“Nt PRO-BRAIN NATRIURETIC PEPTIDE (Nt PRO-BNP) LEVELS INCARDIAC ASYMPTOMATIC TYPE 2 DIABETES”

BY

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ABSTRACT

TITLE OF STUDY: "Nt pro-brain natriuretic peptide (Nt pro-BNP) levels in cardiac asymptomatic Type 2 Diabetes"

NEED FOR THE STUDY:

Cardiovascular diseases are considered the most important cause of mortality and morbidity in diabetic patients and are responsible for nearly 70% of deaths from diabetes. Heart failure is seen twice as often in diabetic men and five times more often in diabetic women than in non-diabetic individuals, which is a preventable cause of morbidity and mortality if a timely diagnosis can be made. However, some patients remain asymptomatic to the occurring left ventricular dysfunction, thus preventing early diagnosis and management of Left ventricular dysfunction. The heart is an endocrine organ that releases many hormones, including four types of Natriuretic peptides. ANP (Atrial Natriuretic Peptide) and BNP (Brain Natriuretic Peptide) are predominately released from the heart.

BNP- is a peptide hormone primarily synthesized 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 endopeptidases Corin and Furin to active C-terminal 32 AA BNP and inactive 76AA N-Terminal-pro-BNP. Nt pro BNP level increases in symptomatic and asymptomatic left ventricular dysfunction with hemodynamic overload. Nt-pro-BNP is more sensitive with a longer half-life of two hours and is preferable to BNP and ANP to detect heart failure and acute myocardial infarction. Several studies have shown that the Pro BNP level is higher in people with diabetes. Ischaemic heart disease is the most important cause of heart failure, while diabetes is the leading one. Recent advances in the

treatment of coronary disease have improved survival for diabetics and non-diabetics. However, the case fatality rate is double in people with diabetes compared with non-diabetics, even with a value of Pro BNP well below the cut-off value for the diagnosis of heart failure. Hyperglycemia induces dysfunction of cardiac myocytes.

The deficiency of intracellular glucose among patients with diabetes leads to higher use of free fatty acids through beta-oxidation in the myocardium. Carbohydrate breakdown is essential for assuming an adequate function of the ion pump, meaning Na /K ATPase and Ca ATPase, which maintains the right cardiomyocyte membrane potential and intracellular Ca transport that triggers relaxation. This balance is disturbed in a diabetic heart, proposing a functional explanation for the impaired relaxation in the myocardium. Thus, Nt Pro BNP is beneficial for screening CVD risk in diabetic patients.

OBJECTIVE: To estimate Nt Pro Brain Natriuretic Peptide (Nt Pro-BNP) levels in asymptomatic cardiac type 2 diabetes mellitus patients.

METHODS: Patients attending BLDE (DU) SHRI BM PATIL MEDICAL COLLEGE HOSPITAL with diagnosed Diabetes Mellitus as per WHO criteria will be selected for the study. The study's nature and purpose will be explained to patients, and informed consent will be taken from those willing to participate. A structural format will be filled in to record personal details.

RESULTS: The study results were conducted to evaluate the correlation between Nt pro-BNP levels and left ventricular diastolic dysfunction and left ventricular ejection fraction.

Correlation between Nt pro-BNP and diastolic dysfunction: There was a positive correlation between Nt pro-BNP levels and diastolic dysfunction. (P value is < 0.0001)

Correlation between Nt pro-BNP and left ventricular ejection fraction: There was a negative correlation between Nt pro-BNP and ejection fraction. (‘r’- 0.882; ‘p’ < 0.001).

CONCLUSION: Grades of diastolic dysfunction and pro-BNP BNP had a positive correlation, and LVEF pro-BNP BNP had a negative correlation. This study can therefore infer that measuring the levels of Nt pro-BNP in patients with diabetes will therefore be helpful in the early detection of heart failure and predicting its prognosis and adverse outcomes.

INTRODUCTION

Diabetes is considered to be one of the leading causes of morbidity and mortality in the world. Therefore, early diagnosis and assessment of the disease's severity are crucial for predicting prognosis, treating the condition, and avoiding/decreasing the mobidity and mortality. [1]

Type 2 diabetes mellitus patients are twice as likely to experience heart failure. Patients with diabetes mellitus experience worse cardiovascular outcomes than those without the condition. Beyond the morphological and functional alterations brought on by diabetic cardiomyopathy, a complicated underlying pathophysiology is present. The high prevalence of heart failure among people with diabetes remains despite the availability of numerous efficient treatments that lower blood sugar levels in patients with type 2 diabetes mellitus. This raises the issue of whether there may be additional causes for the elevated risk of heart failure in diabetes mellitus in addition to hyperglycemia. Several cellular mechanisms are dysregulated in diabetic cardiomyopathy, including inflammation, oxidative stress, aberrant insulin signaling, endoplasmic reticulum stress, variations in the metabolism of cardiac substrates and the lipotoxicity, mitochondrial bioenergetics, altered signal transduction, RAAS (renin-angiotensin-aldosterone system). To lower the risk of HF in patients with diabetes mellitus, several pathophysiological pathways may be susceptible to pharmaceutical therapy. Beyond what is currently accomplished by current antihyperglycemic and HF medications, effective targeting of these pathways may change the outcome of HF. [2,3]

BNP (Brain natriuretic peptide) is a 32-amino acid protein. Primarily it is produced as a 108 amino acid pre-pro BNP (γ-BNP) in the left ventricle of the heart. This hormone is a natriuretic factor that controls the body’s equilibrium of salt and water. It is mainly preserved as BNP-32 in the human heart tissue, with a small quantity of the pre-pro BNP, which is the

precursor form. BNP-32 and the NH2-terminal part of pro-BNP are the forms of BNP that circulate in plasma (Nt-pro BNP). As a result, it is a simple way to evaluate heart function. Pre-pro BNP is produced in response to the myocardial wall stretching. And it is then converted into pro-BNP, which is then converted into the biologically active BNP fragment and the physiologically inactive NT-pro BNP fragment. Even the measurement of left ventricular diastolic dysfunction and left ventricular systolic dysfunction can be helpful in the diagnosis of heart failure. The BNP test's high negative predictive value (NPV) is particularly useful for the exclusion of heart failure. BNP levels are decreased by ACE inhibitors, Angiotensin receptor blockers, spironolactone, and loop diuretics, suggesting that BNP testing is probably useful for monitoring heart failure patients. Patients receiving treatment for chronic, stable heart failure may, however, have BNP values that are within the normal range. An increase in BNP level might result from pulmonary or renal diseases, intrinsic cardiac dysfunction, or both (e.g., chronic hypoxia). BNP measurements are contrasted with various assessments of the state of the heart's function, such as the NYHA (New York Heart Association) classification. When a patient has been given a heart failure or cardiac dysfunction diagnosis, the serum pro BNP level is thought to be a reliable indicator of their risk of cardiovascular events and mortality. **[4,5]**

To aid in the diagnosis of heart failure, the 2016 European Society of Cardiology guidelines for the diagnosis and management of HF (acute and chronic) advise that all patients suspected of having the condition have their serum natriuretic peptide levels (pro-BNP) checked. In a non-acute context, the upper limit of normal for BNP is 35 pg/mL, while the upper limit normal for pro-BNP is considered to be 125 pg/mL. In the acute context, the cut-off result for pro-BNP is around 100 pg/mL, while for pro-BNP, it is 300 pg/mL. Pro BNP levels can be used to distinguish between heart failure and other causes of dyspnea. Patients under 50 years

of age with pro-BNP levels > 450 pg/mL, patients between 50 and 75 75 years old with pro-BNP levels more than 900 pg/mL, and patients over 75 with pro-BNP levels > 1800 pg/mL are all diagnosed with heart failure. In this context, the current study aims to examine Nt pro Brain Natriuretic Peptide (Nt pro-BNP) levels in non-cardiac Type 2 Diabetes Mellitus patients who are asymptomatic. **[6,7,8,9,10]**

AIM AND OBJECTIVES

Aim of the study

To estimate the levels of Nt pro-BNP (Brain Natriuretic Peptide) levels in cardiac asymptomatic Diabetes mellitus patients.

Objectives of the study

- To estimate the Nt pro-BNP (pro-Brain Natriuretic Peptide) levels in patients with Diabetes mellitus with no known cardiac disease.

- To find the significance of pro-BNP in predicting heart failure.

REVIEW OF LITERATURE

Diabetes Mellitus-

History-

The first accepted theories identifying diabetes are around 35 centuries old; the Indian physician Charaka identified the disease and named it ‘madhumea’, which translates to ‘honey urine’ as it attracted flies and ants. Around the same time, an Egyptian physician Hessy-Ra mentions the symptom of excessive urination. The name “diabetes” (Greek: “diabainen,” meaning “to pass through”), which refers to a disease that causes excessive urine output and constant thirst, is generally attributed to the Greek Apollonius of Memphis in 230 B.C [11]. In truth, the sweet taste of urine had been noted by physicians in ancient Greece, China, India, Egypt, and Persia. Willis, in 1676 included the word Mellitus, which means "sweetened like honey,” to refer to the sweetened urinary flavor. When Dobson measured the urine glucose in these patients in 1775, he discovered that it was elevated. The Greek physician Aristaeus of Cappadocia first documented the signs and characteristics of diabetes mellitus in the second century, but it wasn't until 1500 AD that the document was translated into Latin and published in Venice. Von Mering and Makowski, in 1889, discovered that when dogs lost their pancreas, they experienced symptoms like diabetes, which led to a better knowledge of the relationship between the pancreas and diabetes mellitus [12,13]. "Islands of transparent cells that stained differently than the rest of the pancreas" were found by Langerhans in 1869. In 1893, Langerhans verified his results and suggested that these were pancreatic secretory glands, giving the name "islets of Langerhans." De Meyer named the pancreatic juice that is absent in diabetes "insulin" in 1910 to signify that it comes from the insulae of Langerhans [14]. However, Banting, Best, and Macleod first showed in 1921 that the hyperglycemia that is characteristic of diabetes may be

alleviated by giving experimental dogs pancreatic extract from pancreatic island cells. Leonard Thompson, 13, of Canada, was the first patient to get treatment with a pure form of insulin [15]. In the 1920s, the possibility that there are various types of diabetes was proposed. In 1926, MacLean proposed a difference between “hepatic glycosuria” and "true diabetes.” In the 1930s, Himsworth proposed that hyperglycemia is related to either insulin sensitivity or insufficiency while attempting to understand why it occurs [16]. Biguanides and sulfonylureas, two oral glucose-lowering medications, were first released in the 1950s.

Classifications

Diabetes can be classified into the following categories:

1. Type 1 or insulin-dependent diabetes mellitus (absolute/relative insulin deficiency due to autoimmune cell destruction)

2. Type 2 or insulin-independent diabetes mellitus (insulin resistance due to progressive loss of beta cell mass in the pancreas)

3. Gestational diabetes mellitus.

4. Other types of diabetes with specific causes, such as drug or chemical-induced diabetes (such as after organ transplantation, in the treatment of HIV/AIDS, or during glucocorticoid therapy), exocrine pancreas diseases (such as cystic fibrosis and pancreatitis), and monogenic diabetes syndromes (such as maturity-onset diabetes of the young and neonatal diabetes). **[17,18]**

Epidemiology

Prevalence

The IDF (International Diabetes Federation) states that the prevalence of diabetes mellitus worldwide was close to 9% in 2015 and is anticipated to reach 10.4% in 2040 as a result of an ageing population and changes in lifestyle patterns. Age of the population, the nature of the researched population, and the screening techniques employed all have a significant impact on prevalence. About 40% of persons affected by diabetes in western nations are thought to go undiagnosed. [19]

About 460 million persons (aged 20 to 79) had diabetes in 2019, and by 2045, that number is projected to climb to 700 million. In most nations, the percentage of people with type 2 diabetes is rising. Adults with diabetes make up 79% of the population in low- and middle-income nations. In India, the adult population has an estimated 72 million cases of diabetes. The frequency among people aged 20 and older in urban regions is between 10.9% and 14.2%, while it is 3.0–7.8% in rural India, with a substantially greater prevalence among people over 50. [21]

In several European nations, the age-standardized annual incidence of diabetes is rather consistent for both men and women. Over the previous four decades, it has remained steady or perhaps significantly decreased [22].

Risk factors

The most significant risk factors for diabetes, aside from becoming older, are obesity, particularly abdominal obesity, a sedentary lifestyle, and bad eating habits [17,19]. The "metabolic syndrome," which includes diabetes, hypertension, dyslipidemia, abdominal obesity, and insulin resistance, increases the risk of cardiovascular disease [20].

Prognosis

Diabetes also significantly raises the prevalence of macro-vascular problems by a factor of

two to four. The reduction of micro- and macro-vascular problems is attributable to better multifactorial risk factor management. [22,23]

Additionally, although there is still a difference between those with and without the disease, diabetes sufferers' life expectancy is beginning to catch up to that of individuals without the condition. [24,25]

Table 1. Four main groups of diabetes classification according to the ADA [17]

Type	**Details**
Type-1 diabetes	5 to 10 percent of all cases of diabetes frequently manifest during the childhood. It has a sudden onset and is brought on by an autoimmune attack on the pancreatic beta cells, which results in a complete lack of insulin and the requirement for lifelong insulin therapy. Similar to juvenile diabetes, latent autoimmune diabetes in adults (LADA) develops more gradually and only affects adults. Although the aetiology is not entirely understood, a mix of genetic predisposition and environmental variables is thought to be the cause.
Type-2 diabetes	consists of 90 to 95% of all diabetics, which is the vast majority of cases, and generally appears gradually in middle age. characterised by a relative lack of insulin production and insulin resistance, and do not need insulin to survive. Co-existing abdominal obesity, hypertension, dyslipidemia, sedentary lifestyle, smoking, and hereditary

Type	Details
	factors are important risk factors.

