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# Impaired fasting plasma glucose is a risk indicator of interventricular septum thickening among non-diabetic subjects with obesity



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## ABSTRACT

**Aims:** To evaluate whether progressively higher fasting plasma glucose (FPG) is associated to thickening of the interventricular septum (IVS) among non-diabetic subjects with obesity.

**Methodology:** We studied 227 consecutive non diabetic patients (155 women and 72 men, age range 18–72 years) with overweight or obesity (BMI  $\geq$  25 Kg/m<sup>2</sup>), taking no medication or supplement. Hormonal, metabolic and routine laboratory parameters were collected. Echocardiography and ultrasonography echo-color Doppler of intima-media thickness of the common carotid artery (IMT-CCA) were performed to evaluate intima-media thickness of the common carotid artery (IVST) and early signs of atherosclerosis, respectively, in all enrolled subjects.

**Results:** Of the 227 subjects, 48.9% had higher IVST values. Age ( $p$  0.04), waist circumference ( $p$  0.01), systolic ( $p$  < 0.01) and diastolic blood pressure ( $p$  < 0.01), FPG ( $p$  < 0.01), insulin ( $p$  0.04), HOMA IR ( $p$  = 0.01), uric acid ( $p$  < 0.01) serum levels, IMT-CCA ( $p$  < 0.01), and left atrial diameter (LAD) ( $p$  < 0.01) were significantly higher in subjects with pathological IVST. Logistic regression models demonstrated an independent relation of FPG to IVST, both in semi and fully adjusted models (ORs 1.045 and 1.039, respectively). Moreover, graph presentation of the ORs and 95% CIs by FPG quintiles showed a positive risk trend for pathological IVST.

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Conclusions: Higher FPG levels represent an independent sensitive predictor of IVS thickening in subjects with obesity, even before overt diabetes. These results emphasize the importance of preventive management of the diabetes risk in obesity.

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## 1. Introduction

From the perspective of curbing the economic burden weighing down the health-care system, research efforts are focusing on interventions intended to prevent the onset of irrecoverable pathological conditions. From this point of view, obesity, especially the visceral phenotype, plays a pivotal role in the development of multiple cardiometabolic risk factors including dyslipidemia [1,2], hypertension [3,4], impaired glucose metabolism [5], and a prothrombotic state [6,7]. As regards cardiovascular diseases (CVDs), visceral obesity is responsible for a higher prevalence of acute coronary syndromes, atrial fibrillation, and heart failure [8]. Thickening of the arterial wall [9], commonly evaluated on the intima-media thickness of the common carotid artery (IMT-CCA), is an early sign of vascular alterations in obesity [9], as well as of a greater interventricular septal thickening (IVST). This latter, commonly measured by echocardiography, is numbered among early signs of heart deformation in obesity [10]. Higher IVST values result from hypertrophic cardiomyocytes, and occur together with an increased thickness of the left ventricular wall [11].

Asymptomatic pre-diabetes phenotypes such as impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and higher hemoglobin A1c (HbA1c) levels still within the normal range [12], are responsible for carotid atherosclerosis and a higher risk of cardiovascular diseases (CVDs) [13], especially in subjects with obesity. In this context, we previously found that a threshold value of only 90 mg/dl is an independent predictor of higher IMT-CCA [14]. We also reported that in subjects with overweight and obesity, the IMT-CCA is directly associated to insulin resistance [15], a family history of type 2 diabetes mellitus [16] and lower free testosterone levels in men [17].

