Diabetologia (2022) 65:955–963
https://doi.org/10.1007/s00125-022-05678-6

ARTICLE

Diabetes, GDF-15 and incident heart failure: the atherosclerosis risk in communities study

Justin B. Echouffo-Tcheugui[1] · Natalie Daya[2] · Chiadi E. Ndumele[3] · Kunihiro Matsushita[2,3] · Ron C. Hoogeveen[4] · Christie M. Ballantyne[4] · Josef Coresh[2] · Amil M. Shah[5] · Elizabeth Selvin[2]

Received: 22 July 2021 / Accepted: 11 January 2022 / Published online: 11 March 2022

Abstract

Aims/hypothesis Elevated circulating growth differentiation factor-15 (GDF-15), a marker of cellular stress, is associated with both heart failure (HF) and diabetes. However, it is unclear to what extent GDF-15 is associated with HF among individuals with and without diabetes.

Methods We evaluated 10,570 participants free of HF at Visit 3 (1993–1995) of the Atherosclerosis Risk in Communities study. We used Cox regression to evaluate the joint associations of GDF-15 and diabetes with incident HF. Models were adjusted for traditional cardiovascular risk factors.

Results Among a total of 10,570 individuals (mean age of 60.0 years, 54% women, 27% black adults), elevated GDF-15 (≥75th percentile) was more common in people with diabetes compared with those without diabetes (32.8% vs 23.6%, $p<0.0001$). During 23 years of follow-up, there were 2429 incident HF events. GDF-15 (in quartiles) was independently associated with HF among those with and without diabetes, with a stronger association among individuals with diabetes (p-for-diabetes–GDF-15 interaction = 0.034): HR for highest vs lowest GDF-15 quartile (reference): 1.64 (95% CI 1.41, 1.91) among those without diabetes and 1.72 (95% CI 1.32, 2.23) among those with diabetes. Individuals with diabetes and elevated GDF-15 had the highest risk of incident HF (HR 2.46; 95% CI 1.99, 3.03). After accounting for HF risk factors, GDF-15 provided additional prognostic information among participants with diabetes (ΔC statistic for model with vs model without GDF-15: +0.008, $p = 0.001$) and among those without diabetes (+0.006, $p<0.0001$).

Conclusions/interpretation In a community-based sample of US adults, GDF-15 provided complementary prognostic information on the HF risk, especially among individuals with diabetes.

Keywords Growth differentiation factor-15 · Heart failure · Prediction · Type 2 diabetes

✉ Justin B. Echouffo-Tcheugui
jechouf1@jhmi.edu

[1] Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[2] Department of Epidemiology and Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[3] Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[4] Section of Cardiovascular Research, Baylor College of Medicine and Houston Methodist DeBakey Heart & Vascular Center, Houston, TX, USA

[5] Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

Abbreviations

ARIC	Atherosclerosis Risk in Communities
GDF-15	Growth differentiation factor-15
HF	Heart failure
hs-cTnT	High-sensitivity cardiac troponin T
NT-proBNP	N-terminal proB-type natriuretic peptide

Introduction

Growth differentiation factor-15 (GDF-15) is a protein of the TGF-β cytokine superfamily [1], which is expressed in several human tissues [2]. The putative effects of GDF-15 have been described in mechanistic studies [3–5], which point to its role in oxidative stress, mitochondrial function, energy balance and glucose homeostasis.

Research in context

What is already known about this subject?

- Elevated circulating growth differentiation factor-15 (GDF-15), a marker of cellular stress, is strongly associated with both heart failure (HF) and diabetes

What is the key question?

- What is the association between GDF-15 and incident HF among individuals with and without diabetes in the community, and what are the potential differences in the prognostic value of GDF-15 in these individuals?

What are the new findings?

- In a community-based population of US adults, individuals with diabetes and elevated GDF-15 had a greater than twofold higher risk of incident HF than individuals without diabetes and with low GDF-15
- After accounting for HF risk factors, GDF-15 provided important prognostic information, especially in the setting of diabetes

How might this impact on clinical practice in the foreseeable future?

- GDF-15 can help refine the assessment of the risk of HF, particularly among individuals with diabetes. Given its prognostic value, there may be a useful role for GDF-15 in primary and secondary cardiovascular preventive care

Diabetes is an established risk factor for incident heart failure (HF) [6], but the pathways linking diabetes and HF remain poorly understood. Prior epidemiological studies have described a positive association between GDF-15 and diabetes [7, 8], and robust associations of high GDF-15 levels with incident HF [9–12] and HF prognosis [13–15]. GDF-15 is considered a marker of mitochondrial dysfunction [16, 17], reflecting alterations in cellular stress pathways [18]. Diabetes impairs mitochondrial function [19], and adversely affects myocardial energetics even in the absence of overt HF [20, 21]. Laboratory [22] and clinical [20, 23] data suggest that in diabetes-related HF alteration in myocardial metabolism is likely more pronounced than among individuals with HF but without diabetes. These diabetes-related myocardial alterations are directly related to the degree of cellular stress and mitochondrial dysfunction, which can be reflected by GDF-15 levels [16, 17]. This suggests that the association of GDF-15 with incident HF might differ in the presence of diabetes compared with its absence. Despite the accruing evidence on the associations between diabetes and GDF-15, there are limited clinical or population-based data comparing how GDF-15 might improve prediction of HF in people with and without diabetes.

We used data from the community-based Atherosclerosis Risk in Communities (ARIC) study at Visit 3 (1993 to 1995) to examine the associations of GDF-15 and diabetes with incident HF, individually and in combination.

Methods

Study population The ARIC study recruited 15,792 participants from four US communities [24]. The first study visit took place in 1987–1989; since then, participants have returned for subsequent study visits and received annual telephone calls. The third visit (Visit 3) took place in 1993 to 1995.

