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Predictive value of serum irisin for chronic heart failure in patients with type 2 diabetes mellitus

Alexander A. Berezin¹ , Ivan M. Fushchey² , Sergii V. Pavlov³ and Alexander E. Berezin^{4*}

Abstract

We hypothesize that serum irisin can have additional discriminative potency for heart failure (HF) in individuals with type 2 diabetes mellitus (T2DM). The study group comprised 226 consecutive T2DM patients (153 patients with any HF phenotypes and 30 patients without HF) aged 41 to 65 years. The plasma levels N-terminal brain natriuretic propeptide (NT-proBNP) and irisin were detected by ELISA at the baseline of the study. We found that the most appropriate cut-off value of irisin (HF versus non-HF) were 10.4 ng/mL (area under curve [AUC] = 0.96, sensitivity = 81.0%, specificity = 88.0%; $P = 0.0001$). Cutoff point of NT-proBNP that distinguished patients with HF and without it was 750 pmol/L (AUC = 0.78; sensitivity = 72.7%, specificity 76.5%, $p = 0.0001$). Using multivariate comparative analysis we established that concentrations of irisin < 10.4 ng/mL (odds ratio [OR] = 1.30; $P = 0.001$) and NT-proBNP > 750 pmol/mL (OR = 1.17; $P = 0.042$), left atrial volume index (LAVI) > 34 mL/m² (OR = 1.06; $P = 0.042$) independently predicted HF. Irisin being added to NT-proBNP improved predictive modality for HF, whereas combination of NT-proBNP and LAVI > 34 mL/m² did not. In conclusion, we established that irisin had independent predicted potency for HF in patients with established T2DM.

Keywords: Type 2 diabetes mellitus, Heart failure, Irisin, Natriuretic peptides, Predictive model

Introduction

Type 2 diabetes mellitus (T2DM) remains to be a powerful risk factor for newly heart failure (HF) [1]. Moreover, all-cause mortality, cardiovascular (CV) outcomes, and untoward clinical course of the disease including urgent hospital admission, are considered to have been worse for HF patients with T2DM when compared with those who had no diabetes [2]. Along with it, at least of quarter of symptomatic HF patients with different phenotypes of the condition exerts a persistence of hyperglycemia that contributes to the increased T2DM risk in HF patients [3, 4]. In fact, T2DM frequently coexists with HF and modulates each other [5].

Incidence and prognosis of HF in T2DM patients seem to be potentially predictable factors, which are suggested to be attributes of pathophysiological mechanisms playing pivotal role in various maladaptive responses, such as adverse cardiac remodeling, systemic and microvascular inflammation, endothelial and adipose tissue dysfunctions, oxidative stress, hyperglycemia, lipotoxicity, metabolic memory and altered repair system [6–8]. Being involved in vicious circle of HF pathogenesis, these factors roughly overlap and seem to be accurately evaluated by their surrogate circulating indicators [9]. Although the natriuretic peptides (NP) definitely have powerful diagnostic potency to rule out HF, their predictive ability for HF seem to be sufficient limitation in T2DM patients [10]. It has been previously revealed that a discriminative potency of NP for HF with preserved ejection fraction is appeared to be lower than for HF with reduced ejection fraction [11, 12]. These phenotypes of HF distinguish

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each other from a signature of comorbidity including metabolic diseases, it is reasonable to suggest that T2DM could be a factor contributing to limiting predictive value of NP for HF in this population. To up to date our knowledge, multiple biological marker models are regarded to be more predictable than single biomarker ones [13].

Irisin is a multifunctional myokine secreted by adipocytes, cardiac myocytes, and skeletal muscle, possibly mediating a wide range of metabolic processes including 'browning' of white adipose tissue, thermogenesis, insulin resistance, muscle endurance, endothelial function, inflammatory and immune reactions and bone osteoblast activity [14, 15]. In physiological condition, circulating irisin positively associates with skeletal muscle mass, glucose homeostasis, skeletal muscle metabolism and negatively with fasting glycaemia [16]. Although muscle and adipose tissue expressions of irisin mRNA were found to be increased in prediabetes, T2DM was associated with a reduction of the expression and the level of the peptide in plasma [17, 18]. Along with it, HF related to dramatic decrease in circulating irisin levels regardless of a presence of T2DM [19]. There is a hypothesis that irisin acting as peroxisome proliferator-activated receptor gamma coactivator 1-alpha-related protein mediates myocardial contractility and skeletal muscle function and prevent adverse cardiac remodeling, alteration cardiac function and biomechanical stress [20–23]. Thus, dynamic changes of irisin in peripheral circulation seem to be powerful predictor of cardiac remodeling and HF irrespectively from its phenotypes, whereas it remained uncertain whether irisin is comparable to NT-proBNP in its predictive ability in T2DM patients and if add-on of irisin to NT-proBNP is able to improve discriminative potency of the combination. We hypothesize that serum irisin has additional discriminative potency for HF in patients with T2DM.

