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The Impact of Metformin on BNP Levels: A Potential Cardioprotective Role in Type 2 Diabetes

Emre Hoca [1,*], Nilsu Kalaycı [1], Süleyman Ahbab [1], İsmail Engin [2] and Hayriye Esra Ataoğlu [1]

[1] University of Health Sciences, Haseki Training and Research Hospital, Department of Internal Medicine, Istanbul, Turkey

[2] University of Health Sciences, Ümraniye Training and Research Hospital, Department of Endocrinology, Istanbul, Turkey

* Correspondence: emrehoca89@gmail.com; Tel.: +905354611007.

Abstract: Background/Objectives: Cardiovascular complications are the most common cause of mortality and morbidity in diabetic patients. Therefore, the aim of antidiabetic therapy should not only be to provide glucose regulation but also to protect patients from complications and related mortality. Brain natriuretic peptide (BNP) is a peptide secreted as a result of myocardial stress. BNP levels increase in conditions of increased myocardial stress, such as heart failure. It is important not only in diagnosis but also in follow-up. In our study, we aimed to evaluate BNP level and, thus, the factors affecting the risk of developing heart failure in the course of diabetes mellitus. **Methods**: This study was conducted at the University of Health Sciences, Haseki Training and Research Hospital diabetes outpatient clinic. Two hundred fifty-two patients met the inclusion criteria and were enrolled in the study. Laboratory parameters, including BNP values, comorbidities, and anamnesis data, were recorded. **Results**: The mean BNP levels were significantly lower in patients using metformin and pioglitazone. Other antidiabetic medications were not associated with BNP levels. BNP levels were positively correlated with age and diabetes duration and negatively correlated with hemoglobin. According to regression analysis, age, metformin use, and hemoglobin were found to independently affect BNP levels. **Conclusions**: Our findings suggest that metformin could potentially play a significant role in preventing the development of heart failure in diabetic patients without heart failure, owing to its favorable effects on myocardial stress. This suggests metformins potential in preventing heart failure in type 2 diabetic patients.

Keywords: brain natriuretic peptide; cardiovascular complications; heart failure; metformin; type 2 diabetes

1. Introduction

Cardiovascular diseases (CVD) continue to be the most common cause of morbidity and mortality in the course of Type 2 Diabetes Mellitus (T2DM) [1]. Insulin resistance as a main pathophysiologic cause of T2DM is associated with an atherogenic lipid profile, endothelial dysfunction, and increased abdominal obesity, which significantly increase the risk of cardiovascular events [2,3]. Among individuals with type 2 diabetes mellitus, the risk of developing CVD is markedly higher due to shared pathological mechanisms, including chronic inflammation, oxidative stress, and endothelial dysfunction [4]. Heart failure, with a prevalence of up to 30%, is among the most common cardiovascular complications in diabetic patients, together with myocardial infarction [5,6]. Identifying biomarkers that predict cardiovascular risk and understanding the impact of therapeutic interventions on these biomarkers are paramount. B-type natriuretic peptide (BNP), which is produced from pre-proBNP and released from myocytes under myocardial stress and

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stretch, is a well-established biomarker of heart failure [7]. BNP and N-terminal (NT)-proBNP are both natriuretic peptides, but the superiority of these two peptides over each other has not yet been demonstrated. Both peptides are actively used in the diagnosis and follow-up of heart failure [8]. A BNP level below 100 is considered normal, while a level above 400 indicates the probability of heart failure. Values between 100 and 400 are considered a 'grey zone', and heart failure is evaluated according to symptoms, examination findings, and clinical data [9,10]. Elevated levels of BNP have also been associated with subclinical cardiovascular dysfunction and increased cardiovascular risk in non-heart failure populations, including patients with T2DM [10]. Therefore, studies show that BNP levels can be used to monitor heart failure and evaluate its prognostic importance in diabetic patients [12,13]. However, the factors influencing BNP levels in individuals with T2DM who do not have overt heart failure remain poorly understood.