Of the 12,887 participants who attended ARIC Visit 3, we excluded individuals with missing GDF-15 measurements (n = 1427), participants who were black people from Minneapolis and Washington County (n = 35) because of their small number, participants with missing diabetes status (n = 32) and participants with prevalent HF (based on Gothenburg criteria and prior hospitalisation related to HF, n = 823), thus leaving 10,570 participants for this analysis.

All participants provided written informed consent and the study protocol was approved by the Institutional Review Board at each study site.

Laboratory measures GDF-15 was measured in plasma samples collected during ARIC Visit 3 (1993 to 1995) and stored at −70°C prior to analysis using SOMAscan assay (SomaLogic, Boulder, CO, USA) and expressed in relative fluorescence intensity units. For the purposes of analyses, proteins, reported in relative fluorescence units, were $\log_2$ transformed because of skewed distributions, and values outside of 5 SDs on the $\log_2$ scale were winsorised.

The experimental process for proteomic assessment and data normalisation has been previously described. The relative concentration of plasma proteins or protein complexes was measured using a Slow Off-rate Modified Aptamer (SOMAmer)-based capture array [25]. In brief, this method uses short single strands of DNA with chemically modified nucleotides, called modified aptamers, which act as protein-

binding reagents with defined three-dimensional structures and unique nucleotide sequences, which are identifiable and quantifiable using DNA detection technology. The SOMAscan assay has been described in detail previously [26], as have the assay's performance characteristics [27, 28]. Studies have demonstrated a median intra- and inter-run coefficient of variation of approximately 5% and intra-class correlation coefficients of ~0.9 [25, 29]. The SOMAscan assay has a sensitivity that is comparable to that of immunoassays while extending the lower limit of detection (in the femtomolar range) down to below that offered by conventional immunoassay approaches [30].

Ascertainment of diabetes status Prevalent diabetes at Visit 3 was defined by a physician-reported diagnosis of diabetes, self-reported use of diabetes medications, a non-fasting blood glucose level ≥11.1 mmol/l (200 mg/dl) or a fasting plasma glucose (FPG) ≥7 mmol/l (126 mg/dl).

Incident outcome assessment The outcome of interest was incident HF, defined as the first hospitalisation or death related to HF occurring after Visit 3, with follow-up until 31 December 2019. Participants were called on a yearly basis to obtain information regarding hospitalisations, and vital records were examined for all deaths. Hospitalisations and deaths due to incident HF were defined by HF discharge codes (ICD-9 code 428 for hospitalisations early during follow-up and ICD-10 code I50 for later) [31].

Covariates assessment Information on medical history, medication use, current alcohol use and current smoking was obtained using standardised self-report questionnaires. Physical activity was assessed using the interviewer-administered Baecke questionnaire [32], and categorised as per the American Heart Association guidelines as poor, intermediate and recommended [33]. Systolic and diastolic BP measurements were recorded as the mean of two readings. Hypertension was defined as systolic BP ≥130 mmHg, diastolic BP ≥80 mmHg or use of antihypertension medications. BMI was calculated as weight in kilograms divided by the square of height in metres, and obesity was defined as BMI ≥30 kg/m^2. Plasma glucose was measured using the hexokinase method. Serum total cholesterol, triacylglycerol and HDL-cholesterol concentrations were measured by using automated enzymatic assays. LDL-cholesterol was calculated using the Friedewald equation. eGFR was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation [34]. N-terminal proB-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) were also measured using an electrochemiluminescent immunoassay on an automated Cobas e411 analyser (Roche Diagnostics, Mannheim, Germany).

Statistical analysis We compared the baseline characteristics of participants across GDF-15 quartiles using the ANOVA procedure (for continuous variables) or the χ^2 test (for categorical variables).

In cross-sectional analyses, we evaluated the association of diabetes with higher levels of GDF-15 at Visit 3, using multivariable logistic regression. We built a number of sequential models. Model 1 adjusted for age, sex and race/centre. Model 2 included the Model 1 variables as well as current smoking, systolic BP, use of antihypertensive medications, use of cholesterol-lowering medications, total cholesterol, HDL-cholesterol, triacylglycerols, BMI, eGFR and metformin use, as this medication can impact GDF-15 levels [35]. Model 3 adjusted for Model 2 plus NT-proBNP and hs-cTnT.

In prospective analyses, we used Cox proportional hazard regression models to estimate HRs (95% CIs) for the prospective association between GDF-15 at baseline and incident HF by diabetes status, and after adjustment for baseline risk factors, as well as the joint associations of diabetes status and GDF-15 with the incidence of HF. For all the HF incidence models, we initially adjusted for age, sex and race/centre (Model 1). The subsequent adjustments included variables in Model 1 plus education, current smoking, physical activity, systolic BP, use of antihypertensive medications, use of cholesterol-lowering medications, total cholesterol, HDL-cholesterol, triacylglycerols, BMI, eGFR, metformin use, use of diabetes medication other than metformin and diabetes duration (Model 2). We additionally accounted for hs-cTnT and NT-proBNP (Model 3), the use of medication including β-blockers, and angiotensin converting enzyme inhibitors or angiotensin receptor blockers use (Model 4), and for coronary heart disease as a time-varying covariate (Model 5). GDF-15 was modelled in quartiles and as restricted cubic and linear splines to more flexibly evaluate the associations with HF by diabetes status.

We tested for the diabetes and GDF-15 interaction for the incident HF outcome on the multiplicative scale. An interaction between GDF-15 and sex was also investigated. We conducted additional analyses of the prospective associations of cross categories of GDF-15 (in quartiles) and diabetes status (yes vs no) with incident HF; individuals without diabetes and in the lowest GDF-15 quartile served as the reference group.

