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GDF15 reflects beta cell function in obese patients independently of the grade of impairment of glucose metabolism

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Abstract *Background and aims:* Growth differentiation factor 15 (GDF15) is a strong predictor of cardiovascular morbidity and mortality found to be both marker and target of impaired glucose metabolism. GDF15 increases following glucose administration and is up-regulated in obesity and diabetes. We investigate here the relationship between GDF15 and beta cell function.
Methods and results: In this cross-sectional study we evaluated GDF15 concentrations in 160 obese subjects (BMI 35–63 kg/m^2, age 39.4 ± 18.6 years, m/f 38/122) who underwent a 75 g oral glucose tolerance test (OGTT). Based on the OGTT results, the cohort was divided into two groups: 1) normal fasting glucose and normal glucose tolerance (n = 80), 2) impaired fasting glucose, impaired glucose tolerance or type 2 diabetes (n = 80). The relationship of GDF15 to fasting and OGTT-based dynamic insulin sensitivity and insulin secretion parameters was evaluated.

GDF15 was higher in the prediabetes and diabetes groups and correlated with HbA1c, glucose, insulin as well as baseline and dynamic indices of insulin sensitivity and estimated beta cell function. Multiple regression analysis revealed that age, waist-to-height ratio, glomerular filtration rate and prehepatic beta cell function, but not the grade of impairment of glucose metabolism, were independent predictors of GDF15. Subgroup analysis showed that of all parameters of glucose metabolism only C-peptide, fasting prehepatic beta cell function and insulinogenic index remained significantly related to GDF15 in both groups.
Conclusion: We conclude that in patients with severe obesity, GDF15 strongly relates to beta cell function and should be further investigated as a potential therapeutic target and biomarker guiding treatment options.

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Introduction

Growth differentiation factor 15 (GDF15) is a biomarker predicting cardiovascular disease and mortality in several cohorts of healthy individuals and patients [1–4]. GDF15 is associated with nearly all factors related to cardiovascular risk, strongly reflecting classical cardiovascular risk factors such as age, male gender, smoking, hypertension, diabetes mellitus and obesity, but also heart function and low HDL-cholesterol [1,4–6]. In addition, being a stress responsive cytokine, GDF15 is also associated with inflammation and endothelial dysfunction, thereby also reflecting subclinical vascular disease [1,7,8]. The intricate biology of GDF15 is attributed to its expression in many tissues, organs, and its release from different cells including macrophages, endothelial cells, vascular smooth muscle cells, cardiomyocytes and adipocytes [9]. While GDF15 indicates mortality and progression of cardiovascular diseases, it also plays a role in cardioprotection and mice overexpressing GDF15 have an increased life span [9,10], suggesting that elevated GDF15 levels may be either beneficial or detrimental depending on the biological context. Recently, the GDNF family receptor α-like (GFRAL) was identified as the GDF15 receptor mediating its metabolic effects in mice together with the co-receptor RET [11–13].

Among the multiple factors regulating GDF15, several studies have elucidated a strong link between GDF15 and glucose metabolism. GDF15 predicts the future impairment of glucose metabolism in nondiabetic patients and the presence of diabetes in patients with metabolic syndrome [14,15]. In patients with diabetes, GDF15 is a biomarker for cancer incidence, and cardiovascular morbidity and mortality [2,16].

Initially, cross-sectional studies found increased GDF15 concentrations in patients with obesity and diabetes, with GDF15 levels correlating to glucose concentrations, HbA1c and insulin resistance [4–6]. Later on, functional studies revealed that GDF15 directly impacts glucose metabolism since GDF15 transgenic mice display improved glucose tolerance, lower insulin levels, reduced white and brown fat and are resistant to diet-induced obesity [17]. Administration of GDF15 in *ob*/*ob* mice enhanced oxidative metabolism and lipid mobilization from liver, muscle and adipose tissue, improving insulin sensitivity and reducing body weight [18]. On the other hand, GDF15 is also a target of glucose metabolism, as glucose up-regulates not only GDF15 secretion from endothelial and liver cells, but also circulating GDF15 levels in humans [19,20].

To date, the predictive value of GDF15 in patients with diabetes is thought to be due to the relationship between GDF15 and insulin resistance. Therefore, functional studies have been focused on target organs such as muscle and adipose tissue, and nothing is known about a possible role of GDF15 relating to beta cell function. GDF15 was shown to be elevated in diabetes as well as in obesity [5,6,15], both of which are characterized by a combination of insulin resistance and beta cell dysfunction. We therefore aimed to explore the relationship between GDF15 and different parameters of glucose metabolism, insulin sensitivity and beta cell function in a cohort relatively homogeneous with respect to obesity, including 160 obese patients with different grades of impairment of glucose metabolism and no previously diagnosed diabetes.

