Glucose Abnormalities in Urban Hispanics:

diagnosis, prevalence, risk predictive value, and association with metabolic syndrome and high blood pressure

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Abstract

The objective is to study the prevalence of glucose abnormalities (GA), their association with metabolic syndrome (MS), and the screening value of fasting plasma glucose (FPG) and insulin in detecting impaired glucose tolerance (IGT) and diabetes mellitus (DM), were determined in an unselected sample of apparently healthy Urban-Hispanics.

OGGT was conducted in 592 subjects. GA were found in 34% of subjects, defined as impaired fasting glucose (IFG) (13.3%), IGT (6.9%), combined IFG+IGT (7.8%) and type2-DM (6.5%). FPG of 5.6-6.9mmol/l diagnostic of IFG missed 47.1% of subjects with IGT, and FPG ≥7.0mmol/l missed 53.9% of DM. GA were associated with abdominal obesity, hypertriglyceridemia, hyperinsulinemia, hypertension and MS. Prevalence of MS was greater in DM=IFG+IGT>IGT=IFG> controls. Post-load hyperinsulinemia and hyperglycemia was higher in IGT than in IFG; whereas HOMA-IR was higher in IFG. Indices of insulin secretion were markedly reduced in DM, IFG-IGT and IGT. In summary: currently recommended FPG thresholds detect only half of subjects with GA. Diagnosis of GA must include both, fasting and 2-hr post-load glucose levels. Presence of fasting and post-load hyperglycemia-hyperinsulinemia in one individual may explain the increased risk in combined IFG-IGT and in DM. Because of its high prevalence, silent course, and associated increased risk, full-scale screening programs and aggressive management of GA must be implemented.

Key Words: impaired fasting glucose, glucose intolerance, hypertension, metabolic syndrome, Hispanics

Several factors determine the prevalence of glucose abnormalities in a population. Among them are the cutoff limits for the glucose levels employed, the use of fasting and/or post-load plasma glucose levels, the selection criteria for the study subjects, and the ethnic group investigated[1-6]. Because a complete oral glucose tolerance testing (OGGT) or even a single 2-hr post load glucose level are seldom used in primary care, the diagnosis of glucose abnormalities in that setting relies mainly on fasting glucose levels. This practice has been favored by the American Diabetes Association guidelines recommending the creation of the entity impaired fasting glucose (IFG), as a glucose abnormality purportedly able to predict the presence of impaired glucose tolerance (IGT) and risk of developing type 2 DM (DM)[7-9]. Subsequent studies, however, revealed that this practice leaves many patients undiagnosed and consequently untreated[1,3,10-12]. In addition to its prevalence, the clinical value of glucose abnormalities in predicting risk of developing DM and cardiovascular events varies among ethnic groups[1,4,10,11]. Because of these findings, additional measurements and indices have been developed to help in diagnosing and characterizing glucose abnormalities. Among them, there are the insulin levels, insulin/glucose ratios both fasting and after an OGGT, and the Homeostatic Model Assessment ratio (HOMA)[4-12].

Glucose abnormalities are a known risk factor for cardiovascular events[1,4,10,11], which are commonly associated with other risk factors, such as in the metabolic syndrome[13]. However, the extent of the association of glucose abnormalities with other risk factors varies with the type of abnormality, i.e., isolated IFG, isolated IGT or combined IFG and IGT, as well as with the ethnic group studied and the entry criteria employed in the selection of study subjects[4,14-17].

Because of the clinical significance of glucose abnormalities, we investigated a) the prevalence of isolated IFG, isolated IGT, combined IFG/IGT, and of type 2 DM; b) the association and clustering of the different traits of the metabolic syndrome with each of these glucose abnormalities, c) the diagnostic power of fasting serum glucose in detecting IGT and type 2 DM, and d) the clinical benefits of incorporating insulin levels and the Homeostatic Model Assessment (HOMA) ratio in the diagnosis of glucose abnormalities. The study group was an unselected sample of 592 apparently healthy Venezuelans, a previously unstudied ethnic group.

in subjects who self-reported as healthy.

