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Growth Differentiation Factor (GDF)-15 and Cardiometabolic Outcomes among Older Adults: The Atherosclerosis Risk in Communities Study

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INTRODUCTION: Laboratory studies suggest an involvement of growth differentiation factor 15 (GDF-15) in metabolic dysregulation. However, the utility of GDF-15 for assessing risk of cardiometabolic outcomes has not been rigorously examined among older adults.

METHODS: We conducted a cross-sectional analysis of older adults who attended visit 6 (2016–2017) of the Atherosclerosis Risk in Communities (ARIC) Study. We used multivariable logistic regression to quantify cross-sectional associations of GDF-15 (in quartiles) with prevalent diabetes, obesity, atherosclerotic cardiovascular disease (ASCVD), subclinical myocardial stress/injury (assessed by NT-proB-type Natriuretic Peptide [NT-proBNP] and high-sensitivity cardiac troponin T [hs-cTnT]), and heart failure (HF).

RESULTS: Among 3792 ARIC study participants (mean age 80 years, 59% women, 23% Blacks and 77% Whites, mean GDF-15: 2094.9 pg/mL [SD: 1395.6]), higher GDF-15 concentrations (highest vs. lowest quartile) were positively associated with diabetes (adjusted odds ratio [aOR]:] : 2.48, 95% CI : 1.89, 3.26), ASCVD (aOR: 1.57, 95% CI: 1.16, 2.11), increased hscTnT (aOR: 2.27, 95%CI: 1.54, 3.34), increased NT-proBNP (aOR: 1.98, 95%CI: 1.46, 2.70), and HF (aOR: 3.22, 95%CI : 2.13, 4.85), in models adjusted for demographics and traditional cardiovascular risk factors.

CONCLUSIONS: In this sample of older US black and whites, increased GDF-15 was positively associated with diabetes, ASCVD, HF, and markers of subclinical myocardial stress or injury. These results illustrate the diverse aspects of the link between GDF-15 and diseases states, and its potential utility as robust biomarker of adverse cardiometabolic outcomes.

Introduction

Growth differentiation factor 15 (GDF-15) is a member of the transforming growth factor-β (TGF-β) cytokine superfamily (1). GDF-15 is primarily expressed in macrophages and epithelial cells (1), and its expression is positively associated with adiponectin production (2). The putative metabolic effects of GDF-15 have been described in animal studies (3), pointing to a role in energy balance and glucose homeostasis. However, the role of GDF-15 in human metabolism remains poorly understood. In small human and clinical studies, high circulating GDF-15 concentrations have been observed among individuals with diabetes, and positively associated with measures of hyperglycemia and insulin resistance (4, 5). Restoration of GDF-15 concentrations has also been described as a marker of response to obesity treatment using bariatric surgery (6).

Population-based studies have investigated the relation of GDF-15 with CVD, including heart failure and its prognosis (7). However, a limited number of community-based studies have examined the association of GDF-15 with diabetes (8, 9), or with obesity or metabolic syndrome (MetS). Moreover, extant studies of outcomes associated with GDF-15 have also had a limited scope seldom focusing on older adults and mainly including Caucasian participants (8, 9), and have yielded conflicting results with respect to diabetes (8–10). Given the emerging role of GDF-15 as a prognostic biomarker, it is important to clarify its relation with cardiometabolic outcomes among older adults.

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Using data from the Atherosclerosis Risk in Communities (ARIC) Study, we comprehensively assessed the associations of GDF-15 with key cardiometabolic outcomes including diabetes, obesity, MetS, atherosclerotic cardiovascular disease (ASCVD), and heart failure (HF) with a diverse population of older White and Black adults.

Methods

STUDY POPULATION

The Atherosclerosis Risk in Communities (ARIC) Study recruited 15 792 participants from 4 U.S. communities (11). The first study visit took place in 1987–1989. Since then, participants have returned for subsequent study visits and received annual initially and then semi-annual (since 2012) telephone calls. The sixth visit (visit 6) took place in 2016–2017. Of the 4003 eligible participants who attended visit 6, we excluded participants with missing GDF-15 measurements (n = 190), participants who were not Black or White (n = 10), or those who were Blacks from Minneapolis and Washington County (n = 11); leaving 3792 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

Blood samples were collected, centrifuged, and stored at −70°C during ARIC visit 6 (2016–2017). GDF-15 was measured in stored samples in 2018 using an electrochemiluminescence immunoassay on a Cobas e 411 analyzer (Elecsys, Roche Diagnostics). The assay has a limit of detection (LOD) of 400 pg/mL, a measuring range of 400 to 20 000 pg/mL, and an inter-assay imprecision of 4.8%, 4.7%, and 5.1% at GDF-15 concentrations of 699 pg/mL, 1510 pg/mL, and 7264 pg/mL, respectively, in our cohort.

