAS) may cause aggressive deterioration in the course of liver cirrhosis and may have an impact on the development of hepatic cell failure in patients with concomitant diseases. Patients and Methods: 34 patients with OSAS and compensated cirrhosis as well as 30 compensated cirrhotic patients were followed for 1 year to demonstrate the effect of hypoxia and body mass index (BMI) on their prognosis. Polysomnography, abdominal sonography, liver function tests and portal venous pressure were assessed on inclusion. Parameters of hepatic de-compensation (HD) as ascites, hepatic encephalopathy and bleeding esophageal varices (variceal hemorrhage) were recorded. Results: BMI was significantly higher in patients with concomitant OSAS and cirrhosis ($p < 0.01$), and manifestations of hepatic de-compensation occurred in 32.3% of those cases compared to 10% in patients with cirrhosis alone ($p < 0.01$) in one year. Positive correlations were recorded between BMI, desaturation index, sleep duration $SpO_2 < 90\%$ and predictors of HD. Multivariate analysis showed that BMI, AHI, sleep duration $SpO_2 < 90\%$, desaturation index were independent predictors of de-compensation, together with high portal venous pressure and lower serum albumin. Conclusion: Obesity and intermittent hypoxemia in OSAS may have deleterious effect on the natural history of compensated cirrhosis independent of portal venous pressure and liver function. Treatment of OSAS and weight reduction may decrease considerable burden on cirrhosis.

Keywords: OSAS, Liver Cirrhosis, Ascites, Hepatic Encephalopathy, Variceal Hemorrhage, Obesity

1. Introduction

Egypt is a heavily populated country, with a strikingly high prevalence of hepatitis C virus (HCV) infection (26%)⁽¹⁾. Also, in Egypt the total prevalence rates of OSA and OSA syndrome (OSAS) are 13.74% and 3.57% respectively⁽²⁾.

Obstructive Sleep Apnea (OSA) is known as chronic condition characterized by repetitive episodes of upper airway collapse during sleep. The intermittent hypoxia (IH) and re-oxygenation may provoke a number of pathological cascades which involve sympathetic over-activity, systemic inflammation, oxidative stress and endothelial dysfunction. These are believed to be the underlying mechanisms of OSA increased cardio-metabolic risk⁽³⁾. Moreover, OSA is associated with all manifestations of metabolic syndrome, including visceral obesity, hypertension, dyslipidemia, and insulin resistance^(4, 5, 6). Recent clinical data suggests that metabolic dysfunction of OSA is associated with nocturnal

IH, independent of obesity^(5, 6).

Several studies examined levels of liver enzymes in serum of patients with OSA. Chin et al., 2003 were the first to report abnormally elevated morning AST levels in 35% of OSA patients⁽⁷⁾. Others reported that in patients with OSA, the liver enzymes levels as ALT and AST were directly correlated with the severity of nocturnal hypoxia but not with apnea-hypopnea index or BMI⁽⁸⁾.

Obesity is a growing epidemic worldwide, involving 20-35% of the population in Western countries^(9, 10). In addition to its known association with OSAS and several deleterious health consequences outside the liver, obesity is a frequent cause of chronic liver disease that can progress to cirrhosis^(11, 12). There is increasing evidence of a deleterious effect of obesity on preexisting chronic liver disease due to hepatitis C, hepatitis B or alcoholic disease and patients with cirrhosis

due to obesity-related liver disease have a lower survival than patients with viral cirrhosis⁽¹³⁾. It was found that obesity was associated with more advanced fibrosis^(14, 15) and with faster histological and/or clinical progression in longitudinal studies of patients with chronic hepatitis C^(16, 17).

2. The aim of this Study Was

1- To investigate if OSA relates to clinical decompensation in cases with liver cirrhosis.

2- To examine the relation between BMI as a marker of obesity and markers of OSA severity (apnea-hypopnea index [AHI], oxygen desaturation index [DI], minimum oxygen saturation, and percentage of time spent with SpO₂ < 90%), and the occurrence of ascites, hepatic encephalopathy and esophageal variceal hemorrhage.

