Research Article

Sensitivity and Specificity of Serum Furin and Corin in Cardiovascular Complications Diagnosis in Type 2 Diabetes Mellitus Patients - 🔓

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Cite this article: Abu Mustafa AM, Jamee AF, Jaish YE, Zabut BM. Sensitivity and Specificity of Serum Furin and Corin in Cardiovascular Complications Diagnosis in Type 2 Diabetes Mellitus Patients. Int J Clin Cardiol Res. 2019;3(2): 019-025.

ABSTRACT

Background: Cardiovascular Diseases (CVD) are the highest-incidence cause of death and morbidity in patients with type 2 Diabetic (T2DM). The natriuretic peptide is important in controlling blood pressure and salt water balance. Both corin and furin are involved in cleave Pro-Atrial Natriuretic Peptide (ANP) and Pro-BNP (Brian Natriuretic Peptide) into their active forms (ANP and BNP). Recently, studied showed that furin and corin defects could contribute to CVDs.

Methods: This study includes 360 subjects divided into three groups; 120 healthy subjects as controls (Gr I); 120 T2DM patients with no medical history of CVD (Gr II) and 120 T2DM patients confirmed diagnosis of CVD (Gr III). All groups were matched for age and gender. All subjects were investigated for biochemical markers, serum corin and furin levels were determined By ELISA techniques.

Result: Human corin level in T2DM patients with and without CVDs was significantly lower than the control group, while furin level were significantly higher in T2DM with CVDs compared to T2DM patients without CVDs and control groups. Furin was found to be more sensitive than corin (72.5% *vs*. 46.7%, *p* < 0.01), Also furin showed higher specificity when compared with corin (96% *vs*. 84%, *p* < 0.05) and corin (92.5% *vs*. 72.5%, *p* < 0.0001) in predicting cardiovascular complications in T2DM patients.

Conclusions: Results of this study suggested that serum furin and corin associated with CVDs development but furin showed higher specificity and sensitivity so, it may be serve as a biomarker in CVDs diagnoses in T2DM patients.

Keywords: Corin; Furin; Cardiovascular disease; Type-2 Diabetic; Palestinian

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) has become one of the most important chronic public health problems [1]. Cardiovascular Diseases (CVDs) are the primary cause of mortality and morbidity in patients with T2DM [2,3]. An estimated 17.3 million people died from CVDs in 2008 and the number of people who die from CVDs will increase to reach 23.3 million by 2030 [4]. CVDs represented the primary cause of Palestinian mortalities reported in 2010, amounting to 25.4% of the total number of deaths [5,6].

In response to volume or pressure overload, the expression of Atrial Natriuretic Peptide (ANP) and brain or B-Type Natriuretic Peptide (BNP), the cardiac peptide hormones, is highly up regulated, increasing their production in the heart and their release into the circulation. Compared to ANP, BNP has emerged as a superior biomarker for left-ventricular dysfunction and Chronic Heart Failure (CHF) [7].

The human BNP gene encodes a 134-amino acid pre-pro- BNP. The removal of an amino terminal 26-amino acid signal peptide from pre-pro-BNP yields a 108-amino acid pro-BNP. Processing of pro-BNP1-108 by a proprotein convertase during release into circulation, results in the physiologically active 32-amino acid carboxyl-terminal molecule (BNP77-108) and an inactive amino-terminal fragment (NT-pro-BNP1-76) [8,9].

Two proprotein convertases, corin [10] and furin [11], are considered the most likely pro-BNP processing enzymes. Corin is a type II transmem- brane serine protease [11] that has been identified as the physiological "pro-ANP [12] and pro-BNP [13] convertase". The enzyme is highly expressed in the heart [10], primarily in cardiomyocytes [14], where it unique cleaves the inactive natriuretic peptide precursor molecules into biologically active peptide hormones [15]. Furin is a ubiquitously expressed type I transmembrane serine protease involved in the proteolytic processing of a wide range of precursor proteins [16]. In patients with HF, plasma levels of unprocessed natriuretic peptides are highly elevated [8], suggesting that corin and/or furin activity could not be compensated adequately to meet the demand under the pathological condition [17,18].

