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A Study of Pro Brain Natriuretic Peptide (PRO BNP) Levels in Asymptomatic Subjects with Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: Brain natriuretic peptide (BNP) is a thirty two-amino acid peptide. It is synthesized mainly in the left ventricle of the heart as a 108 amino acid prohormone pre-pro BNP (γ-BNP).

Objectives: To measure pro Brain Natriuretic Peptide (pro-BNP) levels in subjects with Type 2 Diabetes mellitus.

Methods: That we have used for the present study prospective, observational, non-interventional cohort study done in patients admitted in Krishna Hospital and Medical Research Centre, Karad with the diagnosis of Type 2 Diabetes Mellitus.

Results: We have seen the Distribution of pulse rate, blood pressure, blood sugar, serum HbA1c and serum creatinine, Distribution of serum lipids, serum pro BNP and Left ventricular ejection fraction (LVEF) in the study population.

Conclusion: The measurement of pro BNP level in a patient with type 2 diabetes mellitus will be valuable for early prediction of heart failure and its outcome.

Key Words: Pro Brain Natriuretic Peptide, Type 2 Diabetes Mellitus, Pulse Rate, Blood Pressure

INTRODUCTION

Diabetes mellitus is one of the leading causes of morbidity and mortality globally. The development of diabetes mellitus requires corresponding amendments in the therapy and identification of the disease severity is therefore important for predicting prognosis, treatment, preventing complications, reducing complications and mortality.[1] Brain natriuretic peptide (BNP) is a thirty two-amino acid peptide. It is synthesized mainly in the left ventricle of the heart as a 108 amino acid prohormone pre-pro BNP (γ-BNP). The hormone is an effective vasodilator and a natriuretic factor regulating salt and water homeostasis in the body. It is stored in the human cardiac tissue predominantly as BNP-32 with a smaller amount of the precursor pre-pro BNP. The circulating plasma forms of BNP are BNP-32 and the NH2-terminal portion pro-BNP (Nt-pro BNP). It is an easy measure for the assessment of cardiac function. As a response to myocardial wall stretch, pre-pro BNP is synthesized and processed to pro-BNP; which is further processed to the biologically inactive NT-pro BNP fragment and the biologically active BNP fragment. These measurements can be useful for diagnosing heart failure, including left ventricular diastolic dysfunction and left ventricular diastolic dysfunction.

Relation between pro BNP and blood pressure

Anuva Mishra et al. observed that the mean systolic blood pressure (SBP) among his study population was 128.2±9.8 mm Hg and had a weak +VE correlation with the pro-BNP levels (p=0.46) whereas the mean DBP among them was 82±7.8 mm Hg and had a weak +VE correlation with pro BNP level (p=0.56). A study conducted by Sasaki N et al, observed a strong +VE correlation of SBP and pro-BNP ($p < 0.001$) however a weak +VE correlation of DBP and pro BNP level was observed (p=0.28). Kursat Dal et al. also reported that the mean SBP was 128.2±9.8 mm Hg and had a strong +VE correlation with the pro BNP level ($p <0.001$); the mean DBP was 82±7.8 mm Hg and had strong +VE correlation with pro BNP level ($p <0.001$).[2,3]

Misurata et al analyzed the pro BNP levels with the blood pressure variability in the Japanese population and reported that mean SBP was 130±13 mm Hg while the mean DBP was 69±6 mm Hg. SBP had a weak +VE correlation with pro

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BNP level (p=0.59) and DBP was also having a weak +VE correlation (p=0.45). A study by Kumiko Hamano et al, too reported that the pro-BNP had a strong +VE correlation with SBP (p=0.027) whereas DBP had a weak +VE correlation (p=0.45).[4, 5]

P Gaede et al also reported a strong +VE correlation (p=0.002) between SBP and pro-BNP while DBP had a weak +VE correlation with pro BNP level (p=0.39); Rosiak M et al reported that pro BNP level had a weak +VE correlation with SBP (p=0.5), and weak +VE correlation with DBP (p=0.33) respectively. Alain G Bertoni et al observed DBP and pro-BNP had a weak +VE correlation (p=0.3). Thus the findings of the above studies are comparable with the present study. [6, 7, 8]

