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SERUM NT-PROBNP:--A NEW SCREENING TOOL IN TYPE 2 DIABETES MELLITUS

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Abstract: NT-PROBNP (N-terminal PRO-BRAIN NATIURETIC PEPTIDE) is an inactive protein moiety that is cleaved off from PRO-BNP to release BNP(Brain Natiuretic Peptide).NT-PROBNP is typically a 76 amino acid residue. Both BNP & NT-PROBNP are useful & established markers for assessment of left ventricular function as the plasma levels of both PROBPNP & NT-PROBNP are typically raised in cardiac failure, myocardial ischaemia & acute coronary syndrome. Diabetes is a complex syndrome characterised not only by hyperglycemia but also functional impairment of various other vital organs of the body such as kidneys, heart, eye & the nervous system to name a few. Various clinical & biochemical studies have proved it beyond doubt that diabetic patients have a many fold higher risk of developing cardiovascular complications than nondiabetics. Diabetes with its entire spectra of complications is turning out to be a single largest killer. In the past few decades it's incidence has been constantly increasing & in the present scenario it is acquiring epidemic proportions. The purpose of our study was to monitor plasma levels of NT-PROBNP (considered as an established marker for myocardial pump failure) in patients with type 2 diabetes & with no history of any cardiovascular disease. The outcome of our study has revealed that type 2 diabetics with no apparent history of cardiovascular disease tend to have significantly higher levels of serum NT-PROBNP as compared to the healthy controls. This is suggestive of the fact that diabetes is associated with a higher prevalence of left ventricular dysfunction than hitherto thought. Serum NT-PROBNP levels thus may act as a screening tool for patients with diabetes who would actually benefit from a echocardiography or a coronary angiogram

Keywords: Cardiovascular Disease, Diabetes, NT-PROBNP, BNP.



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INTRODUCTION

Diabetes & its association with cardiovascular comorbidities is a known fact. Patients with diabetes are twice more prone to suffer from cardiovascular diseases¹ but evaluation of cardiovascular status in diabetics is quite challenging keeping in mind the complexities of the associated symptoms. The earliest complication that is most often evident clinically happens to be coronary atherosclerosis². Studies in the past have revealed that the prevalence of diabetes is quite common in patients with heart failure³. Increased collagen content in the heart of diabetic subjects have been revealed by several autopsy studies. Disproportionate increase in left ventricular mass is also a feature of diabetic heart^{4,6}. All these factors eventually culminate into increased myocardial stiffness & the consequent morbidity & mortality⁷.

Brain natriuretic peptide (BNP) is mainly produced in the left ventricle of the heart as PROBNP which is a 108 amino acid residue. It is then cleaved by a protease to liberate the active BNP (32 amino acid residue) & NT-PROBNP (biologically inactive 76 amino acid portion of PROBNP)^{8,9}.

Regulation of salt & water homeostasis by BNP is well established fact. Increased tension on the ventricular walls due to various pathological states such as cardiovascular disease including ischemia, arrhythmia, fibrosis, cardiac hypertrophy and coronary endothelial dysfunction leads to an increased secretion of BNP.^{10,11} Many studies have suggested that raised NT-PROBNP levels represent a common pathway for various cardiovascular pathological states & it can be used as a cardiac biomarker.^{10,11} Present study was conducted to assess NT-PROBNP levels in diabetic patients who do not have symptoms of cardiovascular disease, the intention being to observe whether any significant variation in NT-PROBNP levels occur in diabetics even without underlying cardiovascular disease as compared to the healthy controls.

MATERIALS & METHODS

This is a case control study carried out at Dept of Biochemistry, IMS & SUM Hospital over a period of 6 months. The subjects for the study were divided into 2 groups:-

1) Group A :-This group comprised of 20 diagnosed cases of type 2 diabetes mellitus who presented to the endocrinology OPD at IMS & SUM Hospital. These patients were diagnosed as having diabetes since last 2 years and were on treatment with oral antidiabetic agents. They were normotensive & with no H/O any form of cardiac events. Age group of the subjects in this group varied between 50 years- 65 years.

