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Serum Homocysteine Level in Patients of Type 2 Diabetes Mellitus with Macrovascular Complications

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ABSTRACT

The risk of CVD in men with DM is 3-fold and in women with DM 5-fold in comparison to those without diabetes(1). Diabetes is a recognized independent risk factor for stroke and is associated with higher morbidity and mortality(2-4). The severity and duration of DM are important predictors of both the incidence and the extent of PAD, as observed in United Kingdom Prospective Diabetes Study, where each 1% increase in glycosylated hemoglobin was correlated with a 28% increase in incidence of PAD, and higher rates of death, microvascular complications and major amputation.(5,6)
Homocysteine concentration is found to be higher in patients with peripheral vascular, cerebrovascular and coronary artery diseases than those without such diseases.(7)
This observational comparative study was done at Ramakrishna Care Hospital, Raipur, from January 2017 to June 2018 involving 100 type 2 diabetes mellitus patients.
Patients were divided into two groups-
Group 1: The Case Group- Type 2 DM patients with macrovascular complications.
Group 2: The Control Group - Type 2 DM patients without any macrovascular complications
With the help of Clinical evaluation and detailed investigations we had determined the presence of macrovascular complications in which we had included Myocardial infarction, CVA and Peripheral vascular disease. Data obtained from these patients were analysed and the results were compared with prior studies of similar objectives. Higher age and duration of diabetes thus had a positive correlation with macrovascular disease. The mean serum homocysteine level was statistically significant and they correlate with higher incidence of macrovascular disease in males and with increasing age.

Keywords: Type 2 Diabetes Mellitus, DM, CVD, CVA, Serum Homocysteine Level, Macrovascular Complications.

INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors. Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system(8).
DM is associated with enhanced development of macrovascular

complications[9], such as myocardial infarction, stroke and peripheral vascular disease.

Table.
Risk Factors for Diabetes-Associated Microvascular and Macrovascular Complications

Risk Factor	Retinopathy	Neuropathy	Nephropathy	Cardiovascular Disease	Cerebrovascular Disease	Peripheral Vascular Disease
Hyperglycemia	Yes	Yes	Yes	Yes	Yes	Yes
Hyperinsulinemia					Yes	
Age	Yes	Yes	Yes	Yes		
Tobacco use	Yes	Yes	Yes	Yes	Yes	
Insulin treatment	Yes					
Dyslipidemia	Yes	Yes	Yes	Yes		
Pregnancy	Yes					
Renal disease	Yes					
Elevated homocysteine level	Yes					
High-fat diet	Yes					
Chronic diabetes mellitus		Yes				Yes
Hypertension		Yes		Yes	Yes	Yes
Obesity				Yes		Yes
Atrial fibrillation					Yes	
Heart failure					Yes	
Proteinuria			Yes		Yes	
Microalbuminuria		Yes	Yes		Yes	
Hyperuricemia					Yes	
Blood inflammatory molecules					Yes	
Elevated blood fibrinogen level						Yes
Physical inactivity				Yes		Yes
Elevated height		Yes				
Ketoacidosis		Yes				
Carotid artery stenosis					Yes	

Pathogenesis of Macrovascular Complications in Type 2 DM

The pathogenesis of macrovascular disease in diabetes is multifactorial; however, the common recipient of injury is the vascular endothelium [10]. Diabetes initially impairs the ability of the vascular endothelium to vasodilate through inhibition of the nitric oxide (NO, a gas molecule that maintains arteriolar vasodilatation) pathway. The presence of hyperglycemia inhibits the enzyme responsible for the production of NO (ie, endothelial nitric oxide synthase [eNOS]) and increases the production of ROS, leading to further inhibition of eNOS [11,12]. The vascular endothelium also loses its ability to produce NO-activated tissue plasminogen activator, a fibrinolytic (anti-clotting) protein that inhibits the ability of inflammatory cells to "stick" to the endothelial surface[13]. Insulin resistance also can contribute to a decrease in NO production and the subsequent impaired vasodilatory response. In addition, insulin resistance can lead to an increase in the release of free fatty acids from adipose tissue[14] and stimulate the PKC pathway, which can directly and indirectly inhibit eNOS activity through increased ROS generation[15]. In addition to the reduction in the vasodilatory response in diabetes, an overproduction of vasoconstrictor substances occurs; these substances include endothelin 1, which has direct vasoconstrictive effects on the endothelium as well as indirect fluid volume effects, including the stimulation of water and salt retention and the activation of the RAS[16].