We assessed the additive predictive value of GDF-15 above and beyond traditional risk factors, including diabetes, by evaluating the changes in C statistic (prediction statistic) associated with the addition of GDF-15 to traditional HF risk factors in the overall sample, as well as, separately, in individuals with and without diabetes.

A p value <0.05 was used to denote statistical significance, including for interaction tests. All analyses were performed using Stata version 15 (StataCorp, USA).

Table 1 Baseline characteristics of ARIC study participants at Visit 3 (1993–1995), by quartiles of GDF-15

Variable	Total	Quartiles of GDF-15 (RFUs)[a]			
		Q1 (12.4–14.1)	Q2 (14.1–14.4)	Q3 (14.4–14.7)	Q4 (14.7–17.1)
N	10,570	2645	2641	2642	2642
Age, years	60.0±5.7	57.4±5.1	59.6±5.5	60.8±5.5	62.4±5.6
Female	5721 (54.1)	1680 (63.5)	1453 (55.0)	1395 (52.8)	1193 (45.2)
Race/centre					
White people, Forsyth Co.	2590 (24.5)	501 (18.9)	617 (23.4)	708 (26.8)	764 (28.9)
White people, Minneapolis	2996 (28.3)	805 (30.4)	818 (31.0)	706 (26.7)	667 (25.2)
White people, Washington Co.	2839 (26.9)	575 (21.7)	652 (24.7)	772 (29.2)	840 (31.8)
Black people, Forsyth Co.	257 (2.4)	79 (3.0)	63 (2.4)	59 (2.2)	56 (2.1)
Black people, Jackson	1888 (17.9)	685 (25.9)	491 (18.6)	397 (15.0)	315 (11.9)
Education[b]					
High school or less	2059 (19.5)	397 (15.0)	478 (18.1)	539 (20.4)	645 (24.4)
High school graduate or equivalent	4474 (42.4)	1112 (42.1)	1117 (42.3)	1139 (43.2)	1106 (41.9)
College or above	4023 (38.1)	1133 (42.9)	1043 (39.5)	958 (36.3)	889 (33.7)
Current drinkers[c]	5671 (53.7)	1459 (55.2)	1511 (57.2)	1381 (52.3)	1320 (50.0)
Current smokers[d]	1857 (17.6)	243 (9.2)	340 (12.9)	501 (19.0)	773 (29.3)
Physical activity[e]					
Poor	3751 (35.6)	901 (34.1)	887 (33.6)	920 (34.9)	1043 (39.6)
Intermediate	2331 (22.1)	605 (22.9)	607 (23.0)	574 (21.8)	545 (20.7)
Ideal	4464 (42.3)	1136 (43.0)	1144 (43.4)	1140 (43.3)	1044 (39.7)
Hypertension[f]	4147 (39.4)	944 (35.9)	996 (37.8)	1037 (39.4)	1170 (44.5)
Systolic BP, mmHg	124.4±19.0	123.1±18.4	123.9±18.6	124.6±18.3	125.9±20.5
Diastolic BP, mmHg	71.7±10.4	72.8±10.1	72.3±10.2	71.4±10.3	70.2±10.9
Antihypertensive medication use	3753 (35.5)	794 (30.0)	873 (33.1)	970 (36.7)	1116 (42.2)
Non-fasting glucose, mmol/l	6.2±2.3	6.1±2.2	6.0±2.1	6.1±2.2	6.4±2.6
Total cholesterol, mmol/l	5.4±1.0	5.5±1.0	5.4±1.0	5.4±1.0	5.3±1.0
HDL-cholesterol, mmol/l	1.4±0.5	1.4±0.5	1.4±0.5	1.3±0.5	1.3±0.5
Triacylglycerol, mmol/l	1.6±1.0	1.6±1.0	1.6±1.0	1.6±1.0	1.6±1.1
Prevalent coronary heart disease	662 (6.3)	118 (4.5)	104 (4.0)	170 (6.4)	270 (10.2)
BMI, kg/m^2	28.3±5.4	28.9±5.4	28.5±5.3	28.1±5.4	27.9±5.5
Diabetes	1567 (14.8)	334 (12.6)	343 (13.0)	376 (14.2)	514 (19.5)
eGFR (CKD-EPI), ml min^{-1} 1.73 m^{-2}	88.3±14.8	93.4±13.9	89.2±13.1	87.5±13.4	83.2±16.8
Metformin use	10 (0.09)	0 (0.00)	1 (0.04)	2 (0.08)	7 (0.26)
Use of other diabetes medications	797 (7.5)	162 (6.1)	155 (5.9)	184 (7.0)	296 (11.2)
Use of β-blockers	1056 (10.0)	207 (7.8)	223 (8.4)	291 (11.0)	335 (12.7)
Use of mineralocorticoid receptor antagonist	278 (2.6)	55 (2.1)	48 (1.8)	62 (2.3)	113 (4.3)
Use of ACE inhibitors/ARBs	915 (8.7)	208 (7.9)	214 (8.1)	232 (8.8)	261 (9.9)
Use of diuretics	1440 (13.6)	292 (11.0)	330 (12.5)	355 (13.4)	463 (17.5)
hs-cTnT[g], ng/l					
Mean±SD among those with detectable values	11.6±13.8	6.8±7.2	7.3±4.9	8.1±8.5	10.7±16.1
Undetectable (<6)	5257 (51.0)	1692 (65.8)	1421 (55.0)	1240 (48.3)	904 (35.0)
6 to <14	4170 (40.5)	785 (30.5)	1014 (39.3)	1107 (43.1)	1264 (48.9)
≥14	877 (8.5)	93 (3.6)	147 (5.7)	221 (8.6)	416 (16.1)
NT-proBNP[h], pg/ml					
Mean±SD among those with detectable values	114.3±300.8	78.0±117.6	90.9±160.4	108.9±189.7	178.2±528.1
<125	8001 (77.6)	2179 (84.8)	2107 (81.6)	1952 (76.0)	1763 (68.2)
≥125	2278 (22.1)	379 (14.7)	468 (18.1)	612 (23.8)	819 (31.7)

