



IMPACT OF HYPERGLYCEMIA AND DIABETIC NEPHROPATHY ON PLASMA N-TERMINAL PRO- BRAIN NATRIURETIC PEPTIDE IN PATIENTS OF TYPE 2 DIABETES MELLITUS

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ABSTRACT

Background: This study aimed to assess NT-pro BNP level and its correlation with glycaemic control and diabetic nephropathy in patients of T2DM without overt cardiovascular disease.

Methods: This study conducted at SMS Hospital, Jaipur by selecting 120 patients of type 2 diabetes mellitus. Information regarding demographic data, clinical symptoms, past medical history, laboratory parameters, NT pro-BNP and 24 h urine protein collected from selected sample population.

Results: The mean value of fasting (140.48 mg/dL) and post-prandial blood sugar (206.64 mg/dL), HbA1c (8.18%), NT pro-BNP (748.58 pg/mL), creatinine (1.24 mg/dL), 24 h urine protein (398.28 mg/24 h) were found to be significantly raised in selected patients of T2DM. 94% patients had underlying proteinuria among which nearly one third of patients had microalbuminuria while remaining two third had macroalbuminuria. Absolute value of NT-pro BNP in patients of T2DM had positive correlation with age of patients ($r = +0.2984$, $p = 0.0009$), duration of diabetes ($r = +0.3165$, $p = 0.0004$), fasting blood sugar ($r = +0.6841$, $p < 0.001$), post prandial blood sugar ($r = +0.2043$, $p = 0.0252$), HbA1c ($r = +0.6858$ and $p < 0.001$) creatinine ($r = +0.4563$, $p < 0.001$) and 24 hours urinary protein ($r = +0.7921$, $p < 0.001$).

Conclusion: Heart failure in patients with T2DM is a most crucial diabetic complication for diagnosis as well as management. NT-pro BNP level in blood stream had an important role for early diagnosis of heart failure. This study suggest that the secretions of NT-pro BNP is increased in patients with T2DM having poor glycaemic control, raised fasting or postprandial blood sugar and diabetic nephropathy. Therefore, measurement of HbA1c, fasting or postprandial blood sugar and 24 h urine proteins are the simple screening tool to identify patients with diabetes at risk for ventricular dysfunction requiring further examination with NT pro-BNP and echocardiography.

Key words: Cardiac dysfunction; Diabetes mellitus; NT pro-BNP; Proteinuria

INTRODUCTION

Diabetes Mellitus (DM) is one of the most challenging public health problems in the 21st century. Diabetes is a major concern for its treatment and prevention of complications. Global burden of diabetes now affecting more than 425 million people, of which one-third are people older than 65 years⁽¹⁾. If nothing is done, the number of people with diabetes may rise to 693 million in 2045⁽²⁾ and by the end of this year, 4 million deaths will happen as a result of diabetes and its complications⁽³⁾. Now a days, in association of other communicable disease, T2DM also increased significantly in the cities of low and middle-income countries. China alone has 121 million people with diabetes and India has a total of 74 million populations with diabetes⁽⁴⁾. In present era, spreading of disease awareness among general public can play a vital role in early detection and prevention of disease. Prevention is far better than treatment to reduce burden of diabetes and its complications on health care and its economic implications are enormous, especially for a developing country like India⁽⁵⁾.

Diabetes mellitus (DM) is a chronic metabolic disorder being characterized by increased blood sugar levels. It is like a termite that insidiously eats up one's own body and, if not controlled, it cripples the body irreversibly. Good glycemic control is essential part for management of diabetes mellitus and its complications. Over time, poor glycemic control can lead to multiple chronic complications like damage to eyes (leading to blindness), kidneys (leading to renal failure) and nerves (leading to numbness in the limbs, impotence and foot disorders/possibly amputation) as well as increased risk of heart diseases and stroke⁽⁶⁾. Quality of life is reduced by complications of diabetes with a devastating long-term effect on their financial and social wellbeing.

Various studies have been conducted in India to look for awareness among diabetics. The Indian Council of Medical Research (ICMR) conducted a study in four regions of India in which they found that only 43.2% of study population know about a disease called diabetes mellitus⁽⁷⁾. Another study found that 17% of their participants had poor knowledge and more than half believe it to be a communicable disease⁽⁸⁾.

