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Correlating BMI, BP and Neck Circumference with AHI to predict OSA

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ABSTRACT

Study Objective: *Obstructive sleep apnea (OSA) is a cause of multiple significant comorbidities and affects hundreds of millions of patients. The prevalence of OSA for adults between the ages of 30 and 70 years old is estimated to be 26%, while the prevalence for the general adult population of more than 18yrs is as high as 38%. Even though OSA affects such a large proportion of the population, the majority of cases are undiagnosed, and approximately 90% of US adults are untreated. These health factors and the economic impact highlight the substantial importance of having accessible and accurate screening tools for OSA.*

Subjects and Methods*: This is a retrospective analysis of adult volunteer subjects who were recruited for this study. Overall well-being was assessed via questionnaire survey, and physical attributes were extracted from EHR. Daytime saliva and serum were collected from participants ranging between 11am-4pm. PSG was used for the diagnosis of OSA according to AASM guidelines.*

Results: *BMI did not correlate with a high blood pressure (BP) in the newly diagnosed OSA patient pool, as well as in the general pool of patients. BMI correlated better with neck circumference in the OSA patients. A high BMI was associated with a high AHI value in the newly diagnosed OSA patients. Systolic and diastolic BP correlated with levels of AHI but not for neck circumference in the OSA patients. ESS was not a good predictor of OSA in patients. Levels of DHEA, afternoon cortisol and 17-OH progesterone in saliva of OSA patients were significantly lower when compared to the normal reference range for each marker.*

Conclusion: *A composite value of large BMI and neck circumference in addition to a high systolic blood pressure may be good indicators of AHI values to assess for OSA risk. Serum glucose was not a good predictor of OSA. However, abnormal levels of products from the adrenal cortex in OSA patients may indicate dys-regulation of the gluconeogenic pathway that may serve as early biomarkers easily accessible from the saliva.*

Keywords

Obstructive Sleep Apnea, Body mass index, Apnea-hypopnea index.

Introduction

The risks of hypertension, type II diabetes mellitus (T2DM), hypercholesteremia, depression, gastro-esophageal reflux disease, heart disease, metabolic dysregulation, and stroke are tied to OSA and are increased when OSA is left undiagnosed [1,2]. In addition to the negative impact on population health, the American Academy of Sleep Medicine (AASM) released an analysis estimating the economic burden of undiagnosed OSA at approximately $150 billion a year. Additionally, an estimated annual savings of approximately $100 billion a year would be produced if all cases of OSA in the US were diagnosed and treated *[3]*. These health and economic factors highlight the substantial importance of having easily accessible and accurate screening tools for OSA.

Current accessible screening for OSA is largely reliant on the following: the STOP-BANG (SB) questionnaire, the Epworth Sleepiness Scale (ESS), and the 4-Variable screening tool (4-V) [4,5]. The SB questionnaire is more targeted to OSA and consists of eight yes/no questions. The first four questions relate to self-assessment, while the subsequent four questions relate to clinical measurements. It has been found to have the highest sensitivity compared to the other two, but importantly it also has the lowest specificity [5]. The ESS is a non-specific measure of daytime sleepiness. It consists of eight questions that are answered on a scale from zero to three that reflect the likelihood of falling asleep during certain daytime activities. The ESS provides the second highest specificity, however it is less specific for more severe OSA and is prone to false-negatives [4,5]. The 4-V screening tool is an equation that uses gender, BMI, blood pressure, and self-reported snoring. It equates to: OSA = (gender*4) + (BMI category value) + (BP category value) + (snoring*4). This equation provides the highest specificity, only when values are >14, at which point sensitivity is only 51% [5]. Overall, each of these screening tools contains inherent weaknesses, and guidelines from the Journal of Clinical Sleep Medicine state none should be used diagnostically [4].

