Prevalence of Metabolic Abnormalities and their Effect on Asthma Symptom Control in Children

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Abstract

Objective The objectives of this study were to determine the prevalence of insulin resistance (IR), dyslipidemia and metabolic syndrome (MS) in children with asthma, aged 10 to 15 years and to determine if these metabolic abnormalities showed an association with asthma symptom control and lung function. **Methods** We conducted a cross-sectional study at a tertiary centre in north India. Consecutive children with physician diagnosed asthma were enrolled. Asthma symptom control over previous four weeks was assessed as per GINA recommendations. Fasting plasma glucose, serum insulin and lipid levels were estimated. HOMA-IR was used as a marker of IR. Spirometry was performed for assessing lung function. **Results** Eighty-three children were enrolled. Median (IQR) age was 12.0 (11.0, 13.5) years and mean (SD) BMI z score was -0.42 (1.0). Median (IQR) Homeostasis Model Assessment- Insulin Resistance (HOMA-IR) was 1.65 (1.06, 2.39). Prevalence of IR was 42.3% (95% CI: 31.7-52.9%). Number of children with elevated triglycerides, total cholesterol, and LDL-cholesterol was 4 (4.8%), 4 (4.8%) and 5 (6%), respectively. 67 (80.7%) children had low HDL-cholesterol. Only one subject was found to have MS. Presence of IR and elevation in serum insulin and triglycerides were associated with poorer asthma control, independent of BMI. None of the metabolic parameters were associated with lung function, after adjusting for height. **Conclusions** A high proportion of children with asthma aged 10-15 years had IR but not MS currently. Increasing serum insulin, triglycerides, and presence of IR were associated with poorer asthma control, after adjusting for BMI.

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Consent: A written informed consent to participate was taken from the attendants. The manuscript does not contain any individual patient's data.

Author contribution statement: KK and RL conceptualized the study. KK, RL, KRJ, VJ and SKK were involved in designing the study. KK performed the data acquisition and analysis, and wrote the first draft. RL, KRJ, VJ and SKK revised and approved the final manuscript. RL will act as the guarantor.

Keywords: Childhood asthma, Insulin resistance, Dyslipidemia, Metabolic syndrome

Running head: Metabolic Abnormalities in Children with Asthma

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Results

Eighty-three children were enrolled. Median (IQR) age was 12.0 (11.0, 13.5) years and mean (SD) BMI z score was -0.42 (1.0). Median (IQR) Homeostasis Model Assessment- Insulin Resistance (HOMA-IR) was 1.65 (1.06, 2.39). Prevalence of IR was 42.3% (95% CI: 31.7-52.9%). Number of children with elevated triglycerides, total cholesterol, and LDL-cholesterol was 4 (4.8%), 4 (4.8%) and 5 (6%), respectively. 67 (80.7%) children had low HDL-cholesterol. Only one subject was found to have MS. Presence of IR and elevation in serum insulin and triglycerides were associated with poorer asthma control, independent of BMI. None of the metabolic parameters were associated with lung function, after adjusting for height.

Conclusions

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Introduction

There is increasing evidence to suggest an association between asthma and obesity, shown by both cross-sectional and prospective studies in adults [1,2]. Mechanisms explaining this link include compromised lung mechanics as a consequence of obesity, decreased physical activity due to asthma leading to obesity, genetic factors shared by both pathologies, asthma associated co-morbidities (gastroesophageal reflux disease and sleep disordered breathing), which are also common in obese subjects and last but not the least, the inflammatory effects of the metabolic changes associated with weight gain [3]. Studies have identified certain

metabolic derangements as potential risk factors, important among them being derangement of lipid profile as well as a state of insulin resistance (IR) [4-6].

The current view is that these metabolic derangements could form the link between obesity and asthma, by resulting in a state of chronic inflammation, also affecting the airway. Logically, the prevalence of these metabolic abnormalities would then be higher in patients with asthma. Not only there is evidence to support this hypothesis, but it can also be demonstrated that there is some influence on the severity of asthma symptoms [7].

