Differences in metabolic parameters and cardiovascular risk between American Diabetes Association and World Health Organization definition of impaired fasting glucose in European Caucasian subjects: a cross-sectional study

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Abstract

Introduction: The American Diabetes Association (ADA) defines impaired fasting glucose (IFG) as fasting plasma glucose concentration of 100–125 mg/dl, whereas the World Health Organization (WHO) and the International Diabetes Federation (IDF) define IFG as fasting plasma glucose levels of 110–125 mg/dl. We identified differences in metabolic parameters and cardiovascular disease (CVD) risk according to the ADA or WHO/IDF definition of IFG.
Material and methods: Healthy drug-naive Caucasian (Greek) subjects ($n = 396$; age 55 ±12 years) participated in this cross-sectional study.
Results: Diastolic blood pressure (DBP) and uric acid levels were higher in the subjects with glucose 100–109 mg/dl compared with those with glucose < 100 mg/dl (87 ±9 mm Hg vs. 84 ±11 mm Hg, $p = 0.004$ for DBP, 5.6 ±1.5 mg/dl vs. 5.0 ±1.0 mg/dl, $p = 0.002$ for uric acid), whereas triglyceride levels were lower in subjects with glucose 100–109 mg/dl compared with those with glucose ≥ 110 mg/dl (169 mg/dl (interquartile range (IQR) = 102–186) vs. 186 mg/dl (IQR = 115–242), $p = 0.002$). Only the ADA definition recognized subjects with significantly increased 10-year CVD risk estimation (SCORE risk calculation) compared with their respective controls (5.4% (IQR = 0.9–7.3) vs. 4.1% (IQR = 0.7–5.8), $p = 0.002$).
Conclusions: The ADA IFG definition recognized more subjects with significantly increased CVD risk (SCORE model) compared with the WHO/IDF definition.

Key words: prediabetes, impaired fasting glucose, American Diabetes Association, World Health Organization, cardiovascular risk, triglycerides.

Introduction

The incidence of type 2 diabetes (T2DM), which is associated with high morbidity and mortality rates, is increasing dramatically [1]. The age-adjusted prevalence of diabetes among Greek adults was 8.2% in 2002 and 9.5% in 2006, corresponding to an increasing rate of 4% per year [2]. In 2006, 12.9% of the adult U.S. population had T2DM, whereas approximately 25% were classified as having "prediabetes" [3]. The term "prediabetes" de-

scribes the intermediate condition in which the fasting plasma glucose level is above the highest normal value and below the cut-off level used to determine the diagnosis of T2DM, including both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). While the definition of IGT is the same for the American Diabetes Association (ADA) and World Health Organization (WHO) – International Diabetes Federation (IDF), IFG is defined as fasting plasma glucose concentration of 100–125 mg/dl according to the ADA definition, but as 110–125 mg/dl according to the WHO/IDF definition [4, 5].

Individuals with prediabetes are at high risk for the development of T2DM. The American Diabetes Prevention Program (DPP) showed that approximately 10% of individuals with IGT developed T2DM on an annual basis [6]. There are sparse reports on the association of IFG with the development of cardiovascular disease (CVD) [7, 8], but data regarding the extent to which CVD risk is increased are inconclusive [9, 10]. In Asian subjects, when IFG was defined as 110–125 mg/dl, it was associated with a significant increase of CVD and/or T2DM mortality, whereas mortality risks diminished substantially when IFG was defined as 100–125 mg/dl [11]. In European subjects, the Diabetes Epidemiology and Collaborative Analysis Of Diagnostic Criteria in Europe (DECODE) study, with approximately 30,000 participants and 11-year follow-up, showed that CVD events were proportionally increased only to 2 h post-challenge plasma glucose, whereas there was a J-shaped relationship between fasting plasma glucose and all-cause mortality [12].

The association of IFG with CVD risk may be associated with the definition used (ADA or WHO/IDF), as well as with other variables such as the presence of other CVD risk factors. The aim of the present study was to identify any differences in metabolic parameters and CVD risk between IFG definition of ADA or WHO/IDF in Caucasian (Greek) subjects.