Methods

Study Participants

The study was performed at the Center for the Detection of Silent Cardiovascular and Metabolic risk factors, a center affiliated with the Clinical Pharmacology Unit at the Central University of Venezuela. A total of 592 apparently healthy subjects were screened for cardiovascular and metabolic risk factors. Patients with known type 1 diabetes mellitus were excluded. The study was conducted in adherence to the Declaration of Helsinki, and the research protocol was approved by the Central University Hospital of the city of Caracas. All participants gave written informed consent. All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

Procedures. Complete history, physical examination and laboratory tests that included hematology, chemistry, fasting lipid panel, fasting and post-load (75g D-glucose) glucose and insulin levels, liver function tests, and urinalysis were obtained. BP was measured with a standard mercury sphygmomanometer and the cuff size was optimized for arm circumference. An average of three consecutive readings differing by no more than 4 mmHg was employed as the subject's BP. Heart rate was obtained from a one-minute pulse. Overall adiposity was assessed by body weight and body mass index (BMI). Waist circumference was measured in the standing position midway between the highest point of the iliac crest and the lowest point of the costal margin in the mid-axillary's line. All anthropometric measurements reflected the average of two measurements.

After at least five days of weight-maintaining diet, the fasting subjects underwent a 75-g OGTT. Blood samples were obtained at baseline, 30, 60, 90,120 and 180 min after the glucose ingestion. Patients were classified into groups based on the ADA and WHO diagnostic criteria[7-9,18], based on glucose levels: no glucose abnormalities (fasting glucose <5.6 mmol/l (<100 mg/dl) and 2-hr glucose < 7.8 mmol/l (<140 mg/dl); IFG (fasting glucose 5.6-6.9 (100-125 mg/dl) and 2-hr glucose < 7.8 mmol/l); IGT (2-hr glucose 7.8-11.0 mmol/l (140-199 mg/dl) and fasting glucose <5.6 mmol/l). Combined IFG and IGT was defined as fasting glucose 5.6-6.9 mmol/l and 2-hr glucose of 7.8-11.0 mmol/l in the same individual. Thus, subjects may present either with isolated IFG, isolated IGT or combined abnormalities. DM was diagnosed as either fasting glucose $\geq$ 7.0 mmol/l ($\geq$126 mg/dl) and/or 2-h postload glucose $\geq$ 11.1 mmol/l ($\geq$200 mg/dl).

HOMA-IR, an index of hepatic insulin resistance, was calculated as (fasting insulin µUI/ml x glucose mmol/l) / 22.5 [19]. The total ($\Delta Insulin_{0-180}$ /$\Delta Glucose_{0-180}$ ratio and early insulin response ($\Delta Insulin_{0-30}$ /$\Delta Glucose_{0-30}$ ratio) during the OGGT, were calculated[20-21].

Plasma glucose was measured using an automated glucose analyzer (Beckman Instruments, Palo Alto, CA), employing a glucose oxidase technique. Plasma insulin was quantitated by solid-phase radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA).

Presence of traits of the metabolic syndrome was based following the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of the High Blood Cholesterol in Adults (ATP III) guidelines: waist circumference: men >102 cm (>40 in), women: >88 cm (35 in); triglycerides >150 mg/dl (>1.7 mmol/l), HDL-cholesterol: men <40 mg/dl (<1.03 mmol/l), women <50 mg/dl (>1.29 mmol/l), BP >130/> 85 mmHg, and fasting glucose >110 mg/dl (>6.1 mmol/l) [13].

