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ORIGINAL A R T I C L E

Evaluation of N-terminal pro-atrial natriuretic peptide and Soluble ST2 as Predictors for Cardiovascular Diseases in Patients with Type 2 Diabetes in Al-Basra, Iraq

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Abstract

Background Cardiovascular disease (CVD) is an umbrella term for a group of illnesses that have an adverse effect on the cardiovascular system. Diabetic cardiomyopathy and atherosclerotic CVD, which may cause heart failure via myocardial infarction and chronic pressure overload, are prevalent metabolic disorders associated with type 2 diabetes mellitus (T2DM).
The Aim Examine the connection between the amount of serum N-terminal pro-atrial natriuretic peptide and Soluble ST2 in patients with type 2 diabetes who have cardiovascular diseases.
Material and Method Examine the connection between the amount of serum N-terminal pro-atrial natriuretic peptide and Soluble ST2 in patients with type 2 diabetes who have cardiovascular diseases.
Results The research findings demonstrated a rise in the N-terminal pro-atrial natriuretic peptide levels in patients with cardiovascular disease (CVD) and diabetes mellitus (DM) compared to those with just DM and the control group. Furthermore, there was a notable disparity in concentrations across the different study groups, with a p-value of less than 0.0001. Furthermore, the findings of this research demonstrated a rise in the concentration of Soluble ST2 in patients with both cardiovascular disease (CVD) and diabetes mellitus (DM) as compared to those with just DM and the control group. There was a notable disparity in the levels of Soluble ST2 across the different groups in the research (p-value <0.0001).
Conclusion Based on the findings of this research, it can be inferred that N-terminal pro-atrial natriuretic peptide and Soluble ST2 have the potential to serve as practical and straightforward indicators for predicting the coexistence of insulin resistance, dysglycemia, and Cardiovascular Diseases in seemingly healthy individuals within the young (<50 years) Al-Basra community.

Keywords: BNP; sST2, Cardiovascular Disease; Diabetes Mellitus and Inflammation

1 Introduction

Long-term cholesterol buildup in coronary arteries causes atherosclerosis and necrosis of heart tissue,

leading to coronary heart disease (CHD). Atherosclerosis's hallmark lesion is the intimal plaque. The formation of a plaque requires the accumulation of lipids, both within macrophages and freely in the tissues, as well as the proliferation of smooth muscle cells and the generation of collagen. A plaque forms as a result of all these events; it has an extracellular lipid core surrounded by a fibrous collagenous shell [1]. Different diseases have different underlying processes. Dietary risk factors are believed to account for 53% of deaths from CVD. Peripheral artery disease, cardiovascular disease, and stroke are all linked to atherosclerosis [2]. Causes include, but are not limited to, stress, anxiety, depression, poor diet, excessive alcohol use, and poor-quality sleep. One in every thirteen deaths from cardiovascular disease is attributed to hypertension, followed by smoking (9%), diabetes (6%), inactivity (6%), and obesity (5%). Rheumatic heart disease may develop if strep throat is not treated [3]. The presence of inflammation inside the blood artery wall initiates endothelial dysfunction, which serves as the first stage in the progression of atherosclerosis. Inflammatory reactions, cell proliferation, and vasculature remodelling help to create atherosclerotic plaques, which are subsequently followed by a range of events, including plaque rupture, thrombosis, and tissue infarction [4].

Obesity and inflammation are closely linked to atherosclerosis, the primary cause of CVD. Foam cell and plaque development on the arterial wall are exacerbated by inflammation and dysregulated lipoprotein metabolism. Secreted by fatty tissue, adipokines influence systemic lipid, glucose, and inflammatory profiles. The dysregulation of adipokine secretions, such as adiponectin, resistin, visfatin, TNF-α, and IL-6, is a direct result of obesity and malfunctioning adipose tissue. Atherosclerosis is exacerbated by the injection of IL-6, and vascular adhesion molecules are upregulated by TNF-α [5, 6].

Diabetes mellitus (DM) is a set of metabolic disorders marked by elevated blood glucose levels caused by either reduced insulin production or inadequate insulin action [7]. Chronic hyperglycemia, or diabetes mellitus, is related to long-term complications, including vision loss, renal failure, nerve damage, heart failure, and blood vessel disorders. DM develops as a result of a combination of events, including autoimmunity that results in the death of the β cells of the pancreas, resulting in insulin insufficiency, and abnormalities that result in resistance to insulin's actions [8].