An adult population-based study in Denmark found that IR was associated with increased risk of aeroallergen sensitization and allergic asthma but not non-allergic asthma [8]. A small cross-sectional pediatric study conducted in Australia showed the prevalence of IR, defined by a HOMA-IR (Homeostasis Model Assessment Insulin Resistance) value of > 1.77 to be much higher among allergic asthmatics (42%) as compared to healthy controls, of whom none had IR[9]. A study conducted in Taiwan in children showed the levels of total cholesterol (TC) and low-density lipoprotein (LDL) to follow the order, obese asthmatics > non-obese asthmatics > obese controls > non-obese controls, thus suggesting a relationship between asthma and dyslipidemia, which was amplified by obesity [10].

However, there are studies that fail to confirm these proposed associations and some that even provide evidence to the contrary[6,11]. For example, spirometry parameters, asthma severity and Asthma Control Test (ACT) scores did not differ between obese and non-obese children with asthma, in Cleveland, Ohio[12]. Consequently, the data regarding the prevalence of metabolic abnormalities in children with asthma are not consistent and the mechanisms relating obesity and asthma have not been clearly elucidated. If adequately proven, this has therapeutic implications, helping in better management and even prevention of development of asthma like symptoms. Therefore, we conducted this study to determine the prevalence of metabolic abnormalities including IR, metabolic syndrome (MS) and dyslipidemia in children with asthma, and to find out if these metabolic abnormalities showed an association with asthma symptom control and lung function.

Methods

We conducted a cross-sectional study from January 2015 to October 2016 at a tertiary care institute in north India. All children with asthma attending the Pediatric Chest Clinic at the institute were screened. Those in follow up for at least six months with good adherence and appropriate technique of taking inhaled medications and willing to participate in the study, were enrolled after receiving a written informed consent from either of the parents or the legally authorized representative. Children with diagnosed diabetes mellitus, chronic illness like renal or liver disease and those on insulin, oral hypoglycemic drugs or statins were excluded. Based on the study conducted by Arshi et al [9], we expected prevalence of IR of 40%; to estimate the same with a precision of 10%, the sample size of 92 was calculated.

The primary outcome measure of the study was the prevalence of IR in children with asthma in the age group of 10 to 15 years. The secondary outcome measures were the prevalence of dyslipidemia and MS in the same population, measures of association between metabolic abnormalities (IR and dyslipidemia) and the level of asthma control, and measures of association between metabolic abnormalities and lung function using spirometry.

Diagnosis of asthma was based on assessment by physician, of reversible airflow obstruction. Global Initiative for Asthma (GINA) guidelines, 2016 were used to classify subjects with different levels of asthma control [13]. HOMA-IR, calculated as the product of fasting plasma glucose (mmol/L) and fasting serum insulin (microU/mL), divided by 22.5, was used as a marker for IR [14,15]. Dyslipidemia was defined as presence of any of these: triglycerides (TG) [?]150 mg/dL, high density lipoprotein cholesterol (HDL-C) <40 mg/dL, TC [?]200 mg/dL or LDL-C [?]130 mg/dL [16,17]. MS was defined using the criteria given by Cook et al, as the presence of three criteria out of these five - TG [?]110 mg/dL, HDL-C <40 mg/dL, waist circumference [?]90th centile, fasting glucose [?]110 mg/dL, and blood pressure [?]90th centile [18].

A questionnaire was used to record demographic information and elicit details regarding symptom onset,

current disease status, drug history, outdoor activity, and family history. All patients were examined in detail and vital parameters, anthropometric measurements and findings on respiratory system examination were recorded. Standing height and weight were measured using a stadiometer and digital scale respectively. Waist circumference was measured using a stretch-resistant tape, applied horizontally just above the upper lateral border of the right ilium, at the end of a normal expiration. Hip circumference was measured around the widest portion of the buttocks. Indian references were used for assigning centiles and 'z' scores to waist circumference, other anthropometric parameters and blood pressure [19-21].