Statistical Analyses

Descriptive statistics were generated for the study population using means (and SEM) for continuous variables and proportions for dichotomous variables. Two-sample comparison for continuous variables was analyzed with the Student's t test or paired t test with Bonferroni's adjustment for repeated testing. Multiple comparisons were analyzed by means of ANOVA. Triglyceride, glucose and insulin levels, HOMA index, and insulin release index were log-transformed for statistical analysis and back-transformed for reporting. Proportions and percentages were compared by Chi-square analysis. Differences were considered significant at values of $P < 0.05$. All statistical analysis was performed with SPSS version 11.0 (SPSS Inc, Chicago, Ill).

Results

Prevalence and predictive value of glucose abnormalities

Fasting and complete (3 hours) OGTT including glucose and insulin plasma levels were obtained in 592 apparently healthy subjects. Glucose abnormalities (IFG, IGT or DM) were found in 34.6% of the subjects evaluated (205/592). Type 2 DM was newly diagnosed in 39 of the 592 individuals studied (6.5%). Employing the 2003 ADA criterion for defining isolated IFG (fasting 5.55-6.9 and 2-hr < 7.8 mmol/l) and the 1985 WHO criterion for IGT (fasting <5.6 and 2-hr 7.8-11.1mmol/l), the prevalence of isolated IFG, isolated IGT, and of combined abnormalities (IFG+IGT) was 13.3, 6.9 and 7.8%, respectively (**Table 1**). Thus, nearly 22% of the apparently healthy, non-diabetic, urban Venezuelans had abnormally elevated fasting glucose levels, and 15% had increased 2-hr post-load glucose levels.

Because of its extensive clinical use, we evaluated how much and how well does fasting glucose predict IGT (**Table 2**). IFG showed a sensitivity of 52.9% (due to its high false-negative rate) and a specificity of 83% (due to its low false positive rate) in predicting IGT. The diagnostic yield, expressed by the positive predictive value was poor (36.8%), whereas the power of the test in excluding IGT, expressed by the negative predictive value, was quite high (90.4%). In fact, fasting plasma glucose levels accounted for 50% of the variance in post-load glucose levels ($r^2 = 0.49$).

DM was newly-diagnosed in 39 subjects (39/592). However, only 18 of 39 subjects (46.1%) met both criteria; i.e., fasting glucose ≥ 7.0 mmol/l (≥126 mg/dl) and/or 2-hr glucose ≥ 11.1 mmol/l (≥200 mg/dl), in the same individual. The other 21 subjects (53.9%), had 2-hr levels in the diabetic range (≥ 11.1 mmol/l), but their fasting glucose levels were below 7.0 mmol/l. Thus, relying only on FPG (≥ 7.0 mmol/l) misses more than half of subjects with DM. Lowering the fasting glucose level to 95 mg/dl allowed to capture 90% of all subjects with ≥ 11.1 mmol/l (≥200 mg/dl) 2-hr postload values.

Clinical value of insulin levels in subjects with glucose abnormalities.

Glucose and insulin levels at baseline and during the OGGT are shown on **Table 3** and **Figure 1**. As expected by their definition, fasting glucose was significantly higher in subjects with IFG and combined IFG/IGT than in those with IGT and GT, whereas 2-hr post-load glucose was higher in those with isolated IGT and combined IGT/IFG. Post-load incremental glucose AUC was greater in IGT and IGT/IFG than in IFG and controls (no glucose abnormalities); whereas, comparable incremental glucose AUC values were observed in IFG and control subjects (**Table 3**).

Post-load plasma insulin levels were significantly associated with the post-load glucose levels; although the level of association was weak ($P=0.005$; $r^2 = 0.08$). There were no significant differences in fasting plasma insulin levels between controls and IGT; whereas 30% higher levels were observed in those with combined IFG/IGT or type 2 DM (**Table 3** and **Figure 1**). Mean plasma insulin levels were higher in IFG than in controls, but the values did not reach statistical significance. After the glucose load, insulin levels peaked at min 60 in glucose tolerant and in isolated IFG, whereas it showed a more gradual rise reaching peak levels at 2-hr in isolated IGT and in combined IGT/IFG. Therefore, 2-hr insulin levels were higher in IGT than in IFG; whilst at min 60 there were no differences in insulin levels between IFG and IGT. Incremental insulin AUC was significantly greater in IGT and IGT/IFG than in IFG and controls. No significant differences in post-load incremental insulin AUC were observed between subjects without glucose abnormalities and those with isolated IFG (Table 3).