NT-proB-type natriuretic peptide (NT-proBNP) and high-sensitive cardiac troponin T (hs-cTnT) were also measured using an electrochemiluminescent immunoassay on an automated Cobas e411 analyzer (Roche Diagnostics). The NT-proBNP assay had an inter-assay imprecision of 4.8% and 4.3% at NT-proBNP concentrations of 152 pg/mL and 4824 pg/mL, respectively. The hs-cTnT assay had an inter-assay imprecision of 5.7% and 4.8% at hs-cTnT concentrations of 27 ng/L and 2230 ng/L, respectively.

Serum glucose was measured using the hexokinase method. Glycosylated hemoglobin (HbA_{1C}) was measured using a high-performance liquid chromatography (Tosoh G8 Analyzer) method certified by the National Glycohemoglobin Standardization Program and aligned to the Diabetes Control and Complications Trial assay. Serum total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol concentrations were measured by using automated enzymatic assays. LDL cholesterol was calculated using the Friedewald equation.

CLINICAL ASSESSMENT AND OUTCOMES

A physical examination and anthropometry were performed at sixth visit (2016–2017). Diabetes was defined as either nonfasting glucose ≥200 mg/dL(≥11.1 mmol/L), fasting serum glucose ≥126 mg/dL((≥6.99 mmol/L), HbA_{1C} ≥6.5%, receiving drug treatment for increased glucose or self-reported physician diagnosis of diabetes. Systolic and diastolic blood pressure (BP) measurements were obtained 3 times and the mean of the second and third values were recorded. Hypertension was defined as systolic BP ≥130 mm Hg, diastolic BP ≥80 mm Hg, or use of antihypertension medications. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters, and obesity was defined as BMI ≥30 kg/m^2. MetS was defined using criteria proposed by the National Cholesterol Education Program—Adult Treatment Panel III (12). The presence of MetS was defined by the presence of any 3 of the following 5 criteria: (1) high triglycerides (≥150 mg/dL[≥1.69 mmol/L) or use of lipid-lowering drugs, (2) increased systolic BP (≥130 mm Hg) or diastolic BP (≥85 mm Hg) or use of antihypertensive drugs, (3) increased fasting blood glucose [≥100 mg/dL(≥5.55 mmol/L)] or known diabetes, (4) low high-density lipoprotein (HDL)–cholesterol [< 40 mg/dL (<1,04 mmol/L) in men and < 50 mg/dL (<1.29 mmol/L) in women], and (5) waist circumference (WC) ≥ 40 inches (men) or 35 inches (women).

Using previously described cut-offs (13, 14), we defined increased hs-cTnT as a value ≥31 ng/L for male and hscTnT ≥17 ng/L for female, and increased NT-proBNP as a value ≥300 pg/mL. The cut-points for NTproBNP were provided by the manufacturer and are commonly used in clinical practice for the staging of heart failure. In the present study, we also used sex-specific hscTnT and NT-proBNP cut-points based on the distribution of our data (≥99th percentile) or 72 ng/dL for hs-cTnT and 416.2 pg/mL for NT-proBNP.

Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation (15). Information on medical history, medication use, alcohol use, and current smoking was obtained using standardized self-report questionnaires.

STATISTICAL ANALYSIS

In the statistical analyses, the values of GDF-15 that were below the LOD were set to 0.5 times LOD

(200 pg/mL). We compared the baseline characteristics of participants across GDF-15 quartiles using the ANOVA procedure for continuous variables or the chi-square test for categorical variables. We used linear regression models to investigate the correlates of GDF-15 with adjustment for age, sex, and race-center. We conducted a similar analysis with GDF-15 modeled as a categorical independent variable (highest quartile vs. other 3 quartiles) using logistic regression.

