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HYPERHOMOCYSTEINEMIA IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract

Objective: *To determine the frequency of Hyperhomocysteinemia in patients with type 2 diabetes mellitus.*

Study design: *Cross-sectional study*

Place and duration: *Medicine Department of LUMHS, Jamshoro, for a duration of 6 months i.e. from Jan/2025 till Mar/2025.*

Patients and methods: *After obtaining written informed consent, 144 patients who met the selection criteria were enrolled. Demographic and baseline clinical details were noted. Serum homocysteine levels were assessed and hyperhomocysteinemia was detected if the levels were > 15 pmol/L. Findings were noted down and were subjected to statistical analysis.*

Results: *A total of 138 patients were enrolled. The median (IQR) age of the patients was 51 (9.5) years. The median (IQR) duration of disease was 10 (9) years and the mean HbA1c was 9.4 (2.5) %. There were 45 (31.3%) males and 99 (68.7%) females in the study. In terms of diabetic complications, retinopathy was seen in 16 (11.1%) patients, nephropathy was present in 43 (29.9%) patients and neuropathy was present in 46 (31.9%) patients. In diabetic patients, hyperhomocysteinemia was documented in 50 (34.7%) patients*

Conclusion: *In patients with T2DM, hyperhomocysteinemia was documented in 34.7% patients and thus must be routinely monitored in such patients in order to avoid cardiovascular risk.*

INTRODUCTION

Since diabetes mellitus (DM) is a prevalent metabolic disease that affects people all over the world, its rising prevalence, chronic nature, and severe consequences have made it a major public health problem[1]. The cross sectional survey conducted in Pakistan showed 19% prevalence of diabetes mellitus[2]. Wound healing problems in diabetics are caused by a number of well-known physiological variables, including reduced cytokine production, decreased growth factor production, angiogenic response, and macrophage function[3]. Furthermore, the normal process of cytokine generation is also disrupted by underlying disease states like hyperglycemia[4].

More and more research is demonstrating the connections between type 2 diabetes mellitus (T2DM) and its vascular consequences and plasma homocysteine (Hc) levels[5]. Hc is a poisonous, non-proteinogenic amino acid that is biosynthesised from methionine and contains sulfur. It is created from methionine as a byproduct of several

transmethylation processes and is situated at the intersection of several metabolic pathways[6]. The 5-methylenetetrahydrofolate reductase (MTHFR) polymorphism is the most prevalent hereditary condition that causes hyperhomocysteinemia. Hyperhomocysteinemia can also occur in those who are deficient in pyridoxine (B6), cobalamin (B12), or folic acid (B9)[7].

It has proven challenging to pinpoint the mechanisms behind T2DM and Hc levels thus far. 5-methyltetrahydrofolate is produced by the conversion of 5,10-methylenetetrahydrofolate by MTHFR[8]. The enzyme lowering activity variation linked to high plasma Hc levels and insulin resistance is impaired by mutations in MTHFR[9]. Insulin resistance is thought to originate from a reduction in insulin secretory response brought on by the harmful generation of reactive oxygen species as a result of high Hc levels[10].

The local literature regarding the homocystelne in relation to type 2 diabetes mellitus is still limited in relation to burden of the disease and its lethal complications. Thus, the current study aimed to determine the frequency of Hyperhomocysteinemia in patients with type 2 diabetes mellitus present at Liaquat University Hospital Hyderabad. The study focused on generating the local data by investigating the magnitude of hyperhomocysteinemia in patients with type 2 diabetes mellitus in our population so that patients could be prospectively rationalized and managed early according to the observations of this study.

PATIENTS AND METHODS:

The study had a cross-sectional design. The study was carried out at the Medicine Department of Liaquat University Hospital, Hyderabad, for a duration of 6 months i.e. from Jan/2025 till Mar/2025. The study enrolled 144 patients with T2DM. The sample size of 144 patients was calculated by taking the prevalence of hyperhomocysteinemia in T2DM as 40%[11] and d=8%. Non-probability consecutive sampling technique was used.

Inclusion criteria: The study included the known cases of diabetes mellitus for > 5 year duration or newly diagnosed (as per operational definitions) patients, of 30-60 years of age and either gender having history of weakness, fatigue and dizziness.