Results

Characteristics of the study patient population

The study patient population composed of mainly male with average age of 51 years and numerous co-morbidities and cardiovascular (CV) risk factors, which included dyslipidemia (83.1%), hypertension (86.3%), stable coronary artery disease (29.5%), smoking (43.2%), and obesity (45.9%) (Table 1). Atrial fibrillation was detected in 17 patients (9.20%) with HF, whereas T2DM patients without HF did not have this condition. LV ventricular hypertrophy, chronic kidney disease and microalbuminuria were found in 73.2%, 21.3% and 30.6%, respectively. Amongst 153 patients with HF 26.2% had HFpEF, 26.8% demonstrated HFmrEF finally HFrfEF was detected in 30.6% individuals. All of them had II/III NYHA class. Therefore, mean LVEF was 53.2%, average levels of

NT-proBNP were 2718 pmol/mL and irisin were 9.85 ng/mL.

We did not notice significant differences between cohorts in demographic and anthropomorphic parameters, presentation of several CV risk factors, and blood pressure. Along with it, HF cohorts composed of more amount of patients with chronic coronary artery disease, LV hypertrophy, chronic kidney disease (1st-to-3rd grades) and having smoking habits than non-HF cohorts ($P=0.001$ for all cases). Therefore, LVEDV, LVESV, LVMMI, LAVI and E/e' were found to be sufficiently higher and LVEF was lower in HF patients than in non-HF individuals. In addition to that, we did not find any difference in HOMA-IR and biochemical parameters between cohorts, apart from NT-proBNP and irisin, the levels of which exerted multidirectional changes. The HF individuals demonstrated significantly higher NT-proBNP and lower irisin than those without HF.

Spearman correlation between circulating levels of irisin and other variables

In entire patient cohort irisin levels were positively associated with NYHA class, LVEF, HOMA-IR, NT-proBNP, and HDL-C, whereas negative associations were found for eGFR, WHR, BMI, systolic and diastolic BP, total cholesterol, triglycerides and LDL-C (Table 2). There were no significant correlations of concomitant medication including SGLT2 inhibitors with HOMA-IR and irisin levels. In T2DM patients with HF irisin exhibited moderate correlation with NT-proBNP, LVEF, and BMI, whereas its association with NYHA class, WHR and diastolic BP were weak. Irisin concentrations in non-HF patients correlated positively with HOMA-IR, NT-proBNP, HDL-C and inversely with WHR, BMI, total cholesterol, LDL-C and also eGFR.

Predictive pattern of models for all HF phenotypes

The reliability of the predictive models for HF is reported Fig. 1. The Receive Operation Characteristics curve analysis yielded that the well-balanced cut-off point for irisin (with HF versus free HF) were 10.4 ng/mL (area under curve [AUC]=0.96, sensitivity=81.0%, specificity=88.0%; $P=0.0001$) (Fig. 1a). Cutoff point of NT-proBNP that distinguished patients with HF and without it was 750 pmol/L (AUC=0.78; sensitivity=72.7%, specificity 76.5%, $p=0.0001$) (Fig. 1b). Along with it, the best cutoff point for LAVI was 34 ml/m² (AUC=0.81; sensitivity=81.6%, specificity 65.4%, $p=0.0001$) (Fig. 1c). E/e' (HF versus non-HF) was 11 unit (AUC=0.69; sensitivity=66.7%, specificity 68.4%, $p=0.0027$) (Fig. 1d). Thus, irisin exhibited more profound discriminative potency for HF when compared with NT-proBNP and featured of diastolic LV dysfunction (LAVI, E/e').