We used logistic regression models to evaluate the associations of GDF-15 (quartiles) with the following cardiometabolic phenotypes: diabetes, obesity, MetS, ASCVD, and HF. For all the outcomes we initially adjusted for age, sex, and race-center (Model 1). The subsequent adjustments depended on the outcomes, as follows:

- Model 2A when analyzing diabetes: Model 1+ current smoking, systolic BP, use of antihypertensive medications, use of cholesterol lowering medications, total cholesterol, HDL-cholesterol, triglycerides and BMI;
- Model 2B when analyzing obesity: Model 1+ current smoking, systolic BP, use of antihypertensive medications, use of cholesterol lowering medications, total cholesterol, HDL-cholesterol, triglycerides and diabetes status;
- Model 2C when analyzing ASCVD and HF: Model 1+ smoking, systolic BP, use of antihypertensive medications, use of cholesterol lowering medications, total cholesterol, HDL-cholesterol, triglycerides, BMI, and diabetes status.
- Model 2D when analyzing increased hsTnT and NT-pro-BNP: Model 1+ smoking, systolic BP, use of antihypertensive medications, use of cholesterol lowering medications, total cholesterol, HDL-cholesterol, triglycerides, BMI, diabetes status, estimated glomerular filtration rate (eGFR), and prevalent HF.
- Model 2E when analyzing MetS: Model 1+ current smoking;

For all the outcomes, we evaluated a third model (Model 3A) which additionally included high sensitivity C-reactive protein (CRP). In persons with diabetes, Model 3B additionally included metformin, as this medication can impact GDF-15 concentrations (16). In a sensitivity analysis, we additionally included adiponectin to evaluate if observed associations with obesity were independent of this variable (Model 4 A). For the diabetes, ASCVD, and HF outcomes, we additionally adjusted for increased hsTnT and NT-pro-BNP. For the diabetes, ASCVD and HF outcomes, we also assessed the additive predictive value of GDF-15 beyond traditional risk factors, by evaluating the changes in *c*-statistic (prediction statistic) associated with the addition of GDF-15 to traditional variables.

We also modeled GDF-15 using restricted cubic and linear splines to more flexibly evaluate its continuous associations with each cardiometabolic outcome.

We conducted sensitivity analyses examining the association of GDF-15 with diabetes, and with increased hsTnT or NT-pro-BNP, in the subset of individuals without a history of ASCVD or HF, as well as the associations of GDF-15 with prevalent ASCVD and HF among individuals without diabetes.

A P value <0.05 was used to denote a 2-sided statistical significance. All analyses were performed using Stata version 15.

Results

A total of 3792 individuals were included, with a mean age of 80 (SD: 5) years, 59% women, 23% Blacks, and 77% Whites. Age, alcohol use, current smoking, diastolic blood pressure, HbA_{1C}, fasting glucose, BMI, waist circumference, triglycerides, as well as the proportion of individuals with diabetes, obesity, hypertension, MetS, and prevalent cardiovascular disease were higher across increasing GDF-15 quartiles (Table 1). HDL-cholesterol and eGFR were lower across GDF-15 quartiles.

CLINICAL CORRELATES OF GDF-15

In age-, sex-, and race-center—adjusted analyses, GDF-15 was correlated with various traits (Table 2). The main correlates of GDF-15 included current smoking (β coefficient: 0.13, 95% confidence interval (CI): 0.07, 0.19), diabetes status (β: 0.31, 95%CI: 0.28, 0.35), BMI (β per 1 SD change: 0.036, 95%CI: 0.021, 0.052), total cholesterol (β per 1 SD change: -0.089, 95%CI: -0.105, -0.073), HDL-cholesterol (β per 1 SD change: -0.097, 95%CI: –0.113, -0.081)) and triglycerides (β per 1SD change: 0.057, 95%CI: 0.042, 0.072). Similar correlates were identified in models including GDF-15 as a categorical outcome, comparing the highest quartile to the other 3 quartiles (Table 2); for example the odds ratio for the diabetes status and GDF-15 association was 4.15 (95%CI: 3.51, 4.91).

ASSOCIATIONS OF GDF-15 WITH CARDIOMETABOLIC OUTCOMES

In analyses examining categorical associations of GDF-15 with outcomes, compared to the lowest quartile, the highest quartile of GDF-15 was significantly associated with diabetes (adjusted odds ratio [aOR]: 2.48, 95% CI1.89, 3.26), ASCVD (aOR: 1.57, 95%CI: 1.16,

Table 1. Baseline characteristics of ARIC study participants at visit 6 (2016–2017), by quartiles of growth derived factor (GDF)-15.