Another major weapon in the management of diabetes is the treatment adherence. The World Health Organization (WHO) defined adherence as "the extent to which a person's behaviour – taking medication, following a diet and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider."⁽⁹⁾ Beside availability of various therapeutic option for type 2 diabetes, less than 50% of patient can able to maintain a status of good glycemic control^(10,11).

Diabetes and heart failure are closely related, When the two diseases are considered individually, heart failure has a much poorer prognosis than diabetes mellitus; therefore, heart failure has to be a priority for treatment in patients presenting with the two conditions⁽¹²⁾. It has been estimated that the proportion of congestive heart failure patients with known T2DM is 20–35 %⁽¹³⁾.

Early identification of vascular and non-vascular risk is a cornerstone of diabetes management and facilitates tailored intervention at an early stage of disease when a useful response is more likely to be obtained. Screening for microalbuminuria identifies patients with early nephropathy at risk for overt disease and targets them for preventive interventions. Microalbuminuria is also strongly associated with cardiovascular disease, but does not identify its presence or severity. As a result of increased cardiac dysfunction, the synthesis and release of cardiac natriuretic peptides rises as a compensatory response. Therefore,

increased B-type natriuretic peptide (BNP) and/or N-terminal pro-BNP (NT-pro BNP) be used as an important marker for symptomatic cardiac dysfunction⁽¹⁴⁾. Hence, in this study, we try to find out the correlation of NT pro-BNP with glycemic control and diabetic nephropathy.

METHODS

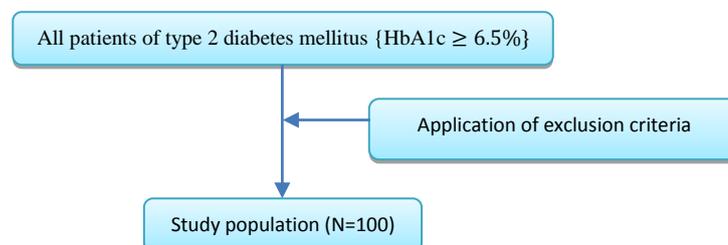
Study Design

This is observational and cross-sectional study, conducted at S.M.S. Medical College and attached Hospital, Jaipur, India from December 2020 to July 2021. This study was approved by the Institutional Ethics Committee. In this study, 120 patients of T2DM selected after application of exclusion criteria (patients of severe illness, past history of cardiovascular disorder, chronic lung disease and chronic kidney disease, hypertension were excluded from this study). The study population underwent detail demographic analysis, clinical manifestation, medical history, treatment history, laboratory investigation especially HbA1c, hemogram, fasting and post-prandial sugar, renal function, urine routine and microscopic examination, 24 hours urine protein, NT-pro BNP. The data obtained were collected, tabulated, compiled, interpreted and analyzed.

Data Collection

All patients of T2DM ($\text{HbA1c} \geq 6.5\%$) undergo detailed medical history to exclude confounding factors especially past history of cardiovascular disorder, chronic lung disease, chronic kidney disease and hypertension. Past history of hypertension detected by any ongoing antihypertensive medications or raised blood pressure at the time of screening. Demographic data obtained in the form age, sex, geographic distribution with clinical manifestations and duration of T2DM and other associated co-morbidities. Vitals of both groups including systolic and diastolic blood pressure, heart rate and temperature were measured by standard protocol. In blood investigations complete blood count, fasting and postprandial blood sugar (2 hour after meal), HbA1c, NT pro-BNP and kidney function test were measured in both groups. 24 hours urine sample collected from time of first urination in morning (Withdrawal sample) to time of urination in next morning at same time to measure protein contents. A special machine is designed to measure the immunoreactive NT-pro BNP (Biomedica Laboratories, Vienna, Austria). Blood samples were drawn in EDTA tube, immediately placed on ice, and promptly centrifuged at 4°C . NT-pro BNP measurements were done using an ELISA.