Methods

Study population

The study included 160 patients routinely attending the obesity outpatient clinic of the Medical University of Vienna. Inclusion criteria were body mass index (BMI) $>$ 35 kg/m^2 and no previous diagnosis of diabetes mellitus, exclusion criteria were concomitant cancer and severe heart, kidney or liver disease. The study protocol was approved by the institutional review board and all participants gave written informed consent. Anthropometric measurements were performed. All subjects underwent a 75 g oral glucose tolerance test (OGTT). Blood samples were collected at baseline and at 30, 60, 90 and 120 min for determination of glucose, insulin and C-peptide as well as GDF15 and clinical chemistry parameters (baseline only).

Type 2 diabetes mellitus (DM) was defined as fasting plasma glucose of $\geq$126 mg/dL (7.0 mmoL/L) or plasma glucose of $\geq$200 mg/dL (11.1 mmoL/L) 2 h after OGTT or glycated hemoglobin (HbA1c) $\geq$ 6.5% ($\geq$48 mmoL/mol). Impaired glucose tolerance (IGT) was defined as a plasma glucose of 140 mg/dL (7.8 mmoL/L) −199 mg/dL (11.0 mmoL/L) 2 h after OGTT, whereas impaired fasting glucose (IFG) was defined as fasting plasma glucose of 100 mg/dL (5.6 mmoL/L) − 125 mg/dL (6.9 mmoL/L). Glomerular filtration rate (GFR) was calculated as [175*(serum creatinine)−1.154*(age)−0.203*0.742 (if female)] using the MDRD formula. Mean arterial blood pressure (MAP) was calculated as [(2*diastolic blood pressure) + systolic blood pressure]/3. The waist-to-height ratio was recently demonstrated to be an indicator of cardiovascular risk in patients with DM [21].

Assays

Samples for GDF15 and insulin measurement were centrifuged at 1500 g for 10 min at 4 °C and serum was immediately frozen at −20 °C until analysis. GDF15 serum levels were measured by quantitative sandwich ELISA (#DGD150, R&D Systems, Minneapolis, MN) with an intra- and inter-assay CV of $<$2.8% and $<$6% respectively, as described [20]. Insulin and C-peptide were measured using commercially available RIAs (LINCO Research, St. Charles, MO) with inter- and intra-assay CV being 2.5 and 3%, respectively, for insulin, and both 4.4% for C-peptide. Glucose, HbA1c, lipid values and clinical chemistry parameters were measured at our Institute of Medical and Chemical Laboratory Diagnostics by routine certified protocols (www.kimcl.at).

Calculations of basal and dynamic insulin secretion and sensitivity parameters

Calculations were performed using established OGTT-derived indices [22]. Areas under the curves (AUCs) were calculated using the trapezoidal rule. The OGTT-derived indices (herein referred to as post glucose load parameters), included the oral glucose insulin sensitivity index (OGIS), the insulinogenic index (IGI) and the adaptation and disposition indices [22–24]. The disposition index, quantifying the capacity of the beta cell to adapt to changes in insulin sensitivity (i.e. posthepatic insulin appearance with respect to changes in insulin sensitivity), was calculated as the ISSI-2 index, as described [24]. The adaptation index provides an estimate of the prehepatic beta cell secretory capacity [22].

Fasting insulin resistance was assessed with HOMA-IR (calculated as (fasting glucose)*(fasting insulin)/405), while post glucose load insulin sensitivity was estimated by OGIS. Beta cell function was estimated by fasting beta cell function, and post glucose load by the IGI. Posthepatic and prehepatic fasting beta cell function was calculated as [(fasting glucose)/(fasting insulin)] or [(fasting glucose)/(fasting C-peptide)], respectively, whereas IGI was calculated based on glucose and insulin or C-peptide AUCs during OGTT. C-peptide levels, which are not subject to a substantial hepatic first-pass effect, were used for the calculation of the prehepatic parameters of beta cell function (IGI and fasting beta cell function) as an approximation of prehepatic insulin secretion, whereas posthepatic parameters of beta cell function were calculated based on insulin levels [22].