Table 1 Characteristics of the study patient population

Variables	Entire T2DM population (n = 183)	HF patients (n = 153)	Non-HF (n = 30)	P-value (HF vs non-HF)
Age, year	51 (41–62)	52 (41–64)	51(41–60)	0.86
Male, n (%)	118 (64.5)	100 (65.4)	18 (60.0)	0.82
Dyslipidemia, n (%)	152 (83.1)	127 (83.0)	25 (83.3)	0.84
Hypertension, n (%)	158 (86.3)	132 (86.3)	26 (86.7)	0.80
Stable CAD, n (%)	54 (29.5)	49 (32.0)	5 (16.7)	0.001
Atrial fibrillation, n (%)	17 (9.2)	17 (9.2)	0	0.0001
Smoking, n (%)	79 (43.2)	63 (41.2)	16 (53.3)	0.044
Abdominal obesity,	84 (45.9)	71 (46.4)	13 (43.3)	0.88
Microalbuminuria, n (%)	56 (30.6)	47 (30.7)	9 (30.0)	0.84
LV hypertrophy, n (%)	134 (73.2)	123 (80.3)	11 (36.7)	0.001
CKD 1–3 grades, n (%)	39 (21.3)	35 (22.9)	4 (13.3)	0.001
HFpEF / HFmrEF / HFrEF, n (%)	48 (26.2) / 49 (26.8) / 56 (30.6)	48 (31.4) / 49 (32.0) / 56 (36.6)	-	-
II/III NYHA class, n (%)	103 (56.3) / 50 (27.3)	103 (67.3) / 50 (23.7)	-	-
BMI, kg/m ²	25.8 ± 2.1	25.6 ± 2.8	26.3 ± 2.6	0.88
Waist circumference, sm	85.6 ± 2.9	85.1 ± 3.2	86.5 ± 3.1	0.86
WHR, units	0.86 ± 0.03	0.85 ± 0.05	0.87 ± 0.03	0.86
SBP, mm Hg	132 ± 5	129 ± 6	135 ± 5	0.81
DBP, mm Hg	80 ± 4	78 ± 5	84 ± 3	0.80
LVEDV, mL	154 ± 6	161 ± 4	147 ± 6	0.001
LVESV, mL	72 ± 7	86 ± 6	59 ± 3	0.001
LVEF, %	53 ± 6	46 ± 3	60 ± 2	0.001
LVMMI, g/m ²	151 ± 6.12	154 ± 5	137 ± 3	0.01
LAVI, mL/m ²	39 ± 8	38 ± 4	30 ± 5	0.042
E/e', unit	14.0 ± 0.46	13.5 ± 0.33	7.2 ± 0.42	0.001
eGFR, mL/min/1.73 m ²	83 ± 6.0	75 ± 4.0	86 ± 3.5	0.01
HOMA-IR	7.65 ± 3.7	7.95 ± 2.3	7.15 ± 2.4	0.14
Fasting glucose, mmol/L	5.84 (4.61–7.02)	5.62 (4.30–6.96)	5.92 (4.61–6.97)	0.28
HbA1c, %	6.65 ± 0.04	6.59 ± 0.02	6.70 ± 0.05	0.70
Creatinine, mcmol/L	108.8 ± 12.0	108.6 ± 8.5	95.1 ± 10.4	0.26
TC, mmol/L	6.41 (6.15–6.82)	6.43 (6.17–6.70)	6.42 (6.35–6.90)	0.82
HDL-C, mmol/L	0.95 (0.73–1.12)	0.97 (0.80–1.07)	0.93 (0.70–1.10)	0.80
LDL-C, mmol/L	4.43 (4.10–4.75)	4.38 (4.27–4.49)	4.51 (4.35–4.68)	0.68
TG, mmol/L	2.26 (2.11–2.31)	2.21 (2.04–2.39)	2.30 (1.18–3.46)	0.64
NT-proBNP, pmol/mL	2718 (1380 – 3720)	3115 (2380 – 3750)	105 (72 – 142)	0.001
Irisin, ng/mL	9.85 (4.34 – 13.60)	6.50 (3.10–10.5)	12.90 (11.2 – 13.4)	0.001

Abbreviations: BMI Body mass index, CKD Chronic kidney disease, DBP Diastolic blood pressure, E/e' Early diastolic blood filling to longitudinal strain ratio, eGFR Estimated glomerular filtration rate, HDL-C High-density lipoprotein cholesterol, HFpEF Heart failure with preserved ejection fraction, HFmrEF Heart failure with mildly reduced ejection fraction, HFrEF Heart failure with reduced ejection fraction, LAVI Left atrial volume index, LVEDV Left ventricular end-diastolic volume, LVESV Left ventricular end-systolic volume, LVEF Left ventricular ejection fraction, LVMMI Left ventricle myocardial mass index, LDL-C Low-density lipoprotein cholesterol, SBP Systolic blood pressure, TG Triglycerides, TC Total cholesterol, WHR Waist-to-hip ratio

Logistic regression analysis

Univariate logistic regression model yielded that the predictors for HF in patients enrolled in the study were the following factors: irisin < 10.4 ng/mL, LV hypertrophy, BMI, NT-proBNP > 750 pmol/mL, age, LAVI > 34 mL/m² and E/e' > 11 (Table 3). Concomitant medications were no remarkable predictors for HF. Multivariate logistic model showed that the serum levels of irisin < 10.4 ng/mL along

with NT-proBNP > 750 pmol/mL and LAVI > 34 mL/m² were independent predictors for HF.