Material and methods

Subjects

Greek subjects ($n = 396$) attending the Outpatient Lipid Clinic of the University Hospital of Ioannina, Greece, participated in the present study. All participants gave their informed consent and the study protocol was approved by the institutional ethics committee.

Definitions

We compared the definition of IFG according to the ADA (fasting glucose levels of 100–125 mg/dl) and WHO/IDF (fasting glucose levels of 110–125 mg/dl). The Framingham risk score was used to determine the 10-year risk of coronary heart disease (CHD) or CVD event (CHD, cerebrovascular disease, peripheral arterial disease and heart failure), based on data from the US population [13, 14]. The Systematic Coronary Risk Evaluation (SCORE) was used to assess the 10-year risk of fatal CHD, non-CHD, and CVD (CHD and non-CHD) events, based on data from the European population [15]. The SCORE system estimates the 10-year risk of a first fatal atherosclerotic event, including heart attack, stroke, other occlusive arterial disease, and sudden cardiac death [15].

Inclusion criteria

All participants were healthy drug-naive European Caucasian (Greek) adults who had their first visit at the outpatient lipid clinic for screening of their cholesterol levels. These subjects were not referred by other clinicians, since the Greek Health System provides free access to outpatient clinics of any type of hospital. Hence, part of the general population chooses outpatient clinics for checking their lipid levels for the first time and receives treatment as needed. For the purposes of this study 1084 individuals were screened between January 2009 and December 2011; 688 subjects with 1 or more exclusion criteria were excluded.

Exclusion criteria

No participant had CHD or any other clinically evident vascular disease (assessed by history, physical examination, electrocardiogram and routine laboratory examination). Subjects with: (i) abnormal hepatic function (aminotransferase activity > 3 times the upper limit of normal, and/or history of chronic liver disease, (ii) serum creatinine levels > 1.8 mg/dl (159 µmol/l) or estimated glomerular filtration rate (eGFR) < 30 ml/min (iii) type 2 diabetes (fasting blood glucose > 126 mg/dl (7.0 mmol/l)), (iv) thyroid-stimulating hormone (TSH) levels < 0.4 or > 5.0 µIU/ml), or, (v) receiving any drug during recruitment were excluded.

Determination of anthropometric and metabolic variables

Body weight, waist circumference and blood pressure

Body weight was determined to the nearest 0.1 kg with a calibrated beam balance and standing height was measured to the nearest 1 cm. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured midway between the lower rib and iliac crest. Blood pressure measurements were obtained at the same time (morning) in the sitting position, in duplicate using the right arm, following a 10 min rest and using a validated mercury sphyg-

Theodosios D. Filippatos, Evangelos C. Rizos, Irene F. Gazi, Konstantinos Lagos, Dimitrios Agouridis, Dimitri P. Mikhailidis, Moses S. Elisaf

momanometer (model no. FC114, Focal Corporation, Toyofuta, Kashiwa City, Chiba Pref., Japan) with an appropriate cuff size.

General biochemical variables

Blood samples were collected in the morning into sterile Vacutainer-SST II advance tubes (Becton Dickinson, Plymouth, UK) after the participants had fasted overnight for 8–12 h. The tubes were refrigerated immediately after collection, were centrifuged at 4°C within 40 min and then were analyzed within 2 h. Serum glucose concentration was measured with the hexokinase method on an Olympus AU600 Clinical Chemistry Analyzer (Olympus Diagnostica GmbH, Hamburg, Germany). To ensure absence of hemolysis, the serum sample was checked automatically in the analyzer with the LIH system (estimation of lipemia, icterus and hemolysis system). The total imprecision (within- and between-run) of the method at the level of 112 mg/dl (6.27 mmol/l) is characterized by CV 0.97% and SD 1.08 mg/dl (0.06 mmol/l). Our laboratory participates in the External Quality Assurance Services (EQAS) program provided by Bio-Rad Laboratories, Inc., where the CV values for glucose in the past 2 years (4 cycles) have ranged between 1.31% and 1.34%. It should be noted that we determined serum glucose levels, a fact that could play a role in our observations since plasma samples are used in the statements for the diagnosis of diabetes. Of note, no difference in glucose values was observed between serum and plasma samples collected from 3692 individuals participating in the Canadian Health Measures Survey [16].