Statistics

Data were tested for normality using the Shapiro–Wilk test. Data shown are means ± standard error of the mean (SEM) for parametric data or medians ± interquartile range (IQR) for nonparametric data, unless otherwise stated. Differences between groups were compared using Mann-Whitney-U Tests, Student's T-tests or Kruskal–Wallis Tests to account for multiple comparisons. Distribution of frequencies was compared using Pearson's chi-squared test. Correlations were computed by Spearman's rank correlation coefficient; stepwise multiple regression analysis was performed entering selected parameters correlating significantly in the whole cohort. Multicollinearity was assessed by the variance inflation factor (VIF); multicollinearity was suspected when the VIF was >2.0. Pairwise exclusion was performed for descriptive statistics in cases with some missing records. Data were analyzed using the IBM SPSS Statistics software.

Results

The baseline clinical, metabolic and biochemical characteristics of the 160 study subjects are summarized in Table 1

Table 1 Baseline characteristics and parameters of glucose metabolism in the whole cohort and differences between the NFG + NGT and the IFG + IGT + DM groups.

	All	NFG + NGT	IFG + IGT + DM	p
Number	160	80	80	
Baseline				
GDF15 (ng/L)	452.4 (293.6)	397.3 (176.8)	534.1 (380.3)	0.001
Sex m/f (%)	38/122 (24/76)	17/63 (21/79)	21/59 (26/74)	n.s.
Age (yr)	39.4 (18.6)	37.0 (17.7)	41.4 (20.3)	0.001
Weight (kg)	132.0 (31.0)	132.0 (32.0)	133.0 (31.3)	n.s.
Waist circumference (cm)	126.5 (18.25)	127.1 (1.4)	126.5 (19.8)	n.s.
Waist-to-height ratio	0.75 (0.11)	0.75 (0.01)	0.77 (0.01)	n.s.
BMI (kg/m^2)	45.9 (9.1)	46.3 (10.4)	45.6 (8.7)	n.s.
GFR (mL/min/1.73 m^2)	86.4 (1.4)	89.1 (1.9)	83.8 (1.9)	0.048
MAP (mmHg)	100.0 (15.0)	98.8 (12.9)	103.3 (16.7)	0.033
Triglycerides (mg/dL)	136.0 (82.8)	128.5 (71.8)	152.0 (86.5)	0.009
Cholesterol (mg/dL)	196.0 (52.5)	192.5 (49.3)	200.5 (55.0)	n.s.
HDL-C (mg/dL)	46.0 (13.0)	46.0 (12.0)	46.0 (13.0)	n.s.
LDL-C (mg/dL)	122.4 (39.0)	120.4 (39.4)	124.0 (41.0)	n.s.
HbA1c (%)	5.5 (0.50)	5.3 (0.50)	5.7 (0.05)	<0.001
Post oral glucose load				
OGIS (mL/min/m^2)	328.8 (5.4)	362.9 (6.1)	290.0 (81.5)	<0.001
IGI prehepatic (nmol/mmol)	48.4 (20.9)	52.7 (1.7)	43.1 (18.5)	0.003
IGI posthepatic (nmol/mmol)	8.6 (6.4)	9.3 (6.5)	7.3 (6.7)	n.s.
Disposition index	14.1 (9.2)	18.2 (0.53)	10.3 (6.3)	<0.001
Adaptation index	15.1 (6.9)	17.7 (7.3)	13.3 (5.1)	<0.001

Shown are mean (SEM) for parametric data or median (IQR) for nonparametric data. DM – type 2 diabetes, GFR – glomerular filtration rate, HbA1c – glycated hemoglobin, HDL-C – high-density lipoprotein-cholesterol, IFG – impaired fasting glucose, IGI – insulinogenic index, IGT – impaired glucose tolerance, LDL-C – low-density lipoprotein-cholesterol, MAP – mean arterial blood pressure, NFG – normal fasting glucose, NGT – normal glucose tolerance, n.s. – not significant, OGIS – oral glucose insulin sensitivity. Differences between groups were tested with independent samples Mann-Whitney-U Tests, independent samples Student's T-test or Chi-Squared Test. p is the level of significance testing for differences between both groups (NFG + NGT, IFG + IGT + DM).

and Fig. 1. Based on the OGTT results, the cohort was divided into groups with different grades of impairment of glucose metabolism: subjects with normal fasting glucose (NFG) and normal glucose tolerance (NGT) were included in the NFG + NGT group (n = 80); patients with IFG, IGT or DM were summarized in the IFG + IGT + DM group; within that group, 13 patients had newly identified mild type 2 diabetes mellitus (HbA1c ≤ 7.0%), 27 patients had IFG only,

