Medical Laboratory Journal
Online ISSN: 2538-4449
Golestan University of Medical Sciences

Relationship between hyperhomocysteinemia and the development of diabetes mellitus and cardiovascular disorders in Indian adult patients

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Abstract

Background: A higher occurrence of raised homocysteine levels has been reported in individuals with type 2 diabetes (T2D), particularly those with macroangiopathy and nephropathy. Given that hyperhomocysteinemia is a risk factor for T2D, mitigating this condition could potentially benefit T2D patients. This study aimed to investigate the influence of homocysteine on T2D and cardiovascular disease (CVD), as well as the factors that modify homocysteine levels.

Methods: This cross sectional, observational study was conducted on 122 individuals in a tertiary care center in Western India. Data related to anthropometry, demography, and biochemistry were gathered following established standards. Statistical analysis was performed using Chi-square test. A P-value of <0.05 was considered statistically significant.

Results: The findings indicated a significantly larger percentage of hyperhomocysteinemia in males, smokers, and individuals with elevated fasting blood sugar and HbA1c levels. The proportion of subjects with high homocysteine levels was notably greater in those with high total cholesterol and triglyceride levels. A significant correlation was observed between increased serum homocysteine levels and decreased serum folic acid and vitamin B12 levels in patients with ischemic heart disease.

Conclusion: Elevated homocysteine levels are observed in smokers and diabetic patients, potentially leading to CVD. Furthermore, this study found a correlation between an increase in serum homocysteine levels and a decrease in serum folic acid and vitamin B12 levels in patients with ischemic heart disease.

Article History

Received: 10 July 2022
Received in revised form: 25 February 2023
Accepted: 20 January 2024
Published online: 25 February 2024
DOI: 10.29252/mlj.18.1.29

Keywords

Diabetes Mellitus
Homocysteine
Body mass index

Article Type: Original Article

Introduction

Homocysteine, an intermediary amino acid containing sulfur, is produced through the demethylation of methionine, the primary source of which is animal protein. The typical range for homocysteine is 5 to 15 µmol/L. When serum homocysteine levels exceed 15 µmol/L, it is traditionally referred to as hyperhomocysteinemia (1). Hyperhomocysteinemia can potentially amplify the negative effects of risk factors, such as hypertension, smoking, and lipid and lipoprotein metabolism, and may also promote inflammation. It is recognized that hyperhomocysteinemia is an important risk factor for atherosclerotic vascular disease and venous thrombosis (2).

Recently, hyperhomocysteinemia has been linked to type 2 diabetes (T2D) (3). Homocysteine levels tend to be elevated in individuals with T2D and are linked with insulin resistance (IR). Given that diabetic individuals are at a high risk for coronary artery diseases (CAD), it becomes crucial to identify advanced markers for assessing CAD risk. The role of homocysteine in the context of T2D and cardiovascular disease (CVD) is of significant importance (4). Hyperhomocysteinemia can arise from a genetic deficiency of the enzymes required for its metabolism, a nutritional deficiency of vitamin cofactors, or medical conditions, such as CVD (5). Reduced intake and plasma concentrations of folic acid, along with vitamins B6 and B12, are associated with elevated plasma homocysteine levels (6).

The mechanism by which hyperhomocysteinemia leads to T2D is complex. Methyl tetrahydrofolate reductase (MTHFR) converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. The 677C→T polymorphism in the MTHFR gene results in an enzyme variant with reduced activity, which is associated with increased plasma homocysteine levels. It is hypothesized that elevated homocysteine levels lead to the production of reactive oxygen species (ROS), which in turn causes a decrease in insulin secretion responsiveness and results in IR. Understanding the significant biological effects of genetic modifiers could enhance our understanding of how homocysteine levels and MTHFR variants contribute to T2D (7).

An increased prevalence of elevated homocysteine levels has been observed in individuals with T2D who also have macroangiopathy and nephropathy. Since hyperhomocysteinemia is a modifiable risk factor with treatment, its correction could potentially have a beneficial impact on the management of T2D (8). The present study was conducted to assess the relationship between homocysteine levels and the lipid profile of individuals with T2D. The aim of this study was to analyze the role of homocysteine in T2D and CVD and also identify the factors that influence homocysteine levels.

Methods

This cross-sectional, observational study was conducted at a tertiary care hospital in Ahmedabad, India. It included individuals whose homocysteine levels were measured. All 122 individuals who were invited to participate in the study agreed and provided informed written consent prior to the onset of any procedures. The study excluded the following groups from participation: Seriously ill patients with changes in sensorium and higher function; patients with impaired hepatic or renal function; pregnant women; women receiving hormonal therapy; individuals with a history of acute infections; individuals with thyroid dysfunctions; and individuals taking vitamin B12, vitamin B6, or folic acid supplements for an extended period. The study was approved by the institutional ethics committee. This study was conducted between November 2017 and July 2019. A sample size of 122 was considered adequate to achieve a power of 0.8 at a significance level of less than 0.05.

