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Original Research Article

Association of Serum Homocysteine, Vitamin B12 And Folate Levels with Metabolic Syndrome in Adults

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Conflict of interest: Nil

Abstract:

Introduction: Central obesity, high blood pressure, poor glucose regulation, and atherogenic lipid abnormalities are the hallmarks of the multifactorial clinical disease known as metabolic syndrome. The risk of type 2 diabetes mellitus, cardiovascular disease, stroke, and other chronic consequences is significantly increased when these interconnected metabolic abnormalities are present.

Aims & Objectives: To assess the association of serum homocysteine, vitamin B12, and folate levels with metabolic syndrome in adults. The study also aims to determine whether alterations in these biochemical parameters are related to the presence of metabolic syndrome.

Materials & Methods: A hospital-based cross-sectional analytical study was conducted in the Department of Biochemistry, Santiniketan Medical College and Hospital, over a period of 1 year. A total of 100 adult patients were included to assess the association of serum homocysteine, vitamin B12, and folate levels with metabolic syndrome.

Result: In 100 participants, mean age was 49.62 ± 12.18 years, with males comprising 56%. Metabolic syndrome was present in 42%. Central obesity was the most common component (58%). Participants with metabolic syndrome had significantly higher homocysteine and significantly lower vitamin B12 and folate levels.

Conclusion: We concluded that decreased levels of vitamin B12 and folate and increased blood homocysteine were linked to metabolic syndrome. Compared to individuals without metabolic syndrome, those with metabolic syndrome had higher levels of homocysteine and lower levels of vitamin B12 and folate. Adults at higher metabolic and nutritional risk may be identified with the help of these biochemical changes.

Keywords: Homocysteine, Vitamin B12, Folate, Metabolic Syndrome, Biochemical Markers, Cardiometabolic Risk.

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Introduction

Atherogenic lipid abnormalities, central obesity, high blood pressure, and poor glucose regulation are the hallmarks of metabolic syndrome (MetS), a multifactorial clinical disease. The risk of type 2 diabetes mellitus, cardiovascular disease, stroke, and other chronic consequences is significantly increased when these interconnected metabolic abnormalities are present.[1] Finding additional biochemical markers that might contribute to the development of MetS has become a crucial field of research due to its rising incidence globally and strong correlation with cardiometabolic morbidity.[2] Homocysteine is an amino acid that contains sulfur and is produced when methionine is metabolized. Remethylation and transsulfuration processes, which both rely on a number of B-group vitamins, are primarily responsible for controlling its content in the blood. Inadequate levels of folate and vitamin B12 may cause homocysteine to build up in the blood because these vitamins are especially crucial for the remethylation of homocysteine to methionine.[3] Endothelial dysfunction, oxidative stress, inflammation, and vascular damage have all been linked to elevated

homocysteine levels, or hyperhomocysteinemia, which may be a factor in cardiometabolic disease.[4]. Essential nutrients for DNA synthesis, cellular metabolism, and one-carbon metabolism are vitamin B12 and folate. A biologically tenable connection between vitamin status and metabolic disorders is provided by their function in homocysteine metabolism. Homocysteine levels and circulating vitamin B12 or folate concentrations have been found to be inversely correlated in earlier epidemiological investigations. Therefore, those with obesity, insulin resistance, dyslipidemia, and other aspects of MetS may be affected by changes in these nutritional indicators. There is mounting evidence that MetS may be linked to homocysteine and B vitamin levels. Higher homocysteine levels were positively correlated with MetS, while higher vitamin B12 levels were inversely correlated with MetS, according to a recent systematic review and meta-analysis involving 66 studies and 87,988 participants. However, folate levels did not show a statistically significant overall association.

These results suggest that there may be a complex association between these biomarkers and MetS that varies depending on lifestyle, dietary status, population characteristics, and other metabolic variables. To assess the association of serum homocysteine, vitamin B12, and folate levels with metabolic syndrome in adults. The study also aims to determine whether alterations in these biochemical parameters are related to the presence of metabolic syndrome.