Spirometry was performed using a portable spirometer (Spirolab III from MIR, Italy). The procedure was explained and supervised by an experienced respiratory nursing officer, and was performed in standing position. The best of three efforts was used for interpretation. The absolute and percentage predicted values of following parameters were recorded: Forced Expiratory Volume – 1 second (FEV_1), Forced Vital Capacity (FVC), FEV_1/FVC ratio, Peak expiratory Flow Rate (PEFR) and Forced Expiratory Flow at 25, 50 and 75% of FVC (FEF_{25}, FEF_{50}, and FEF_{75}). Knudson's equations with correction for Indian population were used for reference values [22].

An enrolled patient was requested to report for collection of blood samples, after eight hours of fasting, within the next seven days. Approximately 2 ml of blood was collected and transported in a fluoride vial for estimation of glucose, done on a Mindray BS200E Autoanalyzer system (Shenzhen Mindray Bio-Medical Electronics Co, Ltd, Shenzhen, China) on the same day. Another 6 ml of blood was collected in a plain vial for estimation of serum insulin and lipid levels. The sample was allowed to clot at room temperature for 10–20 min, centrifuged at 3000 r.p.m. for 20 min for separation of serum, which was stored at -20°C. An electrochemiluminometric assay on a Cobas e411 Autoanalyzer (Roche Diagnostics, Germany GmbH) was used for serum insulin levels and a Beckman Coulter AU480 Autoanalyzer was used for estimation of lipid levels.

Data analysis was done using SPSS version 26, IBM Corp. Mean with standard deviation (SD) and median with interquartile range (IQR) have been used to present continuous data with normal and non-normal distribution respectively. Categorical data are presented as proportions with 95% confidence interval (CI). Comparison of median values of various metabolic parameters across groups based on asthma symptom control was done using Jonckheere-Terpstra test, and Fisher's exact test was used for comparing categorical data. An ordinal logistic regression model, with asthma symptom control as the dependent variable and metabolic parameters as independent variables, was used to adjust for BMI when there was a significant difference in metabolic parameters across asthma control groups. A P value of less than 0.05 was taken to be significant for all statistical tests.

Prior approval was taken from the Institute ethics committee (IESC/T-450/23.12.2014).

Results

Ninety-nine children were screened and found eligible for inclusion during the study period. Two subjects were excluded in view of refusal to provide consent and inability to follow instructions for spirometry on account of developmental delay. Fourteen children were further excluded as they did not report for sampling. Eighty-three participants were included in the study for analysis. Table 1 provides the baseline characteristics of the 83 children. Nine (10.8%) children were overweight where as none were obese.

No significant difference was observed in the average body mass index (BMI), BMI 'z' score, waist circumference, hip circumference, or waist-hip ratio between the three groups based on asthma symptom control.

HOMA-IR index did not show a normal distribution in the population. The median (IQR) HOMA-IR was 1.65 (1.06, 2.39). Thirty-five children were found to have IR taking a HOMA-IR cut-off at 1.77; thus, the prevalence of IR was 42.3% (95% CI: 31.7- 52.9%). The HOMA-IR index showed a significant positive correlation with weight, weight 'z' score, BMI, BMI 'z' score, waist circumference, hip circumference, and waist-hip ratio (E-table 1).

Seventy-two out of 83 children were found to have at least one lipid abnormality. The prevalence of dyslipi-

demia was estimated at 86.7% (79.4-94.0%). Number of children with elevated TG, TC, and LDL-C was 4 (4.8%), 4 (4.8%) and 5 (6%), respectively, whereas 67 (80.7%) children had low HDL-C. Only one subject was found to fulfil the criteria for MS.