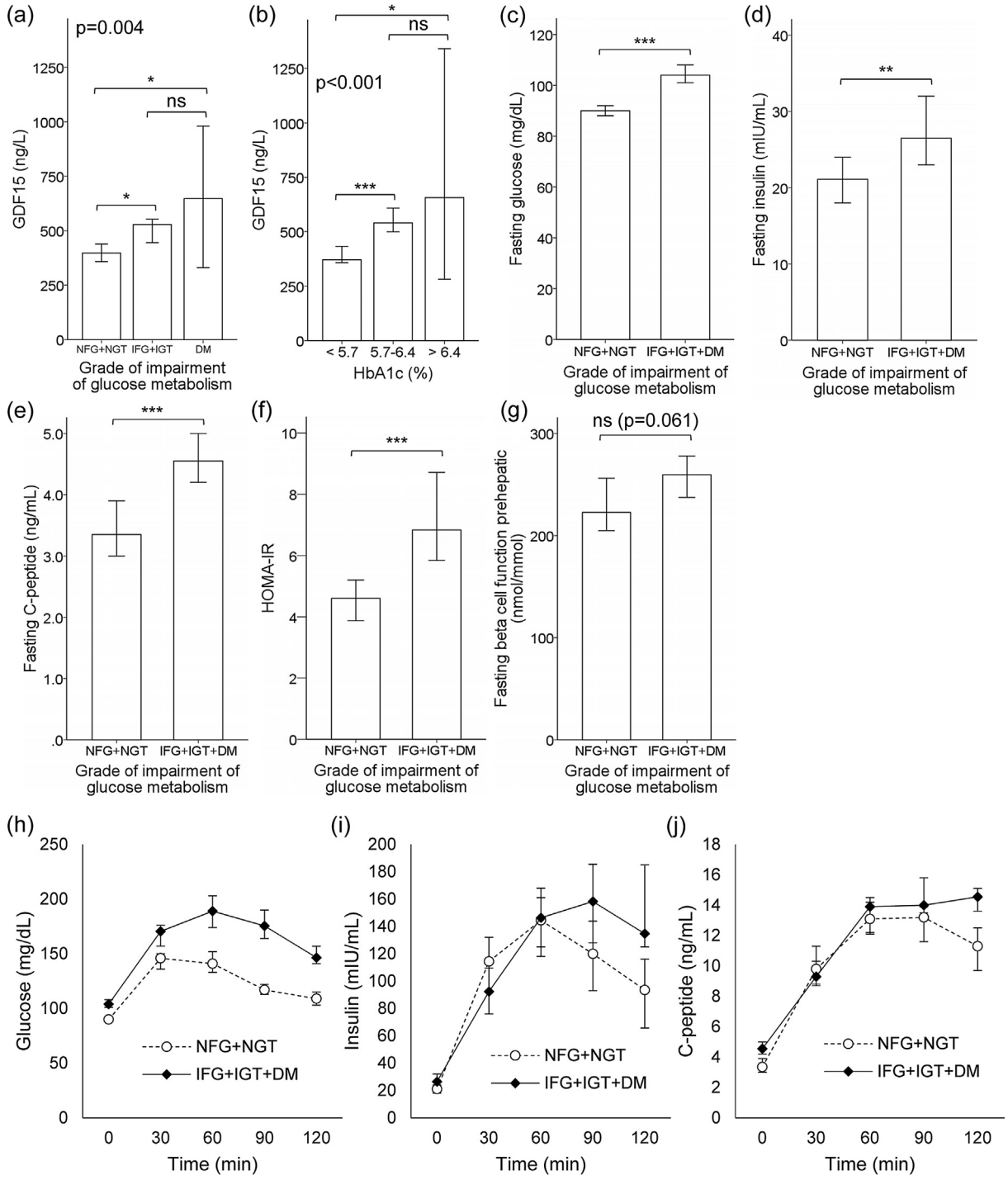

Figure 1 Baseline GDF15, fasting indices of glucose metabolism and OGTT results according to grade of impairment of glucose metabolism and HbA1c. (a) Serum GDF15 in subjects with normal fasting glucose and normal glucose tolerance (NFG + NGT), with prediabetes (IFG + IGT) and type 2 diabetes (DM). (b) Serum GDF15 in subjects with normal HbA1c (<5.7%, <39 mmoL/mol), HbA1c in the prediabetic range (5.7–6.4%, 39–46 mmoL/mol) and HbA1c in the diabetic range (>46 mmoL/mol). (c)–(g) Fasting parameters of glucose metabolism in the NFG + NGT group compared to the IFG + IGT + DM group. (c) Fasting glucose, (d) fasting insulin, (e) fasting C-peptide, (f) HOMA-IR and (g) fasting prehepatic beta cell function. Glucose (h), insulin (i) and C-peptide (j) levels up to 120 min after a 75 g oral glucose tolerance test. Data shown are medians ±95% confidence intervals. Differences between groups were tested with Kruskal–Wallis tests (a and b, exact p-values are given for overall testing) and with independent samples Mann-Whitney-U tests (c–g). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ns not significant (pairwise comparisons).

21 patients had IGT only and 19 patients had IFG + IGT. GDF15 levels were significantly higher in the IFG + IGT + DM compared to the NFG + NGT group (Table 1); there was no significant difference in GDF15 levels between IFG + IGT and DM (Fig. 1A), as well as between IFG and IGT (526.9 vs 423.6 ng/L, p = 0.394). GDF15 levels were significantly higher in patients with HbA1c between 5.7 and 6.4% compared to those with HbA1c in the normal range (Fig. 1B). Patients in the IFG + IGT + DM group were older, had higher HbA1c, mean arterial pressure and triglycerides and a lower GFR (Table 1).

Different indices of beta cell function and insulin sensitivity are shown in Table 1 and Fig. 1. Significant differences between groups were detected in fasting glucose, insulin and C-peptide as well as fasting insulin resistance (HOMA-IR, Fig. C-F). Interestingly, prehepatic IGI (insulinogenic index), reflecting beta cell function after an oral glucose load, was higher in the NFG + NGT group