Serum concentrations of total cholesterol (TC) and triglycerides were determined enzymatically on an Olympus AU600 Clinical Chemistry Analyzer (Olympus Diagnostica, Hamburg, Germany) [17]. High-density lipoprotein cholesterol (HDL-C) was determined by a direct assay (Olympus Diagnostica, Hamburg, Germany). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula, provided that triglyceride levels were < 400 mg/dl (4.5 mmol/l).

Fasting serum insulin levels were measured by microparticle enzyme immunoassay on an AxSYM analyzer (Abbott Diagnostics, Illinois, USA). The homeostasis model assessment (HOMA) index was calculated as follows: fasting insulin (mU/l) × fasting glucose (mg/dl)/405. Creatinine levels were measured by the kinetic Jaffé reaction. The eGFR was estimated by the Modification of Diet in Renal Disease (MDRD) equation formula [18]. Urinary albumin was quantitatively determined by a photometric color test (Olympus Diagnostica GmbH, Hamburg, Germany). Microalbuminuria was estimated by calculating the ratio of urine albumin to urine creatinine (in mg/g) in a single morning-voided urine specimen. The uricase/PAP method (an enzymatic color test) was used for uric acid determinations. The fractional excretions (FE) of uric acid and electrolytes were calculated as follows: FE (%) = urinary [Y] × serum Cr× 100/serum [Y] × urinary Cr, where [Y] equals the concentration of uric acid or electrolytes.

Chronic kidney disease (CKD) was described as stage 2 (MDRD eGFR 60–89 ml/min) and stage 3 (MDRD eGFR 30–59 ml/min) [19].

Statistical analysis

Continuous variables were tested for normality by the Kolmogorov-Smirnov test. Data are presented as mean ± standard deviation (SD) and median (interquartile range) for parametric and non-parametric data, respectively. The differences in the distribution of gender and CKD stages were tested by χ^2 test. Analysis of variance was used to assess differences in biochemical variables between subjects with different glucose levels, followed by post-hoc (least significant difference) tests to compare variables between subjects with glucose levels 100–109 mg/dl and the other groups. The t-test or Mann-Whitney test was used to compare variables between different groups, as appropriate. Differences were considered significant at $p < 0.05$ (two-sided). Analyses were performed using the SPSS 19.0 statistical package for Windows (SPSS Inc., Chicago, Illinois).

Results

Greek (Caucasian) adults (n = 396; 222 females, 174 males, age 54.8 ±11.8 years) were enrolled. For each prediabetes group the respective control group was defined as serum fasting glucose levels < 100 mg/dl for ADA and < 110 mg/dl for WHO/IDF.

Differences between ADA or WHO/IDF definition of prediabetes

Age, gender distribution and smoking did not differ between IFG subjects and the corresponding control group, whereas BMI, waist circumference, and systolic/diastolic blood pressure were significantly higher in subjects with prediabetes compared with the control group, according to both the ADA and the WHO/IDF definition (Table I).

Triglyceride levels were significantly higher only in subjects with prediabetes according to the WHO/IDF definition (but not according to ADA) compared with their respective control group, whereas TC, HDL-C, and LDL-C did not differ significantly between IFG subjects compared with their respective controls (both the ADA and the WHO/IDF definition). As expected, the HOMA index was significantly increased in subjects with prediabetes according to both the ADA and the WHO/IDF definition (Table I).

Uric acid level was significantly higher in subjects with prediabetes according to either the ADA

or the WHO/IDF definition. Aspartate and alanine aminotransferase activity did not differ between groups, whereas γ-glutamyl-transferase (γGT) activity was significantly higher only in WHO/IDF prediabetic subjects compared with their respective controls (Table I).

MDRD eGFR did not differ between prediabetic subjects and their respective controls. Furthermore, the urine albumin/creatinine ratio did not differ between prediabetic subjects and controls, as well as fractional excretion of uric acid, sodium, potassium, phosphorus and magnesium, according to the ADA or WHO/IDF definition (data not shown).

