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ORIGINAL ARTICLE

Putative Role of Cardio Metabolic Risk Among Poorly Controlled Asthmatics in South Indian Population

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Abstract Mortality and morbidity attributed to asthma remains to be the biggest nightmare worldwide. Hence, the study was aimed to compare the cardio metabolic risk factors as assessed by Body mass index (BMI), waist hip ratio (WHR), serum triacylglycerol and uric acid in well controlled and poorly controlled asthmatics and to correlate these parameters with the severity of asthma. A case control study was conducted on 90 subjects who were segregated into well controlled asthmatics (n = 30) and poorly controlled asthmatics (n = 30) who were diagnosed based on Global initiative for Asthma management guidelines and healthy volunteers (n = 30). Centrifuged fasting venous blood samples were used for biochemical analysis, pulmonary function test, BMI, and waist hip ratio (WHR) were measured. The statistical analysis was done using SPSS version 17. There was a significant increase in BMI, WHR, lipid profile, serum uric acid and decrease in forced expiratory volume (FEV1), forced vital capacity (FVC), and FEV1/FVC in poorly controlled asthmatics. There was a significant association between FEV1 and serum uric acid, BMI and Triacylgycerol in poorly controlled asthmatics. Poorly controlled asthmatics have greater risk of developing cardiometabolic problems. Serum uric acid can be used as one of the severity markers in asthma to assess cardio metabolic risk.

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Introduction

Poorly controlled asthma remains a major healthcare burden due to various reasons worldwide. The prevalence of asthma diagnosed clinically ranges from 2 to 9 % and its complications have increased recent times [1]. Several studies have implicated obesity in enhancing the risk of developing asthma, but few studies could not find any association with body mass index (BMI) and disease severity [2–4]. Asthma is a chronic inflammatory condition associated with hypoxia and decrease in physical activity and increased oxidative stress. Adequate control of asthma symptoms is essential; if not controlled, may eventually lead to heart failure in the early part of the life. Study by Ueki et al. documents that asthma and atherosclerosis as chronic comorbid diseases with lipo- metabolic cross-talk [5]. Hence, monitoring the metabolic risk factors could be important in disease prognosis and prevention of complications.

Serum uric acid concentration is increased in tissue hypoxic conditions, namely asthma, impaired glucose tolerance, hyper triacylglycerolemia etc [5]. A study by Clausen et al. has concluded fasting serum uric acid level as a major determinant of the fasting serum triacylglycerol [6]. Studies have documented serum uric acid as a marker of severity, as well as an early predictor of hemodynamic alteration in heart diseases. A study by Aida et al. 2011 showed a significant association between serum uric acid levels and pulmonary function, but Garcia-Larsen et al. in 2009 had demonstrated that mere exist no such relationship between uric acid and pulmonary functions [7, 8]. Given

vague reports and contradictory statements, the present study was aimed to evaluate the physiological and biochemical parameters of cardiometabolic risk in poorly controlled asthma patients, with following objectives:

1. To compare cardio-metabolic risk factor as assessed by BMI, waist-hip ratio, serum triacylglycerol and uric acid in well-controlled and poorly controlled asthma patients.
2. To correlate these parameters with the severity of asthma as assessed by Pulmonary Function Test (FEV1) in poorly controlled asthma patients.

Materials and Methods

A case–control study was conducted after the approval of Institutional Human Ethical Committee (IHEC). Informed written consent was obtained. This study involved thirty healthy controls with normal pulmonary function test (Group I), Sixty diagnosed cases of chronic asthma patients [Thirty well-controlled asthma patients (Group II) and thirty poorly controlled asthma patients (Group III) based on *criteria for asthma symptom severity*, according to the Global initiative for Asthma management (GINA)] [9–13]. Subjects with emphysema, bronchiectasis, infective bronchitis, known diabetes mellitus, hypertension, coronary heart diseases, cyanotic heart diseases, renal failure, gout, endocrine disorder, patient on drugs other than anti-asthmatic agents and those on vitamin supplements were excluded from the study. Three ml of fasting venous blood sample was withdrawn in test tube and subjected to centrifugation at 5000 rpm for 10 minutes. Separated serum was used for estimation of various biochemical parameters using Roche Hitachi 902 automated clinical chemistry analyzer which includes: Glucose estimation by Glucose oxidase and peroxidase method, serum uric acid by uricase-peroxidase enzymatic method, Total cholesterol by cholesterol oxidase method, Triacylglycerols by Glycerol kinase enzymatic method, High density cholesterol (HDL) by direct colorimetric method and Low density cholesterol (LDL) was calculated by Friedwald's formula. All reagent kits were procured from Crest Biosystems, a division of *Coral clinical system*. Pulmonary function tests: Forced expiratory volume (FEV1), Forced vital capacity-FVC, FEV1/FVC using Portable *spirometer—MIR Winspiro—Spirobank II* instrument. Physiological parameters included Body mass index (BMI) calculated based on the formula: BMI = weight in kilograms/height in meters^2 (Quetelets Index), waist circumference and hip circumference were measured by measuring tape and waist-hip ratio (WHR) was calculated.

