

RESEARCH PAPER

Relationship of Lung Function with Homocysteine, Vitamin B₁₂ and Folic Acid Level in Metabolic Syndrome

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Abstract

Background: Metabolic syndrome (MetS) is a complex metabolic disorder and with debilitating effects on many organs including lung function impairment. Hyperhomocysteinaemia is caused by nutritional deficiency of vitamin B₁₂ and folic acid can increase this risk further. Both the metabolic syndrome and hyperhomocysteinaemia adversely affect the lung function. But no study was found in Bangladeshi MetS in this regard.

Objective: To assess the relationship of lung function with serum homocysteine, vitamin B₁₂ and folic acid level in metabolic syndrome.

Methods: This cross-sectional study was conducted in the department of physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from November, 2019 to April, 2020. A total of 60 female subjects were selected with the age ranging from 25-45 year by purposive sampling. Among them 30 metabolic syndrome patients were included in the study group (group A) and 30 age and sex matched apparently healthy subjects constituted comparison group (group B). Serum homocysteine, vitamin B₁₂, folic acid and other biochemical parameters and the lung function of all subjects were assessed. Data were expressed as mean±SD. Spirometric measures were expressed as percent of predicted value. Statistical analysis was done by Independent sample 't' test and Pearson's correlation coefficient test.

Results: In this study, the mean percentage of predicted value of FVC, FEV₁ and, PEFr were significantly lower ($p<0.001$) in group A than those of group B. The mean serum homocysteine level was higher and vitamin B₁₂ and folic acid level were lower in metabolic syndrome patients compared to comparison group and the difference was statistically significant only for homocysteine ($p<0.05$). In addition, the FVC and FEV₁ were significantly negatively correlated ($p<0.05$) with serum homocysteine and FVC was significantly positively correlated ($p<0.05$) with serum folic acid level in group A.

Conclusion: The present study reveals that impairment of lung function is related to higher level of homocysteine and lower level of folic acid in metabolic syndrome.

Keywords: Metabolic syndrome, lung function test, homocysteine, folic acid

Introduction

The constellation of metabolic abnormalities including centrally distributed obesity, raised triglyceride, increased blood pressure, fasting plasma glucose and reduced high density lipoprotein cholesterol (HDL-C) is known as metabolic syndrome. According to IDF definition, central obesity (defined as waist circumference, ≥ 90 cm for men or ≥ 80 cm for women of South Asia) is obligatory criteria of MetS.¹ Along with it, presence of any ≥ 2 of following criteria are needed to diagnose this syndrome- (1) Raised

triglyceride (TG ≥ 150 mg/dL); (2) Reduced HDL cholesterol (<40 mg/dl in men, <50 mg/dl in women); (3) Raised blood pressure (Systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg) (4) Raised fasting plasma glucose (FPG- ≥ 100 mg/dL). Around the world prevalence of MetS is 20-25% and in Bangladesh overall prevalence 30%; female- 32%; male- 25%.²

Multiple metabolic impairment in metabolic syndrome are risk factors for cardiovascular disease, kidney disease, chronic lung disease and fatty liver disease. Impaired lung function associated with hypertension, type 2 diabetes, low density lipoprotein cholesterol, overall obesity and abdominal obesity.³ Previous studies reported restrictive, obstructive and mixed pattern of lung function impairment in metabolic syndrome.³⁻⁶ Spirometry is the principal method used

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to evaluate ventilatory function of lung. It is widely used and well recognized procedure for assessing lung function⁷.

Several studies found higher level of homocysteine and/or lower level of vitamin B₁₂ and folic acid in MetS⁸⁻¹⁰. On the contrary, some studies found no significant changes in homocysteine, vitamin B₁₂ and folic acid level in this group of patients.^{11, 12}

Homocysteine is toxic, nonproteogenic sulfur containing amino acid which is produced from demethylation of dietary methionine in the liver. Homocysteine is metabolised either via transsulfuration or remethylation pathway. About half of the intracellular homocysteine remethylated to methionine by methionine synthase. Vitamin B₁₂ and folic acid are required for this reaction. Other half of homocysteine transsulfurated to cysteine with the help of cystathionine β-synthase which require vitamin B₆ as a cofactor. The cysteine ultimately converted to sulfate and cleared from the body via urine.¹³⁻¹⁵

Aberrant homocysteine metabolism leads to cytotoxicity by redox imbalance and oxidative stress by elevated protein, nucleic acid and carbohydrate oxidation and lipoperoxidation.¹⁶ Lower level of vitamin B₁₂ strongly correlates with lipid peroxidation and folic acid minimize oxidative stress.^{17,18} Hyper-homocysteinaemia causes oxidative stress in rat lung by lipid peroxidation, oxidative damage to protein and disrupted enzymatic and non-enzymatic antioxidant defense.¹⁹

Several studies observed the relationship of lung function with homocysteine, vitamin B₁₂ and folic acid in general population and in COPD patients.²⁰⁻²²

Despite reports regarding relationship between lung function and homocysteine, vitamin B₁₂ and folic acid level in general population and in COPD patients, there is no evidence of investigating relationship between them in MetS. Exploring this relationship may be helpful in prevention, early diagnosis and effective management of impaired lung function related morbidity in this group of patients.