The gold standard objective diagnostic procedure for OSA is a polysomnographic recording [6]. Polysomnography (PSG) is an overnight measurement of several physiological signals, including electroencephalography (EEG) to measure sleep and a comprehensive recording of respiratory parameters. The recording is annotated by a sleep technician and evaluated, together with symptomatology, to diagnose the presence of sleep-related disorders [7]. The number of annotated respiratory events divided by the sleep time yields the apnea-hypopnea index (AHI) [8]. AHI thresholds of 5, 15, 30 events/h correspond to mild, moderate and severe OSA, respectively.

While polysomnography is a preferred tool for diagnosing OSA, it has its challenges [9], and is not as cost-effective or as convenient as a biomarker. OSA biomarkers provide a promising avenue of research that could overcome the flaws of the above screening and diagnostic tools by cost-effectively providing high specificity and sensitivity while also measuring disease severity.

The objective of this pilot study was to determine if a combination of vital signs and biomarkers from the saliva may predict OSA and its severity in adult patients. Such combinations may be further investigated and validated for measurable biochemical characteristics that can be associated with the severity of OSA, as a diagnostic tool that is both more cost-effective and convenient than polysomnography.

Material and Methods

The study was approved by the institutional review board at participating center and carried out in accordance with The Code of Ethics of the Declaration of Helsinki. Written informed consent was obtained from all subjects. Adult volunteer OSA patients were diagnosed via attended polysomnography for confirmation of diagnosis within the AASM accredited center and as per routine clinical practice. All PSG data were scored by a certified registered polysomnography technologist (RPSGT) using American Academy of Sleep Medicine (AASM) criteria. Apnea–hypopnea index (AHI) was used in the diagnosis and assessment of severity according to AASM approved guidelines [4].

Clinical evaluation included a sleep history, physical examination, and follow up under the supervision of a board-certified sleep medicine specialist. Questionnaires were completed and medical histories were obtained before the subjects underwent sleep studies. Daytime sleepiness was assessed by the Epworth Sleepiness Scale (ESS); ESS scores range from 0 to 24; a score >10 indicates excessive daytime sleepiness [9].

Overall well-being was assessed via a questionnaire survey at the beginning and at follow-up during the study. Additionally, data from health records were collected, recorded, analyzed, and compared for changes in blood pressure, body weight, neck circumference, serum glucose and lipids, and saliva for mid-day DHEA-S, cortisol, and 17-OH progesterone at initial diagnosis of OSA. Data from all other patients not evaluated for OSA were analyzed and used for comparison where relevant.

Measurements

The questionnaire survey assessment tool was divided into three sections: socio-demographic factors, anthropometric measures, and biochemistry. The questionnaire gathered information on demographics such as age, gender, and educational background; risk factors of chronic diseases such as smoking, alcohol intake, diet, and physical exercise; prevalence of chronic diseases including hypertension, diabetes mellitus, and dyslipidemia.

The anthropometric measures evaluated height and body weight as measured in the upright position to the nearest 0.5cm and 0.1kg, respectively. Volunteers underwent measurement of neck or waist circumference taken at specified times throughout the study.

Blood pressure for each subject was taken in the sitting position after 30 minutes of rest and recorded in their medical chart at each visit. Three readings each of systolic and diastolic blood pressures were recorded with an interval of five minutes at the least, and the mean of each measure was used for the data analysis.

Sample collection and biomarker testing

Saliva, collected during the day between 11 am and 4 pm with no specific prior restrictions to subjects were immediately stored in -80 C and then shipped with coded labels to a third party commercial laboratory for processing.

Biochemical analysis

Sampling of easily accessible bodily fluids (serum and urine) were collected and sent under appropriate standardized conditions to an external commercial laboratory for biochemical analysis.

Results

Figure 1

Approximately 247 participants were enrolled and pooled for this study. To determine if there is a relationship between systolic and diastolic blood pressure (BP) relative to neck circumference in the newly diagnosed OSA patients, systolic and diastolic values were plotted against neck circumference from data obtained from EMR charts. Figure 1a shows no specific pattern of correlation of BP with neck circumference in the general pool of patients. Figure 1b shows a linear trend towards an increase in neck circumference with higher systolic and diastolic BP levels in newly diagnosed OSA patients. Patients with a primary diagnosis of OSA had a BMI greater than 27.53; however, the BMI of OSA patients did not correlate with BP Figure 1d. The general pool demonstrated a trend that higher systolic and diastolic BP could be associated with higher BMI levels (Figure 1c).