The role of corin and furin in the pathophysiology of CVDs remains incompletely understood. In view of the clinical importance of predicting the development of CVDs in patients with T2DM, the present study was designed to compare the diagnostic accuracy of corin and furin in predicting CVDs in T2DM patients.

PATIENTS AND METHODS

Study design and population

A total of 240 patients were recruited in this case–control study, including 120 T2DM patients without CVDs, who were referred to the outpatient clinic of the diabetic clinic center, Gaza strip, Palestine and 120 T2DM patients with CVDs, who were referred to the cardio care unit of the Cardiology Department, El-Shifa Hospital, Gaza strip, Palestine. In addition, 120 healthy subjects, who underwent routine medical checkups at El-Shifa Hospital and had no medical history of CVDs, were recruited as controls who were selected based on normal clinical and laboratory findings. Participants who had conditions that might affect the natriuretic system such as diseases of the liver, chronic kidney disease, pulmonary hypertension, chronic obstructive lung disease, congenital heart disease, critical valvular heart disease, autoimmune diseases or malignant disease were excluded. The study protocol was approved by the scientific ethical committee of Faculty of Science, Islamic University, Gaza strip, Palestine. A written informed consent was obtained from all the enrolled patients and healthy subjects prior to inclusion into the study in accordance with the Declaration of Helsinki.

Clinical evaluation of the participants

At the time of study baseline, each participant enrolled in the study was thoroughly surveyed according to a self- administered questionnaire which was recorded by trained research staff. Clinical diagnosis and definitions DM was diagnosed according to criteria set by the American Diabetes Association. DM was defined as the presence of one of the following: (1) a fasting plasma glucose of 126 mg/dl or (2) a self-reported history of DM and current use of either insulin or an oral hypoglycemic medication (American Diabetes Association, 2009). The diagnosis of CVDs was performed according to the current guidelines by experienced cardiologists who cared for the patients but were blinded to the study [19,20].

Measurement of plasma corin and furin levels

Venous blood samples were collected into Ethylenediaminetetraacetic Acid (EDTA) - vacutainer tubes (BD diagnostics, Franklin Lakes, NJ) by venipuncture. Plasma samples

were immediately obtained, aliquoted in sterile polypropylene tubes and stored at 80°C until analysis. Plasma levels of Corin and furin were measured using commercial enzyme-linked immunosorbent assays (ELISAs; Abnova, Taipei, Taiwan) following the manufacturer's instructions.

Corin ELISA is capable of recognizing both recombinant and natural human corin. According to the manufacturer's protocol, the minimum detectable concentration of corin ELISA was found to be 5.64 pg/ mL. Moreover, no significant corin ELISA cross-reactivity with Enterokinase, Histone acetyltransferase or Spinesin.

Furin ELISA is able to recognize both recombinant and natural human furin. According to the manufacturer s protocol, the minimum detectable concentration of furin ELISA was found to be 15 pg/ mL. Furthermore, no significant furin ELISA cross-reactivity was observed with any of the following proteins and cytokines: Angiogenin, Brain-derived neurotrophic factor, Leptin, Granulocyte-macrophage colony- stimulating factor, Monocyte chemoattractant protein-1 (MCP-1), MCP-2, MCP-3, Transforming growth factor beta, Tumor necrosis factor alpha (TNF-a), TNF-b, Vascular endothelial growth factor, Interleukin1 (IL-1), IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12, IL-13, IL-15 and Interferon gamma.