Flow chart



Statistical analysis

The descriptive statistics for quantitative data was expressed as mean and standard deviation and qualitative data was expressed as proportions. The parameters were compared among different Groups using chi-square and z-score test for significant differences. The level of significance was assigned at a p-value less than 0.05.

RESULTS (Table 1)

A total of 120 patients of T2DM selected for study at SMS Medical College and attached group of Hospital, Jaipur, Rajasthan. All necessary data were collected, evaluated, interpreted and correlated to assess different manifestations of T2DM. Value of NT-pro BNP in patients of T2DM correlated with HbA1c, fasting and post-prandial blood sugar, serum creatinine and 24 hours urine protein. The overall mean age of patients of T2DM was 55.6 year (55.60 ± 6.36) and sex ratio (female to male) for patients of T2DM were found to be 0.58. The mean heart rate in study population were found to be 79.43/minute (79.43 ± 9.62) at the time of enrolment. The mean systolic and diastolic blood pressure was found to be 128.4 mmHg and 82.5 mmHg respectively.

All patients of study groups go through base line investigations with special focus on diabetes, renal and cardiac parameters. The mean value of hemoglobin was 12.14 g/dL (12.14 ± 1.38), total leukocyte counts was $7.64 \times 10^3 /\mu\text{L}$ (7.64 ± 1.82) and platelet counts were 2.53 lac/ μL (2.53 ± 0.45) for patients of T2DM. The mean fasting and post-prandial blood sugar for selected patients of T2DM were found to be 140.48 mg/dL (140.48 ± 38.41) and 206.64 mg/dL (206.64 ± 60.51) respectively, which was much higher than normal limit. Blood level of sugar in last three months, a direct reflection of sugar control was estimated by HbA1c in all patients and found that mean value of HbA1c in patients of T2DM was 8.18% (8.18 ± 1.41).

NT-pro BNP released from heart as a consequence of increased load on myocardium and supposed to be an indirect reflection of reduced functional capacity of heart. In our study the mean NT-pro BNP for patients of T2DM was 748.58 pg/mL (748.58 ± 704.46). Absolute value of NT-pro BNP in patients of T2DM also varied widely which ranges from a minimum value of 65 pg/mL to maximum value of 3832 pg/mL. The proportion of individuals with a NT-pro BNP value above the cut off value (300 pg/mL) was nearly about 67%. The mean value of serum urea and creatinine in selected group of patients was found to be 32.22 mg/dL (32.22 ± 9.84) and 1.24 mg/dL (1.24 ± 0.42) respectively.

The mean value of parameters in selected patients of Type 2 DM	
Characteristics	Type 2 DM (N=120)(Mean \pm SD)
Age (Year)	55.6 \pm 6.36
Sex ratio (Female to Male)	0.58
General Physical examination	
Systolic Blood Pressure (mm of Hg)	128.4 \pm 7.98
Diastolic Blood Pressure (mm of Hg)	82.5 \pm 5.24
Heart Rate (per minute)	79.43 \pm 10.4
Laboratory Investigations	
Haemoglobin (g/dL)	12.14 \pm 1.38
TLC ($\times 10^3/\mu\text{L}$)	7.64 \pm 1.82
Platelets (x Lac/ μL)	2.53 \pm 0.45
Fasting blood sugar (mg/dL)	140.48 \pm 38.41
PP- blood sugar (mg/dL)	206.64 \pm 60.51
HbA1c (%)	8.18 \pm 1.41
NT-pro BNP (pg/mL)	748.58 \pm 704.46
Urea (mg/dL)	32.22 \pm 9.84
Creatinine (mg/dL)	1.24 \pm 0.42
24 h urine protein	398.28 \pm 243.49

Table 1: The mean value of parameters in selected patients of Type 2 DM (Quantitative data expressed as mean \pm S D while qualitative data expressed as numbers with percentage).

Renal function in study groups also estimated by 24 hours urinary protein excretion. In this study, the mean value of excreted urinary protein in 24 hours was found to be 398.28 mg/24 h (398.28 ± 243.49) which was significantly higher in the range of macroproteinuria. In our study, 94% patients had underlying proteinuria among which nearly one third of patients had microalbuminuria while remaining two third had macroalbuminuria. In 43 patients, proteinuria was in the range of diabetic nephropathy (>500 mg/24h) (Table 2).

