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Systemic hemodynamics in relation to glucose tolerance: the Health 2000 Survey

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Abstract

The influence of impaired glucose metabolism—that is, impaired fasting glucose, impaired glucose tolerance (IGT), and type 2 diabetes mellitus diabetes (DM2)—on systemic hemodynamics is largely unknown. Therefore, we investigated the associations of glucose metabolism disturbances with stroke index (SI), cardiac index, systemic vascular resistance index (SVRI), arterial pulse wave velocity (PWV), and heart rate among Finnish adults (N = 389; mean age, 58.3 ± 7.9 years) participating in the Health 2000 Survey. Systemic hemodynamic parameters were measured using the whole-body impedance cardiography device, and an oral glucose tolerance test (OGTT) was performed to evaluate glucose tolerance status. We found a decreasing trend for SI and increasing trends for SVRI and PWV according to the worsening of glucose tolerance (P for trend < .003 for all). In pairwise comparisons, SI was lower in the impaired fasting glucose group (P = .041) and the IGT group (P < .001) as compared with the normal glucose tolerance (NGT) group. Systemic vascular resistance index was higher in the IGT group (P = .045) and the DM2 group (P = .043) than in the NGT group. Subjects with IGT or DM2 had higher arterial PWV (10.7 ± 0.2 m/s, P < .001 and 11.7 ± 0.5 m/s, P = .001, respectively) than subjects with NGT (9.5 ± 0.1 m/s). Moreover, 2-hour glucose in OGTT was an independent determinant of SVRI and PWV (P < .001 and P = .005, respectively) in multivariable linear regression models. In conclusion, the present study demonstrates that glucose intolerance, even without DM2, associates with several adverse changes in systemic hemodynamics and that 2-hour glucose in OGTT is an independent determinant of SVRI and PWV. These findings support the systematic evaluation of glucose tolerance status in the estimation of cardiovascular risk among the middle-aged population.

1. Introduction

Impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and type 2 diabetes mellitus (DM2) have been shown to associate with cardiovascular disease as well as increased all-cause and cardiovascular mortality [1-4]. The mechanisms of these associations are not fully understood but might involve increased sodium sensitivity in insulin-resistant states, which may lead to hypertension [5] and increased arterial stiffness [6,7] due to structural changes in the large arteries. Increased peripheral resistance, stiffening of large arteries, and higher venous tone [8] may, in turn, lead to concentric and/or eccentric left ventricular (LV) hypertrophy [9,10] and to decreased LV contractility [11,12]. Especially arterial pulse wave velocity (PWV), a commonly used marker of arterial stiffness, has been shown to be increased in subjects with IFG, IGT, or DM2 [13,14]; and increased PWV has been found to associate with cardiovascular disease and mortality in subjects with a glucose metabolism disorder [15]. In addition, echocardiography studies have suggested that the worsening of glucose tolerance has adverse cardiac effects, including decreased LV systolic and diastolic function [16-19].

More insight into systemic hemodynamics and cardiovascular function in subjects with a glucose metabolism disorder could be achieved by simultaneous evaluation of several systemic hemodynamic parameters—including

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stroke volume (SV), a measure of cardiac function indicating the volume of blood pumped by the heart on every cardiac cycle; systemic vascular resistance (SVR), the force the LV must overcome to expel blood into arteries and a known determinant of blood pressure; and PWV. Previously, diabetes has been found to associate with decreased SV [20]; but the relation between SV and impaired glucose metabolism, that is, IFG or IGT, is less known. Moreover, associations between SVR and glucose metabolism disorders have not been described thoroughly.

To address the above-mentioned gaps in the literature, the present study was undertaken to evaluate systemic hemodynamics in adult Finnish individuals with normal glucose tolerance (NGT), IFG, IGT, or DM2 participating in the Health 2000 Survey.

2. Methods

2.1. Study population

The source of the study population was a large Finnish health examination survey (the Health 2000 Survey) carried out in 2000-2001 [21]. The overall study cohort was a 2-stage stratified cluster sample (8028 subjects) representing the entire Finnish population 30 years and older. To study cardiovascular disease and diabetes more thoroughly, a supplemental study (1867 subjects; participation rate, 82%) was carried out in the catchment areas of 5 Finnish university hospitals. Whole-body impedance cardiography (ICG_{WB}) monitoring and an oral glucose tolerance test (OGTT) were included in the study protocol in the catchment areas of Tampere and Turku University Hospitals (402 subjects, aged 46-76 years) to gain better insight into systemic hemodynamic alterations related to disturbances in glucose metabolism. Subjects with DM2 using insulin did not participate in the OGTT. Subjects with incomplete cardiovascular risk factor, OGTT, or systemic hemodynamics data (n = 11) and subjects with type 1 diabetes mellitus or undetermined diabetes (n = 2), were excluded. Therefore, a total of 389 subjects were included in the present analysis. In this study population, 4 subjects had self-reported cerebrovascular disease; and 10 subjects had self-reported ischemic heart disease.