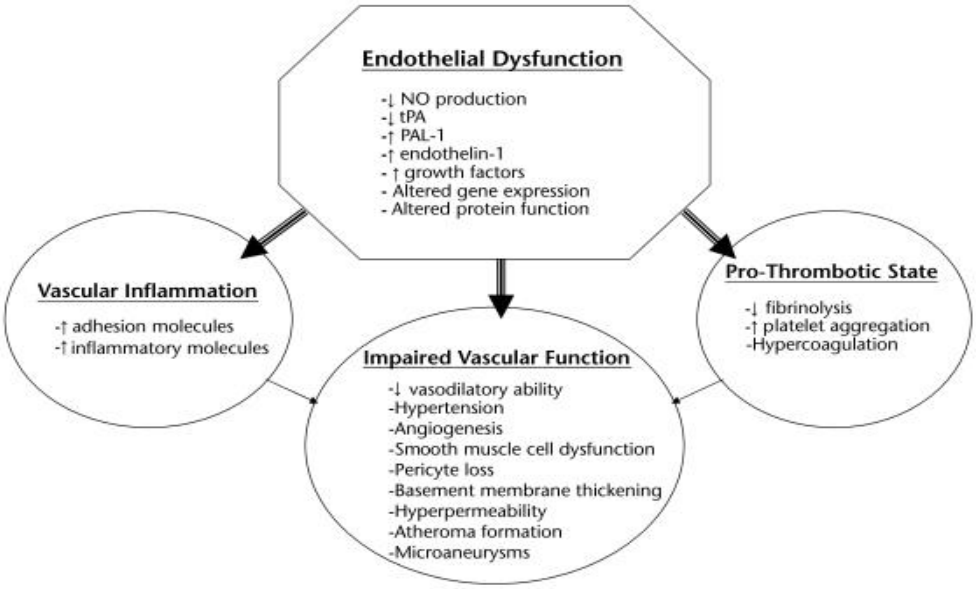

Figure-1

Homocysteine is believed to cause atherogenesis and thrombogenesis via endothelial damage, vascular smooth muscle proliferation, and coagulation abnormalities. High homocysteine levels are associated with increased risk of cardiovascular and cerebrovascular disease [(17)].

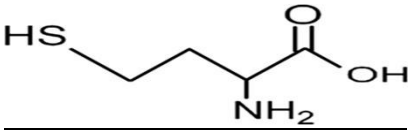

Figure -2

Homocysteine, a sulfhydryl-containing amino acid, is an intermediate product in the normal biosynthesis of the aminoacids methionine and cysteine [(18)]. It is present in plasma in four different forms: around 1% circulates as free thiol, 70–80% remains disulphide-bound to plasma proteins, mainly albumin and 20–30% combines with itself to form the dimer homocysteine or with other thiols [(19)]. Homocysteine is a key determinant of the methylation cycle as shown below[(20)].