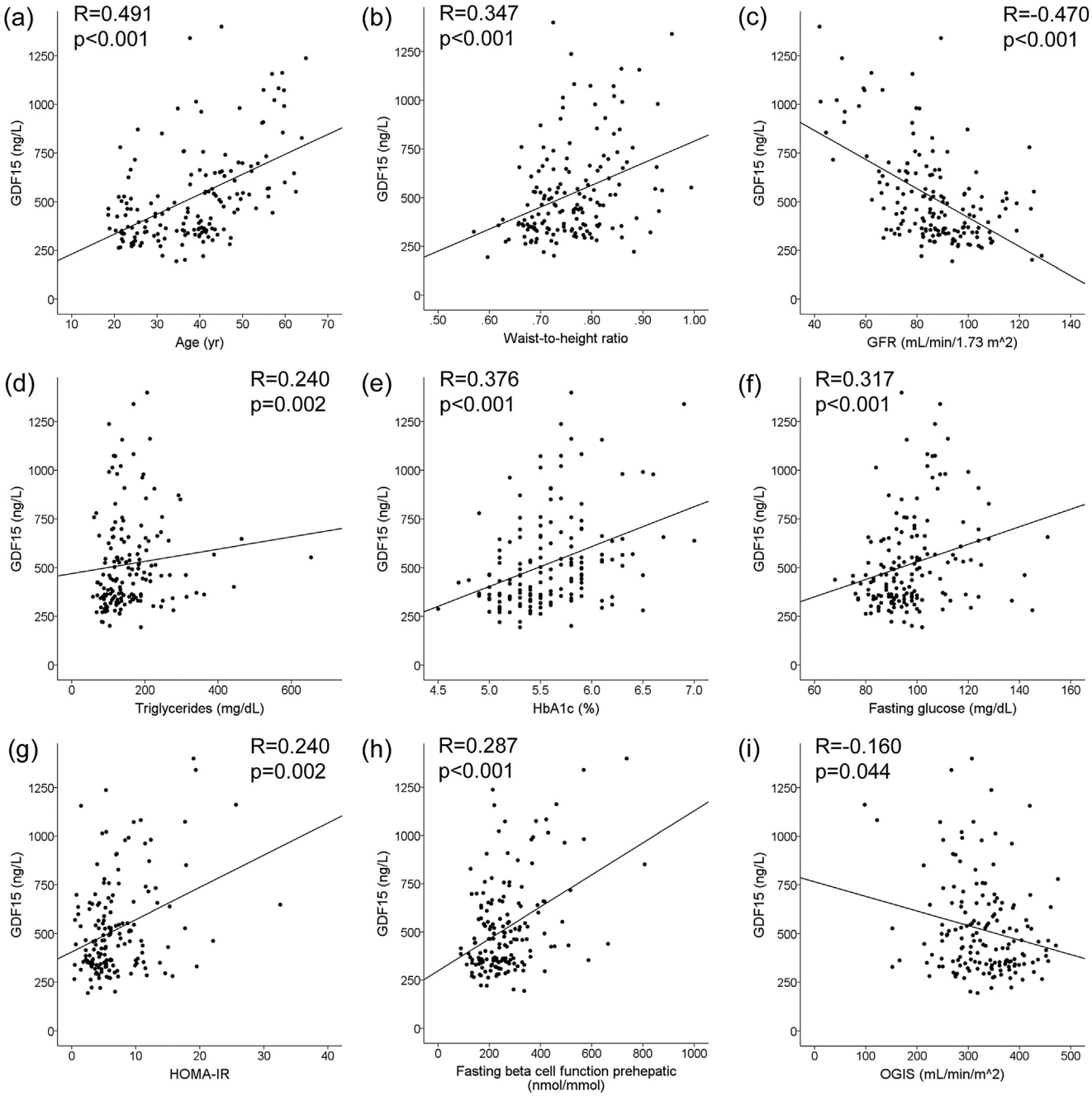

Figure 2 Scatter plots showing the relationship between GDF15 levels and different baseline parameters and parameters of glucose metabolism. Shown are the correlations between GDF15 and (a) Age, (b) Waist-to-height ratio, (c) GFR (glomerular filtration rate), (d) Triglycerides, (e) HbA1c (glycated hemoglobin), (f) fasting glucose, (g) HOMA-IR (homeostasis model assessment insulin resistance index), (h) prehepatic fasting beta cell function, (i) OGIS (oral glucose insulin sensitivity). Correlations were computed by Spearman's rank correlation coefficient, correlation coefficients (Spearman's R) and significances are shown in the plots.

compared to the IFG + IGT + DM group (Table 1) whereas fasting prehepatic beta cell function was not significantly different between groups (Fig. 1E), narrowly missing significance ($p = 0.061$).

The relationships between GDF15 and baseline characteristics as well as indices of insulin sensitivity and beta cell function are shown in Fig. 2. Waist-to-height ratio correlated better with GDF15 levels than waist circumference ($R = 0.320$, $p < 0.001$), waist-to-hip ratio ($R = 0.292$, $p < 0.001$) or BMI (n.s.). We found a significant correlation of GDF15 levels with prehepatic but not posthepatic fasting beta cell function.

The following variables correlating with GDF15 in univariate analysis were entered into stepwise multiple regression: age, waist-to-height ratio, GFR, triglycerides, HbA1c, glucose, HOMA-IR, fasting beta cell function prehepatic, OGIS, disposition index and the grade of impairment of glucose metabolism (see above, and Fig. 2). In this model, only GFR, waist-to-height ratio, fasting prehepatic beta cell function