Materials and Methods

This was a cross sectional study, conducted in the department of physiology, BSMMU from November 2019 to April 2020. The protocol of this study was approved by Institutional Review Board, BSMMU, Dhaka. Thirty diagnosed MetS patients with age range

25-45 years were included in the study group. Another 30 age and sex matched apparently healthy subject were taken as comparison group who were in good physical health. All the subjects were free from respiratory, cardiac, renal and chronic liver disease. Individual having thyroid disorders, malignancy, menopause and on nutritional supplement like multivitamins (within 120 days) were excluded from the study. The study group were selected from the Department of Endocrinology, OPD, BSMMU, Dhaka who were diagnosed as metabolic syndrome. The comparison group were collected among the relatives and attendants of patients, hospital staff and subjects available in the BSMMU campus and also through personal contacts from different areas of Bangladesh.

After selection of the subjects, thorough information was given to them about the objectives and study procedure. Informed written consent was obtained from all the participants who were voluntarily participated. The patients were also allowed freedom to withdraw herself from the study even after participation whenever they feel. Detail dietary, family, menstrual and medical history were taken and thorough physical examination, anthropometric measurement including waist circumference were recorded on a data schedule. Then 10 ml venous blood was collected in fasting condition from ante-cubital vein of each subject of both groups for estimation of FPG, fasting lipid profile, serum creatinine, serum alanine aminotransferase. If these were normal, the other biochemical variables were estimated.

After final selection serum homocysteine, vitamin B₁₂, folic acid were assessed from the preserved blood by chemiluminescent immunoassay. The selected subjects were again requested to attend the department of physiology with all preparation of lung function test on next day. To assess lung function, spirometry was done using a portable spirometer (PONY FX, cosmed, Italy) in the lung function laboratory in the department of physiology.

Data were expressed as mean ± SD. Spirometric measures were expressed as percent of predicted value. Independent sample 't' test was done to compare mean value of all parameters between study group and comparison group. Pearson's correlation test was done to see the relationship of lung function parameters with serum homocysteine, vitamin B₁₂ and folic acid level in metabolic syndrome patients by using SPSS.

Results

In this study, total 60 subjects were enrolled. Among them 30 were study subjects and 30 were age, sex matched apparently healthy comparison subjects. Data were collected from all the subjects. The mean percentage of predicted value of FVC and FEV₁ were significantly lower in group A than that of group B [74.07 (SD= 8.49); 85.77 (SD= 6.20) and 73.77 (SD= 9.58); 84.00 (SD=8.54) respectively; $p<0.001$, $p<0.001$]. Actual value of FEV₁/FVC % was higher in group A than that of group B but the difference was statistically non-significant between the groups [85.46 (SD=5.95) and 84.07 (SD=4.40) respectively; $p>0.05$]. The mean percentage of predicted value of PEFR was significantly lower in group A than that of group B [56.37 (SD= 15.84) and 83.77 (SD=19.98) respectively; $p<0.001$]. There was lower but statistically non-significant difference found in mean percentage of predicted value of FEF_{25-75%} in group A than that of group B [62.07 (SD=14.31) and 68.57 (SD=12.77) respectively; ($p>0.05$) (table I).

The mean value of serum homocysteine was significantly higher in group A than that of group B

[10.89 (SD= 4.01) $\mu\text{mol/L}$ and 8.91 (SD= 2.85) $\mu\text{mol/L}$ respectively $p<0.05$]. The difference of serum vitamin B₁₂ and folic acid were lower in group A than those of group B but these were statistically non significant [396.90 (SD= 150.52) pg/mL; 462.50 (SD=143.17) pg/mL and 8.77 (SD=2.29) ng/mL; 8.81(SD= 3.90) ng/mL respectively; $p>0.05$] (table II). In the group of metabolic syndrome FVC, FEV₁, FEV₁/FVC, PEFR and FEF_{25-75%} were negatively correlated ($r = -0.435$, -0.417 , -0.052 , -0.309 and -0.293 respectively) with serum homocysteine level but it was statistically significant for FVC and FEV₁ ($p<0.05$, $p<0.05$ respectively) (table III). In the study group FVC, FEV₁, FEV₁/FVC, PEFR and FEF_{25-75%} were negatively correlated ($r = -0.293$, -0.312 , -0.124 , -0.258 and -0.151 respectively) with serum vitamin B₁₂ level but these were statistically non significant ($p>0.05$) (table IV). In the MetS group FVC, FEV₁, FEV₁/FVC, PEFR and FEF_{25-75%} were positively correlated ($r = 0.378$, 0.359 , 0.031 , 0.238 and 0.124 respectively) with serum folic acid level but it was statistically significant only for FVC ($p<0.05$) (table V).