Comparison and reclassification of the predictive values of the models

We established that inclusion of irisin to reference predictive model constructed from NT-proBNP significantly added discriminatory information of the model, whereas

Table 2 Spearman correlations between irisin levels and other parameters

Factors that correlate with the levels of irisin	Entire population		HF patients		None-HF patients	
	r Spearman	P value	r Spearman	P value	r Spearman	P value
HOMA-IR	0.34	0.001	0.14	0.12	0.44	0.003
NT-proBNP	0.33	0.001	0.38	0.001	0.38	0.001
LVEF	0.26	0.044	0.32	0.001	0.17	0.54
NYHA class	0.24	0.01	0.16	0.05	-	-
TC	-0.27	0.001	-0.11	0.06	-0.24	0.042
HDL-C	0.24	0.02	0.13	0.42	0.29	0.001
LDL-C	-0.29	0.001	-0.13	0.22	-0.31	0.001
TG	-0.28	0.001	-0.20	0.050	-0.32	0.001
eGFR	-0.32	0.024	-0.21	0.054	-0.30	0.001
WHR	-0.40	0.001	-0.25	0.001	-0.42	0.001
BMI	-0.32	0.001	-0.30	0.001	-0.34	0.001
SBP	-0.28	0.001	-0.06	0.26	-0.20	0.046
DBP	-0.26	0.001	-0.21	0.001	-0.22	0.044

Abbreviations: BMI Body mass index, BP Blood pressure, DBP Diastolic blood pressure, eGFR Estimated glomerular filtration rate, HDL-C High-density lipoprotein cholesterol, HOMA-IR Homeostasis Model Assessment of insulin resistance, LDL-C Low-density lipoprotein cholesterol, LVEF Left ventricular ejection fraction, NT-proBNP N-terminal brain natriuretic pro-peptide, NYHA New York Heart Association, SBP Systolic blood pressure, TC Total cholesterol, TG Triglycerides, WHR Waist-to-hip ratio

LAVI did not exhibit modality to increase the discriminative potency of NT-proBNP (Table 4). Thus, irisin remarkably improved the predictive value of NTproBNP for HF in T2DM patients, whereas we did not find a difference between isolated irisin and irisin + reference model that seems to show an independent discriminative value of irisin for HF.