Type	Details
Gestational diabetes	During pregnancy, hyperglycemia is first noticed, and it goes away 12 weeks after delivery. During and immediately after birth, there is an increased risk for a variety of problems for both the mother and the foetus, and these women are more likely to later acquire type 2 diabetes.
Other specific types	Examples include diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young).

Treatment

Recommendations [25]

1. The most effective initial pharmacologic treatment for type 2 diabetes is metformin (biguanides).
2. As long as metformin is tolerated well and there are no contraindications, it should be continued once taken.; additional medications, such as insulin, should be added to metformin.
3. To lengthen the period preceding treatment failure, early combination therapy may be explored in some patients at the time of treatment initiation.
4. An early introduction of insulin therapy should be considered if there is evidence of ongoing catabolism (weight loss), or if symptoms of hyperglycemia are present, or when HbA1C levels are high (10% [86 mmol/mol]) or blood glucose levels (300 mg/dL [16.7 mmol/L]).
5. A patient-centered approach should be used to select the choice of pharmacologic agents. Cardiovascular complications, risk of hypoglycemia, cost, impact on weight, risk of serious side effects, and patient preferences should be considered.
6. Among patients with type 2 diabetes who have any cardiovascular disease or, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist which have proven cardiovascular benefit is recommended as part of the glucose-lowering regimen independent of A1C and in consideration of patient-specific factors.

7. In individuals with type 2 diabetes who require higher insulin, oral medications like glucagon-like peptide 1 receptor agonists can lower blood sugar levels and are, if practical, preferred to insulin.

Heart Failure

History

In 1628, Harvey published the first contemporary understanding of the circulatory system in his "Excercatio anatomica," setting the basis for modern understanding of the function of the heart. He showed how the blood was pumped from the heart through vessels to the tissues and back through vessels. This revolutionised science and runs contrary to Galen's ancient viewpoint. [31]

The 18th century saw a considerable amount of interest in anomalous heart structure. According to Berlin, in 1833, dilation was thought to happen as a result of the contractile force is decreased. Osler reported his findings that though hypertrophy is initially adaptive, it can eventually become maladaptive and impair the heart's capability to pump blood. Chamber dilatation and fluid accumulation associated with heart failure became better understood with Rontgen's 1895 X-rays discovery that could see inside the body. Understanding the typical circulatory physiology was made possible by Starling's demonstration in 1918 that a greater end-diastolic volume significantly increases the contractility of the heart, as stated in his "Law of the heart." Insights into the disturbed hemodynamic status brought on by reduced myocardial contractility, which results in a decrease in cardiac output and an increase in filling pressures, were provided by cardiac catheterization, which was first explained by Forssmann and later developed by Cournand and Richards. Since the invention of echocardiography by Edler and Hertz in 1954, non-

invasive examinations of cardiac function have been made possible. When Olson, for instance, claimed that "the problem underlying heart failure is reduced energy consumption by the contractile apparatus," implying that heart failure is an energy-depleted state, myocardial biology began to draw attention in the 1950s. In the 1960s, theories of how decreased myocardial contractility contributes to heart failure emerged. This markedly improved our understanding of the pathology underlying heart failure. [32,33,34,35]

For a long time, only medications that increased the failing heart's power could be used as a treatment for heart failure. Cardiovascular glycosides, notably Scilla Maritima, were used by ancient Egyptians, Romans, Greeks, and Syrians (sea onions). Withering made the first statement about Digitalis' beneficial cardiac benefits in 1785. Bloodletting leaches and, subsequently, Southey's tubes were used to drain the excess fluid accumulation that had accumulated in the swollen, edematous legs in an effort to treat the fluid retention that resulted from heart failure. Diuretics were made available in the 20th century and provided wonderful symptom relief. [35,36,37,39]

Definition and classification of heart failure

The ESC (European Society of Cardiology) defines heart failure as a syndrome that includes signs and symptoms like increased jugular venous pressure, pulmonary crepitations, tachycardia, and pedal edema. The symptoms include breathlessness, persistent cough or wheeze, pedal edema, and easy fatiguability. These symptoms, though, might not be obvious in the beginning or individuals receiving appropriate diuretic therapy. When present, they are the result of a structural or functional anomaly of the heart that causes systolic and/or diastolic ventricular dysfunction, which lowers cardiac output and/or elevates intracardiac pressures when the heart is at rest or under stress. Recent ESC guidelines state that in addition to physical examination and clinical examination, laboratory testing, and chest

radiograph, an ECG should be included in the initial evaluation of patients with suspected heart failure. The diagnosis of heart failure can be verified by echocardiography. Beyond the detection of myocardial abnormality, other impairments like valvular abnormalities, pericardial abnormalities, and endocardial abnormalities may be found. However, the diagnosis of heart failure and its management depend heavily on the determination of the underlying cause [40].

The cornerstone to diagnosing HF is proving an underlying cardiac cause. Systolic and/or diastolic ventricular dysfunction is typically caused by a myocardial dysfunction. However, HF can also result from abnormalities with the heart's valves, endocardium, pericardium, and conduction (often, more than one of these abnormalities is present). For therapeutic purposes, it is essential to identify the underlying cardiac problem because the exact pathology dictates that particular treatment used. [41]

Diastolic dysfunction-related heart failure has been distinguished from systolic dysfunction-related heart failure in clinical practice. The former refers to a decreased ability of the ventricle to expel blood, whereas the latter is caused by limited ventricular filling as a result of hampered myocardial relaxation. Since they were not mutually exclusive, this terminology was later dropped. The classification used at the moment is based on the left ventricular ejection fraction (LVEF). Heart failure with preserved ejection fraction (HFpEF; LVEF 50%) is a condition that affects heart failure patients in spite of a normal ejection fraction. In the most recent European management guidelines for heart failure, patients having an ejection fraction of 40 - 49% are classified as having "mid-range" heart failure (HF-Mr-EF). In comparison, those with an ejection fraction of less than 40% are classified under "heart failure with reduced ejection fraction" (HF-r-EF). The most understood entity is HF-r-EF, and only this group is eligible for the recent guideline-based therapy, which affects mortality and morbidity. [40,41]

Epidemiology

Depending on the definition, the HF prevalence varies from 1 to 2 percent of adults in developed countries and up to 10 percent among those above 65. A 65-year-old who visits their health care provider complaining of dyspnea with exertion likely has undiagnosed HF (mainly HFpEF). At age 55, the lifetime risk of heart failure is 28% for women and 33% for men. According to the definition used, the clinical environment, the age and gender of the study group, any prior myocardial infarctions, the year of study and publication, and other factors, the proportion of patients with HFpEF ranges from 25% to 75%. [26]

Patients with HFmrEF share characteristics with HFrEF and HFpEF patients. However, further research is required to fully understand this patient population. Within and between various geographical areas of the world, the etiology of HF varies. The causes of HF-, which cross over into other classifications, do not have a single, widely acknowledged classification system. [19,42,43,44]

Heart failure is recognized to be caused by a variety of diseases, both cardiovascular and non-cardiovascular, in many patients. These numerous diseases should be recognized as part of the diagnostic process for heart failure since they may offer chances for target-specific treatments. Many individuals with IHD and HF have had myocardial infarctions or other revascularization procedures in the past. A healthy coronary angiography does not, however, rule out myocardial scarring or poor coronary microcirculation.

According to the most recent statistics from Europe (ESC-HF pilot research), hospitalized and stable heart failure patients had annual all-cause mortality rates of 17% and 7%, respectively, and annual hospitalization rates of 44% and 32%, respectively [45].

Cardiovascular causes, particularly sudden cardiac death and deteriorating HF, are the most common causes of death in people with HF (both inpatient and ambulatory). Nearly always, HFrEF has higher all-cause mortality than HFpEF. Particularly in patients with HFpEF,

hospitalizations are frequently caused by non-cardiovascular conditions. From 2000 to 2010, there was no change in hospitalization for cardiovascular causes, however, there was an increase for non-cardiovascular causes. [45,46]

Prevalence - Heart failure affects 1-2% of adult populations in India who are older than 25 years of age. The prevalence rises with age, reaching 10% over 65. The prevalence is rising as the population ages, but more critically, as survival rates have improved, especially for ischemic heart disease. [44,45,46]

Risk factors

A list of the risk factors leading to AHF is provided in Table 2. Failure results in a little less than half of the hospital admissions. EVEREST trial shows that 45% of hospital admissions were due to cardiac failure, while 37% were due to non-cardiac conditions. [47,48]

Table 2: Risk factors for Heart failure [48]

Cardiac	**Non-cardiac**	**Iatrogenic or Patient-related**
• Acute myocardial infarction (AMI) • Acute valvular regurgitation • Acute pulmonary embolism • Uncontrolled hypertension • Bradycardias (i.e., third-degree atrioventricular block) • Tachycardia (i.e., atrial fibrillation)	• Anemia • COPD exacerbation or asthma • Strenuous exercise • Infections and febrile states • Hyperthyroidism • Hypothyroidism	• Increased salt or fluid intake • Poor treatment compliance • Surgery • Alcohol abuse • Drugs (i.e., NSAID, thiazolidinediones)

• Aortic dissection • Cardiac tamponade • Myocarditis	• Renal dysfunction • Emotional stress • Pregnancy (peripartum cardiomyopathy)	

The most frequent etiological factors are hypertension and ischemic heart disease, which account for about 40% of all cases (IHD). Pulmonary illness, valvular heart diseases, atrial fibrillation, myocardial infiltrative and toxic interactions are less frequent. Heart failure, diabetes, obesity, and classic IHD risk factors are significant [25].

The three different types of heart failure, i.e., HFrEF, HFmrEF, HFpEF, are thought to have slightly different risk factor profiles, with HFpEF being more likely to occur in advanced age, chronic hypertension, diabetes, atrial fibrillation, and female sex. At the same time, HFrEF is more likely due to IHD, smoking, and the male sex. [41]

Pathophysiology of heart failure

Heart failure occurs when the heart cannot pump out enough blood to meet tissue needs or must increase filling pressures to maintain it must increase filling pressures to keep up an adequate output. Myocyte loss and malfunction, cardiac remodeling, or a combination of the two may be the cause. Three adaptive mechanisms will be triggered to maintain an acceptable cardiac output. This explains how people with heart failure, at least in the early stages, may not exhibit many symptoms while having impaired cardiac function. [48]

1) The Starling rule states that an increase in preload, which is demonstrated by an increase in end-diastolic volume, improves ventricular function.

2) To maintain mean artery pressure (MAP) and the perfusion of essential organs, neurohormonal activation - which results in increased function – enhances the sympathetic tone by stimulating the RAAS (Renin-Angiotensin-Aldosterone System).

3) Cardiac remodeling, including hypertrophy and dilatation, in order to accommodate the higher demand.

The first two are due to an immediate response, which is advantageous during the initial stages.

Brain natriuretic peptide (BNP)

Initially extracted from animal brain extracts, brain natriuretic peptide (BNP) was later recognized as a cardiac natriuretic hormone. It creates the heart's dual natriuretic peptide couplet and the homologous atrial natriuretic peptide (ANP). The myocyte stretch is the primary trigger for pro-BNP and secretion from the heart. The physiologically inactive N-terminal prohormone BNP (NT-pro BNP) and biologically active BNP are separated from the pro-peptide during secretion. Increased wall strains, hypoxia, and neurohormonal stimulation contribute to an increased BNP secretion in heart failure. [49, 50, 51]

Uncertain pathogenic significance surrounds the surprising finding that activated cardiac fibroblasts produce BNP. Contrary to ANP, the mature peptide is stored less extensively within cells when the hormone BNP is produced. Usually, the atrial serves as the primary manufacturing site, but ventricular NT-pro BNP synthesis is dramatically enhanced as heart failure progresses BNP has various effects on distant tissues, including diuresis, vasodilation, and a reduction in renin and aldosterone secretion. BNP binding to the natriuretic peptide clearance receptor type-C and proteolysis by peptidase NEP are two known pathways of BNP clearance from the citation. NT-pro BNP has a higher plasma concentration than BNP due to its longer half-life. [51, 52, 53]

A 32-amino acid cardiac natriuretic peptide hormone, brain natriuretic peptide (BNP), was first discovered in the brain tissue of pigs. On chromosome 1, the human BNP gene may be found. This gene produces the pro-hormone BNP, encoded by the BNP protein [54,55]. The residual prohormone, NT-pro BNP (76 amino acids), and the physiologically active BNP may be ted in human blood using an immunoassay [57]. The main primary of BNP and the peptides it is connected to is cardiac

myocytes. The primary trigger for peptide production and secretion is myocyte strain. Recently, it has also been demonstrated that cardiac fibroblasts produce BNP. In many cardiac cell types, several neurohormones may promote cardiac BNP synthesis. [58, 58, 60]

Ventricular (NT-pro BNP) production is markedly increased locally in the vicinity of myocardial infarction and cardiac failure. BNP stimulates the synthesis of intracellular cGMP by binding to the natriuretic peptide receptor type A in peripheral organs [61,62]. Diuresis, vasodilatation, suppression of renin and aldosterone synthesis, and inhibition of cardiac and vascular myocyte development are among the physiologic consequences. [63, 64, 65]