Metformin is the most commonly used antidiabetic agent to improve insulin sensitivity in treating type 2 DM and conditions characterized by insulin resistance, such as pre-diabetes, obesity, and polycystic ovary syndrome [14]. Studies show that metformin contributes favorably to mitochondrial energy metabolism in cardiac cells by activating AMP-dependent kinase (AMPK). Some other studies show that metformin has properties such as reducing oxidative stress in cardiac cells, contributing to an increase in endothelial function, and positively affecting inflammation [15,16]. There are very few studies evaluating the beneficial effects of metformin on the development of heart failure in diabetic patients or comparing its cardiac effect profile head-to-head with agents such as sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, whose positive cardiovascular effects have been well established. In addition, very few studies evaluate the effects of metformin on cardiac stress through BNP levels.

In this retrospective cross-sectional study, we aimed to investigate the effects of antidiabetic drugs on cardiac stress and their possible cardioprotective effects in diabetic patients without heart failure by evaluating the measured BNP levels.

2. Materials and Methods

2.1. Study Participants

The study protocol was approved by the ethics committee of Haseki Training and Research Hospital (reference no: 58-2024, date: 01.08.2024). This study was conducted using the principles of good clinical practice and the Declaration of Helsinki. The data of patients who attended the diabetes outpatient clinic between January 1, 2024, and October 1, 2024, were retrospectively reviewed. A total of 6,299 patients were screened, and those meeting the inclusion criteria (n:252) were enrolled in the study. Patient and laboratory data were collected and analyzed using the hospital information operating system. Being older than 18 years of age, having a BNP level below 400 pg/ml, being diagnosed with type 2 diabetes, and having accessibility to the anamnesis of the treatments used by the patients were determined as inclusion criteria. Exclusion criteria were a BNP level above 400 pg/ml suggestive of heart failure, echocardiographically proven heart failure, or the presence of symptoms of heart failure (New York Heart Association Heart Failure Functional Classification-Class 2,3,4 patients). Patients with chronic kidney disease (CKD) stage 4-5, acute kidney injury, or hepatic failure were also excluded.

2.2. Data Collection

Demographic data (such as age and gender) and clinical characteristics (comorbidities and medications used) were recorded. The laboratory parameters (BNP, aspartate aminotransferase [AST], alanine aminotransferase [ALT], triglycerides, high-density lipoprotein [HDL]-cholesterol, low-density lipoprotein [LDL]-cholesterol, total cholesterol, complete blood count, HbA1c, glucose, urea, creatinine) obtained following an overnight fasting period of at least 8 hours were recorded. Diabetes duration was calculated and recorded by analyzing the anamnesis, medication usage reports, and patients' past prescriptions. In order to complete the missing data, the hospital

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information operating system was used. BNP levels were determined using a chemiluminescence immunoassay (CLIA) method using a BNP kit in Siemens Advia Centaur XP (Mannheim, Germany) device and recorded in nanograms per liter.

2.3. Statistical Analysis

Statistical analyses were performed using SPSS 25.0 for Windows software (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as mean ± standard deviation and minimum-maximum and median values. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Comparisons between groups were conducted using the independent samples t-test or Mann-Whitney U test, depending on relevant data distribution. Categorical variables were compared using the chi-square test. Correlations between BNP levels and clinical or laboratory parameters were evaluated using Pearson or Spearman correlation coefficients. Different multivariate linear regression models were constructed to identify independent factors associated with BNP levels. While constructing different regression models, in addition to the data that we found to be associated with BNP in our study, some other parameters associated with BNP in other studies were also used. A p-value of <0.05 was considered statistically significant.

3. Results

A total of 252 patients meeting the inclusion criteria were included in the analysis. The mean age of the study population was 56.82 ± 9.2 years, with a diabetes duration of 9.96 ± 5.04 years. Of the participants, 132 were female and 120 were male. The mean BNP level was 37.43 ± 39.59 pg/ml. The mean HbA1c level was 7.90 ± 1.77%, and the mean fasting glucose level was 152.24 ± 59.59 mg/dL. Lipid profile results showed a mean total cholesterol level of 176.73 ± 42.13 mg/dL, HDL-cholesterol of 43.64 ± 12.05 mg/dL, LDL-cholesterol of 101.58 ± 35.52 mg/dL, and triglycerides of 160.45 ± 94.06 mg/dL. Mean hemoglobin (Hb), urea, and creatinine levels were 13.55 ± 1.58 g/dL, 35.03 ± 11.26 mg/dL, and 0.90 ± 0.22 mg/dL, respectively (Table 1). Comorbidities with diabetes were hyperlipidemia in 51%, hypertension in 41%, coronary artery disease in 10%, and hypothyroidism in 5% of patients. (Table 1).