Among the whole group of 396 participants, 263 (66%) had CKD stage 2 and 26 (6.5%) had CKD stage 3. Among the group of subjects with CKD, the ADA definition recognized significantly more subjects with CKD stage 2 and stage 3 compared with the WHO/IDF definition ($p < 0.05$).

It should be noted that 77% of subjects who had IFG according to the ADA definition had metabolic syndrome compared with 78% of subjects who had IFG according to the WHO/IDF definition (p = NS).

Subjects with prediabetes according to both definitions had increased 10-year Framingham CHD and CVD risk (Table II). In contrast, when the SCORE risk was calculated, only prediabetic subjects according to the ADA definition had significantly greater CVD risk compared with their respective control group (Table II).

Differences between different glucose levels

In order to better evaluate the differences shown above from the comparison between prediabetic subjects and controls according to their IFG definition, we further focused on the particular group of

Table I. Anthropometric and metabolic variables in subjects with IFG according to ADA or WHO/IDF definition

Variable	Differences between subjects with ADA definition of IFG and subjects with glucose < 100 mg/dl			Differences between subjects with WHO/IDF definition of IFG and subjects with glucose < 110 mg/dl		
	IFG definition according to ADA (glucose ≥ 100 mg/dl)	Control group (< 100 mg/dl)	Value of p	IFG definition according to WHO/IDF (glucose ≥ 110 mg/dl)	Control group (< 110 mg/dl)	Value of p
N (females/males)	183 (100/83)	213 (122/91)	NS	62 (32/30)	334 (190/144)	NS
Age [years]	55 ±12	54 ±12	NS	55 ±12	55 ±12	NS
Current smokers [%]	30	21	NS	26	19	NS
BMI [kg/m2]	31.2 ±5.2	29.2 ±4.2	< 0.001	33.4 ±6.3	29.6 ±4.4	< 0.001
Waist circumference [cm]	105 ±12	101 ±12	< 0.001	108 ±13	102 ±12	< 0.001
Systolic BP [mm Hg]	139 ±16	134 ±19	0.001	141 ±16	135 ±18	0.002
Diastolic BP [mm Hg]	87 ±9	84 ±11	0.001	88 ±10	85 ±10	0.003
Total cholesterol [mg/dl]	241 ±38	238 ±39	NS	238 ±36	239 ±39	NS
Triglycerides [mg/dl]	170 (108–198)	159 (102–194)	NS	188 (115–242)	159 (102–189)	0.01
HDL-C [mg/dl]	51 ±11	53 ±11	NS	50 ±10	52 ±11	NS
LDL-C [mg/dl]	158 ±32	154 ±33	NS	149 ±30	155 ±33	NS
HOMA index	3.5 (2.0–4.8)	1.9 (1.2–2.7)	< 0.001	4.0 (3.1–6.3)	2.0 (1.4–3.2)	< 0.001
Uric acid [mg/dl]	6 ±2	5 ±1	0.001	5.9 ±1.6	5.3 ±1.5	0.002
AST [U/l]	21 (18–26)	21 (18–25)	NS	21 (18–26)	21 (18–25)	NS
ALT [U/l]	23 (17–32)	22 (16–29)	NS	23 (17–35)	22 (16–30)	NS
GT [U/l]	21 (14–32)	19 (14–30)	NS	22 (18–33)	19 (13–30)	0.002
eGFR MDRD [ml/min/1.73 m2]	79 (70–90)	80 (71–89)	NS	78 (72–88)	80 (71–90)	NS
CKD stage 2 [%]	67	68	NS	73	67	NS
CKD stage 3 [%]	7	7	NS	7	7	NS

Values are given as mean ± SD or median (interquartile range) for parametric and non-parametric variables, respectively. IFG – impaired fasting glucose, ADA – American Diabetes Association, ALT – alanine aminotransferase, AST – aspartate aminotransferase, BMI – body mass index, BP – blood pressure, eGFR – estimated glomerular filtration rate, γGT – γ-glutamyltranspeptidase, HDL-C – high-density lipoprotein cholesterol, HOMA – homeostasis model assessment, LDL-C – low-density lipoprotein cholesterol, MDRD – Modification of Diet in Renal Disease, CKD – chronic kidney disease, NS – not significant, WHO/IDF – World Health Organization/International Diabetes Federation