and age, but neither fasting glucose, HbA1c nor the grade of impairment of glucose metabolism (NFG + NGT versus IFG + IGT + DM) were independent predictors of GDF15 concentrations ($F(4, 151) = 37.072$, $p < 0.001$, $R^2 = 0.495$) (Table 2, "full model"). When fasting C-peptide levels were added to the variables included in the analysis, fasting C-peptide, GFR, waist-to-height ratio and age were independent predictors of GDF15 ($F(4, 151) = 38.360$, $p < 0.001$, $R^2 = 0.504$) (Table 3). Implications of multicollinearity were detected between HbA1c, fasting glucose, fasting C-peptide and fasting beta-cell function using a stringent cutoff (VIF > 2.0). To exclude the impact of multicollinearity, we performed a regression analysis using a simplified model including only the following variables: GFR, age, waist-to-height ratio and prehepatic fasting beta-cell function, finding again that beta-cell function is an independent predictor of GDF15 concentrations ($F(4, 153) = 37.885$, $p < 0.001$, $R^2 = 0.498$) (Table 2).

Group-specific correlations between GDF15 and baseline characteristics as well as indices of insulin sensitivity and beta cell function are shown in Table 3. GDF15 correlated positively with age and negatively with GFR in the NFG + NGT and the IFG + IGT + DM groups, mirroring the results of the whole cohort. Within parameters of glucose metabolism, only parameters of prehepatic fasting and glucose-induced beta cell function (prehepatic fasting beta cell function, IGI) as well as C-peptide were significantly related to GDF15 in both groups.

Table 2 Different models of multiple regression indicating significant independent predictors of GDF15 as well as corresponding measures of collinearity.