Materials and Methods

Type of Study: Hospital-based cross-sectional analytical study

Place of Study: Department of Biochemistry, Santiniketan Medical College and Hospital

Study Duration: 1 year

Sample Size: 100 adult patients to assess the association of serum homocysteine, vitamin B12 and folate levels with metabolic syndrome.

Inclusion Criteria

- Adults aged ≥18 years.
- Participants willing to provide written informed consent.
- Participants willing to undergo anthropometric, clinical and biochemical assessment.
- Participants with complete data on metabolic syndrome components and serum homocysteine, vitamin B12 and folate levels.

Exclusion Criteria

- Pregnant or lactating women.
- Patients with severe renal or hepatic dysfunction.
- Patients with known malignancy.
- Patients with known hematological disorders affecting vitamin B12 or folate levels.
- Patients with acute illness or infection at the time of assessment.
- Participants unwilling to provide consent or incomplete clinical/biochemical data.

Study Variables

- Age, sex
- Height, weight, BMI, waist circumference
- Blood pressure, history of diabetes mellitus, hypertension and other relevant comorbidities
- Fasting blood glucose, triglycerides, HDL cholesterol
- Serum homocysteine, serum vitamin B12, serum foliate

Statistical Analysis: Data were entered into Excel and subsequently analyzed using SPSS and GraphPad Prism. Continuous variables were summarized as means with standard deviations, while categorical variables were presented as counts and percentages. Comparisons between independent groups were performed using two-sample t-tests, and paired t-tests were applied for correlated (paired) data. Categorical data were compared using chi-square tests, with Fisher's exact test applied when expected cell counts were small. A p-value of ≤ 0.05 was considered statistically significant.

Result

Table 1: Sociodemographic characteristics of study participants

Variable	Category	Number (n)	Percentage (%)
Age	18–30 years	12	12
	31–40 years	20	20
	41–50 years	28	28
	51–60 years	25	25
	>60 years	15	15
Sex	Male	56	56
	Female	44	44
Residence	Rural	42	42
	Urban	58	58
Smoking	Yes	28	28
	No	72	72
Alcohol consumption	Yes	24	24
	No	76	76

Table 2: Clinical and biochemical characteristics of study participants

Parameter	Mean ± SD	Minimum	Maximum	Median
Age (years)	49.62 ± 12.18	19	74	50
BMI (kg/m²)	26.84 ± 4.12	19.1	38.7	26.5
Waist circumference (cm)	91.24 ± 10.82	68	116	91
Systolic BP (mmHg)	132.68 ± 16.42	98	172	130
Diastolic BP (mmHg)	83.14 ± 10.26	60	108	82
Fasting blood glucose (mg/dL)	108.52 ± 28.64	72	198	102
Triglycerides (mg/dL)	168.34 ± 62.18	72	342	154
HDL-C (mg/dL)	43.82 ± 9.16	27	68	43
LDL-C (mg/dL)	119.46 ± 31.28	58	194	117
Homocysteine (µmol/L)	15.84 ± 6.72	5.8	36.4	14.6
Vitamin B12 (pg/mL)	324.62 ± 128.54	96	682	306
Folate (ng/mL)	8.14 ± 3.62	2.1	18.6	7.8

Table 3: Distribution of metabolic syndrome and its components among study participants

Metabolic syndrome component	Present n (%)	Absent n (%)	P-value
Central obesity	58 (58.0)	42 (42.0)	0.115
Elevated triglycerides	46 (46.0)	54 (54.0)	0.424
Reduced HDL-C	49 (49.0)	51 (51.0)	0.92
Elevated blood pressure	43 (43.0)	57 (57.0)	0.18
Elevated fasting glucose	38 (38.0)	62 (62.0)	0.016
Metabolic syndrome	42 (42.0)	58 (58.0)	0.115

