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Original Article

Metabolic changes in normal- and underweight children with obstructive sleep-disordered breathing

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ABSTRACT

Objective: This study evaluates the metabolic profile of normal- and underweight children with sleep-disordered breathing (SDB) due to adenotonsillar hypertrophy.
Methods: A total of 39 children aged 3–15 years with SDB and 28 age- and gender-matched controls were included in the study. Body mass index *z* score, blood pressure, and fasting serum levels of triglycerides (TGs), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, very-low-density lipoprotein (VLDL), blood glucose, plasma insulin, and homeostatic model assessment (HOMA) were determined in both case patients and controls.
Results: We observed significantly lower levels of fasting blood glucose ($p = 0.015$) and higher levels of HDL ($p = 0.002$), LDL ($p = 0.002$), and cholesterol ($p = 0.001$) in case patients than in controls. The mean values of fasting insulin and HOMA were higher in case patients (6.42 ± 6.47 and 1.40 ± 1.48) than in controls (5.31 ± 3.40 and 1.20 ± 0.84) respectively. No direct correlation between indices of severity of SDB and various metabolic and blood pressure parameters was found. When the effect of body weight was studied by subgrouping case patients according to normal weight and underweight, significant increases in the levels of fasting insulin ($p = 0.039$), HOMA ($p = 0.017$), and fasting blood glucose ($p = 0.021$) were observed. Also, a significant correlation was observed between the duration of illness and fasting insulin ($p = 0.023$), HOMA ($p = 0.020$), fasting glucose ($p = 0.004$), and diastolic blood pressure ($p = 0.030$).
Conclusion: This study shows an independent effect of body weight and duration of illness on various metabolic and blood pressure parameters in normal- and underweight children with SDB

1. Introduction

Sleep-disordered breathing (SDB) is characterized by repeated episodes of partial or complete obstruction of the upper airway and is associated with recurrent sleep disruption, intermittent hypoxemia, or periods of sustained hypoventilation. The prevalence of SDB is approximately 1%–3% in children aged 2–18 years, and is equal in boys and girls [1]. In a questionnaire-based study, the authors determined the prevalence of SDB in school children of Delhi to be 4.9% in boys and 4.7% in girls [2]. Metabolic syndrome (Met-S), a well-known risk factor for increased cardiovascular morbidity and mortality, is characterized by high blood pressure and abnormalities in blood glucose and lipid metabolism, and is frequently associated with insulin resistance and obesity [3–7]. Higher levels of blood pressure, insulin resistance, and dyslipidemia have been observed in patients with SDB [8–12]. These metabolic abnormalities have also been found to be independent of obesity in adult patients [13–16]. This has been further supported by studies that have shown significant improvement in parameters of glucose impairment and diabetes control after treatment of SDB with nasal continuous positive airway pressure (CPAP) [17,18]. Intermittent hypoxemia and sleep fragmentation have been shown to be associated with insulin resistance, increased inflammatory markers, and endothelial dysfunction, which may ultimately result in increased cardiovascular morbidity and mortality [19–21]. Few data are available in the literature regarding the role of SDB in metabolic dysfunction in the pediatric population. A few studies conducted in obese adolescent patients with SDB have found similar results and reported a significant association between fasting insulin levels and various indices of severity of SDB independent of body mass index (BMI) [10–12,22–25]. Met-S occurs in 25%–30% of overweight children and 50% of severely obese children [25–27]. Unlike in adults, the improvement of metabolic parameters following CPAP therapy has not been documented in children [28]. Some studies

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that included prepubertal children (one of them having excluded the obese group) did not find any significant association between indices of SDB and fasting insulin levels [29,30]. Whether the effect of SDB on the metabolic abnormalities is independent or is due to the concomitant obesity has always been a matter of debate, and, on this issue, the data conflict. Another factor that has been proposed to be responsible for nonsignificant changes in metabolic parameters is probably the short duration of illness in this population of patients [31].

This study evaluated the metabolic profiles of largely normal-weight or underweight children with SDB due to adenotonsillar hypertrophy. It also examined the exclusive influence of SDB and the effect of duration of illness on metabolic parameters and blood pressure of these patients, independent of the impact of body weight.