BNP was first identified in the swine brain in 1998 and given the label "brain natriuretic peptide," but later research has revealed that ventricular myocytes primarily produce and secrete BNP. [66]

Under any pathological circumstance, the mRNA can quickly synthesize the pre-pro BNP (a precursor protein containing 134 amino acids) and remove the 26 amino acid signal peptides from the N-terminus to form a 108 amino acid BNP (pro-BNP). Pro BNP is then cleaved by the pro-BNP convertases, which are Corin and furin, into Nt-pro BNP, which is an inactive 76 amino acid and BNP, which is an active 32 amino acid, respectively [67,68]. Plasma contains both NT-pro BNP and physiologically active BNP. [69]

Receptors of natriuretic peptides

NPR-A, NPR-B, and NPR-C are the three membrane-bound natriuretic peptide receptors (NPR) for natriuretic peptides. Vascular endothelium and a few other tissues, including the brain and kidney, are rich reservoirs of NPR-A [70, 71, 72]. While the NPR-B receptor mediates CNP, the NPR-A receptor is the primary receptor for both ANP and BNP effects. After NPR-A and NPR-B receptors are activated, the levels of cyclic guanylate monophosphate (cGMP) increase. BNP works against the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system to mediate its biological effects after binding with NPR-A. This increases the glomerular filtration rate and has

diuretic, natriuretic, and vasodilatory effects. [73, 74, 75, 76]

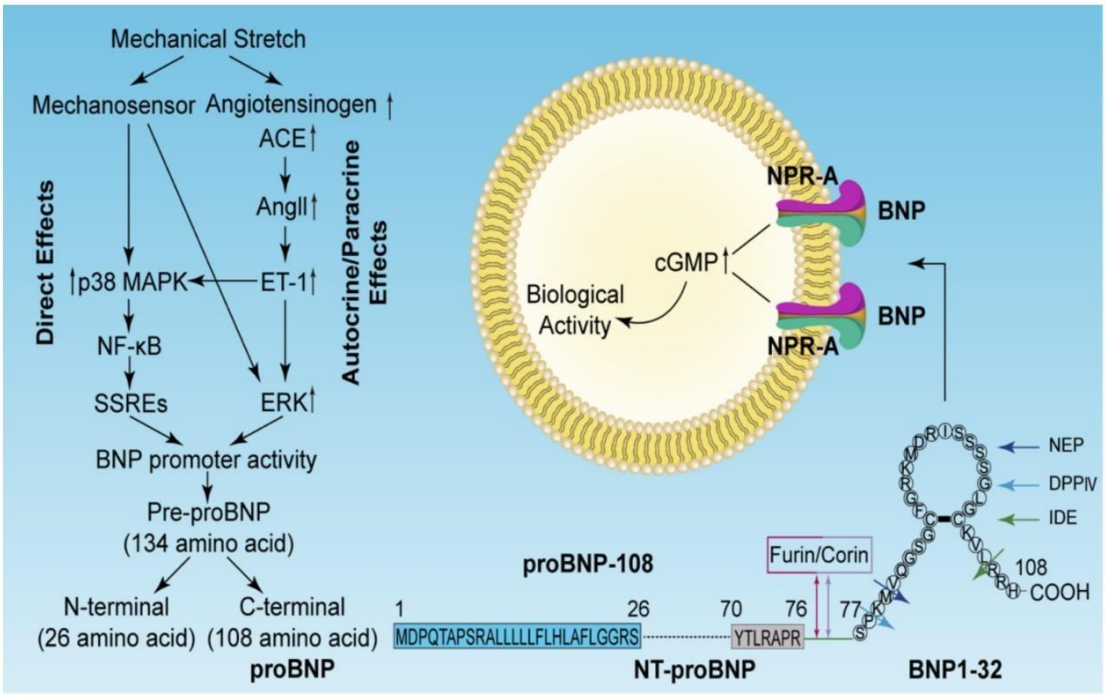


Figure 1: Effects of mechanical stretch on the heart. [77]

Clinical biomarkers for the diagnosis of HF include BNP and NT-pro BNP. About 1 to 2% of adults in the United States are affected by the multifactorial systemic disease known as HF. Depending on the ejection fraction, cases of HF are currently classified as either HFrEF or "heart failure with normal or preserved ejection fraction" (HFrEF or HFpEF) (EF) [78,79]. BNP and NT-pro BNP are regarded as the most valuable and trustworthy biomarkers for detecting HF and cardiac dysfunction, according to the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) and European Society of Cardiology (ESC) guidelines. Additionally, they are in charge of determining the severity, directing the appropriate treatment plans, and determining the prognosis of heart disease. [80, 81]

Diagnostic Role in a Failing Heart

BNP and NT-pro BNP levels can rise as a result of HF and cardiac dysfunction, which can be caused on by a range of conditions, including ischemic heart disease, various forms of arrhythmias,

and cardiomyopathy. [82, 83, 84]

BNP and NT-pro BNP have been linked to arrhythmias and cardiomyopathies in addition to ischemic heart disorders. Patients with atrial fibrillation were shown to have higher levels of BNP and NT-pro BNP. In an animal experiment, it has been shown that BNP mRNA and its protein rise as soon as 10 minutes following transiently fatal ventricular arrhythmias. Takotsubo cardiomyopathy has markedly elevated BNP levels, and early BNP/cTnT and BNP/CK-MB ratios distinguish Takotsubo cardiomyopathy from acute myocardial infarction (AMI) more precisely than BNP alone. [85, 86]

This suggests that BNP assays may be used to help differentiate between different cardiac disorders when combined with other indicators. [85]

Assessing the Severity and Prognosis of HF

BNP and NT-pro BNP are extremely important in the diagnosis of HF, but they are also very helpful in determining the severity and prognosis of HF. According to Doppler-echocardiography, BNP and NT-pro BNP were the best independent predictors for HFpEF. [86]

The New York Heart Association (NYHA) classification system was used to construct this experiment. Patients who were judged to be in NYHA classes I to IV had steadily rising plasma BNP concentrations, which suggests that plasma BNP concentration rises with the severity of HF.In patients with cardiovascular illnesses, plasma levels of BNP and NT-pro BNP have predictive significance, and a decrease in these levels signals an improvement in clinical symptoms. The evaluated BNP or NT-pro BNP and the risk of mortality are positively correlated. BNP and NT-pro BNP were the best predictors of sudden cardiac death, even after accounting for clinical factors such as EF, according to a study of 521 AMI patients. Additionally, plasma BNP and NT-pro BNP are used clinically to direct the management of patients with HF and cardiac dysfunction. They are also used as prognostic indicators, which can assist clinicians in modifying their treatment

plan and assessing the efficacy of their interventions to increase patient survival. [87, 88, 89, 90]

STUDY DESIGN:

This is an observational prospective study.

SOURCE OF DATA:

This study has included patients diagnosed with Diabetes mellitus attending the outpatient or inpatient of BLDE (Deemed to be University) - Sri B.M. Patil Medical College, Hospital and Research Center, Vijayapura.

- All these patients were informed regarding the study in all aspects, and an informed consent was taken.
- The period of study was from JANUARY 2021 to JUNE 2022.

METHODS:

Patients attending BLDE (Deemed to be University) Sri B.M. Patil Medical College, Hospital and Research Center, Vijayapura diagnosed with Diabetes Mellitus as per WHO criteria were selected for the study.

The study's nature and purpose were explained to patients, and informed consent was taken from those willing to participate.

Patients' present and past medical histories were recorded, and a detailed physical examination was done.

METHOD OF COLLECTION OF DATA

Study patients:

An in-detail history, general examination, systemic examination, and necessary investigations were done for all the patients who met the required inclusion criteria. Both males as well as females attended the outpatient department and admitted to Sri B.M. Patil Medical College, Hospital and Research Center, Vijayapura.

SAMPLE SIZE:

With the anticipated Proportion of Nt-pro BNP value (above 350 pmol/l) among Type 2 Diabetes patients at 61.3%, the study required sample size of 64 patients with a 95**%** level of confidence and 12% precision**.**

Formula used

$$n = \frac{z^2\, p * q}{d^2}$$

Where Z = Z statistic at α level of significance

d^2= Absolute error

P =Proportion rate

Q = 100 - p

Statistical Analysis

- The data thus obtained was entered into an MS Excel sheet, and THE statistical analysis was performed using an (SPSS) statistical package for the social sciences (Version 20).
- The results are presented as Mean (Median)±Standard deviation, count and percentage, and diagram.
- Categorical variables between variables were compared using the Chi-square test.
- A correlation coefficient was used to find the correlation between the quantitative variables.
- The receiver Operative curve (ROC) was performed to find Sensitivity and specificity.

INCLUSION CRITERIA:

- Patients with Diabetes Mellitus diagnosed according to WHO criteria **i.e.**

1. Fasting blood sugar levels more than or equal to 126 mg/dl **(OR)**

2. Post-prandial blood sugar more than or equal to 200 mg/dl **(OR)**

3. HbA1c $\geq$ 6.5 %.

EXCLUSION CRITERIA:

- Diabetic Patients with any cardiovascular disease like IHD, MI, Cardiomyopathies, Congestive Cardiac Failure, or congenital heart disease.
- Patients aged >75 years.
- Patients with chronic liver and kidney diseases.

RESULTS

Age distribution of the study subjects.

Totally 64 patients were taken up for the present prospective observational research. Total of 4 subjects was of less than 30 years of age, 4 subjects were in the 31 to 40 years age group, and 10 subjects were in the 41 to 50 years age group, while 12 subjects were in the 51 to 60 years age group, 22 subjects were between 61 to 70 years, and remaining patients were above 70 years of age. Majority of the patients were of age group above 50 years of age.

Table 4: Frequency distribution of subjects according to age

Age (Years)	No. of patients	Percentage
20 - 29	4	6.3
30 - 39	4	6.3
40 - 49	10	15.6
50 - 59	12	18.8
60 - 69	22	34.4
70+	12	18.8
Total	64	100.0

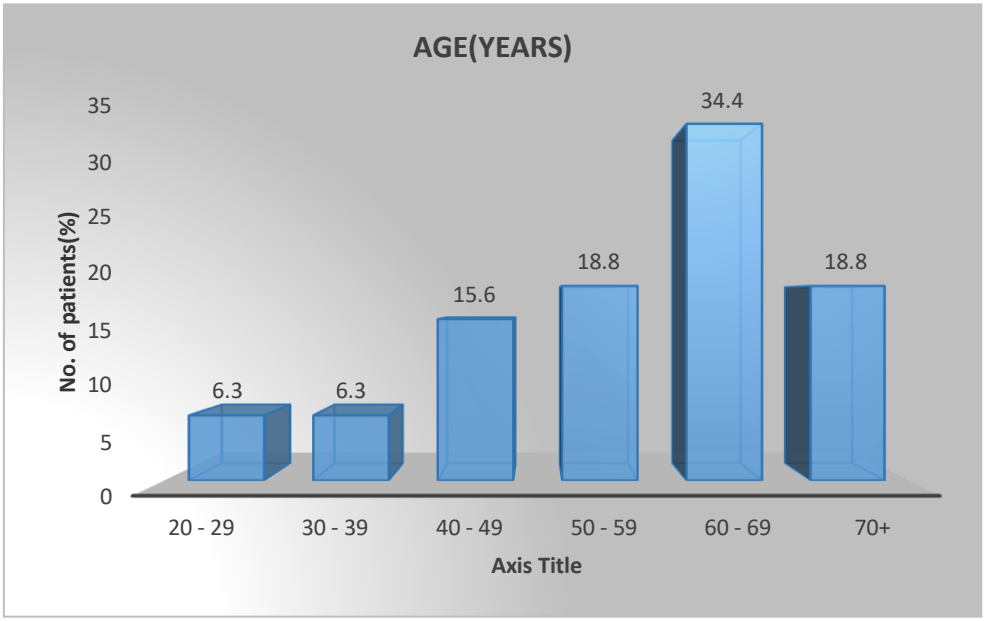


Figure 2: Frequency distribution of subjects according to age

Gender distribution of study population

Of the total 64 subjects, 34 (53%) study subjects were males and 30 (47%) study subjects were females.

Table 5: Frequency distribution of subjects according to gender

Gender	n=64	%
Males	34	53.00
Females	30	47.00
Total	64	100.00

Distribution of mean plasma Nt pro-BNP levels in study subjects and its correlation with diastolic function

64 patients admitted to the hospital with Diabetes Mellitus were taken up for the study. We observed that the subjects with normal diastolic function had mean pro BNP levels of 374.32 ± 220.793 pg/ml, while with grade I diastolic dysfunction had 1201.35 ± 258,552 pg/ml, with grade II diastolic dysfunction, had 1698.21 ± 578.522 pg/ml and with Grade III diastolic dysfunction had 7963.50 ± 5844.544 pg/ml. The P value of the correlation is 0.0001.