A detailed history, including the patient's age, sex, place of residence, religion, occupation, marital status, and personal history (e.g., dietary habits, alcohol consumption, history of cigarette smoking, blood pressure, medical history of ischemic heart disease (IHD), family history of diabetes and hypertension, and physical activity), was collected using questionnaires.

The participants' height (portable Seca stadiometer, Hamburg, Germany; accuracy of up to 0.1 cm) and body weight (flat Seca 876 scale, Hamburg, Germany; accuracy of up to 100 g) were measured based on standard protocols.

Individuals with a BMI of 18.5-24.9 kg/m2 were considered to have a normal weight, individuals with a BMI of 25.0-29.9 kg/m2 were classified overweight, and individuals with a BMI⩾30.0 kg/m2 were considered obese (9).

Blood samples were collected in the morning after eight hours of fasting in both plain and EDTA vials. The blood samples were immediately centrifuged for 10 minutes at 3000 rpm. The serum was removed and stored in the freezer compartment of a refrigerator for measuring homocysteine, lipid profile, vitamin B12, and folic acid levels. The homocysteine and vitamin B12 levels were estimated using the ADVIA Centaur XPT system through a chemiluminescence immunoassay (CLIA). The serum lipid profile was also estimated using the ADVIA 1800 system through photometry. Moreover, the HbA1c levels were estimated using the D10 (BIORAD) system through high-performance liquid chromatography (HPLC).

Statistical analyses were performed using SPSS for Windows, Version 26 (SPSS, Chicago, IL, USA). Prior to the analyses, all outcome variables were checked for normality. The differences in mean values were evaluated using the student's t-test for parametric data and the Mann–Whitney U test for non-

parametric data. The Chi-square test was used for categorical variables. A P-value of less than 0.05 was considered statistically significant.

Results

The study enrolled 122 subjects, with males comprising 65.5% and females 34.4%. The age distribution was as follows: 4.9% were under 45 years, 34.4% were between 46 and 55 years, 36% were between 56 and 65 years, and 24.5% were over 66 years. In terms of health history, 33.6% were smokers, 68.03% had a history of diabetes, and 76.2% had a history of CVD.

The study found a significantly higher proportion of hyperhomocysteinemia in males, smokers, and subjects with high fasting blood sugar levels (>100 mg/dL) and high HbA1c levels (>5%) (P<0.05). Specifically, homocysteine levels exceeded 15 µmol/L in 69 men and 29 women, as well as in 38 smokers and 60 non-smokers. Furthermore, among diabetic patients (FBS>125), 82 out of 83 patients had homocysteine levels higher than 15 µmol/L. Similarly, 82 out of 83 patients with HbA1c levels higher than 5% also had elevated homocysteine levels (>15 µmol/L).

Table 1 presents the associations between lipid profile, fasting blood sugar levels, and serum homocysteine levels. It was found that total cholesterol and HDL levels did not show a significant association with impaired blood sugar levels. However, triglyceride and LDL levels had a significant association with impaired blood sugar levels. In terms of homocysteine levels, a significantly higher proportion of subjects with elevated homocysteine levels had high total cholesterol and high triglyceride levels (P<0.05). Interestingly, no significant association was observed between elevated homocysteine levels and abnormal LDL and HDL levels.

Figure 1 illustrates the relationship between the BMI categories and the history of T2D and CVD among the participants. It was found that a significantly higher proportion of individuals with a history of T2D and CVD were obese (P<0.05).

Table 2 demonstrates a significant association between elevated serum homocysteine levels and decreased serum folic acid and vitamin B12 levels in patients with IHD.

Table 1. Association of homocysteine and fasting blood sugar with lipid profile parameters

Homocysteine level (µmol/L)						Fasting blood sugar (mg/dL)				
Lipid profile	**Unit mg/dL**	**≤ 15**	**> 15**	**Chi-square value**	**P-value**	**<100**	**100-125**	**≥126**	**Chi-square value**	**P-value**
Total cholesterol	< 200	20	59	4.52	0.034	25	5	49	4.64	0.098
	≥ 200	4	39			6	3	34		
Triglyceride	< 150	16	31	9.99	0.002	21	3	23	15.3	0.001
	≥ 150	8	67			10	5	60		
HDL	≤ 40	12	44	0.202	0.653	13	3	40	0.600	0.741
	> 40	12	54			18	5	43		
LDL	< 100	13	36	2.44	0.118	21	4	24	14.5	0.001
	≥ 100	11	62			10	4	59		