Table 4: Comparison of homocysteine, vitamin B12 and folate levels according to metabolic syndrome status

Biochemical parameter	Metabolic Syndrome Present	Metabolic Syndrome Absent	p-value
Homocysteine (µmol/L)	19.24 ± 7.12	13.38 ± 5.08	<0.001
Vitamin B12 (pg/mL)	276.48 ± 108.62	359.46 ± 132.18	0.001
Folate (ng/mL)	6.92 ± 2.84	9.02 ± 3.82	0.002

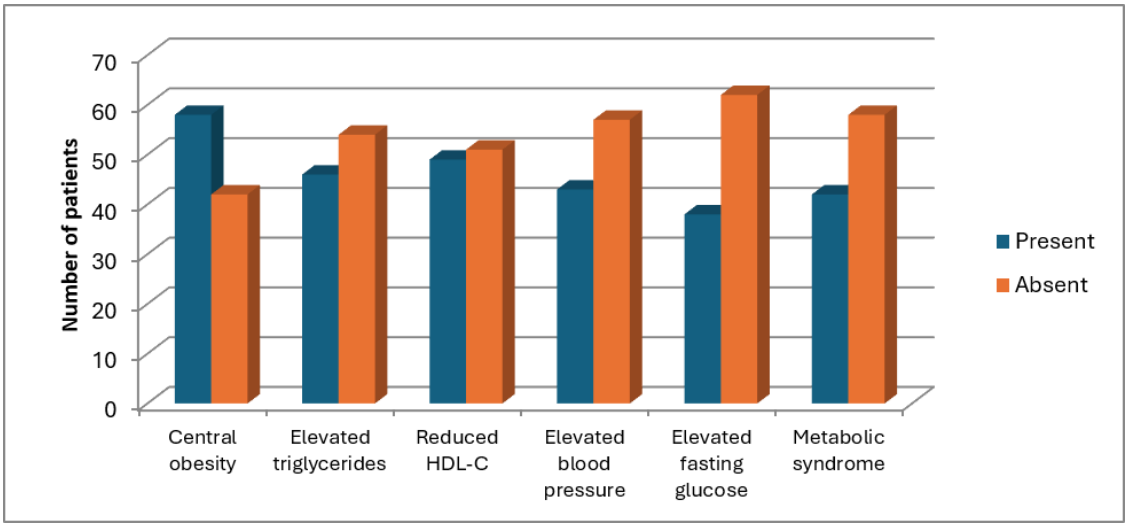

Figure 1: Distribution of metabolic syndrome and its components

In the present study of 100 participants, the mean age was 49.62 ± 12.18 years, with a range of 19–74 years. The largest proportion belonged to the 41–50 years age group (28.0%), followed by 51–60 years (25.0%) and 31–40 years (20.0%). Males constituted 56.0% of the participants, while females constituted 44.0%. The majority were from urban areas (58.0%). Smoking and alcohol consumption were reported by 28.0% and 24.0% of participants, respectively (Table 1). The mean BMI was 26.84 ± 4.12 kg/m², and the mean waist circumference was 91.24 ± 10.82 cm. The mean systolic and diastolic blood pressures were 132.68 ± 16.42 mmHg and 83.14 ± 10.26 mmHg, respectively. The mean fasting blood glucose was 108.52 ± 28.64 mg/dL. Mean triglycerides, HDL-C and LDL-C were 168.34 ± 62.18 mg/dL, 43.82 ± 9.16 mg/dL and 119.46 ± 31.28 mg/dL, respectively. The mean serum homocysteine level was 15.84 ± 6.72 µmol/L, while mean vitamin B12 and folate levels were 324.62 ± 128.54 pg/mL and 8.14 ± 3.62 ng/mL, respectively (Table 2).