The median fasting serum insulin level and HOMA-IR index were compared between the asthma symptom control groups. An increasing trend was observed from controlled to partly controlled and uncontrolled, which was statistically significant in case of insulin level but not HOMA-IR. A similar statistically significant increasing trend was observed for median TG and LDL-C levels. There was no significant difference in the median TC and HDL-C levels. A significant difference was not seen for prevalence of IR (HOMA-IR [?]1.77). These comparisons are summarized in table 2, figures 1A, B and C.

We used an ordinal logistic regression model to adjust for BMI, separately for each significant variable, including fasting insulin, serum TG and LDL-C. Except for LDL-C, the rest of the variables showed a significant positive correlation with poorer asthma symptom control, after adjusting for BMI.

We correlated individual spirometry indices, including observed and percentage predicted values of FEV_1, FVC, FEV_1/FVC, PEFR, FEF_{25}, FEF_{50} and FEF_{75} to HOMA-IR index, fasting serum insulin and lipid levels. Interestingly, HOMA-IR index showed a statistically significant but weak positive correlation with FEV_1 and FEV_1 percentage predicted, and serum insulin level showed a similar correlation only with FEV1 percentage predicted. These correlations, however, were not significant on adjusting for height. Also, serum TG, TC, LDL-C, and HDL-C all showed a statistically significant weak negative correlation with PEFR, which were again not significant on adjusting for height. These results are summarized in table 3.

A HOMA-IR cut off of 2.5 has been shown to be more sensitive and specific in Indian adolescents 10 to 17 years of age [23]. On taking this higher cut-off at 2.5, 17 children were found to have IR [prevalence 20.5% (11.8-29.2%)] in our study population. The prevalence of IR (HOMA-IR [?]2.5) also showed a statistically significant increase, from controlled to partly controlled, and further to uncontrolled asthma, after adjusting for BMI.

Discussion

The prevalence of IR observed in our study (42.3%) is very close to that reported by Arshi et al (42.9%) in an Australian population, using the same cut off of HOMA-IR [?]1.77 [9]. Literature on IR in Indian children is scarce. A recent study reporting on Indian children with asthma, aged 6-18 years, estimated the prevalence to be 15.5% [24]. The study had used a HOMA-IR value of 2.5, which has been suggested to be more accurate for the Indian population[23]. Applying the same threshold, the prevalence of IR in our population comes to 20.5%, which is comparable. Unfortunately, our study did not include a control group. Overall, the median HOMA-IR in our cohort of children with asthma was lower than the average reported in a study conducted in schoolchildren aged 6 to 16 years, in the eastern part of the country [25]. However, in the latter study, 28.2% participants were overweight and obese, compared to only 10.8% in our population. In addition, there might be other factors accounting for the difference, like a differential distribution of post-pubertal children, as HOMA-IR values have been shown to increase with increase in sexual maturation [23].

IR has been suggested to be an early biochemical marker of MS, developing at age 18-19 years [26]. We, therefore, believe our result to be significant because relying on anthropometry alone, the risk of developing MS in our population would appear to be lower. If the prevalence of IR in Indian children with asthma is confirmed to be as high in larger studies, this might indicate the need to adopt stricter lifestyle measures in early adolescence.

The prevalence of dyslipidemia in our study was 86.7% (79.4-94.0%). The high prevalence was predominantly because of commonly observed low HDL-C in our study subjects, seen in 80.7% (72.2-89.2%). In a population of 695 Indian urban adolescents, in the age group of 10-18 years, low HDL-C was reported in 27.3% [27]. One reason for our group to have a low HDL-C could be the higher proportion of males, as it has been shown that boys typically show a sudden decline the HDL-C levels around the pubertal age, compared to females[28]. We believe it is extremely unlikely that asthma alone would be responsible for such a drastic abnormality.

Only one child in our study fulfilled the criteria for MS. Similarly, in another Indian cohort of 90 children, only two had MS[24]. Ross et al found 12 children to qualify for presence of MS in a group of 116 children with asthma[12]. However, contrary to Ross's study where 52 children (44.8%) were obese, none of the children sampled in our study were obese. This might possibly explain the observed low prevalence of MS in our study. However, as previously stated, we believe that a higher proportion of children, who have IR currently might be at risk for developing MS later.

