Clinical significance of chitotriosidase in outpatients with advanced heart failure

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ABSTRACT

The previous studies have shown that plasma chitotriosidase (CHIT) levels increase in many diseases with inflammation. However, there are no reported studies investigating the relationship between CHIT and chronic heart failure (CHF) which is an inflammatory process. Therefore, we aimed to investigate the role of CHIT in diagnosis and severity of CHF in this study. 36 patients (50% male, mean age 63.17±10.18 years) with left ventricular ejection fraction <40% and 27 controls (44% male, mean age 61.33±8.73 years) were included in this study. Patients with CHF were divided into two groups as ischemic heart failure (IHF) and non-ischemic heart failure (NIHF) according to the underlying etiology. Plasma CHIT and N-terminal pro brain natriuretic peptide (NT-proBNP) levels were measured by ELISA method. Plasma CHIT and NT-proBNP levels were higher in patients with CHF than in controls (CHIT 931.25±461.39 ng/mL, 232.79±61.28 ng/mL, p<0.001; NT-proBNP, 595.31±428.11 pg/mL vs 78.13±30.47 pg/L; p<0.001). Also, the levels of these parameters increased in IHF compared with NIHF (CHIT, 1139.28±495.22 ng/mL, 671.22±237.21 ng/mL, p=0.002; NT-proBNP, 792.87±461.26 pg/mL vs 348.36±202.61 pg/mL, p=0.001) and there was a strong correlation between NT-proBNP and CHIT (r=0.969, p<0.001). According to this study findings, plasma CHIT level increases in CHF and its increased levels are correlated with NT-proBNP which is used diagnosis and prognosis of HF.

Significance of this study

What is already known about this subject?

- Chitotriosidase (CHIT) is an enzyme secreted by active macrophages and neutrophils and its increased levels have been shown in various diseases such as tuberculosis, sarcoidosis, multiple sclerosis and neurodegenerative diseases that are associated with inflammatory processes.
- CHIT measurements are also used in evaluation of treatment response in the lysosomal storage diseases today.

What are the new findings?

- The recent studies demonstrated that CHIT activation increases 55-fold in atherosclerotic tissues and this elevation is directly proportional to the number of diseased vessels.
- Also, there are only few studies that reported its increased levels in acute stroke. Therefore, most of the scientists agree that CHIT has an important role in the development and progression of atherosclerosis accompanied by the inflammatory process.

How might these results change the focus of research or clinical practice?

- In this study, we investigated the role of CHIT in heart failure (HF), which has inflammation in its pathophysiology and is closely related with coronary artery disease, and found that CHIT can indicate both the presence of HF and its severity. Its strong relationship with N-terminal pro brain natriuretic peptide (NT-proBNP), which is used in the diagnosis, exclusion of diagnosis and treatment follow-up of HF, suggests that this biomarker may be used in clinical practice with the same indications.
- In particular, CHIT enzyme activity may be measured in patients with mismatch between symptoms and clinic findings which may not be distinguished by NT-proBNP (gray zone) or in patients with right and left ventricular dysfunction coexistence or false positive results of NT-proBNP.

INTRODUCTION

Chronic heart failure (CHF) is a clinical syndrome that represents the last stage of various heart diseases and is characterized by the failure of the heart to meet the body's metabolic demands.[1] Despite advanced modern medical treatments, it is still associated with high mortality and morbidity.[2] Its incidence increases due to advanced age, hypertension and ischemia, so it imposes a great economic burden on societies by increasing healthcare costs.[3] CHF has a wide spectrum ranging from a mild disease that can be easily managed to advanced disease that requires treatment with mechanical support or heart transplantation. Therefore, early diagnosis of disease, determination of appropriate treatment strategies and estimation of prognosis are very important. Although New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF) and natriuretic peptide level measurements are used for the severity and prognosis, these parameters may not still adequately

predict major adverse cardiac events. For these reasons, new biomarkers are needed to better understand the pathophysiology of HF and to determine new treatment strategies.[4]