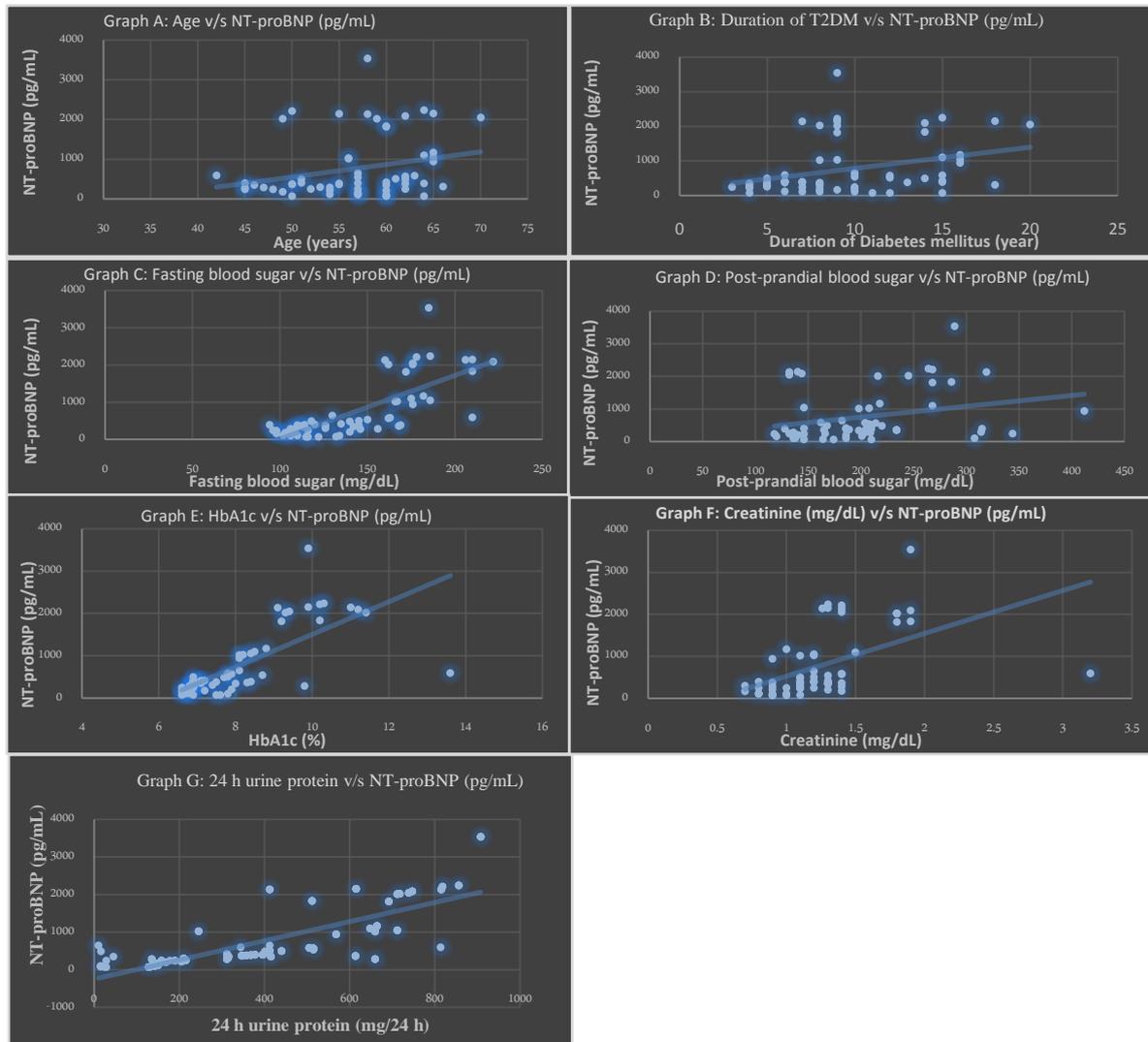
Range of proteinuria	Number of patients	%
Microalbuminuria (30 - 300)	34	28.33%
Macroalbuminuria (300 - 3000)	79	65.83%
Diabetic nephropathy (>500)	43	35.83%

Table 2: Range of proteinuria in selected group of patients.