Table 1. Descriptive variables and laboratory parameters of patients.

Variable	Mean±std	Min.-Max. (Median)
Age (years)	56.82±9,2	23-75 (58)
Diabetes duration (years)	9.96±5.04	1-17 (12)
Gender (F/M)	132/120	
BNP (ng/l)	37.43±39.59	2-314 (25.7)
HbA1c (%)	7.90±1.77	4.8-15.5 (7.45)
Glucose (mg/dl)	152.24±59.59	47-430 (137)
Total cholesterol (mg/dl)	176.73±42.13	77-335 (174)
HDL-cholesterol (mg/dl)	43.64±12.05	16-95 (42)
LDL-cholesterol (mg/dl)	101.58±35.52	20-251 (94.8)
Triglyceride (mg/dl)	160.45±94.06	37-602 (133.5)
Hemoglobin (g/dl)	13.55±1.58	9.2-17.1 (13.5)
Urea (mg/dl)	35.03±11.26	12-96 (33)
Creatinine (mg/dl)	0.90±0.22	0.48-1.84 (0.87)
AST (U/l)	16.71±14.59	4-188 (14)
ALT (U/l)	27.17±19.19	8-160 (22)
Comorbidities	**N (%)**	
Hyperlipidemia	131 (51.9)	
Hypertension	104 (41.2)	
Coronary artery disease	26 (10.3)	

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Hypothyroidism	14 (5.5)

(**Std:** standart deviation**, min:** minimum**, max:** maximum**, F:** female**, M:** male**, BNP:** brain natriuretic peptide**, HDL:** high-density lipoprotein**, LDL:** low-density lipoprotein**, AST:** aspartate aminotransferase**, ALT:** alanine aminotransferase).

The mean BNP levels were significantly lower in patients using metformin (33.68 ± 36.78 pg/ml) than non-users (49.18 ± 45.69 pg/ml; p: 0.034). Similarly, pioglitazone users had significantly lower BNP levels (27.37 ± 22.85 pg/ml) than non-users (41.46 ± 43.98 pg/ml; p: 0.021). However, no significant differences in BNP levels were observed for users versus non-users of SGLT2 inhibitors, DPP-4 inhibitors, sulfonylureas, insulin, statins, or fibrates, as shown in Table 2.

Table 2. Antidiabetic/antihyperlipidemic medications and BNP levels.

Medications (n)		BNP	p
Metformin	Non-user (61)	49,18±45,69	**0,034**
	User (191)	33,68±36,78	
SGLT2 inhibitors	Non-user (110)	42,02±45,49	0.162
	User (142)	33,88±34,08	
DPP-4 inhibitors	Non-user (122)	40,47±40,03	0.523
	User (130)	34,58±39,12	
Pioglitazone	Non-user (180)	41,46±43,98	**0.021**
	User (72)	27,37±22,85	
Sulfonylureas	Non-user (215)	38,12±41,49	0.764
	User (37)	33,42±25,99	
Insulin	Non-user (104)	31,44±27,07	0.195
	User (148)	41,64±46,04	
Statins	Non-user (165)	40,12±40,33	0,060
	User (87)	32,33±37,85	
Fibrates	Non-user (232)	37,84±40,51	0.714
	User (20)	32.70±26,99	

(**SGLT2:** Sodium-glucose cotransporter-2, **DPP-4:** dipeptidyl peptidase-4).

A significant positive correlation was found between BNP levels and age (r= 0.410, p: <0.001) as well as diabetes duration (r= 0.149, p = 0.018). BNP levels showed a negative correlation with hemoglobin (r= -0.284, p: <0.001) and alanine aminotransferase (ALT) levels (r= -0.151, p: 0.016). No significant correlations were observed between BNP levels and HbA1c, fasting glucose, lipid profile, urea, creatinine, or AST levels (Table 3).