	GDF-15 Quartiles				
Characteristics	**Q1 (470.1-1285 pg/mL) (n = 950)**	**Q2 (1286-1703 pg/mL) (n = 947)**	**Q3 (1704-2432 pg/mL) (n = 949)**	**Q4 (2433-17254 pg/mL)) (n = 946)**	***P*-value**
Age, mean (SD)	77.5 (3.7)	79.2 (4.4)	80.5 (5.0)	81.1 (5.0)	<0.001
Female, n (%)	658 (69.3%)	596 (62.9%)	513 (54.1%)	465 (49.2%)	<0.001
Race/Center, n (%)					<0.001
Whites, Forsyth Co.	196 (20.6%)	215 (22.7%)	214 (22.6%)	200 (21.1%)	
Whites, Minneapolis	310 (32.6%)	288 (30.4%)	277 (29.2%)	242 (25.6%)	
Whites, Washington Co.	196 (20.6%)	238 (25.1%)	242 (25.5%)	307 (32.5%)	
Blacks, Forsyth Co.	22 (2.3%)	19 (2.0%)	8 (0.8%)	14 (1.5%)	
Blacks, Jackson	226 (23.8%)	187 (19.7%)	208 (21.9%)	183 (19.3%)	
Drinking status, n (%)					<0.001
Current	539 (57.7%)	478 (51.9%)	432 (45.6%)	396 (43.0%)	
Former	225 (24.1%)	245 (26.6%)	283 (30.5%)	335 (36.4%)	
Never	171 (18.3%)	198 (21.5%)	213 (23.0%)	189 (20.5%)	
Current smoker, n (%)	49 (5.2%)	54 (5.9%)	74 (8.0%)	82 (8.9%)	0.005
Systolic blood pressure, mm Hg	134.8 (18.5)	135.3 (18.0)	134.9 (18.7)	135.6 (20.0)	0.78
Diastolic blood pressure, mm Hg	69.6 (10.4)	68.3 (10.2)	67.1 (10.1)	65.6 (10.9)	<0.001
Hypertension, n (%)	665 (71.7%)	735 (78.9%)	759 (81.4%)	806 (87.4%)	<0.001
Anti-hypertensive medication use, n (%)	618 (65.5%)	701 (74.6%)	764 (80.9%)	833 (88.5%)	<0.001
HbA_{1C}, %	5.8 (0.6)	5.9 (0.8)	6.0 (0.9)	6.3 (1.0)	<0.001
Glucose, mg/dL	100.6 (18.0)	103.8 (27.4)	107.0 (29.3)	113.3 (30.8)	<0.001
Triglycerides, mg/dL	108.8 (54.4)	110.2 (51.1)	116.0 (54.7)	123.5 (70.3)	<0.001
Total cholesterol, mg/dL	185.5 (38.2)	177.2 (39.9)	172.4 (39.3)	161.8 (40.6)	<0.001
HDL-cholesterol, mg/dL	56.2 (13.7)	53.6 (14.2)	51.3 (13.9)	47.8 (13.0)	<0.001
eGFR-cr, mean (SD)	76.3 (12.4)	70.1 (13.7)	65.2 (15.8)	54.4 (19.2)	<0.001
Prevalent CVD, n (%)	118 (12.4%)	170 (18.0%)	236 (24.9%)	341 (36.1%)	<0.001
Prevalent heart failure, n (%)	42 (4.4%)	56 (5.9%)	81 (8.5%)	187 (19.8%)	
Waist circumference, inches	38.3 (5.2)	39.3 (5.4)	40.1 (5.5)	40.5 (5.4)	<0.001
Body mass index, kg/m^2	27.7 (5.3)	28.4 (5.4)	28.5 (5.5)	28.4 (5.4)	0.010
Obese, n (%)	279 (29.6%)	321 (34.3%)	297 (31.8%)	306 (33.3%)	0.16
Diabetes, n (%)	195 (20.9%)	251 (27.3%)	312 (34.0%)	525 (58.1%)	<0.001
Metformin Use n (%)	22 (2.3%)	64 (6.8%)	114 (12.0%)	254 (26.8%)	<0.001
Metabolic syndrome components, n (%)	501 (52.7%)	566 (59.8%)	622 (65.5%)	710 (75.1%)	<0.001
Increased triglycerides	530 (55.8%)	557 (58.8%)	612 (64.5%)	694 (73.4%)	<0.001
Increased blood pressure	797 (83.9%)	847 (89.4%)	867 (91.4%)	892 (94.3%)	<0.001
Increased glucose	371 (39.1%)	418 (44.2%)	463 (48.9%)	572 (60.6%)	<0.001
Low HDL-cholesterol	219 (23.1%)	269 (28.5%)	330 (34.8%)	405 (42.9%)	<0.001
Large waist circumference	577 (62.2%)	621 (68.2%)	610 (67.7%)	612 (70.1%)	0.003
Metabolic syndrome, n (%)	340 (46.1%)	349 (52.2%)	353 (58.4%)	217 (57.4%)	<0.001

Values are mean±SD for continuous variables, and n (%) for categorical variables. BMI, body mass index; CVD, cardiovascular diseases; HDL, high-density lipoprotein; Metabolic syndrome was estimated among those without diabetes (n = 2390).
To convert glucose, triglycerides, total cholesterol and HDL cholesterol from mg/dL to mmol/L multiply by 0.0555, 0.0113, 0.0259, and 0.0259, respectively.