The recent studies have suggested that many complex biological stages such as inflammation, oxidative stress, neurohormonal activation, myocyte damage and vascular remodeling intertwine in the underlying pathophysiology of heart failure (HF).[5] Many biomarkers such as chemokines, adhesion molecules and endothelin-1 and cytokines such as tumor necrosis factor-α (TNF-α), interleukin 1 (IL-1) and interleukin 6 (IL-6) have been investigated in the pathogenesis.[6] Although increased levels of these parameters have been demonstrated in patients with HF, their role in the progression of HF is not yet clear. In addition, high success has not been achieved with treatment strategies targeting these cytokines.[7]

Chitotriosidase (CHIT) is a member of the 18-glycosyl hydrolase family and is the first active chitinase identified in human plasma.[8] CHIT is released from polymorph nuclear neutrophils and mainly activated macrophages. CHIT plays an important role in the immune response against fungi, bacteria and pathogens including chitin.[9] Therefore, CHIT activity measurement is used as a biochemical marker in lysosomal storage diseases such as Gaucher disease and Nieman Pick, in which macrophage accumulation and activity increase.[10] In addition, increased levels in plasma have been shown in diseases such as chronic lung diseases, tuberculosis, sarcoidosis, multiple sclerosis, malignancy, thalassemia, familial Mediterranean fever, Alzheimer's and stroke.[11] According to recent studies, CHIT may play a role in innate immunity and may act as an immunomodulator indirectly in antigen presentation and induction of cell-mediated immunity.[12]

The role of CHIT in the development and progression of atherosclerosis has been supported by many studies.[13] One study showed that CHIT enzyme activation increased 55-fold in atherosclerotic tissues, another study also demonstrated the association between CHIT and the severity of coronary artery disease (CAD) defined by the number of diseased vessels.[14 15] However, no study has been reported investigating the role of CHIT in HF, an inflammatory process like CAD. Therefore, we aimed to evaluate the role of CHIT in determining the diagnosis and severity of HF and its relationship with N-terminal pro brain natriuretic peptide (NT-proBNP) in this study.

MATERIALS

Study population

This cross-sectional case-control study was carried out with 36 patients with LVEF <40% and 27 control subjects who admitted to the Pamukkale University Faculty of Medicine Cardiology department outpatient clinic between 01.05.2014 and 01.11.2014. Acute coronary syndrome in the last 3 months, newly diagnosed HF (<6 months), acute myocarditis and pericarditis, congenital heart diseases, malignancies, hematological disorders, chronic renal failure (glomerular filtration rate (GFR) calculated by the Cockcroft-Gault formula <50 mL/min/1.73 m^2), lysosomal storage disorders, acute and chronic infections, severe chronic obstructive pulmonary diseases, autoimmune diseases, thyroid dysfunctions, sepsis, severe malnutrition, neurodegenerative diseases, cerebrovascular diseases, pregnancy and lactation were determined as exclusion criteria.

CHF was divided into ischemic and non-ischemic according to the underlying etiology. HF with objective findings of CAD in coronary angiography or functional tests was defined as ischemic HF (IHF).[16] The development of HF due to genetic, viral infections, arrhythmia, infiltrative diseases, heart valve diseases was defined as non-ischemic HF (NIHF).[17] NYHA functional class was determined by experienced cardiologists who were blinded to the study, based on symptoms and clinical data. The subjects with other comorbidities except hypertension, especially diabetic subjects because of high prevalence of occult ischemia due to diabetic neuropathy, were not included in the control group due to the use of only medical history and clinical findings to rule out CAD.

Demographic and clinical data

Demographic and clinical data such as age, gender, smoking, body mass index, medical history and drug use were collected from all subjects. The detailed physical examination and ECG were performed. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, the current use of antihypertensive treatment or a combination of them.[18] Diabetes was defined as the use of current insulin or oral agents or having a fasting serum glucose level ≥126 mg/dL (7.0 mmol/L) or HbA1c≥6.5% or a known history of diabetes.[19]

Echocardiography

Two-dimensional transthoracic echocardiography (Vivid 7, General Electric Vingmed Ultrasound, Horten, Norway) was performed by the same operator in the left lateral decubitus position. Left ventricular morphology and functions were evaluated by parasternal long-short axis, apical and subcostal imagings. Left ventricular end-systolic diameter (LVESD) and left ventricular end-diastolic diameter (LVEDD) were measured using M-mode and LVEF was calculated by biplanar Simpson method.