3. Patients and Methods

In this cohort observational study, the study population consisted of patients recruited from the Sleep Lab. Chest Department, Assiut University Hospital, between January 2010 and January 2013, who were referred for clinically indicated sleep study as well as patients with compensated liver cirrhosis (all Hepatitis C patients recruited from National Program Against Hepatitis C Clinic, Assiut, Egypt) referred to Abdominal Sonography unit, Gastroenterology and Hepatology Department, Assiut University Hospital, for follow-up. Thirty-four patients with OSAS and concomitant compensated liver cirrhosis (Group A), and 30 patients with compensated cirrhosis with no OSAS (Group B) were followed for one year for manifestations of hepatic decompensation (ascites, hepatic encephalopathy and variceal hemorrhage).

Patients were treated by liver support measures, diuretics for ascites, spironolactone for portal hypertension, esophageal band ligation or sclerotherapy if needed, and hepatic encephalopathy measures in those who needed it. Treatment with continuous positive airway pressure (CPAP) was available for 11 patients in Group A (for socioeconomic reasons); weight reduction was successful in only 4 patients.

Patients were considered for inclusion if they had compensated cirrhosis and portal hypertension (defined by hepatic vein pressure gradient (HVPG) \geq 6 mmHg), without gastro esophageal varices. The diagnosis of cirrhosis was either biopsy proven or clinically suspected and confirmed by the presence of an HVPG \geq 10 mmHg. Child-Pugh score was calculated in all patients to assess the prognosis in all subjects. At baseline clinical history, physical examination including body weight, blood tests (fasting glucose, lipid profile, and liver function tests), upper gastrointestinal endoscopy, abdominal ultrasonography, and HVPG measurement were performed. Demographic characteristics, sleep and medical history, including cardiovascular diseases (CVD) and metabolic diseases, medication use and habits, were recorded in a standardized questionnaire before the sleep study. Patients were followed every 3 months after

random assignment (1:1 cross-over) until the primary end point of the study (development of hepatic encephalopathy, ascites, or variceal hemorrhage), or until the end of the study.

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters measured by a scale, and patients with BMI >30 kg/m² were defined as obese.

Exclusion criteria were: patients with central sleep apnea, upper airway resistance and narcolepsy. Patients with cerebrovascular diseases or lung diseases with hypoxemia, e. g. chronic obstructive pulmonary disease, smokers and alcoholics were also excluded. Patients with hepatopulmonary syndrome, Porto-pulmonary hypertension, ascites, on diuretic treatment, hepatocellular carcinoma, splenic or portal vein thrombosis, comorbidity with life expectancy < 1 year, use of drugs affecting splanchnic hemodynamics or portal pressure, primary biliary cirrhosis or primary sclerosing cholangitis and pregnancy were excluded at the start of the study. All cirrhotic patients received the same treatment when needed.

4. Polysomnography

Overnight polysomnography was performed in all subjects by a computerized system (Somnostar alpha; Sommedics, Yorba Linda, Calif., USA) at the Sleep Lab, Chest Department, Assiut University, and included the following: electro-oculogram (2 channels), electroencephalogram (4 channels), electromyogram of the sub-mental muscles (2 channels), electromyogram of the anterior tibialis muscle of both legs (2 channels), electrocardiogram and airflow (with an oro-nasal thermistor). Chest and abdominal efforts (2 channels) were recorded and arterial oxy-hemoglobin saturation (SaO₂; 1 channel) was recorded by pulse oximeter with a finger probe. Apnea Hypopnea index AHI was calculated as the number of apneas plus hypopneas per hour of sleep. Patients with AHI \geq 5 events/h were diagnosed as having OSAS. The excessive day time sleepiness of the patients was assessed according to the Epworth Sleepiness Scale (ESS) and values >10 were regarded as pathological. Polysomnographic reports and ESS were revised blindly by 2 expert investigators.

The study was approved by the Ethics Committee of the Faculty of Medicine, Assiut University, and all patients gave written informed consent.

5. Statistical Analyses

SPSS software (Statistical Package for the Social Sciences, version 16.0, SSPS, Chicago, Ill, USA) was used for statistical analyses. The results were expressed as means \pm SD. For comparison of non-parametric values between OSAS patients and controls, the Mann-Whitney test was used. The paired Student's t test was performed within groups to show significant differences. The Pearson correlation test was used to assess the strength of association between clinical and polysomnographic parameters and predictors of hepatic de-

compensation of cirrhosis. Significant determinants identified from these analyses were studied in a stepwise multiple regression. P value <0.05 was considered statistically significant.

