Cardiovascular Risk Profile in Subjects With Prediabetes and New-Onset Type 2 Diabetes Identified by HbA_{1c} According to American Diabetes Association Criteria

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OBJECTIVE

We investigated the cardiovascular risk profile in subjects with prediabetes and new-onset type 2 diabetes identified by glycated hemoglobin A_{1c} (HbA_{1c}) according to the new American Diabetes Association criteria.

RESEARCH DESIGN AND METHODS

Arterial stiffness, intima-media thickness (IMT), soluble receptor for advanced glycation end products (sRAGEs), and oral glucose tolerance test (OGTT) were evaluated in 274 subjects without a previous history of diabetes. The subjects were stratified into three groups according to the HbA_{1c} levels.

RESULTS

The subjects with prediabetes (*n* = 117, HbA_{1c} 5.7–6.4% [39–46 mmol/mol]) showed a higher augmentation (Aug), augmentation index (AugI), and IMT compared with those with lower HbA_{1c}; however, these values were similar to those of subjects with HbA_{1c} >6.5% (48 mmol/mol). When we further analyzed the subjects with prediabetes but included only subjects with normal glucose tolerance (NT) in the analysis, AugI and IMT still remained significantly higher than their levels in control subjects with HbA_{1c} <5.7% (39 mmol/mol). After multiple regression analyses including several cardiovascular risk factors, only HbA_{1c}, age, and sRAGE were significantly correlated with the IMT, whereas age and 1-h postload glucose were the major determinants of AugI.

CONCLUSIONS

Our data show that subjects with prediabetes according to HbA_{1c}, but with both NT according to the OGTT and normal fasting glycemia, have an altered IMT and AugI. These data suggest that a simple, reproducible, and less expensive marker such as HbA_{1c} may be better able to identify prediabetic subjects at high cardiovascular risk compared with fasting glycemia or OGTT alone.

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In 2011, the American Diabetes Association (ADA) proposed that glycated hemoglobin A_{1c} (HbA_{1c}) should be used as a diagnostic test for diabetes and prediabetes. An HbA_{1c} value ≥6.5% (48 mmol/mol) was recommended for the diagnosis of diabetes, and an HbA_{1c} of 5.7–6.4% (39–46 mmol/mol) was identified as a new indicator of prediabetes in addition to impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (1). Evidence indicates that subjects who are at high risk for type 2 diabetes also have an increased cardiovascular risk; therefore, the value of a predictive test for type 2 diabetes is also determined by its ability to indicate a high risk of cardiovascular disease (CVD) (2).

The ADA recommendations are mainly based on the relationship between HbA_{1c} and microvascular complications, especially retinopathy (1,3). The association of macrovascular diseases, which are the primary causes of mortality in patients with type 2 diabetes, with HbA_{1c} compared with other glucose homeostasis parameters (fasting and 1- and 2-h post–oral glucose tolerance tests [OGTTs]) is currently less conclusive (4).

Glycosylationof the arterial wall might play a role in vascular damage by affecting arterial stiffness, a progressive process that is accelerated by many age-associated disorders, including diabetes, hypertension, and metabolic syndromes. In large arteries, aging is characterized by the decreased turnover of collagen and elastin and increased levels of advanced glycation end products (AGEs) and cross-links. Elastic fibers undergo lysis and disorganization subsequent to their replacement by collagen and other matrix components (5). These events cause a loss of elasticity and induce stiffening. Moreover, recent data have shown that the interaction between AGEs and their receptor (RAGE) plays an important role in the development of diabetes complications and accelerated atherosclerosis (6,7). RAGE is upregulated in the atherosclerotic plaques of diabetic subjects, and interaction with its ligands induces proinflammatory gene activation and contributes to tissue injury and arterial stiffening (8).

Our first aim was to investigate the cardiovascular risk profile of subjects with prediabetes (HbA_{1c} 5.7–6.4% [39–46 mmol/mol]) and new-onset type 2 diabetes (HbA_{1c} ≥6.5 [48 mmol/mol]) according to HbA_{1c}. We studied early markers of atherosclerosis, such as arterial stiffness (pulse wave analysis and its central hemodynamic correlates, such as augmentation pressure [Aug], augmentation index [AugI], and pulse wave velocity [PWV]) and intima-media thickness (IMT). In addition, we characterized the association between serum soluble RAGE (sRAGE) and early markers of cardiovascular damage. Our second aim was to investigate whether HbA_{1c} is a better indicator of cardiovascular risk compared with other glucose homeostasis parameters, such as fasting and 1- or 2-h post-OGTTs.