Estimated indices of insulin resistance and insulin secretion were calculated. HOMA-IR ratio, a marker of hepatic muscle insulin resistance[19,21], was significantly higher in DM (140%; $P<0.001$), combined IFG-IGT (85%;

P<0.001) and in IFG (34%; P<0.05) than in controls. The HOMA ratio in IGT although 18% higher than that of normal glucose tolerant, it did not reached statistical significance (P=0.09). Indexes of total and early, insulin secretion, $\Delta I(AUC)/\Delta G(AUC)$ and $\Delta I_{0-30}/\Delta G_{0-30}$, respectively, were markedly reduced in IGT, combined IGT and IFG, and in DM, compared to IFG and controls (no abnormalities)(Table 3).

Association of glucose abnormalities with risk factors and traits of the metabolic syndrome

Compared to normal fasting-glucose tolerant subjects, those with glucose abnormalities were on average 7 years older, were heavier, had larger waists, and higher WHR ratios, triglyceride and BP levels. A greater prevalence of hypertension and metabolic syndrome was observed in subjects with glucose abnormalities compared to controls (Table 1). There were no significant differences in indices of obesity, BP, lipid levels, prevalence of HT and metabolic syndrome in subjects with isolated IFG and isolated IGT. Those with combined IFG/IGT or with type 2 DM presented a significantly worse metabolic profile than those with isolated IFG or IGT. Metabolic syndrome was found in 54% of subjects with combined IFG/IGT or with type 2 DM, compared to a prevalence of 23% in normal fasting-glucose tolerant subjects, 34% in those with isolated IFG and of 37% in subjects with isolated IGT (P<0.01) (Table 1).

Figure 1. Fasting and post-load plasma glucose and insulin levels in control subjects (no glucose abnormalities-NGT), and in subjects with IFG, IGT and combined IFG + IGT.

Shown are mean values ± S.E.M. for plasma glucose and plasma insulin levels taken during fasting and at different times after a 75-g oral glucose load.