Relation of pro-BNP with the duration of diabetes mellitus

Kumiko Hamano et al had reported the mean duration of diabetes mellitus as 9±5 years and had a strong +VE correlation with pro-BNP (p=0029). A study conducted by Kursat Dal et al reported that the mean duration of diabetes was 7.5 ± 3.5 years and there was a significant decrease in pro BNP levels after improving the glycaemic control in the study population (p<0.001). Misurata et al [4] also reported that the duration of diabetes mellitus had a strong correlation with pro BNP level (p=0.05). Similarly, P. Gaede et al in their study reported that the duration of diabetes mellitus had a strong correlation with pro BNP level (p=0.003). Alain Bertoni et al also observed a strong correlation with duration of diabetes mellitus and pro BNP (p<0.05). [6, 5, 9, 7]

Pro BNP and blood sugar levels

Ashok Sahu et al also studied the pro BNP levels in the diabetic population in central India and reported that FBS had a +VE correlation with pro BNP level (p<0.001). Mishra A et al, also reported that FBS had a strong +VE correlation with pro BNP level (p<0.001). Similarly, Kursat Dal et al too in their study observed that mean fasting plasma glucose levels were 306.3 ± 119.4 mg/dL and it had a strong association with serum pro BNP level (p=0.002). Thus, the above studies were comparable with the present study. [2, 10, 9]

Pro BNP and HbA1C

Kursat Dal et al, reported that the mean HbA1c level was 11.0 ± 2.5% and a significant decrease in pro BNP level was observed after improving glycemic control (p<0.001). Misurata et al also reported that HbA1c had a +VE correlation with pro-BNP levels (p=0.002). Anuva Mishra et al in their study too observed a strong +VE correlation of serum HbA1c and serum pro BNP levels. Rosiak M et al also reported high mean HbA1c levels were associated with high pro BNP values (p<0.001). Alain G Bertoni et al, also reported that HbA1c level had a strong +VE correlation with pro BNP level(p<0.001) [7,8, 9]

Pro BNP and LV functions

Amulya et al. reported that LV systolic dysfunction had a strong +VE correlation with the pro-BNP levels (p<0.001). Hui Gong et al. also observed a strong +VE correlation of LV systolic dysfunction and pro BNP level (p<0.05) and a strong +VE correlation of LV diastolic function and pro BNP level (p=0.045). A study by Carsten Taschö pe et al also had described that LV systolic dysfunction and LV diastolic dysfunction were +VEly associated with pro-BNP levels [p=0.09, p=0.001 respectively]. [11,12,13]

OBJECTIVES

- To measure pro Brain Natriuretic Peptide (pro-BNP) levels in subjects with Type 2 Diabetes mellitus.

MATERIALS AND METHODS

Type of study:-

This was a prospective, observational, non-interventional cohort study done in patients admitted in Krishna Hospital and Medical Research Centre, Karad with the diagnosis of Type 2 Diabetes Mellitus

Sample size calculation:

According to a study conducted by Bertoni A .G et al, the prevalence of Congestive Heart Failure in patients of diabetes was found 11.8%.[14]

So, p = 11.8%

Using formula for sample size (n) calculation,

$$n = \frac{4 \times p \times q}{e^2}$$

Where, p = 11.8% = 0.118

q = 1 - p = 0.882

Taking e, absolute error of 10%, e = 0.1

So, $n = \frac{4 \times 0.118 \times 0.882}{0.1 \times 0.1}$

$n = 41.63 \approx 42$

According to the formula, a total of 42 subjects were taken in the present prospective observational study. The study population, therefore, is A total of 42 subjects admitted in wards and ICU were enrolled in the present study. This study was conducted over 18 months (October 2018 to May 2020). This study was conducted on patients admitted with the diagnosis of Type 2 Diabetes Mellitus according to American Diabetes Association criteria at Krishna Hospital and Medical Research Centre, Karad.

Inclusion Criteria:

- Patients with Type 2 Diabetes Mellitus who were asymptomatic for heart failure were included in the study
- All gender between 18 to 70 years were included in the study

Exclusion Criteria:

- Patients with established heart failure, renal failure, Chronic Obstructive Pulmonary Disease, liver cirrhosis, stroke, hyperthyroidism, septic shock, patients with nephropathy
- Patients with valvular heart disease, coronary artery disease

This study was approved by Institutional Ethics Committee (IEC). The written and informed consent was taken from all the participants in local and English language before including them in the study.

A detailed physical examination was done. The blood pressure was recorded using a well-calibrated mercury sphygmomanometer in the supine position (Diamond BP MR-120 Mercurial BP Deluxe). At least two readings were taken, with one-minute intervals between them, and the average of the measurements was recorded. Other parameters such as pulse rate were checked in the radial artery for the whole one minute.

