IOSR Journal of Biotechnology and Biochemistry (IOSR-JBB)
ISSN: 2455-264X, Volume 4, Issue 1 (Jan. - Feb 2018), PP 12-16
www.iosrjournals.org

An Interrelationship betweenNt Pro-Bnp Level, Glycemic Control And Myocardial Ischemia in Type 2 Diabetes Without Overt Cardiac Disease

*Dr.Anuva Mishra[1], Dr.SangeetaSanghamitraBhanja[2]
[1](Assoc. Prof, Dept. of Biochemistry, MKCG Medical College, Berhampur, India)
[2](Senior Resident, Dept. of Biochemistry,Institute of Medical Sciences and SUM Hospital, Bhubaneswar, India)
Corresponding Author:Dr.SangeetaSanghamitraBhanja.

Date of Submission: 15-01-2018 Date of acceptance: 31-01-2018

I. Introduction

Cardiovascular complications are the most important cause of mortality and morbidity in diabetic patients and are responsible for nearly 75% of deaths from diabetes.[1,2]Heart failure is encountered twice as often in diabetic men, and five times more often in diabetic women, compared to non-diabetic individuals which is a preventable cause of morbidity and mortality if timely diagnosis can be made.Heart is considered an endocrine organ that releases many hormones including four types of Natriuretic peptides out of which ANP and BNP are predominately released from heart.BNP- is a peptide hormone synthesized largely by myocytes in response to myocardial stretch, in the form of pre-pro-BNP (134 amino acids). It is cleaved to pro-BNP (108 amino acids), and then proteolyzed by serine endopeptidasescorin and furin to active C-terminal 32 aa BNP and inactive 76aa N-Terminal-pro-BNP. NT-pro BNP level increases in the presence of both symptomatic and asymptomatic left ventricular dysfunction with haemodynamic overload. NT-pro-BNP is more sensitive with a longer half-lifeof two hours and preferable to BNP and ANP for the detection of heart failure and acute myocardial infarction. Several studies have shown that NT pro BNP level is higher in diabetics.[3-6]Ischaemic heart disease is currently considered the most important cause of heart failure with diabetes as the leading cause.Recent advances in the treatment of coronary disease have improved survival for diabetics and non-diabetics, but still the case fatality rate is double in diabetics compared with non-diabetics even with a value of NT pro BNP well below the cut off value for diagnosis of heart failure.[4,5]The reason between hyperglycemia and BNP levels is not obvious. Hyperglycemia may induce dysfunction of cardiac myocytes. Endoplasmic reticulum stress associated with diabetes leads to myocytes apoptosis and Cardiomyopathy as well.[7,8]
Diabetic cardiomyopathy is also not uncommon leading to sudden cardiac death and an early diagnosis by measuring NT Pro BNP can initiate timely intervention.[9]

II. Aim And Objective

To find out the correlation between NT Pro BNP and glycated haemoglobin HbA1C to find out the relation with severity of diabetes and NT pro BNP level with indicator of silent myocardial ischemia ie: MPI(Myocardial Performance Index) in type 2 diabetes mellitus patients.

III. Material And Methods

The current case control study was undertaken in the Department of Biochemistry in collaboration with the Department of Cardiology, S.C.B. Medical College, Cuttack.50 patients with diabetes mellitus of at least 5 years duration without overt heart disease and under regular medication (biguanides or sulfonylurea) are enrolled as cases and an equal number of age and sex matched healthy controls are taken for the evaluation of the following tests.3.1. Routine tests:were carried out using standard reagent kits with TOSHIBA 120 FR auto analyzer by taking 5ml of fasting venous blood in non-vacutainer tubes.

1. FBS (fasting blood sugar) – glucose oxidase / peroxidase method
2. Serum urea – UV-kinetic method using enzyme glutamate dehydrogenase
3. Serum creatinine – creatinine-kinase enzymatic method
4. Serum electrolytes (Na+/K+) – electrolyte analyzer by Ion Selective Electrode method
5. Lipid profile:Total Cholesterol (TC) – cholesterol oxidase method Triglycerides (TG) – enzymatic method,
6. 3.2.Hb A1C- By HPLC method CG (Electrocardiography) and Echocardiography- for evaluation of LVEF (left ventricular ejection fraction) and MPI[Myocardial performance index: This numeric value is defined as the sum of isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) divided by

ejection time (ET) and could be calculated for each ventricle individually]3.4. Special tests: NT Pro -BNP: ByELISAmethod with LISASCAN EM using standard kit.Conditions that tend to increase the NT-Pro BNP level like patients having history of major surgery or trauma within six months, malignancy, pregnancy, acute coronary syndrome,LVEF less than 45%, hypertension and serum creatinine more than 2.5 mg% were excluded from the study.