Statistical Analysis

Results were expressed as mean ± standard deviation. One way ANOVA followed by Tukey HSD was used to compare the means of the parameters. The correlation study was done using Pearson's correlation method. 'p' value of less than 0.05 was considered as significant for all statistical tests. SPSS version 17 was used for statistical analysis.

Results

In the present study, all the study subjects were males between the age group of 20–40 years. Age matched controls were recruited. Glycaemic status in the study subjects showed no significant difference (p value = 0.8) when compared to healthy controls. BMI and WHR level were significantly higher in poorly controlled asthma subjects. There was a decrease in FEV1 and FVC/FEV1 ratios in poorly controlled asthma subjects when compared to control and well-controlled asthma ($p = 0.001$). Serum Total cholesterol, TAG levels, VLDL-cholesterol and uric acid levels were significantly higher in poorly controlled asthma ($p \leq 0.05$) as in Tables 1 and 2.

There was a negative correlation between serum TAG and FEV1 in poorly controlled asthma ($R = -0.6$; p value = 0.04). There was a positive association between BMI and serum uric acid levels in poorly controlled asthma ($R = 0.91$; p value = 0.03). There was a negative correlation between TAGs and FEV1in poorly controlled asthma ($R = -0.84$; p value = 0.04).

Discussion

In our geographical region, till date, very few research studies has been carried out on investigating the potential cardiovascular risk in asthma subjects. So, we segregated chronic asthmatics into two groups based on severity. The mean age of the poorly controlled and well-controlled asthma was 25 years [7]. Some of the common triggering factors as obtained from history were dust, smoke, cold weather, and seafood. There were increased levels of TAG, total cholesterol, and VLDL-cholesterol in poorly controlled asthma subjects. The commonly measured anthropometric measurements: waist-hip ratio and BMI were increased in poorly controlled asthma subjects when compared to control ($p < 0.05$). Whereas, in well-controlled asthmatics TAG alone was higher. These findings suggest us that there are increased cardiovascular risk factors among poorly controlled asthma subjects than in well-controlled asthma subjects. A study by Iribarren et al. has documented an increased risk ratio (RR) for coronary

Table 1 Comparison of study parameters between well controlled and poorly controlled asthma patients

Parameters	Control (N = 30)	Well controlled asthma (N = 30)	Poorly controlled asthma (N = 30)	*p* value
Age (years)	26 ± 8.4	26 ± 7.3	25 ± 6.4	0.83 (Ns)
BMI	21.97 ± 2.69	21.56 ± 2.38	25.8 ± 6.29*#	0.002 (S)
Waist Hip Ratio	0.86 ± 0.24	0.85 ± 0.31	0.89 ± 0.08*#	<0.001(S)
FEV1 % predicted	90.7 ± 15.5	84.03 ± 16.02	46.31 ± 20.64*#	<0.001(S)
FVC % predicted	92 ± 16.1	91.03 ± 16.47	67 ± 24.94*#	<0.001(S)
FEV1: FVC %	86.9 ± 5.5	92.9 ± 7.0	69.1 ± 5.54*#	<0.001(S)
Blood glucose (mg/dL)	90.6 ± 17.0	91.13 ± 11.9	95.53 ± 11.92	0.19 (NS)
Uric acid (mg/dL)	4.10 ± 0.32	4.38 ± 0.82	5.3 ± 0.54*#	<0.001(S)

Data presented as mean ± SD

Analysis of data was done by one-way ANOVA and post hoc Tukey-Krammer test

S significant, *Ns* Not significant

* Depicts comparison with control group and the # depicts comparison with well controlled asthma group