The incidence of diabetes is seeing a significant surge; it has been projected that the global incidence would rise by over 50%. Diabetes mellitus is a genetically diverse collection of illnesses characterized by a shared resistance to glucose, indicating that it is not a single disease. The introduction of the notion of genetic heterogeneity, which refers to the idea that several genetic and environmental variables may lead to comparable phenotypes, has had a profound impact on the genetic study of this prevalent condition [9].

Soluble ST2 (sST2) is categorized as a component of the interleukin 1 receptor family, often known as interleukin 1 receptor-like 1 (IL1RL-1) [10]. ST2 stands for "suppression of tumorigenicity 2". It was discovered in 1989, but only in 2002 Weinberg et al. [11]. Studies have shown that cardiac cells have the capacity to generate it as a reaction to myocardial stress, therefore drawing the interest of experts about its potential significance in the cardiovascular system. The two primary isoforms of ST2 are the transmembrane or cellular version (ST2L) and the soluble or circulating variant (sST2) [10].

The neurohormone B-type natriuretic peptide (BNP), a neurohormone, plays a crucial role in regulating cardiovascular function [12]. BNP is mostly produced in the ventricular myocardium, with some synthesis taking place in the atrial myocardium and the brain. Production is stimulated in the ventricles by the activation of stretch receptors. The pro-B-type natriuretic peptide acts as a precursor protein and is cleaved to produce BNP and the N-terminal pro-B-type natriuretic peptide (NT-proBNP). These two peptides are later detected in the bloodstream inside the plasma [13, 14].

2 Materials and Methods

2.1 The ethical considerations

The study included the acquisition of blood samples and the use of experimental techniques, both of which were authorized by the Ethical Committee of AL Basra Teaching Hospital in Iraq and Sousse University in Tunisia. Before collecting samples, explicit consent was obtained from all participants included in the study. Moreover, all techniques and processes were carried out in compliance with the criteria and laws established by the Ethical Committee of the Faculty of Medicine Ibn Al Jazzar, Sousse, which is associated with Sousse University in Tunisia.

2.2 Study design

This case-control study was performed on patients who attended Al-Basrah Teaching Hospital.

2.3 The subjects

This study comprised 60 patients who visited Al-Basrah Teaching Hospital in Basrah and had diabetes mellitus (DM), with a mean age of 56.02± 1.395 years and an age range of (40 - 80) years, and 60 patients who had cardiovascular diseases and diabetes (CVD &

DM), with a mean age of 59.20± 1.478 years and an age range of (40 - 80) years. The research also included 60 healthy controls. The healthy control group's mean age was 54.72± 1.405 years. During the period of September 2022 to September 2023, clinical and laboratory testing confirmed the diagnosis made by specialized physicians for all the participants in this research. An informed consent form was signed in writing by each subject. Body weight (kg) divided by squared height (meters) was the formula used to compute BMI.

2.4 Body mass index measurement

The same scale was used to measure each subject's height and body weight. The weight (kg) divided by the square of the height (metres) was used to compute the body mass index (BMI). According to the World Health Organisation (WHO) and American Diabetes Association (ADA) recommendations, the patients were categorized based on BMI. The following categories were used to categorize people's weight: normal (BMI 18.5-24.9), overweight (BMI 25-29.9), and severely obese (BMI >30) [15].

2.5 The criteria of the healthy controls group

The healthy control group samples were collected from the experimental group after ensuring the adequacy of the criteria specified in this study. The selection of the healthy control group was based on several criteria, including:

1. The healthy control participants should not have any medical history of heart disorders.
2. They have not undergone any surgical intervention or illness requiring hospitalization.
3. A health questionnaire determines the subjective perception of good health.
4. With the approximate age range of the patient's group.

2.6 Human N-terminal pro atrial natriuretic peptide and human soluble ST2

This ELISA kit uses the Sandwich-ELISA principle.

Assay procedures summary

1. Add 100μL standard or sample to the wells. Incubate for 90 min at 37 °C
2. Discard the liquid, and immediately add 100 μL Biotinylated Detection Ab working solution to each well. Incubate for 60 min at 37 °C
3. Aspirate and wash the plate for 3 times
4. Add 100 μL HRP conjugate working solution. Incubate for 30 min at 37 °C. Aspirate and wash the plate 5 times
5. Add 90 μL Substrate Reagent. Incubate for 15 min at 37°C
6. Add 50 μL Stop Solution
7. Read the plate at 450nm immediately. Calculation of the results

2.7 Statistical analysis

Microsoft Office Excel 2013 and GraphPad Prism 9.2.0 were used to gather, analyze, and present the data. Numbers were used to represent categorical data, while mean Standard Error of Mean was used to convey numerical data. An unpaired t-test and a one-way ANOVA were used to compare the mean values across the different groups for variables that were regularly distributed. Chi-square analysis was performed on the qualitative data. Using Pearson's correlation coefficient, a bivariate correlation was carried out. When the P-value was less than 0.05, it was deemed significant.