Statistical analysis

Categorical variables were reported as the number of cases (percentage) and compared using the Pearson's chi-square test. The continuous variables were expressed as mean ± Standard Deviation (SD) if normally distributed and compared using the independent Student's t-test or one-way analysis of variance as appropriate. Normality was assessed by the Shapiro-Wilk test. A two-sided probability (p) value was used for all statistical analyses, and a p value of 0.05 was considered statistically significant. The correlation of corin and furin levels with continuous variables was analyzed using Pearson correlation coefficient because data were normally distributed. Receiver Operating Characteristic (ROC) curve analysis was performed to determine the diagnostic value of corin and furin levels (Table 1). Data statistical analyses were performed using the statistical package for the social sciences (SPSS Statistics for Windows, Version 23.0; IBM Corp., Armonk, NY).

RESULTS

Baseline characteristics of the study cohort. The study cohort was divided into three groups: 120 healthy subjects, 120 T2DM patients without CVDs and 25 T2DM patients with CVDs. The clinical and biochemical characteristics of the patients and healthy subjects are listed in tables 2,3, respectively. Furin levels was found to be significantly higher in T2DM patients with CVDs than those in T2DM patients without CVDs and those in healthy subjects. Furthermore, furin levels was higher in T2DM patients without CVDs than those in healthy subjects. However, corin levels appeared to be significantly higher in healthy subjects than those in T2DM patients with or without CVDs. Moreover, corin levels were higher in T2DM patients without CVDs than those in T2DM patients with CVDs (Table 3).

Correlation of plasma corin and furin levels with other variables

Corin level was positively correlated with Height, SBP, Hb and HDL-C levels in study population. In contrast, corin level was negatively correlated with SBP, Furin, FBS, Creatinine, Uric Acid, Cholesterol, TG, LDL-C, CK, CK-MB and LDH (Table 4). Corin

Table 1: Demographic data of the studied groups.

Demographic variables	Groups			p - value
	Controls (n = 120)	**T2DM without CVD (n = 120)**	**T2DM with CVD (n = 120)**	
Smoking				
Yes	22 (18.3)	23 (19.2)	27 (22.5)	0.694
No	98 (81.7)	97 (80.8)	93 (77.5)	
Employ				
Yes	47 (39.2)	68 (56.7)	41 (34.2)	0.001
No	73 (60.8)	52 (43.3)	79 (65.8)	
HTN				
Yes	0 (0)	29 (24.2)	85 (70.8)	0.000
No	120 (100)	91 (75.8)	35 (29.2)	
HTN				
Yes	0 (0)	29 (24.2)	85 (70.8)	0.000
No	120 (100)	91 (75.8)	35 (29.2)	
Family history HTN				
Yes	3 (2.5)	23 (19.2)	72 (60)	0.000
No	117 (97.5)	97 (80.8)	48 (40)	
Family history DM				
Yes	8 (6.7)	12 (10)	85 (70.8)	0.000
No	112 (93.3)	108 (90)	35 (29.2)	
Family history CAD				
Yes	0 (0)	0 (0)	19 (15.8)	0.000
No	120 (100)	120 (100)	101 (84.2)	
Family history stroke				
Yes	0 (0)	3 (2.5)	13 (10.8)	0.000
No	120 (100)	117 (97.5)	107 (89.2)	
Family history PAD				
Yes	3 (2.5)	3 (2.5)	13 (10.8)	0.004
No	117 (97.5)	117 (97.5)	107 (89.2)	

level was positively correlated with BMI, duration DM, SBP, FBS, creatinine, uric acid, cholesterol, TG, LDL-C, CK, CK-MB, LDH levels in study population. In contrast, corin level was negatively correlated with height, weight, diastolylic BP, Hb and HDL-C (Table 5).

ROC curve analysis

The sensitivity of CVDs diagnosis in T2DM patients by furin level was higher than that by corin. Furthermore, in T2DM patients, the specificity of CVDs diagnosis by furin level higher than that by corin. Differences in the Positive Predictive Value (PPV), Negative Predictive Value (NPV), accuracy and Area under the Curve (AUC) between furin and corin (Table 6 and Figure 1).