Table 2. Correlates of GDF-15 among ARIC study participants at visit 6 (2016–2017).

	GDF-15 (log-transformed)	GDF-15–quartile 4 vs. quartiles 1 to 3
Predictors	**Beta Coefficient (95% CI)**[i]	**Odds Ratio (95% CI)**[i]
Current smoking	0.13 (0.07, 0.19)	1.64 (1.23, 2.18)
Systolic blood pressure (mm Hg)[ii]	0.002 (-0.013, 0.018)	1.02 (0.94, 1.10)
Use of antihypertensive medications	0.21 (0.18, 0.25)	2.63 (2.10, 3.29)
Use of cholesterol lowering medication	0.13 (0.10, 0.16)	1.72 (1.47, 2.02)
Total cholesterol (mg/dL)[ii]	−0.089 (-0.105, -0.073)	0.67 (0.62, 0.74)
High-density lipoprotein–cholesterol (mg/dL)[ii]	−0.097 (-0.113, -0.081)	0.65 (0.59, 0.71)
Triglycerides (mg/dL)[ii]	0.057 (0.042, 0.072)	1.23 (1.15, 1.33)
Body mass index (kg/m^2)[ii]	0.036 (0.021, 0.052)	1.11 (1.02, 1.20)
Diabetes status	0.31 (0.28, 0.35)	4.15 (3.51, 4.91)

[i]Estimates are adjusted for age, sex, and race/center.
[ii]Per 1 SD change (1 SD: Systolic blood pressure = 18.80 mm Hg; Total cholesterol = 40.41 mg/dL; High-density lipoprotein- cholesterol =14.02 mg/dL; Triglycerides= 58.37 mg/dL; Body mass index = 5.41 kg/m^2).

2.11), increased hscTnT (aOR: 2.27, 95%CI: 1.54, 3.34), increased NT-proBNP (aOR: 1.98, 95%CI: 1.46, 2.70), and HF (aOR: 3.22, 95%CI: 2.13, 4.85) in multivariable-adjusted models (Table 3). For the diabetes, ASCVD, and HF outcomes, additionally adjusting for hscTnT and NT-proBNP did not materially affect our results (Model 4A, Table 3). For the obesity outcome, additionally accounting for adiponectin did not significantly change our results (Model 4B, Table 3). Regarding the increased NT-proBNP and hscTnT outcomes, the use of alternative definitions based on the cohort and sex-specific distributions of these markers showed similar results (Supplemental Table 1).

GDF-15 was not significantly associated with obesity (aOR for highest vs. lowest quartile: 0.84, 95%CI: 0.65, 1.07). We observed roughly linear associations of GDF-15 with diabetes, obesity, ASCVD, and HF (Fig. 1). GDF-15 appeared to have a J-shaped association with obesity. The exploration of MetS revealed a positive association with GDF-15 (aOR: 3.09, 95% CI; 2.49, 3.82) (Supplemental Table 2).

In the subpopulation of ARIC participants without a history of ASVCD or HF, we found a significant association of GDF-15 with diabetes (aOR for diabetes for highest vs. lowest quartile: 4.81, 95% CI 3.61, 6.40) (Supplemental Table 3). In the participants without diabetes, GDF-15 was significantly associated with HF (aOR 3.99, 95%CI: 2.31, 6.9) but not significantly associated with ASCVD (aOR: 1.41, 95%: 0.95, 2.11) (Supplemental Table 3).

Among individuals without prevalent CVD or HF (Supplemental Table 4), GDF-15 remained significantly associated with increased hscTnT (aOR: 2.22, 95%CI: 1.42, 3.48), and increased NT-proBNP (aOR: 1.90, 95%CI: 1.32, 2.75).

The addition of GDF-15 to a model including traditional risk factors (Model 3A or 3B, Table 3) showed that GDF-15 significantly improved risk prediction for diabetes (*c*-statistic for model without GDF-15: 0.829 vs. *c*-statistic for model with GDF-15: 0.836, P value for difference: 0.007), and for HF (0.714 vs. 0.742, P value for difference: 0.001), but not for ASCVD (0.753 vs. 0.756, P value for difference: 0.071).