Blood samples

Peripheral venous blood samples were collected after 8–12 hours of fasting. Routine biochemical tests including plasma fasting glucose, lipids, kidney function tests were analyzed on Cobas Integra 800 autoanalyzer using the electrochemilumization method (Roche Diagnostics GmbH, Mannheim, Germany). Hemogram parameters such as complete blood count and leukocyte count were evaluated with the ADVIA-120 system using flow cytometry method. Serum NT-pro BNP concentrations were determined by enzyme linked immunosorbent assay (ELISA) using DRG NT-proBNP direct (EIA-4827) from DRG International, USA. The detected concentration range was 0–640 pmol/L and then pmol/L unit was converted to pg/mL.

CHIT levels measurement

Blood samples were taken in an EDTA-containing tube and centrifuged at 3000 ×g for 10 min and stored at −70°C for later analysis. Plasma CHIT levels were measured with the commercial CY-8074 CircuLex Human Chitotriosidase ELISA kit (MBL International, Woburn, Massachusetts,

USA) according to the manufacturer's protocol. The concentration range was between 56.25 and 3600 pg/mL. Absorbance was read on a microplate reader at 450 nm wave length. The concentrations of CHIT in each sample were calculated by a four-parameter mounting method based on the standard curve, using blank, corrected and averaged over replicate values.

Statistical analysis

The data were analyzed with SPSS 25.0 (IBM SPSS Statistics 25 software; IBM, Armonk, New York, USA) package program. Shapiro Wilk test was used for determination of normal distribution. Continuous variables were defined by the mean±SD and categorical variables were defined by numbers and percentages. For independent groups comparisons, Independent samples t test was used when parametric test assumptions were provided and Mann-Whitney U test was used when parametric test assumptions were not provided. The spearman correlation analysis was performed to analyze the relationships between continuous variables. Differences between categorical variables were tested with χ^2 analysis. The statistical significance point (alpha) was chosen as 0.05.

RESULTS

Comparison of the groups is summarized in table 1. Mean ages of the groups (63.17±10.18 vs 61.33±8.73; p=0.455) and male population ratios were similar (50% vs 44%; p=0.662). There was no significant difference between hypertension incidences in the groups. The LVEF in patients with CHF was significantly lower (27.27%±5.23 %, 60.17%±3.21%; p<0.001) and CHF patients showed high NT-proBNP and CHIT levels according to controls (NT-proBNP, 595.31±428.11 pg/mL vs 78.13±30.47; p<0.001; CHIT, 931.25±461.39 ng/mL vs 232.79±61.28; p<0.001) (figure 1). In addition, fasting plasma glucose, creatinine, GFR, sodium, triglycerides, high-density lipoprotein cholesterol, white blood cells (WBC) and albumin levels differed significantly in groups (p<0.05).

Baseline characteristics, clinical and laboratory findings of IHF (n=20, 50% male, mean age 63.45±10.49 years) and NIHF (n=16, 50% male, 62.81±10.11) groups are shown in table 2. The incidences of hypertension, diabetes mellitus and atrial fibrillation were similar. LVEF in IHF patients was significantly lower than in patients with NIHF (25.57±5.14 vs 29.39±4.67; p=0.027). However, no differences in LVEDD and LVESD measurements were found. According to clinical symptoms and data, the number of patients in NYHA III-IV functional class was higher in the IHF group (70% vs 30%; p=0.05). There were significant differences in CHIT and NT-proBNP levels between groups and these parameters' concentrations were more increased in patients with IHF (CHIT; 1139.28±495.22 vs 671.22±237.21; p=0.002; NT-proBNP; 792.87±461.26 and 348.36±202.61; p=0.001) (figure 2). In addition creatinine, GFR, HDL-C and WBC also showed significant differences in the groups (p<0.05). In correlation analysis, CHIT was associated with age, LVEF, creatinine, GFR, WBC and albumin (table 3). There was also a strong correlation between CHIT and NT-proBNP which is used for determination of HF diagnosis and HF prognosis in clinical practice (figure 3).