Values are mean ± SD for continuous variables, and *N* (%) for categorical variables

[a] Values of GDF-15 in RFUs were $\log_2$ transformed because of skewed distributions, and values outside of 5 SDs were winsorised, for the purposes of the analyses

[b] 14 participants (Q1: 3, Q2: 3, Q3: 6, Q4: 2) were missing data on education level

[c] Alcohol use was ascertained using the two questions: 'Do you presently drink alcoholic beverages?', and, 'Have you ever consumed alcoholic beverages?' Participants who answered yes to the first question were considered to be current drinkers

[d] For smoking, participants were asked if they currently smoked cigarettes or whether they had done so in the past, and were categorised into: never smokers, former smokers and current smokers

[e] 24 participants (Q1: 3, Q2: 3, Q3: 8, Q4: 10) were missing data on physical activity

[f] 46 participants (Q1: 16, Q2: 4, Q3: 11, Q4: 15) were missing hypertension status

[g] 266 participants (Q1: 75, Q2: 59, Q3: 74, Q4: 58) were missing data on hs-cTnT

[h] 264 participants (Q1: 75, Q2: 59, Q3: 72, Q4: 58) were missing data on NT-proBNP

ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; Co., County; Q, quartile; RFU, relative fluorescence intensity unit

Results

A total of 10,570 individuals were included in our analysis (mean age of 60.0 [SD: 5.7] years, 54% women, 27% black participants, mean GDF-15: 14.4 [SD: 0.50]). Table 1 shows the baseline characteristics of participants by quartile of GDF-15. Individuals in the highest GDF-15 quartile were older and more likely to have hypertension, diabetes or coronary heart disease, as well as elevated hs-cTnT and NT-proBNP, but were less likely to be women, drinkers, smokers or to be obese. The characteristics of participants by diabetes and by HF status are shown in electronic supplementary material (ESM) Tables 1, 2.

Diabetes and GDF-15 levels association Elevated GDF-15 was more common in people with diabetes compared with those without diabetes (32.8% vs 23.6%, $p<0.0001$). Diabetes status was associated with elevated GDF-15 levels (≥75th percentile), even after adjustment for traditional HF risk factors (ESM Table 3). After adjusting for relevant risk factors, the OR for the association of diabetes with elevated GDF-15 was 1.59 (95% CI 1.38, 1.84) (Model 2, ESM Table 3). After an additional adjustment for NT-proBNP and for hs-cTnT levels the association was attenuated but remained significant (OR 1.56; 95% CI 1.39, 1.78; Model 2, ESM Table 3).

Diabetes, GDF-15 and HF Over a median of 23 years of follow-up, 2429 incident HF events occurred within the study sample (ESM Table 4). Higher GDF-15 at baseline was associated with an increase in the risk of HF (Model 2, Table 2, ESM Fig. 1), with an HR for the highest GDF-15 quartile (GDF-15 values: 14.7–17.1) vs the lowest quartile (GDF-15 values: 12.4–14.1) of 1.70 (95% CI 1.49, 1.94). There was a statistically significant interaction between GDF-15 and diabetes status on the outcome of incident HF (p for interaction = 0.034). In analyses stratified by diabetes status (Model 2, Table 2), GDF-15 was significantly associated with incident HF among those without diabetes (HR for the highest GDF-15 quartile vs the lowest quartile: 1.64 [95% CI 1.41, 1.91]), but more so among those with diabetes (HR for the highest GDF-15 quartile vs the lowest quartile: 1.72 [95% CI 1.32, 2.23]). Additionally, accounting for cardiac biomarkers (hs-cTnT and NT-proBNP), medication use (β-blocker use, and angiotensin converting enzyme inhibitors or angiotensin receptor blockers) and coronary heart disease as a time-varying covariate did not appreciably affect the magnitude or significance of the effect estimates (ESM Table 5).

Among individuals with diabetes, we observed roughly J-shaped associations of GDF-15 with HF (Fig. 1b), whereas among those without diabetes, the association of GDF-15 and incident HF was roughly linear (Fig. 1c).

In the overall study population, the addition of GDF-15 to a model including traditional risk factors, among which diabetes (Model 2, Table 2), showed that GDF-15 significantly improved risk prediction for HF (C statistic for model without GDF-15: 0.753 vs C statistic for model with GDF-15: 0.758, C statistic improvement [ΔC statistic]: +0.005, p for difference: <0.0001). Among individuals with diabetes, the C statistic for the model without GDF-15 was 0.721 vs C statistic for model with GDF-15: 0.729, and ΔC statistic was +0.008 (p = 0.0001). In those without diabetes, the C statistic for the model without GDF-15 was 0.736 vs C statistic for model with GDF-15: 0.742, and ΔC statistic was +0.006 ($p<0.0001$).