Discussion

In a cross-sectional investigation of a large community-based sample of Black and White older adults, we examined the association of GDF-15 with major cardiometabolic outcomes. Circulating GDF-15 was positively associated with diabetes, ASCVD, subclinical myocardial injury and stress, and HF. However, the association of GDF-15 with obesity was more complex, with evidence for a J-shape. The divergent directions of the associations of GDF-15 with diabetes and obesity suggest that the former is most probably the main driver of the association with the MetS outcome. The observations made suggest that GDF-15 is potentially a robust biomarker for various disease states. Our findings reflect the complexity of GDF-15 metabolism which involves various tissues (e.g., myocardium, vessels, and adipose tissue) and multiple pathways such as those involved in glucose regulation. Indeed, GDF-15 has been implicated in various processes including inflammation, apoptosis, and vascular injury (3, 17).

Table 3. Association of growth derived factor (GDF)-15 with cardiometabolic outcomes among ARIC study participants at visit 6 (2016–2017).

		Odds Ratio (95% Confidence Interval)					
Models	GDF-15 quartiles	Diabetes	Obesity	Prevalent ASCVD	Prevalent HF	High TnT (hscTnT $\geq$ 31 ng/L for male and hscTnT $\geq$ 17 ng/L for female)	High NT-proBNP (BNP $\geq$ 300 pg/mL)
Model 1	Q1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
	Q2	1.60 (1.28, 1.99)	1.44 (1.18, 1.76)	1.31 (0.99, 1.72)	1.31 (0.87, 1.98)	1.74 (1.24, 2.46)	1.45 (1.14, 1.86)
	Q3	2.33 (1.87, 2.90)	1.41 (1.15, 1.74)	1.80 (1.38, 2.35)	1.84 (1.24, 2.73)	2.72 (1.95, 3.78)	1.98 (1.55, 2.52)
	Q4	6.77 (5.41, 8.48)	1.57 (1.28, 1.94)	2.46 (1.90, 3.20)	4.96 (3.45, 7.14)	8.06 (5.88, 11.05)	4.78 (3.77, 6.05)
Model 2	Q1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
	Q2	1.41 (1.11, 1.79)	1.28 (1.03, 1.60)	1.21 (0.90, 1.63)	1.08 (0.69, 1.69)	1.13 (0.78, 1.63)	1.12 (0.85, 1.48)
	Q3	1.78 (1.40, 2.26)	1.03 (0.82, 1.29)	1.48 (1.11, 1.98)	1.47 (0.96, 2.24)	1.36 (0.95, 1.97)	1.21 (0.91, 1.60)
	Q4	4.86 (3.80, 6.21)	0.89 (0.70, 1.14)	1.58 (1.17, 2.13)	3.20 (2.13, 4.82)	2.28 (1.55, 3.35)	2.03 (1.49, 2.77)
Model 3	Q1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
	Q2	1.12 (0.87, 1.45)	1.27* (1.02, 1.58)	1.21 (0.89, 1.63)	1.08 (0.69, 1.69)	1.13 (0.78, 1.63)	1.11 (0.85, 1.47)
	Q3	1.17 (0.90, 1.53)	1.00 (0.80, 1.25)	1.47 (1.10, 1.97)	1.47 (0.96, 2.25)	1.36 (0.95, 1.96)	1.19 (0.90, 1.58)
	Q4	2.48 (1.89, 3.26)	0.84 (0.65, 1.07)	1.57 (1.16, 2.11)	3.22 (2.13, 4.85)	2.27 (1.54, 3.34)	1.98 (1.46, 2.70)
Model 4	Q1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)		
	Q2	1.10 (0.85, 1.43)	1.26 (1.01, 1.58)	1.19 (0.88, 1.60)	1.05 (0.67, 1.64)		
	Q3	1.14 (0.88, 1.49)	0.97 (0.77, 1.23)	1.42 (1.06, 1.90)	1.36 (0.89, 2.10)		
	Q4	2.23 (1.68, 2.96)	0.88 (0.68, 1.13)	1.27 (0.93, 1.74)	2.19 (1.43, 3.37)		