2. Methods

2.1. Participants and procedures

A total of 39 children 3–15 years of age, who presented to the outpatient department (OPD) of a tertiary-care teaching hospital with the chief complaints of snoring, mouth breathing, recurrent upper respiratory infections, and adenotonsillar hypertrophy, were included in the study. In addition, 28 age- and gender-matched individuals were included as controls. The controls were selected from children attending the pediatric OPD who were being evaluated for minor illnesses that were considered to have little or no effect on their metabolic profile. None of the controls had any clinical evidence of SDB. The study was approved by the ethics committee of the institution, and written informed consent was obtained from the parents of the children. A detailed analysis of symptoms and meticulous clinical examination were carried out. Children who had chronic medical disease or were on any medication that could affect the metabolic profile were excluded from the study. The duration of illness was calculated from the time that the symptoms (eg, snoring) first appeared. A general survey included noninvasive blood pressure (systolic and diastolic), height, and weight measurement. Blood pressure was measured in the sitting position, and mean of three consecutive measurements was recorded. BMI was then calculated [body weight in kilograms/(height in meters)^2]. The BMI *z* score was determined on the basis of age, gender, and BMI for each patient. A BMI *z* score or standard deviation score indicates how many units of the standard deviation a child's BMI is above or below the average BMI value for that individual's age group and sex [22]. The World Health Organization–recommended cut points of BMI-for-age *z* score were used to assess the child's growth and nutritional status. Children with BMI *z* score of >1 and >2 were classified as "overweight" and "obese," respectively, and those with BMI-for-age *z* score of ≤2 and ≤3 were classified as "thin" and "severely thin," respectively [23]. In our study, we grouped "thin" and "severely thin" together as "underweight." Blood pressure *z* scores were also calculated using recommendations by the National High Blood Pressure Education Program Working Group [24]. Serum levels of triglycerides (TGs), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, very-low-density lipoprotein (VLDL), and blood glucose in the fasting state were estimated using enzymatic methods. Plasma insulin was measured using a commercially available radioimmunoassay kit. The homeostatic model assessment (HOMA) was calculated as a product of fasting insulin and glucose. A HOMA value of >3.16 was considered to be evidence of insulin resistance [30].

The children then underwent fully attended, in-laboratory level-I polysomnography (PSG). Whole-night PSG was performed (Alice 5; Philips Respironics, Murrysville, PA) for 6–7 hours by a trained technologist. The following parameters were measured: two channels each for electroencephalography, electrooculography, and electromyography with submental electrodes, electrocardiography, airflow recording through the nose and mouth by a thermistor and nasal pressure cannula, thoracic and abdominal efforts by plethysmography, oxygen saturation by pulse oximetry, and tracheal sound recording using a microphone attached to the neck. Respiratory events such as apneas, hypopneas, and respiratory effort-related arousals (RERAs) were scored in accordance with the revised American Association of Sleep Medicine scoring rules (2012) [25]. Apnea was scored when there was ≥90% amplitude reduction with more than 90% event's duration meeting the amplitude reduction criteria for the duration of two breaths in association with respiratory effort. Hypopnea was scored when there was ≥30% reduction in amplitude on nasal pressure tracing for a duration of two breaths or more and was associated with either ≥3% oxygen desaturation or an arousal. RERA was scored if there was a sequence of breaths lasting for at least ten seconds characterized by increasing respiratory effort or flattening of the nasal pressure waveform, leading to an arousal from sleep, when the sequence of breaths did not meet criteria for an apnea or hypopnea. The severity of obstructive sleep apnea (OSA) was then scored on the basis of Respiratory Distress Index (RDI), which was calculated by adding apneas, hypopneas, and RERAs divided by total sleep time. Patients were classified as normal (RDI < 1), mild (RDI 1 to <5), moderate (RDI 5–10), and severe (RDI > 10).

2.2. Statistical methods

The data were entered into a Microsoft Excel spreadsheet and were analyzed using SPSS software, version 19 (SPSS Inc., Chicago, IL). Summary statistics [ie, mean and standard deviation (SD)] were presented for the metabolic parameters, and the association of these parameters with patients with SDB and controls was tested using the Student *t* test. A *t* test was also used for testing the association of metabolic parameters with the normal- and underweight individuals. Correlation of RDI, BMI *z* score, and oxygen saturation and duration of illness with the metabolic parameters was studied using the Pearson correlation coefficient. Multivariate regression analysis was carried out to eliminate the confounding effect of *z* scores and duration of illness on the metabolic parameters.

3. Results

A total of 39 children with SDB (henceforth termed case patients) and 28 controls were studied; there were no significant differences in their age and gender (Table 1). However, a significant difference was observed in the *z* score of case patients (0.37 ± 1.92) and controls (1.30 ± 0.64; $p = 0.017$). The mean fasting blood glucose value was found to be significantly lower in case patients ($p = 0.015$), which became nonsignificant after adjusting for body weight. The mean levels of HDL ($p = 0.002$), LDL ($p = 0.002$), and cholesterol ($p = 0.001$) were higher in case patients than in controls, even after adjustment for the *z* score (Table 1). The mean values of fasting insulin and HOMA were higher in case patients (6.42 ± 6.47) than in controls (5.3 ± 3.40), although they did not reach statistical significance. No significant difference was observed in the mean values of TGs and blood pressure.

Using RDI as the criterion for grading severity, 77% of the patients were found to have moderate to severe disease, whereas using apnea-hypopnea index (AHI) as the criterion, approximately 75% of the patients were found to have mild to moderate disease (Table 2). This differentiation was done to see the specific effect of RERAs on metabolic and hemodynamic parameters.

To discern the impact of the severity of SDB, degree of desaturation, *z* score, and duration of illness on various metabolic parameters and blood pressure, linear correlation was performed using the Pearson correlation coefficient. No significant correlation