As to the heart structure and physiology, glucose metabolism alterations have an impact on cardiovascular risk parameters and, in particular, a prolonged exposure to higher glucose levels and insulin-resistance has proved to foster adverse cardiac remodeling and subclinical dysfunctions, even before the diagnosis of diabetes [18,19]. In this regard, the multi-center community-based ECHO-SOL Study on Hispanics/Latinos in the United States, that collected the largest dataset of echocardiographic parameters, reported a close relationship between glucose intolerance, insulin resistance and increased left ventricular mass, that is a preclinical marker of an impaired cardiac structure among pre-diabetic subjects [20]. Accordingly, a previous report had demonstrated that fasting plasma glucose (FPG) may be prognostic for incident congestive heart failure (CHF) hospitalization and the combined endpoint of CHF/CV death, regardless of the presence of diabetes [21,22].

In this scenario, early screening for echocardiographic signs of cardiac hypertrophy may be very useful. However, no study has yet explored the role of higher glucose levels still within normal range on preclinical markers of alterations of cardiac structure and function in subjects with obesity. This study was aimed at investigating this aspect, focusing on the relationship between FPG levels and IVST in a population of apparently healthy non-diabetic subjects with overweight and obesity.

## 2. Methods

### 2.1. Study patients

From January 2019 to January 2020, 227 consecutive patients (155 females and 72 males, aged  $42.4 \pm 13.3$  years) were recruited at the "Population Health Unit" of the National Institute of Gastroenterology "S. de Bellis," Research Hospital, Castellana Grotte, Apulia, Italy. All data were collected at the baseline examination. Inclusion criteria were overweight or obesity ( $BMI \geq 25 \text{ Kg/m}^2$ ), in subjects taking no supplements or medication, including oral contraceptives or medicines for osteoporosis. Exclusion criteria were any history of endocrinological diseases (diabetes mellitus, hypo or hyperthyroidism, hypopituitarism, etc.), chronic inflammatory diseases, stable hypertension, angina pectoris, stroke, transient ischemic attack, atrial fibrillation, heart infarction, congenital heart disease, any malignancies, renal and liver failure and inherited thrombocytopenia.

The study protocol (ClinicalTrials.gov Identifier: NCT04264091) met the principles in the Declaration of Helsinki and was approved by the Ethics Committee of the National Institute of Gastroenterology "S. De Bellis" Research Hospital (Castellana Grotte, Apulia, Italy). All participants gave informed consent prior to enrollment in accordance with the Helsinki Declaration of 1964 and subsequent revisions.

### 2.2. Physical examination and laboratory biomarkers collection

At baseline, hormonal, metabolic and routine biochemistry parameters were closely examined in all subjects. A brief interview, including questions on medical history and lifestyle, was conducted by a senior physician. Extemporaneous outpatients diastolic (DBP) and systolic blood pressure (SBP) was determined in a sitting position after at least a 10-min rest, a minimum of three different times, using an OMRON M6 automatic Blood Pressure monitor. Blood samples were drawn between 08:00 and 09:00 h am, after overnight fasting.

Fasting blood glucose, insulin, total cholesterol, high- and low-density lipoprotein (HDL, LDL) cholesterol, and triglycerides serum levels were assayed. Serum insulin concentrations were measured by radioimmunoassay (Behring, Scoppito, Italy) and all samples were analyzed in duplicate. Plasma glucose was determined using the glucose oxidase method (Sclavus, Siena, Italy), while the concentrations of plasma lipids (triglycerides, total cholesterol, HDL cholesterol) were quantified by automated colorimetric method (Hitachi; Boehringer Mannheim, Mannheim, Germany). LDL cholesterol was calculated using the Friedewald equation [23]. TSH, FT3 and FT4 serum concentrations were measured by a competitive luminometric assay based on the SPALT (solid-phase antigen luminescence technique) principle (LIAISON FT3, FT4, TSH, DiaSorin, Saluggia, Italy). Serum uric acid was measured by the URICASE/POD method implemented in an autoanalyzer (Boehringer Mannheim, Mannheim, Germany). Insulin resistance was assessed using the Homeostasis Model Assessment – Insulin Resistance (HOMA-IR) [24].