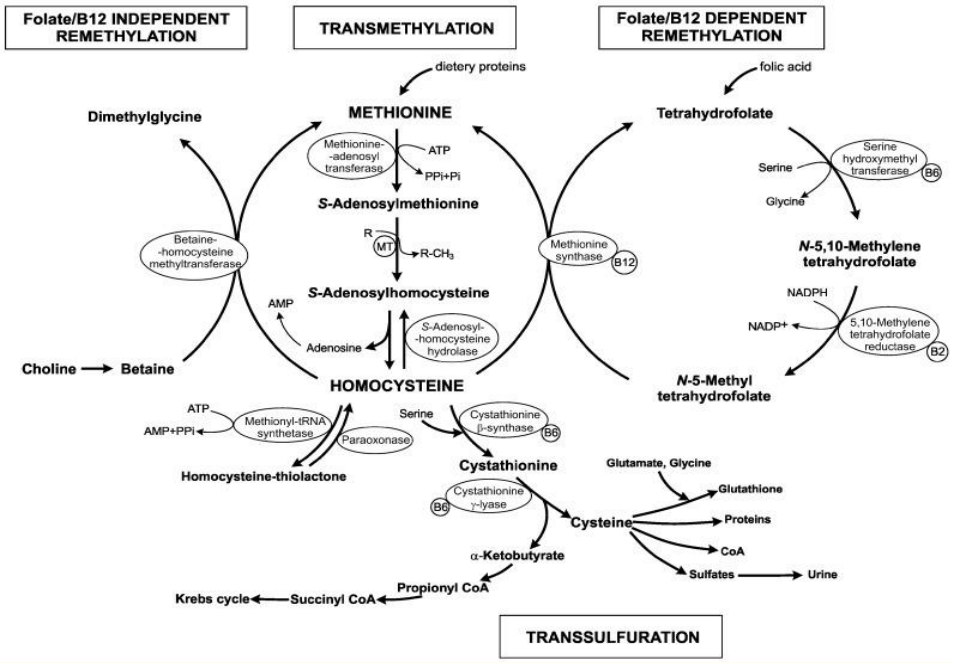

Figure 3: The schematic overview of homocysteine metabolism and its relationship with folic acid and vitamins. ATP: adenosine triphosphate; AMP: adenosine monophosphate; PPi: pyrophosphate; Pi: orthophosphate; B2/B6/B12: vitamins B2/B6/B12; CoA: coenzyme A; R: acceptor; R-CH3: methylated product; MT: methyltransferases.

HYPERHOMOCYSTEINEMIA

The definition of hyperhomocysteinemia differs between studies[18]. Hyperhomocysteinemia is defined as a medical condition characterized by an abnormally high level (above 15 µmol/L) of homocysteine in the blood [22]. Total concentration of homocysteine in plasma of healthy humans (fasting) is low and its level is between 5.0 and 15.0µmol/L when assessed with the use of HPLC, or 5.0-12.0µmol/l when immunoassay methods are used[23]. When the level is between 16-30 µmol/L it is classified as moderate, 31-100 µmol/L is considered intermediate and a value above 100 µmol/L is classified as severe hyperhomocysteinemia[19].

Hyperhomocysteinemia can also arise from nutritional deficiencies of folate, vitamin B_6, and vitamin B_{12} [24]. Several diseases such as renal and thyroid dysfunction, cancer, psoriasis, and diabetes as well as various drugs, alcohol, tobacco, coffee, older age and menopause, are believed to be associated with moderately elevated homocysteine concentrations[18].

A rise in serum creatinine also leads to a rise in fasting total homocysteine. The major route of homocysteine clearance from plasma is the kidney, and the rise is due to defective metabolism of homocysteine by the kidney. Total homocysteine levels are found to be considerably higher in patients with chronic renal disease than the moderately raised concentrations commonly found in patients with atherothrombotic vascular disease, and this may be the probable cause that contributes to the high incidence of vascular complications in patients with chronic renal failure [19]. Plasma homocysteine concentrations can be increased by various drugs and diseases that interfere with folate, vitamin B_6, and B_{12} metabolism, hence an abnormal homocysteine concentration may have a probable use as a diagnostic aid for some of these conditions[19].

There has been an indication towards a significant correlation between hyperhomocysteinemia and cardiovascular disease and its complications such as heart attacks and strokes[23]. It is believed that hyperhomocysteinemia leads to endothelial cell damage, reduction in the flexibility of vessels, and alters the process of haemostasis [23].

Because of the association between homocysteine level and macrovascular complications of Diabetes Mellitus, physicians and diabetologists should have thorough understanding of this association which will help them in managing patients.