RESEARCH DESIGN AND METHODS

Study Subjects

Subjects (n = 274) with no previous diagnosis of diabetes were recruited from patients attending our University Hospital for diabetes and cardiovascular risk evaluation. The inclusion criteria were an age range of 18–65 years. All patients were Caucasian and underwent a physical examination and review of their clinical history, smoking status, and alcohol consumption. None of them had lost weight or changed dietary habits during the 3 months preceding the study. The exclusion criteria were a previous history of diabetes, previous history of overt cardiovascular events (stroke, ischemic heart disease, chronic obstructive peripheral arteriopathy, or heart failure), anemia, or hemoglobinopathies, use of medications known to affect glucose metabolism, positivity for antibodies to hepatitis C virus or hepatitis B surface antigen, clinical evidence of advanced liver or renal disease, chronic gastrointestinal diseases associated with malabsorption, rheumatic diseases, and/or recent history of acute illness, malignant disease, and drug or alcohol abuse.

Body weight and height were measured, and BMI was calculated as weight (kg)/[height (m)]^2. Waist circumference was measured in a standing position at the level of the umbilicus. Blood pressure (BP) was measured with a calibrated sphygmomanometer after the subject had rested in the supine position for 10 min. Venous blood samples were drawn from the antecubital vein on the morning after an overnight fast. Baseline venous blood samples were obtained for the measurement of plasma glucose, total cholesterol, HDL cholesterol, triglycerides, high-sensitivity C-reactive protein (hs-CRP), and sRAGE. LDL cholesterol concentrations were estimated using the Friedewald formula. All subjects underwent a 75-g OGTT with 0-, 30-, 60-, 90-, and 120-min sampling for plasma and insulin as previously described (9). According to their 2-h glucose levels, the subjects were classified into the following categories: normal glucose tolerance (NT), IGT, or type 2 diabetes. NT was defined as a 2-h plasma glucose level <140 mg/dL. IGT was defined as a 2-h plasma glucose level of 140–200 mg/dL. Type 2 diabetes was defined as a 2-h plasma glucose level ≥200 mg/dL (1).

Biochemical Analyses

Plasma glucose, serum total cholesterol, triglycerides, HDL cholesterol, and hs-CRP were measured using available enzymatic methods as previously described (9). A commercially available ELISA kit (Human sRAGE ELISA; Biovendor, Brno, Czech Republic) was used according to the manufacturer's instructions to quantify the plasma concentration of sRAGE.

HbA_{1c} was measured via high-performance liquid chromatography using a National Glycohemoglobin Standardization Program and standardized to the Diabetes Control and Complications Trial (DCCT) (10) assay reference. Chromatography was performed using a certified automated analyzer (HPLC; HLC-723G7 hemoglobin HPLC analyzer; Tosoh Corp.) (normal range 4.25–5.9% [23–41 mmol/mol]).

Pulse Wave Analysis

All measurements were made from the right radial artery by applanation tonometry using a Millar tonometer (SPC-301; Millar Instruments, Houston, TX) (11). The measurements were performed by a single investigator with the subject in the supine position. The data were collected directly with a desktop computer and processed with

SphygmoCorCvMS (AtCor Medical, Sydney, Australia). The aortic waveform has two systolic pressure peaks, the latter of which is caused by wave reflection from the periphery. With arterial stiffening, both the PWV and the amplitude of the reflected wave are increased such that the reflected wave arrives earlier and adds to (or augments) the central systolic pressure. The aortic waveform in pulse wave analysis was subjected to further analysis for the calculation of the aortic Aug, AugI (calculated by dividing augmentation by pulse pressure), central BP, ejection duration (duration of the systolic period in milliseconds), and Buckberg subendocardial viability ratio (SEVR; area of diastole divided by area of systole during one cardiac cycle in the aorta). Pulse pressure is the difference between the systolic and diastolic BPs.