### 2.3. Anthropometric assessment

Clinical procedures were carried out by two qualified nutritionists (RZ and FC), trained for equivalent measuring performances. All anthropometric measurements were taken with participants dressed in lightweight clothing and without shoes. Variables were all collected at the same time between 7:00 and 10:00 a.m. in the morning, after overnight fasting. Height was measured to the nearest 0.5 cm using a wall-mounted stadiometer (Seca 711; Seca, Hamburg, Germany). Body weight was determined to the nearest 0.1 kg using a calibrated balance beam scale (Seca 711; Seca, Hamburg, Germany). BMI was calculated by dividing body weight (Kg) by the square of height (m<sup>2</sup>) and classified according to World Health Organization criteria for normal weight (18.5–24.9 kg/m<sup>2</sup>), overweight (25.0–29.9 kg/m<sup>2</sup>), grade I obesity (30.0–34.9 kg/m<sup>2</sup>), grade II obesity (35.0–39.9 kg/m<sup>2</sup>), and grade III obesity ( $\geq 40.0$  kg/m<sup>2</sup>) [25]. Waist circumference (WC) was measured at the narrowest part of the abdomen, or in the area between the tenth rib and the iliac crest (minimum circumference).

### 2.4. Ultrasound measurement of carotid Intima–Media thickness

All subjects underwent high-definition vascular ultrasound according to the following protocol to measure IMT-CCA, a useful tool for evaluating early atherosclerosis. Ultrasonographic echo-color Doppler studies of the left and right common carotid arteries were performed by the same physician with a Philips Sonos 5500 using a 7.5 MHz high-resolution probe. Patients were placed in supine position, with the neck extended and rotated contralaterally by 45°, and the common carotid arteries were examined on the sagittal axis with a lateral view. We used the Pignoli et al. [26] method to define IMT-CCA, as described in our previous studies [6]: by focusing and freezing images on the distal wall of the common carotid artery on the lengthwise axis during end-diastole, the IMT-CCA was calculated as the distance between the leading borders of the first hyperechoic line and of the second

hyperechoic line, separated by a hypoechoic space (“double-track pattern”). The measurements were performed bilaterally 1 cm proximally to the carotid bulb, three times, and the IMT-CCA value was calculated as the arithmetical mean of each side. The IMT-CCA value considered for statistical analyses was the mean of right and left measurements. For IMT detection, we excluded arterial segments presenting atherosclerotic plaque.

### 2.5. Echocardiography

All patients underwent a full echocardiographic evaluation in line with international guidelines [27]. To avoid bias, only one experienced cardiologist performed all the echocardiographic examinations, using a GE Vivid T8 (Health Care, Italy) with a standard phase-array multi-frequency transducer, 3.5 MHz, and ECG trigger. Transthoracic echocardiography was performed with the patient in left lateral decubitus, after 10 min resting, with the exam table slanted to 30°. The examination included measurements of the diastolic interventricular septum (IVS) and anteroposterior diameter of the left atrium (LAD). Cardiac valves were evaluated by color Doppler to detect regurgitation and/or stenosis. Subjects were divided according to the IVST cut-off set by the latest ASE/EACVI guidelines:  $>9$  mm in women and  $> 10$  mm in men [11].

## 3. Statistics

We performed statistical analysis of baseline variables, expressed as mean  $\pm$  standard deviation (SD), median and range for continuous variables, and proportion (%) for the frequency of categorical variables. The whole sample ( $N = 227$ ) was divided into two groups according to the diagnosis of pathological IVST. The normality of distribution was assessed for each variable using Shapiro’s test. Wilcoxon sum rank test and independent samples t-test were performed on the basis of methodological suitability, to assess differences in variables between groups. Spearman’s correlation matrix was built for all continuous biochemical and anthropometric variables to check for interrelated variables, to avoid co-linearity effects in the model. P-values less than or equal to 0.05 were considered statistically significant, with 95% confidence intervals. Logistic regression analyses were built to define the Odds Ratio (OR) for pathological IVST. To avoid known confounding effects, two models were run: 1) Partially adjusted model including age, and WC; 2) Fully adjusted model including age, WC, uric acid, SBP, DBP and IMT-CCA (Table 2).