Table 1 Baseline characteristics, laboratory data and medications

	Patients (n=36)	Controls (n=27)	P value
Baseline characteristics			
Mean age (years)	63.17±10.18	61.33±8.73	0.455
Males, n (%)	18 (50)	12 (44)	0.662
Body mass index (kg/m^2)	28.38±5.13	28.91±4.97	0.682
Hypertension, n (%)	17 (47)	9 (33)	0.268
Diabetes mellitus, n (%)	–	14 (39)	0.0001
Smoking, n (%)	3 (8)	5 (19)	0.272
Systolic blood pressure (mm Hg)	119.89±13.44	117.37±13.57	0.466
Diastolic blood pressure (mm Hg)	76.72±10.56	73.48±8.73	0.200
Heart rate (beats/min)	74.58±13.24	70.78±13.29	0.177
Atrial fibrillation, n (%)	10 (28)	–	0.003
LVEDD (mm)	60.86±5.56	46.19±3.78	<0.001
LVESD (mm)	49.11±6.40	29.04±3.03	<0.001
LVEF (%)	27.27±5.23	60.17±3.21	<0.001
Laboratory findings			
FPG (mg/dL)	115.33±28.64	95.44±10.57	0.002
Creatinine (mg/dL)	0.96±0.16	0.72±0.10	<0.001
GFR (mL/min/m^2)	75.15±13.77	89.04±13.69	<0.001
Sodium (mEq/L)	139.22±3.46	140.74±1.81	0.028
T-chol (mg/dL)	188.78±46.34	197.11±39.71	0.456
TG (mg/dL)	163.64±77.40	117.41±64.47	0.002
LDL-C (mg/dL)	110.17±31.27	118.56±30.65	0.292
HDL-C (mg/dL)	40.61±7.27	54.85±13.43	<0.001
Hemoglobin (g/L)	137.00±13.00	142.50±13.30	0.08
WBC (cells/µL)	9.07±2.07	6.6±1.46	<0.001
Albumin (g/dL)	4.27±0.26	4.56±0.25	<0.001
NT-proBNP (pg/mL)	595.31±428.11	78.13±30.47	<0.001
Chitotriosidase (ng/mL)	931.25±461.39	232.79±61.28	<0.001
Medication, n (%)			
ACE inhibitor/ARB	27 (75)	8 (30)	<0.001
Beta-blockers	32 (89)	2 (7)	<0.001
Statins	13 (36)	1 (4)	0.002
Loop diüretics	23 (64)	–	<0.001
Aldosterone antagonist	19 (53)	–	<0.001
Antiplatelet agents	34 (94)	5 (19)	<0.001
Digoxine	9 (25)	–	<0.001

ACE, angiotensin-converting enzyme; ; ARB, angiotensin receptor blocker; FPG, fasting plasma glucose; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; NT-proBNP, N-terminal pro hormone brain natriuretic peptide; T-chol, total cholesterol; TG, triglycerides; WBC, white blood cells.

DISCUSSION

In this study, we investigated the role of CHIT in the diagnosis and severity of HF. We found increased plasma CHIT levels in patients with CHF than in control subjects. When we categorized patients with CHF into two groups according to baseline etiology, we showed that patients with IHF had higher plasma CHIT enzyme levels than in patients with NIHF and there was a strong positive correlation between NT-proBNP and CHIT.

The underlying pathophysiology of CHF is complex. The mechanisms that trigger the development of HF can be

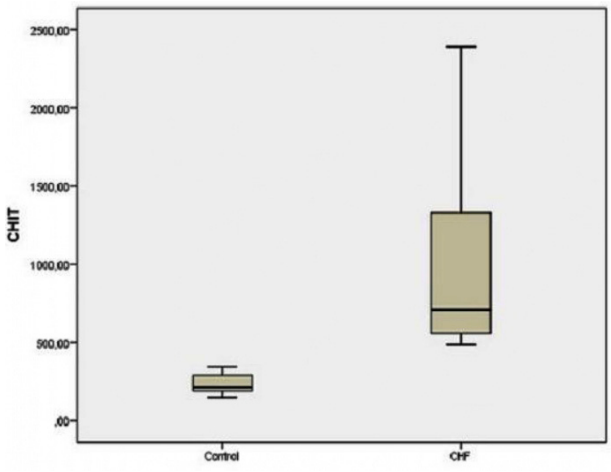

Figure 1 The comparison of plasma CHIT levels in patients with CHF and controls. CHF, chronic heart failure; CHIT, chitotriosidase.