DISCUSSION

The incidence of diabetes is escalating worldwide and, consequently, this has become a major healthcare problem. Moreover, T2DM is associated with significantly accelerated rates of microvascular and macrovascular complications [1]. However, the molecular mechanisms underlying the high incidence of diabetic complications are still not fully understood. When cardiovascular complications progress to an end stage, medical options are limited. Thus, timely diagnosis and early intervention are important for managing these life-threatening diseases [2]. BNP is a cardiac hormone, released from the cardiac ventricles in response to increased myocardial stretch or wall tension [21]. When ventricular myo- cytes secrete pro-BNP108, furin, corin or other currently unknown proteases are thought to cleave pro-BNP108 to pro- BNP77-108 (BNP-32), which is considered to be the biologic-

Table 2: Demographic data of the studied groups.

Parameters	Controls (n = 120)	T2DM without CVD (n = 120)	T2DM with CVD (n = 120)	F	t	p - value
		Groups		**Statistical test**		
Age (years) Mean ± SD Range	58.2 ± 7.2 (48-73)	59.1 ± 7.3 (46-70)	57.6 ± 11.2 (20-79)	0.949		0.388
Height (cm) Mean ± SD Range	172.6 ± 7.5 (155-191)	173.3 ± 8.7 (150-195)	166.3 ± 8.7$^{\$\#}$ (140-190)	25.885		< 0.001*
Weight(Kg) Mean ± SD Range	87 ± 12.6 (61-113)	88.5 ± 14.4 (53-135)	81 ± 13.6 (51-127)	10.451		< 0.001*
BMI (kg/m²) Mean ± SD Range	29.2 ± 3.6 (20.9-39.1)	29.5 ± 4.6 (19.5-42.7)	29.4 ± 5.2 (17.9-43.4)	0.172		0.842
WC (cm) Mean ± SD Range	80 ± 9.4 (61.1-110)	87.6 ± 10.5$^{\$}$ (69.3-118.4)	109.7 ± 14.6$^{\$\#}$ (72-149)	209.210		< 0.001*
Systolic BP (mmHg) Mean ± SD Range	121 ± 8.3 (105-140)	128.9 ± 23.1$^{\$}$ (95-190)	131.5 ± 20.8$^{\$\#}$ (90-180)	10.421		< 0.001*
Diastolylic BP (mmHg) Mean ± SD Range	79.3 ± 4.4 (70-85)	82.3 ± 9.3$^{\$}$ (65-100)	75.6 ± 11.2$^{\$\#}$ (50-104)	17.404		< 0.001*
Heart rate (b/min) Mean ± SD Range	73.5 ± 7.2 (60-90)	79.2 ± 7.7$^{\$}$ (60-100)	77.5 ± 14$^{\$}$ (35-117)	10.009		< 0.001*
Duration DM (years) Mean ± SD Range		7.1 ± 5.8 (1-25)	10.4 ± 5.6 (2-25)		4.471	< 0.001*
Duration HTN (years) Mean ± SD Range		7.0 ± 4.6 (1-19)	9.0 ± 4.9 (1-20)		2.025	0.042
Duration CVD (years) Mean ± SD Range			7.9 ± 4.9 (1-20)			

p (*, #: significant at $p ≤ 0.05$); *: T2DM with CVD & T2DM without CVD versus control group, #: compares T2DM without CVD versus T2DM with CVD.

ally active hormone and an inactive amino terminal pro-BNP1-76 (NT-pro-BNP-76) [22]. Corin and furin were identified as the most likely pro- BNP processing enzymes [23]. To date, despite numerous studies devoted to the assessment of the clinical significance of pro-BNP-derived peptides, the clinical importance of corin and furin in the pathophysiology of CVDs remains incompletely understood.