The examination of the joint association of diabetes and GDF-15 with HF showed that individuals in the top quartile of GDF-15 with diabetes had an HR of 2.46 (95% CI 1.99, 3.03) for incident HF relative to those in the lowest GDF-15

Table 2 HRs (95% CIs) for the associations of GDF-15 and incident HF post ARIC Visit 3, stratified by diabetes status

Model	GDF-15 quartile	HR (95% CI)		
		Overall	Diabetes	No diabetes
Model 1	Q1	1 (Reference)	1 (Reference)	1 (Reference)
	Q2	1.12 (0.98, 1.27)	1.03 (0.79, 1.34)	1.13 (0.98, 1.31)
	Q3	1.35 (1.19, 1.53)	1.23 (0.94, 1.59)	1.36 (1.18, 1.57)
	Q4	2.20 (1.95, 2.49)	2.39 (1.88, 3.05)	1.99 (1.73, 2.30)
Model 2	Q1	1 (Reference)	1 (Reference)	1 (Reference)
	Q2	1.04 (0.91, 1.19)	0.90 (0.68, 1.18)	1.08 (0.93, 1.26)
	Q3	1.19 (1.05, 1.36)	0.99 (0.75, 1.30)	1.22 (1.06, 1.42)
	Q4	1.70 (1.49, 1.94)	1.72 (1.32, 2.23)	1.64 (1.41, 1.91)

Model 1: adjustment for age, sex and race/centre

Model 2: Model 1 + education, current smoking, physical activity, systolic BP, use of antihypertensive medications, use of cholesterol-lowering medications, total cholesterol, HDL-cholesterol, triacylglycerols, BMI, eGFR, metformin use, use of diabetes medication other than metformin and diabetes duration

Q, quartile

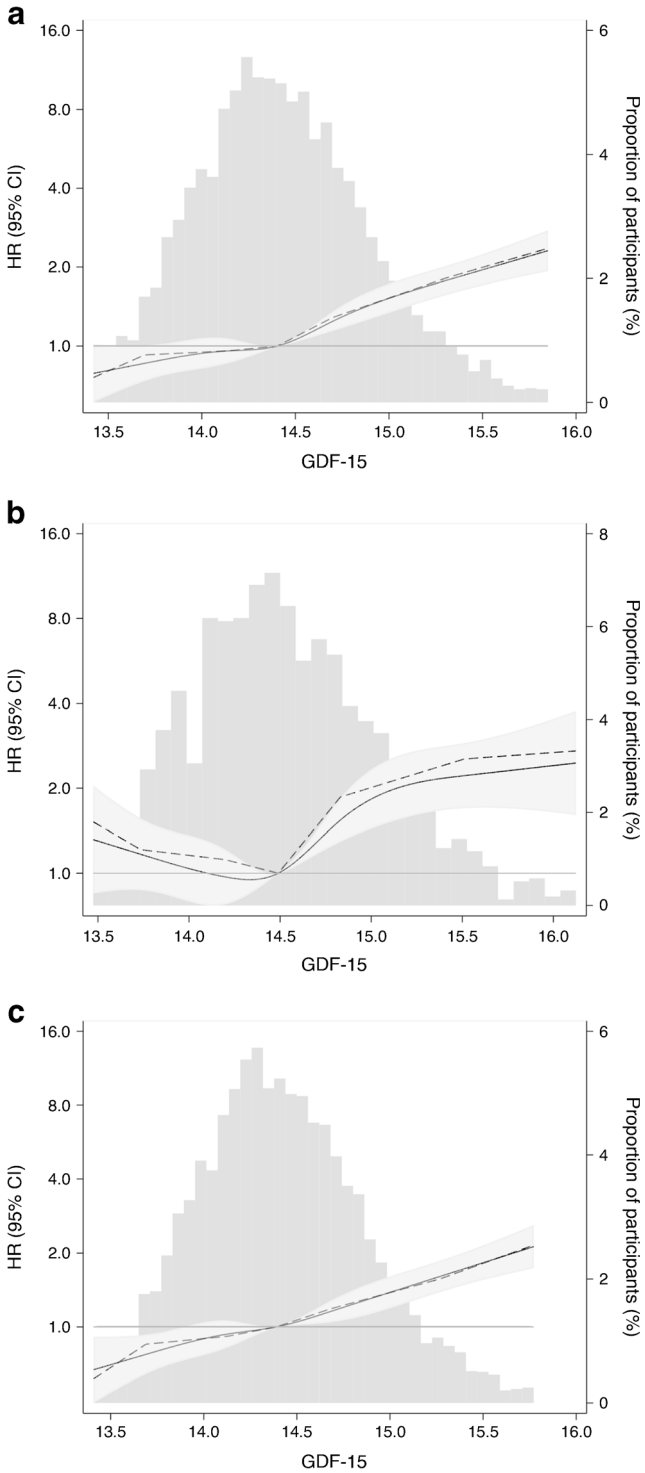

Fig. 1 HRs (95% CIs) for the association of GDF-15 with incident HF overall and according to diabetes status. GDF-15 was modelled as a restricted cubic spline (solid line) and as a piece-wise linear spline (dashed line) (knots at percentiles 5, 27.5, 50, 72.5 and 95); *y*-axes are plotted on a logarithmic scale. (**a**) Overall sample. (**b**) Diabetes. (**c**) No diabetes

quartile without diabetes (Model 2, Table 3). Additional adjustments for cardiac biomarkers (NT-proBNP and hs-cTnT), the use of medications (β-blockers use, and angiotensin converting enzyme inhibitors or angiotensin receptor blockers) and coronary heart disease as time-varying covariates did not affect the magnitude of the effect estimate and its significance (ESM Table 6).

Given the significance of the GDF-15 and sex interaction (p for interaction = 0.0034), we also conducted sex-specific analyses. Among men (ESM Table 7), GDF-15 was significantly associated with incident HF among those without diabetes (HR for the highest GDF-15 quartile vs the lowest quartile: 1.63 [95% CI 1.31, 2.03]), but not among those with diabetes (HR for the highest GDF-15 quartile vs the lowest quartile: 1.32 [95% CI 0.91, 1.92]). In women (ESM Table 7), GDF-15 was significantly associated with incident HF among those without diabetes (HR for the highest GDF-15 quartile vs the lowest quartile: 1.56 [95% CI 1.26, 1.94]), but to a greater extent among those with diabetes (HR for the highest GDF-15 quartile vs the lowest quartile: 2.30 [95% CI 1.58, 3.34]).