Table 3. Correlation of BNP levels with clinical data and laboratory parameters.

	R	p
Age	0.410	**<0.001**
Diabetes duration	0.149	**0.018**
HbA1c	0.091	0.150
Fasting glucose	0.095	0.131
HDL-cholesterol	0.092	0.145
LDL-cholesterol	-0.100	0.115
Triglyceride	-0.034	0.589
Urea	0.072	0.253
Creatinine	0.000	0.995
Hemoglobin	-0.284	**<0.001**
ALT	-0.151	**0.016**
AST	-0.044	0.491

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When subgroup analyses were performed, the BNP level was found to be 44.77±47.52 in females and 29.35±26.36 in males (p:0.001). There was no difference between the mean ages of male and female patients (57.23±8.82 and 56.37±9.60, respectively, p: 0.459).

Multivariate linear regression analysis (model 1) identified age (B: 1.305, p: <0.001), male gender (B: -12.915, p: 0.006), and metformin use (B= -11.312, p= 0.040) as independent predictors of BNP levels. In an alternative regression model (model 2), age (B: 1.293, p: <0.001), metformin use (B: -11.857, p: 0.047) remained, and also hemoglobin (B: -3.980, p: 0.020) was found as significant predictors. Pioglitazone use, HbA1c, LDL-cholesterol, HDL-cholesterol, and creatinine were not significant predictors of BNP levels according to these regression models, as shown in Table 4.

Table 4. Linear regression models determining factors affecting BNP levels.

Model 1				
	B	**S.E.**	**%95 CI for B (lower-upper)**	**p**
(Constant)	-21.180	15.936	-52.569 – 10.209	0.185
Age	1.305	0.281	0.750 – 1.859	**<0.001**
Diabetes duration	0.078	0.504	-0.915 – 1.071	0.877
Male gender	-12.915	4.653	-22.080 - -3.750	**0.006**
Metformin	-11.312	5.474	-22.094 - -0.530	**0.040**
Pioglitazone	-5.486	5.297	-15.920 – 4.947	0.301
Model 2				
	B	**S.E.**	**%95 CI for B (lower-upper)**	**p**
(Constant)	31.531	33.886	-35.216 - 98.279	0.353
Age	1.293	0.266	0.769 - 1.816	**<0.001**
Metformin	-11.857	5.948	-23.573 - -0.142	**0.047**
Male gender	-6.218	5.724	-17.494 - 5.057	0.278
HbA1c	0.738	1.373	-1.966 - 3.442	0.591
LDL-cholesterol	-0.040	0.068	-0.174 – 0.093	0.551
HDL-cholesterol	0.069	0.209	-0.344 – 0.481	0.743
Hemoglobin	-3.980	1.701	-7.331- - 0.628	**0.020**
Creatinine	-7.106	12.807	-32.333 – 18.121	0.580

4. Discussion

The aim of the treatment of diabetic patients should not only be to reduce blood glucose and HbA1c levels but also to prevent possible complications and serious morbidity and even mortality that may develop as a result of these complications [17,18]. Since cardiovascular events are the most common cause of death among these complications, favorable cardiovascular effects are at the forefront when developing diabetes treatments or evaluating the effects of existing antidiabetic agents. Considering that all diabetic patients are at risk for cardiovascular diseases, we aimed to evaluate the factors affecting BNP levels, which are indicators of cardiac stress and thus the risk of developing heart failure, in diabetic patients without a diagnosis or symptoms of heart failure. Thus, we demonstrated that BNP levels may be important antidiabetic treatment selection. In our study, only metformin had a decreasing effect on BNP levels among all antidiabetic drugs. This fact revealed that metformin is the agent of first choice in diabetic patients at risk of cardiovascular disease.