2.2. Clinical characteristics

Venous blood samples were taken after an overnight fast. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations were determined enzymatically (Olympus System Reagent; Olympus, Hamburg, Germany, for total cholesterol and triglycerides; Roche Diagnostics, Mannheim, Germany, for HDL cholesterol) with a clinical chemistry analyzer (Olympus AU400). Low-density lipoprotein (LDL) cholesterol concentration was calculated using the Friedewald formula [22].

The OGTT was carried out after 10 to 12 hours of fasting. Subjects were given 75 g of glucose in a 10% solution. Venous blood samples for glucose and insulin determinations were taken before and 2 hours after the glucose load. Plasma glucose was determined by the glucose dehydrokinase method (Diagnostica Merck, Darmstadt, Germany) in a clinical chemistry analyzer (Konelab, Vantaa, Finland). In addition, plasma insulin was determined by the radio immunoanalysis method (Pharmacia, Uppsala, Sweden).

Height and weight were measured, and body mass index (BMI) was calculated. Continuous blood pressure was measured after 15 minutes of rest using a Finapres digital plethysmograph (Ohmeda, Engelwood, CO) placed on the middle finger of the left hand. An average blood pressure value of 30-second measurement was used. To verify the Finapres results, blood pressure was also measured from the upper arm using the automatic Omron M4 oscillometry manometer (Omron, Matsusaka, Japan, and Omron Healthcare Europe, Hoofddorp, the Netherlands). Smoking habits were ascertained with a questionnaire, defined as smoking on a daily basis. Informed written consent was obtained from all subjects, and the study was approved by local ethics committees.

2.3. Glucose tolerance

We used the World Health Organization criteria for diabetes mellitus [23] in the classification of subjects with no previously diagnosed diabetes: (1) NGT—fasting venous plasma glucose less than 6.1 mmol/L and 2-hour venous plasma glucose less than 7.8 mmol/L in an OGTT; (2) IFG—fasting venous plasma glucose of 6.1 to 6.9 mmol/L and 2-hour venous plasma glucose less than 7.8 mmol/L; (3) IGT—fasting venous plasma glucose less than 7.0 mmol/L and 2-hour venous plasma glucose of 7.8 to 11.0 mmol/L; and (4) DM2—fasting venous plasma glucose of at least 7.0 mmol/L or 2-hour venous plasma glucose of at least 11.1 mmol/L. Subjects taking oral diabetes medication were considered as having DM2 regardless of their OGTT results.

2.4. Hemodynamic measurements

An ICG_{WB} device (CircMon B202; JR Medical, Tallinn, Estonia) was used to determine blood flow (SV and cardiac output [CO]), SVR, arterial stiffness (PWV), and heart rate (HR). A pair of electrically connected current electrodes (Blue Sensor type R-00-S; Medicotest, Ölstykke, Denmark) was placed on the extremities just proximally to the wrists and the ankles. The outer electrodes feed current; and the inner electrodes measure the pulsatile changes in voltage that occur because of pulsatile changes in whole-body impedance as related to the change in the size of the aorta, reflecting SV. Cardiac output was estimated as HR ∗ SV; and SVR, as mean blood pressure (MBP) divided by CO. An additional pair of electrodes was placed on knee joint level and on the calf to measure PWV. The CircMon software measures the time difference between the onset of the decrease (“foot”) in impedance in the whole-body impedance signal and, subsequently, the popliteal artery signal. By means of this

time difference and the estimated distance between the electrodes, the software calculates the PWV. Stroke volume, CO, and SVR were indexed to body surface area to reduce the influence of body size on measurement results; and they were defined as follows: stroke index (SI) (SV/body surface area, in milliliters per square meter), cardiac index (CI) (CO/body surface area, in liters per minute per square meter), and systemic vascular resistance index (SVRI) (SVR/body surface area, dyne∗s/cm^{5}m^2). The procedure and evaluation as well as the good repeatability and reproducibility of the ICG_{WB} method have been described in more detail previously [24-26].