ASCVD: atherosclerotic cardiovascular disease, HF: heart failure, hs-cTnT: High-sensitive cardiac troponin T, NT-proBNP: NT-proB-type Natriuretic Peptide.
Model 1 adjusts for age, sex, and race-center.
Model 2a (diabetes outcome): Model 1 + current smoking, systolic blood pressure, use of antihypertensive medications, use of cholesterol lowering medications, total cholesterol, HDL cholesterol, triglycerides and body mass index; Model 2 b (obesity outcome): Model 1 + current smoking, systolic blood pressure, use of antihypertensive medications, use of cholesterol lowering medications, total cholesterol, HDL cholesterol, triglycerides, and diabetes status; Model 2c (ASCVD or HF): outcomes includes for Model 1 + current smoking, systolic blood pressure, use of antihypertensive medications, use of cholesterol lowering medications, total cholesterol, HDL cholesterol, triglycerides, BMI, and diabetes status; Model 2d: (increased hsTnT or BNP): Model 1 + current smoking, systolic blood pressure, use of antihypertensive medications, use of cholesterol lowering medications, total cholesterol, HDL cholesterol, triglycerides, body mass index, diabetes status, eGFR and prevalent CVD/HF.
Model 3 adjusts for Model 2 + C-reactive protein–Model 3 for the diabetes outcome adjusts for Model2 + C reactive protein+ metformin use.
Model 4a (diabetes, ASCVD and HF): Model 3 + hs-cTnT and NT-proBNP.
Model 4 b (obesity): Model 3 + adiponectin (Visit 5).

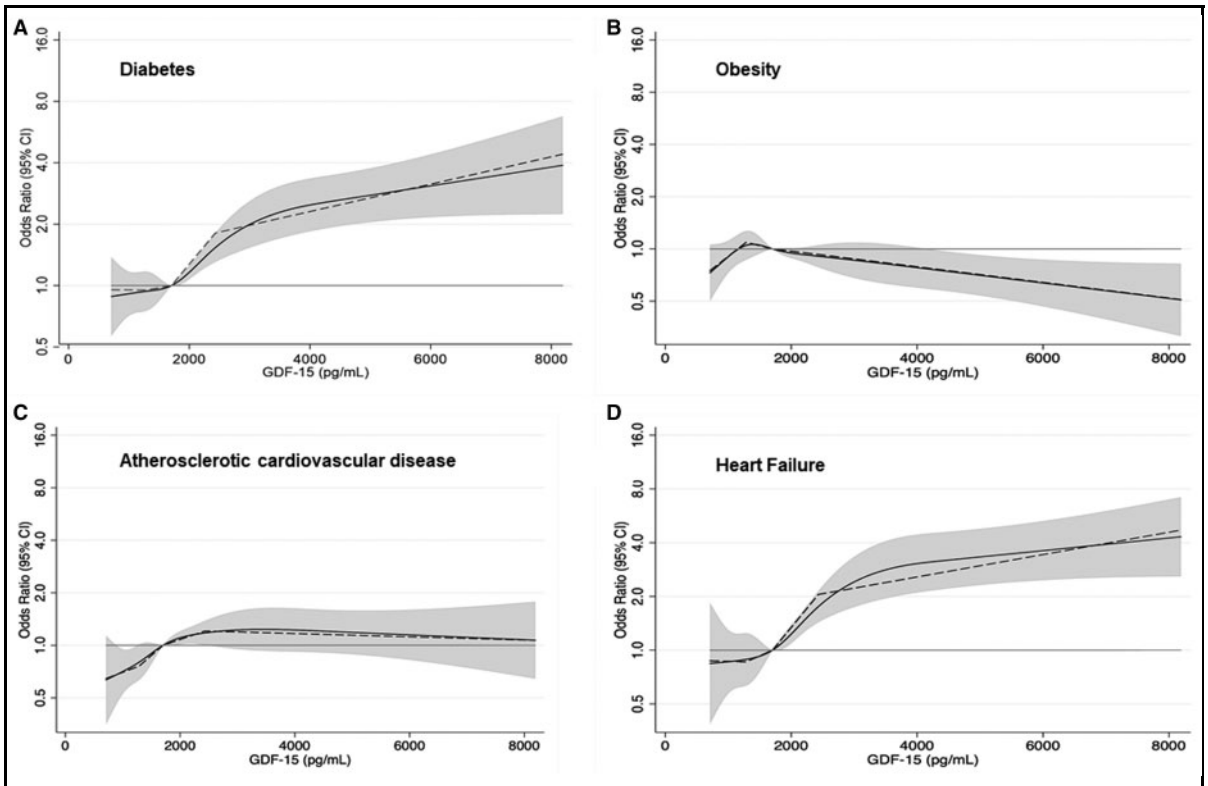

Fig. 1. Restricted cubic (solid) and piece-wise linear (dashed) splines of GDF-15 associations with various outcomes–Panel (A) diabetes, panel (B) obesity, panel (C) atherosclerotic cardiovascular disease, and panel (D) heart failure.