Among the metabolic syndrome components, central obesity was the most common component (58.0%), followed by reduced HDL-C (49.0%), elevated triglycerides (46.0%), elevated blood pressure (43.0%), and elevated fasting blood glucose (38.0%). Overall, 42.0% of participants had metabolic syndrome, while 58.0% did not. Elevated fasting blood glucose showed a statistically significant association (p=0.016), whereas central obesity, elevated triglycerides, reduced HDL-C, elevated blood pressure, and overall metabolic syndrome status were not statistically significant (Table 3).

When biochemical parameters were compared according to metabolic syndrome status, participants with metabolic syndrome had significantly higher homocysteine levels than those without metabolic syndrome (19.24 ± 7.12 vs. 13.38 ± 5.08 µmol/L; p<0.001). Conversely, vitamin B12 levels were significantly lower among participants with metabolic syndrome (276.48 ± 108.62 vs. 359.46 ± 132.18 pg/mL; p=0.001). Similarly, folate levels were significantly lower in the metabolic syndrome group (6.92 ± 2.84 vs. 9.02 ± 3.82 ng/mL; p=0.002). These findings indicate that metabolic syndrome was characterized by higher serum homocysteine and lower vitamin B12 and folate levels (Table 4).

Discussion

The present study included 100 adult participants, of whom 42 (42.0%) had metabolic syndrome and 58 (58.0%) did not have metabolic syndrome. The mean age of the total study population was 49.62 ± 12.18 years, ranging from 19 to 74 years. The largest proportion of participants belonged to the 41–50 years age group (28.0%), followed by 51–60 years (25.0%) and 31–40 years (20.0%). Males constituted 56 (56.0%) participants, while females constituted 44 (44.0%). Urban residents accounted for 58 (58.0%), whereas 42 (42.0%) were from rural areas. In terms of lifestyle characteristics, 28 (28.0%) participants were smokers and 24 (24.0%) reported alcohol consumption. These characteristics indicate that the study population represented adults with a considerable burden of conventional cardio metabolic risk factors. The anthropometric and clinical findings further demonstrated the presence of several metabolic risk factors among the 100 participants. The mean BMI was 26.84 ± 4.12 kg/m², while the mean waist circumference was 91.24 ± 10.82 cm. The mean systolic and diastolic blood pressures were 132.68 ± 16.42 mmHg and 83.14 ± 10.26 mmHg, respectively. The mean fasting blood glucose was 108.52 ± 28.64 mg/dL. The mean triglyceride and HDL-C levels were 168.34 ± 62.18 mg/dL and 43.82 ± 9.16 mg/dL, respectively, while the mean LDL-C level was 119.46 ± 31.28 mg/dL. These findings demonstrate the coexistence of adiposity, dysglycaemia, elevated blood pressure and lipid abnormalities in the study population, which are characteristic features of metabolic syndrome. Among the 100 participants, central obesity was the most frequently observed metabolic syndrome component, being present in 58 (58.0%) participants. This was followed by reduced HDL-C in 49 (49.0%), elevated triglycerides in 46 (46.0%), elevated blood pressure in 43 (43.0%), and elevated fasting blood glucose in 38 (38.0%) participants. Overall, 42 (42.0%) participants fulfilled the criteria for metabolic syndrome, whereas 58 (58.0%) did not. The predominance of central obesity in the present study is important because visceral adiposity is closely associated with insulin resistance, chronic inflammation, oxidative stress and adverse lipid metabolism, all of which contribute to the development of metabolic syndrome. The most important biochemical finding of the present study was the significantly higher serum homocysteine level among the 42 participants with metabolic syndrome compared with the 58 participants without metabolic syndrome. The mean serum homocysteine concentration was 19.24 ± 7.12 µmol/L in the metabolic syndrome group compared with 13.38 ± 5.08 µmol/L in the non-metabolic-syndrome group, and this difference was statistically significant (p<0.001). Thus, the findings suggest a strong positive association between elevated serum homocysteine and metabolic syndrome in the present population.This observation is consistent with the findings of Narang et al., who studied patients with metabolic syndrome and reported an association between elevated homocysteine and abnormalities of vitamin B12 and folate metabolism.[5] Their findings support the possibility that disturbed homocysteine metabolism may contribute to the cardiometabolic abnormalities associated with metabolic syndrome. The similarity between their findings and the present study is particularly relevant because both studies were conducted in populations where nutritional factors may influence vitamin B12, folate and homocysteine concentrations. Similarly, Butkowski et al. investigated the relationship between homocysteine and metabolic syndrome and reported that homocysteine was associated with the accumulation of metabolic syndrome components.[6] In the present study, the difference in homocysteine concentration between the 42 metabolic syndrome participants and 58 non-metabolic-syndrome participants was marked, supporting the possibility that hyperhomocysteinaemia may be related to the clustering of metabolic abnormalities. The findings are further supported by Srećković et al., who studied obese individuals with and without metabolic syndrome and reported an association between homocysteine and the metabolic syndrome