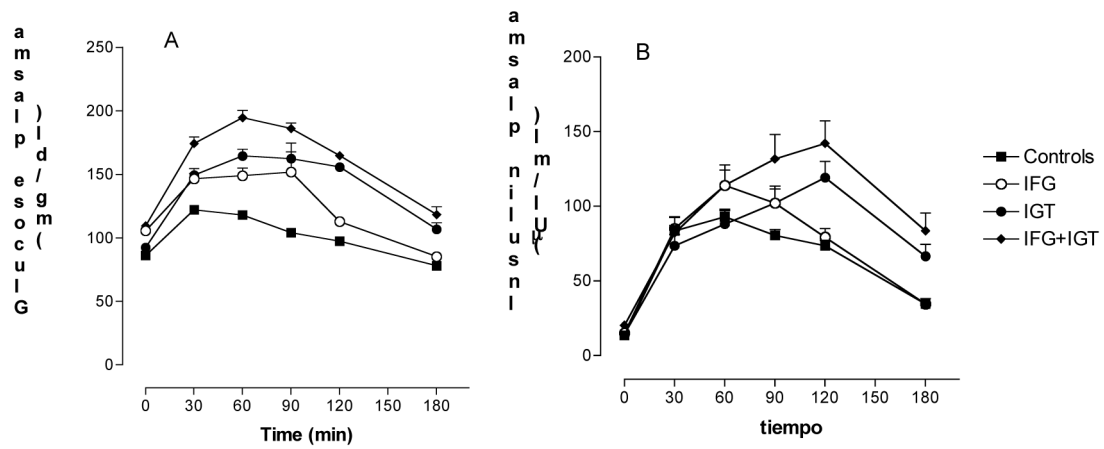

Table 1. Characteristics of GT, DM, IFG and IGT study subjects

	GT (n=387)	Isolated IFG (n=79)	Isolated IGT (n=41)	IFG/ITG (n=46)	DM (n=39)
Criteria	**Basal < 100 2hr < 140**	**Basal >100 < 126 2hr < 140**	**Basal < 100 2 h >140 < 200**	**Basal >100< 126 2 h > 140 < 200**	**Basal ≥ 126 2h ≥ 200**
M/W	95/292	32/47	10/31	19/27	23/16
Age	41.3±0.7	47.4±1.2 *	50 ±1.6*[a]	50 ± 1.8*[a]	51.2 ± 1.5*[a]
BMI	28.8±0.3	30.4±0.5*	30.2±0.7*	31.5±0.6*	30.8±0.9*
Weight	75.1±0.8	80± 1.6*	78.5± 2.1	83.8 ± 2*[b]	82.5±2.5*[b]
Waist	92.2 ± 0.7	98.8 ± 1.4*	99.2 ± 1.8*	101.5 ± 1.7*	101.6±2.2*
WHP	0.89±0.005	0.93±0.01*	0.92±0.01*	0.94±0.01*	0.96±0.01*[ab]
SBP	120 ± 0.8	125 ± 1.7*	126 ± 3.2*	128 ± 2.7*[a]	134±3.1*[ab]
DBP	78 ± 0.6	81 ± 1*	81 ± 1.9*	83 ± 1.5*[a]	86±2.1*[ab]
% HT	20.3	30.8*	34.1*[a]	37.8*[a]	36.8*[a]
Triglyceride	136 ± 4	152 ± 10*	152 ± 12*	152 ± 12*[a]	145±11
HDL-C	42 ± 0.7	42 ± 1.2	39.2 ± 1.9	41.6 ± 1.7	42.1±1.9
% MS	23.3	34.3*	36.8*[a]	54.1*[ab]	54.3*[ab]

Shown are mean values SEM, or as percentage of subjects with hypertension (HT) or metabolic syndrome (MS). M: men; W: women; BMI: body mass index (kg/m2); weight in kg; waist in cm; WHP: waist to hip ratio; BP in mmHg; glucose, triglyceride and HDL-Cholesterol in mg/dl. GT: normal fasting and glucose tolerant; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; IFG/IGT: subjects with both IFG and IGT; DM: diabetes mellitus.*P<0.01 from controls; [a] P<0.01 from IFG; [b]P<0.01 from IGT.

Table 2. The value of fasting plasma glucose in predicting IGT in non-diabetics

A. Fasting plasma glucose cut-off level of 6.1 mmol/l

Fasting glucose	2-hr glucose	2-hr glucose
	<7.8 mmol/l	**7.8 – 11.0 mmol/l**
< 6.1 mmol/l n= 520	n= 453 (GT)	n= 67 (IGT)
6.1-6.9 mmol/l n=33	n=13 (IFG)	n=20 (IFG+IGT)

B. Fasting plasma glucose cut-off level of 5.6 mmol/l

Fasting glucose	2-hr glucose	2-hr glucose
	< 7.8 mmol/l	**7.8 – 11.0 mmol/l**
< 5.6 mmol/l n= 428	n= 387 (GT)	n= 41 (IGT)
5.6-6.9 mmol/l n=125	n=79 (IFG)	n= 46 (IFG+IGT)

C. Predictive value of fasting plasma glucose at 5.6 and 6.1 mmol/l cut-off levels

	IFG at 5.6-6.9 mmol/l	IFG at 6.1-6.9 mmol/l
Specificity	387/466 = 83%	453/466= 97.2%
Sensitivity	46/87 = 52.9%	20/87= 23%
Positive Predictive Value	46/125= 36.8%	20/33= 60.6%
Negative Predictive Value	387/428= 90.4%	433/520= 87.1%

Two cut-off values for fasting plasma glucose were evaluated as predictors of IGT. A total of 553 non-diabetic, apparently healthy subjects were studied. The specificity, sensitivity, negative and positive predictive values were calculated for each of the cut-off values. Values shown are number of subjects, percentages and fasting and 2-hr post-load plasma glucose levels in mmol/l.