Exclusion criteria: Patients were excluded if they were known cases of type 1 diabetes mellitus, gestational diabetes and hypothyroidism, individuals who were already on corticosteroids, immune-suppressive therapy, vitamin B-12, folic acid, pyrazinamide, thiazides, lipidlowing or antioxidant therapy, known cases of chronic liver diseases as chronic viral hepatitis, chronic renal failure and the pregnant and lactating ladies.

T2DM was identified when there were known cases of diabetes mellitus for more than five years, or when fasting blood sugar (FBS) was greater than 126 mg/dl or random blood sugar (RBS) was greater than 200 mg/dl at least twice (newly diagnosed). Hyperhomocysteinemia was considered when serum homocysteine levels were > 15 pmol/L. Effect modifiers were also assessed. Hypertension was by the presence of history for >01 year duration and baseline blood pressure (>140/90) on presentation (on physical examination) while already on treatment but non-compliance, smoking history was considered positive if there was clinical history of tobacco use (>5 cigarettes per day) for > 02 years duration (on clinical history). Obesity was labeled when the body mass index (BMI) was ≥30 kg/m^2. According to a biochemical measure, hyperlipidemia was characterized as unusually high blood levels of any one or all lipoproteins, including HDL (<40 mg/dl), triglycerides (>150 mg/dl), low density lipoprotein (>100 mg/dl), and cholesterol (>200 mg/dl). Non-alcoholic fatty liver disease (NAFLD) was defined by the appearance of liver as hyperechogenic (bright), vessel blurring and lumen narrowing of the hepatic veins on ultrasonography along with no history of alcohol consumption and steatogenic medication. Low platelet count was labeled if there were less than 150,000 platelets per microliter of blood. Uncontrolled DM was labeled when Hemoglobin A1c (HbA1c) was greater than 6.5% while already on treatment. Diabetic retinopathy was evaluated by ophthalmoscope by detecting either tiny bulges within vessels, bleeding in the retina, new blood vessels and scar tissue or leakage of blood vessels on clinical examination by researcher. Diabetic nephropathy was labeled when urinary albumin excretion (microalbuminuria) was greater than 30 mg / 24 hours. The urine collection was done through a urine bag. Diabteic neuropathy was labeled when the

patient had decreased sensitivity (reduced / decrease response) to external stimuli to touch on soft nylon fiber (monofilament) applied on the planter aspect of patient's foot [clinical examination] by clinician and was considered as diabetic neuropathy (diabetic neuropathy +ve) when there was reduced / decrease response to touch on monofilament. There were five different categories for educational status: primary (1–5 years), middle (6–8 years), secondary (9–10 years), higher (11+ years of education completed, including professional or university degrees), and no education, or illiterate (someone who cannot read or write).

After taking written informed consent, a total of 144 patients were enrolled. The relevant individuals were further evaluated for the serum homocysteine level by taking a 2cc venous blood sample in a 5cc disposable syringe by the principal investigator and sent to the laboratory for analysis. The senior pathologist who had more than 5 years of clinical laboratory experience analyzed the specimen. The hyperhomocysteinemia was labeled as per operational definition while the data was collected on pre-designed proforma whereas all the financial burden of the study was paid by the researcher herself. The effect modifiers and other explanatory variables were assessed. All findings were noted down and were subjected to statistical analysis.

The data of all patients will be analyzed in SPSS version 21.00. The frequency and percentage was calculated for age, gender and residence (urban or rural), educational status, hypertension, smoking, obesity, hyperlipidemia, NAFLD, low platelet count, un-controlled DM, diabetes related complications (retinopathy, nephropathy, neuropathy) and hyperhomocysteinemia. The Shapiro-Wilk test was used to determine the normality of the data. The median and interquartile range (IQR) was calculated for quantitative variables such as age, duration of diabetes mellitus & hemoglobin A1C (HbA1c) as the data was non-normal in distribution. The stratification was done for the effect modifiers to see the effect on outcome and to control the effect modifiers. The post stratification chi-square test was applied and a p value of ≤0.05 was considered significant.

RESULTS:

A total of 138 patients were enrolled. The median (IQR) age of the patients was 51 (9.5) years. The median (IQR) duration of disease was 10 (9) years and the mean HbA1c was 9.4 (2.5) % (Table-I).