We hypothesized that corin and furin might serve as biomarkers to predict the development of CVDs in T2DM patients. To test this hypothesis, we measured plasma corin and furin in T2DM patients with or without CVDs as well as in healthy subjects. The present study shows that corin levels were significantly lower in T2DM patients with or without CVDs than those in healthy subjects. Similarly, corin levels were lower in T2DM patients with CVDs than those in T2DM patients without CVDs. These results suggest that the reduction of corin levels may be related more closely to the pathological changes associated with DM than that of CVDs. The reduced levels of corin observed in T2DM patients with CVDs are likely to reflect either the chronic loss of cardiomyocytes and/or diminished cardiac corin protein expression. It is possible that the expression/activity of corin sheddase, which remains unknown, is reduced in CVDs, leading to low levels of plasma corin. Alternatively, corin cleaves itself on the cell surface and in CVDs such a process is inhibited or impaired, resulting in lower corin levels in plasma. Other possibilities may also include

accelerated plasma corin degradation or clearance [24]. In the current study, there was a significant negative correlation between corin and BNP levels in T2DM patients with or without CVD. Furthermore, a negative correlation was found between corin and furin levels in T2DM patients with CVD. It has been previously reported that plasma corin levels were reduced significantly in patients with HF and that the reduction of corin levels appeared to correlate with the severity of HF [25,26]. These results are consistent with the elevated levels of unprocessed natriuretic peptides in patients with HF, suggesting that corin deficiency may be a contributing factor in failing hearts [27]. Recently, low serum corin levels were found to be an independent predictor for poor clinical outcomes in patients with coronary disease [28]. Interestingly, it has been recently demonstrated that there were no significant differences in the plasma corin concentration/activity among the Acute Decom- Pensated Heart Failure (ADHF), non-cardiac dyspnea (non- ADHF), and CHF patient groups. Additionally, there was no significant correlation between corin concentration/activity and pro-BNP, NT-pro-BNP or BNP levels [29].

Surprisingly, it has been reported that the furin-mediated cleavage of pro-BNP resulted in BNP1-32, whereas corin- mediated processing of pro-BNP results in the formation of truncated BNP4-32, suggesting that corin is unlikely to be the primary candidate for the role of pro-BNP processing enzyme [23][30].

Table 3: Biochemical parameters of the studied groups.

Parameters	Groups			F	*p* - value
	Controls (n = 120)	T2DM without CVD (n = 120)	T2DM with CVD (n = 120)		
Corin (ng/ l) Mean ± SD Range	138.8 ± 72.4 (5.9-355)	81.2 ± 60.1$ (7-262)	63.5 ± 40.9$ (18-245)	53.069	< 0.00*
Furin (pg/ l) Mean ± SD Range	161.4 ± 37 (100-257)	200.8 ± 85.7 (93-540)	1092.3 ± 819.7$# (107.1-3158.4)	146.580	< 0.00*
Hb (g/ dl) Mean ± SD Range	13.3 ± 1.7 (10.5-16.7)	12.3 ±1.9$ (9.1-16.4)	11.6 ± 1.4$# (8-16.9)	28.554	< 0.00*
FBS (mg/ dl) Mean ± SD Range	84.1 ± 9.1 (66-113)	166.1 ± 55.1$ (101-378)	199.5 ± 73.5$# (75-482)	148.990	< 0.00*
Creatinine (mg/ dl) Mean ± SD Range	0.74 ± 0.22 (0.28-1.11)	1 ± 0.32$ (0.28-1.94)	1.22 ± 0.46$# (0.27-2.3)	57.826	< 0.00*
Uric Acid (mg/ dl) Mean ± SD Range	4.3 ± 0.8 (3-6.5)	5 ± 1.1$ (3.3-9.4)	5.6 ± 2.4$# (2.3-12.9)	20.437	< 0.00*
Cholesterol Mean ± SD Range	159.4 ± 24.9 (99-213)	188.9 ± 47.6$ (89-336)	208 ± 55.5$# (117-378)	36.139	< 0.00*
TG (mg/ dl) Mean ± SD Range	144.1 ± 66.6 (79-424)	174.2 ± 67.4$ (72-411)	234 ± 94$# (93-501)	42.337	< 0.00*
HDL-C (mg/ dl) Mean ± SD Range	45.4 ± 9.3 (27-66)	37.7 ± 7.9$ (23-53)	33.9 ± 7.9$# (17-56)	58.848	< 0.00*
LDL-C (mg/ dl) Mean ± SD Range	85.2 ± 35.6 (17-192)	116.5 ± 47$ (17-256)	126.9 ± 53$ (52-291)	27.084	< 0.00*
CK (U/ L) Mean ± SD Range	86.2 ± 22 (55-167)	119.6 ± 47.7 (41-207)	353.2 ± 473.1$# (40-2212)	33.629	< 0.00*
CK-MB (U/ L) Mean ± SD Range	8.9 ± 2.5 (2.8-17.3)	12.3 ± 4.4 (4.7-28.1)	57.6 ± 94.8$# (7.4-418)	29.567	< 0.00*
LDH (U/L) Mean ± SD Range	314.9 ± 67 (218-529)	355.3 ± 89.2 (233-612)	576.3 ± 442.3$# (213-1976)	34.272	< 0.00*