Table I: FVC, FEV₁, FEV₁/FVC, PEFR and FEF_{25-75%} in two groups (N=60)

Variables	Group A (n=30)	Group B (n=30)	p value
FVC (% of predicted value)	74.07±8.49 (59.00-92.00)	85.77±6.20 (74.00-96.00)	0.000 ^{***}
FEV ₁ (% of predicted value)	73.77±9.58 (59.00-96.00)	84.00±8.54 (70.00-100.00)	0.000 ^{***}
FEV ₁ /FVC % (actual value)	85.46±5.95 (67.00-96.00)	84.07±4.40 (74.00-91.00)	0.304 ^{ns}
PEFR (% of predicted value)	56.37±15.84 (32.00-93.00)	83.77±19.98 (35.00-109.00)	0.000 ^{***}
FEF _{25-75%} (% of predicted value)	62.07±14.31 (32.00-95.00)	68.57±12.77 (47.00-98.00)	0.068 ^{ns}

Data were expressed as mean±SD. Values in parentheses indicate ranges; Statistical analysis was done by Independent sample 't' test; Group A-subjects with metabolic syndrome; Group B-comparison group; FVC-forced vital capacity; FEV₁-forced expiratory volume in 1st second; PEFR-peak expiratory flow rate; FEF_{25-75%}-forced expiratory flow in middle half of FVC; ns-non significant ($p>0.05$); ^{***} $p<0.001$; N=total number of subjects; n = number of subjects in each group.

Table II: Serum homocysteine, vitamin B₁₂ and folic acid levels in two groups (N=60)

Variables	Group A (n=30)	Group B (n=30)	p value
Homocysteine ($\mu\text{mol/L}$)	10.89 \pm 4.01 (5.19-22.98)	8.91 \pm 2.85 (5.07-14.82)	0.031*
Vitamin B ₁₂ (pg/mL)	396.90 \pm 150.52 (166.00-878.00)	462.50 \pm 143.17 (311.00-925.00)	0.089 ^{ns}
Folic acid (ng/mL)	8.77 \pm 2.29 (4.00-14.10)	8.81 \pm 3.90 (3.50-17.30)	0.961 ^{ns}

Data were expressed as mean \pm SD. Values in parentheses indicate ranges; Statistical analyses were done by Independent sample 't' test; Group A-subjects with metabolic syndrome; Group B-comparison group; ns-non significant ($p>0.05$); * $p<0.05$; N=total number of subjects; n= number of subjects in each group.

Table III: Correlations of FVC, FEV₁, FEV₁/FVC, PEFR and FEF_{25-75%} with serum homocysteine level in group A (n=30)

Variables	Group A (n=30)	
	r value	p value
FVC	-0.435	0.016*
FEV ₁	-0.417	0.022*
FEV ₁ /FVC	-0.052	0.785 ^{ns}
PEFR	-0.309	0.096 ^{ns}
FEF _{25-75%}	-0.293	0.116 ^{ns}

Statistical analysis was done by Pearson's correlation coefficient (r) test. Group A-subjects with metabolic syndrome; FVC-forced vital capacity; FEV₁-forced expiratory volume in 1st second; PEFR-peak expiratory flow rate; FEF_{25-75%}-forced expiratory flow in middle half of FVC; * $p<0.05$; ns-non significant ($p>0.05$); n-number of subjects in group A.

Table IV: Correlations of FVC, FEV₁, FEV₁/FVC, PEFR and FEF_{25-75%} with serum vitamin B₁₂ level in group A (n=30)

Variables	Group A (n=30)	
	r value	p value
FVC	-0.293	0.116 ^{ns}
FEV ₁	-0.312	0.094 ^{ns}
FEV ₁ /FVC	-0.124	0.514 ^{ns}
PEFR	-0.258	0.169 ^{ns}
FEF _{25-75%}	-0.151	0.427 ^{ns}

Statistical analysis was done by Pearson's correlation coefficient (r) test. Group A- subjects with metabolic syndrome; FVC-forced vital capacity; FEV₁-forced expiratory volume in 1st second; PEFR-peak expiratory

flow rate; FEF_{25-75%}-forced expiratory flow in middle half of FVC; ns-non significant ($p>0.05$); n-number of subjects in each group.