RESULTS

Distribution of pulse rate and blood pressure in the study population

A total of 42 subjects were enrolled in the present study. The pulse rate, systolic blood pressure and diastolic blood pressure were measured in them. The mean pulse rate of males was 87.76 ± 11.35 per minute and the mean pulse rate of females was 90.28 ± 15.95 per minute (Table 1). The pulse rate of male and female subjects was not statistically significant (p=0.576). The mean SBP of males was 119.52 ± 18.02 mm Hg and the mean SBP of females were 108.57 ± 16.77 mm Hg. The mean SBP between males and females was statistically not significant (p=0.235). The mean DBP of males was 72.85 ± 7.83 mm Hg and the mean DBP of females was 77.61 ± 8.30 mm Hg. The mean DBP between males and females was statistically significant (p=0.0475).

Distribution of blood sugar, serum HbA1c and serum creatinine level in the study population

In the present study, we assessed the fasting and postprandial blood sugar, serum creatinine and serum HbA1c levels. The mean fasting blood sugar level of males was 187.52 ± 73.95 mg/dL, the mean level of blood sugar in the case of ladies when observing fast remained 184.90 ± 56.65 mg/dL. The mean postprandial fasting blood sugar level between males and females was not statistically significant (p=0.989). The mean HbA1c of males was 8.47 ± 2.30 mg/dL and the mean HbA1c of females was 8.07 ± 2.30. The mean HbA1c between males and females was not statistically significant (p=0.480). The mean serum creatinine level of males was 0.94 ± 0.17 mg/dL and the mean serum creatinine level of females was 0.95 ±0.19 mg/dL. The mean serum creatinine level between males and females was not statistically significant (p=0.878). (Table 1).

Distribution of serum lipids in the study population

The mean serum triglyceride level of males was 135.95 ± 35.36 mg/dL and the mean serum triglyceride level of females was 120.42 ± 37.59 mg/dL. The mean serum triglyceride level between males and females was not statistically significant (p=0.261). The mean serum total cholesterol level of males was 153.19 ± 32.34 mg/dL and the mean serum total cholesterol level of females was 141 ± 41.31 mg/dL. The mean serum total cholesterol level between males and females was not statistically significant (p=0.287). (TABLE 1)

Distribution serum pro BNP and Left ventricular ejection fraction (LVEF) in the study population

The mean LVEF of males was 44.33 ± 10.93% and the mean LVEF of females was 45.70 ± 12.85%. The mean LVEF between males and females was not statistically significant (p=0.667). The mean serum pro BNP level of males was 4545.28 ± 7989.80 pg/mL and the mean serum pro BNP level of females was 4388.4 ± 5322.70 pg/mL. The mean serum pro BNP level between males and females was not statistically significant (p=0.45).Table 1

Table 1: Distribution of various parameters in the study population

Variables	Males (Mean ± SD)	Females (Mean ± SD)	Significance (p-value)
Pulse rate (per minute)	87.76 ± 11.35	90.28 ± 15.95	=0.576
SBP (mm Hg)	119.52 ± 18.02	108.57 ± 16.77	=0.235
DBP (mm Hg)	72.85 ± 7.83	77.61 ± 8.30	=0.047
BSL F (mg/dL)	187.52 ± 73.95	184.90 ± 56.65	=0.892
BSL PP (mg/dL)	203.57 ± 52.17	203.80 ± 54.19	=0.989
HbA1C (%)	8.47 ± 2.30	8.07 ± 2.30	=0.480
Serum creatinine (mg/dL)	0.94 ± 0.17	0.95 ±0.19	=0.878

Table 1: ***(Continued)***

Variables	Males (Mean ± SD)	Females (Mean ± SD)	Significance (p-value)
Serum TG (mg/dL)	135.95 ± 35.36	120.42 ± 37.59	=0.261
Serum total cholesterol (mg/dL)	153.19 ± 32.34	141 ± 41.31	=0.287
Serum HDL (mg/dL)	44.33 ± 11.12	40.95 ± 7.99	=0.190
Serum LDL (mg/dL)	104.19 ± 33.55	91.95 ± 29.60	=0.170
Serum VLDL (mg/dL)	26.57 ± 5.19	25.09 ± 5.96	=0.451
LVEF (%)	44.33 ± 10.93	45.70 ± 12.85	=0.667
pro BNP (pg/mL)	4545.28 ± 7989.80	4388.4 ± 5322.70	=0.45

Distribution of the study population according to the duration of Type 2 Diabetes Mellitus

