Sleep Medicine 15 (2014) 1547–1553

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Impact of sleep-disordered breathing on metabolic dysfunctions in patients with polycystic ovary syndrome

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ARTICLE INFO

Article history:
Received 19 March 2014
Received in revised form 10 June 2014
Accepted 30 June 2014
Available online 16 September 2014

Keywords:
Polycystic ovary syndrome (PCOS)
Sleep-disordered breathing (SDB)
Metabolic dysfunction
Hyperandrogenism
Insulin resistance
Metabolic syndrome

ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is the most common endocrinological disorder among women in the reproductive age group. These women are prone to develop sleep-disordered breathing (SDB) and metabolic disorders. SDB is also associated with metabolic dysfunctions. We hypothesized that SDB is an independent risk factor contributing to metabolic dysfunctions in women with PCOS.
Methods: Prospective cross-sectional study in which 50 women with PCOS and not on any treatment were selected. They were divided into two groups: Group 1 - PCOS with SDB and Group 2 - PCOS without SDB.
Results: Thirty-three (66%) women with PCOS had SDB. Women in Group 1 had significantly higher systolic blood pressure (SBP) ($P = 0.002$); diastolic blood pressure (DBP) ($P = 0.044$); fasting blood sugar ($P = 0.006$), triglyceride levels ($P = 0.014$) and mean Ferriman-Gallwey score ($P = 0.028$). The HDL was significantly lower in group 1 ($P = 0.006$). In group 1, 42.4% of women had metabolic syndrome ($P < 0.001$). Excessive daytime sleepiness (EDS) was significantly higher in Group 1 ($P = 0.04$). Respiratory distress index significantly correlated positively with waist circumference ($r = 0.551$, $P < 0.001$), SBP ($r = 0.455$, $P = 0.001$), DBP ($r = 0.387$, $P = 0.006$), FBS ($r = 0.524$, $P = 0.000$), homeostatic model assessment ($r = 0.512$, $P = 0.000$), triglycerides ($r = 0.384$, $P = 0.006$), free testosterone ($r = 0.390$, $P = 0.005$), and negatively with HDL ($r = -0.555$, $P < 0.001$).
Conclusion: Women with PCOS and SDB had significantly increased metabolic abnormalities as well as more severe hyperandrogenism. Women with PCOS who have metabolic abnormalities or severe hyperandrogenism should undergo an overnight PSG.

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most prevalent (5–10%) gynecological conditions in premenopausal women [1,2]. It is characterized by anovulation, hyperandrogenism, insulin resistance (IR), obesity, and polycystic ovaries [3,4]. The pathogenesis of PCOS is multifactorial, with IR and compensatory hyperinsulinemia being the key factors. Insulin plays a direct role by acting synergistically with luteinizing hormone (LH) to stimulate androgen secretion from theca cells [5]. It also exerts an indirect effect by decreasing the sex hormone-binding globulin (SHBG) production from the liver, further enhancing androgen levels. This androgenic milieu inhibits the selection of dominant follicles, resulting in accumulation of dysfunctional cystic follicles in the ovary and anovulation [6–8].

Though the clinical presentation of most of these patients shows oligomenorrhea, hirsutism, and obesity, it is the metabolic dysfunctions that can have far-reaching, serious consequences. Several studies have shown that women with PCOS are prone to metabolic disorders such as glucose intolerance, type II diabetes mellitus (DM), hypertension, dyslipidemia, and cardiovascular diseases such as hypertension, stroke, and coronary artery disease (CAD) [9–15]. A recent addition to this list of health risks is obstructive sleep apnea (OSA), which has been reported to be higher in women with PCOS in comparison to the general population [6].

Sleep-disordered breathing (SDB) is characterized by repeated episodes of partial or complete cessation of breathing for ≥10 s during sleep. It constitutes a spectrum of disorders of varying severity with intermittent snoring as the mildest and obesity hypoventilation syndrome as the most severe. Heavy snoring, upper airway resistance syndrome, and mild/moderate/severe OSA lie between these two extremes [16]. Prevalence of SDB in women increases with age and body mass index (BMI), and has been reported to be between 2% and 9% [17,18].

The pathogenesis of SDB involves a number of interrelated mechanisms such as anatomically small upper airway and abnormal respiratory control mechanism. The risk of OSA is increased as a function of both total body mass and its distribution. The quantity of visceral fat appears to correlate highly with OSA [19].

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http://dx.doi.org/10.1016/j.sleep.2014.06.023
1389-9457/

Testosterone hormone has also been shown to be a contributory factor in the development of SDB [20]. However, estrogen and progesterone are found to be protective [21].

SDB has several adverse outcomes on the cardiovascular system with increased prevalence of hypertension, CAD, ischemic heart disease (IHD), and stroke. It is also associated with increased prevalence of IR, glucose intolerance, type II DM, and dyslipidemia [22–25].

The overall prevalence of both SDB and PCOS in general population is similar, ranging from 2% to 10%. Both of these conditions have very similar metabolic and cardiovascular complications, indicating a close association between the two.

We hypothesized that SDB is an independent risk factor contributing to the metabolic dysfunctions in women having PCOS. To test this hypothesis, we decided to study the impact of SDB on metabolic dysfunctions in patients with PCOS.