PWV

The SphygmoCor CvMS (AtCor Medical, Sydney, Australia) system was used for the determination of the PWV. This system uses a tonometer and two different pressure waves obtained at the common carotid artery (proximal recording site) and at the femoral artery (distal recording site). The distance between the recording sites and suprasternal notch was measured using a tape measure. An electrocardiogram was used to determine the start of the pulse wave. The PWV was determined as the difference in travel time of the pulse wave between the two different recording sites and the heart, divided by the travel distance of the pulse waveform. The PWV was calculated on the mean basis of 10 consecutive pressure waveforms to cover a complete respiratory cycle.

Carotid Ultrasound Examinations

Ultrasound scans were performed using a high-resolution B-mode ultrasound system (MyLab 50 XVision; Esaote Biomedica SpA, Florence, Italy) equipped with a 7.5-MHz linear array transducer. To exclude interobserver variability, all ultrasound examinations were performed by a single physician who was blinded to the clinical and laboratory characteristics of the patients. The subjects were examined in the supine position. Longitudinal images from the angle with the best visibility were displayed bilaterally for the common carotid artery. Scans were performed, and measurements were conducted at a total of six plaque-free sites 1 cm proximal to the carotid bulb. The obtained values were averaged and are presented as the mean of the IMT of the common carotid artery. Plaques, defined as a clearly isolated focal thickening of the intima-media layer with a thickness of 1.4 mm, were not observed in any individuals. All measurements were obtained in diastole, assessed as the phase in which the lumen diameter is at its smallest and the IMT is at its largest.

The study was approved by the local ethics committee. Informed consent was obtained from each participant.

Statistical Analyses

The sample size was calculated based on AugI using a level of significance (α) set to 5% and a power ($1 - \beta$) set to 80%. Statistical comparisons of the clinical and biomedical parameters were performed using Stat View 6.0 for Windows. The data are presented as the means $\pm$ SD. The distributional characteristics of each variable, including normality, were assessed by the Kolmogorov-Smirnov test. The statistical analyses were performed with the unpaired Student *t* test and ANOVA for continuous variables and the χ^2 test for noncontinuous variables. A *P* value <0.05 was considered statistically significant. When necessary, numerical variables were logarithmically transformed for statistical analysis to reduce skewness (triglycerides, hs-CRP, homeostasis model assessment of insulin resistance [HOMA-IR], sRAGE, and IMT), and values were expressed as median and interquartile range.

Simpleregression analysis was performed to relate AugI and IMT to the following variables: HbA_{1c}, fasting glucose, and 1- and 2-h postload glucose. Subsequently, variables reaching statistical significance were inserted into a multivariate regression model to identify independent relationships between cardiovascular risk factors (age, sex, smoking status, systolic and diastolic BP, total cholesterol, HDL cholesterol, triglycerides, hs-CRP, HOMA-IR, and sRAGE) and variations in AugI and IMT. The variance inflation factor was used to check for the problem of multicollinearity among the predictor variables in multiple regression analysis.

RESULTS

In total, 274 subjects participated in the study. The study population was divided into the following three groups (based on HbA_{1c} levels) according to the ADA recommendation (1): 97 control subjects (HbA_{1c} <5.7% [39 mmol/mol]), 117 patients with prediabetes (HbA_{1c} 5.7–6.4% [39–46 mmol/mol]), and 60 patients with type 2 diabetes (HbA_{1c} ≥6.5% [48 mmol/mol]). Of the subjects who were prediabetic based on the HbA_{1c} levels, 80 (68%) showed NT after the OGTT, and only 8 showed IFG. Therefore, many of these subjects should be classified as normal according to fasting glycemia and OGTT.

As shown in Table 1, BMI, waist circumference, and total cholesterol were not significantly different among the three groups. Subjects with an HbA_{1c} of 5.7–6.4% (39–46 mmol/mol) were older and had higher systolic BP, diastolic BP, fasting glucose, triglycerides, HOMA-IR, and hs-CRP but lower HDL cholesterol than the control subjects. Moreover, these subjects had anthropometric and metabolic characteristics similar to patients with diabetes, except for the higher HDL cholesterol and lower fasting glycemia. No differences were observed in the sRAGE levels among the three groups.

Because a 1-h postload glucose level ≥155 mg/dL has been reported as a key marker for cardiovascular and type 2 diabetes risks (12,13), we also stratified all subjects according to their 1-h plasma glucose levels. We found that 82% of patients with a 1-h glucose ≥155 mg/dL presented HbA_{1c} >5.7%.