2.5. Statistics

Statistical analyses were performed using SPSS for Windows (version 16.0; SPSS, Chicago, IL). The skewed distribution of triglycerides was corrected logarithmically before statistical analyses. Analysis of variance was used in testing differences between unadjusted group means with Dunnett T3 post hoc test for multiple comparisons for continuous variables. χ^2 was used for categorical variables. Adjusted mean systemic hemodynamic parameters were analyzed using SPSS general linear models (analysis of covariance). Adjusted multivariable regression models were constructed to study independent effects of fasting glucose, 2-hour glucose in OGTT, fasting insulin, and 2-hour insulin in OGTT on systemic hemodynamic parameters. To limit the effects of collinearity and control the number of covariates, glucose and insulin measures were analyzed separately in multivariable models. There were no interactions between sex, glucose tolerance groups, and systemic hemodynamic parameters; and therefore, analyses were performed as sexes combined. All analyses were repeated after excluding subjects having self-reported cerebrovascular or ischemic heart disease (n = 14), with essentially similar results. A P value of < .05 was considered statistically significant.

3. Results

Table 1 shows the baseline characteristics of the study population according to glucose tolerance status. The prevalence of IFG, IGT, and DM2 was 9.3%, 19.5%, and 8.7%, respectively. Subjects with a glucose metabolism disorder had higher BMI, triglycerides, 2-hour glucose, and 2-hour insulin in OGTT as well as fasting glucose and fasting insulin values, than subjects with NGT. In comparison with the NGT group, systolic blood pressure (SBP) was higher in the IGT and DM2 groups; and MBP was higher in the DM2 group. Moreover, SBP was higher in subjects with DM2 than in those with IGT; and MBP was higher in subjects with IGT than in those with IFG. Compared with the NGT group, both the IFG and the IGT groups had lower HDL cholesterol values. Antihypertensive medication was more frequently used in the glucose metabolism disorder groups than the NGT group. Higher use of statin therapy was seen in subjects with DM2 than in those with NGT.

Independent associations of fasting glucose, fasting insulin, 2-hour glucose in OGTT, and 2-hour insulin in OGTT with systemic hemodynamic parameters are shown in Table 2. Multivariable regression models for SI and PWV included fasting glucose, fasting insulin, 2-hour glucose in OGTT or 2-hour insulin in OGTT, age, sex, HR, BMI, SBP, diastolic blood pressure (DBP), HDL cholesterol, LDL cholesterol, triglycerides, and smoking. For SVRI, similar

Table 1
Characteristics of the study population

	Glucose tolerance				
	NGT n = 243	IFG n = 36	IGT n = 76	DM2 n = 34	P for trend
Age (y)	57.5 ± 7.8	59.6 ± 7.3	59.0 ± 8.1	61.5 ± 8.0	.020
Men (%)	39.1	61.1*	48.7	44.1	.063
BMI (kg/m²)	26.1 ± 3.6	28.5 ± 4.9*	28.3 ± 4.4†	29.8 ± 5.4†	<.001
Smoking (%)	23.5	33.3	18.4	23.5	.386
Fasting glucose (mmol/L)	5.3 ± 0.4	6.3 ± 0.2‡	5.8 ± 0.5‡¶	7.3 ± 2.4‡‖	<.001
2-h glucose in OGTT (mmol/L)	5.5 ± 1.2	6.2 ± 1.1*	8.9 ± 0.8‡¶	14.1 ± 4.3‡¶	<.001
Fasting insulin (mmol/L)	7.0 ± 2.9	10.8 ± 4.9‡	10.2 ± 5.7‡	13.8 ± 10.4†	<.001
2-h insulin in OGTT (mmol/L)	37.1 ± 24.3	67.3 ± 52.7*	72.7 ± 38.7‡	82.7 ± 56.3‡	<.001
SBP (mm Hg)	126.2 ± 21.0	124.1 ± 18.5	134.0 ± 21.7*	146.7 ± 18.8‡§	<.001
DBP (mm Hg)	66.2 ± 13.0	64.1 ± 8.5	68.9 ± 12.0	71.4 ± 14.2	.035
MBP (mm Hg)	86.2 ± 14.5	84.1 ± 10.8	90.6 ± 14.0§	96.6 ± 14.0†	<.001
Antihypertensive medication (%)	19.3	36.1*	31.6*	67.6‡¶	<.001
Total cholesterol (mmol/L)	5.6 ± 0.9	5.9 ± 1.1	5.7 ± 1.0	5.4 ± 1.1	.053
LDL cholesterol (mmol/L)	3.4 ± 0.8	3.8 ± 1.0	3.5 ± 0.9	3.2 ± 1.0	.030
HDL cholesterol (mmol/L)	1.6 ± 0.4	1.4 ± 0.4*	1.5 ± 0.4*	1.4 ± 0.5	<.001
Triglycerides (mmol/L)	1.1 (0.8-1.4)	1.5 (1.0-2.2)*	1.5 (1.1-2.0)‡	1.5 (1.1-2.2)‡	<.001
Statin medication (%)	7.0	11.1	10.5	23.5†	.021