In terms of age group, there were 35 (24.3%) patients of age group 30 to 45 years and 109 (75.7%) patients of age group 46 to 60 years. There were 45 (31.3%) males and 99 (68.7%) females in the study. The educational status of the patients revealed that 15 (10.4%) patients were illiterate, 27 (18.8%) had done matric, 41 (28.4%) patients studied till secondary, 42 (29.2%) patients did graduation and 19 (13.2%) patients had above graduation degree. Hypertension was present in 75 (52.1%) patients, smoking history was positive in 48 (33.3%) patients, 71 (49.3%) patients were obese, 60 (41.7%) patients had hyperlipidemia, NAFLD was present in 40 (27.8%) patients, low platelet count was observed in 18 (12.5%) patients and uncontrolled diabetes was present in 60 (41.7%) patients. In terms of diabetic complications, retinopathy was seen in 16 (11.1%) patients, nephropathy was present in 43 (29.9%) patients and neuropathy was present in 46 (31.9%) patients. In diabetic patients, hyperhomocysteinemia was documented in 50 (34.7%) patients (Table-II).

Data was stratified for baseline demographical and clinical effect modifiers and it was revealed that hyperhomocysteinemia was significantly more frequent in patients who had hyperlipidemia (p=0.029), however, there was no significant association between other effect modifiers and hyperhomocysteinemia (Table-III).

Table-I: Median (IQR) of Quantitative Variables (n=138)

Variables	Median (IQR)
Age (in years)	51 (9.5)
Duration of disease (in years)	10 (9)
HbA1c (%)	9.4 (2.5)

Table-II: Frequency of baseline demographic and clinical characteristics (n=138)

Variables	**Frequency (percentage)**
Age group: 30 to 45 years 46 to 60 years	 35 (24.3%) 109 (75.7%)
Gender: Male Female	 45 (31.3%) 99 (68.7%)
Educational status: Illiterate Matric Secondary Graduate Above graduate	 15 (10.4%) 27 (18.8%) 41 (28.4%) 42 (29.2%) 19 (13.2%)
Hypertension: Yes No	 75 (52.1%) 69 (47.9%)
Smoking: Yes No	 48 (33.3%) 96 (66.7%)

Obesity: Yes No	 71 (49.3%) 73 (50.7%)
Hyperlipidemia: Yes No	 60 (41.7%) 84 (58.3%)
NAFLD: Yes No	 40 (27.8%) 104 (72.2%)
Low platelet count: Yes No	 18 (12.5%) 126 (87.5%)
Uncontrolled diabetes: Yes No	 60 (41.7%) 84 (58.3%)
Diabetic retinopathy: Yes No	 16 (11.1%) 128 (88.9%)
Diabetic nephropathy: Yes No	 43 (29.9%) 101 (70.1%)
Diabetic neuropathy: Yes No	 46 (31.9%) 98 (68.1%)
Hyperhomocysteinemia: Yes No	 50 (34.7%) 94 (65.3%)

Table-III: Stratification of hyperhomocysteinemia with respect to effect modifiers (n=144)

Effect Modifiers	Hyperhomocysteinemia		p value
	Yes	No	
Age group: 30 to 45 years 46 to 60 years	 15 (10.4%) 35 (24.3%)	 20 (13.9%) 74 (51.4%)	0.245
Gender: Male Female	 13 (9%) 37 (25.7%)	 32 (22.3%) 62 (43%)	0.322
Educational status: Illiterate Matric Secondary Graduate Above graduate	 6 (4.2%) 10 (6.9%) 13 (9%) 13 (9%) 8 (5.6%)	 9 (6.3%) 17 (11.8%) 28 (19.4%) 29 (20.1%) 11 (7.6%)	0.889
Hypertension: Yes No	 28 (19.4%) 22 (15.3%)	 47 (32.6%) 47 (32.6%)	0.493
Smoking: Yes No	 13 (9%) 37 (25.7%)	 35 (24.3%) 59 (41%)	0.173
Obesity: Yes No	 21 (14.6%) 29 (20.1%)	 50 (34.7%) 44 (30.6%)	0.201
Hyperlipidemia: Yes No	 27 (18.8%) 23 (16%)	 33 (22.9%) 61 (42.4%)	0.029
NAFLD: Yes			