Table 6: Distribution of plasma Nt pro-BNP levels in the study subjects and its correlation with diastolic function

Diastolic function	**Mean ± SD (pg/mL)**
Normal (n=25)	374.32 ± 220.793
Grade I Diastolic Dysfunction (n=17)	1201.35 ± 258,552
Grade II Diastolic Dysfunction (n=14)	1698.21 ± 578.522
Grade III Diastolic Dysfunction (n=8)	7963.50 ± 5844.544

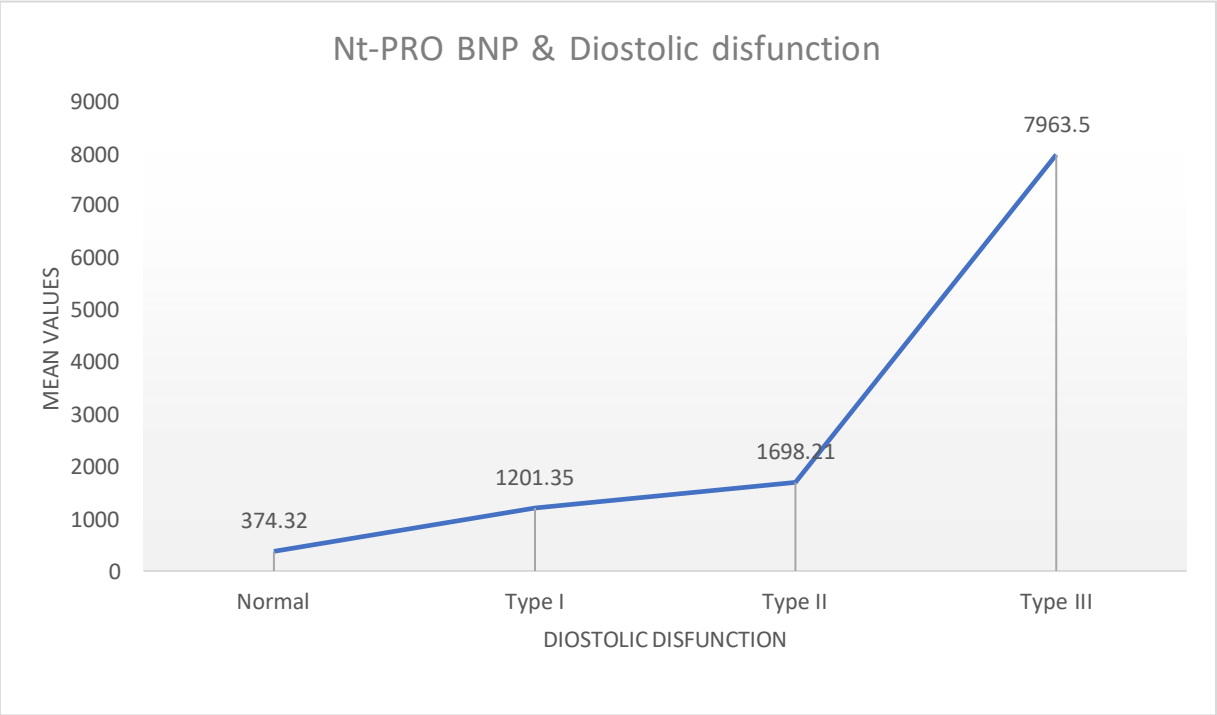


Figure 3: Distribution of plasma Nt pro-BNP levels in the study subjects and its correlation with diastolic function

Association between age and pro level BNP

The association of pro BNP level in subjects according their age was evaluated. The mean pro BNP level in subjects who had age less than 50 years had mean pro BNP of 747.3747.3±1005.987 pg/mL while in subjects with age more than 50 years had mean pro BNP of 6067.37±7506.701pg/mL. The association was between them was statistically significant (‘t’-2.52, ‘p’=0.007).

Table: Frequency distribution of pro BNP levels according to age of the study population

Age	Mean ± SD	‘t’ value	‘p’ value
< 50 years	747.3 ± 1005.987	-2.52	0.007
> 50 years	6067.37 ± 7506.701		

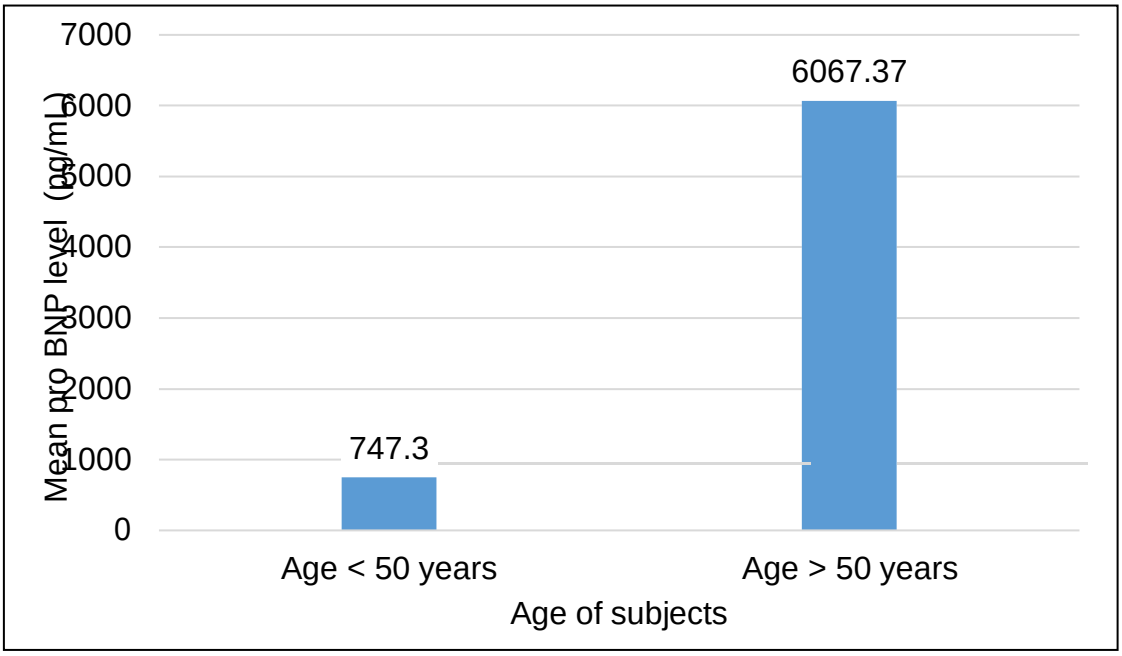


Figure 4: Frequency distribution of pro-BNP levels according to the age of the study population

Association between gender of the research population and pro-BNP

The association between pro-BNP levels in subjects according to their gender was evaluated. The mean of Nt pro-BNP level in male patients was 4544.27 ± 7987.81 pg/mL and in female patients was 4295.07 ± 5321.71 pg/mL. There is no statistically significant correlation between Nt pro-BNP plasma levels of males and females. ('t'=0.118**,** 'p' =0.452)

Table 7: Frequency distribution of pro-BNP levels according to the gender of the study population

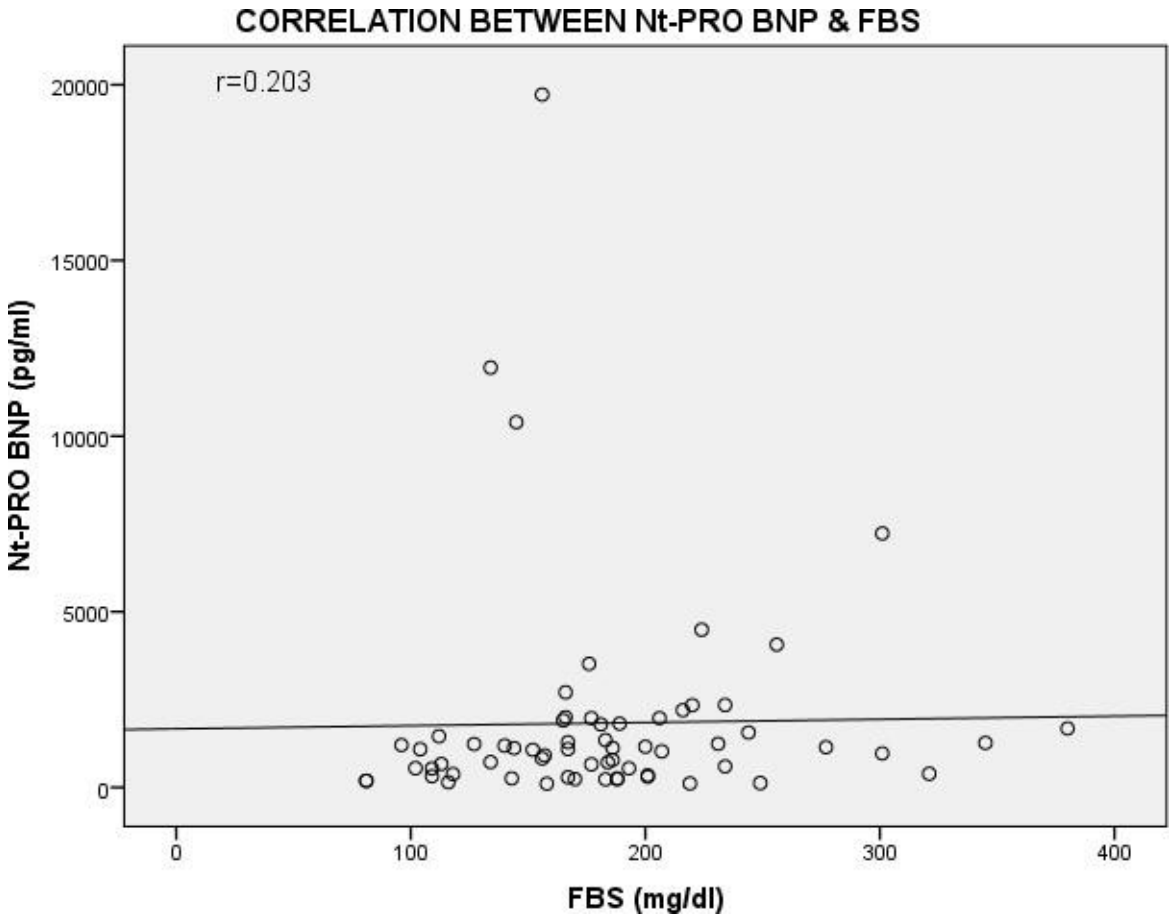
Gender	**Mean ± SD**	**'t'- value**	**'p-value**
Males	4544.27 ± 7987.81	0.118	0.452
Females	4295.07 ± 5321.71		

Association between fasting blood sugar level and pro BNP level

The association between fasting blood sugar level (FBS) and the pro-BNP level was studied. There was a significant positive correlation present between the fasting blood sugar level and pro-BNP level ('r'= 0.203; 'p' = 0.108).

Table 8: Association between fasting blood sugar level and pro-BNP

Pearson's correlation coefficient		**FBS**
pro BNP (pg/mL)	'r' value	0.203
	'p' value	0.108

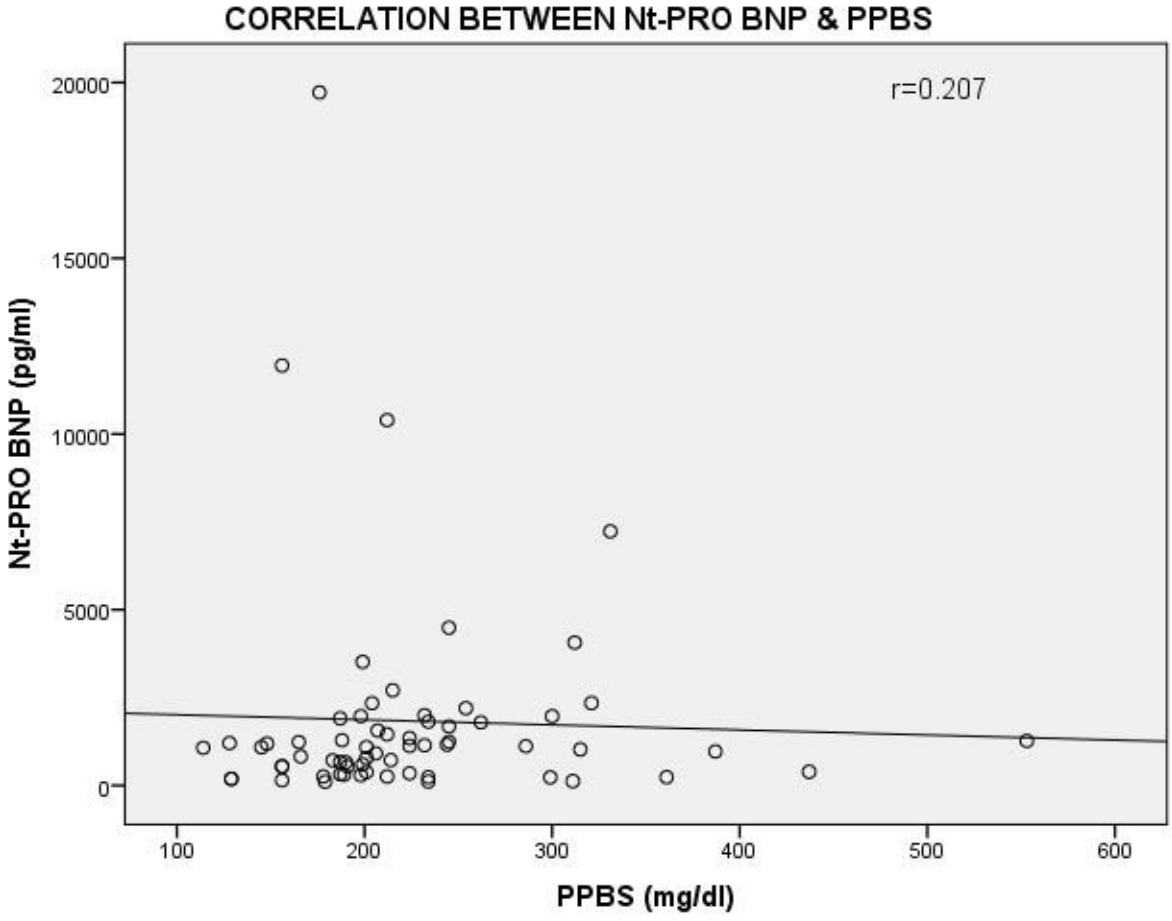


Association between postprandial blood sugar and pro-BNP level

The association between postprandial blood sugar (PPBS) and the pro-BNP level was studied. A positive correlation was found between postprandial blood sugar and pro BNP level ('r'= 0.207; 'p' = 0.101).