To assess the effect trend of FPG on IVST, FPG was divided into quintiles. Two multivariate models (partially and fully adjusted) were run, using quintiles as regressors to assess an increasing trend of the Odds Ratio (OR) for pathological IVST (Fig. 1). Statistical analyses were performed using RStudio software, Version 1.2.5042 (RStudio, Inc., Boston, MA, USA).

## 4. Results

The whole sample featured a majority of women (68.3%). Mean age was  $42.4 \pm 13.3$  years. Mean BMI was  $32.9 \pm 5.4$

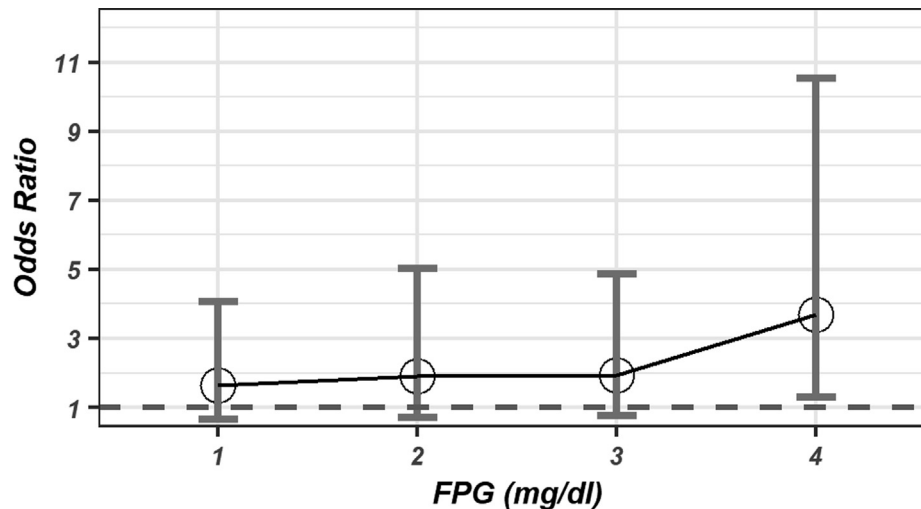


Fig. 1 – Fully adjusted estimated ORs and 95% CIs for pathological IVST by FPG quintiles.

Kg/m<sup>2</sup>. Table 1 summarizes the general, anthropometric, hormonal, metabolic and routine laboratory parameters of the enrolled subjects, subdivided by pathological IVST (yes/no), expressed as mean ± SD, median and range for continuous variables, and as percentage (%) for proportions. The prevalence of pathological IVST was 48.9% (N = 111), dominated

by men (55%, N = 61). The pathological IVST group were significantly older ( $p$  0.04), with higher WC ( $p$  0.01), SBP ( $p$  < 0.01), DBP ( $p$  < 0.01), HOMA IR ( $p$  0.01), FPG ( $p$  < 0.01), insulin ( $p$  0.04), acid uric ( $p$  < 0.01) serum levels, IMT-CCA ( $p$  < 0.01), IVST ( $p$  < 0.01) and LAD ( $p$  < 0.01). Table 2 shows the linear regression models (partially and fully adjusted) for

Table 1 – Characteristics of the whole sample divided by IVST pathological cut-offs.