BNP levels increase with age due to impaired ventricular compliance, endothelial dysfunction, and increased preload and afterload due to increased activity of the Renin-Angiotensin-Aldosterone System. Therefore, studies suggest that age-specific cut-off values of BNP levels should be determined [19,20]. Similarly, there are studies showing that an increase in the duration of diabetes is also associated with an increase in BNP levels [21]. In our study, we found a positive correlation between both age and diabetes duration and BNP levels. Later, when we performed regression

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analysis, although age was found to be one of the factors independently affecting BNP levels, in the second model, it was observed that diabetes duration was not one of the factors independently affecting BNP levels. This finding suggests that the effect of diabetes duration on BNP levels may be due to other factors such as age and medications used.

In the majority of studies, BNP levels were found to be higher in women than in men among patients without a diagnosis of heart failure. Although the underlying pathophysiology has not been fully elucidated, the main factors are thought to be that testosterone upregulates neprilysin activity and leads to a decrease in cardiac natriuretic peptide levels. At the same time, estrogen hormone increases gene expression and release of natriuretic peptides [22–24]. In our study, BNP levels were found to be significantly higher in female patients, supporting these findings. In addition to the possible pathophysiologies suggested, the fact that hemoglobin levels were lower in the female patient group and hemoglobin levels were negatively correlated with BNP, the lower hemoglobin levels in women mediate a possibility of BNP elevation. The second regression analysis model created with demographic data and laboratory parameters found that hemoglobin levels were an independent parameter affecting BNP levels, but gender had no effect on BNP. This suggests that the difference in BNP levels between genders may have arisen due to different hemoglobin levels. Low hemoglobin levels are thought to increase BNP levels by increasing the stress on the myocardium and leading to an increase in left ventricular wall thickness in later periods. In studies conducted by Wold Knudsen et al. and Karakoyun et al., an inverse relationship was observed between hemoglobin levels and BNP levels in different patient groups with and without a diagnosis of heart failure [25,26].

While cholesterol levels are associated with processes resulting in atherosclerosis, BNP levels reflect the level of cardiac stress through different pathophysiological mechanisms independent of atherosclerosis. As a result, there may be no correlation between cholesterol levels and BNP levels. Similar to our study, no significant correlation was found between BNP levels and LDL-cholesterol and HDL-cholesterol levels in the study conducted with elderly patients by He et al. [27].

Srisawasdi et al. showed that BNP levels were less affected by creatinine levels than NT-proBNP levels, and even in male patients, patients with stage 3 CKD had similar levels to men with stage 1 CKD when other factors were eliminated. This is thought to be the higher renal excretion of NT-proBNP compared to BNP. It has been shown that BNP levels start to be affected by creatinine levels, usually in patients with advanced CKD (stage 4 or 5) [28]. Similarly, Vickery et al. demonstrated that the levels of natriuretic peptides, mostly NT-proBNP, started to be affected in advanced CKD patients [29]. Like the aforementioned studies, we found no correlation between creatinine levels and BNP levels in our patient groups. Our study did not include advanced CKD patients and used BNP measurements as natriuretic peptides.

Studies are showing that BNP levels in diabetic patients have a close relationship with glycemic control and that BNP levels decrease as HbA1c and glucose levels normalize, as well as studies showing that BNP levels do not correlate with glycemic control and may even have a negative correlation in some cases [30,31]. This may be because BNP protects against insulin resistance by increasing fat metabolism, increasing adiponectin levels, and decreasing inflammation [32,33]. Our study did not find any correlation between glucose or HbA1c levels and BNP levels. We thought that this was normal because the majority of the type 2 DM patients admitted to our diabetes outpatient clinic also had concomitant metabolic syndrome.

Most publications evaluating the cardioprotective effects, particularly changes in natriuretic peptides of SGLT2 inhibitors, have been conducted in patients with heart failure. SGLT2 inhibitors have been found to cause a significant decrease in BNP in these patients. The study by Chen et al. found similar results [34]. On the other hand, there are very few studies evaluating the relationship between SGLT2 inhibitors and natriuretic peptides in patients without a diagnosis of heart failure or symptoms of heart failure. In the SOCOGAMI study and the EMBODY trial, the effect of SGLT2 inhibitors on cardiometabolic parameters in patients without a diagnosis of heart failure was evaluated, and it was found that SGLT2 inhibitors had no significant effect on BNP levels in these patients [35,36]. SGLT2 inhibitors act by decreasing increased congestion and preload in patients with

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heart failure, leading to a decrease in BNP levels as a result of decreased ventricular tension. However, since there is no increase in congestion and preload in patients without heart failure, SGLT2 inhibitors may not have the extra effect of reducing ventricular tension and changing BNP levels. Similarly, in our study, no significant difference was observed in BNP levels in patients using SGLT2 inhibitors compared to non-users.