Figure 2

In this study, OSA was assessed based on the Apnea-hypopnea index (AHI) which were plotted as arbitrary units to compare with systolic and diastolic blood pressure (A), BMI (B) and neck circumference (C). In the subset of patients newly diagnosed with OSA we observe trends that correlate systolic and diastolic blood pressures with AHI (A). Additionally, the peaks for BMI and AHI overlap and coincide with higher BMI correlating with increased AHI values (B). However, no significant association or trend is observed for AHI and neck circumference (C).

Figure 3

Figure 3 shows no difference in the pattern of expression or trend for the Epworth Sleepiness Scale (ESS) between the newly diagnosed OSA patients and the rest of the participants.

Figure 4

DHEA-S and 17-OH progesterone are commercially available tests that can be easily performed from saliva of patients. Here we measured the values of DHEA-S and 17-OH in afternoon saliva in OSA patients, which were significantly lower than the established reference range. Additionally, while measuring afternoon saliva cortisol may be challenging due to several factors that may influence its secretion, our data shows a trend towards a lower than reference value in saliva of afternoon cortisol levels.

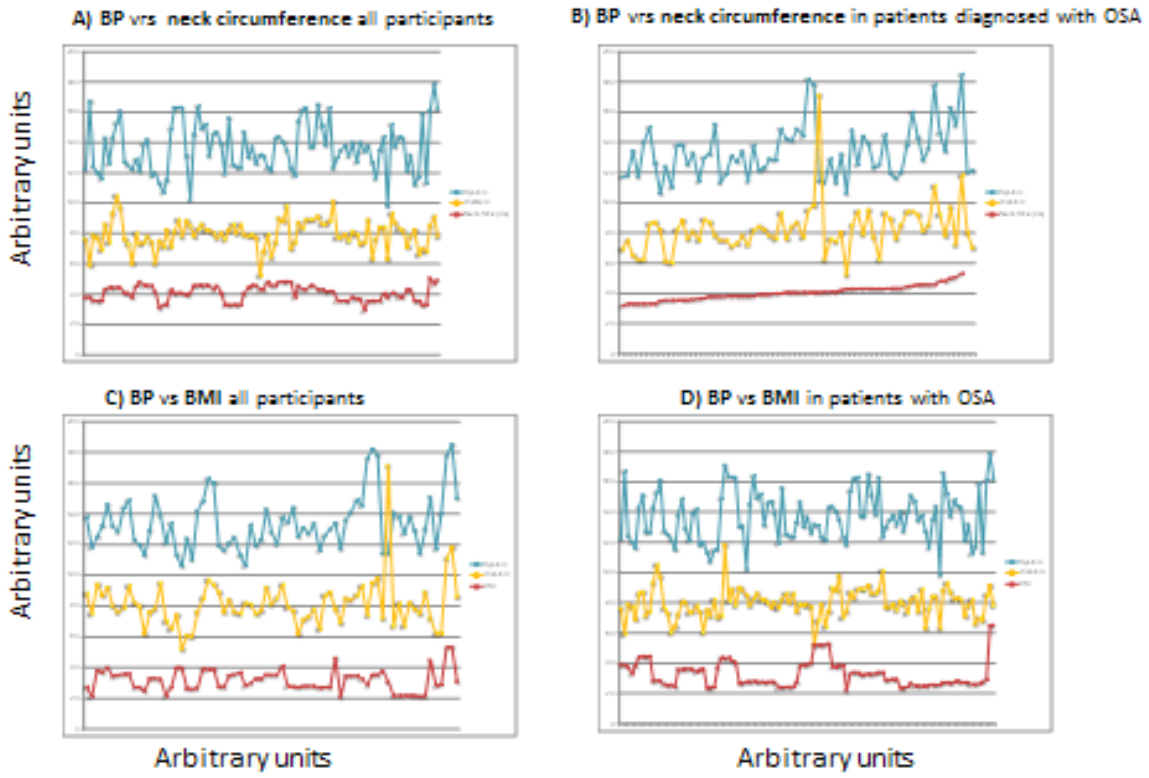

Figure 1: Blood Pressure (BP) correlates better with neck circumference compared to BMI in newly diagnosed OSA patients. No specific pattern of correlation of BP with neck circumference or BMI can be observed in the general pool of patients.

A) Separation of systolic (blue) and diastolic (yellow) BP values in arbitrary units, plotted against neck circumference from a general pool of patients.

B) Separation of systolic (blue) and diastolic (yellow) BP values in arbitrary units, plotted against neck circumference from newly diagnosed patients with OSA.

C) Separation of systolic (blue) and diastolic (yellow) BP values in arbitrary units, plotted against body mass index (BMI) from a general pool of patients.

D) Separation of systolic (blue) and diastolic (yellow) BP values in arbitrary units, plotted against body mass index (BMI) from newly diagnosed patients with OSA.