Studies have shown that among children & adolescents with asthma, IR and MS are associated with higher bronchial hyperresponsiveness and severe asthma [7,29]. Also, dyslipidemia has been shown to be associated with higher airway resistance measured by forced oscillation technique [30]. We hypothesized that it might be possible to demonstrate an association between metabolic parameters and asthma symptom control. To test this, we compared the groups with controlled, partly controlled, and uncontrolled asthma. While there was no statistically significant difference in median HOMA-IR of the groups, there was a significant increasing trend in serum insulin level, associated with poorer asthma control. There was a similar association seen with presence of IR, defined as HOMA-IR [?]2.5.

Further, we performed a similar comparison for lipid levels and there was a significant increase in serum TG and LDL-C with poorer control. The association of poor asthma control with fasting serum insulin, presence of insulin resistance (HOMA-IR [?]2.5) and serum TG persisted after adjusting for BMI. Simply put, children with asthma who had higher fasting serum insulin, higher serum TG or HOMA-IR [?]2.5 were at a higher risk of having a poorer asthma control, irrespective of their BMI.

These results show that metabolic derangements are directly associated with clinically relevant outcomes like asthma symptom control. To the best of our knowledge, this is the first study demonstrating a correlation between lipid profile and asthma control in children. Unfortunately, the current study design doesn't permit further delineation between association and causality. It might be worthwhile to explore these metabolic parameters in children with poor asthma control and see if treatment addressing these has a beneficial effect on asthma symptoms.

We also explored correlations between metabolic parameters and spirometry indices (table 3) and found a weak negative correlation between lipid levels and PEFR. The correlation was not significant statistically on adjusting for height. Similar negative correlations with metabolic markers have been reported by a few pediatric studies but the results are not consistent and have often lacked confidence[24,31,32]. The most likely explanation for the same is that there are several mechanical and non-mechanical factors influencing lung function, and consequently the effect of a single metabolic parameter might not be very strong.

Our study is unique because we have focused on the relationship between metabolic derangements and clinically useful outcomes like symptom control, which are helpful in clinical decision making. Our group included children with physician diagnosed asthma rather than relying on self-reported symptoms. We used population specific standards for anthropometry, blood pressure centiles and spirometry indices.

We acknowledge a few limitations in our study. Of the initially enrolled 97 children, only 83 reported for sampling. There was disproportionate representation of the genders with boys predominating. As there was no control population, prevalence of metabolic derangements could not be compared to that in healthy children. Also, the cross-sectional design prevents us from exploring the temporal association and hence, causality between poor symptom control and metabolic abnormalities.

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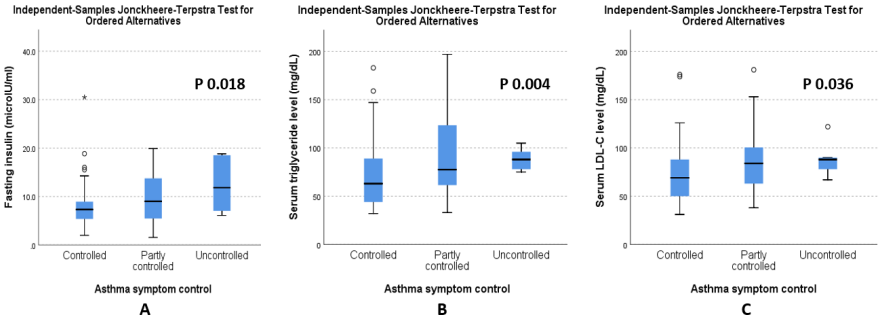
Figure Captions

Figure 1A: Distribution of serum insulin level among children with different levels of asthma symptom control

Figure 1B: Distribution of serum triglyceride level among children with different levels of asthma symptom control

Figure 1C: Distribution of serum LDL-C level among children with different levels of asthma symptom control



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