Arterial Stiffness According to HbA_{1c} Levels

Aug and AugI were significantly higher in the prediabetic group (HbA_{1c} 5.7–6.4% [39–46 mmol/mol]) than in the control group (HbA_{1c} <5.7% [39 mmol/mol]) (11.6 $\pm$ 6.5 vs. 9.5 $\pm$ 7.3, $P < 0.05$; 28.8 $\pm$ 11 vs. 24.4 $\pm$ 13.7, $P < 0.05$; respectively). In contrast, SEVR and

Table 1—Clinical and metabolic characteristics of the study population according to HbA_{1c} levels

	HbA_{1c} <5.7% (39 mmol/mol) (*n* = 97)	HbA_{1c} 5.7–6.4% (39–46 mmol/mol) (*n* = 117)	HbA_{1c} ≥6.5% (48 mmol/mol) (*n* = 60)
Age (years)	41.5 ± 12.2	48.3 ± 10.7†	51 ± 7.2*
BMI (kg/m^2)	30.6 ± 5.5	31.8 ± 6.1	31.7 ± 5.3
Waist circumference (cm)	102 ± 13.5	103.3 ± 11.9	106.6 ± 11.6
Fasting glucose (mg/dL)	86.4 ± 9.3	93.1 ± 11.6†	114 ± 21.1*‡
1-h glucose post-OGTT (mg/dL)	129.1 ± 33.8	161 ± 40†	206.7 ± 31.8*‡
2-h glucose post-OGTT (mg/dL)	106.2 ± 28.1	133.2 ± 42.3†	204.2 ± 71.4*‡
Total cholesterol (mg/dL)	187 ± 34.2	194.7 ± 34.9	182.1 ± 34.6
HDL cholesterol (mg/dL)	47.3 ± 12.6	44 ± 12.3†	39.5 ± 8*‡
Triglycerides (mg/dL)	86 (138–64)	107 (141–80)†	116 (141.5–87.5)
LDL cholesterol (mg/dL)	117.8 ± 31.6	124.9 ± 26.5	118.3 ± 30
Systolic BP (mmHg)	116 ± 15.8	123.8 ± 14.4†	127 ± 15.3*
Diastolic BP (mmHg)	70.7 ± 10.8	76 ± 10.8†	76 ± 11.7*
hs-CRP (mg/dL)	0.15 (0.3–0.1)	0.27 (0.55–0.12)†	0.36 (0.65–0.17)*
HOMA-IR	1.5 (1.9–1.1)	2 (3–1.4)†	2.7 (3.2–1.4)*
sRAGE (pg/mL)	387.9 (517.8–282.7)	394.4 (475.4–278.4)	391 (502.5–274.6)
1-h glucose post-OGTT ≥155 mg/dL	27 (9%)	70 (59%)	58 (96%)
Active smokers	40 (41%)	57 (48%)	34 (56%)*
Hypertension	22 (22%)	40 (34%)†	22 (37%)*

Data are presented as mean ± SD or as median (interquartile range) for continuous variables and percentage for the categorical variables. Smoking was quantified (number of cigarettes and years smoked), and smoking status was classified in active smokers and nonsmokers. Hypertension was defined as systolic BP >135 mmHg or diastolic BP >85 mmHg or taking any hypertension medications. †$P < 0.05$, HbA_{1c} <5.7% vs. HbA_{1c} 5.7–6.4%. *$P < 0.05$, HbA_{1c} <5.7% vs. HbA_{1c} ≥6.5%. ‡$P < 0.05$, HbA_{1c} 5.7–6.4% vs. HbA_{1c} ≥6.5%.

PWV were similar between these two groups. In individuals with type 2 diabetes, Aug and AugI were significantly increased compared with the control subjects. No difference was observed between the subjects with prediabetes and those with type 2 diabetes (HbA_{1c} ≥6.5% [48 mmol/mol]). Furthermore, in the subjects with diabetes, SEVR was impaired, and PWV was significantly increased compared with the normal and prediabetic individuals (Table 2).

To minimize the impact of glucose tolerance alteration as a confounding factor, we examined the prediabetic subjects and excluded all those subjects with diabetes or IGT after the OGTT from the analysis. As shown in Fig. 1, AugI remained significantly higher in the NT group with HbA_{1c} >5.7 (39 mmol/mol) compared with the NT subjects with HbA_{1c} <5.7% (39 mmol/mol). We found no difference between the NT group with HbA_{1c} >5.7 (39 mmol/mol) and the subjects with IGT or type 2 diabetes.