Table 2 Comparison of lipid profile between well controlled and poorly controlled asthma patients

Parameters	Control (N = 30)	Well controlled asthma (N = 30)	Poorly controlled asthma (N = 30)	*p* value
Total Cholesterol (mg/dL)	164 ± 25.2	172.39 ± 5.8	190.3 ± 35.25*	<0.026 (S)
HDL (mg/dL)	43 ± 9.5	42 ± 7.5	43 ± 7.12	0.92 (NS)
LDL (mg/dL)	105 ± 23	101.78 ± 22.61	101.9 ± 38.90	0.88 (NS)
VLDL (mg/dL)	15.84 ± 5.3	27.66 ± 11.57	42.7 ± 44.78*	<0.001 (S)
TAG (mg/dL)	79.4 ± 26.3	138.40 ± 58.16*	137.5 ± 56.91*	<0.001 (S)

Data presented as mean ± SD

Analysis of data was done by one-way ANOVA and post hoc Tukey-Krammer test

S significant, *NS* Not significant

* Depicts comparison with control group

heart disease (CHD) in female asthmatics [14]. Enright et al. has documented cross-sectional positive associations between the diagnosis of asthma and fibrinogen levels with high density lipoprotein (HDL) cholesterol levels [15]. A similar study carried out by Bellocchia et al. documented that in asthma or COPD, there were slightly higher prevalence of cardiovascular diseases as compared to the general population and they also have suggested that other factors, namely age and severity of obstruction as predictors of cardiovascular risk [16].

In our study, the PFT as assessed by FEV1, FVC& FEV1/FVC ratios by spirometer were comparatively lower in poorly controlled asthma than well controlled asthma and normal subjects (Table 1). There was an inverse relationship between serum uric acid and FEV1($R = -0.6$; $p = 0.04$). A study by Aida et al. has shown significant association between the same in asthmatics [7]. It is now widely recognized that oxidative stress and inflammation have a nexus and play a vital role in the initiation of the pathogenesis of diseases [17, 18]. Uric acid, which is considered as a marker of antioxidant status and a marker of cardiovascular risk, was significantly higher in poorly controlled asthma subjects. There was a positive association between uric acid and BMI in poorly controlled asthma subjects ($R = 0.91$; $p = 0.3$). Numerous other studies have documented the recognized role of oxidative stress and BMI in several diseases viz., Diabetes mellitus, hypertension, etc. [19, 20]. Our study corroborates the documented report on Asthma as an inflammatory condition; characterized by persistent rise in markers of inflammation along with serum uric acid which can potentiate CVD risk.

Asthma is complex immune inflammatory diseases triggered by various pathways; these pathways either benefit as a short term to overcome stress or infections or else, it may persist for a longer period as in chronic uncontrolled asthma. The immune response acts through two different arms: Type 1 response and Type 2 response.

The two types of responses are mediated by helper T cells (Th1 and Th2) which in turn release interferons and other pro-inflammatory cytokines. Both the types (Th1 and Th2) interact with each other, but Type 2 response is evident and predominant which release Tumour necrosis factor –alpha (TNF-α) and Interleukin-6 which are elevated in sustaining inflammation in asthmatic patients. They play significant roles in the activation of platelets, fibrinogen and smooth muscle proliferation to form mature plaques in humans [14, 21, 22]. In concordance with our study, article by Satocompos et al. has documented cardiovascular disease as a most frequent cause of death in asthma [23].

Conclusion

Poorly controlled asthma patients are prone to cardiometabolic risk. Hence, determination of anthropometric parameters (BMI, waist-hip ratio) and estimation of serum uric acid can be recommended and considered as useful parameters during the course of the treatment.

Limitations of the Study

Due to time and financial constraints, our study has limitations e.g. estimation of other lipid parameters, history and duration of asthma, medications and gender study and other markers of oxidative stress and inflammation in different age groups could have been better with a larger sample size. We would like to have a comprehensive study in future to assess their specific effects as related to CHD risk.

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Compliance with Ethical Standards

Conflict of interest SathishBabu Murugaiyan, K. P. Sreesoorya, Surendra K. Menon, SubimanSaha, Srinivasan AR, Arul Vijaya Vani. S, Reeta R, Kuzhandai Velu V, declare no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Present study was conducted after getting institute ethical clearance and consent from all the study subjects.

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