Table V: Correlations of FVC, FEV₁, FEV₁/FVC, PEFR and FEF_{25-75%} with serum folic acid level in group A (n=30)

Variables	Group A (n=30)	
	r value	p value
FVC	0.378	0.040*
FEV ₁	0.359	0.052 ^{ns}
FEV ₁ /FVC	0.031	0.870 ^{ns}
PEFR	0.238	0.205 ^{ns}
FEF _{25-75%}	0.124	0.514 ^{ns}

Statistical analysis was done by Pearson's correlation coefficient (r) test. Group A- subjects with metabolic syndrome; FVC-forced vital capacity; FEV₁-forced expiratory volume in 1st second; PEFR-peak expiratory flow rate; FEF_{25-75%}- forced expiratory flow in middle half of FVC; * $p<0.05$; ns- non significant ($p>0.05$); n-number of subjects in each group.

Discussion

In the study, FVC was significantly lower ($p<0.001$) in metabolic syndrome patients when compared to healthy subjects. Almost similar findings were reported by Choi et al, Yeh et al, Chen et al, Choudhary and Jani and Negm et al^{3,5, 23- 25}.

But Rogliani et al and Van Huisstede et al found FVC was lower but nonsignificant in MetS patients in comparison to healthy individuals.^{26, 27}

In the present study, FEV₁ was significantly lower ($p<0.001$) in metabolic syndrome patients compared

to healthy comparison group. Consistent finding also observed by Yeh et al, Chen et al, Choudhary and Jani and Negm et al^{3, 5,24,25}.

But Rogliani et al and Van Huisstede et al found FEV₁ was lower but nonsignificant in MetS patients in comparison to healthy individuals.^{26, 27}

The present study revealed that, FEV₁/FVC ratio is higher but non significant in metabolic syndrome patients when compared to healthy subjects. Almost similar findings were reported by Soares et al.⁶ Whereas, Negm et al reported significantly higher FEV₁/FVC ratio in metabolic syndrome patient than healthy subjects.³ On the other hand, Choi et al and Choudhary and Jani found significantly lower FEV₁/FVC ratio in MetS patients compare to healthy individual.^{5,23}

This study found that PEFR was significantly lower ($p<0.001$) in MetS patients in comparison to healthy individuals. No previous study was available to compare this finding.

The current study revealed that FEF_{25-75%} was lower in MetS patients in comparison to healthy individuals but it was statistically non-significant. Van Huisstede et al reported similar finding about FEF_{25-75%} in their study.²⁷ Whereas, Choudhary and Jani found significantly lower FEF_{25-75%} in MetS patients when compared with healthy subjects.⁵

This study found that serum homocysteine was significantly higher ($p<0.05$) in MetS patients in comparison to healthy individuals. This finding was consistent by Guven and Inanc and Narang, Singh and Dange.^{8, 10} But Nabipour et al. and Vaya et al. found higher but nonsignificant difference of this parameter in MetS patients in comparison to healthy individuals.^{11, 12}

The current study revealed that serum vitamin B₁₂ and folic acid were lower in MetS patients than those of comparison group but those were statistically non-significant. But Guven and Inanc, Maiti and Das and Narang, Singh and Dange found significantly lower these parameters in MetS patients in comparison to healthy individuals.⁸⁻¹⁰

In this study, Pearson's correlation coefficient (r) test was performed to observe the relationship of lung function measures with serum homocysteine, vitamin B₁₂ and folic acid level in metabolic syndrome.

In metabolic syndrome group mean FVC, FEV₁, FEV₁/FVC, PEFR and FEF_{25-75%} were negatively correlated with serum homocysteine level but only

FVC and FEV₁ were statistically significant ($p<0.05$). Almost similar findings were observed by Nunomiya et al. in general population.²²

In metabolic syndrome group, mean FVC, FEV₁, FEV₁/FVC, PEFR and FEF_{25-75%} were negatively correlated with serum vitamin B₁₂ level but these were statistically non-significant. No previous study was available to compare these findings.

In metabolic syndrome group, mean FVC, FEV₁, FEV₁/FVC, PEFR and FEF_{25-75%} were positively correlated with serum folic acid level but it was statistically significant only for FVC ($p<0.05$). No previous study was available to compare these findings.

Conclusion

Based on the results of the present study, it can be concluded that, impairment of lung function is related to higher level of homocysteine and lower level of folic acid in metabolic syndrome.

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