Both simple and multiple regression analyses were performed to evaluate the independent contributions of the glycemic parameters and other cardiovascular risk factors to AugI.

Table 2—Arterial Stiffness and thickness parameters according to HbA_{1c} levels

	HbA_{1c} <5.7% (39 mmol/mol) (*n* = 97)	HbA_{1c} 5.7 to 6.4% (39–46 mmol/mol) (*n* = 117)	HbA_{1c} ≥6.5% (48 mmol/mol) (*n* = 60)
Augmentation pressure (mmHg)	9.5 ± 7.3	11.6 ± 6.5†	12.6 ± 6.1*
AugI (%)	24.4 ± 13.7	28.8 ± 11†	30.5 ± 10.7*
SEVR (%)	156 ± 24.9	157 ± 29.7	144.3 ± 31.6*‡
PWV (m/s)	7.5 ± 2	7.7 ± 1.4	8.8 ± 1.8*‡
IMT (mm)	0.65 (0.7–0.6)	0.73 (0.81–0.64)†	0.79 (0.91–0.69)*

Data are presented as mean ± SD or as median (interquartile range). †$P < 0.05$, HbA_{1c} <5.7% vs. HbA_{1c} 5.7–6.4%. *$P < 0.05$, HbA_{1c} <5.7% vs. HbA_{1c} ≥6.5%. ‡$P < 0.05$, HbA_{1c} 5.7–6.4% vs. HbA_{1c} ≥6.5%.

The simple regression analysis included HbA_{1c}, fasting glucose, and 1- and 2-h postload glucose. AugI was significantly correlated with HbA_{1c} ($r = 0.15$, $P < 0.05$), 1-h postload glucose ($r = 0.24$, $P < 0.05$), and 2-h postload glucose ($r = 0.19$, $P < 0.05$). Then, we performed multiple regression analysis using two models. The first model included HbA_{1c} and 1- and 2-h postload plasma glucose and showed a significant ($P < 0.05$) correlation between AugI and 1-h postload glucose. The second model included a variety of atherosclerosis risk factors (age, sex, smoking status, systolic and diastolic BP, total cholesterol, HDL cholesterol, triglycerides, hs-CRP, HOMA-IR, and sRAGE) and showed that the only variables that remained significantly associated with AugI were age ($P < 0.0001$) and 1-h postload glucose ($P < 0.05$) (Table 3).

IMT According to HbA_{1c} Levels

The IMT was significantly higher ($P < 0.05$) in patients with prediabetes and type 2 diabetes than in subjects with low HbA_{1c} (Table 2). We found that the IMT was higher in the NT subjects with HbA_{1c} 5.7–6.4% than in the NT subjects with

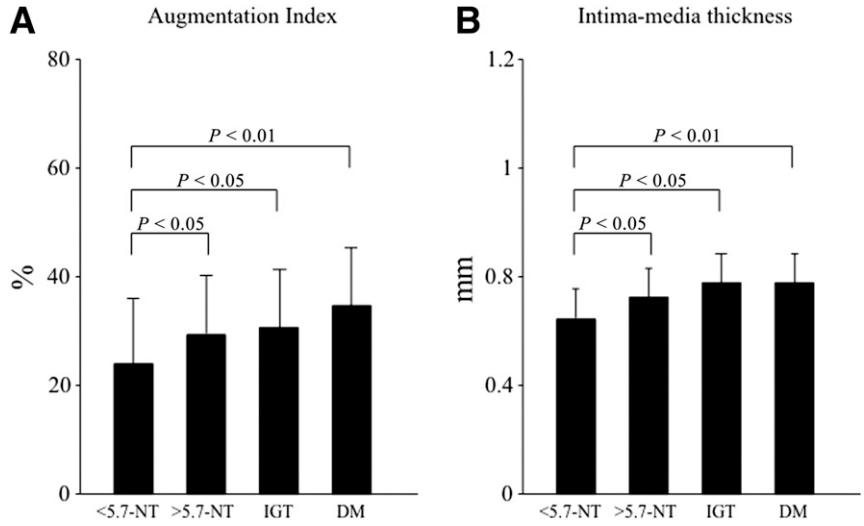

Figure 1—AugI (mean ± SD) (*A*) and IMT (mean ± SD) (*B*) by normotolerant (NT) with HbA_{1c} <5.7% (*n* = 86), NT with HbA_{1c} >5.7% (*n* = 80), IGT (*n* = 62), and type 2 diabetes (*n* = 46).