LITERATURE REVIEW

The correlation between hyperhomocysteinemia and atherosclerotic disease was first proposed more than 40 years ago. It was first identified by McCully in 1969. Atherosclerosis is the most common pathological process that leads to cardiovascular diseases such as myocardial infarction (MI), heart failure, stroke and claudication [25].

Some of the presumed mechanisms of these effects include an increase in proliferation of vascular smooth muscle cells, endothelial dysfunction, oxidative damage, an increase is synthesis of collagen and deterioration of arterial wall elastic material[26]. Examination of the effect of homocysteine on CRP expression and investigation on the related mechanism in vascular smooth muscle cells (VSMCs) revealed that homocysteine significantly induced mRNA and protein expressions of CRP in VSMCs both in vitro and in vivo [27].

It also has role in increasing the activity of HMG Co A reductase which in turn increases cholesterol synthesis [28]. An increased cholesterol level promotes atherosclerosis and hence it is a risk factor for CAD. Serum levels of homocysteine were found to be significantly higher in CAD than in non CAD subjects. Increased serum homocysteine levels positively correlated with severity of CAD[28].

Several studies demonstrated that homocysteine is capable of triggering neuronal damage via oxidative stress, DNA

damage and activation of pro-apoptotic factors in cell cultures or animal models[24].

In fact, Hcy suppresses NO production by endothelial cells and platelets and increases generation of reactive oxygen species (ROS) by the release of arachidonic acid from the platelets. It also inhibits glutathione peroxidase and thus stimulates proliferation of endothelial cells[29]. In addition, Hcy has been shown to inhibit methyltransferases, to suppress DNA repair and to facilitate apoptosis when accumulated inside the cells. Autooxidation of Hcy metabolites results in H202 accumulation[30] and challenging neurons to Hcy metabolites for longer period leads to necrotic cell death[31].

Humphrey et al. [32] analyzed has also demonstrated that increased 5 µmol/L Hcy concentration will increase approximately 20% risk of CAD events. Chauhan et al. (2012) reported that hyperhomocysteinemia, a risk factor for cardiovascular disorder, obesity, and type 2 diabetes, is prevalent among Indians who are at high risk of these metabolic disorders[33]. Page et al.[34] & Souissi et al.[35] found independent association between high serum homocysteine and increased risk of myocardial infarction.

In another study done in the Department of Endocrinology, Eskisehir, Turkey in type 2 diabetic patients, comparison was done between patients who had atherosclerotic vascular disease and no vascular disease. Homocysteine levels and markers of inflammation were measured. Both Homocysteine levels and inflammation markers were all significantly elevated in patients with atherosclerotic vascular disease when compared with patients without vascular disease. Impaired renal functions were significantly associated with both Homocysteine levels and inflammatory markers. There was no correlation between Homocysteine levels and inflammation markers except for TNFα, implying that inflammation is not involved in the process by which Homocysteine leads atherosclerosis in type 2 diabetes[36].

A study done by Usman Khan et al on UK black stroke population concluded that homocysteine levels were elevated and highest levels were found in lacunar stroke with leukoaraiosis[37].

A study done by Tan NC et al concluded that hyperhomocysteinemia is an independent risk factor for ischemic strokes in young Asian adults. The relationship between increasing homocysteine and stroke risk is strong, graded, and significant. The association with large-artery strokes suggests that hyperhomocysteinemia may increase stroke risk via a proatherogenic effect[38].

Obaidi et al.'s [39] study where the authors observed that the rise in cardiac troponin-I most notably occurred in homocysteine level >16.5µmol/L in AMI patients.

A study done by Kittner SJ et al concluded that there is an independent association between elevated homocysteine level and stroke in young women[40].

MATERIALS & METHODS

Study site: - Study was conducted at Ramakrishna Care Hospital Raipur.