Table 9: Association between postprandial blood sugar and pro-BNP level

Pearson's correlation coefficient		**PPBS**
pro BNP (pg/mL)	'r' value	0.207
	'p-value	0.101



Association between pro-BNP and HbA1c level

Mean Nt pro-BNP levels in patients with a glycosylated hemoglobin level of less than seven percent was 927.85±3662.094 pg/mL, and in those with a glycosylated hemoglobin level of more than seven percent was 5486.6±7635.7671 pg/mL. This correlation was found to be significant ('r'-2.214**,** 'p'=0.016)

Table 10: Frequency distribution of pro BNP levels in subjects based on HbA1c levels

HbA1c	Mean ± SD	'r' value	'p-value
< 7%	927.85 ± 3662.094	-2.214	0.016
> 7%	5486.6 ± 7635.767		

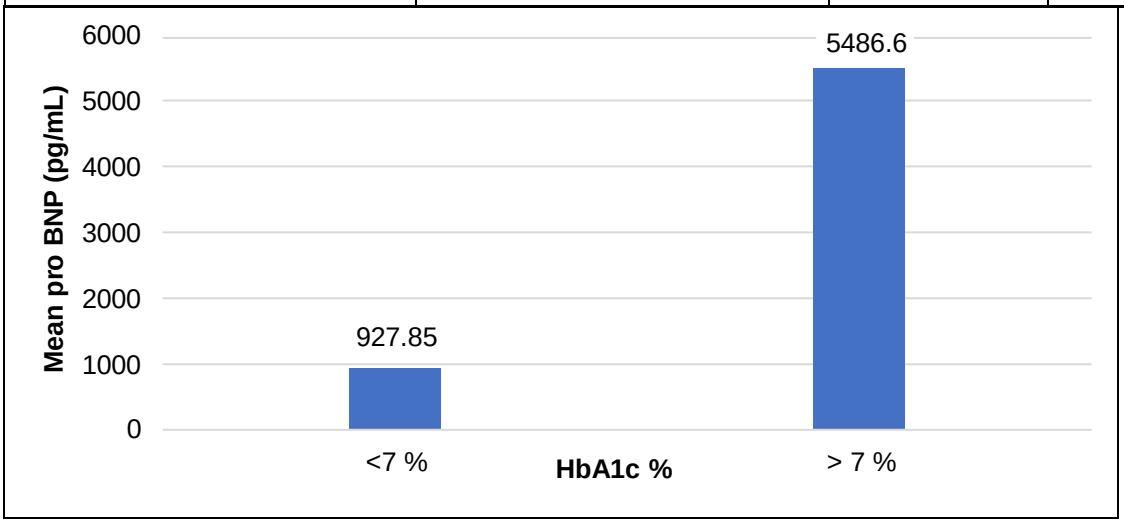


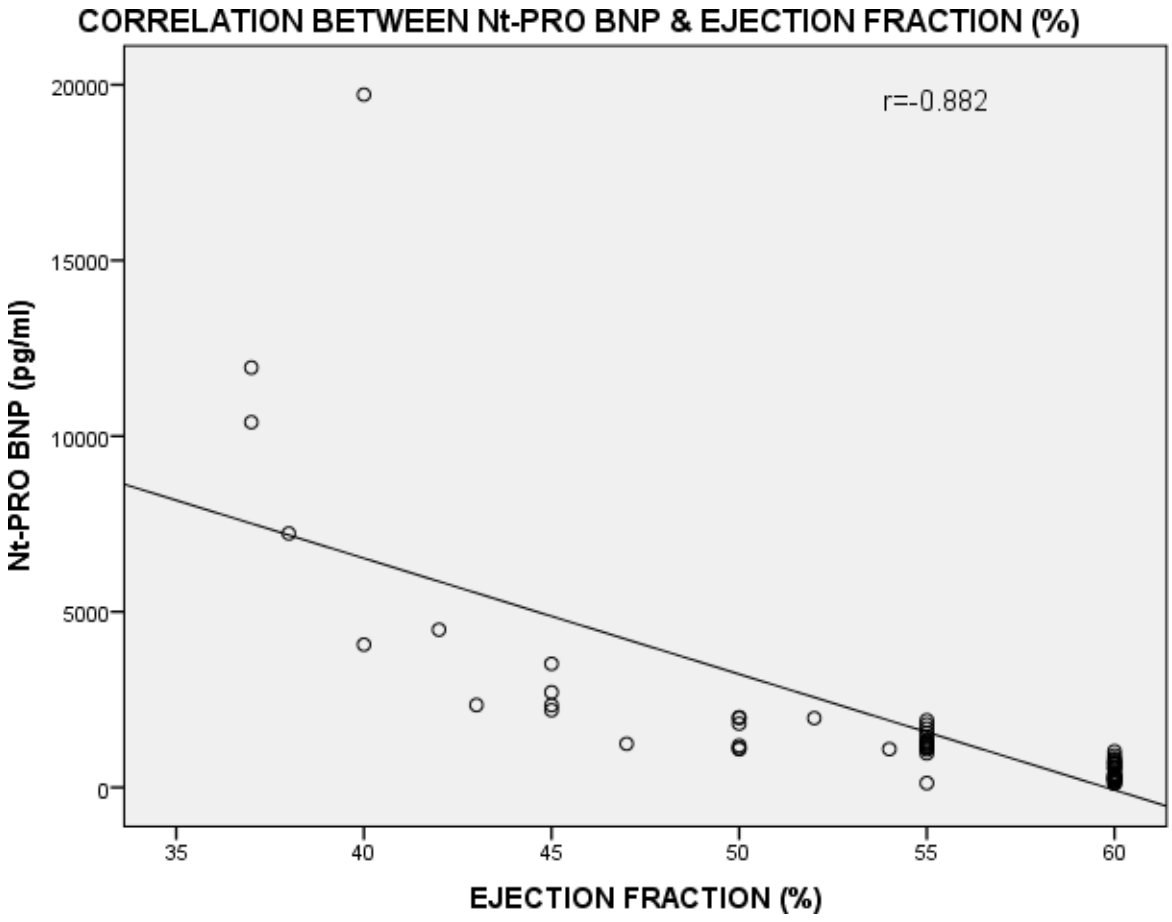
Figure 7: Frequency distribution of pro BNP levels in subjects based on HbA1c levels

Association between LVEF and Nt pro-BNP

The association between LVEF and serum Nt pro-BNP level was evaluated with Pearson's correlation coefficient. A negative correlation was found between LVEF and Nt pro-BNP level ('r'-0.882; 'p' < 0.001).

Table 11: Association between LVEF and pro BNP

Pearson's correlation coefficient		**LVEF**
BNP (pg/mL)	'r' value	-0.882
	'p' value	<0.001



Association between serum triglycerides and pro BNP

The association between serum triglycerides and pro BNP was studied. A positive correlation was found between triglycerides and pro BNP levels ('r'= 0.106; 'p'= 0.502).

Table 12: Association between serum triglycerides and pro BNP

Pearson's Correlation Coefficient		**Triglycerides**
Nt pro-BNP (pg/mL)	'r'- value	0.106
	'p' - value	0.502

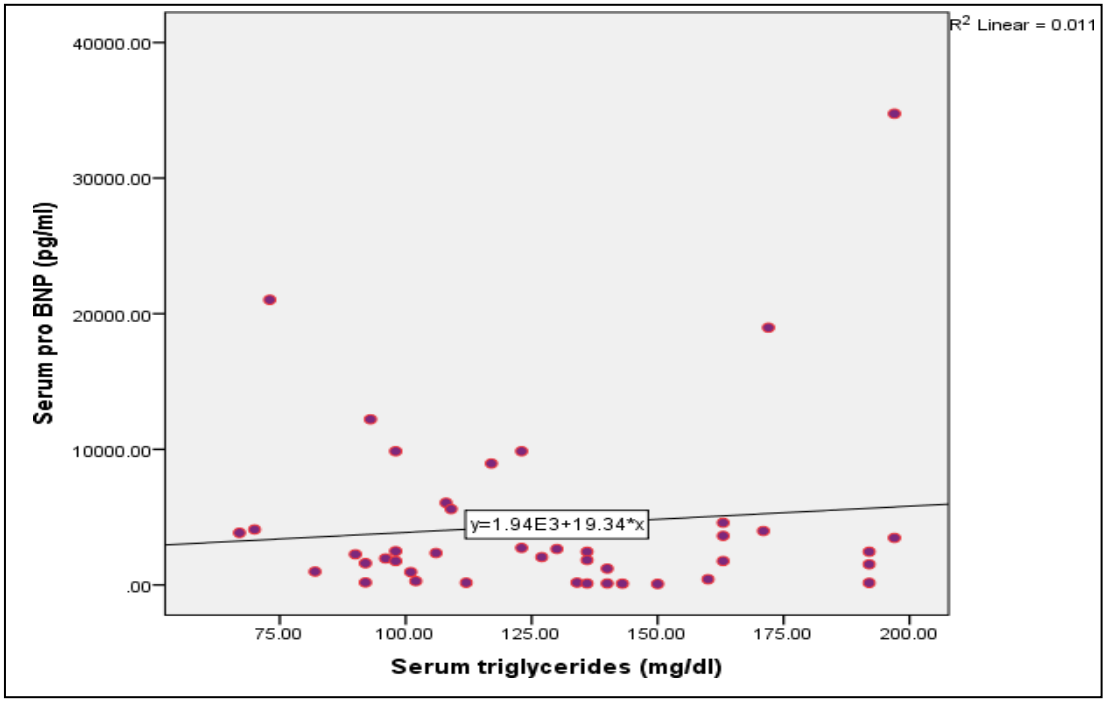


Figure 9: Graph showing association between serum triglycerides and pro BNP

Association between serum total cholesterol and pro-BNP

The association between serum total cholesterol and pro-BNP was studied. A positive correlation was found between total cholesterol and serum pro BNP levels. ('r'= 0.023; 'p'= 0.887)

Table 13: Association between serum total cholesterol and pro-BNP

Pearson's Correlation Coefficient		**Total cholesterol**
Nt pro-BNP (pg/mL)	'r'- value	0.023
	'p - value	0.887

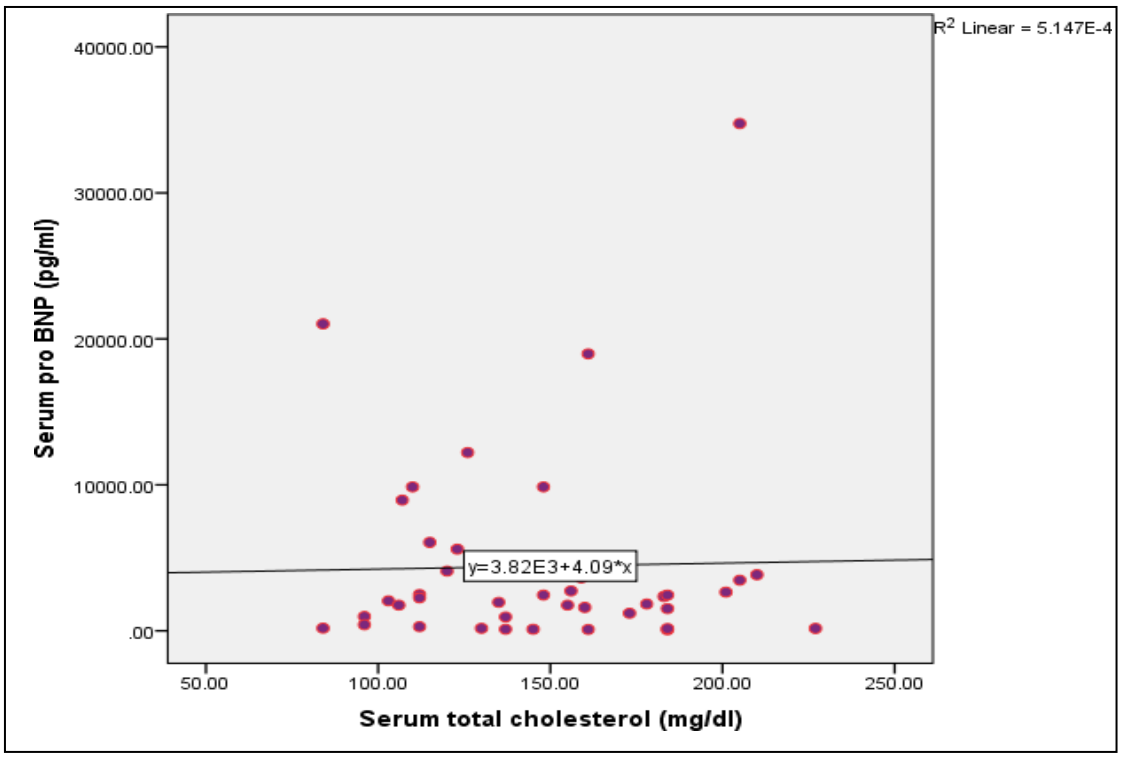


Figure 10: Graph showing association between serum total cholesterol and pro BNP

Association between plasma HDL and plasma Nt pro-BNP levels.

