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Early markers of renal damage in obstructive sleep apnea syndrome (OSAS) patients with or without diabetes mellitus

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ABSTRACT

Background: Although obstructive sleep apnea syndrome (OSAS) has been associated with chronic kidney disease CKD, there are little data about early screening of renal affection in OSAS patients.

Aim of the work: To evaluate renal function in OSAS patients with or without diabetes mellitus (DM) using blood indices [mean platelet volume (MPV) and red cell distribution width (RDW)] and serum neutrophil gelatinase associated lipocalin (NGAL) as early markers of kidney injury.

Patients and methods: This case control analytic study was designed to enroll 20 OSAS patients with DM, 20 OSAS patients without DM, and 20 non OSAS diabetic patients as control group. All patients underwent full over-night attended diagnostic polysomnography. Those with AHI $\geq$5 were considered to have OSAS. Laboratory parameters including complete blood count with MPV and RDW, serum glucose, urea, creatinine, Hemoglobin A1c, urine albumin creatinine ratio UACR and serum NGAL were done to all enrolled participants.

Results: Urine albumin creatinine ratio UACR $\geq$ 3 mg/mmol was found in 11 (55%) of OSAS diabetic group, 6 (30%) of non diabetic OSAS group and in 11 (55%) of D.M group. Both diabetic and non diabetic OSAS patients had significantly higher RDW and NGAL compared to non OSAS diabetic. The diabetic OSAS group had also significantly higher serum urea and creatinine compared to DM group. In OSAS patients, RDW had significant positive correlation with UACR. Meanwhile both RDW and NGAL were determined to have significant positive correlation with desaturation index during sleep, but not correlated to AHI.

Conclusion: Renal impairment is common in OSAS patients but more frequent if associated with diabetes mellitus. RDW% can be used as simple screening test for early detection of renal injury in OSAS patients with or without diabetes mellitus.

Introduction

The process of intermittent, and repeated obstruction of upper airway is known as obstructive sleep apnea syndrome (OSAS), [1] it is considered as risk factor for several pathological conditions e.g. cardiovascular disease, including hypertension, ischemic heart disease, congestive heart failure, cardiac arrhythmias and cerebrovascular stroke [2,3].

Several researches have been carried out on the association between OSAS and chronic kidney disease (CKD) [4]. OSAS has been observed in (41–65%) of patients with CKD [5,6] and CKD occurs in about eighteen percent of patients with severe OSAS [7]. The possible mechanisms for developing CKD in OSAS patients are; apnea related chronic intermittent desaturation, increased both sympathetic and renin angiotensin activity. In addition to oxidative stress, which causes endothelial dysfunction [8], increased platelet conjunction, systemic inflammation, insulin insensitivity, and failure of metabolic regulation [9]. Diabetic nephropathy also has similar physiological risk factors as OSAS [10]. Hyperglycemia leads to the increase of both oxidative and nitrosative burden. Moreover activation of the rennin-angiotensin-aldosterone (RAAS) and endothelin systems result in

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increased pressure either systemic or intraglomerular, with resulting hyperfiltration and albuminuria [11]. It is documented that ratio between albumin and creatinine in urine (UACR) is indicated for diagnosis, classification, and assessment of prognosis of CKD, where a value of (3–29.9) mg albumin/mmol creatinine is considered moderate albuminuria [12].

Red blood cell distribution width (RDW) is an indicator of variability of erythrocyte size. Ineffective erythropoiesis or increased destruction of red cell lead to variable sized red blood cells and a higher RDW [13]. The higher RDW values the more the risk of developing cardiovascular disease and nephropathy in diabetic patients [14]. Mean platelet volume (MPV) is simple, inexpensive and informative parameter [15] which had been found to be increased in patients with glomerular disease and could predict disease progression [16].

Neutrophil gelatinase associated lipocalin (NGAL) (a 25-kDa secretory glycoprotein) is an innate immunity antibacterial factor released by both neutrophils and also cells of renal tubules in response to different injurious processes [16]. Several studies have identified NGAL as a good early marker of chronic renal injury [17–19].

The present study was done aiming to evaluate renal function in OSAS patients with or without DM using blood indices (MPV and RDW) and serum NGAL as early markers of kidney injury.

Patients and methods

This case control analytic study was designed to enroll OSAS and diabetes mellitus patients at Chest department and Internal Medicine department, Assiut University Hospital over a period of 8 months (from June 2016 to January 2017). It included 40 patients diagnosed as OSAS based on polysomnography (AHI $\geq$ 5) of whom 20 patients were diabetic and 20 were non diabetic. Twenty age, sex, and BMI matched patients diagnosed as DM [20] without OSAS was included as a control group. All patients with diabetes were type 2 DM and the duration of diabetes ranges from 10 to 15 years. Informed written consents were obtained from all individuals according to National Ethics Committee. The study was approved by the medical ethics of Faculty of Medicine at Assiut University.