classified as ischemia-related damages, metabolic syndrome including hypertension, diabetes mellitus and obesity, genetic causes, mechanical factors and activation of the native or acquired immune system.[20 21] Although CHF was previously thought as a hemodynamic disorder caused by sympathetic system and neurohormonal system activation, the failure of treatments targeting these systems has led to investigation of other underlying mechanisms.[2 22]

Many studies have shown increased circulating levels of inflammatory cytokines such as TNF-α, IL-1β, IL-6 and chemokines such as monocyte chemoattractant peptide-1, IL-8 and macrophage protein-1a in HF. As a result of these studies, it has been claimed that CHF may develop as a result of a neurohormonal disorder and inflammation and HF may be strongly linked and they may affect each other.[23–25]

The immune cells which play an important role in inflammation also provide the modulation of the development and progression of HF. One of the immune modulator cells which play a role in CHF development is monocyte-derived macrophages. Monocyte-derived macrophages lead to cardiac remodeling in cardiac tissue damage and they are divided into resident macrophages derived from embrionic progenitors and infiltrative CCR2+ monocyte-derived macrophages with different functions in the heart tissue. Under normal conditions, resident macrophages derived from embryonic progenitors are of dominant type in the heart tissue and they are activated in minimal inflammation and tissue repair. However, in severe cardiac damage, CCR2+ monocyte-derived macrophages become dominant and initiate the inflammatory process.[26 27] Although the main sources of cytokines are lymphocytes, fibroblasts and endothelial cells, the monocyte-derived macrophages may secrete these proinflammatory cytokines during inflammation and cardiomyocytes are one of the main source of cytokines in this process.[28]

CHIT plays a role in the pathogenesis of many diseases by contributing to reverse remodeling in the inflammation process. It provides cellular-mediated immunity, especially in defense against pathogens, and accelerates eosinophil, lymphocyte and macrophage migration by stimulating the secretion of many chemokines. It also contributes to tissue healing (fibrosis) by increasing TGF-β1 expression in organ damages.[12 29] As previously mentioned, CHIT is produced by activated and differentiated macrophages and neutrophils which play important role in inflammation process and its production increase depending on the number of activated macrophages.[8] Considering the active role of macrophages in CHF process, the secretion of CHIT by these immune cells is possible in CHF. CHIT may lead to reverse remodeling in CHF by tissue repair and triggering the secretion of various chemokines in cardiac damage such as pulmonary fibrosis, non-alcoholic fatty liver disease and neurodegenerative diseases.[12]