Study population: - patients with type 2 diabetes mellitus

Study design: - one and half year observational comparative study, January 2017-June 2018

Inclusion Criteria:

1. subjects who have given consent for participation in the study
2. The diagnosis of DM is based on WHO criteria;
   - A fasting plasma glucose of ≥ 126 mg/dl (7.0 mmol/L) after minimum 12-h fast, with symptoms of diabetes
   - 2 h of postprandial glucose level of ≥ 200 mg/dl (11.1 mmol/L) after 75 g oral glucose load.
   - HBA1C levels greater than or equal to 6.5%
3. Subjects of either sex - male or female.
4. Diagnosis of macrovascular disease based on history, clinical findings.

Exclusion Criteria:

1. Patients who have not given written informed consent.
2. Patients with Type 1 diabetes
3. Pregnancy
4. Cardiomyopathy, congenital heart diseases, valvular heart disease
5. Severe renal impairment
6. Severe hepatic impairment
7. Patient on lipid-lowering drugs
8. Patient on vitamin B supplements
9. Trauma, surgery or amputation involving the lower limb.
10. Deep vein thrombosis
11. Alcoholics
12. Smoking
13. Patients on treatment with drugs known to cause diabetic state like steroids and risperidone.

Statistical Analysis

Sample size: From earlier study: Lakshman Ramachandran, NS Negi, B Gupta. Prevalence of hyperhomocysteinemia in type-2 diabetes mellitus and its correlation with its complications. Journal, Indian Academy of Clinical Medicine. October-December, 2012. 13(4): 277-81.

Formula:

Minimum sample size is

$$N = \frac{2(1.96+0.84)^2\, SD^2}{D^2} = 48 \text{ in each group}$$

Where:

N = the sample size in each of the groups

M1 = mean Plasma homocysteine level in type 2 diabetic with complication=3.0095

M2 = mean Plasma homocysteine level in type 2 diabetic without complication=2.4919

D = the difference in mean= M1-M2=0.5176

SD^2 = Squared pooled deviation=0.806

1.96 = conventional multiplier for alpha = 0.05

0.84 = conventional multiplier for power = 0.80

Analysis of quantitative data using %, mean and standard deviation, unpaired' test

Qualitative data were analyzed using chi square test or fisher exact test.

Statistical significance

P<0.05 is significant

P<0.01 is highly significant

P>0.05 is not significant

Statistical Software is SPSS 16.0

Sampling Method: Purposive random sampling

RESULT

1. In our study most of the patients belonged to age group 51-60 years.
2. Mean age was 58.66 ± 5.87 in case group while in control group; mean age was 54.72 ± 6.63 which was statistically highly significant. (p value<0.001)
3. In case group, 66% were males, 34% were females while in control group 64% were males and 36% were females which was not statistically significant.(p value 0.83)
4. Mean duration of type 2 DM was 9.14±2.38 in case group and 5.34±1.61 in control group which was statistically significant. (p value<0.0001)
5. Except for mean serum creatinine, there was statistically significant difference in both the groups for blood investigations done that is, mean FBG, PP-BG, HbA1c, serum homocysteine, serum cholesterol, serum TG and serum LDL.
6. In case group, 84% patients presented with anginal equivalents, 28% came with focal neurological deficits and only 10% had claudication. Of total patients presenting with anginal equivalents, 93.94% were males and 64.70% were females which was highly significant. (p value 0.007) However sex distribution for CVA and PAD was not statistically significant. (p value 0.066 and 0.48 respectively).

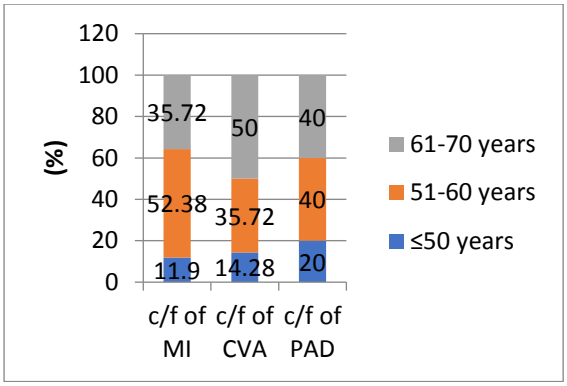

Chart-1 shows that out of 50 patients, 8 patients were in age group ≤50 years in which 5 patients had c/f of MI, 2 patients had c/f of CVA and 1 patient had c/f of PAD.