6. Results

There was no significant difference in the baseline clinical and biochemical parameters in both groups except the significant increased BMI in Group A compared to Group B ($p < 0.05$) (Table 1).

The data in Table 2 showed the basic differences in polysomnographic parameters that lead to assignment of patient in either group with or without OSAS. Table 3 illustrated that obesity in Group A and Group B was associated with significantly higher AHI, Desaturation index, longer sleep duration $SpO_2 < 90\%$, less minimum O_2 saturation and less sleep efficiency.

During one year of follow up, 32.2% of patient in Group A developed clinical hepatic de-compensation compared to 10% in Group B. Ascites was the commonest presentation (18% vs. 10% in Group A vs. Group B, $P < 0.001$), while hepatic encephalopathy was recorded in 15% Group A and 0.04% Group B ($P < 0.01$) and variceal hemorrhage was recorded in 15% of Group A vs. 0.07% in Group B ($P < 0.01$) (Figure 1).

There was positive correlation between the occurrence of clinical hepatic de-compensation (ascites, hepatic encephalopathy and variceal bleeding) and the BMI in the studied groups as well as the desaturation index, duration of sleep $SpO_2 < 90\%$, PVP and decrease in serum albumin (Table 4, 5).

7. Discussion

Obesity, OSAS and liver cirrhosis are very common in Egypt. With nearly 70 % of its adult population overweight or obese, Egypt is the fattest African country. It is also the 14th fattest country in the world, according to the most recent World Health Organization statistics. The diagnostic criteria for obstructive Sleep apnea (OSA) in the general population, reported to be as high as 24% in Egyptian men and 9% in Egyptian women⁽¹⁸⁾. And unfortunately, Egypt holds a unique position in the epidemiology of hepatitis and liver cirrhosis. Egypt is the home of the highest prevalence of hepatitis C virus (HCV) in the world, with an overall rate of approximately 22%⁽¹⁹⁾.

7.1. Effect of Obesity, OSAS on the Liver

The present study illustrated that BMI (as indicator of obesity), was significantly higher in patients with OSAS and liver cirrhosis (Group A) and obesity in the same group was associated with less AHI, Desaturation index, longer sleep duration $SpO_2 < 90\%$, less minimum O_2 saturation and less sleep efficiency. During the period of follow-up, one-third of patients in Group A developed ascites, hepatic encephalopathy or hematemesis compared to 10% in Group B. In agreement, many studies illustrated that OSAS is

associated with insulin resistance and hyperlipidemia and both conditions are associated with non-alcoholic fatty liver disease (NAFLD)^(20, 21). Berzigotti added that in patients with HCV, the most common cause of cirrhosis, the BMI was an independent predictor of de-compensation⁽¹⁷⁾.

It was suggested that obesity-related variables (specifically insulin resistance and histological features of fatty liver), but not obesity itself, were independently associated with a worse outcome, as defined by histological and/or clinical events, in patients with advanced HCV liver disease. The strong predictive value of BMI suggests that this easily measured variable should be routinely recorded in every patient with compensated cirrhosis as obesity was significantly associated on univariate analysis with the development of outcomes (histological and/or clinical)⁽²²⁾.

The current study illustrated that there was a significant positive correlation between BMI and clinical hepatic de-compensation. Many authors suggested that the exact mechanism underlying the association between obesity and the development of clinical de-compensation in cirrhosis is not clearly identified. Although the effects of hypoxia on the adipose tissue are still incompletely defined, adipose tissue hypoxia was shown to occur in obesity⁽²³⁾, and adipocytes exposed to hypoxia in vitro produced less Adiponectin⁽²⁴⁾. Therefore, hypoxia may be a patho-physiological important link between OSAS, obesity and persistent state of inflammation⁽²⁵⁾. Also, it is worth noting that adipose tissue in obesity is known to acquire a pro-inflammatory, pro-fibrogenic and pro-angiogenic phenotype resulting in the production of adipokines and cytokines (leptin, IL-1 and TNF- α)^(25, 26, 27) with deleterious vascular effects on hepatic inflammation, fibrogenesis and angiogenesis, which may mediate a further worsening of intrahepatic resistance and portal hypertension⁽²⁸⁾.