Table 1: Anthropometric measurements of controls and case

Parameter (mean ± SD)	Controls	Cases	'p' value
Age in years	51.42±9.49	53.04±15.64	>0.05
Systolic blood pressure (mm Hg)	122.0±2.5	128.2±9.8	>0.05
Diastolic blood pressure (mm Hg)	77.0±2.5	82.0±7.8	>0.05
Body Mass Index	25.65±3.69	28.78±4.66	<0.05*
Waist hip ratio	0.96±0.06	1.07±0.04	>0.05

* Statistically significant

Table II: Comparison of routine biochemical tests between controls and cases

Parameter (mean±SD)	Controls	Cases	'p' value
FBS in mg %	90.94±14.25	125.78±63.18	p<0.001*
S.urea in mg %	25.61±6.09	31.36±11.19	p>0.05
S.creatinine in mg %	0.89±0.17	0.97±0.52	P>0.05
S. Cholesterol in mg %	153.71±35.41	184.12±48.77	p<0.001*
S. Triglycerides in mg %	123.13±33.11	199.6±73.29	P<0.001*
S.HDL in mg %	38.42±6.05	35.28±8.34	p<0.05*
S.LDL in mg %	86.19±23.28	106.64±39.96	p<0.01*
S.VLDL in mg %	25.53±8.51	40.14±14.73	P<0.05*
S. Na+ in m Eq /L	137.61±2.2	134±14.45	p>0.05
S.K+ in m Eq /L	3.67±0.29	4.52±1.29	P<0.05*
* Statistically significant			

Table III: Comparison of NT Pro BNP level as marker of Glycemic control in controls and cases.

Name of test	**Controls Mean ± SD**	**Cases Mean ± SD**	**'p' value**
NT Pro BNP in pg/ml	37 ± 11	91 ± 26	< 0.001*
HbA1C in gm%	5.58 ± 1.08	7.21 ± 2.15	<0.001*

* Statistically significant

Correlation of NT Pro BNP with HbA1c as Marker of Glycemic Index in Cases and Controls.