p (*, #: significant at *p* ≤ 0.05); *: T2DM with CVD & T2DM without CVD versus control group, #: compares T2DM without CVD versus T2DM with CVD.

In the present study, furin levels appeared to be significantly higher in T2DM patients with CVDs than those in T2DM patients without CVDs and healthy subjects. In addition, furin levels were higher in T2DM patients without CVDs than those in healthy subjects. These results suggest that the elevation of furin levels may be related more closely to the pathological changes associated with CVDs than that of DM. Furthermore, there was a significant positive correlation between furin and BNP levels in healthy subjects, T2DM patients with or without CVDs. Moreover, a negative correlation was found between furin and corin levels in T2DM patients with CVDs.

Recently, [29] reported that there were no significant differences in the plasma furin concentration among the ADHF, non-ADHF and CHF patient groups. Furthermore, there was no significant correlation between plasma furin concentration and pro-BNP, NT-pro-BNP or BNP levels.

In our study, the sensitivity of CVDs diagnosis in T2DM patients by furin level was significantly higher than that by corin. However, both furin and BNP have a similar sensitivity in diagnosing CVDs. Furthermore, the specificity of CVDs diagnosis by furin level was significantly higher than that by corin. In the current study, since furin produced a similar sensitivity to BNP and better specificity, PPV, NPV, diagnostic accuracy and AUC than BNP in the biochemical diagnosis of CVDs, furin measurements could add important information to clinical judgment in establishing a final diagnosis of CVDs.

Likelihood of altering protein function. However, it may be argued that a more comprehensive examination of the total allelic

Table 4: Correlation between serum corin level and studied parameters among study population

Parameters	Serum corin level (ng/ml)	
	Pearson correlation (r)	p - value
Age (years)	0.038	0.474
Height (cm)	0.126	0.017*
Weight(Kg)	0.053	0.319
BMI (kg/m²)	-0.031	0.564
duration Heart disease (years)	0.004	0.968
Duration DM (years)	-0.087	0.178
DurationHTN (years)	-0.141	0.113
Systolic BP (mmHg)	-0.160	0.002*
Diastolylic BP (mmHg)	0.018	0.734
Heart rate (b/min)	-0.105	0.048*
Furin (pg/l)	-0.349	< 0.001*
Hb (g/dl)	0.277	< 0.001*
FBS (mg/dl)	-0.441	< 0.001*
Creatinine (mg/dl)	-0.358	< 0.001*
Uric Acid (mg/dl)	-0.153	< 0.001*
Cholesterol (mg/dl)	-0.192	<0.001*
TG (mg/dl)	-0.267	< 0.001*
HDL-C (mg/dl)	0.221	< 0.001*
LDL-C (mg/dl)	-0.189	< 0.001*
CK (U/L)	-0.176	< 0.001*
CK-MB (U/L)	-0.190	< 0.001*
LDH (U/L)	-0.187	< 0.001*

*p - value significant at $p \leq 0.05$

Table 5: Correlation between serum corin level and studied parameters among study population.