No	16 (11.1%) 34 (23.6%)	25 (16.7%) 70 (48.6%)	0.409
Low platelet count: Yes No	 4 (2.8%) 46 (31.9%)	 14 (9.7%) 80 (55.6%)	 0.234
Uncontrolled diabetes: Yes No	 23 (16%) 27 (18.8%)	 37 (25.7%) 57 (39.6%)	 0.442
Diabetic retinopathy: Yes No	 6 (4.2%) 44 (30.6%)	 10 (6.9%) 84 (58.3%)	 0.804
Diabetic nephropathy: Yes No	 19 (13.2%) 31 (21.5%)	 24 (16.7%) 70 (48.6%)	 0.120
Diabetic neuropathy: Yes No	 12 (8.3%) 38 (26.4%)	 34 (23.6%) 60 (41.7%)	 0.136

DISCUSSION:

The current study findings revealed that in patients with T2DM, hyperhomocysteinemia was present in 34.7% patients. The majority of the patients in our study were of age group 46 to 60 years, were females and had education till secondary or were graduate. There was significant association between the frequency of hyperhomocysteinemia and hyperlipidemia in our study.

Globally, T2DM is becoming more and more common[12]. Finding modifiable factors is crucial for diabetes prevention because of the high costs associated with healthcare[13]. It is well recognized that T2DM is a complicated and diverse illness caused by a number of interrelated elements, both environmental and genetic, each of which contributes differently to the disease's etiology[14]. Numerous lifestyle, environmental, behavioral, nutritional, and cultural factors are also important predictors of T2DM risk. Recent research has increasingly demonstrated the connections between T2DM and associated vascular consequences and plasma Hc levels[15]. However, research showing differences in plasma Hc levels between individuals with and without diabetes make the correlation with T2DM less than conclusive. Furthermore, little is known about this association in our local population. Therefore, there was a dire need to conduct a study locally to assess the rate of hyperhomocysteinemia in patients with T2DM.

Our results showed that hyperhomocysteinemia was present in 34.7% patients. In the study by Ansari *et al.* the hyperhomocysteinemia in patients with type 2 diabetes mellitus was seen in 40% of the patients[11]. Hoogeveen *et al.* revealed that hyperhomocysteinemia was present in 25.8% patients with T2DM[16]. Buysschaert *et al.* found 31% of the patients with T2DM had hyperhomocysteinemia[17]. In another

study Mundu *et al.* hyperhomocysteinemia was seen in 72% of the patients who had microvascular complications and in 36.6% patients who did not have complications[18]. These studies support our study findings that hyperhomocysteinemia is frequently encountered in patients with T2DM.

Our study findings showed that hyperlipidemia was significantly more frequent in T2DM patients who had hyperlipidemia, however, there was no significant association with other effect modifiers such as age, gender, complications of diabetes, uncontrolled diabetes, NAFLD, smoking, hypertension and low platelet count. Wei *et al.* also revealed that hyperhomocysteinemia was significantly associated with hyperlipidemia[19]. Tarkun *et al.* similarly revealed that in diabetic patients, there was no significant association between hyperhomocysteinemia and effect modifiers such as age, lipid profile, blood sugar levels and diabetes duration[20]. These findings arein line with our study findings that the demographic and diabetes related factors have no association with the presence of hyperhomocysteinemia.

In T2DM patients, plasma homocysteine levels must be checked, and if hyperhomocysteinemia is found, it must be appropriately treated in order to prevent cardiovascular morbidity.

Conclusions:

The current study concluded that in patients with T2DM, hyperhomocysteinemia was documented in 34.7% patients. The current study findings proposed that to avoid cardiovascular morbidity, plasma homocysteine levels in T2DM patients must be monitored, and if hyperhomocysteinemia is discovered, it must be properly treated. To validate the results of the current study, larger samples must be used in future research.

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LIMITATIONS:

The study was subject to important limitations. Because this study was conducted at a single center therefore, its findings cannot be broadly applied. Secondly, we did not assess the vitamin deficiencies in our study which could have affected the metabolism of homocysteine. Hence, deficiencies such as those of vitamin B12, B6 and folic acid must be checked in order to avoid development of further complications.

Conflict of interest: None

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