Theodosios D. Filippatos, Evangelos C. Rizos, Irene F. Gazi, Konstantinos Lagos, Dimitrios Agouridis, Dimitri P. Mikhailidis, Moses S. Elisaf

Table II. Indices of 10-year cardiovascular risk according to ADA or WHO/IDF definition of IFG

Variable	Differences between subjects with ADA definition of IFG and subjects with glucose < 100 mg/dl			Differences between subjects with WHO/IDF definition of IFG and subjects with glucose < 110 mg/dl		
	IFG definition according to ADA (glucose ≥ 100 mg/dl)	Control group (< 100 mg/dl)	Value of p	IFG definition according to WHO/IDF (glucose ≥ 110 mg/dl)	Control group (< 110 mg/dl)	Value of p
FRAMINGHAM CHD RISK [%]	9.6 (6.1–12.8)	7.9 (4.5–12.4)	0.001	9.8 (7.4–12.9)	8.7 (4.9–12.5)	0.003
FRAMINGHAM CVD RISK [%]	16.6 (8.6–21.2)	13.8 (6.1–20.1)	0.001	18.1 (9.9–22.3)	14.5 (6.5–20.6)	0.003
SCORE CHD RISK [%]	3.3 (0.6–4.0)	2.6 (0.4–3.4)	< 0.001	3.4 (0.5–4.7)	2.9 (0.4–3.7)	NS
SCORE NON-CHD RISK [%]	2.1 (0.4–2.9)	1.6 (0.2–2.1)	0.001	2.2 (0.4–3.2)	1.8 (0.3–2.3)	NS
SCORE CVD RISK [%]	5.4 (0.9–7.3)	4.1 (0.7–5.8)	0.002	5.7 (0.9–7.8)	4.6 (0.7–6.0)	NS

Values are given as median (interquartile range). ADA – American Diabetes Association, WHO/IDF – World Health Organization/International Diabetes Federation, IFG – impaired fasting glucose, CHD – coronary heart disease, CVD – cardiovascular disease, NS – not significant

subjects with glucose levels 100–109 mg/dl for whom the 2 definitions of IFG differ. For this purpose, subjects were divided into 3 groups, i.e. glucose levels < 100 mg/dl (low-risk for T2DM with both definitions), 100–109 mg/dl (low-risk for diabetes with WHO/IDF but IFG with ADA definition), and ≥ 110 mg/dl (IFG with both definitions) and, when analysis of variance between these groups was significant, we compared the group with glu-cose 100–109 mg/dl with the groups with glucose > 110 mg/dl or < 100 mg/dl (Table III).

Body mass index and waist circumference pro-gressively increased in parallel with glucose levels (Table III). A progressive increase was also evident for systolic/diastolic blood pressure levels. However, subjects with serum glucose of 100–109 mg/dl did not have significantly different blood pressure com-pared with the group with glucose levels ≥ 110 mg/dl,

Table III. Anthropometric-metabolic variables and indices of 10-year cardiovascular risk according to serum fasting glucose levels

Variable	Glucose < 100 mg/dl	Glucose between 100–109 mg/dl	Glucose ≥ 110 mg/dl	Value of p (ANOVA)
N (females/males)	213 (122/91)	121 (68/53)	62 (32/30)	NS (gender)
BMI [kg/m²]	29.2 ±4.2	30.1 ±4.1	33.4 ±6.3[&#]	< 0.01
Waist circumference [cm]	101 ±12	104 ±11[&]	108 ±13[&]	< 0.01
Systolic BP [mm Hg]	134 ±19	138 ±16	141 ±16[&]	< 0.01
Diastolic BP [mm Hg]	84 ±11	87 ±9[&]	88 ±10[&]	< 0.01
Total cholesterol [mg/dl]	238 ±39	241 ±31	237 ±36	NS
Triglycerides [mg/dl]	159 (102–194)	169 (102–186)	186 (115–242)[&#]	< 0.01
HDL-C [mg/dl]	53 ±11	52 ±11	49 ±10[&]	< 0.05
LDL-C [mg/dl]	154 ±33	157 ±28	149 ±30	NS
Uric acid [mg/dl]	5.0 ±1.0	5.6 ±1.5[&]	5.9 ±1.6[&]	< 0.01
FRAMINGHAM CHD RISK [%]	7.9 (4.5–12.4)	9.3 (5.6–12.9)	9.8 (7.4–12.9)[&]	< 0.01
FRAMINGHAM CVD RISK [%]	13.8 (6.1–20.1)	15.9 (7.8–20.9)	18.1 (9.9–22.2)[&]	< 0.01
SCORE CHD RISK [%]	2.7 (0.4–3.4)	3.4 (0.7–3.9)[&]	3.4 (0.5–4.7)[&]	< 0.01
SCORE NON-CHD RISK [%]	1.6 (0.2–2.1)	2.1 (0.4–2.6)[&]	2.2 (0.4–3.2)[&]	< 0.01
SCORE CVD RISK [%]	4.2 (0.7–5.7)	5.5 (1.0–6.8)[&]	5.7 (0.9–7.8)[&]	< 0.01