Table 3. Fasting and post-load plasma glucose and insulin levels and indexes of insulin sensitivity and secretion in subjects with and without glucose abnormalities

	GT (387)	IFG (79)	IGT (41)	IFG+IGT (46)	DM (39)
FSG (mg/dl)	86±0.5	106±0.5*	92±1	109 ± 0.9*[b]	137±8*[ab]
2-hr G (mg/dl)	98±1	113±2*	156±2*[a]	164 ± 2*[a]	259±14*[ab]
F Ins (µUI/ml)	12.8±0.5	14.1±0.9	13.9±1.1	18.2 ± 2*[ab]	19±2.1*[ab]
2-hr I (µUI/ml)	71±3	78± 5	115±9*[a]	132 ± 13*[ab]	113±16*[a]
AUC-G	55 ± 2	76 ± 11	135 ± 7*[a]	148 ± 6*[a]	250±20*[ab]
AUC-I	166 ± 6	186 ± 10	221± 14*[a]	264 ± 23*[ab]	237±25*[a]
HOMA-IR	2.7 ± 0.1	3.7±0.2*	3.2±0.2*	5.0 ± 0.6*[ab]	6.6±0.9*[ab]
$\Delta I_{0-30}/\Delta G_{0-30}$	2.2 ± 0.3	2.1 ± 0.3	1.1 ± 0.1*[a]	0.9 ± 0.1*[a]	0.66±0.3*[a]
ΔI(AUC) /ΔG(AUC)	2.8 ± 0.4	2.5 ± 0.3	1.6 ± 0.2*[a]	1.7 ± 0.2*[a]	0.95±0.2*[a b]

FSG: fasting plasma glucose; FSI: fasting plasma insulin; 2-hr G: 2-hr postload plasma glucose; 2-hr I: 2-hr postload plasma insulin; AUC-G: incremental area under the curve for the glucose plasma concentrations following an OGGT ($mg.dl^{-1}.h^{-1}$); AUC-I: incremental area under the curve for insulin plasma concentrations following an OGGT ($U.ml^{-1}.h^{-1}$); HOMA-IR: (fasting insulin UI/ml x glucose mmol/l) / 22.5. $I_{0-30}/\Delta I_{0-30}$: ratio of increases in insulin and glucose plasma levels from fasting to 30 min after the OGGT (U/ml per mg/dl). ΔI(AUC) /ΔG(AUC): ratio of increases in insulin and glucose plasma levels from fasting to 180 min after the OGGT (U/ml per mg/dl). *P<0.01 from controls; [a] P<0.01 from IFG; [b] P<0.01 from IGT.

Table 4. Prevalence of glucose abnormalities in non-diabetics by ethnicity

	Sample	Threshold for IFG (mmol/lt)	GT (%)	IFG (%)	IGT (%)	IFG+IGT (%)
Caracas, Venezuelan (present study)	Unselected	≥5.6	70	14.3	7.4	8.3
Gran Canaria Island-Spain [15]	Unselected	≥5.6	73.6	14.6	6.5	5.3
Taiwan [16]	Unselected	≥5.6	66	7.7	17.1	6.4
Singapore [4]	Unselected	≥5.6		3.5	10.2	3.4
Italy [1]	Unselected	≥6.1	74.9	5.8	15.5	3.7
Caracas, Venezuela (present study)	Unselected	≥6.1	81.9	2.4	12.1	3.6
Germany [10]	Selected Subjects with relatives with either type 2DM, obesity and/or dyslipidemia	≥6.1	55.2	13.6	15.2	16
Finland [24]	Selected Subjects with families of two members with type2 DM	≥6.1	69.8	12.2	11.1	6.8