The association between plasma HDL level and plasma Nt pro-BNP levels was studied. A negative correlation was found between plasma HDL level and plasma pro BNP levels. ('r'- 0.082; 'p'= 0.604)

Table 14: Association between serum HDL level and serum pro BNP level

Pearson's Correlation Coefficient		**HDL**
Nt pro-BNP (pg/mL)	'r'- value	-0.082
	'p'- value	0.604

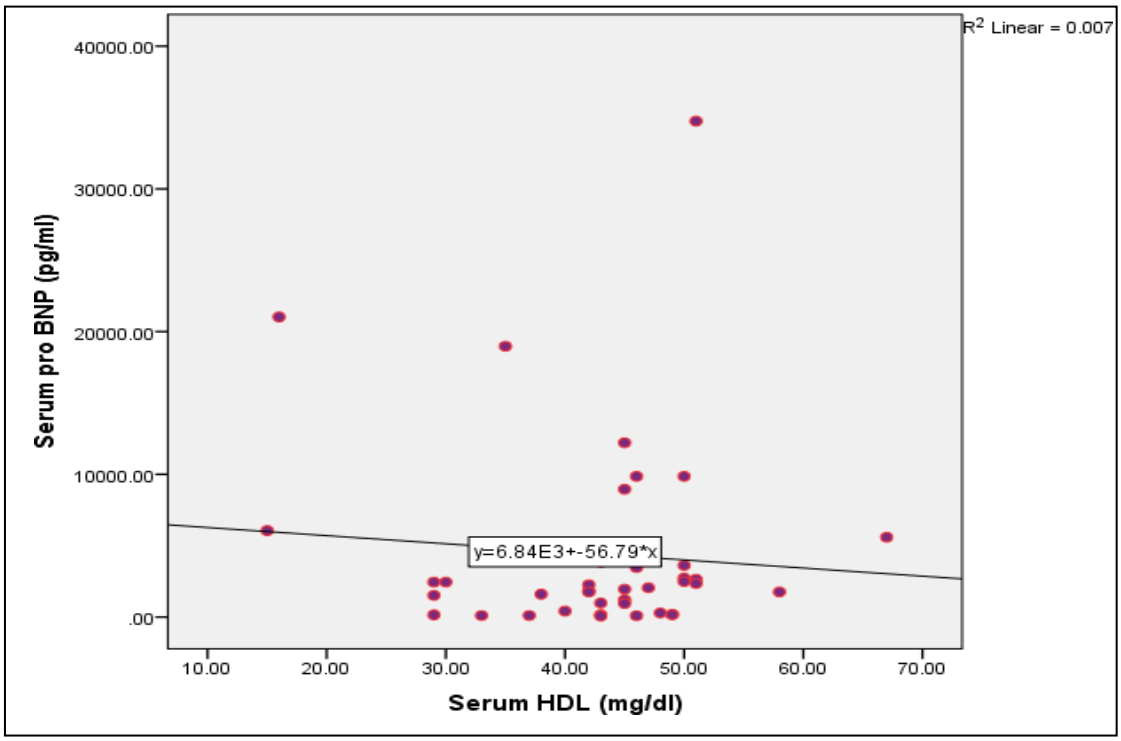


Figure 11: Graph showing association between serum HDL and pro BNP

Association between serum LDL and pro-BNP

The association present between plasma LDL level and plasma pro BNP level was studied. A weak correlation was found between serum LDL level and pro BNP level. ('r'=0.519; 'p'< 0.001)

Table 15: Association between serum LDL and pro BNP level

Pearson's Correlation Coefficient		**LDL**
Nt pro-BNP (pg/mL)	'r'- value	0.519
	'p'- value	<0.001

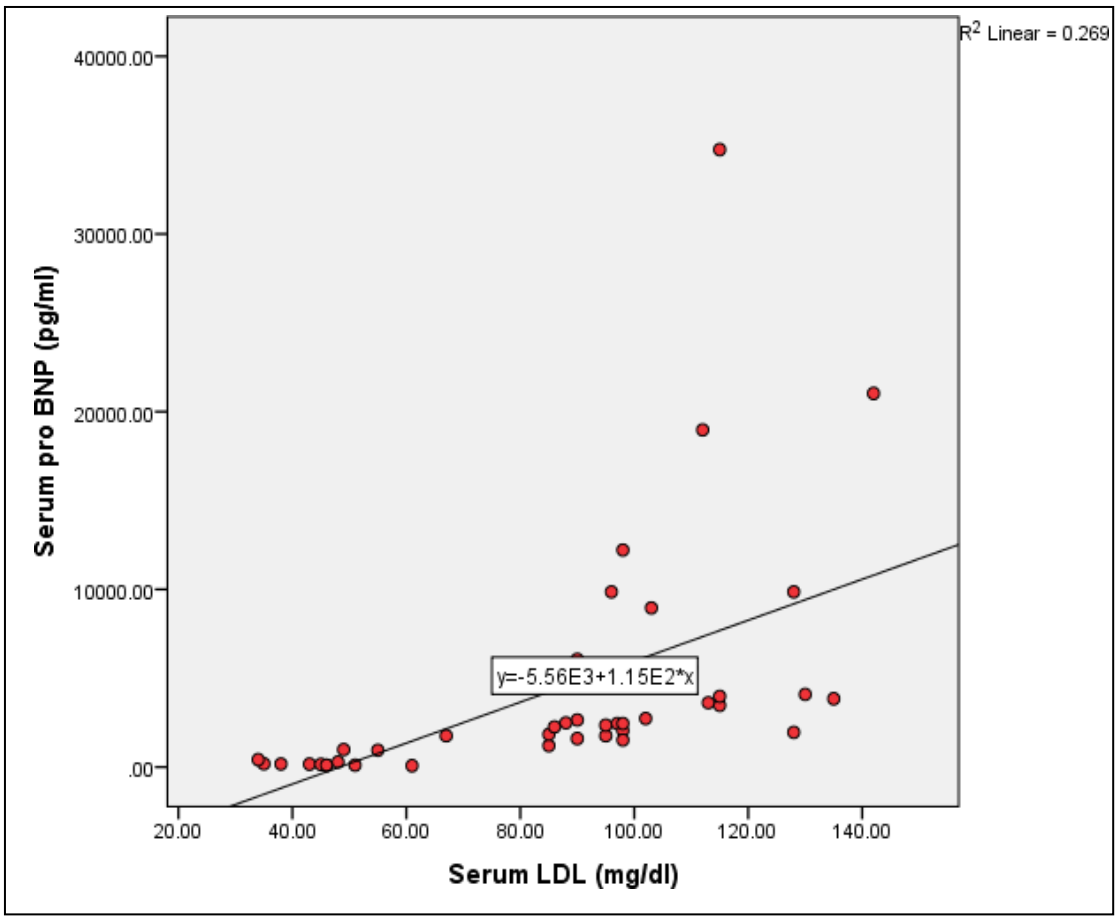


Figure 12: Graph showing association between serum LDL and pro BNP

Association between serum VLDL level and pro BNP level

The association between serum VLDL level and pro BNP level was studied. A positive correlation was found between serum LDL level and pro-BNP level. ('r'=0.111; 'p'= 0.483)

Table 16: Association between serum VLDL and pro-BNP level

Pearson's Correlation Coefficient		**VLDL**
Nt pro-BNP (pg/mL)	'r'- value	0.111
	'p - value	0.483

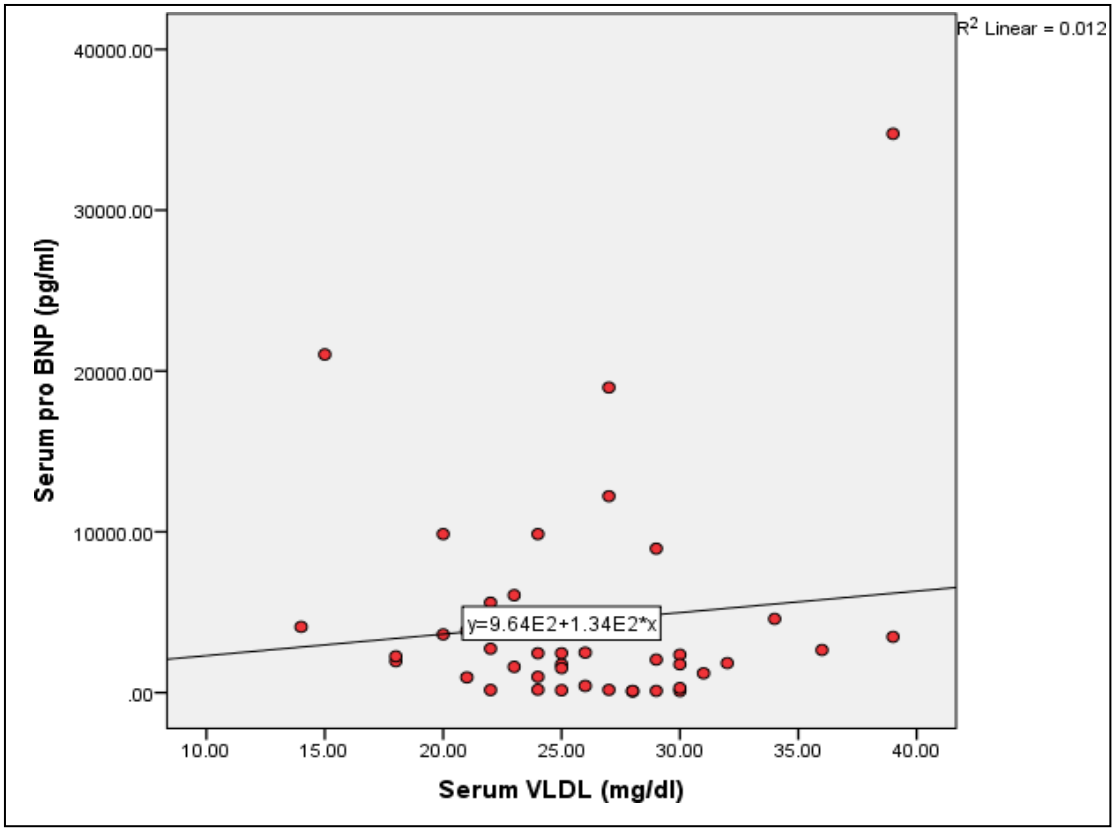


Figure 13: Graph showing association between serum VLDL level and pro BNP level

Association between Pulse rate and serum pro BNP level

The association between the pulse rate of the subjects and serum pro BNP level was studied. A positive correlation was found between pulse rate & serum pro-BNP levels ('r'= 0.029; 'p'= 0.854).

Table 17: Association between Pulse rate and pro-BNP

Pearson's Correlation Coefficient		**Pulse rate**
Nt pro-BNP (pg/mL)	'r'- value	0.029
	'p - value	0.854

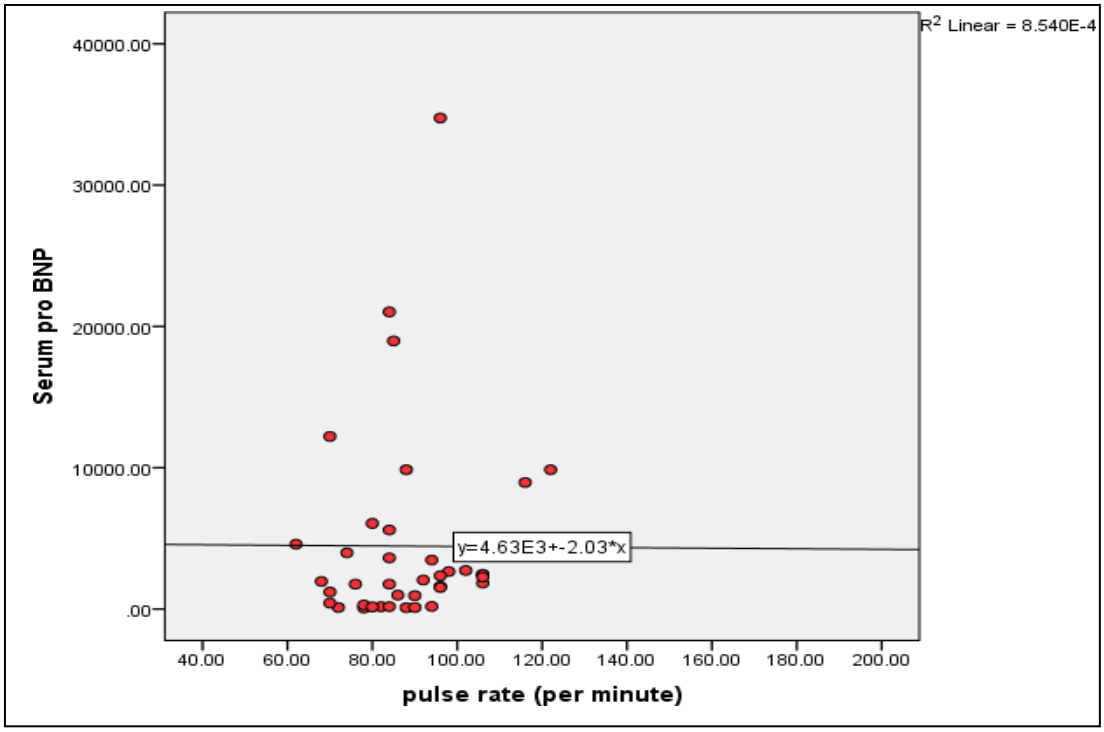


Figure 14: Graph showing association between Pulse rate and pro BNP

Association between systolic blood pressure, diastolic blood pressure and pro BNP

The association between SBP, DBP of the subjects & serum Nt pro-BNP level was studied. A positive correlation was found between pro-BNP and SBP ('r'= 0.455; 'p' =0.0021); while there was very weak positive correlation between pro BNP level and DBP ('r'= 0.564; 'p'=0.001).