Variables	Normal IVST		Pathological IVST		P Value *
	Mean/Median	Range/SD	Mean/Median	Range/SD	
Proportion (%)	<b>116.00 (51.10)</b>	–	<b>111.00 (48.90)</b>	–	–
Age (years)	42.00	18.00 to 71.00	46.00	18.00 to 72.00	<b>0.04</b>
Gender					
Male	11.00 (9.50)	–	61.00 (55.00)	–	<b>&lt;0.01<sup>†</sup></b>
Female	105.00 (90.50)	–	50 (45.00)	–	
WC (cm)	105.90	11.68	110.00	13.46	<b>0.01<sup>‡</sup></b>
BMI (Kg/m <sup>2</sup> )	31.30	25.10 to 47.30	32.00	25.10 to 47.60	0.79
SBP (mmHg)	124.80	14.82	134.00	16.97	<b>&lt;0.01<sup>‡</sup></b>
DBP (mmHg)	80.16	10.18	86.05	12.56	<b>&lt;0.01<sup>‡</sup></b>
Total Cholesterol (mg/dl)	192.00	97.00 to 297.00	194.00	118.00 to 310.00	0.88
HDL-Cholesterol (mg/dl)	53.00	24.00 to 116.00	49.00	29.00 to 89.00	0.06
LDL-Cholesterol (mg/dl)	117.50	32.00 to 216.00	121.00	52.00 to 262.00	0.44
Triglycerides (mg/dl)	84.50	34.00 to 361.00	101.00	33.00 to 541.00	0.06
FPG (mg/dl)	86.00	66.00 to 122.00	90.00	65.00 to 121.00	<b>&lt;0.01</b>
Insulin (UI/ml)	9.55	2.90 to 112.00	10.90	2.40 to 46.50	<b>0.04</b>
HOMA IR	1.99	0.61 to 30.14	2.49	0.52 to 10.90	<b>0.01</b>
HbA1c (%)	5.30	4.50 to 6.40	5.35	4.35 to 6.45	0.12
Uric acid (mg/dl)	4.15	2.10 to 8.70	4.90	2.20 to 10.40	<b>&lt;0.01</b>
TSH (mU/l)	1.79	0.29 to 6.37	1.58	0.33 to 5.49	0.06
FT3 (pg/ml)	2.91	1.64 to 3.95	3.00	2.05 to 4.60	0.08
FT4 (pg/ml)	10.20	7.10 to 16.50	10.30	6.80 to 13.80	0.41
IMT-CCA (cm)	0.65	0.30 to 1.15	0.73	0.44 to 1.20	<b>&lt;0.01</b>
IVST (mm)	9.00	7.00 to 10.00	12.00	10.00 to 15.00	<b>&lt;0.01</b>
LAD (mm)	36.00	28.00 to 44.00	38.00	28.00 to 44.00	<b>&lt;0.01</b>

\* Wilcoxon sum rank test, <sup>†</sup>Chi squared test, <sup>‡</sup>Two Sample t-test,

Data are shown as mean ± SD, median and range for continuous variables and as (%) for proportions

Significance shown in bold

Abbreviations: BMI (Body Mass Index); WC (Waist Circumference); SBP (Systolic Blood Pressure); DBP (Diastolic Blood Pressure); FPG (Fasting Plasma Glucose); HOMA IR (Homeostasis Model Assessment for Insulin- Resistance); TSH (Thyroid-Stimulating Hormone); FT3 (Free Triiodothyronine); FT4 (Free Thyroxine); IMT-CCA (Intima-Media Thickness of Common Carotid Artery); IVST (Interventricular Septal Thickening); LAD (Left Atrium Diameter)

pathological IVST. In both models, the results demonstrated an independent relationship between FPG and IVST (OR 1.039, CI 95% 1.010 to 1.068 and OR 1.039, CI 95% 1.008 to 1.072, respectively, for the semi and fully adjusted models). IMT-CCA and uric acid both showed independent associations with IVST (OR 67.180 CI 95% 5.240 to 86.12 and OR 1.317 CI 95% 1.049 to 1.653, respectively). By contrast, the other variables showed no significance. Fig. 1 clearly shows the increasing effect trend, fully adjusted for confounders, of the association between FPG quintiles and pathological IVST.