The joint association of diabetes and GDF-15 with HF showed that women in the top quartile of GDF-15 with diabetes had an HR of 2.53 (95% CI 1.86, 3.43) for incident HF relative to those in the lowest GDF-15 quartile without diabetes (ESM Table 7). The corresponding estimate in men was 1.69 (95% CI 1.37, 2.09).

Discussion

In a large community-based sample of black and white adults, we found an independent association between GDF-15 and incident HF, which was more pronounced among people with diabetes. There were sex differences in the relation of GDF-15 and HF by diabetes status, with the stronger associations among men without diabetes and women with diabetes. Even after adjustment for traditional HF risk factors, as well as markers of subclinical cardiac disease (hs-cTnT and NT-proBNP), medication use and coronary artery disease, individuals with diabetes and high GDF-15 levels had a greater than threefold higher risk of incident HF than individuals without diabetes and with lower levels of GDF-15. Moreover, GDF-15 added prognostic information to that of diabetes for HF risk prediction. These findings may have clinical implications, as diabetes status and GDF-15 are both independently associated with an increased risk of incident HF. While the observed change in C statistic after the addition of GDF-15 was statistically significant, the magnitude of the change was small and the role of GDF-15 for monitoring HF risk in clinical practice remains unclear.

Previous studies have demonstrated associations between diabetes and HF, between GDF-15 and diabetes, and between GDF-15 and incident HF. Indeed, higher GDF-15 concentrations have been described among individuals with impaired glucose tolerance vs those without glycaemic impairment [36, 37], and have also been prospectively associated with diabetes

Table 3 HR (95% CI) for the joint associations of diabetes and GDF-15 with incident HF post ARIC Visit 3

Diabetes status	Quartile of GDF-15	HR (95% CI)	
		Model 1	Model 2
No diabetes	Q1	1 (Reference)	1 (Reference)
	Q2	1.17 (1.01, 1.35)	1.12 (0.96, 1.30)
	Q3	1.42 (1.23, 1.63)	1.28 (1.11, 1.49)
	Q4	2.09 (1.82, 2.41)	1.73 (1.50, 2.01)
Diabetes	Q1	2.75 (2.21, 3.41)	1.58 (1.24, 2.02)
	Q2	2.50 (2.02, 3.10)	1.30 (1.02, 1.66)
	Q3	2.99 (2.44, 3.67)	1.47 (1.16, 1.86)
	Q4	5.67 (4.80, 6.71)	2.46 (1.99, 3.03)

Model 1: adjustment for age, sex and race/centre

Model 2: Model 1 + education, current smoking, physical activity, systolic BP, use of antihypertensive medications, use of cholesterol-lowering medications, total cholesterol, HDL-cholesterol, triacylglycerols, BMI, eGFR, metformin use, use of diabetes medication other than metformin and diabetes duration

Q, quartile

[7, 8]. Similarly, a number of studies have shown associations of GDF-15 with incident HF [9, 10, 12] and adverse HF prognosis [13–15]. However, the existing population-based studies of diabetes and GDF-15 have not examined their combined role in the pathogenesis of HF. The present analysis extends prior research by showing the additional prognostic implications of both dysglycaemia and elevated GDF-15 levels for incident HF risk. Our findings suggest that GDF-15 is an informative biomarker in the setting of diabetes, with the practical implication being that GDF-15 can be used for HF risk stratification among individuals with diabetes, thus allowing a better selection of candidates for effective HF prevention, possibly using novel therapies such as sodium–glucose cotransporter 2 (SGLT2) inhibitors [38, 39]. Indeed, the addition of GDF-15 to diabetes-specific risk prediction tools such as the UK Prospective Diabetes Study (UKPDS) engine [40, 41] could be considered to refine HF risk stratification among individuals with diabetes. There is not agreement upon GDF-15 cut-off for clinical diagnosis or prognosis purposes and specific cut-points merit exploration in future studies.

Mechanistic studies suggest that elevated GDF-15 levels reflect mitochondrial dysfunction, which contributes to the adverse myocardial effects [16, 17]. Mitochondrial dysfunction may be particularly pronounced in the setting of diabetes [19], with potentially more severe consequences on myocardial energetics and function [20, 22, 23], ultimately translating into a higher HF frequency. GDF-15 also has pro-atherogenic effects possibly through LDL oxidisation [42], as well as reflecting myocardial fibrosis [43] and endothelial dysfunction [44]; all of these processes are also more common in the setting of diabetes.

There are limitations to our study. First, the diagnosis of incident HF was based on hospital discharge and death certificate codes, which may have resulted in some misclassification, as the HF cases seen in the outpatient setting (i.e., potentially less severe or chronic stable forms of HF) were not captured. Second, our analysis does not account for the potential impact of all HF- or diabetes-directed therapies during the follow-up period. Third, we only had one measure of GDF-15, an inherently time-varying measure. Fourth, GDF-15 was measured using an aptamer assay and expressed in relative fluorescent units, although the correlation between this assay and GDF-15 measured using a targeted (ELISA) assay is known to be high (Pearson's correlation >0.8) [25]. Fifth, cardiac imaging data were not available to assess the subtypes of HF (HF with reduced ejection fraction [HFrEF] and HF with preserved ejection fraction [HFpEF]), and the combined effects of diabetes and elevated GDF-15 levels on HF incidences may differ by HF subtype. Sixth, we lacked detailed information on the type of diabetes, and the extent of glycaemic control (as assessed by glycosylated haemoglobin).