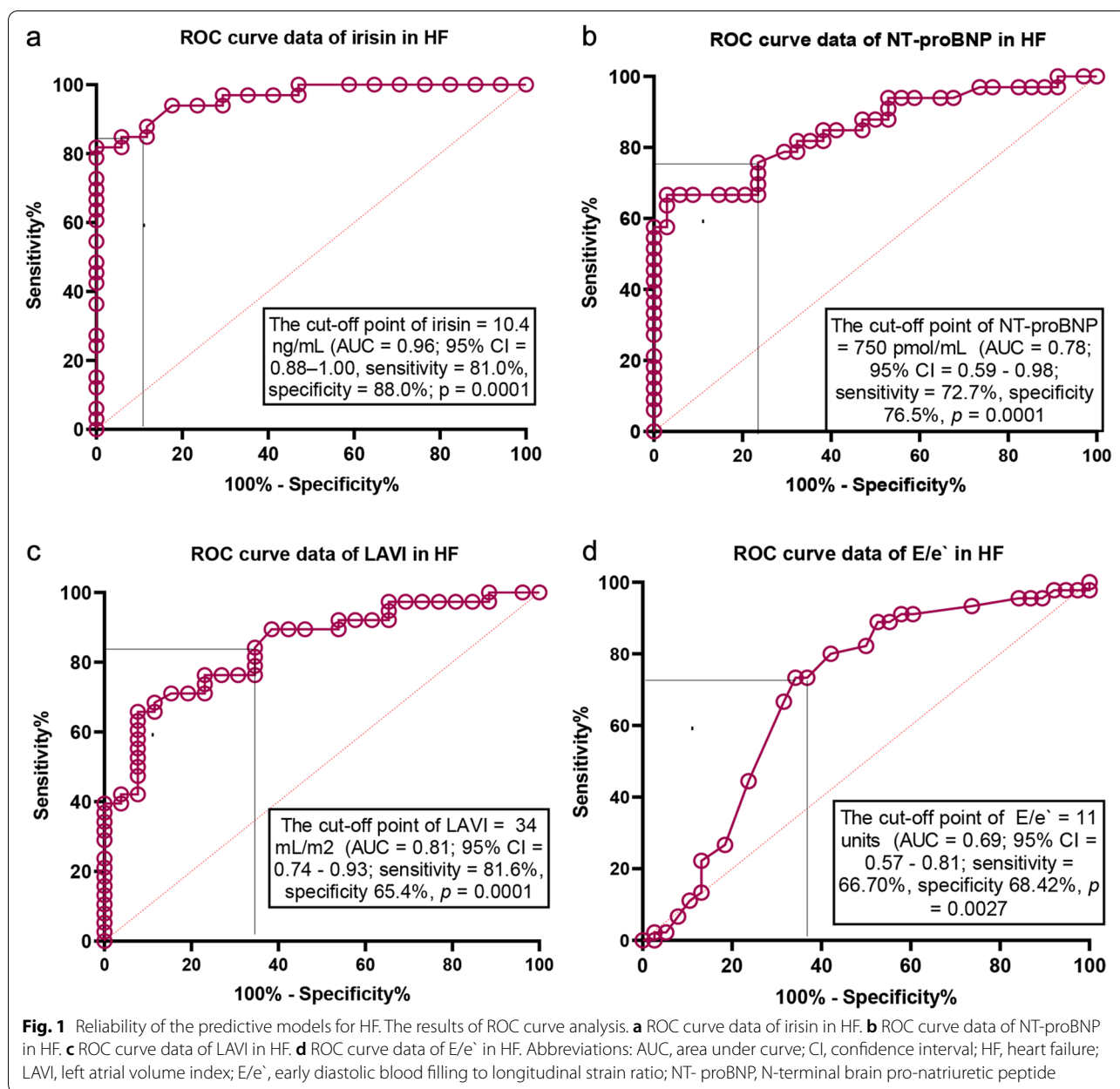
Discussion

Our study demonstrated that irisin concentrations were lower in T2DM patients with established HF independently from its phenotypes. Aline with it, well balanced cutoff level for irisin that distinguished HF cohort from non-HF cohort was found to be 10.4 ng/mL. Yet, addition of irisin level to the predictive HF model constructed from elevated levels of NT-proBNP remarkably exerted its additive potency.

We hypothesize that these findings may be promising for personified transitional management of HF regardless of a signature of comorbidities including T2DM and profile of HF phenotypes. Indeed, previously received data showed that acute / acutely decompensated HF was strongly associated with an increase in both NT-proBNP and irisin, whereas opposite changes of these biomarkers in terms of increase in NT-proBNP and decrease in irisin accompanied chronic HF [24, 25]. Moreover, there is a strong reason to believe that reduced levels of irisin more typical for maladaptive shifts in adverse cardiac remodeling due to inflammation and fibrosis than elevation of NT-proBNP in circulation reflecting non-specific biomechanical stress [26]. Irisin is sometimes referred to as the

'universal indicator' of early stages of cardiac remodeling as it is capable of attenuating hypoxia / ischemia-induced apoptosis of cardiac myocytes and cardiac hypertrophy [27]. Acting via microRNA-19b/AKT/mTOR and AMPK/mTOR signaling pathways, irisin promotes cardiac protective activity and modulate preconditioning [28, 29]. Finally, its ability to suppress oxidative stress and inflammation is considered to be clear explanation of the cause by which circulating levels of irisin was found to be high in acute HF along with natriuretic peptides and other biomarkers of biomechanical stress and myocardial injury [30]. Thus, a trend to decrease in circulating levels of irisin in HF diabetics when compared to non-HF patients with T2DM seems to be a sign of incapability of endogenous repair system to compensate initial myocardial damage, so it illustrates an occurrence of maladaptive stage in cardiac remodeling directly related to T2DM-induced microvascular inflammation, endothelial dysfunction and skeletal muscle myopathy [31, 32].

On the other hand, weak physical endurance in T2DM is regarded to be a plausible cause of low levels of circulating irisin in comparison with healthy individuals [33, 34]. It has been noticed that skeletal muscle expression of irisin in chronic HF inversely correlated to the levels of inflammatory cytokines [34, 35]. Because T2DM is a well-known factor contributing to atherosclerosis, systemic and microvascular inflammation including adipose tissue inflammatory-related remodeling, skeletal muscle dysfunction and persistently exists among HF including HFpEF, irisin can be a promising predictor of cardiac remodeling and HF [36, 37]. This hypothesis has



been confirmed in some clinical studies, which yielded optimistic results in respect with the predictive role of irisin for both HFpEF and HFrfEF in patients with T2DM or insulin resistance [38, 39]. The findings of our study showed that irisin levels being positively correlated with LVEF did not exhibit strong correlation with several metabolic parameters including fasting glucose, HOMA-IR in HF cohort, whereas in non-HF T2DM patients these associations were noticed. In fact, these data clarify that the initial trigger for irisin production in HF and non-HF populations can be different and that thereby low levels of irisin is considered a surrogate biomarker of advanced

cardiac remodeling and the risk of HF manifestation. Indeed, there is strong evidence of the fact that is consisted of this assumption [39, 40].