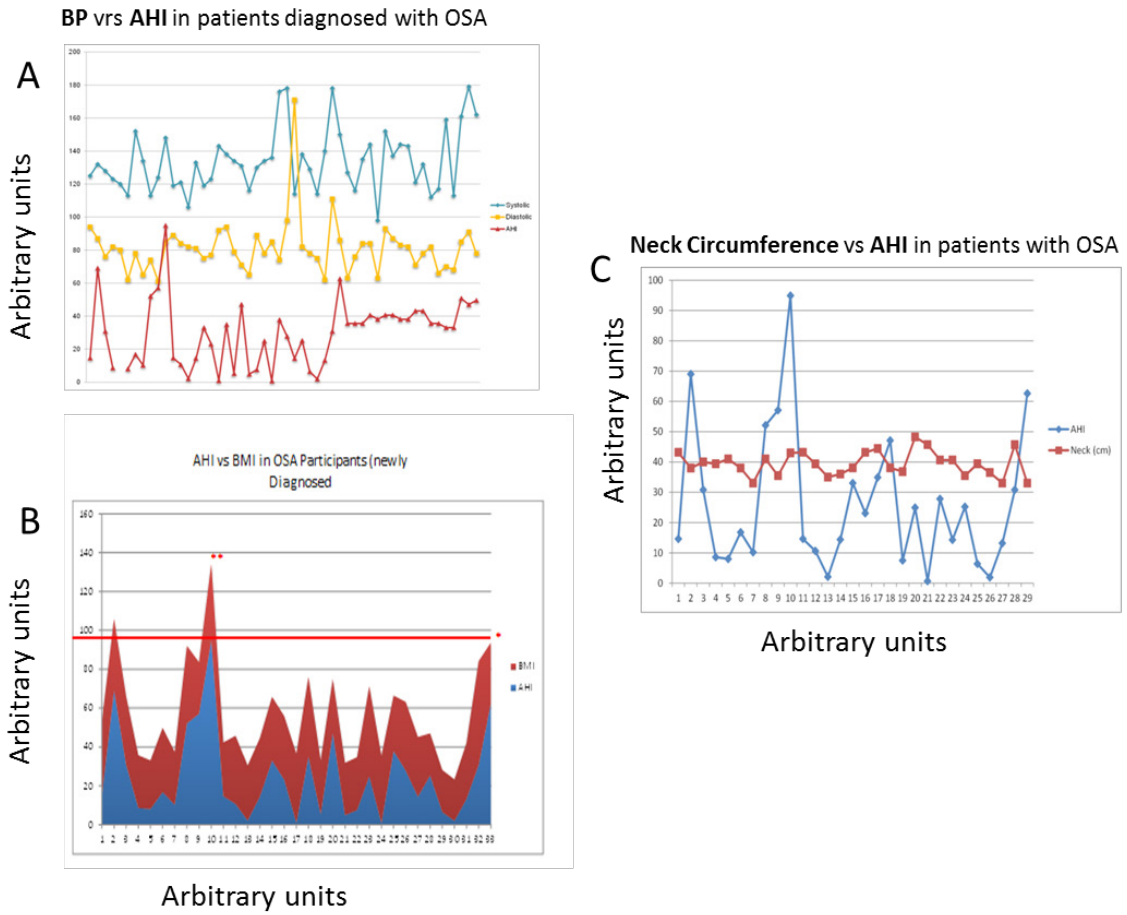

Figure 2: Values for AHI and BMI plotted at arbitrary units showed correlations for both newly diagnosed patients with OSA as well as all subjects. Overall, the BMI for the newly diagnosed OSA patients trended higher compared to all subjects.

Values for BMI (red) and AHI (blue) were plotted for both newly diagnosed OSA patients and all subjects. Insert shows the levels in all subjects. Red horizontal line is the