Regression models	Entered variables	Estimated model coefficients		Collinearity statistics
		Standardized β	p	VIF
Full model	GFR	−0.308	<0.001	1.719
	Waist-to-height ratio	0.179	0.008	1.337
	Prehepatic fasting beta cell function	0.291	<0.001	1.258
	Age	0.292	<0.001	1.823
	Triglycerides		n.s.	
	HbA1c		n.s.	
	Glucose		n.s.	
	HOMA-IR		n.s.	
	Disposition index		n.s.	
	OGIS		n.s.	
	Grade of impairment of glucose metabolism (NFG + NGT, IFG + IGT + DM)		n.s.	
Model including C-peptide	GFR	−0.301	<0.001	1.716
	Waist-to-height ratio	0.164	0.016	1.365
	C-peptide	0.313	<0.001	1.298
	Age	0.255	0.001	1.717
	Triglycerides		n.s.	
	HbA1c		n.s.	
	Glucose		n.s.	
	HOMA-IR		n.s.	
	OGIS		n.s.	
	Disposition index		n.s.	
	Grade of impairment of glucose metabolism (NFG + NGT, IFG + IGT + DM)		n.s.	
Simplified model	GFR	−0.306	<0.001	1.716
	Waist-to-height ratio	0.182	0.007	1.349
	Fasting beta cell function	0.296	<0.001	1.268
	Age	0.291	<0.001	1.822

DM – type 2 diabetes mellitus, GFR – glomerular filtration rate, HbA1c – glycated hemoglobin, HOMA-IR – homeostasis model assessment insulin resistance index, NFG – normal fasting glucose, NGT – normal glucose tolerance, OGIS – oral glucose insulin sensitivity; VIF – variance inflation factor.

Table 3 Univariate correlations of GDF15 with baseline characteristics, fasting and OGTT-based indices of glucose metabolism in the NFG + NGT and the IFG + IGT + DM groups.

	NFG + NGT		IFG + IGT + DM	
	r	p	r	p
Number	80		80	
Baseline				
Age	0.278*	0.013	0.559***	<0.001
Sex (male gender)	0.245*	0.029	−0.007	n.s.
Weight	0.024	n.s.	0.086	n.s.
Waist-to-height ratio	0.202	n.s.	0.422***	<0.001
BMI	−0.049	n.s.	0.183	n.s.
GFR	−0.347**	0.002	−0.530***	<0.001
MAP	0.091	n.s.	0.038	n.s.
Triglycerides	0.269*	0.016	0.114	n.s.
Cholesterol	0.174	n.s.	0.025	n.s.
HDL-C	−0.154	n.s.	0.080	n.s.
LDL-C	0.133	n.s.	0.009	n.s.
HbA1c	0.191	n.s.	0.283*	0.011
Fasting				
Fasting glucose	0.086	n.s.	0.236*	0.035
Fasting insulin	0.145	n.s.	0.194	n.s.
Fasting C-peptide	0.317**	0.004	0.307*	0.006
HOMA-IR	0.138	n.s.	0.232*	0.039
Fasting beta cell function prehepatic	0.303*	0.006	0.282*	0.011
Fasting beta cell function posthepatic	0.164	n.s.	0.139	n.s.
Post glucose load				
OGIS	−0.012	n.s.	−0.051	n.s.
IGI prehepatic	0.233*	0.037	0.224*	0.046
IGI posthepatic	0.099	n.s.	0.037	n.s.
Disposition index	−0.081	n.s.	−0.145	n.s.
Adaptation index	0.234*	0.038	0.102	n.s.

BMI – body mass index, DM – type 2 diabetes, GFR – glomerular filtration rate, HbA1c – glycated hemoglobin, HDL-C – high density lipoprotein-cholesterol, HOMA-IR – homeostasis model assessment insulin resistance index, IGI – insulinogenic index, LDL-C – low density lipoprotein-cholesterol, MAP – mean arterial pressure, NFG – normal fasting glucose, NGT – normal glucose tolerance, OGIS – oral glucose insulin sensitivity, ***$p < 0.001$, **$p < 0.005$, *$p < 0.05$, n.s. not significant.

Discussion

GDF15 is a glucose- and stress-responsive cytokine secreted mainly by endothelial cells, macrophages and the liver. Here we describe the relationship between GDF15 and different parameters of insulin secretion and sensitivity in a cross-sectional cohort of severely obese patients, finding that GDF15 correlated with all fasting parameters of glucose metabolism: fasting glucose, insulin, estimated fasting beta cell function and insulin resistance and sensitivity indices, but only estimated fasting prehepatic beta cell function was an independent predictor of serum GDF15 concentrations.