However, we noticed that irisin being added to NTproBNP was better predictor for HF than LAVI, so metabolic response in T2DM at high risk of HF occurred ahead of hemodynamic left-side heart changes. Aline with it, we established that isolated use of irisin is taken into account to be because the same predictable of HF as its combination with the based model. This clarifies independent discriminative potency of the biomarker and opens new prospective in further discovery of clinical

Table 3 Predictors for HF in T2DM patient populations

	Logistic Regression Models			
	Univariate		Multivariate	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value
NT-proBNP (> 750 pmol/mL vs ≤ 750 pmol/mL)	1.54 (1.06–2.33)	0.001	1.17 (1.02–1.26)	0.042
Irisin (< 10.4 ng/mL vs ≥ 10.4 ng/mL)	1.52 (1.16–2.86)	0.001	1.28 (1.08–2.15)	0.001
LAVI (> 34 mL/m ² vs ≤ 34 mL/m ²)	1.19 (1.11–1.36)	0.001	1.06 (1.02–1.13)	0.044
LVH (present vs absent)	1.12 (1.06–1.20)	0.044	1.05 (1.00–1.11)	0.14
E/e' (> 11 units vs ≤ 11 units)	1.12 (1.06–1.21)	0.001	1.04 (1.00–1.06)	0.42
BMI (present vs absent)	1.07 (1.02–1.11)	0.046	1.05 (1.00–1.08)	0.062
Age	1.03 (1.02–1.05)	0.048	1.03 (1.00–1.04)	0.16

Abbreviations: BMI Body mass index, E/e' Early diastolic blood filling to longitudinal strain ratio, LAVI Left atrial volume index, LVH Left ventricular hypertrophy, NT-proBNP N-terminal brain natriuretic pro-peptide

Table 4 The comparisons of predictive models for HF: The results of model fit statistics

Models	Depending variable: HF					
	Area under curve		Net-reclassification improvement		Integrated discrimination indices	
	M ± SD	P-value	M ± SD	P-value	M ± SD	P-value
Reference Model 1 (NT-proBNP)	0.78 ± 0.16	-	-	-	-	-
Model 2 (NT-proBNP + LAVI)	0.82 ± 0.06	0.05	0.15 ± 0.04	0.64	0.17 ± 0.03	0.42
Model 3 (NT-proBNP + irisin)	0.97 ± 0.01	0.0001	0.63 ± 0.02	0.045	0.56 ± 0.03	0.012
Model 4 (Irisin)	0.96 ± 0.01	0.0001	0.53 ± 0.01	0.044	0.42 ± 0.01	0.024

Abbreviations: LAVI Left atrial volume index, M Median, SD Standard deviation, HF Heart failure, NT-proBNP N-terminal brain natriuretic pro-peptide