3 Results

Table 1 displays the demographic details of the other groups and control participants. The mean age of the diabetes mellitus groups was 56.02± 1.395 years, whereas the control participants' mean age was 54.72± 1.405 years. As shown in Figure 1, there was no significant difference in the mean age across the study groups (p = 0.0760). The groups with diabetes and cardiovascular disease were 59.20± 1.478 years mellitus. The BMI (kg/m2) of the control group was 24.58 ± 0.2385), while the patients with diabetes mellitus and cardiovascular disease and DM had BMIs of 25.15 ± 0.2875) and 27.03 ± 0.3339), respectively. Table 1 and Figure 2 demonstrate that there was a significant difference (p-value <0.0001) in the mean age across the research groups.

Table 1: Demographic characteristics of control subjects and other Groups.

Characteristic	Control	D.M	CVD & D.M	P Value
	n=60	n=60	n=60	
		Age(years)		
Range	40- 80	40 - 80	40 - 80	0.0760
Mean ± SEM	54.72± 1.405	56.02± 1.395	59.20± 1.478	ns
		BMI (kg/m2)		
Range	21.78 - 26.81	22.03 - 28.4	22.84 - 29.78	<0.0001
Mean ± SEM	24.56 ± 0.1985	25.28 ± 0.2454	27.13 ± 0.2501	****
		Gender		
Male, n (%)	30 (50.0 %)	30 (50.0 %)	30 (50.0 %)	0.9723
Female, n (%)	30 (50.0 %)	30 (50.0 %)	30 (50.0 %)	ns

n: number of cases; SEM: Standard Error of Mean; ns: not significant at p > 0.05 ;****: significant at p <0.0001

There were 30 (50.0%) men and 30 (50.0%) women in the control group. Thirty (50.0%) men and thirty (50.0 %) females made up the diabetes mellitus group, whereas twenty (50.0%) females and thirty (50.0%) males made up the cardiovascular disease and diabetes mellitus group. Regarding gender, there was no discernible difference between the research groups' control participants and other groups (p = 0.9723).

3.1 Age

The measurement of age showed a non-significant difference in mean values between the control and DM (p-value = 0.7958). In addition, the a non-significant difference in mean values between control and CVD & DM (p-value = 0.0702), and there was a non-significant difference in mean value between DM and CVD & DM (p-value = 0.2579) (Figure 1).

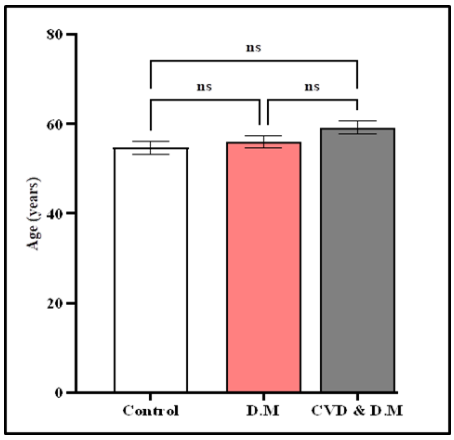

Figure 1: Estimation of the Age in patients and control.

3.2 BMI

The measurement of BMI showed a non-significant difference in mean values between the control and DM (p-value = 0.0769). In addition, the a significant difference in mean values between the control and CVD & DM (p-value <0.0001), and there was a significant difference in mean value between DM and CVD & DM (p-value <0.0001) (Figure 2).

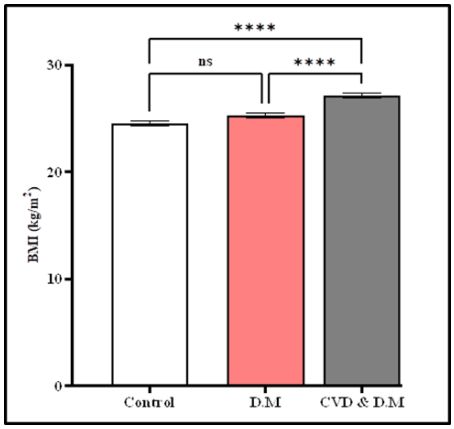

Figure 2: Estimation of mean body mass index BMI (kg/m^2) in control and other groups.