Values are given as mean ± SD or median (interquartile range) for parametric and non-parametric variables, respectively. [#]p < 0.05 vs. glucose between 100–109 mg/dl (post-hoc analysis). [&]p < 0.05 vs. glucose < 100 mg/dl (post-hoc analysis). ADA – American Diabetes Association, BMI – body mass index, BP – blood pressure, CHD – coronary heart disease, CVD – cardiovascular disease, eGFR – estimated glomerular filtration rate, HDL-C – high-density lipoprotein cholesterol, HOMA – homeostasis model assessment, LDL-C – low-density lipoprotein cholesterol, MDRD – Mod-ification of Diet in Renal Disease, NS – not significant, WHO/IDF – World Health Organization/International Diabetes Federation

whereas they had significantly increased diastolic blood pressure compared with the group with glucose < 100 mg/dl (Table III).

TC, HDL-C and LDL-C did not differ between the group with glucose levels of 100–109 mg/dl and other groups, whereas triglyceride levels were significantly higher in subjects with glucose ≥ 110 mg/dl compared with the other groups (Table III).

Subjects with glucose 100–109 mg/dl had significantly increased uric acid concentration compared with subjects with glucose < 100 mg/dl, but not with those with glucose ≥ 110 mg/dl (Table III).

All indices of cardiovascular risk were progressively increased in parallel with the increase of glucose levels. In subjects with glucose 100–109 mg/dl, all indices of SCORE risk were significantly increased compared with subjects with glucose < 100 mg/dl. In contrast, there was no difference in the indices of Framingham and SCORE risk between subjects with glucose 100–109 mg/dl and subjects with glucose ≥ 110 mg/dl (Table III).

Discussion

Our study shows that if we use the 2 different definitions of IFG (ADA or WHO/IDF) we find consistent changes in most of the anthropometric variables and metabolic parameters in subjects with IFG compared with their respective controls. However, we noticed certain differences in a limited number of metabolic parameters and CVD risk factors (triglycerides, γGT, uric acid, and diastolic blood pressure), as well as differences in cardiovascular risk estimation between the 2 different definitions of IFG.

The definition of prediabetes includes subjects with IFG or IGT or both. Since IGT is defined in the same way using either ADA or WHO/IDF statements, prediabetes differentiates only in the different definitions of IFG according to the ADA or WHO/IDF. In our study we examined the differences in laboratory parameters or surrogate markers for CVD development, focused on the disputed (ADA vs. WHO/IDF definition) group of subjects with glucose levels 100–109 mg/dl. Our data showed that diastolic BP and uric acid levels were higher in the disputed group compared with subjects with glucose < 100 mg/dl. Blood pressure is a major risk factor and a major target of therapy in subjects with increased CVD risk [20, 21]. Additionally, elevated uric acid levels may marginally increase the risk of CHD events, independently of traditional CHD risk factors [22]. On the other hand, TG levels were lower in the disputed group compared to the group of subjects with glucose ≥ 110 mg/dl. The differences in CVD risk factors resulted in the important finding that the cardiovascular risk estimation (SCORE risk calculation) was significantly higher only in IFG subjects according to the less stringent ADA definition compared with their respective controls, whereas the CVD risk estimation based on the Framingham equation was higher for IFG subjects according to both the ADA and the WHO/IDF definition. Moreover, there was also a noticeable increase of cardiovascular risk (SCORE) when the grey-zone group of subjects with fasting glucose 100–109 mg/dl was compared with subjects with fasting glucose < 100 mg/dl. As a result, the threshold of fasting glucose ≥ 100 mg/dl proposed by the ADA discriminates better the individuals with increased cardiovascular risk compared with the more stringent criteria proposed by the WHO/IDF for the definition of IFG. This interesting finding seems clinically relevant, since the definition of WHO/IDF for IFG may miss a group of subjects with increased CVD risk.