HbA_{1c} <5.7% (39 mmol/mol) (0.73 ± 0.11 vs. 0.68 ± 0.13, $P < 0.05$).

In the simple regression analysis, the IMT was associated with HbA_{1c} ($r = 0.32$, $P < 0.01$), fasting glucose ($r = 0.29$, $P < 0.01$), 1-h postload glucose ($r = 0.23$, $P < 0.01$), and 2-h postload glucose ($r = 0.24$, $P < 0.01$). To estimate the independent contributions of the glycemic parameters (HbA_{1c} and 1- and 2-h postload plasma glucose), we performed multivariate regression analysis with two models. The first model included the glycemic parameters (HbA_{1c} and 1- and 2-h postload plasma glucose), and the second model included several CVD risk factors (age, sex, smoking status, systolic and diastolic BP, total cholesterol, HDL cholesterol, triglycerides, hs-CRP, HOMA-IR, and sRAGE). The first model showed a significant correlation between the IMT and HbA_{1c} ($P < 0.05$). In the second model, the only variables that remained significantly associated with the IMT were HbA_{1c} ($P < 0.05$), age ($P < 0.0001$), and sRAGE ($P < 0.05$) (Table 3).

Table 3—Multiple regression analysis evaluating AugI and IMT as dependent variable

	Coefficient β	*P* value
AugI		
Multiple regression: model 1*		
1-h glucose (mg/dL)	0.063	<0.05
Multiple regression: model 2**		
1-h glucose (mg/dL)	0.032	<0.05
Age (years)	0.35	0.0001
IMT		
Multiple regression: model 1*		
HbA_{1c}	0.27	<0.05
Multiple regression: model 2**		
HbA_{1c} (%)	0.016	<0.05
Age (years)	0.02	0.0001
sRAGE (pg/mL)	0.08	<0.05

*Model 1 was adjusted for HbA_{1c}, fasting glucose, and 1- and 2-h glucose. **Model 2 was adjusted for age, sex, smoking status, systolic BP, diastolic BP, total cholesterol, HDL cholesterol, triglycerides, hs-CRP, HOMA-IR, and sRAGE.

CONCLUSIONS

In this study, we investigated the impact of ADA diagnostic criteria on the cardiovascular risk profile in a population without a previous history of diabetes (14–17). We evaluated arterial stiffness and arterial thickness, known as early markers of atherosclerosis and predictive of cardiovascular events.

We found that arterial stiffness was altered in subjects with higher HbA_{1c} levels. Both Aug and AugI were significantly increased in the subjects with prediabetes compared with the control subjects. Additionally, in type 2 diabetic subjects (HbA_{1c} ≥6.5% [48 mmol/mol]), Aug and AugI were also increased to a similar extent as that observed in the individuals with prediabetes. Furthermore, the IMT was higher in both prediabetic and type 2 diabetic subjects compared with the control subjects.

When we divided our study population into NT patients and those with altered glucose tolerance (including subjects with IGT and diabetes), we noted several interesting and original observations. Our data showed that Aug and AugI were increased in the NT subjects with HbA_{1c} 5.7–6.4% compared with their levels in the NT individuals with HbA_{1c} <5.7%; however, these values were similar to those of the IGT and type 2 diabetic patients. Moreover, the NT subjects with HbA_{1c} 5.7–6.4% showed higher IMT values compared with the NT subjects with low HbA_{1c}, and there were no significant

differences with respect to the IMT values of the IGT and type 2 diabetic patients. These results suggest that an HbA_{1c} cutoff of 5.7% is more sensitive for the identification of subjects at high cardiovascular risk as many of these subjects (72 out of 117) were classified as NT after the OGTT with a normal fasting glucose level.