3.3 N-terminal pro-atrial natriuretic peptide

The study's findings indicated that, in comparison to DM and control subjects, the levels of N-terminal pro atrial natriuretic peptide (NT-proANP) in CVD and DM patients were higher (30.46 ± 1.263) (ng/dL) and (13.791±0.2731) (ng/dL), respectively. The concen-

trations of NT-proANP varied significantly (p-value <0.0001) across the research groups. A significant difference in mean values was observed between the control and DM groups in the NT-proANP assay (p-value <0.0001). Furthermore, a noteworthy distinction was seen in the average values between the control group and CVD & DM (p-value <0.0001), as well as a noteworthy difference in the average value between DM and CVD & DM (p-value <0.0001). (as showing Figure 3).

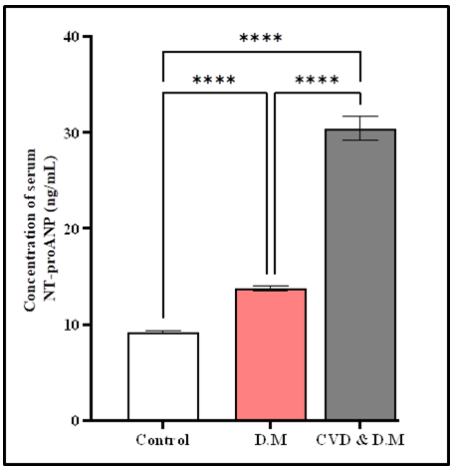

Figure 3: Estimation of serum concentrations of NT-proANP (ng/d).

Data are expressed as means ± SEM. p-values were determined by One-way ANOVA ** p-value ≤0.01, and **** p- value ≤ 0.0001).

3.4 Soluble ST2

According to the study's findings, soluble ST2 (sST2) levels in CVD and DM patients were higher than those in DM and the control group (10.69 ± 0.2849 and 3.786 ± 0.2810) mg/dL, respectively. Between study groups, there was a significant difference in sST2 concentrations (p-value <0.0001). A significant difference in mean values was observed between the control and DM groups in the sST2 assessment (p-value <0.0001). Furthermore, a noteworthy distinction was seen in the average values between the control group and CVD & DM (p-value <0.0001), as well as a noteworthy difference in the average value between DM and CVD & DM (p-value <0.0001). (as showing Figure 4).

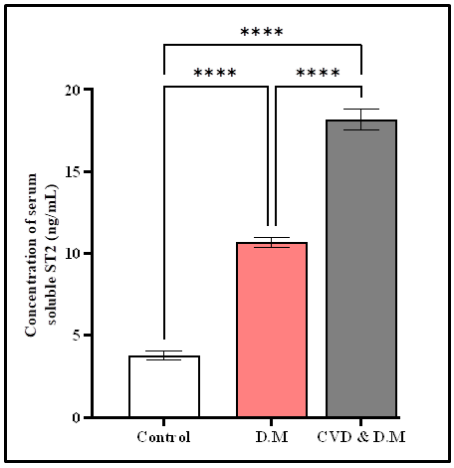

Figure 4: Estimation of serum concentrations of sST2 (ng/mL).

Data are expressed as means ± SEM. P-values were determined by One-way ANOVA (**** p- value ≤ 0.0001).

4 Discussion

In most developed countries, cardiovascular disease (CVD), mostly caused by coronary artery atherosclerosis, is one of the main causes of death. The incidence of CVD is influenced by age, gender, economic position, and other variables. Lipid abnormalities, thrombosis, inflammation, activation of vascular smooth cells and platelets, endothelial dysfunction, oxidative stress, and genetic factors are among the highly linked processes seen in atherosclerosis [16, 17]. There was no significant difference in the mean age among the study groups; the mean age of the control subjects was 54.72± 1.405 years, the mean age of the diabetes mellitus groups was 56.02± 1.395 years, and the mean age of the cardiovascular disease and diabetes groups was 59.20± 1.478 years. These results are consistent with [18], who found that the mean age of patients with CVD was 55 years. Furthermore, the findings corroborated the observation made by [19] that the mean age of CVD patients was 64.72 years (55.6-73.8 years).

Our research supported the results of [20], which showed that older adults and populations on the rise are more susceptible to CVD. A variety of broader ageing processes, such as the buildup of morbidity, a decrease in homeostasis, and the long-lasting negative impacts of CVD risk factors, are linked to high age-related CVD incidence. Another cause of heart disease is subtle age-related changes in the shape and function of CVD [21]. One such constant aging phenomenon is the diastolic perfusion changes, increased afterload stress, increased cardiac workload, and vascular stiffening of the central vasculature, which usually start

by middle age and eventually lead to ischemia, heart failure, arrhythmia, and other CVD disorders [22].