## 5. Discussion

The present study had the goal of evaluating whether progressively higher FPG is associated with interventricular septum (IVS) thickening among non-diabetic subjects with overweight and obesity. The findings clearly demonstrate that FPG is one of the determinant factors for subclinical cardiac alterations in subjects with excessive body weight, even before overt diabetes. In particular, we found that higher FPG levels, even within a non-diabetic range, influence IVS thickening, regardless of the major risk factors commonly associated with early signs of cardiac wall thickening.

Thus, our investigation demonstrates that a direct influence of FBG on IVST begins early in the natural history of diabetes, before the clinical diagnosis. The role of FBG was confirmed by a positive effect trend of FBG on IVST, expressed by a positive trend of ORs through the FBG quintiles. A further remarkable finding was that pathological IVST values, diagnosed according to the latest ASE/EACVI guidelines [11], were present in almost half of our population sample (48.9%, N = 111 of 227), despite their being apparently free of overt CVDs. It is noteworthy that we recently found hypertension in 69% of a population of apparently healthy subjects with obesity [4] and this finding, together with the results of the present study showing a high percentage of patients with greater IVST, emphasize the importance of preventing obesity, and supporting weight loss in subjects with obesity.

Our findings on FBG are in line with accumulated evidence from population-based studies focused on cardiovascular outcomes. A bi-racial report from the Atherosclerosis Risk In the Community (ARIC) Study reported that both diabetes and pre-

diabetes are associated with an increased LV mass, worse diastolic function, and an insidious reduction in left ventricular systolic function in subjects without prevalent coronary heart disease or heart failure (HF), suggesting that hyperglycemic status may contribute to an insidious subclinical impairment of cardiac structure and function [28]. Likewise, the Multi-Ethnic Study of Atherosclerosis (MESA), investigating four ethnic cohorts, found a progressive increase in wall thickness from normal glucose metabolism to IFG and type 2 diabetes in Caucasian subjects, but the differences were not significant after adjustment for other cardiovascular risk factors [29]. Again in pre-diabetes contexts, the CARDIA study highlighted that in middle-aged subjects, a longer exposure to glycemic abnormalities, with poor glucose and insulin resistance, may adversely influence cardiac remodeling and function over a 25-year period, predisposing to HF in later life [18]. Consistently, major findings from the ECHO-SOL study reinforce the concept that alterations in cardiac structure and function may begin even in pre-diabetes conditions [20]. In this regard, it should be noted that more and more evidence pointed to the critical role of post-prandial glucose in relation to body weight control, as an additional trigger factor for the development of oxidative stress, diabetes and CVDs [30].

Among the confounding variables included in the logistic regression model, IMT-CCA maintained an independent association with IVST, regardless of other confounders. This relationship suggests that progressive thickening of the arterial wall may be responsible for a parallel thickening of the IVS in subjects affected by obesity, even in the absence of diabetes, hypertension and other diseases known to affect heart structure and function. In line with the concept of possible cardiovascular alterations induced by higher FBG levels still in the normal range, we had previously found that even a threshold value of 90 mg/dl is an independent predictor of early signs of atherosclerosis, as evaluated by the IMT-CCA [13]. Accordingly, a retrospective study of 2052 non-diabetic participants, whose coronary artery calcium (CAC) score was measured repeatedly over 4 years, demonstrated that subjects with a higher baseline haemoglobin glycation index (HGI), defined as the difference between measured and predicted HbA1c levels, had a higher risk for incident CAC than those with a low baseline HGI [31].