cut-off value point for all subjects at ~ 100 arbitrary units*. The highest BMI peak was at ~ 140** arbitrary units for the OSA patients.

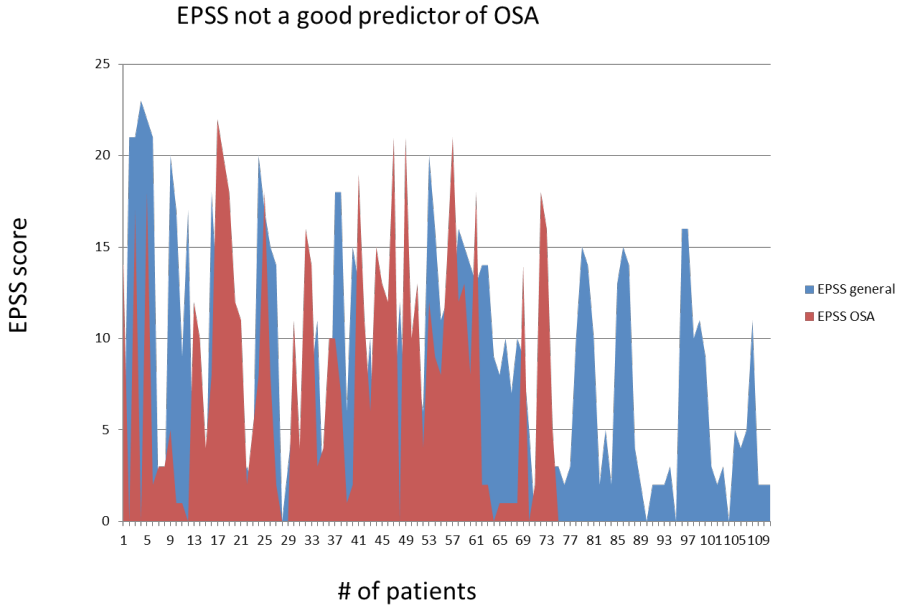

Figure 3: No difference in the Epworth sleepiness scale (EPSS) obtained from questionnaire in new diagnosed OSA patients and the general pool of patients.

The score values of EPSS obtained from the general pool of patients (blue) compared to patients newly diagnosed with OSA (red).