In this study, absolute value of NT-pro BNP in patients of T2DM group correlated with demographic and laboratory parameters (Table 3). In this study, absolute value of NT-pro BNP raised with age of patients with 'r' value of +0.2984 ($p=0.0009$). NT-pro BNP also have significant positive correlation with duration of diabetes in patients of T2DM ('r' = +0.3165, $p=0.0004$). Absolute value of NT-pro BNP has positive correlation with fasting blood sugar ('r' = +0.6841, $p<0.001$) and post prandial blood sugar ('r' = +0.2043, $p=0.0252$). NT-pro BNP also raised with value of HbA1c as both have positive correlation with 'r' = +0.6858 and $p<0.001$. In this study, absolute value of NT-pro BNP also positively correlated with serum level of creatinine ('r' = +0.4563, $p<0.001$). 24 hours urinary protein excretion also had significant positive correlation with NT pro-BNP ('r' = +0.7921, $p<0.001$).

Correlation between NT-pro BNP with various parameters		
Characteristics	Correlation Coefficient 'r'	P value
Age and NT-pro BNP	0.2984	0.0009 (S)
Duration of Diabetes and NT-pro BNP	0.3165	0.0004 (S)
Blood Sugar (F) and NT-pro BNP	0.6841	<0.001 (S)
Blood Sugar (PP) and NT-pro BNP	0.2043	0.0252 (S)
HbA1c and NT-pro BNP	0.6858	<0.001 (S)
Creatinine and NT-pro BNP	0.4563	<0.001 (S)
24 hours Urine Protein and NT-pro BNP	0.7921	<0.001 (S)

Table 3: Correlation of NT pro-BNP with various quantitative data of selected patients of T2DM



Graph 1: Correlation of NT pro-BNP with (A) Age of patients, (B) Duration of T2DM, (C) Fasting blood sugar, (D) Postprandial blood sugar, (E) HbA1c, (F) Creatinine, (G) 24 h urine protein in selected patients of T2DM

DISCUSSION

The incidence and prevalence of T2DM increases worldwide. There is multifactorial contribution for this which includes: increasing incidence of T2DM in young people and increasing incidence of T2DM in adults as a result of sedentary living, high-energy dietary intakes and the intergenerational effects of hyperglycemia in pregnancy and the general ageing of the global population. On the other hand, earlier diagnosis of T2DM and better management of all types of diabetes leading to greater life-expectancy are also contributing to this rise in prevalence.

Heart failure is a major health issue and a risk factor for early death and disability in type 2 diabetes. This study was therefore done at the SMS medical college and attached hospital, Jaipur, in order to assess cardiac dysfunction by using NT-pro BNP as a marker and its correlation with glycemic control and diabetic nephropathy.

In this study nearly half of patients are in their sixth decades (51 to 60 year) of life and male populations are predominant involving 63.29% in patients of T2DM. All patients of study groups go through base line investigations with special focus on diabetes, renal and cardiac parameters. In patients of T2DM mean value of hemoglobin, total leukocyte counts and platelet counts were found to be within normal range without any specific deviation in absolute value. The mean fasting blood sugar (140.48 mg/dL) and post prandial blood sugar (206.64 mg/dL) were found to be significantly higher than normal limit in selected patients of T2DM. Higher value of blood sugar in patients of T2DM has been responsible for precipitations of diabetes related complication especially micro vascular, macrovascular and cardiac complications including heart failure.

BNP seems to be elevated in early left ventricular systolic as well as in diastolic dysfunction⁽¹⁵⁾. In this study, the NT-pro BNP level was shown to be significantly elevated in the selected patients of T2DM. Hence, patients of T2DM are more prone to develop cardiac failure as detected by higher NT-pro BNP level in these patients. In this study serum level of urea and creatinine also higher significantly in patients of T2DM.