It is thought that pioglitazone may increase BNP levels due to its water-retaining effect, thus possibly increasing myocardial volüme [37]. In our study, BNP levels were found to be lower in the patient group using pioglitazone, which may contradict this situation. However, the regression analysis later found that pioglitazone use was not an independent factor affecting BNP levels. When we performed subgroup analysis, we found that the mean age of pioglitazone users was lower than non-users, and most of these patients were pioglitazone users.

Until a while ago, it was recommended that metformin should not be used in patients with heart failure due to the possible risk of lactic acidosis. In light of current information, it is thought that metformin can be used in patients even with heart failure, as well as in diabetic patients at risk of developing heart failure, due to its anti-inflammatory, myocardial oxidative stress-reducing, and endothelial function-correcting effects [16]. Also, some studies have shown that there is no significant increase in the risk of lactic acidosis with metformin use in patients with heart failure [38]. In addition to these favorable effects of metformin use, there are very few large-scale studies evaluating the relationship between BNP levels and metformin use in patients without a diagnosis of heart failure, and the results are contradictory. In the study by Top et al., no change was observed in BNP levels in the patient group using metformin, but we thought that the fact that all of the patients included in the study were using insulin might have caused no change in BNP values due to the effects of insulin [39]. In the study conducted by Sabbar et al. on non-diabetic patients diagnosed with heart failure, the addition of metformin to standard heart failure treatment resulted in a significant reduction in BNP levels during follow-up [40]. Similarly, Sokolova et al. observed that metformin use led to a decrease in BNP levels in patients with diabetes but without heart failure [41]. Although both studies were conducted with a relatively small number of patients, they are valuable in demonstrating the potential cardioprotective effects of metformin. Consistently, our study also found that metformin use was associated with a significant reduction in BNP levels, independent of other factors. Although SGLT2 inhibitors and GLP-1 agonists have demonstrated significant cardiovascular benefits, metformin's direct effect on BNP levels remains less explored. Our findings highlight a unique role for metformin in reducing myocardial stress, which could have implications for future diabetes treatment strategies. These findings suggest that, in addition to its beneficial effects on blood glucose regulation and insulin resistance, metformin may play an unexpectedly crucial role in cardioprotection in diabetic patients.

The limitations of our study include the fact that it was retrospective and cross-sectional; we evaluated the status of the patients at the time of data collection, and we could not observe changes in the parameters during follow-up.

5. Conclusions

Heart failure, one of the most common cardiovascular complications that may develop in the course of diabetes mellitus, is a pathology whose morbidity and mortality can be reduced if its development can be prevented. The positive effects of metformin use on BNP levels, and thus on the risk of developing heart failure, even in diabetic patients without heart failure, are quite valuable. If these benefits of metformin can be demonstrated in studies that include follow-up data of patients and can be conducted with a larger patient group, this under-emphasized effect of metformin will allow metformin to become again the first choice in the treatment of diabetics, especially those at risk of developing heart failure.

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writing—original draft preparation, E.H. and S.A.; writing—review and editing, E.H. and H.E.A.; visualization, E.H. and İ.E.; supervision, E.H. and H.E.A.; project administration, E.H. and S.A.; funding acquisition, N.K. and İ.E. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

BNP	Brain natriuretic peptide
CVD	Cardiovascular diseases
T2DM	Type 2 diabetes mellitus
AMPK	AMP-dependent kinase
SGLT-2	Sodium-glucose cotransorter 2
GLP-1	Glucagon-like peptide-1
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
CLIA	Chemiluminescence immunoassay
Hb	Hemoglobin

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