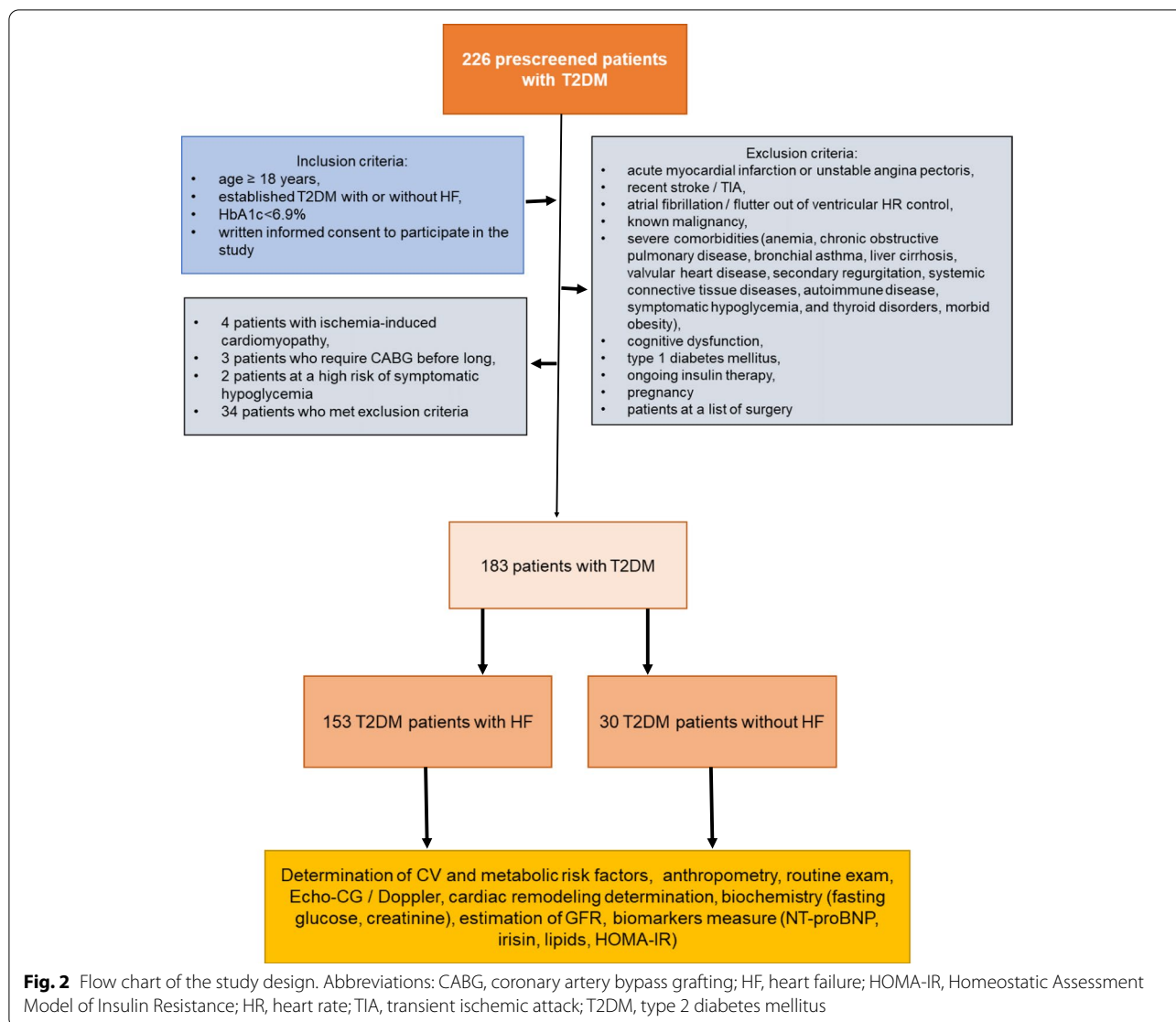
implication of the model. Perhaps, irisin being abundantly produced by skeletal muscles and adipocytes and other tissues out of myocardium may mediate different variants of peripheral tissue dysfunction, which intervene in an exceedingly progression of HF in T2DM [17, 19]. During this context, irisin seems to point out quite optimistic results that deserve investigating in large clinical trials. Indeed, a metabolic signature of HFpEF frequently collides to serious difficulty within the interpretation of its role in prediction of clinical course of the disease [2, 19]. Yet, there is uncertain whether the patients with HFpEF and T2DM could also be beneficially treated and demonstrate a strict resemblance in clinical outcomes having a major difference in irisin. These findings are regarded to be another target for further studies. Taking into consideration the results of several studies of positive impact of irisin on cardiac function and structure [41, 42], we hypothesized that a decrease in irisin concentration is superior to diastolic and systolic cardiac dysfunction markers in prediction of HF. Finally, we received strong evidence of our hypothesis when the full model including NT-proBNP and irisin became more predictable for HF than others.

There are several limitations in the study, the first of them relates to one center open cohorts study design. Yet, we also do not include T2DM patients having history TIA / stroke, also as those with coronary revascularization or other surgical procedures. The second limitation was that we did not use phenotypes of HF (HFpEF, HFrfEF and HFmrEF) for further analysis. The last limitation was a lack of serial measures of circulating biomarkers in a protocol of the study. However, we believe that these limitations are not conclusive and allow extrapolating the results of the study on other populations.

Methods

Study design

A total of 226 T2DM patients who were under investigation in the Private Multidisciplinary Hospital Vita-Centre LTD (Zaporozhye, Ukraine) were consecutively included in the study from October 2020 to December 2021. The following criteria such as age > 18 years, established T2DM regardless of HF, and the levels of HbA1c less 6.9% were used as inclusion ones. The study design, inclusion / exclusion criteria and reasons to exclusion at the prescreening are reported Fig. 2. Then since the patients were checked in compliance to inclusion / exclusion criteria 183 patients were finally included in the study.



CV risk factors and co-morbidities

We evaluated CV risk factors and co-morbidities according to current guidelines of the European Society of Cardiology (ESC) [43–46] so as to work out HF during the study we used ESC guidelines [47, 48].

Routine anthropometric examinations

We evaluated conventional anthropometric parameters including body mass index (BMI), height, weight, and hip-to-waist ratio (WHR) [49].

B-mode Echocardiography and Doppler examination

Conventional B-mode echocardiography and impulse Doppler examination on Vivid T8 (“GE Medical Systems”, Freiburg, Germany) were performed with the aim of elucidating hemodynamic features (left ventricular ejection fraction [LVEF], left atrial volume [LAV], left atrial

volume index [LAVI], E/e` ratio) in compliance with current guidelines [50]. Left ventricular hypertrophy (LVH) was detected per conventional echocardiographic criteria, including the following: LV mass / body area ≥ 125 g/m2 in male or ≥ 110 g/m2 in female [51].