The correlates of GDF-15 identified in our study were similar to those described in prior reports, including the PIVUS study which included older adults (18), the Rancho Bernardo study (19), and younger individuals in the Framingham Heart Study (20). Our study complements and extends the later findings. Our findings of GDF-15 associations with most of the examined cardiometabolic outcomes are consistent with results from previous studies. Higher GDF-15 concentrations have been described among individuals with diabetes or impaired glucose tolerance as compared to individuals without glycemic impairment (4, 5, 8, 20), and have also been prospectively associated with insulin resistance and diabetes (9, 21). Our ASCVD results complement the evidence from prior investigations, which showed a positive relation of GDF-15 with overt ASCVD (7, 18, 22–24) and subclinical atherosclerosis (25, 26). Similarly a number of studies have also shown high concentrations of GDF-15 among individuals with prevalent HF (27–30). While prior studies have investigated the HF prognostic utility of GDF-15 above and beyond that of hsTcnT and/or NT-proBNP (27, 31), these have seldom examined the direct link between GDF-15 and subclinical measures of myocardial injury and stress (27). The observed relations of GDF-15 with diabetes and other metabolic traits as captured in the MetS entity may partially explain the associations between GDF-15 and CVD, including atherosclerotic conditions and HF (7, 26, 32). The observation of an attenuation of the GDF-15 and ASCVD association after the exclusion of individuals with diabetes in our study, suggests that dysglycemia may play a role in the GDF-15 and atherosclerosis pathway.

The exact mechanisms by which GDF-15 may modulate the risk of cardiovascular disease and affects metabolic regulation are still not clearly understood. GDF-15 appears to be a stress-induced cytokine reflecting damages in a variety of tissues, including the heart and the vessels (17). The effects on GDF-15 on the vascular system include pro-atherogenic effects possibly through LDL oxidization (33). GDF-15 has been described as a marker of myocardial fibrosis (34), though it may also limit excessive myocardial hypertrophy (35). Regarding its metabolic effects, GDF-15 may act as an adipokine (2), thus its link to an activation of the transcription factor p53, which contributes to inflammation and insulin resistance (36). Increased GDF-15

concentrations may also reflect mitochondrial dysfunction (3), which contributes to the adverse vascular and myocardial effects and impairment of glucose tolerance. Our findings on obesity are congruent with data from experimental models showing that GDF-15 has anorexic or weight loss effects (37, 38), through a counter-regulatory energy feedback loop including the hypothalamus (where GFD-15 receptors are located (39)), which upon stimulation by GDF-15 attempts to limit excess energy intake in the setting of obesity (40).

Strengths of our study include the community-based design, the large sample of Blacks and White older individuals, the examination of a wide spectrum of cardiometabolic outcomes, and the rigorous measurement of potential confounding factors. Nonetheless, there are limitations that should be considered in the interpretation of our results. First, the observational cross-sectional nature of our study limits causal inferences, especially as GDF-15 may both contribute to and be a marker of cardiometabolic risk. Second, while we were able to account for many measured clinical factors, our effect estimates may be subject to residual confounding. Finally, we included many comparisons in this study which raises the concern of a false positive result.

Conclusion

In conclusion, GDF-15 concentrations were associated with diabetes, MetS, prevalent ASCVD, and HF in a large community-based sample of older individuals. Our findings illustrate the complexity of the link between GDF-15 and diseases states. Specifically, this points to a potential adverse impact of increased concentrations GF-15 on glucose metabolism, vascular biology, and myocardial function, whereas of the association of GDF-15 with obesity was not robust. The findings also support a potential role for GDF-15 as a clinical biomarker of cardiometabolic risk in the community. Prospective investigations and interventional studies are needed to further characterize how the GDF-15 pathway modulates the occurrence of cardiometabolic outcomes.

Supplemental Material

Supplemental material is available at *Clinical Chemistry* online.

Nonstandard Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor 15; HDL, high density lipoprotein; HF, heart failure; hs-cTnT, high-sensitivity cardiac troponin T; LDL, low density lipoprotein; LOD, limit of detection; MetS, metabolic syndrome; NT-proBNP, NT-proB-type natriuretic peptide; WC, waist circumference

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