The relationship between hyperglycemia and cardiovascular risk in diabetic patients has been well established (4,18,19). The risk of CVD is increased before glycemia reaches diabetic levels, as previously observed in IFG and IGT subjects and as recently demonstrated in NT individuals with a 1-h postload glucose ≥155 mg/dL (20). However, which among the glucose homeostasis parameters (fasting plasma glucose, 1-h postload glucose, 2-h postload glucose, and/or HbA_{1c}) could be a better predictor of CVD in prediabetic patients remains unclear. In the current study, HbA_{1c} was initially associated with AugI in an unadjusted model. After adjustment for conventional risk factors, fasting and postload glucose (including 1- and 2-h plasma glucose), the association with HbA_{1c} disappeared, and only 1-h postload glucose remained significantly associated with AugI, suggesting that 1-h postload glucose may be a better glycemic marker of vascular damage. This finding thus might highlight the importance of undergoing OGTT and obtaining intermediate values during glucose load, as previously indicated (20,21). However, we found that most subjects with a 1-h glucose exceeding 155 mg/dL are included in the group with HbA_{1c} in the 5.7–6.4 (39–46 mmol/mol) range, leading to the conclusion that HbA_{1c} could be used to identify subjects at a higher cardiovascular risk. Furthermore, only HbA_{1c} was associated with the IMT after a multiple regression analysis in two models, including glucose homeostasis parameters and multiple atherosclerosis risk factors. These findings are in agreement with previous studies (22) and suggest the importance of HbA_{1c} as an early marker of cardiovascular risk, although the metabolic alterations that lead to an increased cardiovascular risk are multiple and complex, and not a single laboratory test can adequately identify or classify an individual cardiovascular risk.

We did not find any differences in the sRAGE levels among our three groups. However, sRAGE was significantly associated with the IMT in the simple and multiple regression analyses, suggesting the adverse effect of sRAGE on the cardiovascular profile.

Previous studies reported that higher sRAGE levels are associated with cardiovascular events and all-cause mortality in subjects with type 1 diabetes; however, the findings regarding the circulating total sRAGE levels in both type 1 and type 2 diabetes are controversial (23,24). sRAGE reflects the total pool of soluble RAGE in the plasma. Splice variants, including endogenous secretory RAGE, appear to act as decoys, binding inflammatory RAGE ligands such as AGEs. In contrast, cleaved-type soluble RAGE, derived from the cell surface, appears to be modulated by the RAGE-ligand interaction, leading to increased receptor expression (25). In this work, we measured the total pool of plasma sRAGE; therefore, we could not discern whether the variants of sRAGE might have different associations with the morphological and functional markers of CVD.

Our findings are in good agreement with previously published data. In a longitudinal study in a population without diabetes at intermediate-to-high cardiovascular risk, glycated hemoglobin predicted all-cause and cardiovascular mortality independently of fasting glucose (26). Furthermore, Liang et al. (27) reported that HbA_{1c} was related to high PWV independently of conventional cardiovascular risk factors in a healthy Chinese population. In our study, we found a significant and strong correlation between HbA_{1c} and AugI, Aug, and IMT; in contrast, no correlation was observed with the PWV. This discordance could be due, at least in part, to ethnic differences in the study population or differences in the sample size. Accordingly, another study on a Chinese population showed that the AugI and PWV were differentially affected in subjects with diabetes (28). Thus, the discordance between PWV and AugI is not surprising. Previous studies have also showed that wave reflection indices and aortic stiffness do not always change in parallel. AugI is primarily determined by the magnitude and timing of the reflected pressure waves, which depend on the tone and elasticity of the small muscular arteries at the major sites of pressure wave reflection; PWV is a measure of elastic-type large artery stiffness and is inversely related to aortic distensibility and compliance (29). Therefore, AugI may be changed independently of PWV due to alterations in vascular smooth muscle tone that do not affect the elastic aorta. Increases in oxidative stress and reduced endothelial nitric oxide availability may impact the peripheral arteries more than the aorta.

In this study, SEVR, which is an estimate of myocardial perfusion, was not significantly different when we compared prediabetic subjects with control subjects. These findings are in agreement with the findings we reported in a recent study (11), in which SEVR was affected by metabolic syndrome but not by altered glucose tolerance.

Our study has several limitations. Our results could be affected by age, although such an effect would not be surprising, considering that aging is strongly correlated with arterial stiffness (30). However, previous studies have indicated that the deterioration of glucose tolerance is associated with increased arterial stiffness and that many of these changes occurred before the onset of type 2 diabetes (31). In addition, the OGTT was performed once; thus, intraindividual variation in plasma glucose levels cannot be taken into account.

In conclusion, our data suggest that a simple, reproducible, and less expensive marker such as HbA_{1c} may be better able to identify prediabetic subjects at high cardiovascular risk compared with the use of fasting glycemia or OGTT alone.

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