The strengths of our study include the community-based design, the large sample of black and white individuals, with long-term follow-up for incident HF events, and the extensive adjustment for potential confounding factors. The high number of HF events provided power to stratify by both the diabetes status and GDF-15 concentrations, in order to fully examine the contributions of both of these variables to incident HF risk.

Conclusion In this analysis of community-dwelling black and white people, we found an independent association between GDF-15 concentrations and incident HF, which was more pronounced among individuals with diabetes. Individuals with both diabetes and high GDF-15 levels had a markedly increased HF risk. Our results also indicate that GDF-15 can be used to better stratify people with diabetes for HF risk, and thus help select patients who should be aggressively targeted

for HF prevention. Our results suggest that GDF-15 may have an eventual role in clinical practice for monitoring cardiovascular risk and guiding preventive strategies.

Supplementary Information The online version contains peer-reviewed but unedited supplementary material available at https://doi.org/10.1007/s00125-022-05678-6.

Acknowledgements The authors thank the staff and participants of the ARIC study for their important contributions.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Funding The Atherosclerosis Risk in Communities study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services (under contract nos. (75N92022D00001, 75N92022D00002, 75N92022D00003, 75N92022D00004, 75N92022D00005). The content of this work is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. SomaLogic Inc. conducted the SomaScan assays in exchange for use of ARIC data. This work was supported in part by NIH/NHLBI grant R01 HL134320. JBE-T was supported by NIH/NHLBI grant K23 HL153774. ES was supported by NIH/NHLBI grant K24 HL152440 and NIH/NIDDK grant R01 DK089174. AMS was supported by NIH/NHLBI grants R01HL135008, R01HL143224, R01HL150342, R01HL148218 and K24HL152008. CEN was supported by NIH grant R01HL146907. ES, CEN and JBE-T were supported by AHA grant 20SFRN35120152.

Authors' relationships and activities ES is a member of the Editorial Board for *Diabetologia*. The other authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement JBE-T was involved in the study conception and design, literature search, data analysis and data interpretation, and drafted the manuscript. ND was involved in the data analysis and the writing of the manuscript. CEN, KM, RCH, CMB and AMS were involved in data interpretation and writing of the manuscript. JC was involved in acquisition of data, data interpretation and writing of the manuscript. ES was involved in the study design, supervision of data collection, data analysis, data interpretation and writing of the manuscript. All authors contributed meaningfully to this manuscript and approved the final version. JBE-T is the guarantor of this work.

References

1. Bootcov MR, Bauskin AR, Valenzuela SM et al (1997) MIC-1, a novel macrophage inhibitory cytokine, is a divergent member of the TGF-beta superfamily. Proc Natl Acad Sci U S A 94:11514–11519
2. Unsicker K, Spittau B, Krieglstein K (2013) The multiple facets of the TGF-β family cytokine growth/differentiation factor-15/macrophage inhibitory cytokine-1. Cytokine Growth Factor Rev 24:373–384
3. Macia L, Tsai VWW, Nguyen AD et al (2012) Macrophage inhibitory cytokine 1 (MIC-1/GDF15) decreases food intake, body weight and improves glucose tolerance in mice on normal & obesogenic diets. PLoS One 7:e34868
4. Wang X, Chrysovergis K, Kosak J et al (2014) hNAG-1 increases lifespan by regulating energy metabolism and insulin/IGF-1/mTOR signaling. Aging (Albany NY) 6:690–704
5. Chrysovergis K, Wang X, Kosak J et al (2014) NAG-1/GDF-15 prevents obesity by increasing thermogenesis, lipolysis and oxidative metabolism. Int J Obes 38:1555–1564
6. Ohkuma T, Komorita Y, Peters SAE, Woodward M (2019) Diabetes as a risk factor for heart failure in women and men: a systematic review and meta-analysis of 47 cohorts including 12 million individuals. Diabetologia 62:1550–1560
7. Bao X, Borné Y, Muhammad IF et al (2019) Growth differentiation factor 15 is positively associated with incidence of diabetes mellitus: the Malmö diet and Cancer–cardiovascular cohort. Diabetologia 62:78–86
8. Kempf T, Guba-Quint A, Torgerson J, Magnone MC, Haefliger C, Bobadilla M, Wollert K (2012) Growth differentiation factor 15 predicts future insulin resistance and impaired glucose control in obese nondiabetic individuals: results from the XENDOS trial. Eur J Endocrinol 162:913–917
9. Wang TJ, Wollert KC, Larson MG et al (2012) Prognostic utility of novel biomarkers of cardiovascular stress: the Framingham heart study. Circulation 126:1596–1604
10. Stenemo M, Nowak C, Byberg L et al (2018) Circulating proteins as predictors of incident heart failure in the elderly. Eur J Heart Fail 20:55–62
11. Fluschnik N, Ojeda F, Zeller T et al (2018) Predictive value of long-term changes of growth differentiation factor-15 over a 27-year-period for heart failure and death due to coronary heart disease. PLoS One 13:e0197497
12. Bansal N, Zelnick L, Go A et al (2019) Cardiac biomarkers and risk of incident heart failure in chronic kidney disease: the CRIC (chronic renal insufficiency cohort) study. J Am Heart Assoc 8:e012336
13. Kempf T, von Haehling S, Peter T et al (2007) Prognostic utility of growth differentiation Factor-15 in patients with chronic heart failure. J Am Coll Cardiol 50:1054–1060
14. Anand IS, Kempf T, Rector TS et al (2010) Serial measurement of growth-differentiation factor-15 in heart failure: relation to disease severity and prognosis in the valsartan heart failure trial. Circulation 122:1387–1395
15. Cotter G, Voors AA, Prescott MF et al (2015) Growth differentiation factor 15 (GDF-15) in patients admitted for acute heart failure: results from the RELAX-AHF study. Eur J Heart Fail 17:1133–1143
16. Fujita Y, Taniguchi Y, Shinkai S, Tanaka M, Ito M (2016) Secreted growth differentiation factor 15 as a potential biomarker for mitochondrial dysfunctions in aging and age-related disorders. Geriatr Gerontol Int 16(Suppl 1):17–29
17. Ji X, Zhao L, Ji K et al (2017) Growth differentiation factor 15 is a novel diagnostic biomarker of mitochondrial diseases. Mol Neurobiol 54:8110–8116
18. Kalko SG, Paco S, Jou C et al (2014) Transcriptomic profiling of TK2 deficient human skeletal muscle suggests a role for the p53 signalling pathway and identifies growth and differentiation factor-15 as a potential novel biomarker for mitochondrial myopathies. BMC Genomics 15:91
19. Pinti MV, Fink GK, Hathaway QA, Durr AJ, Kunovac A, Hollander JM (2019) Mitochondrial dysfunction in type 2 diabetes mellitus: an organ-based analysis. Am J Physiol Endocrinol Metab 316:E268–E285
20. Scheuermann-Freestone M, Madsen PL, Manners D et al (2003) Abnormal cardiac and skeletal muscle energy metabolism in patients with type 2 diabetes. Circulation. 107:3040–3046
21. Levelt E, Rodgers CT, Clarke WT et al (2016) Cardiac energetics, oxygenation, and perfusion during increased workload in patients with type 2 diabetes mellitus. Eur Heart J 37:3461–3469