A total of 42 subjects were enrolled for the present study. Total 23 (54.77%) subjects had a duration of diabetes mellitus of fewer than 5 years of which 13 (61.9%) subjects were males and 10 (33.33%) subjects were females. Total 14 (33.33%) subjects had a duration of diabetes mellitus of 5 to 10 years of which 6 (28.57%) subjects were males and 8 (38.10%) subjects were females, Total of 5(11.90%) subjects had a duration of diabetes mellitus between 10 to 15 years of which 2 (9.52%) subjects were males and 3 (14.29%) subjects were females. The was no statistical significance between the duration of diabetes mellitus of male and female subjects (p=0.644). **Table 2**

Table 2: Frequency distribution of subjects according to the duration of Type 2 Diabetes Mellitus

Duration of Type 2 DM	Males		Females		Total	
	n=21	%	n=21	%	n=42	%
Less than 5 years	13	61.9	10	33.33	23	54.77
5 to 10 years	6	28.57	8	38.10	14	33.33
10 to 15 years	2	9.52	3	14.29	5	11.90
Total	21	100.00	21	100.00	42	100

(DF-9;χ^2=20.53;p=0.644)

DISCUSSION

The prevalence of diabetes mellitus is increasing day by day in developing countries like India. Heart failure is the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus.In this study, we evaluated pro-BNP as a marker in predicting heart failure in patients with type 2 diabetes mellitus and was compared with various other studies.

Distribution of age in the study population and its association with pro-BNP

Total 42 subjects were enrolled in the present study, the majority of them were of age group 61 to 70 years (42.86%), followed by 51 to 60 years(26.19%) and then less than 40 years (16.67%). The mean age of the study subjects was 55.40 ± 11.42 years. It was observed that there was a weak +VE correlation between pro-BNP levels and the age of the study subjects. (p-value = 0.031).

A study conducted by Hui Gong et al reported that the mean age of the study population was 64 ± 8 years and there was a +VE correlation of pro BNP level and age of the subjects (p<0.05).[15] In the same way, Kumiko Hamano et al. also reported that the mean age of the study population was 64.3±12 years and its correlation with pro BNP level was strong +VE (p=0.001).[5] In a study done by P. Gaede et al it was observed that the mean age of the study population was 58±6 years and its correlation with pro BNP level was found to be strong +VE (p<0.001).[6] Carsten Taschö pe et al. had also reported the mean age of the study population as 49±13 years and its correlation with pro BNP level was weak +VE (p=0.061). [13] Similarly, Rosiak M et al also reported the mean age of the study population as 64.4 ± 8.2 years and its correlation with pro BNP level as strongly +VE (p<0.01). [8] Alain Bertoni et al, had described that the mean age of the study population was 59.5±6.8 years and it had a strong +VE correlation with pro BNP level (p=0.05). [7] Thus findings of the above studies are comparable with the present study.[9-12]

Distribution of gender in the study population and its association with pro-BNP

A total of 42 subjects was enrolled in the present study, among them 21 (50%) subjects were males and 21 (50%) were females. The mean pro BNP level reported among males was 4545.28±7989.80 pg/mL and among females, it was 4296.09±5322.70 pg/mL and there was no statistical difference between the pro-BNP levels among them (p= 0.45). However, a study reported by Kursat Dal et al. reported higher levels of pro-BNP in females as compared to males. These findings were not comparable with the present study as the population in the study of Kursat Dal et al. were predominantly females.[13,14]

Distribution of pulse rate in the study population and its association with pro BNP level

The mean pulse rate in the present study population was 89.02 ± 13.55 per minute and there was a weak +VE correlation with pro BNP level (p =0.854). A study by Kursat Dal et al. reported that the mean pulse rate was 72.8±10.4 per minute; Masugata et al, reported the mean pulse rate as 68±5 per minute and was weakly associated with pro-BNP levels (p=0.024). [4] Similarly, the study of Ruihua Cao et al. reported a +VE correlation with pro-BNP and pulse rate

(p=0.41).[13] Thus observation of the present study was similar to previous studies and amplifies the importance of pulse rate in diabetic patients.[14]

Distribution of systolic blood pressure (SBP), diastolic blood pressure (DBP) and its association with pro-BNP

In the present study, the mean SBP among males was 119.52±18.02 mm Hg while among females it was 108.57±16.77 mm Hg and there was no statistical significance among both (p=0.23) however it had a strong +VE correlation with pro-BNP levels (p=0.002). The mean DBP among males was 72.85±7.83 while among females it was 77.61±8.30 mm Hg. There was a statistical significance between DBP of males and females and also DBP showed a weak +VE correlation with pro BNP values (p=0.72).