A biomarker called N-terminal pro-A-type natriuretic peptide (NT-proANP) is often utilized in clinical settings to evaluate cardiac function and identify cardiovascular disease (CVD), especially heart failure [23]. The heart releases a hormone called atrial natriuretic peptide (ANP) in reaction to increased pressure and straining of the atria, the heart's upper chambers. A portion of the prohormone created during the synthesis of ANP is known as NT-proANP [4]. The results of this study showed an increase in the level of N-terminal pro atrial natriuretic peptide (NT-proANP) in CVD & DM patients as compared with DM and control, respectively. There was a significant difference in concentrations of NT-proANP among study groups (p-value <0.0001).

The relationship between NT-proANP and cardiovascular disease (CVD) and diabetes mellitus (DM) is complex and multifaceted: NT-proANP levels tend to increase in response to cardiac stress, such as in cases of heart failure, atrial fibrillation, and hypertensive heart disease [24]. Elevated levels of NT-proANP can indicate atrial or ventricular stretch and stress, which are common in various forms of CVD. NT-proANP is often used as a marker to aid in the diagnosis, prognosis, and monitoring of heart failure and other cardiac conditions [25]. Higher NT-proANP levels are associated with a higher risk of adverse outcomes in heart failure patients [26].

Some studies have suggested a link between higher NT-proANP levels and diabetes. Elevated NT-proANP levels have been observed in individuals with type 2 diabetes, especially those with impaired glucose tolerance or insulin resistance [27]. It's important to note that while NT-proANP can provide valuable information about cardiovascular health, it is just one piece of the puzzle. Other factors, such as clinical history, physical examination, other biomarkers (e.g., B-type natriuretic peptide, troponins), and imaging studies, are typically considered alongside NT-proANP levels to make accurate diagnoses and treatment decisions [28, 29]. Individual responses to NT-proANP and its relationship with CVD and DM can vary widely based on a person's overall health, genetics, lifestyle factors, and the presence of other medical conditions(31).

Numerous investigations have shown that NT-proBNP has comparable diagnostic efficacy to BNP in the context of heart failure identification [30, 31], This phenomenon occurs due to the enzymatic cleavage of proBNP, resulting in the production of BNP and NT-proBNP. The heart releases both BNP and NT-proBNP in equal amounts. Nevertheless, it is important to note that the metabolic processes of B-type natriuretic peptide (BNP) in plasma vary from those of N-terminal pro-B-type natriuretic peptide (NT-proBNP), resulting in NT-proBNP being more susceptible to age-related influences [32].

In their study, Januzzi et al. [33] previously conducted a study in which they found that the levels of NT-proBNP, a biomarker for acute heart failure, are significantly affected by age. Based on their findings, the authors suggested an effective approach to diagnose acute heart failure using NT-proBNP by using age-specific thresholds. Specifically, they proposed cutoff values of 450, 900, and 1800 pg/mL for individuals aged less than 50, between 50 and 75, and over 75 years old, respectively. In contrast, when diagnosing acute heart failure using the measurement of B-type natriuretic peptide (BNP), it is worth noting that the cutoff threshold remains consistent regardless of the patient's age [34–36]. Additionally, it is crucial to acknowledge that the NT-proBNP value may be significantly affected by renal function. Consequently, even a little renal impairment has the potential to inflate the actual NT-proBNP measurement.

Soluble ST2 (sST2) is a biomarker that has been studied in the context of CVD and various other health conditions. sST2 is a member of the interleukin-1 receptor family and is produced in response to tissue injury and inflammation [37, 38]. It has been associated with cardiac remodelling, fibrosis, and inflammation, making it of interest in the field of cardiology [39]. The results of this study showed an increase in the level of soluble ST2 (sST2) in CVD & DM patients as compared with DM and control, respectively. There was a significant difference in concentrations of sST2 among study groups (p-value <0.0001). It's important to note that while there is evidence suggesting the involvement of sST2 in cardiovascular disease and its potential link to diabetes mellitus, research in this field is ongoing. The specific mechanisms and clinical implications of sST2 in relation to CVD and DM are still being investigated.

5 Conclusion

This research suggests that N-terminal pro-atrial natriuretic peptide and Soluble ST2 may be useful indicators for predicting insulin resistance, dysglycemia, and cardiovascular disease in a community of seemingly healthy under-50s in Al-Basra. This study compared N-terminal pro-atrial natriuretic peptide and Soluble ST2 as surrogate insulin resistance markers to identify asymptomatic people with atherogenic lipoprotein profiles, which increase cardiovascular disease risk. Standardized reference values ensured clinical applicability throughout the investigation.

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Conflict of Interest: No conflicts of interest exist between the authors and the publication of this work.
Ethical consideration: The ethical committee approved the study at University of Basra, Iraq.

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