In our study the majority of our subjects had CKD stage 2 and 3. This finding shows that many subjects considered otherwise healthy with 1 or more CVD risk factors may still have impaired renal function. It seems that, among the whole group of subjects with CKD, the definition of ADA recognizes a significantly greater percentage of subjects with CKD stage 2 and CKD stage 3 compared with the WHO/IDF definition. In other words, the definition of ADA is more sensitive to identify prediabetic individuals with CKD. The European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) acknowledge CKD as a CHD risk equivalent in their latest guidelines and propose more aggressive treatment to prevent the future development of CVD for CKD subjects [23–25].

The rationale for establishing the intermediate categories of impaired glucose regulation was based on their ability to predict future T2DM. The reason to change the initially proposed from ADA lower cut-off point of fasting glucose from 110 mg/dl to 100 mg/dl was the much lower proportion of the population that is included in the IGT compared to the IFG category, resulting in decreased sensitivity for predicting the development of T2DM [26]. In the DECODE study, which used an IFG threshold of ≥ 110 mg/dl, only a quarter of the 2766 individuals without T2DM who had IGT also had IFG, and nearly a third of the 2411 individuals without T2DM who had IFG had IGT [27]. The authors concluded that subjects with IFG constitute a heterogeneous population, with possibly different CVD risk factors [27]. The other factors that should influence the choice of the lower cut-off point of fasting glucose for IFG diagnosis is that prediabetes classification represents a risk factor for the development of T2DM as well as CVD, rather than a clinical entity per se. IFG and IGT have been associated with obesity, dyslipidemia with high triglycerides and/or low HDL-C levels, and hypertension [5]. In our study we applied the 2 different definitions of IFG in healthy

Theodosios D. Filippatos, Evangelos C. Rizos, Irene F. Gazi, Konstantinos Lagos, Dimitrios Agouridis, Dimitri P. Mikhailidis, Moses S. Elisaf

Greek adults and we found that the risk for future CVD is significantly increased in those subjects with fasting glucose levels higher than 100 mg/dl. As a result, the diagnosis of IFG for these individuals would help to categorize them in a higher risk group not only for future T2DM but also for CVD development.

It is difficult to establish a strict rule for the definition of prediabetes universally, since it is based on fasting glucose, a continuous variable with a wide range of measurements. Moreover, if we were able to define from epidemiological data on a certain population the exact value above which the diagnosis of IFG should be clearly made, it would be extremely difficult to apply this rule in general, due to the heterogeneity of the population. Greece is one of the low-risk European countries for the development of CVD [15]. In this study we used in Greek (Caucasian) subjects the ADA definition of IFG which applies to the US population, and the WHO/IDF definition which applies in general, and estimated the CVD risk using the Framingham (US population-based data) or SCORE (European) risk calculation. Although this looks confusing, it is what happens in clinical practice in countries where solid epidemiological data are lacking. Our findings indicate certain differences in favor of the less strict ADA definition of IFG, and should be validated in larger studies with diverse ethnicities. It should be mentioned that a large prospective study, which enrolled Framingham offspring participants free of CVD, showed that both IFG definitions were associated with increased CHD risk in women, whereas neither IFG definition identified men at increased short-term risk for CVD [28]. We did not find any difference between genders. This difference may be due to the different population, since we enrolled Greek subjects.

In conclusion, the definition of ADA recognized European subjects with significantly increased CVD risk (using the SCORE model) compared with the WHO/IDF IFG definition.

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