Values are presented as unadjusted mean ± standard deviation or geometric mean (25th-75th percentiles) or percentages of subjects.
*P < .05, †P < .01, and ‡P < .001 in pairwise comparison with the NGT group.
§P < .05, ‖P < .01, and ¶P < .001 in pairwise comparison IGT vs IFG and DM2 vs IGT.

Table 2
Independent glucose/insulin effects on systemic hemodynamic parameters in multivariable regression models (N = 389)

	SI		SVRI		PWV	
	$\beta \pm$ SE	P	$\beta \pm$ SE	P	$\beta \pm$ SE	P
Fasting glucose (mmol/L)	−0.277 ± 0.381	.467	58.217 ± 36.654	.113	0.193 ± 0.091	.034
2-h glucose in OGTT (mmol/L)	−0.153 ± 0.127	.227	45.352 ± 11.717	<.001	0.085 ± 0.030	.005
Fasting insulin (mmol/L)	0.014 ± 0.078	.857	−2.026 ± 7.627	.791	0.033 ± 0.019	.075
2-h insulin in OGTT (mmol/L)	−0.012 ± 0.010	.223	2.666 ± 0.970	.006	0.002 ± 0.002	.331

Regression coefficients (β) are age, sex, HR, BMI, SBP and DBP (for SI and PWV only), HDL cholesterol, LDL cholesterol, triglycerides, and smoking adjusted.

multivariable regression models were constructed (with the exception that SBP and DBP were not included in the model because blood pressure was used in the calculation of SVRI). Two-hour glucose in OGTT ($P < .001$; adjusted model R^2, 12.9%) and 2-hour insulin in OGTT ($P = .006$; adjusted model R^2, 11.2%) were directly and independently associated with SVRI. Other risk factors associated with SVRI were sex and HR ($P < .02$ for both). In addition, fasting glucose ($P = .034$; adjusted R^2, 51.9%) and 2-hour glucose in OGTT ($P = .005$; adjusted model R^2, 52.3%) were directly and independently associated with PWV. Other risk factors associated with PWV were age, sex, HR, and SBP ($P < .02$ for all). High-density lipoprotein cholesterol ($P = .022$), HR ($P < .001$), BMI ($P = .039$), and DBP ($P = .032$) were independent predictors explaining 15.7% of the variation in SI; but glucose or insulin measures were not associated with SI.

Mean values of SI, SVRI, and PWV according to glucose tolerance status are shown in Fig. 1. Stroke index was observed to decrease (P for trend < .001) and SVRI and PWV to increase (P for trend = .002 and P for trend < .001, respectively) with the worsening of glucose tolerance. In pairwise comparisons, SI was lower in the IFG and IGT groups when compared with the NGT group ($P = .041$ and $P < .001$, respectively); but there was no statistically significant difference between the DM2 and NGT groups ($P = .221$). Systemic vascular resistance index and PWV were higher in the IGT and DM2 groups than in the NGT group (SVRI: IGT vs NGT, $P = .045$ and DM2 vs NGT, $P = .043$; PWV: IGT vs NGT, $P < .001$ and DM2 vs NGT, $P = .001$). The difference between the IFG and the NGT groups was not statistically significant. In addition, there was no statistically significant difference in CI or HR between the groups (data not shown). After adjusting for age, sex, HDL cholesterol, LDL cholesterol, triglycerides, smoking, SBP (for SI and PWV only), and DBP (for SI and PWV only), decreasing trend of SI and increasing trends of SVRI and PWV with the worsening of glucose tolerance remained statistically significant (analysis of covariance P for trend < .03 for all).