Table 2 Characteristics of study patients according to the etiology

	IHF (n=20)	NIHF (n=16)	P value
Baseline characteristics			
Mean age (years)	63.45±10.49	62.81±10.11	0.855
Males, n (%)	10 (50)	8 (50)	1.000
Body mass index (kg/m^2)	29.19±6.13	27.38±3.45	0.272
Hypertension, n (%)	10 (50)	7 (44)	0.709
Diabetes mellitus, n (%)	9 (45)	5 (31)	0.400
Smoking, n (%)	2 (10)	1 (6)	1.000
Systolic blood pressure (mm Hg)	120.65±16.78	118.94±7.92	0.69
Diastolic blood pressure (mm Hg)	75.20±12.25	78.63±7.97	0.404
Heart rate (beats/min)	73.15±12.03	76.38±14.81	0.476
Atrial fibrillation, n (%)	5 (25)	5 (31)	0.722
LVEDD (mm)	61.90±6.46	59.56±4.02	0.386
LVESD (mm)	50.45±7.39	47.44±4.60	0.290
LVEF (%)	25.57±5.14	29.39±4.67	0.027
NYHA I–II, n (%)	6 (30)	10 (63)	0.05
NYHA III–IV, n (%)	14 (70)	6 (37)	0.05
Laboratory findings			
FPG (mg/dL)	121.90±29.01	107.13±26.81	0.062
Creatinine (mg/dL)	1.02±0.19	0.89±0.07	0.012
GFR (mL/min/m$^{2)}$	70.24±14.68	81.29±9.84	0.011
Sodium (mEq/L)	139±3.29	139.5±3.74	0.44
T-chol (mg/dL)	177.35±43.16	203.06±47.54	0.099
TG (mg/dL)	167.40±90.53	158.94±59.64	0.888
LDL-C (mg/dL)	108.35±32.05	112.44±31.14	0.703
HDL-C (mg/dL)	38.45±7.81	43.31±5.65	0.02
Hemoglobin (g/L)	139.40±13.10	133.90±12.60	0.215
WBC (cells/μL)	9.70±2.07	8.29±1.84	0.049
Albumin (g/dL)	4.24±0.27	4.30±0.26	0.508
NT-proBNP (pg/mL)	792.87±461.26	348.36±202.61	0.001
Chitotriosidase (ng/mL)	1139.28±495.22	671.22±237.21	0.002
Medication, n (%)			
ACE inhibitor/ARB	13 (65)	14 (88)	0.245
Beta-blockers	18 (90)	14 (88)	0.813
Statins	12 (60)	1 (6)	0.001
Loop diüretics	15 (75)	8 (50)	0.121
Aldosterone antagonist	10 (50)	9 (56)	0.709
Antiplatelet agents	18 (90)	16 (100)	0.492
Digoxine	5 (25)	4 (25)	1.000

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; FPG, fasting plasma glucose; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IHF, ischemic heart failure; LDL-C, low-density lipoprotein cholesterol; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; NIHF, non-ischemic heart failure; NT-proBNP, N-terminal pro hormone brain natriuretic peptide; NYHA, New York Heart Association; T-chol, total cholesterol; TG, triglycerides; WBC, white blood cells.

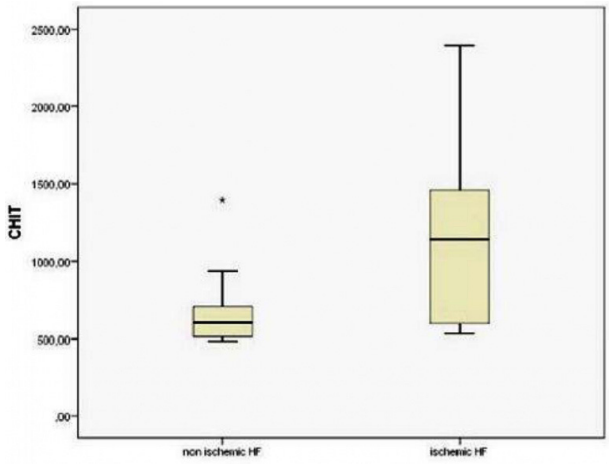

Figure 2 The comparison of plasma CHIT levels according to etiology of heart failure. CHIT, chitotriosidase; HF, heart failure.

Also, it has been shown that the NLRP3 inflammatory system increases CHIT expression by TNF-α induction and the NF-B signaling pathway by stimulation of IL-1β[30 31] playing important role in progression of CHF.[32] Therefore, there may be a possibility that these cytokines may indirectly increase plasma CHIT levels by stimulating of monocyte-derived macrophages. Also, a study showed the prolongation of the life span of neutrophils in congestive HF and the neutrophils which is another source of CHIT may affect the CHIT secretion in our study.[33] Based on these inferences, CHIT measurements may be used in diagnosis of patients with HF with impaired left ventricular systolic function.

Table 3 The correlation analysis of chitotriosidase in patients with heart failure

Variables	R	P value
Mean age	0.515	0.001
Body mass index	−0.146	0.397
Systolic blood pressure	−0.082	0.635
Diastolic blood pressure	−0.186	0.277
Heart rate	0.164	0.340
LVEDD	0.008	0.962
LVESD	0.076	0.660
LVEF	−0.491	0.002
FPG	0.183	0.284
Creatinine	0.345	0.04
GFR	−0.693	<0.001
Sodium	−0.267	0.116
T-chol	−0.057	0.743
TG	0.226	0.229
LDL-C	0.101	0.557
HDL-C	−0.068	0.692
Hemoglobin	−0.241	0.157
WBC	0.680	<0.001
Albumin	−0.422	0.01
NT-proBNP	0.969	<0.001

FPG, fasting plasma glucose; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; NT-proBNP, N-terminal pro hormone brain natriuretic peptide; T-chol, total cholesterol; TG, triglycerides; WBC, white blood cells.