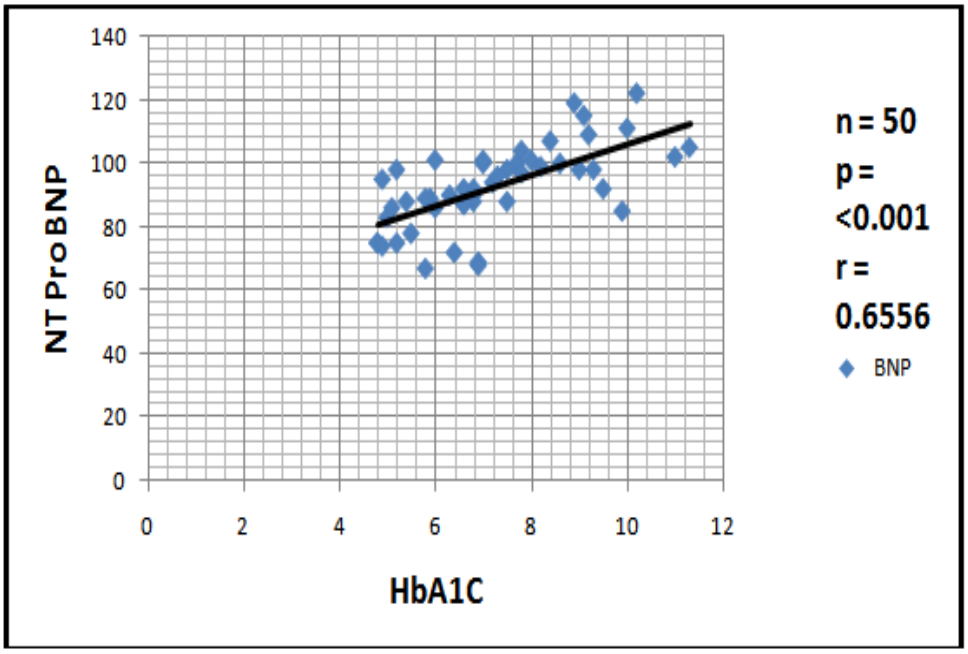


Table IV: **Comparison of NT Pro BNP level, MPI and LVEF in controls and cases**

NT pro-BNP (pg/ml)	37±11	91±26	**<0.001***
MPI	0.38±0.05	0.59±0.14	**<0.001***
LVEF%	61±3.7	59±4.1	>0.05

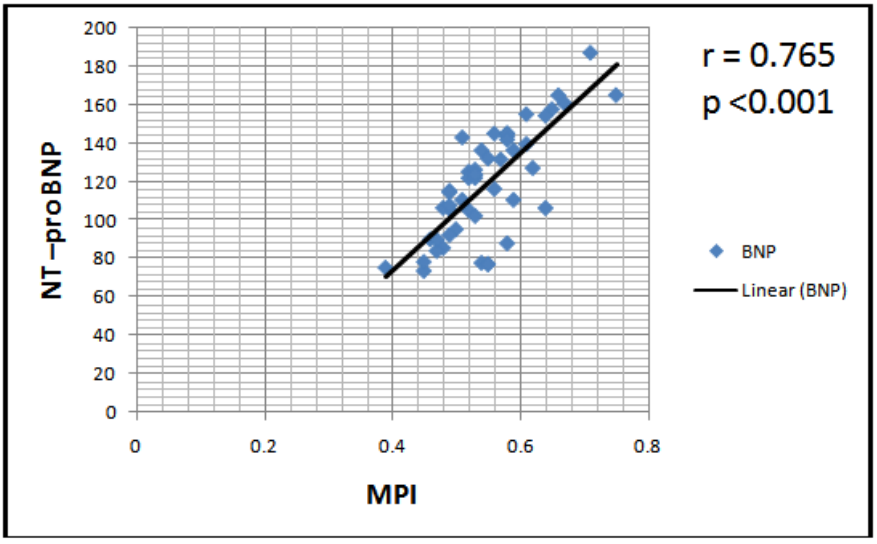
* Statistically significant

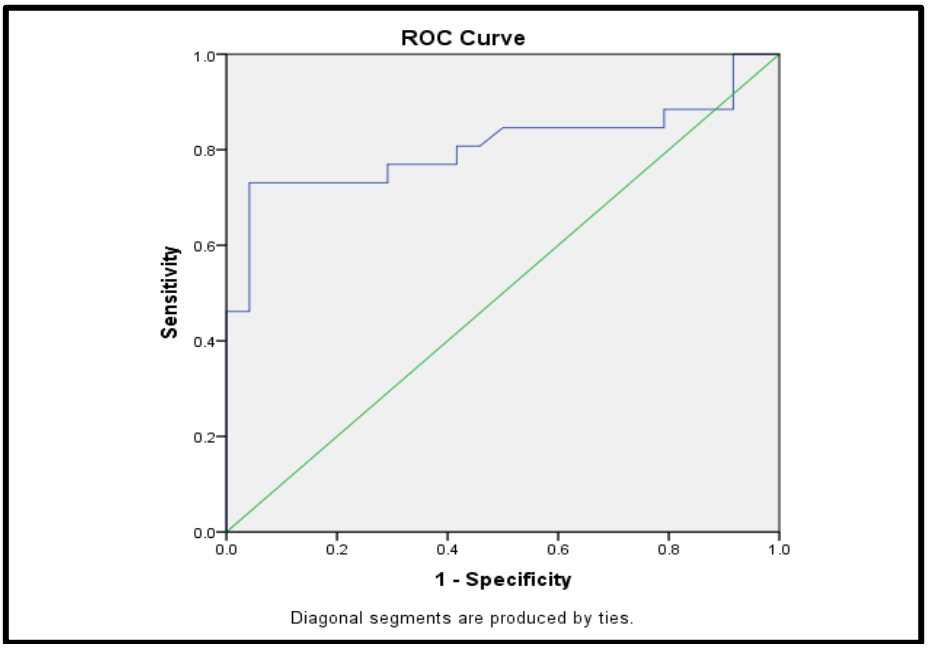
Table V: Comparison of NT Pro BNP level and MPI in diabetic patients with or without ischemia