In this study 24 hours urine sample also collected to detect excretion of 24 hours urinary protein and found that excretion of protein in urine significantly higher in patients of T2DM. Proteinuria a microvascular complication which reflect diabetic nephropathy in patients of T2DM. V Mohan et al in their study⁽¹⁶⁾ suggest that the frequency of proteinuria was assessed in a cohort of 1848 diabetic patients attending a diabetes center in south India. A total of 127 (6.9%) patients had evidence of macroproteinuria and 49 (2.5%) patients had microproteinuria. Thus overall, 9.4% of patients had diabetes related proteinuria. In addition, 70 patients (3.8%) had evidence of proteinuria with no evidence of retinopathy. The frequency of both microproteinuria and macroproteinuria increased linearly with duration of diabetes. Multiple logistic regression analysis showed that duration of diabetes, serum creatinine, and glycated hemoglobin were risk factors for macroproteinuria. In our study, 94% patients had underlying proteinuria among which nearly one third of patients had microalbuminuria while remaining two third had macroalbuminuria. In 43 patients, proteinuria was in the range of diabetic nephropathy (>500 mg/24h).

In this study absolute value of NT-pro BNP continuously increased with age of patients in T2DM as maximum value of NT-pro BNP was observed in patients of more than 60 year of age. This might be explanation of higher prevalence of heart failure (HF_rEF or HF_pEF) in advancing age. A linear regression model for age as an independent and NT-pro BNP as a dependent variable suggests an age-related increase in NT-pro BNP. However absolute cut off value for NT-pro BNP also varied as per age of patients as suggested by Bernstein LH⁽¹⁷⁾ the median NT-pro BNP for patients under 50 years is 60.5 pg/ml with an upper limit of 462 pg/ml, and for patients over 50 years the median was 272.8 pg/ml with an upper limit of 998.2 pg/ml.

The mean value of NT-pro BNP has positive correlation with fasting blood sugar ($p < 0.001$), post prandial blood sugar ($p = 0.0252$) and HbA1c ($p < 0.001$). Hyperglycemic state responsible for increased vascular complication and heart failure in patients of T2DM. It is well known that glucose level is directly linked to CVD risk. A prospective observational study (UKPDS-35) revealed that every 1% reduction in baseline HbA1c levels decreases the incidence of myocardial infarction by 5%⁽¹⁸⁾. It is estimated that approximately 5 million individuals with HF in the US have co-existing diabetes. It confirms that significantly elevated HbA1C is

associated with increased risk in this population and efforts should be made to treat these patients with proven HF therapies and consider glucose lowering therapy.

In this study NT-pro BNP have positive correlation with serum level of creatinine or impaired renal function test. Patients of T2DM are more prone to develop diabetic nephropathy as a long-term microvascular complication. However, mean value of creatinine were found to be within normal range in patients of T2DM.

NT-pro BNP also have positive correlation with excreted urinary protein in patients of T2DM. Hulya Taskapan et al ⁽¹⁹⁾ provide evidence of an association between NT-pro BNP and proteinuria in type II diabetic patients with macroalbuminuria. Patients with high NT-pro BNP may have more tubular injury. There is accumulating evidence suggesting that the risk for developing diabetic nephropathy ^(20, 21) and cardiovascular disease ⁽²²⁾ starts when urinary albumin excretion values are still within the normoalbuminuric range. Progression to micro or macroalbuminuria was more frequent in patients with type 2 diabetes with baseline Urine albumin excretion above the median (2.5 mg/24 h) ⁽²⁰⁾. After 10 years of follow-up, the risk of diabetic nephropathy was 29 times greater in patients with type 2 diabetes with UAE values 10 g/min ⁽²¹⁾.

CONCLUSION

Heart failure in patients with T2DM is a most crucial diabetic complication for diagnosis as well as management. NT-pro BNP level in blood stream had an important role for early diagnosis of heart failure. This study suggest that the secretions of NT-pro BNP is increased in patients with T2DM having poor glycemic control, raised fasting or postprandial blood sugar and diabetic nephropathy. Therefore, measurement of HbA1c, fasting or postprandial blood sugar and 24 h urine proteins are the simple screening tool to identify patients with diabetes at risk for ventricular dysfunction requiring further examination with NT pro-BNP and echocardiography.

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