**Table 2 – Logistic regression models on IVST categories as dependent variable.**

	Variables	OR	CI 95%	P value
Semi adjusted*	FPG (mg/dl)	1.039	1.010 to 1.068	0.01
	Age (years)	1.012	0.990 to 1.034	0.27
	WC (cm)	1.019	0.996 to 1.042	0.09
Fully adjusted†	FPG (mg/dl)	1.039	1.008 to 1.072	0.01
	Age (years)	0.984	0.957 to 1.011	0.25
	WC (cm)	0.998	0.972 to 1.025	0.93
	Uric Acid (mg/dl)	1.317	1.049 to 1.653	0.01
	DBP (mmHg)	1.014	0.977 to 1.052	0.45
	SBP (mmHg)	1.020	0.993 to 1.048	0.13
	IMT-CCA (cm)	67.180	5.240 to 86.12	<0.01
	Insulin (UI/ml)	0.995	0.966 to 1.025	0.76

Significance shown in bold

\*corrected for age and WC

†corrected for semi adjusted plus SBP, DBP, IMT-CCA, uric acid, and insulin levels

As regards the other metabolic parameters, this study shows that subjects with pathological IVST have higher uric acid levels, and this association was maintained in the fully adjusted logistic regression models with IVST as the dependent variable, corroborating previous data reporting hyperuricemia to be an independent driver of left ventricular hypertrophy (LVH) [32].

No significant difference of LDL-cholesterol levels resulted from the two groups (normal/pathological IVST) belonging to the study sample, although this represents a well-known risk parameter for CVDs, especially among studies on diabetic subjects [33]. However, our sample included non-diabetic subjects only complicated by obesity, without analysing a parallel normal-weight control group, and this aspect is likely to mask part of the multiple risk factors for CVDs, including serum LDL-cholesterol. Moreover, since UKPDS has been performed in UK and this study has been carried out in the south of Italy, genetic and food differences may partly contribute to explain this result.

Insulin levels and insulin resistance, evaluated by HOMA IR, were significantly higher in subjects with greater IVST and since insulin is a well-known growth factor, it may well be that hyperinsulinemia and insulin resistance may contribute to IVS thickening, as demonstrated in previous studies conducted in women with obesity [34]. However, the association between insulin and IVST was not maintained after adjustment of data for FBG, uric acid and IMT-CCA, thus excluding a strong independent influence of insulin and insulin-resistance on IVS thickening in subjects with uncomplicated obesity.

Lastly, systolic and diastolic BP were significantly higher in subjects with greater IVST and, since hypertension is a well-known factor leading to interventricular septum and left ventricular hypertrophy [35], it could well be that higher SBP and BDP may contribute to greater IVST. However, the association between SBP and DBP and IVST was not maintained after logistic regression and adjustment of data either, excluding a strong independent influence of BP on IVS thickening in subjects with uncomplicated obesity.

Some limitations of this study should be considered. Because of the cross-sectional setting, the direction of any causal relationship could not be established, so our data provide a description rather than an explanation. Prospective studies are needed to clarify a causal relationship. A strong point is that we examined only individuals taking no medication, thus avoiding a possible interference with biomarkers assays and hence investigated outcomes.

In conclusion, this study demonstrates that higher FPG levels within a non-diabetic range represent an independent sensitive predictor of IVS thickening in subjects with overweight and obesity, even before the onset of diabetes. Given the current obesity epidemic and consequently increased prevalence of glycemic disturbances, these results have important public health implications. They emphasize the point that delaying or halting progression from IGF to diabetes may prevent harmful thickening of the ventricular walls and the subsequent onset of cardiovascular complications.

Ethics approval and consent to participate

The study protocol was approved by the was approved by the Ethics Committee of the National Institute of Gastroen-

terology "S. De Bellis" Research Hospital (Castellana Grotte, Apulia, Italy). Written informed consents were obtained from all participants before data collection.

Consent for publication

All authors have declared their consent for this publication.

Availability of data and materials

Data can be obtained on request and are not publicly available.

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Not applicable.

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## Authors contributions

GDP, RS and GG contributed to the planning of the study; FC had access to data and conducted analyses; RZ wrote the first draft; All authors critically reviewed the intellectual content of manuscript drafts and approved the final version for submission. GDP and EG are the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable.

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