Table 18: Association between systolic blood pressure, diastolic blood pressure and pro BNP

Blood pressure	**'r' value**	**'p' value**
Systolic Blood Pressure	0.455	0.0021
Diastolic Blood Pressure	0.564	0.001

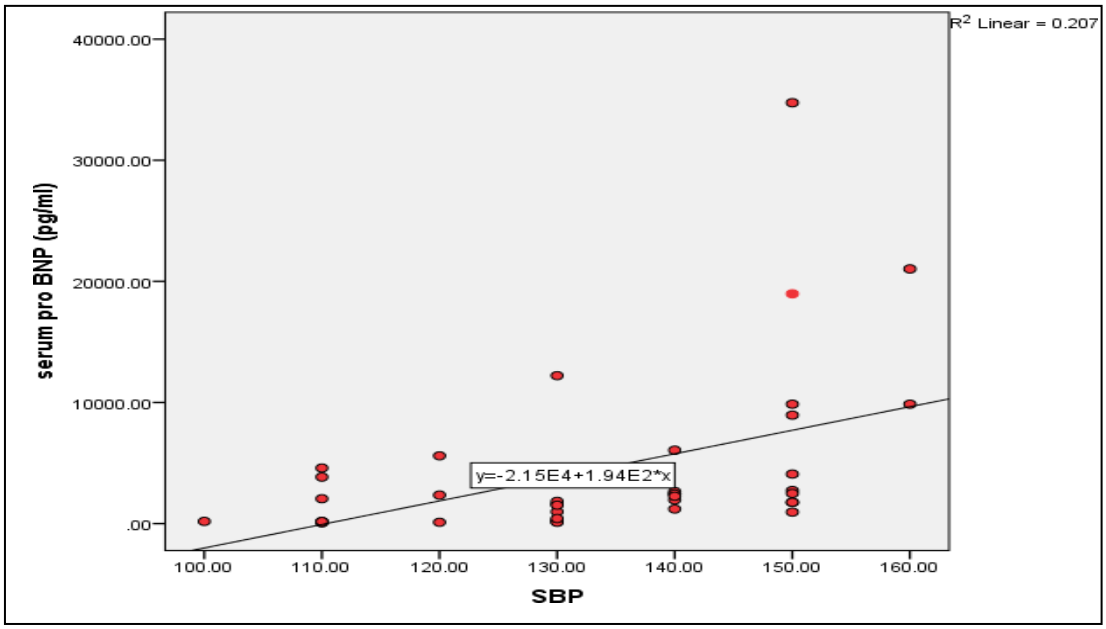


Figure 15: Graph showing association between systolic blood pressure and serum pro BNP level

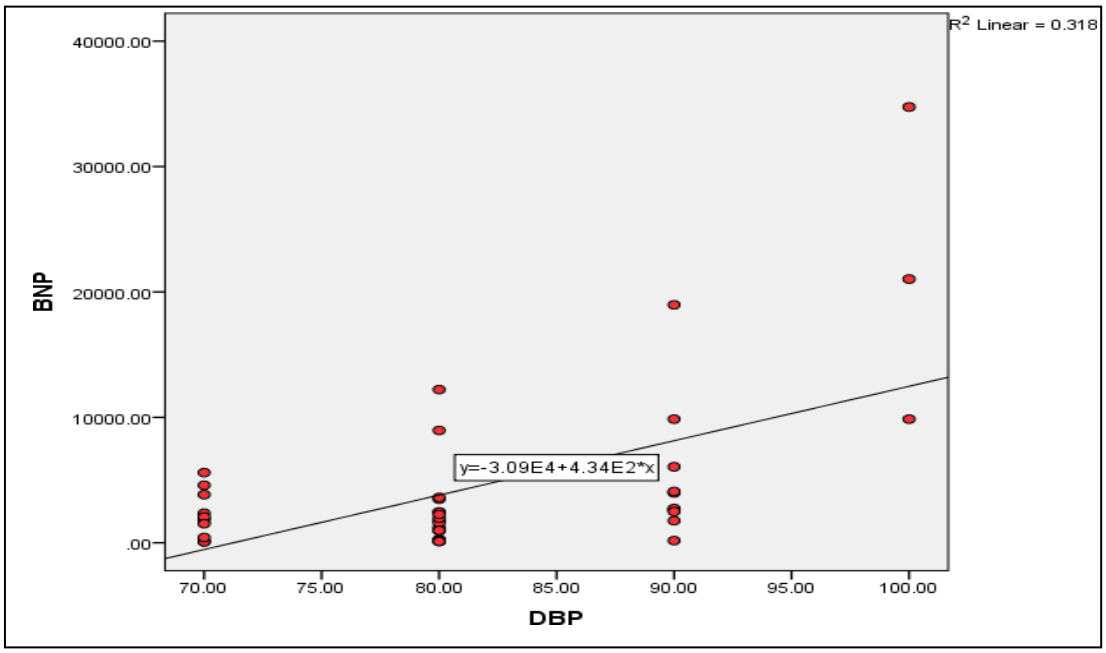


Figure:

Graph showing association between diastolic blood pressure and pro BNP

DISCUSSION

Diabetes mellitus is becoming more common every day in emerging nations like India. The primary reason for illness & mortality among people with diabetes mellitus is heart failure. In the present study, pro-BNP was studied and compared to results from different other studies.

Age distribution in the study group & the association with Nt pro-BNP

64 patients were selected for this prospective observational study. A total of 4 subjects were of less than 30 years age, 4 subjects were of 31 to 40 years age group, and 10 subjects were of 41 to 50 years age group, while 12 subjects were of 51 to 60 years age group, 22 subjects were between 61 & 70 years and all the remaining patients, above 70 years of age. Most of the patients were of age group above 50 years of age. It was found that the age of the study participants and pro-BNPBNP levels had a slight positive correlation. (P value is 0.031).

According to research conducted by Huei Gang et al., the mean age of the study population was 63 ± 9 years, and a positive correlation was found between pro-BNP levels & individuals' ages ('p' 0.05) [94]. Similarly, Kumiko Hamano et al. stated that the study population's mean age was 64.312 years, and that was a strong positive correlation between age and the pro-BNP level ('p'= 0.001) [105]. In a study, it was pointed out that the population's mean age was 58.6 years and that a strong positive correlation was there between age & the Nt pro-BNP level (p 0.001) [104]. The average age of the study population was 49 years and 13 months, according to Carsten Taschö pf et al. The connection between age and the pro-BNP level was weakly positive ('p'=0.061) [112]. Similar to what Rosiak M et al. observed, a positive correlation ('p' 0.01) was present between age and Nt pro-BNP levels [109]. The study population's mean age was 59.5 ± 6.8 years, according to Alain Bertoni et al. (p=0.05), and there was a significant positive correlation between age and the pro- BNP level [107]. Thus, the results of the studies mentioned above can be compared to those of the current study.

Sex distribution in the subjects and the association with Nt pro- BNP

34 (53%) and 30 (47%) of the 64 total study participants were men and women, respectively. The mean pro BNP level was 4544.27 ± 7988.81 pg/mL in men & 4296.08 ± 5321.71 pg/mL in women; there is no significant difference between the pro-BNP levels between the sexes (‘p'= 0.45). However, a study published by Kurshat Daal et al. revealed that females had higher amounts of pro-BNP than males [101]. These results could not be compared to the current study since Kurshat Daal et al. sample’s population was predominately female.

Distribution of the SBP, DBP and its association with pro-BNP

In the current study, the mean Systolic BP for men was 117.54±17.04 mm Hg, while the mean Systolic BP for women was 106.56±17.78 mm Hg. Although neither value showed a significant difference statistically (p=0.23), pro-BNPBNP levels were strongly positively correlated with both (p=0.002). Males had a mean DBP of 72.85± 7.83 mm Hg, whereas females had a mean DBP of 77.63±7.31 mm Hg. The difference in DBP between males and females and the slight positive correlation between DBP and pro-BNP levels (p = 0.72) were statistically significant.

Sasaki N. et al. study found a slight positive association between DBP and pro-BNP levels (‘p'=0.28) but a significant positive correlation between SBP and pro-BNP levels (‘p’0.001) [102]. According to Kurshat Daal, the mean Systolic Blood Pressure was 126.4 mm Hg on average and had a substantial positive correlation with the pro BNP level (‘p’ = 0.001); the mean Diastolic Blood Pressure was 84 mm Hg on average and had a similar correlation (‘p’ = 0.001) [106]. In a study of blood pressure variability in the Japanese population, Masugata et al. found that the mean SBP was 130±13 mm Hg and the mean DBP was 69±6 mm Hg. SBP and DBP had weak positive correlations with pro-BNP levels (‘p'=0.59 and ‘p'=0.45, respectively) [103]. The pro-BNP had a

strong positive correlation with SBP (‘p'=0.027) and a weak positive correlation with DBP (‘p'=0.45), according to a study by Kumiko Hamano et al. [105]. P Gaede et al. discovered a weakly positive association between DBP and pro-BNP level (‘p'=0.39) and a high positive correlation between SBP and pro-BNP (‘p'=0.002) [104]. The results of the earlier investigations can thus be compared to those of the current study.

Distribution of mean serum pro BNP levels in the study subjects and its correlation with diastolic function

A total of 64 patients with type 2 diabetes mellitus were taken up for the study. We observed that the subjects with normal diastolic function had mean pro BNP levels of 374.32 ± 220.793 pg/ml, while with grade I diastolic dysfunction had 1201.35 ± 258,552 pg/ml, with grade II diastolic dysfunction, had 1698.21 ± 578.522 pg/ml and with Grade III diastolic dysfunction had 7963.50 ± 5844.544 pg/ml. The P value of the correlation is 0.0001. There is a strong correlation between pro-BNP and diastolic dysfunction.

Distribution of FBS level and PPBS level and its association with the pro-BNP level

The association between fasting blood sugar level (FBS) and the pro-BNP level was evaluated with Pearson´s correlation coefficient. There was a positive correlation between fasting blood sugar level and pro BNP level (‘r’=0.203; ‘p’ 0.108). The association between postprandial blood sugar (PPBS) and the pro-BNP level was evaluated with Pearson´s correlation coefficient. There was a positive correlation between postprandial blood sugar and pro BNP level (‘r’= 0.207; ‘p’ = 0.101).

In a study of pro-BNP levels in diabetic patients in India, Ashok Sahu found a positive correlation between pro-BNP levels and FBS (‘p’ 0.001) [108]. Additionally, according to Mishra A et al. (p 0.001), FBS and pro-BNP levels showed a strong positive correlation FBS, and pro-BNP levels showed a strong positive correlation, according to Mishra A et al. (p 0.001) [101]. As a result, the study above and current studies and the present study were comparable.

Distribution of serum HbA1c level and the correlation with the pro-BNP levels

The mean pro BNP level in subjects with a glycosylated hemoglobin level of less than seven percent was 927.85±3662.094 pg/mL, and in those with a glycosylated hemoglobin level of more than seven percent was 5486.6±7635.7671 pg/mL. The correlation was statistically significant ('r'-2.214**,** 'p'=0.016)

In the studies that support the current research, Kurshat Daal found that the mean of HbA1c level was 11.1 ± 2.4% and that improved glycemic control resulted in a significant drop in pro-BNP level ('p'- 0.001). [106] Misurata also noted that pro-BNP levels and HbA1c positively correlated ('p'=0.002) [103]. Anuva Mishra et al. also reported a strong positive association between blood pro-BNP levels and serum HbA1c levels in their study. So, the research mentioned above can be compared to the current study's research (p'0.001) of the present study.

Distribution of lipid profile parameters in these research patients and its correlation with the pro-BNP levels

In the present study, the mean serum triglyceride level was 128.19 ± 36.89 mg/ dL, the mean total cholesterol level was 147.09 ± 37.16 mg/ dL, the mean HDL level was 42.64 ± 9.71 mg/ dL, the mean LDL level was 98.07 ± 31.35 mg/ dL, and the mean VLDL level was 25.83 ±5.57 mg/ dL. The pro-BNP level was correlated with various lipid profile parameters. The correlation between pro-BNP and total cholesterol was weakly positive ('p'=0.887), the correlation between pro-BNP and triglyceride levels was weakly positive ('p'=0.502), there was a negative correlation of pro-BNP and HDL levels ('p'=0.604), pro-BNP and LDL level had negative correlation ('p'=0.52) whereas pro BNP had weak positive correlation with VLDL ('p'=0.483).

SUMMARY

This study was a prospective, analytical, observational, non-interventional study conducted at Shri B M Patil Medical College, Hospital and Research center, Vijayapura. The study was conducted over a period of 18 months.