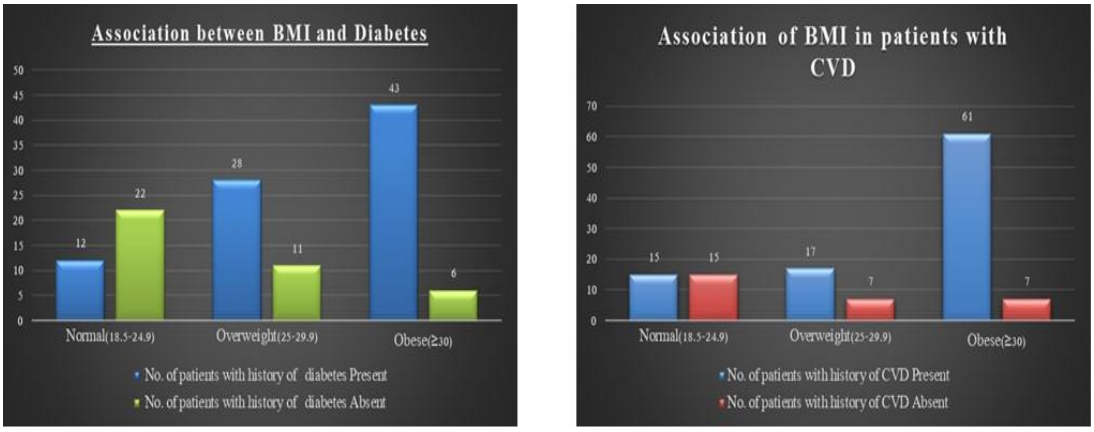

Figure 1. A: Represented association between BMI and diabetes
B: Represented association between BMI in patients with CVD

Table 2. Plasma homocysteine levels and other parameters in ischemic heart disease (IHD) patients

Study subjects				Chi-square value	P-value
Parameters	**Unit**	**No. of patients without a history of myocardial infarction or chronic stable IHD**	**No. of patients with a history of CVD**		
Homocysteine (µmol/L)	≤ 15	22	2	76.0	< 0.001
	> 15	7	91		
Serum folic acid (ng/mL)	< 2.7	8	74	27.1	< 0.001
	2.7-17	21	19		
Serum vitamin B12 (ng/mL)	< 200	9	57	8.15	0.004
	200-900	20	36		

Discussion

Our study found a significantly higher proportion of hyperhomocysteinemia in males, smokers, and subjects with high fasting blood sugar and HbA1c levels. We also observed that subjects with high total cholesterol and high triglyceride levels had significantly elevated homocysteine levels. Furthermore, there was a significant association between raised serum homocysteine levels and reduced serum folic acid and vitamin B12 levels in patients with IHD.

Indeed, our findings align with those reported by Macko et al., who also reported higher levels of serum homocysteine in men. They attributed this to factors, such as sex hormone status, body size, muscle mass, and vitamin status (10). In line with our study, Ganji et al. also reported a higher homocysteine level in smokers and attributed it to the direct effect of smoking, reflecting different nutritional statuses (11). Significant positive associations were also reported between homocysteine levels and glucose and HbA1c levels in other studies (12, 13,14,15). The positive correlation observed between glycemic parameters and homocysteine levels supports the hypothesis that hyperhomocysteinemia could play a pathophysiological role in the development of T2D.

Our findings align with those reported by Okumura et al., who also observed a significant positive association with triglyceride levels. However, in contrast to our results, they found a significant negative association with HDL-C (16). The observed mutual increase in homocysteine levels with an increase in triglyceride levels and a decrease in HDL-C could provide additional evidence for the involvement of hyperhomocysteinemia in the pathophysiology of diabetes mellitus. This finding is in line with the results of studies by Anand et al. and El Oudi et al., who also found a strong positive association between homocysteine levels and cholesterol and LDL-C levels, as well as an inverse association with HDL-C (17,18). Serum folic acid and serum vitamin B12 levels also showed a significant association in IHD patients with raised homocysteine levels, as folic acid and vitamin B12 deficiency leads to raised homocysteine levels, and raised homocysteine levels cause CVD (19).

Conclusion

Our study found that homocysteine levels are elevated in smokers and diabetic patients, which can contribute to CVD. Furthermore, we observed a correlation between an increase in serum homocysteine levels and a decrease in serum folic acid and vitamin B12 levels in patients with IHD.

Acknowledgement

Not applicable.

Funding sources

None.

Ethical statement

The institutional ethics committee approved the study.

Conflicts of interest

The contributing authors declare no conflicts of interest.

Author contributions

All authors contributed to data collection, data analysis, and writing of the manuscript.

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How to Cite:
Antani M, Goyal A, Rana J. Relationship between hyperhomocysteinemia and the development of diabetes mellitus and cardiovascular disorders in Indian adult patients. *Med Lab J.* 2024;18(1):29-31.