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Modelling obstructive sleep apnea susceptibility using non-invasive inflammatory biomarkers

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ABSTRACT

Background: Obstructive sleep apnea (OSA) is considered systemic inflammatory disease but airway and systemic inflammatory markers roles in OSA prediction are not widely used in sleep clinics.
Aims: To study some simple inflammatory markers in the serum or exhaled breath that may predict OSA diagnosis or severity.
Methods: The study included 60 participants, 43 OSAS and 17 healthy control. Cases were recruited from Respiratory Sleep Disorders Clinic full night PSG was done, the next morning, fractional exhaled nitric oxide (FENO) was measured, blood sample were collected for measuring Erythrocyte sedimentation rate (ESR) and high sensitivity C- reactive protein (HS-CRP).
Results: Statistically Significant increase in Basal and minimal oxygen saturation, arousal index, FENO, ESR (1st, 2nd hour), HS-CRP with in OSA patients versus controls. While significant increase of HS-CRP, basal, minimal oxygen saturation and arousal index were found in severe OSA no significant differences were founded in (FENO, or ESR (1st, 2nd hour)).The predicted cut off point of FENO, HS-CRP, ESR(1st, 2ndhrs) that can be used in OSA diagnosis were (8,5.5,6.5,13.5) with sensitivity (0.88,0.95,0.83,0.93) and specificity (0.77,0.88,0.63,0.63). While in severe OSA were (24.5, 19.4, 9, 18.5) with sensitivity (0.82, 0.91, 0.82, 0.82) and specificity (0.72, 0.72, 0.72, 0.68) respectively.
Conclusion: OSA patients have increased level of HS-CRP, ESR, and Exhaled FENO which confirm association of inflammation in OSA. These simple inflammatory markers may be used also as simple non invasive predictors to diagnose OSA. Moreover, the HS-CRP may be used as a useful parameter to predict OSA severity.

Introduction

OSA has been associated with increased in biochemical markers of inflammation. Different inflammatory markers are proved to be elevated in OSA patients such as FENO, CRP, IL-6 and (TNF- a), but they are not routinely used in all sleep clinic [1]. However repetitive airway occlusion associated with intermittent nocturnal desaturation may induce the production of oxygen free radicals and cause local and systemic inflammation [2].

Nitric oxide (NO) plays a significant role in regulating vascular tone and airway in humans, It can be easily measured in exhaled air to diagnose and evaluate the severity of airway and alveolar inflammation [3].

C-reactive protein (CRP) is synthesized in the liver and regulated by cytokines. Unlike cytokines, CRP levels are stable in the same individual over 24 h and may reflect the level of inflammatory response [4].

Erythrocyte sedimentation rate (ESR) can asses the ability of red blood cells to aggregate and reported to be increased in different inflammatory diseases [5].

Although ESR is low cost, simple and applicable test for prediction of cardio- vascular disease, few studies were done on the relationship between the degree of plasma ESR level and OSA severity [6,7].

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So we aimed to investigate the levels of some inflammatory markers in the serum and exhaled breath of OSA patients such as: ESR, HS-CRP, and Fractional Exhaled Nitric Oxide (FENO) and if they could help to predict OSA diagnosis or severity.

Patients and methods

We conducted a case- control study including 60 patients (43) newly diagnosed as OSA and (17) healthy control. All participants included in this case-control study were non-smokers and free of any inflammatory disorders (allergy, bronchial asthma, gastro-esophageal reflux disease, cardiovascular diseases and cerebrovascular diseases) or use of any medication including (systemic or inhaled corticosteroids, antihistaminic, cysteinyl leukotriene receptor inhibitors), or had upper or lower respiratory tract infection 2 weeks before sampling. Control healthy subjects were also free from any sleep disorders symptoms. Cases were recruited from Sleep disorders breathing clinic in Pulmonary Medicine Department – Mansoura University – Egypt.

All participants in this study had in laboratory, attended, full night polysomnography using (SONMOscreen™ plus, SOMNOmedics, Germany) with AASM standard montage, where it was interpreted according to the recent manual scoring criteria [8] were they diagnosed as OSA or normal participant according to the third international classification of sleep disorders [9]. Then they were classified according to apnea hypopnea index (AHI) into two main groups: cases (AHI $\geq$ 5) with symptoms suggestive of OSA (e.g. sleepiness, fatigue, nocturnal chocking, witnessed apnea and insomnia) or when the individual has 15 or more obstructive respiratory events/hour can be classified as OSA regardless of symptoms and co morbidities (n = 44) and control (AHI < 5) (n = 17). Cases were classified into two subgroups into severe OSA (AHI $\geq$ 30) (n = 34) and non-severe OSA (AHI < 30) (n = 9).