Medications

T2DM patients received diet together with personally adjusted dose of metformin and sodium-glucose cotransporter-2 (SGLT2) inhibitor optionally. HF patients were treated in line with conventional clinical recommendation with beta-blockers, antagonists of renin–angiotensin–aldosterone system, loop diuretics, while possible use of SGLT2 inhibitions or i/f blocker ivabradine were also recommended as adjunctive therapies. Lipid-lowering agents were prescribed in subjects with known

dyslipidemia, T2DM or established CVD without conventional contraindications. Antiplatelet drugs were added to the therapy when needed.

Biochemical analyses

Blood samples were collected for biochemical analysis after overnight fasting. After centrifugation (3000 r/min, 30 min) pooled serum aliquots were stored at $\leq -70^{\circ}\text{C}$ until analysis. Concentrations of irisin and NT-proBNP were measured with commercial ELISA kits (Elabscience, Houston, Texas, USA). All ELISA data were evaluated in step with the quality curve and every sample was measured twice because the norm was finally analyzed. Conventional biochemistry parameters were routinely measured in local laboratory using Roche P800 analyzer (Basel, Switzerland). We used CKD-EPI formula to estimate glomerular filtration rate (GFR) [52]. Insulin resistance was detected as Homeostatic Assessment Model of Insulin Resistance (HOMA-IR) [53].

Statistical analyses

We used v. 23 SPSS (IBM, Armonk, New York, USA) software and v. 9 GraphPad Prism (GraphPad Software, San Diego, CA, USA) software for statistical analysis. The Kolmogorov–Smirnov test was accustomed evaluate distribution of variables. Baseline characteristics were expressed as counts with percentages or mean \pm variance (SD) or median (interquartile range – IQR) for continuous variables and as proportions for categorical variables. For the normally distributed continuous variables, Student's t-test was used. Otherwise, the Mann–Whitney U-test was chosen instead. We used Spearman coefficient of correlation to represent the connection between variables. With the aim of obtaining a receiver operating characteristic (ROC)-determined biomarker cut-points Youden method was performed. For the optimal cut-of value, the realm under the curve (AUC), 95% confidence Intervals (95% CI), also as a sensitivity and specificity were estimated. Univariate logistic regression was accustomed elucidate plausible predictive factors for HF. The potential candidates ($P < 0.05$) included in multivariate logistic regression. Predictive value of things for HF were confirmed using estimation of integrated discrimination indices (IDI) and net-reclassification improvement (NRI). All the tests performed were 2 sided, and p value < 0.05 was considered statistically significant.

Conclusion

Current predictive model for HF based on measurement of concentrations of natriuretic peptides and detection of cardiac dysfunction or alteration of cardiac structure seems to show the best predictive value for

HFrEF, whereas the discriminative potency for HFmrEF/HFpEF is significantly lower than for HFrEF. Therefore, coexisting comorbidities including obesity and T2DM intervene in problematic issue to interpretation of the variability of NT-proBNP. In this connection, discovery of new biomarkers that are able to improve predictive capability of current model is promising. Irisin ensures a metabolic regulation of cardiac function and structure and tackles skeletal muscle activity with common clinical features of HF such as fatigue and low tolerability to physical exercise along with direct impact on adverse cardiac remodeling. Yet, irisin seems to show their predictive potency regardless of NT-proBNP and any HF phenotype.

We established that serum irisin levels were significantly decreased in HF in patients with established T2DM when compared with individuals with T2DM without this condition. Along with it, we established that the concentrations of irisin less than 10.4 ng/mL not only had discriminative information for HF, but also was able to improve the discriminative potency of NTproBNP for the disease in T2DM patients. The irisin seem to show optimistic results in terms of its predictive ability for HF independently from NT-proBNP and cardiac features characterized LV diastolic function (LAVI). This finding seem to have promising importance in discovering new predictive models for HF in these patient populations.

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Authors' contributions

AEB, IMF, and AAB contributed to the conception and design of the study, wrote the first draft of the manuscript. AAB performed echocardiography, collected blood samples and executed the data analyses. AEB and IMF supervised the manuscript. SVP contributed to data analysis and corrected the first draft of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Availability of data and materials

The data in the present study will be available upon request to the corresponding authors.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee of Zaporozhye Medical Academy of Post-graduate Education ethics committee's approval (protocol number: 8; date of approval: 10 October 2020). The authors declared that the study was conducted following the Declaration of Helsinki and good clinical practice. All patients signed the informed consent before to be included in the study.

Competing interests

The authors declare no potential conflict of interest.

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