Out of 50 patients, 26 patients were in age group 51-60 years in which 22 patients had c/f of MI, 5 patients had c/f of CVA and 2 patients had c/f of PAD.

Out of 50 patients, 16 patients were in age group 61-70 years in which 15 patients had c/f of MI, 7 patients had c/f of CVA and 2 patients had c/f of PAD.

7. The difference in age distribution of c/f of MI, c/f of CVA, c/f of PAD was found to be statistically not significant. (p value was 0.14, 0.22 and 0.85 respectively). In the present study age distribution of the macrovascular complications was found to be statistically not significant.
8. Mean homocysteine level in case group was 16.52±3.56 in study group and was 11.74±2.76 in control group which was statistically significant. (p value <0.001)
9. In case group we found that males had mean homocysteine levels of 18.36±2.55 while females had mean homocysteine level of 12.94±2.30. Mean homocysteine level in males in control group was 12.72±2.42 and in females it was 10±2.19. values were statistically significant.(p value<0.001).

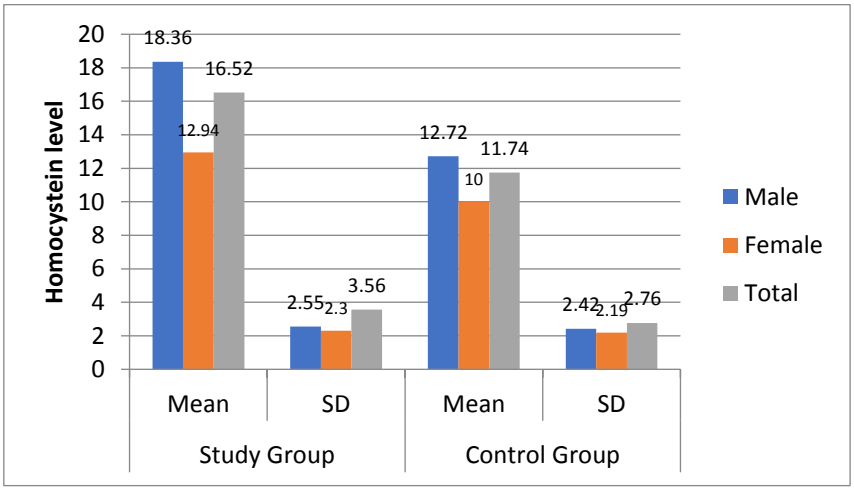

Chart 2 shows mean homocysteine level in case group was 16.52±3.56 and in control group it was 11.74±2.76. This difference was found to be statistically significant. (p value <0.001)

Serum homocysteine level in males in case and control group was 18.36±2.55 and 12.72±2.42 respectively and this was found to be statistically significant. (p value <0.001).

10. Serum homocysteine level in females in case and control group was 12.94±2.30 and 10±2.19 respectively and this was found to be statistically significant. (p value <0.001)
11. Highly significant difference (P<0.001) in mean serum homocysteine level was found in age group 51-60 years and 61-70 years which was 15.61±3.63 and 19±2.16 respectively. Also highly significant difference (P<0.001) exists between mean homocysteine level in age group≤50 years which was 14.5±3.16 and age group 61-70 years in which it was 19±2.16.

DISCUSSION

- **The prevalence of macrovascular complications in type 2 DM patients:**

In the present study it was found that in case group 84% patients had MI , 28% patients had CVA and 10% patients had peripheral arterial disease. The mean duration of type 2 DM in case group v/s control group was 9.14±2.38 v/s 5.34±1.61 respectively. This difference was statistically significant (p value<0.0001). Also The mean age in case group was 58.66±5.87 and in control group it was 54.72±6.63 which was found to be statistically significant (p value<0.001). Higher age and duration of diabetes thus had a positive correlation with macrovascular disease.