score.[7] Homocysteine was also related to metabolic parameters such as insulin resistance and HbA1c in their study. These findings provide a possible biological explanation for the significantly higher homocysteine concentration observed among the 42 participants with metabolic syndrome in the present study. Genetic epidemiological evidence has also suggested a positive relationship between homocysteine and metabolic syndrome. A Mendelian randomization study published in 2021 demonstrated that higher homocysteine levels were associated with an increased likelihood of metabolic syndrome.[8] Such findings provide additional support for the association identified in the present study, although the cross-sectional nature of the current investigation means that a causal relationship cannot be established. The present study also demonstrated a significant difference in serum vitamin B12 concentrations between the 42 participants with metabolic syndrome and the 58 participants without metabolic syndrome. The mean vitamin B12 concentration was significantly lower among participants with metabolic syndrome (276.48 ± 108.62 pg/mL) compared with those without metabolic syndrome (359.46 ± 132.18 pg/mL), with a statistically significant difference (p=0.001). This inverse association between vitamin B12 and metabolic syndrome is biologically plausible because vitamin B12 is an essential cofactor in the remethylation of homocysteine to methionine. The findings are consistent with the systematic review and meta-analysis by Ulloque-Badaracco et al., which included 66 studies involving 87,988 participants.[9] The authors reported an inverse association between vitamin B12 concentration and metabolic syndrome, with higher vitamin B12 levels being associated with lower odds of metabolic syndrome. They also reported a positive association between homocysteine and metabolic syndrome.[9] Therefore, the biochemical pattern observed in the present study—higher homocysteine and lower vitamin B12 among the 42 participants with metabolic syndrome—is consistent with the broader published evidence. Prospective evidence from the CARDIA cohort further supports this observation. Zhu et al. studied 4,414 participants and reported that higher serum vitamin B12 levels were associated with a lower risk of incident metabolic syndrome.[6] They also demonstrated an inverse relationship between serum B-vitamin concentrations and homocysteine and found that higher homocysteine concentrations were associated with an increased risk of incident metabolic syndrome.[10] These longitudinal findings strengthen the relevance of the association identified in the present study of 100 participants, although prospective studies are needed to establish temporal relationships. Serum folate was also significantly lower among the 42 participants with metabolic syndrome than among the 58 participants without metabolic syndrome. The mean folate concentration was 6.92 ± 2.84 ng/mL in the metabolic syndrome group compared with 9.02 ± 3.82 ng/mL in the non-metabolic-syndrome group. This difference was statistically significant (p=0.002). The finding may be explained by the important role of folate in one-carbon metabolism and homocysteine remethylation. Reduced folate availability may impair homocysteine metabolism and consequently contribute to elevated circulating homocysteine levels. The present finding regarding folate is biologically plausible but should be interpreted cautiously because previous studies have reported inconsistent associations. In the systematic review and meta-analysis conducted by Ulloque-Badaracco et al., folate was not significantly associated with metabolic syndrome overall.[9] The difference between that meta-analysis and the present study may be related to variations in dietary intake, nutritional status, supplementation, laboratory methods, population characteristics and adjustment for potential confounding variables. Villatoro-Santos et al. also demonstrated heterogeneous relationships between B-vitamin biomarkers and metabolic syndrome among 524 participants from Mesoamerican populations.[11] Their findings suggest that the relationship between vitamin B12, folate, homocysteine and metabolic syndrome may differ between populations. In contrast, the present study of 100 participants demonstrated a consistent pattern of higher homocysteine and lower vitamin B12 and folate among the 42 participants with metabolic syndrome. The combined biochemical pattern observed in the present study is particularly noteworthy. Among the 42 participants with metabolic syndrome, serum homocysteine was elevated while vitamin B12 and folate levels were lower compared with the 58 participants without metabolic syndrome. These three biomarkers are closely interconnected through the one-carbon metabolic pathway. Vitamin B12 and folate are required for the remethylation of homocysteine to methionine; therefore, reduced availability of either vitamin may contribute to accumulation of homocysteine. Elevated homocysteine may subsequently promote oxidative stress, endothelial dysfunction, inflammation and vascular injury, potentially contributing to cardiometabolic abnormalities.[9,12] The review by Ashok et al. also highlighted the potential role of vitamin B12 and folate metabolism in metabolic syndrome and cardiovascular risk.[12] The authors described possible mechanisms involving homocysteine, oxidative stress, insulin resistance and endothelial dysfunction. These mechanisms provide a plausible explanation for the findings observed among the 42 participants with metabolic syndrome in the present study. From a clinical perspective, the findings