Parameters	Serum furin level (Pg/ml)	
	Pearson correlation (r)	p - value
Age (years)	-0.029	0.584
Height (cm)	-0.273	0.000*
Weight(Kg)	-0.155	0.003*
BMI (kg/m²)	0.029	0.581
duration Heart disease (years)	-0.023	0.801
Duration DM (years)	0.177	0.006*
DurationHTN (years)	0.169	0.057
Systolic BP (mmHg)	0.119	0.023*
Diastolylic BP (mmHg)	-0.128	0.015*
Heart rate (b/min)	0.060	0.257
Hb (g/dl)	-0.188	< 0.001*
FBS (mg/dl)	0.490	< 0.001*
Creatinine (mg/dl)	0.485	< 0.001*
Uric Acid (mg/dl)	0.293	< 0.001*
Cholesterol (mg/dl)	0.309	< 0.001*
TG (mg/dl)	0.341	< 0.001*
HDL-C (mg/dl)	-0.224	< 0.001*
LDL-C (mg/dl)	0.238	< 0.001*
CK (U/L)	0.336	< 0.001*
CK-MB (U/L)	0.307	< 0.001*
LDH (U/L)	0.269	< 0.001*

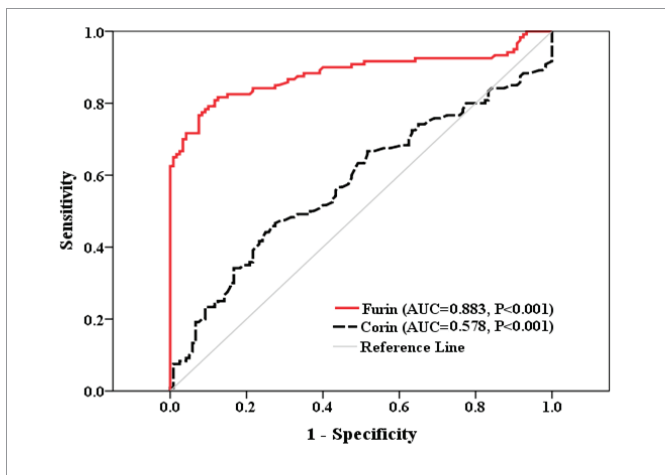*p - value significant at $p \leq 0.05$

Figure 1: Receiver Operating Characteristic Curve (ROC) to diagnostic CVDs

variation of the corin locus in more diverse populations using a haplotype-based approach will yield additional insights In conclusion, to the best of our knowledge, the present study is the first to provide a preliminary elucidation of the clinical value of the furin levels in the risk assessment of CVDs in T2DM patients. Our findings indicate that a routine measurement of furin levels can improve the predictive ability of CVDs in T2DM patients. Our findings are expected to encourage designing future studies with larger cohorts of patients from different ethnic populations. Further studies are warranted to determine if plasma furin levels are changed in patients with cardiovascular complications over a longer period following medical treatment and if the changes correlate with the underlying pathology. Such studies shall help to understand the diagnostic and prognostic values of furin and may also help to translate basic discoveries in furin research into novel strategies to treat cardiovascular complications.

Table 6: Youden index cut-off points, sensitivity, specificity, positive predictive value, negative predictive value and area under the curve of furin, corin and for diagnostic CVDs in T2DM patients.

Biomarker	T2DM without CVDs (n = 120)	T2DM with CVDs (n = 120	Cut-off point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	AUC (95% CI)	p - value
Furin (pg/ml)	111	33	≤ 353.95	72.5	92.5	90.6	77.1	82.5	0.883 (0.836-0.930)	< 0.001*
	9	87	> 353.95							
Corin (ng/ml)	33	56	≤ 68.2	46.7	72.5	62.9	57.6	59.6	0.578 (0.505-0.651)	0.036*
	87	64	> 68.2							

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