NT pro BNP(pg/ml)	121±23	84±19	< **0.001***
MPI	0.62±0.16	0.54±0.14	< **0.001***

* Statistically significant

Graph showing correlation of NT pro BNP with MPI





- The usefulness of NT-pro BNP as a marker of Ischemic heart disease (IHD) in patients with type 2 diabetes was assessed by ROC curve analysis. The AUC was found to be 0.807 with a cut off value of 118.95pg/ml showed 83% sensitivity and 71% specificity for diagnosis of IHD (95% CI, 0.676 – 0.938).

Area Under the Curve				
Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.807	.067	.000	.676	.938

IV. Discussion

Type 2 diabetes leads to cardiovascular diseases and heart failure in a significant number of cases.[4,5,10]NT pro BNP is a sensitive marker in predicting cardiac dysfunction and is an indicator of myocardial stiffness.[10]Various authorshave given possible explanations for the association of increased NT Pro BNP in diabetics like higher prevalence of diastolic dysfunction, increased levels of blood lipids and consequent atherosclerosis, increased collagen content in heart muscles and decreased relaxation of heart muscles due to ATP deficiency.[11,12,13]Furthermore, Natriuretic peptides may function as endogenous inhibitors of cardiac hypertrophy and fibrosis.[14,15]*Natriuretic* peptides exert their biological effect through NPR- A and NPR- B receptors which are membrane bound guanylylcyclases that generate cyclic GMP and subsequent stimulation of cGMP dependent protein kinase activating nitric oxide signal transduction pathway and consequent relaxation of myocytes.[16,17]In the present study we have tried to find out the correlation between severity of diabetes and markers of myocardial dysfunction in patients without diagnosed cardiac disease. Table 1 shows significantly increased values of BMI in cases as compared to controlswhich explain the association of obesity in diabetes. Though the SBP and DBP are slightly on a higher side in cases, these are non-significant as we have intentionally excluded hypertensives from the study population who can interfere with study results.Table 2 shows a comparison of routine biochemical parameters between cases and controls. Here we find significantly increased levels of FBS, total cholesterol, triglycerides, LDL and VLDL and decreased level of HDL in diabetic cases which are already established.There is a positive correlation of NT pro BNP with HbA1C (r value = +0.6556) showing the association between poor glycemic control and myocardial stress. There are many hypotheses for deterioration of left ventricular function like microvascular changes, alterations in blood chemistry, metabolic changes, deposition of advanced glycosylation end products and myocardial stiffening by increased fibrosis.[18-24]We also found a strong positive correlation of NT pro BNP and MPI(r value of +0.765), which is a marker of silent myocardial ischemia. The isovolumetric contraction and relaxation times were also longer in diabetics as compared to healthy controls which indicate both systolic and diastolic dysfunction which corroborates with the study of other authors.[25]The usefulness of NT-pro BNP as a marker of Ischemic heart disease (IHD) in patients with type 2 diabetes was assessed by ROC curve analysis. The AUC was found to be 0.807 with a cut off value of 118.95pg/ml showed 83% sensitivity and 71% specificity for diagnosis of IHD (95% CI, 0.676 – 0.938) which is similar to the study of *E. Babes et al.*[26]As silent myocardial ischemia and diastolic dysfunction can develop relatively early in diabetes, we can identify these conditions by estimations of NT Pro BNP and MPI.Thus, NT pro BNP may be considered as an indicator of impending cardiovascular disease in type 2 DM.

V. Summary And Conclusion

1. Diabetic patients have high incidence of silent cardiac disease, particularly with poor glycemic control.
2. So, screening with a simple biochemical test like estimation of NT pro BNP is a very logical approach which correlates well with indicators of myocardial dysfunction like MPI.
3. It is equally efficacious but more economical and easily estimated in comparison to Echo-cardiography in predicting silent MI in type II DM.

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IOSR Journal of Biotechnology and Biochemistry (IOSR-JBB) is UGC approved Journal with Sl. No. 4033, Journal no. 44202.

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