2. Methods

This was a cross-sectional study in which 50 women with PCOS attending the gynecology outpatient department and reproductive endocrinology clinic of Vardhaman Mahavir Medical College (VMMC) and Safdarjung Hospital were randomly selected.

PCOS was defined by the Rotterdam criteria, that is, the presence of any two of the following three features: (1) chronic oligomenorrhea (six or fewer spontaneous menses per year); (2) biochemical or clinical evidence of hyperandrogenism; and (3) polycystic ovaries on ultrasonography [1,26]. Women on any form of treatment for PCOS were not included in the study. Patients with thyroid disorders, hyperprolactinemia, congenital adrenal hyperplasia, smokers, and those with neurological or psychiatric disorders were also excluded from the study.

All women gave written informed consent before participation in this study, which had the approval of the ethics committee of VMMC and Safdarjung Hospital.

2.1. Subject evaluation

Each woman underwent a detailed examination including measurement of height, weight, waist circumference, blood pressure (BP), and general physical and systemic examination. Clinical severity of hirsutism was also determined using Ferriman–Gallwey (FG) score [27]. BMI was calculated and classified according to Indian Standardization [28]. BMI of <18.4 qualified for underweight; 18.5–22.9 was normal; 23–24.9 was overweight; and >25 was obese.

All the women filled out a detailed sleep questionnaire that also included a subjective evaluation of daytime sleepiness (EDS) using the Epworth Sleepiness Scale. Each subject was asked to rate the probability of falling asleep in eight situations on a score of 0–3. The higher the score, the greater was the sleepiness [29–31].

2.2. Biochemical and hormonal assays

A 75 g oral glucose tolerance test was performed on all the patients. Simultaneously, a fasting and postprandial insulin measurement was carried out using enzyme-linked immunosorbent assay. IR was calculated using homeostatic model assessment (HOMA). A value >3.8 was taken as a marker for IR [32,33]. The fasting sample was also subjected to lipid profile including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride levels. Hormonal assays conducted were serum thyroid-stimulating hormone, serum prolactin, free testosterone, dehydroepiandrostenedione sulfate (DHEAS) and SHBG levels.

Metabolic syndrome (MBS) was defined by the National Cholesterol Education Programme, Adult Treatment Panel (NCEP ACT III) criteria as presence of any three of the following (female-specific range) [34]: FBS ≥110 mg/dL; BP ≥130/85; waist circumference >88 cm; triglyceride ≥150 mg/dL; HDL <50 mg/dL.

2.3. Polysomnography

All 50 patients underwent an overnight polysomnography (PSG), which was performed according to standard laboratory protocol. Data recorded included three-channel electroencephalography (EEG), two-channel electro-oculography, submental and anterior tibialis electromyography, nasal airflow by thermistor, nasal pressure by pressure cannula, thoracic and abdominal efforts by strain gauges, oxygen saturation by pulse oximetry, and tracheal sound recording using microphone attached to the neck. The three EEG channels used were F3M2, C3M2, and O1M2. All signals were simultaneously recorded and stored using a digital PSG system (ALICE 5; Respironics, Inc., Murrysville, PA, USA). A minimum of 7 h of sleep was recorded in each subject. All the PSG records were scored by an experienced sleep medicine consultant.

2.3.1. Definitions of respiratory parameters

- Apnea was diagnosed when there was a drop in the peak thermal sensor excursions by >90% of baseline lasting for ≥10 s. Further, ≥90% of the event duration should have met the amplitude reduction criteria.
- Hypopnea was diagnosed when the nasal pressure signal excursions dropped by ≥50% of the baseline lasting for ≥10 s and were accompanied by a ≥3% drop in oxygen saturation from pre-event baseline or an arousal. Further, ≥90% of the event duration should have met the amplitude reduction criteria.
- Respiratory effort-related arousal (RERA) was defined as an event of increasing respiratory effort or flattening nasal pressure waveform of >10 s followed by an arousal from sleep but which did not meet the criteria for an apnea or hypopnea.
- Respiratory distress index (RDI) was defined as the number of obstructive apneas, hypopneas, and RERAs per hour of sleep. This was calculated by dividing total number of respiratory events with total sleep time in hours.
- SDB was defined as an RDI of ≥5 along with symptoms or an RDI of >15/h with or without associated symptoms. The symptoms include any one of the following: EDS, unrefreshing sleep, gasping or choking, witnessed apneic spells, or nocturia [35].
- Severity of OSA according to RDI was defined as [16,35]: mild OSA, 5 to <15/h; moderate OSA, 15–30/h; severe OSA, >30/h.

The patients were divided into two groups according to their PSG findings. Those with SDB were termed as group 1 and those without SDB were termed as group 2.

The results were tabulated and subjected to statistical analysis. Independent sample *t*-test was used for comparison of continuous variables between the subgroups of PCOS, that is, PCOS with and without SDB. A two-tailed *t*-test was used to calculate the *P* values between these groups. For all analyses, $P < 0.05$ was considered as statistically significant. χ^2-Test was applied to calculate the associations and significance of the categorical values. A multivariate analysis was applied to establish association between these two groups after controlling for BMI. Correlation curves using Pearson correlation (r) were determined for certain variables in the subgroups of PCOS to further emphasize the strength of correlation. For parameters that were not normally distributed, such as free testosterone and diastolic blood pressure (DBP), Spearman's rank correlation coefficient was used instead of Pearson's correlation.