suggest that measurement of serum homocysteine, vitamin B12 and folate may provide additional information regarding cardiometabolic risk in adults with metabolic abnormalities. In particular, the combination of central obesity, impaired glucose regulation and altered homocysteine–B-vitamin metabolism may identify individuals requiring closer metabolic evaluation. However, based on the present study, these biomarkers cannot be considered independent diagnostic markers of metabolic syndrome. The present study has several limitations. First, the study included only 100 participants, with 42 participants having metabolic syndrome and 58 without metabolic syndrome, which limits the statistical power and generalisability of the findings. Second, the cross-sectional/observational nature of the study does not allow a causal relationship between homocysteine, vitamin B12, folate and metabolic syndrome to be established. Third, factors such as dietary intake, vitamin supplementation, renal function, medication use and genetic variations affecting homocysteine metabolism were not fully considered and may influence the observed associations. Larger prospective studies with appropriate multivariable adjustment are therefore required. Despite these limitations, the present study has the strength of simultaneously evaluating serum homocysteine, vitamin B12 and folate in all 100 participants and comparing these biomarkers according to metabolic syndrome status.

The findings demonstrated that the 42 participants with metabolic syndrome had significantly higher homocysteine and significantly lower vitamin B12 and folate levels than the 58 participants without metabolic syndrome. This pattern is broadly consistent with recent observational, prospective and meta-analytic evidence.[6,12]

Conclusion

We concluded that serum homocysteine, vitamin B12, and folate levels were significantly associated with metabolic syndrome among adults. Participants with metabolic syndrome had significantly higher serum homocysteine levels (19.24 ± 7.12 vs. 13.38 ± 5.08 µmol/L; $p<0.001$) and significantly lower vitamin B12 levels (276.48 ± 108.62 vs. 359.46 ± 132.18 pg/mL; $p=0.001$) and folate levels (6.92 ± 2.84 vs. 9.02 ± 3.82 ng/mL; $p=0.002$) compared with those without metabolic syndrome. These findings suggest that elevated homocysteine along with reduced vitamin B12 and folate levels may be associated with the presence of metabolic syndrome.

Assessment of these biochemical parameters may therefore provide useful additional information for identifying adults at increased metabolic risk and may contribute to a better understanding of the nutritional and biochemical factors associated with metabolic syndrome.

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