2) Group B:-This group comprised of 20 age & sex matched healthy controls who presented to the hospital for regular health check up. They neither had diabetes, nor did they have any H/O any other major illness. This group served as the control group.

A written informed consent from all the cases & controls were taken about their willingness to participate in the study. The study was approved by the institutional ethical committee which follows the Helsinki guidelines. All the samples for blood investigations in this study were sent to a NABL accredited private lab in Kolkata namely CHIKITSA MEDICARE Pvt Ltd. Statistical analysis was done by SPSS V 17.0.

ESTIMATION OF NT-PROBNP

NT-PROBNP was estimated using a commercially available kit supplied by Roche Diagnostic Ltd on Elecsys 2010 fully automated immunoassay system.

NT-PROBNP levels ≥ 125 pg/ml were considered as high.

ESTIMATION OF LIPID PROFILE

Total cholesterol was estimated using a commercially available kit supplied by Roche Diagnostics which involves the CHOD/PAP enzymatic method. Triglyceride was assessed by kit involving enzymatic GPO/PAP method. HDL, LDL & VLDL were estimated by a commercially available kit supplied by Roche Diagnostics which involves the enzymatic CHOD/PAP method.

ESTIMATION OF BLOOD SUGAR

Blood sugar was estimated using fully automated auto analyser using enzymatic assay kit which employs the GODPOD method.

RESULTS & DISCUSSION

Table 1. Demographic data (Mean \pm SD) for the study population.

FACTOR	GROUP A	GROUP B
Age	52.02 \pm 9.47	38.56 \pm 5.35
BMI	25.43 \pm 3.45	24.50 \pm 3.56
BPS	124.72 \pm 3.35	122.76 \pm 2.96
BPD	78.80 \pm 8.13	80.36 \pm 4.36
FS	176.32 \pm 16.51	82.30 \pm 12.60
TC	165.26 \pm 22.84	148.64 \pm 29.76
TG	183.10 \pm 65.20	167.23 \pm 63.32
HDL	43.28 \pm 7.34	42.40 \pm 9.20
LDL	110.08 \pm 29.29	92.08 \pm 22.72
VLDL	34.74 \pm 9.19	32.30 \pm 13.25
NTproBNP	37.558 \pm 30.727	23.562 \pm 23.395

As the above data indicates, our study has revealed significantly higher value of NT-PROBNP in diabetic subjects who are not known to suffer from any cardiovascular symptoms as compared to the healthy controls. The increase in serum NT-PROBNP levels in these diabetic subjects can have multiple explanations:-

1) Peripheral & distal atherosclerotic changes in the coronary tree due to increased blood lipids as is evident from our data.

2) Increased collagen content of the diabetic heart has been proved by various autopsy studies. Metamorphosis of a cardiac fibroblast into a collagen secreting cell occurs by same mechanism by which NT-PROBNP secretion increases.¹²

3) Endothelial dysfunction, increased intimal medial thickness & arterial stiffness has been found to be more prevalent in diabetic subjects than non diabetics.^{13,14} Myocardial stretching results due to endothelial dysfunction, increased intimal medial thickness which in turn results in elevated levels of NT-PROBNP in blood as a compensatory mechanism.

4) Inherent ATP deficiency in diabetes due to intracellular glucose deficiency leads to an increased free fatty acid oxidation in cardiomyocytes. A sufficient amount of carbohydrate break down is of great importance for assuming an adequate function of the ion pumps,

meaning Na⁺/K⁺- ATPase and Ca²⁺ - ATPase, which maintains the right cardiomyocytes membrane potential and intracellular Ca⁺ transport, that triggers relaxation. In the diabetic heart, this balance is disturbed, proposing a functional explanation to the impaired relaxation in the myocardium.¹⁵⁻¹⁸

Our study has an inherent disadvantage of being a onetime observation for each individual, but still we were able to detect difference in NT-PROBNP levels between the two groups in question. Serum NT-PROBNP level estimation could thus serve as an important screening tool to identify diabetic patients who are at risk of cardiovascular disease. It could also serve as a screening tool to separate diabetic patients who are eligible for an echocardiography or a coronary angiogram. However this is a very small study that requires confirmation from further larger scale studies.

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