Exclusion criteria:

1. Patients with other respiratory diseases (COPD, bronchial asthma, interstitial lung disease …etc.)
2. Patients with cardiac diseases.
3. Patients with known renal disease.
4. Patients with hypertension.

All participants were subjected to the following

Polysomnography

All patients underwent full over-night attended diagnostic polysomnography (Somnomedics Somnoscreen plus device (Somnomedics, Randersacker, Germany). Sleep stages were recorded by central and frontal EEG channels. Oxygen variables (Desaturation index (DI), average oxygen level and minimum oxygen level) were recorded by pulse oximeter, nasal and oral flow by oronasal flow thermistor while respiratory effort (thoracic and abdominal motion) by inductive plethysmography. Other channels as ECG leads and bilateral lower limb channels were also recorded. The test was then manually scored by a sleep specialist blinded to the study [21]. Those with AHI $\geq$ 5 with obstructive and mixed apneas were considered as cases of OSAS.

Laboratory investigations

Venous blood samples were collected from all patients under standardized conditions. After centrifugation of serum samples, they were divided and stored in aliquots at −80 °C until analysis. Complete blood count (CBC) for all patients were done by ABX Pentra XL80 HORIBA ABX-France. Serum Glucose, urea, creatinine, and creatinine in urine and Hemoglobin A1c were measured by conventional methods using Cobas Integra c311 autoanalyzer, (Roche, Switzerland).

Microalbuminuria was measured by rapid quantitative test which is based on fluorescence immunoassay technology using Fine care. Then urine albumin creatinine (UACR) ratio was calculated. Patients with UACR $\geq$ 3 were considered to have moderate albuminuria and renal injury [12]. Serum NGAL level was measured by Sandwich ELISA technique using wuhan ElAab Science kit (Co. ltd 430074 China).

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 16.0 for Windows (SPSS Inc.; Chicago, IL; USA) was used for data analysis. As the study data were detected to be non parametric using tests of normality (Shapiro-Wilk and Kolmogorov-Smirnov Tests), data were presented as median ± SE (standard error). Chi-square was applied for comparison of qualitative data and Mann Witney *U* test for comparison of continuous data. Spearman test was used for correlation analysis. To determine the best cut-off for RDW% associated with UACR $\geq$ 3 mg/mmol as indicator of renal injury, we calculated the area under the receiver operating characteristic curve (AUC). A P value $\leq$0.05 was considered significant.

Results

We included a total of 60 patients; 40 with OSAS [9 (22.2%)] patients were moderate, and 31 (73.8%) patients were severe]. Twenty OSAS patients were diabetic [mean AHI is 42.5 event/h and mean DI is 65.6/h] and 20 were non diabetic [mean AHI is 33.8 event/h and mean DI is 46.8/h]. Also, 20 non OSAS diabetic patients were included as control cases. There were no significant differences regarding age, gender and BMI among the studied groups. (Demographic data of the studied groups were shown in Table 1). Urine albumin creatinine ratio UACR $\geq$ 3 mg albumin/mmol creatinine as indicator of renal injury was found in 11 (55%) of OSAS diabetic group, 6 (30%) of non diabetic OSAS group and in 11 (55%) of D.M group.

Results of hematologic variables in the studied groups were demonstrated in Table 2. There were no significant differences in all blood variables between diabetic OSAS group and non diabetic OSAS group ($p > .05$). However both diabetic OSAS and non diabetic OSAS patients had significantly higher RDW compared to DM group (13.45 ± 0.43 vs. 11.5 ± 0.18, $p < .001$; 12.85 ± 0.51 vs. 11.5 ± 0.18, $p = 0.017$ respectively). In OSAS patients, RDW was determined to have significant positive correlation with, urine albumin creatinine ratio ($r = 0.474$, $p = .003$) but had significant negative correlation with minimum oxygen saturation during sleep ($r = -0.423$, $p = .008$) (Fig. 1). By applying the receiver operating characteristic curve ROC, the optimum cut off level of RDW associated with UACR $\geq$ 3mg/mmol in OSAS patients was $\geq$13 giving sensitivity 84.6% and specificity 64% (Fig. 2).

Regarding chemical variables, the diabetic OSAS group had significantly higher serum urea and serum creatinine compared to DM group (7.25 ± 0.87 vs. 4.37 ± 0.40, $p = .001$; 80.7 ± 10.54 vs. 59 ± 4.39, $p = .030$ respectively). Despite that there was no significant difference in urine albumin creatinine ratio between the three

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