Previous studies have found increased GDF15 concentrations in patients with obesity and diabetes [5,6,14]. To date, the strong relationship between GDF15 and insulin resistance was thought to be the main determinant of increased GDF15 concentrations in obesity and diabetes. Nevertheless, GDF15 was found to be the only biomarker increased in patients with metabolic syndrome and diabetes, when compared to age-, sex- and BMI-matched patients with metabolic syndrome without diabetes [15]. Both these groups displayed similar HOMA insulin resistance indices [15], revealing that other factors relating to glucose metabolism might impact serum GDF15 concentrations. The present manuscript examines in detail different parameters of glucose metabolism in relation to circulating GDF15 concentrations, revealing the estimated fasting prehepatic beta cell function as an independent predictor of GDF15 concentrations. Factors determining fasting prehepatic fasting beta cell function are fasting glucose and fasting C-peptide; Of these two parameters, only C-peptide was found to independently predict GDF15 concentrations. Calculations based on C-peptide minimize the impact of the hepatic first-pass effect which influences insulin concentrations, thereby providing a more accurate estimate of pancreatic secretory capacity [25]. The post-hepatic fasting beta cell function, which reflects not only pancreatic insulin secretion but also hepatic insulin clearance, did not significantly correlate with GDF15 levels in the whole group and subgroups, underlining the importance of fasting pancreatic insulin secretory function in relation to GDF15 levels. Interestingly, fasting pre-hepatic beta cell function narrowly missed significance in the comparison between the NFG + NGT and the IFG + IGT + DM groups ($p = 0.061$); we attribute this to the heterogeneity of beta cell function especially in the IFG + IGT + DM group. Nevertheless, GDF15 levels correlated well with the fasting prehepatic beta cell function, highlighting again that factors in addition to the presence of impaired glucose metabolism act to determine GDF15 levels in our cohort.

To date, the pathways regulating the increase in GDF15 found in patients with impaired glucose tolerance and diabetes are not completely understood. We and others recently described that increased glucose concentrations enhance GDF15 release from human hepatic and endothelial cells [19,20]. GDF15 was also up-regulated by inflammatory stimuli, and increased GDF15 concentrations in obesity and type 2 diabetes reflected the degree of their accompanying subclinical inflammation [7]. Both hyperglycemia and inflammation impact beta cell function [26,27], and seem to be part of the pathophysiological mechanisms underlying the relationship between GDF15 and glucose metabolism.

GDF15 expression in the normal pancreas is nearly zero, but it is highly up-regulated in pancreatitis and pancreatic cancer [28]. To date, no data exist on the pancreatic GDF15 expression in patients with obesity, prediabetes and diabetes. Mechanistic studies are needed to evaluate the role of GDF15 in the pathogenesis of beta cell dysfunction and diabetes.

While recent studies explored GDF15 mainly as a therapeutic target in weight regulation in the context of its newly discovered receptor GFRAL which is expressed in the brainstem in mice, primates and humans, GDF15 is expressed in response to multiple stimuli and in many tissues, suggesting additional weight-independent functions [11].

Our present study is limited by its cross-sectional design, which allows only inferences on the causality between GDF15 levels and parameters of glucose metabolism and beta cell function. Furthermore, our cohort consists of severely obese and highly insulin resistant individuals; these patients were selected since we aimed to uncover potential variations of GDF15 levels on the basis of subtle differences in insulin resistance and beta cell function in the knowledge that body weight and the presence of diabetes both strongly influence GDF15 levels. Hence we cannot comment on the relationship between GDF15 and measures of glucose metabolism and beta cell function in patients with lower grades of obesity and insulin resistance. Lastly, we provide only estimated measures of insulin resistance and beta cell function; our results should be confirmed by the direct measurement of beta cell function and insulin resistance using the hyperglycemic and the hyperinsulinemic/euglycemic clamp techniques in lean and obese subjects.

In summary, we show here for the first time that beta cell function is an independent predictor of GDF15 concentrations in obese patients. These results contribute to the understanding of the pathophysiology of GDF15 in obesity, beta cell function and diabetes; should our results be confirmed by direct measurement of beta cell function, GDF15 should be investigated as a potential therapeutic target and biomarker guiding treatment options.

Disclosure

The authors declare no conflict of interest.

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