In the present study, one-year changes in portal pressure (as determined by HVPG) were significantly different among Group A and Group B (Group A had significant increased BMI), with HVPG significantly increased in overweight patients. This observation may suggest that the mechanism by which obesity leads to a greater incidence of clinical de-compensation is, at least in part, by an increase in HVPG, as portal hypertension is responsible for the clinical complications that define this late stage of cirrhosis.

As regards intermittent hypoxia, this study showed that in patients with concomitant liver cirrhosis and OSAS, the levels of AHI, sleep duration $SpO_2 < 90\%$, desaturation index were independent predictors of hepatic de-compensation.

In a previous study, it was demonstrated that sympathetic hyperactivity in OSAS patients is generally considered a major consequence of intermittent hypoxia, and contribute to inflammatory activation and increase release of Hs-CRP, IL-6 and TNF- α ⁽²⁵⁾. In patients with OSAS, hypoxia was considered as one of the aggravating factors for development of NAFLD⁽²⁰⁾, and OSA was also regarded as one of the factors that accelerate the progression of NAFLD to non-alcoholic steatohepatitis (NASH)⁽²¹⁾.

Theoretically it was suggested that free fatty acid (FFA)

flux to the liver induced by intermittent hypoxia may up-regulate I κ B kinase β resulting in phosphorylation and degradation of I κ B followed by activation of NF- κ B and this leads to synthesis of many pro-inflammatory cytokines like: tumor necrosis factor- α (TNF- α), interleukin6 (IL-6), and macrophage inflammatory protein-2 (MIP-2)^(29,30). In the presence of obesity and hepatic steatosis, intermittent hypoxia increased mRNA and protein levels of pro-inflammatory cytokines as TNF- α , IL-1, MIP-2 and CRP in liver tissue⁽³¹⁾. Intermittent hypoxia may also lead to NASH by up-regulating reactive oxygen species (ROS) generation via NADPH oxidase system⁽³²⁾. The NADPH oxidase stimulates hepatic stellate cells to produce collagen via angiotensin II leading to liver fibrosis⁽³³⁾. Reactive oxygen may also directly stimulate NF- κ B inducing down-stream inflammatory pathways⁽³⁴⁾. Savransky et al., 2007 added that in the absence of obesity, chronic intermittent hypoxia (CIH) leads to mild liver injury via oxidative stress and excessive glycogen accumulation in hepatocytes and sensitizes the liver to a second insult⁽³⁵⁾.

Taken together, intermittent hypoxemia and obesity can interact to induce NASH and accelerate cirrhosis via accelerated adipose tissue lipolysis.

From a clinical point of view the findings of this study may have important implications. Up to now the only modifiable lifestyle-associated risk factor for decompensation in cirrhosis was alcohol ingestion in patients with alcoholic cirrhosis. The current data suggests that in patients with concomitant OSAS and liver cirrhosis, intermittent hypoxia and overweight might play important and independent role in the progression of compensated to decompensated cirrhosis, and might become new non-pharmacological targets for preventing clinical events in this population. Ratzu and his colleagues added that in patients with advanced chronic hepatitis C, weight may be associated with a better outcome, confirming that it can modify progression of chronic liver diseases⁽¹³⁾.

The limitations of this study were: the small sample size as many patients did not complete the follow-up period or were scheduled to Interferon-gamma therapy for hepatitis C during the study. Also this group most of OSAS patient didn't receive any treatment by CPAP due to economic reasons. Finally, the exact details of dietary habits of the included subjects should have been considered as it may be a factor contributing to the development of de-compensation. Further studies on non-obese subjects and on the effect of CPAP in those patients are recommended.

In conclusion, Obesity as defined by increased BMI and intermittent hypoxemia in patients with concomitant OSAS and liver cirrhosis may have deleterious effect on the natural history of compensated cirrhosis independent of increased portal pressure and decreased serum albumin level. Treatment of OSAS by CPAP and weight reduction may decrease considerable burden on cirrhosis.

7.2. Compliance with Ethical Requirements

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Ibrahim declare that they have no conflict of interest. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

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