The prevalence of glucose abnormalities reported for different ethnicities is presented. Prevalence, expressed as %, is shown for two cut-off levels of fasting glucose (≥5.6 or ≥6.1), as available. Study patient selection is described as either an unselected sample (no criteria for selection employed), or as selected samples. FHx: family history

Discussion

The worldwide raise in the cost of health care and the increasing difficulties in accessing adequate health care, urges the development of simple, inexpensive, highly sensitive and specific screening tests for disease diagnosis and decision making. For many ethnicities, "normal" laboratory values and cutoff limits are unavailable. Consequently, patient management is commonly based on reference values obtained from studies conducted in other countries. In this investigation, employing an OGGT, we determined the prevalence of glucose abnormalities defined as isolated IFG, isolated IGT, combined IFG/IGT and type 2 DM in an unselected sample of 592 apparently healthy Venezuelans. It was striking to observe the very high incidence of glucose abnormalities in subjects who self-reported as healthy. Glucose abnormalities were present in 35% of the subjects, of which IFG was present in 13.3%, IGT in 6.9%, combined IFG and IGT in 7.8%, and type 2 DM in 6.5% of subjects. The results indicate that nearly 20% of the apparently healthy subjects had IFG, and 15% IGT. The observed prevalence of IFG and IGT in this unselected group of Venezuelans is quite different of that reported for Taiwanese[4] and people of Singapore[16], where a much greater prevalence of IGT than of IFG was observed. Prevalence of glucose abnormalities in urban Venezuelans were comparable to those reported in unselected subjects from the Canary Islands[15] and Italy[1], irrespectively of whether the 5.6 or the 6.1 cut-off limit for fasting serum glucose was employed (**Table 4**). Expectedly, a much higher prevalence of IFG was observed when studies included subjects with a positive family history of type 2 DM (Table 4)[22-24].

The similarities of Venezuelans, with Spanish, Italians and Caucasians in general observed in this work, have also been reported in studies on gene polymorphisms. The allele frequency of mutations in genes encoding for alpha-adducin, endothelial nitric oxide synthase and Nicotinamide Adenine Dinucleotide Phosphate-oxidase in Venezuelans was found to be comparable to that reported for Caucasians, but quite different from that of subjects of African descent and Asians[25-27]. The results suggest that despite the interracial mix existing in Venezuelans, the genetic composition seems to reflect a strong European influence.

In this work, we report that fasting glucose levels as defined by ADA[7-9], were quite insensitive in detecting IGT, even though its power in excluding IGT was quite high (~90%). Because of its high false–negative rate, the sensitivity of IFG in predicting IGT was only 50%. Nearly half of the subjects with 2-hr values diagnostic of IGT had fasting glucose levels below the 5.6 mmol/l threshold for IFG[9]. Similarly, diagnosis of DM based on fasting glucose levels was also at fault. Nearly half of the newly diagnosed diabetics by a 2-hr post-load glucose level, were missed with the use of fasting glucose cutoff level of ≥7 mmol/l. Thus, if only fasting glucose levels were to be employed, nearly half of subjects with IGT and/or type 2 DM would be left undiagnosed and untreated. These findings strongly support the view that both fasting and OGGT tests are complementary and not mutually exclusive[1,3,10-12]. More importantly, that we cannot rely exclusively on fasting glucose levels to diagnose glucose intolerance or even worse DM. Inclusion of the 2-hr post-load glucose levels must be an integral part of our practices. In additions, the prevalence of glucose abnormalities is largely underestimated if diagnosis is based solely on fasting plasma glucose.