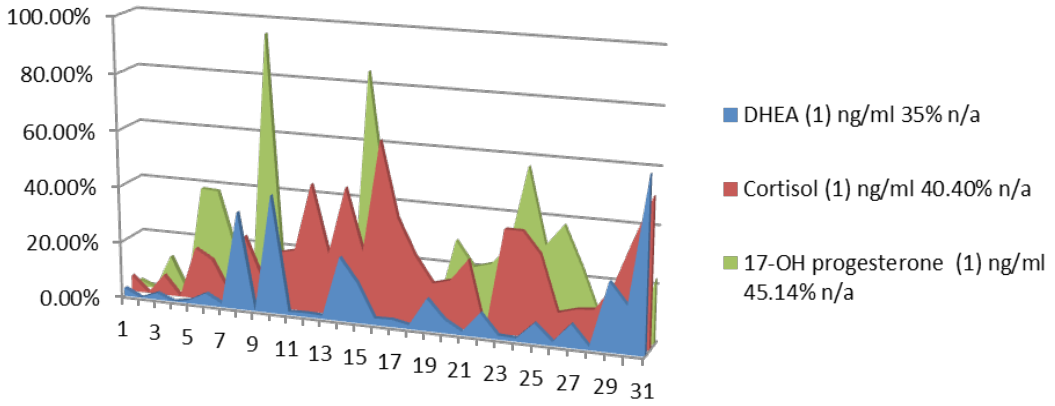

Figure 4: Set at a normal reference range of 100% the relative values of morning (11am) DHEA, Cortisol and 17-OH progesterone plotted from the saliva of newly diagnosed OSA patients show significantly lower levels compared to reference range.

Reference range set at a 100% the graphs shows 11am saliva expression of DHEA-s(blue), cortisol (red) and 17-OH progesterone (green).

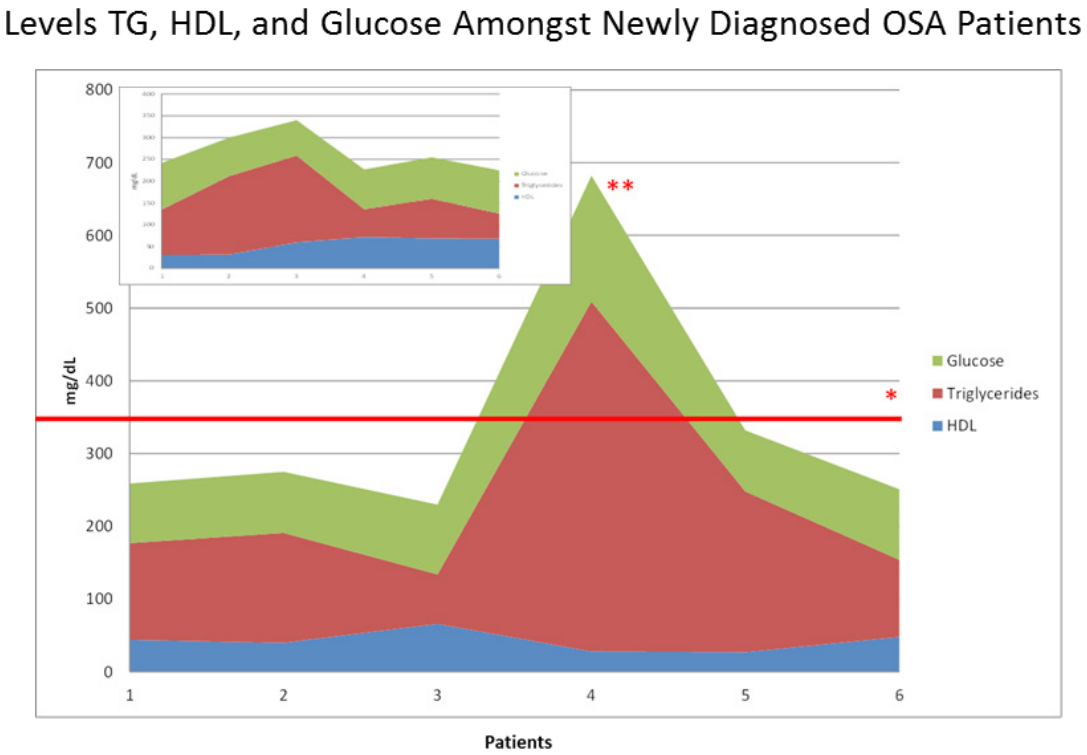

Figure 5: Serum levels of triglycerides (TG), HDL and Glucose in mg/dl measured in patients Figure 5: Newly diagnosed with OSA showed higher levels of glucose and triglycerides compared to all subjects. There were no observed differences with HDL levels.