Similar to the present study, Anuva Mishra et al observed that the mean SBP among his study population was 128.2±9.8 mm Hg and had a weak +VE correlation with the pro-BNP levels (p=0.46) whereas the mean DBP among them was 82±7.8 mm Hg and had a weak +VE correlation with pro BNP level (p=0.56).[2] A study conducted by Sasaki N et al, observed a strong +VE correlation of SBP and pro-BNP (p<0.001) however a weak +VE correlation of DBP and pro BNP level was observed (p=0.28).[3] Kursat Dal et al, also reported that the mean SBP was 128.2±9.8 mm Hg and had a strong +VE correlation with the pro BNP level (p<0.001); the mean DBP was 82±7.8 mm Hg and had strong +VE correlation with pro BNP level (p<0.001).[9] Masugata et al, analysed the pro BNP levels with the blood pressure variability in the Japanese population and reported that mean SBP was 130±13 mm Hg while the mean DBP was 69±6 mm Hg. SBP had a weak +VE correlation with pro BNP level (p=0.59) and DBP was also having a weak +VE correlation (p=0.45). [4] A study by Kumiko Hamano et al, too reported that the pro-BNP had a strong +VE correlation with SBP (p=0.027) whereas DBP had weak +VE correlation (p=0.45).[5] P Gaede et al, also reported a strong +VE correlation (p=0.002) between SBP and pro-BNP while DBP had a weak +VE correlation with pro BNP level (p=0.39).[6] Rosiak M et al reported that pro BNP level had weak +VE correlation with SBP (p=0.5), and weak +VE correlation with DBP (p=0.33) respectively. [8] Alain G Bertoni et al observed DBP and pro-BNP had a weak +VE correlation (p=0.3). [7] Thus the findings of the above studies are comparable with the present study.

Distribution of duration of diabetes mellitus and its association with pro-BNP

In the present study, 42 study subjects were enrolled. The majority of the 23(54.77%) had a duration of fewer than 5 years of diabetes mellitus and among 19 (45.23%) subjects with the mean duration of diabetes mellitus were 4.6 ± 4.32 years. The mean pro BNP level in subjects with the duration of diabetes mellitus less than 5 years was 1235.08 ± 1217.54 pg/mL and the mean pro BNP level in subjects with the duration of diabetes mellitus more than 5 years was 8276.94 ± 8483.48 pg/mL. There was a statistical significant correlation with subjects who had a duration of DM less than 5 years and who had more than 5 years (p=0.01). There was a moderate +VE correlation of duration of DM and pro-BNP ('r'=0.63)

Similar to the present study Kumiko Hamano et al. had reported the mean duration of diabetes mellitus as 9±5 years and had a strong +VE correlation with pro-BNP (p=0.029).[5] A study conducted by Kursat Dal et al. reported that the mean duration of diabetes was 7.5 ± 3.5 years and there was a significant decrease in pro BNP levels after improving the glycaemic control in the study population (p<0.001). [9] Masugata et al. also reported that the duration of diabetes mellitus had a strong correlation with pro BNP level (p=0.05). [4] Similarly, P. Gaede et al in their study reported that the duration of diabetes mellitus had a strong correlation with pro BNP level (p=0.003).[6] Alain Bertoni et al. also observed a strong correlation with the duration of diabetes mellitus and pro BNP (p<0.05).[7] Thus the above studies were comparable with the present study.

CONCLUSION

Type 2 diabetes mellitus is a major risk factor for heart failure. With the increase in the number of patients with type 2 diabetes mellitus in India, it is evident that the burden of heart failure in the Indian population will be the mirror of the global picture in future. Considering this, in the present study the association between serum pro BNP levels and various factors in patients with type 2 diabetes mellitus was evaluated. There was a significant correlation of pro BNP levels with systolic and diastolic blood pressure, duration of diabetes mellitus, glycosylated haemoglobin levels, impaired fasting and postprandial blood sugar levels, triglyceridemia, albuminuria, glycosuria and retinopathy as determined by linear regression analysis. There was a negative correlation with LVEF and pro-BNP and a +VE correlation with pro-BNP and grades of diastolic dysfunction. Thus we can conclude that the measurement of pro BNP level in a patient with type 2 diabetes mellitus will be valuable for early prediction of heart failure and its outcome.

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Both authors read and approved the final manuscript.

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