Spirometry was done to all participants in the same condition with three trials and the highest acceptable recordings was considered, Forced Vital Capacity (FVC), Forced Expiratory Volume after 1 s (FEV1) and FEV1/FVC were measured.

At the next morning of the sleep study blood samples were collected, HS-(CRP) samples were collected by standard method and measured by turbidimetry using CRP LATEX: Biosystems reagents and instruments [10] while ESR was measured by the standard method [11].

FENO was measured next morning after full night polysomnography by a portable electrochemistry-based device (NO breath″, Bedfont Scientific Ltd., UK). The subjects were advised to avoid vigorous exercise, smoking and heavy meals one hour before test. All tests were conducted according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [12]. Results were documented in part per billion (ppb). Subjects were asked for 10 s expiration with a constant flow (50 ml/s) and pressure (10 cm H2O) in a sitting position. Measurements were repeated until we obtained at least two acceptable maneuvers with FENO differences less than 4 ppb. The mean of two tests was reported as the final result [12].

Statistical analysis

Data was analyzed using SPSS version 16 for Windows® (SPSS Inc, Chicago, IL, USA). Qualitative variables were described as number and percent. Chi-square test or Fisher exact test of significance was used for comparison between groups, as appropriate. Quantitative variables were first tested for normality distribution by Shapiro test. Normally distributed variables were described by mean ± SD, then compared by unpaired *t*-test (t). Non normally distributed variables were described by median (min-max) and compared by independent Mann-Whitney test (Z) was used. P value $\leq$ .05 was considered statistically significant Receiver operating characteristics (ROC) curve for detection of accuracy of test and cut off points for severity of OSA.

Results

Demographic data of the studied group were shown in Table 1, they were (60) participants (43) were newly diagnosed OSA and (17) were healthy control with no statistically significant differences between two groups as regard (age, sex, BMI and FEV1/FVC). While there were statistical significant increase in (Basal and minimal oxygen saturation, arousal index, FENO, ESR (1st, 2nd hour), HS-CRP) in OSA patients versus control group with *p* value < .001 for all (Table 2).

In comparison between severe and non- severe OSA, there were statistically significant higher (basal oxygen saturation, minimal oxygen saturation arousal index, and HS-CRP) in OSA group, while there were no significant differences were found as regard (age, BMI, FENO, ESR (1st, 2nd hour) between two groups (Table 3).

The validity of predicted cut off point of FeNO, HS-CRP, ESR-1& ESR-2 in prediction of OSA were (8, 5.5, 6.5, 13.5) with sensitivity (0.88, 0.95, 0.83, 0.93) and specificity (0.77, 0.88, 0.63, 0.63) while in severe OSA prediction were (24.5, 19.4, 9, 18.5) with sensitivity (0.82, 0.91, 0.82, 0.82) and specificity (0.72, 0.72, 0.72, 0.68) respectively.

Discussion

Airway inflammation in OSA is mostly caused by release of inflammatory mediators due to nocturnal apneas and hypopneas [13].

Many studies reported that patients with OSA have systemic inflammation, with elevated inflammatory mediators such as intercellular adhesion molecules (ICAM) and C-reactive protein [14,15].

So our study aimed to investigate measurement of levels of some inflammatory markers in the serum and exhaled breath of OSA patients such as, ESR, HS-CRP and (FENO) and if they could help to predict OSA or its severity.

Our results revealed that exhaled NO (FENO), ESR (1st, 2nd hour), and HS-CRP measured during daytime in standard conditions in subjects with OSA, as well as basal and minimal oxygen saturation, and arousal index were significantly higher than in subjects without OSA That seems to be similar to multiple previous studies [1,2,16,17] who documented increased level of exhaled NO (FENO) and HS-CRP in OSA subjects so we are supporting previous studies who confirmed that OSAS is associated with both airway and systemic inflammation [14,15]. However, we did not find significant difference in FENO level between subjects with severe versus non severe OSA in our study which differ in (Fortuna et al.) [17] who showed high FENO level and low alveolar nitric oxide [CANO] in severe OSA patients vs healthy subjects.

The result of our study showed also that the specificity of FENO to diagnose OSA was best at 77% when the level of FENO exceeded 8 ppb in subjects with OSA, while the sensitivity was 88%This result were near to (Zhang et al.) [18] who had 16 studies to assess the difference in FENO levels between patients with OSA and controls by a meta-analysis and 5 studies for alveolar nitric oxide [CANO] in OSA patients, he concluded that FENO levels were significantly higher in patients with OSA compared with the control group (6.32 ppb, 95% confidence interval [CI] 4.46–8.33, P < .001). however no significant difference in CANO between both groups

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