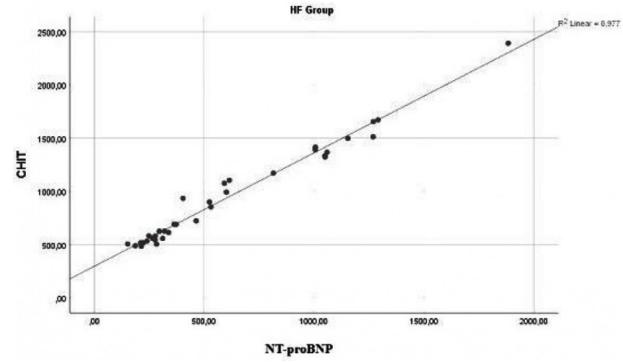

Figure 3 The correlation between CHIT and NT-proBNP in heart failure according to underlying etiology. CHIT, chitotriosidase; HF, heart failure; NT-proBNP, N-terminal pro brain natriuretic peptide.

Many studies have shown that IHF has a worse prognosis than NIHF and the parameters such as advanced age, poor NYHA functional class and impaired renal functions are associated with the severity and prognosis of HF.[34 35] In particular, lower LVEF is a major risk factor for cardiac and all-cause mortality.[36] NT-proBNP is another biomarker that indicates the HF progression and prognosis and its increased levels were associated with lower LVEF and advanced NYHA functional class.[37] In our study, the worse LVEF, advanced NYHA functional class and higher NT-proBNP levels and impaired renal functions in patients with IHF confirmed that IHF has a worse prognosis, similar to previous reports. In addition, the demonstration of higher plasma CHIT levels in ischemia etiology and the significant correlation of CHIT with age, LVEF, creatinine, GFR and NT-proBNP also suggest that CHIT may be used in determining the severity and indirectly prognosis of HF.

The incidence of hypoalbuminemia in patients with HF is higher than in healthy population and is associated with increased NT-proBNP levels and mortality rate.[38] In a prospective study involving middle-aged men, leukocyte count increase was correlated with hospitalization frequency in HF.[39] In our study, the correlation between CHIT and hypoalbuminemia and increased leukocyte count confirms our hypothesis that CHIT may play a role in determining the severity of CHF and indirectly prognosis.

We agree that CHIT may be used in the diagnosis/severity of HF, in outpatient follow-up of patients with HF, evaluation of response to treatment and in the differential diagnosis of acute dyspnea instead of NT-proBNP, especially in emergency units. However, it may be more appropriate to use it in only selected patients because of its high cost and non-practical measurements unlike NT-proBNP. Also, CHIT enzyme activity may be measured in patients with mismatch between symptom and clinic findings which cannot be distinguished by NT-proBNP (gray zone). In addition, both biomarkers may be used together in very elderly patients (age >80 years), right and left ventricular dysfunction coexistence and false positive results of NT-proBNP.

There were some limitations in this study. This study was performed in a single center and it had relatively small sample. The categorization of NYHA functional class level was based on the patient's subjective symptoms rather than objective evidence. Also, HF therapy may affect the plasma CHIT levels indirectly by affecting the macrophage activation and

functions. Finally, control subjects were included in the study according to their medical history and clinical findings, and CAD was not ruled out by non-invasive or invasive imaging tests.

In conclusion, plasma CHIT level increases in CHF and may be used as a biomarker in the diagnosis of CHF. In addition, its increased levels are associated with worse LVEF and higher NT-proBNP levels. So, it may be useful for demonstration of the severity and indirectly estimation of prognosis in HF. However, long-term follow-up and large scale prospective studies are needed to determine the prognostic significance of CHIT.

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