In a similar study conducted by *Alaboud AF et al.* on microvascular and macrovascular complications of type 2 diabetic mellitus showed approximately 63 (8.7%) had myocardial infarction (MI), 49 (6.6%) had cerebrovascular accident (CVA). Age (years) , duration of DM (years) were significant variables associated with macrovascular complications found in this study[(41)].

- **Comparison of serum homocysteine levels in type 2 DM patients with and without macrovascular complications.**

In the present study it was found that the mean serum homocysteine level was 16.52±3.56 in case group and was 11.74±2.76 in control group. This difference was statistically significant (p value<0.001). All these differences are statistically significant and they correlate with higher incidence of macrovascular disease in males and with increasing age. In a similar study conducted by *Chang N et al.* they found that in diabetic patients without macroangiopathy, the plasma homocysteine level was 11.4 ± 3.1 µmol/l. In the diabetic patients with macroangiopathy, the plasma homocysteine level was 14.2 ± 5.8 µmol/l, which was significantly higher[(42)].

In another similar study conducted by *El Oudi et al*. a strong association was found between type 2 diabetes and hyperhomocysteinemia (P<0.001)[(43)].

- **Correlation of serum homocysteine with age and sex**

In the present study it was found that serum homocysteine in males was 18.36±2.55 and 12.72±2.42 in case and control group respectively. While in females it was 12.94±2.30 and 10±2.19 in case and control group respectively. Also mean serum homocysteine level for age group < 50 years was 14.5±3.16 , from 51-60 years it was 15.61±3.63 and from 61-70 it was 19±2.16. All these differences are statistically significant and correlate with higher incidence of macrovascular disease in males and with increasing age. In a similar study conducted by *Nygård O et al* study it was found that the level of plasma total homocysteine was higher in men than in women and increased with age. In subjects 40 to 42 years old, geometric means were 10.8 mumol/L for (5918 men) and 9.1 mumol/L for (6348 women). At age 65 to 67 years, the corresponding tHcy values were 12.3 mumol/L (1386 men) and 11.0 mumol/L (1932 women)[(44)].

Correlation between Serum homocysteine and HbA1c

In the present study it was found that there was statistically significant correlation between serum homocysteine and HbA1c level. (p value <0.002).

A study done at Department of Public Health, Kyorin University School of Medicine, Tokyo, Japan. in diabetic subjects, HbA1c was associated with higher total homocysteine in diabetic patients. (p value < 0.001) [(45)]

- **Correlation between Serum homocysteine and hypertriglyceridemia.**

In the present study it was found that there was significant correlation between serum homocysteine and serum TG as shown in table 12 (p value<0.04)

A study done at Department of Public Health, Kyorin University School of Medicine, Tokyo, Japan. in diabetic subjects serum triglyceride levels were strongly associated with total homocysteine. (p value < 0.024)[45]

Also in a study conducted by *El Oudi et al.* it was found that diabetics had elevated serum levels of triglycerides (P<0.001) and hyperhomocysteinemia [43].

CONCLUSION

In summary, hyperhomocysteinemia could be a risk factor accounting for chronic complications in diabetic patients. Hyper homocysteinemia may be acting as an additional risk factor for macrovascular disease in patients of type 2 DM. The results of this study have shown that homocysteine levels were significant in type 2 DM with developed macrovascular complications and was correlated with HbA1c, dyslipidemia. Results have shown that hyperhomocysteinemia is a risk factor in etiology of vascular complications in type 2 DM.

Serum homocysteine estimation at the time of initial work up of all patients of type 2 DM and periodically in yearly follow up should be recommended. Hyperhomocysteinemia when discovered should be treated with supplements and suitable vitamins.

Nevertheless, these statements need further confirmation with more elaborate trials.

It is necessary to perform more large scale based prospective and interventional studies to clarify the independent risk of homocysteine in type 2 DM.

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Conflict of Interest: None

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Ethical Approval: Approved

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