22. Anderson EJ, Rodriguez E, Anderson CA, Thayne K, Chitwood WR, Kypson AP (2011) Increased propensity for cell death in diabetic human heart is mediated by mitochondrial-dependent pathways. Am J Physiol Heart Circ Physiol 300:H118–H124
23. Rijzewijk LJ, van der Meer RW, Lamb HJ et al (2009) Altered myocardial substrate metabolism and decreased diastolic function in nonischemic human diabetic cardiomyopathy: studies with cardiac positron emission tomography and magnetic resonance imaging. J Am Coll Cardiol 54:1524–1532
24. The ARIC Investigators (1989) The atherosclerosis risk in communities (ARIC) study: design and objectives. Am J Epidemiol 129: 687–702
25. Tin A, Yu B, Ma J, Masushita K (2019) Reproducibility and variability of protein Analytes measured using a multiplexed modified aptamer assay. J Appl Lab Med 4:30–39
26. Gold L, Ayers D, Bertino J et al (2010) Aptamer-based multiplexed proteomic technology for biomarker discovery. PLoS One 5: e15004
27. Kim CH, Tworoger SS, Stampfer MJ et al (2018) Stability and reproducibility of proteomic profiles measured with an aptamer-based platform. Sci Rep 8:8382
28. Candia J, Cheung F, Kotliarov Y et al (2017) Assessment of variability in the SOMAscan assay. Sci Rep 7:14248
29. Ganz P, Heidecker B, Hveem K et al (2016) Development and validation of a protein-based risk score for cardiovascular outcomes among patients with stable coronary heart disease. JAMA 315: 2532–2541
30. Williams SA, Kivimaki M, Langenberg C et al (2019) Plasma protein patterns as comprehensive indicators of health. Nat Med 25:1851–1857
31. Avery CL, Loehr LR, Baggett C et al (2012) The population burden of heart failure attributable to modifiable risk factors: the ARIC (atherosclerosis risk in communities) study. J Am Coll Cardiol 60:1640–1646
32. Richardson MT, Ainsworth BE, Wu HC, Jacobs DR Jr, Leon AS (1995) Ability of the atherosclerosis risk in communities (ARIC)/ Baecke questionnaire to assess leisure-time physical activity. Int J Epidemiol 24:685–693
33. Piercy KL, Troiano RP, Ballard RM et al (2018) The physical activity guidelines for Americans. JAMA. 320:2020–2028
34. Levey AS, Stevens LA, Schmid CH et al (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150:604–612
35. Coll AP, Chen M, Taskar P et al (2020) GDF15 mediates the effects of metformin on body weight and energy balance. Nature 578:444–448
36. Vila G, Riedl M, Anderwald C et al (2011) The relationship between insulin resistance and the cardiovascular biomarker growth differentiation factor-15 in obese patients. Clin Chem 57: 309–316
37. Ho JE, Mahajan A, Chen MH et al (2012) Clinical and genetic correlates of growth differentiation factor 15 in the community. Clin Chem 58:1582–1591
38. Zelniker TA, Wiviott SD, Raz I et al (2019) SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 393:31–39
39. Zannad F, Ferreira JP, Pocock SJ et al (2020) SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-reduced and DAPA-HF trials. Lancet 396:819–829
40. Stevens RJ, Kothari V, Adler AI, Stratton IM, Holman RR (2001) The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). Clin Sci 101:671–679
41. Kothari V, Stevens RJ, Adler AI et al (2002) UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK prospective diabetes study risk engine. Stroke. 33:1776–1781
42. Schlittenhardt D, Schober A, Strelau J et al (2004) Involvement of growth differentiation factor-15/macrophage inhibitory cytokine-1 (GDF-15/MIC-1) in oxLDL-induced apoptosis of human macrophages in vitro and in arteriosclerotic lesions. Cell Tissue Res 318:325–333
43. Lok SI, Winkens B, Goldschmeding R et al (2012) Circulating growth differentiation factor-15 correlates with myocardial fibrosis in patients with non-ischaemic dilated cardiomyopathy and decreases rapidly after left ventricular assist device support. Eur J Heart Fail 14:1249–1256
44. Xu J, Kimball TR, Lorenz JN et al (2006) GDF15/MIC-1 functions as a protective and antihypertrophic factor released from the myocardium in association with SMAD protein activation. Circ Res 98:342–350