The following observations were made in this study:

1. A total of 64 patients admitted with the diagnosis of type 2 diabetes mellitus were included in the prospective observational study. Out of the total, males were 34 in number (53%), and females were 30 in number (47%). The mean value of pro-BNP in male patients was 4546.27 ± 7988.80 pg/mL, while in female patients, it was 4295.08 ± 5323.71 pg/mL, and it was not statistically significant ('p'=0.452).
2. The mean age of the study population was 55.50 (±12.32) years. The mean pro-BNP level in subjects with age less than 50 years was 747.3 pg/mL, while in subjects with age more than 50 years was 6067.37 pg/mL and the association between them was statistically significant ('t'-2.52, 'p'=0.007). There was a weak positive correlation between pro BNP level and the age of the subjects. ('r'= 0.334; 'p'= 0.031)
3. In the study population, the mean pulse rate among males was 88.77 (± 12.45) per minute, while among females, it was 90.28 (±15.95) per minute, and there was a weak positive correlation between pulse rate and pro-BNP levels ('r'=0.029).
4. The mean systolic blood pressure among the male patients was 129.51 (±16.01) mm Hg, while among the female patients was 118.56 (±14.76) mm Hg; the mean diastolic blood pressure among male patients was 74.86 (±7.84) mm Hg, and among the female patients was 78.62 (± 8.32). There was a moderate positive correlation between pro-BNP with SBP and DBP ('r'=0.45, 'r'=0.56 respectively).
5. The mean fasting blood sugar level among males was 187.52 ± 73.95 mg/dL and among

females was 184.90 ± 56.65 mg/dL and there was a statistical significance among them ('p'=0.108). The mean postprandial blood sugar level among males was 203.57 ± 52.17 mg/dL and among females was 203.80 ± 54.19 mg/dL, and it was statistically significant ('p'=0.101). There was a moderate positive correlation of pro BNP with fasting BSL ('r'=0.203) and a weak positive correlation of pro BNP with postprandial BSL ('r'=0.207).

6. The mean HbA1c of males was 8.57 ± 2.20 % and the mean HbA1c of females was 8.17 ± 2.30 %. The mean HbA1c was not statistically significant ('p'=0.480) among males and females. The mean pro-BNP in subjects with HbA1c <7% was 927.85 ± 3662.094 pg/mL, and in subjects with HbA1c >7% was 5486.6 ± 7635.767 pg/mL, this was found to statistically significant ('p'=0.01). There was a positive correlation between pro BNP levels and HbA1c ('r'=0.48).
7. The mean triglyceride level was 128.19 (± 36.89) mg/dL, the mean total cholesterol level was 147.09(±37.16) mg/dL, the mean HDL level was 42.64 (± 9.71) mg/dL, the mean LDL level was 98.07 (± 31.35) mg/dL and the mean VLDL level was 25.83 (± 5.57) mg/dL.
8. The mean level of pro-BNP in male patients was 4546.27 (±7979.81) pg/mL, and in female patients was 4388.4 (±5332.71) pg/mL. There was no statistical significance of pro-BNP level among males and females ('p'= 0.44).
9. The mean LVEF among male patients was 43.30(± 11.92) % and among female patients was 44.71 (± 13.75) %. There was no statistical significance of LVEF among males and females ('p'=0.66). It had a negative correlation with pro-BNP ('r = -0.882).
10. Total of 25 subjects had a normal diastolic function; 17 subjects had grade I diastolic dysfunction; 14 subjects had grade II diastolic dysfunction; 8 subjects had grade III diastolic dysfunction. There was a strong positive correlation between pro-BNP and

grades of diastolic dysfunction ('r'= 0.47). The p-value of the correlation was < 0.0001, which is statistically significant

CONCLUSION

Heart failure has a high-risk factor associated with type 2 diabetes mellitus. Indeed, the prevalence of heart failure in the Indian population would eventually reflect the overall situation due to the rise in type 2 diabetes mellitus patients in India. In light of this, the current study assessed the relationship between the plasma Nt pro-BNP levels & several variables in individuals with diabetes. According to a linear regression study, there was a significant correlation between Nt pro-BNP values and systolic blood pressure and the diastolic blood pressure, the diabetes mellitus duration, HbAIC levels, elevated fasting (FBS) and postprandial (PPBS) blood sugar levels, and elevated triglyceride levels. Grades of diastolic dysfunction and pro-BNP BNP had a positive correlation, and LVEF pro-BNP BNP had a negative correlation. This study can therefore infer that measuring the levels of Nt pro-BNP in patients with diabetes will therefore be helpful in the early detection of heart failure and predicting its prognosis and adverse outcomes.

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PROFORMA

Name: I.P./OPNo.:

Age: Hospital:

Sex: Address:

HISTORY

Chief complaint

BRIEF HISTORY OF PRESENTING ILLNESS

PAST AND ASSOCIATED ILLNESS

FAMILY HISTORY:

PERSONAL HISTORY:

Diet

Appetite

Sleep

Bowel and bladder

General physical examination

Pulse

BP

Temp.

RR

Height

Weight

SYSTEMIC EXAMINATION

Cardiovascular system:-

Central nervous system:-

Respiratory system:-

Per abdomen examination:-

PROVISIONAL DIAGNOSIS

Treatment detail

INVESTIGATION:

FBS: mg/dL

PPBS: mg/dL

HbA_1c: %

Urea: mg/dL

Creatinine: mg/dL Urine Routine:

Serum fasting insulin

Hematological

Hemoglobin

TLC/DLC

Glycosylated hemoglobin

X-ray chest (P.A.) view

Electrocardiogram

FINAL DIAGNOSIS:

DATE:

SIGNATURE

B.L.D.E. (DEEMED TO BE UNIVERSITY) IEC/NO-09/2021 Date-22/01/2021

(Declared vide notification No. F.9-37/2007-U.3 (A) Dated. 29-2-2008 of the MHRD, Government of India under Section 3 of the UGC Act, 1956)

The Constituent College

SHRI. B. M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Institutional ethical committee of this college met on 11-01-2021 at 11am to scrutinize the synopsis of Postgraduate students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has been accorded Ethical Clearance

Title: NT Pro Brain in Natriuretic peptide (NT RPO BNP) levels in Type 2 Diabetes patients without any cardiovascular diseases

Name of PG student: Dr Sai Santosh Jajimi, Department of Medicine

Name of Guide/Co-investigator: Dr S S Devarmani, Professor of Medicine

DR .S.V.PATIL
CHAIRMAN
Institutional Ethical Committee
B L D E (Deemed to be University)
Shri B.M. Patil Medical College,
VIJAYAPUR-586103 (Karnataka)

Following documents were placed before Ethical Committee for Scrutinization:

1. Copy of Synopsis / Research project
2. Copy of informed consent form
3. Any other relevant documents.

11

INFORMED CONSENT FORM:

TITLE OF RESEARCH: A STUDY OF PRO BNP (BRAIN NATRIURETIC PEPTIDE) IN TYPE 2 DIABETES MELLITUS PATIENTS WITHOUT CARDIOVASCULAR DISEASE.

GUIDE: **DR S S DEVARAMANI (**M.D GENERAL MEDICINE)

P.G. STUDENT: **DR SAI SANTOSH JAJIMI**

All aspects of this consent form are explained to the patient in the language understood by them.

PURPOSE OF STUDY:

I have been informed that the purpose of this study is to estimate Nt PRO BNP levels in asymptomatic cardiac type 2 diabetes mellitus patients.

PROCEDURE:

I understand that I will undergo a detailed history and clinical examination and investigations.

BENEFITS:

I understand that my participation in this study will have no direct benefit to me other than the potential benefit of treatment, which is planned to prevent further morbidity and mortality.

CONFIDENTIALITY:

I understand that the study's medical information will become a part of hospital records and will be subjected to confidentiality and privacy regulation of the hospital. If the data is used for publication, the identity will not be revealed.

REQUEST FOR MORE INFORMATION:

I understand that I may ask for more information about the study at any time.

WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary, and I may refuse to participate or withdraw from the study at any time.

(Signature of Guardian) (Signature of the patient)

MASTER CHART CODING:

Diastolic function	Normal	0
	Grade I Diastolic Dysfunction	1
	Grade II Diastolic Dysfunction	2
	Grade III Diastolic Dysfunction	3

MASTER CHART

	B	C	D	F	G	H	I	J	K
1	Name	Age (Years)	Sex	FBS (mg/dl)	PPBS (mg/dl)	HbA1C (%)	Nt-PRO BNP (pg/ml)	DIASTOLIC DYSFUNCTIO	EJECTION FRACTION (%)
3	Rachappa Dundrappa	61	M	231	245	10	1243	2	47
4	Gurubasayya Irayya	65	M	134	156	6.3	11951	3	37
5	Parasanar Bhimappa	35	M	301	387	15.6	967	1	55
6	Renuka M Belkod	48	F	167	201	5.8	1092	1	54
7	Mallama Biradar	63	F	224	245	7	4489	3	42
8	Devakki Ningappa	55	F	156	166	5.5	822	0	60
9	Niyaz Siraju Inamdar	34	M	234	321	12.1	2345	3	43
10	Shamala Prabhakar Ku	68	F	145	212	8.3	10393	3	37
11	Devu Pawar	68	M	177	198	8.9	1970	2	52
12	Kasturi Sangayya	64	F	109	187	9.9	318	0	60
13	Bhavani Kumbar	20	F	201	189	5.6	304	0	60
14	Babu Pawar	50	M	156	176	10	19718	3	40
15	Bheemappa Wadayar	57	M	167	188	7.9	1288	1	55
16	Sharada Patil	65.00	F	109.00	156.00	5.60	537.00	-	60.00
17	Laxmibai Sharnappa	65	F	104	145	6.1	1088	2	50
18	Ningappa	73	M	181	262	9.7	1793	1	55
19	Sudhindra Shamarao	64	M	189	234	6.8	1814	2	50
20	Gurubasappa	70	M	177	190	7.1	657	1	60
21	Sidamma Hunnur	60	M	165	187	8.5	1908	2	55
22	Vaishali	41	F	216	254	8.1	2200	2	45
23	Allabi Dastageenab	70	F	176	199	6.8	3518	3	45
24	Shivashankar Gollapp	50	M	256	312	11.9	4065	3	40
25	Chandrashekar Ratho	70	M	134	214	7.6	721	0	60
26	Belagavi S G	73	M	166	232	11.2	1998	2	50
27	Rajeshwari Pujari	25	F	167	198	6.9	289	0	60
28	Geetha S Patel	39	F	118	201	6.9	378	0	60
29	Sheik Jainu	65	M	96	128	6	1205	1	55
30	Shankar Gouda	42	M	81	129	6.5	188	0	60
31	Saraswati	70	F	301	331	13	7229	3	38
32	Gurupadrappa	66	M	127	165	7.3	1234	1	55
33	Siddamma Vandar	65	M	321	437	14.1	390	0	60

	B	C	D	F	G	H	I	J	K
1	Name	Age (Years)	Sex	FBS (mg/dl)	PPBS (mg/dl)	HbA1C (%)	Nt-PRO BNP (pg/ml)	DIASTOLIC DYSFUNCTIO	EJECTION FRACTION (%)
30	Shankar Gouda	42	M	81	129	6.5	188	0	60
31	Saraswati	70	F	301	331	13	7229	3	38
32	Gurupadrappa	66	M	127	165	7.3	1234	1	55
33	Siddamma Vandar	65	M	321	437	14.1	390	0	60
34	Devendrappa	55	M	186	201	6.1	782	0	60
35	Laxman	74	M	158	179	12.6	104	0	60
36	Mamataj Begam	70	F	219	234	6.4	112	0	60
37	Shankargouda	44	M	81	129	6.5	188	0	60
38	Subbaratnamma A	72	F	183	224	10.1	1347	1	55
39	Sunanda G	60	F	249	311	13	123	0	55
40	Mahesh Dashwant	45	M	188	212	8.9	252	0	60
41	Sangamma	45	F	157	206	10	912	1	60
42	Laxmibai	54	F	201	224	8.8	345	0	60
43	Mahamma	65	F	183	299	7.7	231	0	60
44	Drakshayani	65	F	207	315	7.7	1025	1	60
45	Kenchamma	46	F	277	232	12.6	1145	1	55
46	Ashok	55	M	188	234	10.1	234	0	60
47	Shivabai	70	F	184	183	7.7	716	0	60
48	Shivaganga	57	F	140	148	8.9	1189	1	50
49	Siddappa	64	M	220	204	8.9	2341	2	45
50	Bhimray	57	M	144	286	7.9	1117	2	50
51	Firam	62	F	193	191	7	542	0	60
52	Niyaz	34	M	152	114	13.2	1072	2	55
53	Ashok Gowda	66	M	200	244	7.9	1160	1	55
54	Hanumanth	48	M	143	178	7.2	256	0	60
55	Mahananda	45	F	116	156	7.6	145	0	60
56	Lakshmibai	58	F	113	187	6.4	668	2	60
57	Devu Pawar	68	M	206	300	12.1	1970	2	50
58	Yamanappa	60	M	112	212	9.9	1456	1	55
59	Basappa Talawar	56	M	166	215	11	2708	2	45
60	Somala	72	F	102	156	7	546	0	60
61	Aishwarya	29	F	170	361	9.4	236	0	60
62	Mohnish	56	M	244	207	7.8	1564	1	55
63	Annapurna Koli	74	F	380	245	10.4	1678	2	55
64	Padeppa Sonad	62	M	345	553	13.3	1266	1	55
65	Jayawant Laxman	24	M	234	199	11	599	0	60