Levels of triglycerides (TG) in red, Glucose (green) and HDL (blue) were assessed in serum of patients newly diagnosed with OSA. Insert shows the levels in all subjects. Red horizontal line is the cut-off value point for all subjects at ~350 mg/dl*. The highest peak was for glucose in the OSA patients at ~ 700mg/dl ** followed by triglycerides at ~500mg/dl; compared to 350mg/dl and 250mg/dl, respectively for all patients.

Figure 5

OSA has been directly tied to metabolic dysfunction, specifically, glucose regulation and T2DM. Studies are suggestive of OSA contributing to impaired glucose metabolism secondary to sleep fragmentation, sympathetic excitation, and intermittent hypoxia effecting pancreatic B-cell function, insulin sensitivity, and systemic inflammation. We plotted the levels of triglycerides (TG), HDL, and glucose obtained from the EMR of subject's routine lab results. The values for glucose and TG trended higher in the subjects diagnosed with OSA and peaked at twice the levels for glucose in the OSA subjects as compared to the overall subjects.

Discussion

Serious public health consequences are associated with being overweight and obese [10]. Obesity is a major risk factor for the development of OSA. OSA is an established risk factor for

insulin resistance and other cardio-metabolic disorders [11]. The enigma remains whether OSA has any causal role in the adverse metabolic profile, independent of or beyond that due to obesity. Approximately one third of the US population was overweight or obese in 2003-2004 and since then, percentages of overweight individuals have increased exponentially [12]. OSA is one of the most serious medical squeals from obesity, in association with heart disease, hypertension and type 2 diabetes [13]. The costs associated with diagnosis of OSA remain very high and cumbersome i.e. with PSG [14,15]; thus, there is a need for identifying biomarkers that are easily accessible for early identification and stratification of OSA at point-of-care. Biomarkers associated with OSA may also be used as pharmaceutical targets that reduce weight and mitigate adverse effects of obesity, including hyperlipidemia and insulin resistance.

This study sought to compare trends of biometric measurements in OSA patients versus the general patient population and to discern whether specific combination of metrics could predict OSA, as well as serve as an objective biomarker to further the evaluation for OSA in a general patient population.

Neck circumference has been suggested to be a more reliable measure of obesity [16], and a risk factor for hypertension [17], in relation to increasing systolic and diastolic blood pressures. There are several conflicting reports on the studies previously done on the association of neck circumference with AHI or OSA [18-20]. In our study, while a correlation was not observed with AHI, a large neck circumference was associated with a greater BMI.

As previously reported by others, ESS was not effective in differentiating and discriminating newly diagnosed OSA patients with the general population [21,22].

DHEA-S [23,24] and 17-OH progesterone [25] are commercially available tests that are performed from saliva of patients for routine clinical assessment and evaluation. This study showed that the values of DHEA-S and 17-OH Progesterone were significantly lower than the established reference range in the newly diagnosed OSA patients. This finding warrants further investigation and with a larger population pool for validation.

Additionally, while measuring afternoon saliva cortisol may be challenging due to several factors that may influence its secretion and collection [26], our data shows a trend towards a decrease in afternoon salivary cortisol levels. This also warrants further investigation and validation in a larger pool of newly diagnosed OSA patients. Furthermore, the effect of treatment with CPAP on these parameters can determine if the combination of these biomarkers can predict the diagnosis of OSA [27,28].

In summary, our data suggest the following combination: High BP=high BMI=High AHI, where high BMI correlates with a larger neck circumference. A combination of high systolic and diastolic blood pressures, large BMI, and abnormally low DHEA levels may be an objective biomarker signal for the presence of OSA with a high AHI score at diagnosis. These anthropometric measures which are routinely obtained during doctor's visit, in addition to commonly used sleep assessment tools, can help easily identify potential OSA patients that can then be fully evaluated and diagnosed with polysomnographic (PSG) testing.

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