The value of plasma insulin levels, the HOMA-IR ratio and the insulin/glucose ratios as a diagnostic aid for glucose abnormalities was investigated. It was found that insulin levels were more useful in understanding the mechanisms rather than in diagnosing a specific glucose abnormality. This is partly due to the finding that changes in insulin levels followed increases in plasma glucose. In fact, compared to IFG, the sustained increase in post-load plasma glucose in subjects with IGT was associated with larger and more sustained increases in plasma insulin. In addition, fasting insulin levels in subjects with IFG often overlapped with those of subjects with no abnormalities or with IGT. We thus believe that incorporating fasting and/or post-load insulin levels as a routine in our practices it is not cost-effective since it provides little additional diagnostic and therapeutic information. In fact, IFG was characterized by higher fasting glucose and insulin levels, with increase in HOMA-IR, normal post-load glucose disposal, and no changes in indices of insulin secretion. These findings support the view that hepatic insulin resistance is the major culprit of the IFG abnormality, as shown in studies employing the euglycemic clamp[2,21,28,29]. Conversely, IGT was characterized by early defects in insulin secretion leading to gradual and sustained increases in post-load insulin, combined with an inefficient disposal of the glucose load. In IGT, skeletal muscle insulin resistance together with defective secretion seem responsible for the abnormal glucose disposal[2,21].

In this Venezuelan population, subjects with either IFG or IGT were found to have a comparable risk profile. The degree and rates of obesity, abdominal obesity, high BP, high triglyceride levels, low HDL-C concentrations, and increased prevalence of metabolic syndrome, were not different in IFG and IGT. The prevalence of metabolic syndrome in subjects with isolated IFG or isolated IGT averaged 34 and 37% respectively, compared to 23% in control subjects with no glucose abnormalities. Similar metabolic risk profile for IFG and IGT has also been reported by others[15,23,30]; however, IGT was found to be associated with a worse cardiovascular risk profile than

IFG by others[16,17,22]. In all studies reviewed, as well as in ours, subjects with combined abnormalities were found to be at a higher risk for metabolic and cardiovascular events than those with isolated IFG or IGT[4,15-17,23,28], present study. Our findings support the results of the Framingham Offspring study revealing that risk for type-2 DM and cardiovascular disease increases continuously across the spectrum of glucose abnormality categories[31]. Additionally, conversion to DM is heightened in patients with combined compared to those with isolated abnormalities (IFG or IGT)[32]. Further, longitudinal studies on disease progression revealed that fasting and post-load hyperglycemia have distinct evolutions toward DM[33]. In conclusion, glucose abnormalities should be aggressively managed due to their associated increased risk for metabolic and cardiovascular disease, in particular when both fasting and post-load abnormalities are present in the same individual[4,14-16,30], present study. Presence of both fasting and post-load hyperglycemia-hyperinsulinemia in one individual, may explain the increased risk observed in combined IFG-IGT and in DM, compared to that of subjects with isolated IFG (fasting hyperglycemia-hyperinsulinemia) or isolated IGT (post-load hyperglycemia-hyperinsulinemia).

In summary, a large prevalence (35%) of glucose abnormalities was found in an unselected sample of 592 self-referred as healthy urban Venezuelans. As for other risk factors such as high cholesterol, low HDL cholesterol, high triglycerides, lipid abnormalities and high blood pressure, glucose abnormalities appear to be asymptomatic in nature. This allows the defects in fasting and/or post-load glucose disposal with its associated alterations in insulin metabolism, to transit undetected for long periods. Glucose abnormalities were strongly associated with other risk factors for cardiovascular and metabolic disease, including hypertension and the metabolic syndrome; the later was present in 54% of subjects with combined IFG and IGT. Fasting glucose and insulin levels were found to be very poor screening tests for diagnosing IGT and type 2 DM, failing to detect half of glucose intolerant or diabetic subjects, diagnosed by a 2-hr post-load measurement. Consequently, 2-hr glucose values after a 75-oral glucose load must be incorporated in our clinical practices to identify a significant additional number of subjects with normal or elevated fasting glucose that are at an increased risk toward or that already have DM. Because of its high prevalence, silent course, and associated increased risk, full-scale screening programs and aggressive management of GA must be implemented.

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