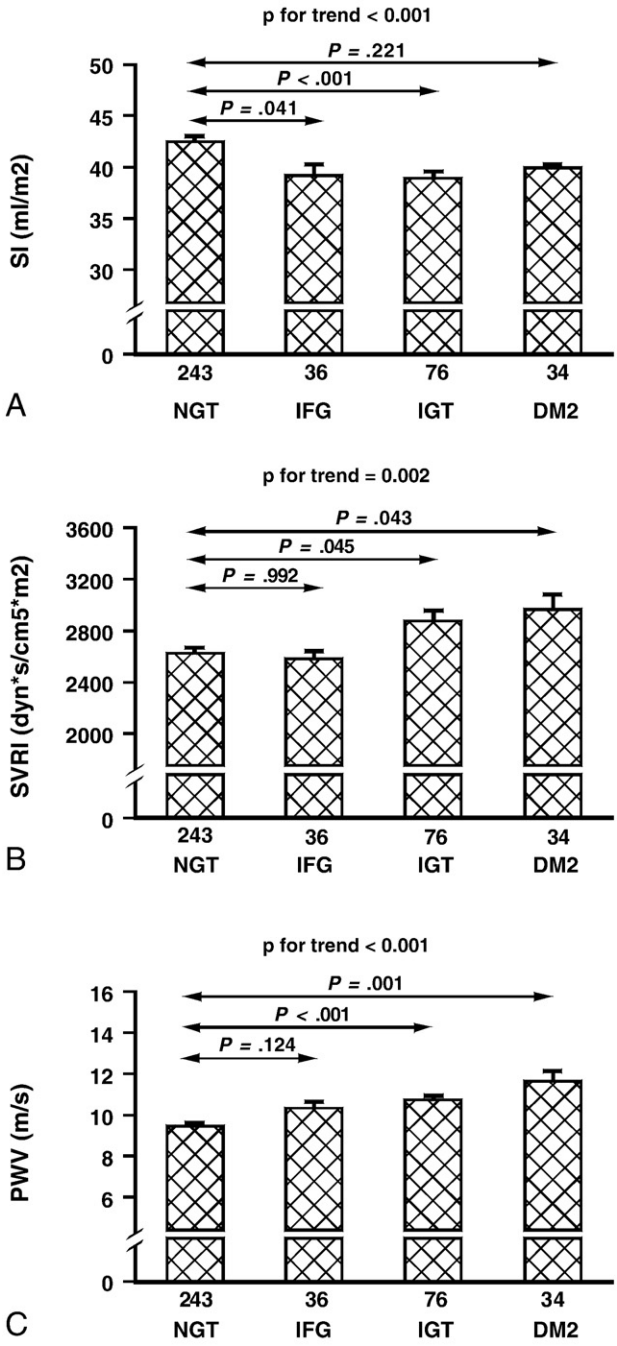

Fig. 1. Stroke index (A), SVRI (B), and PWV (C) means and standard errors according to glucose tolerance status.

4. Discussion

The aim of the present report was to study several systemic hemodynamic parameters simultaneously in

subjects with a different glucose tolerance status to achieve a deeper understanding of cardiovascular function in glucose metabolism disorders. We found that deteriorating glucose tolerance was associated with increased SVRI and PWV and with decreased SI. In addition, 2-hour glucose and insulin in OGTT were associated with SVRI independently of other cardiovascular risk factors; and fasting glucose and 2-hour glucose in OGTT were independent determinants of increased PWV.

We observed higher arterial stiffness, expressed as PWV, in subjects with DM2 [14,27,28] and IGT [13] compared with subjects with NGT, which is in line with previous reports. Previously, PWV has also been shown to be higher in subjects with IFG than in subjects with NGT [13,28]. In the present study, there was an increasing trend of PWV according to worsening of glucose tolerance, although in pairwise comparison, there was no statistically significant difference between IFG and NGT groups. Notably, the difference in PWV between subjects with IGT and those with NGT was 1.3 m/s; and that between subjects with DM2 and NGT was 2.2 m/s. This difference is worthy of mention because Blacher et al [29] observed an all-cause mortality odds ratio of 1.39 for each PWV increase of 1 m/s in patients with end-stage renal failure. In multivariable regression analysis, we found that sex, age, fasting glucose, 2-hour glucose in OGTT, SBP, and HR were determinants of PWV—a finding that is in agreement with previous studies [27,30]. Altogether, models including fasting glucose and 2-hour glucose in OGTT explained 51.9% and 52.3% of the variance in PWV, respectively. Thus, deteriorating glucose tolerance has unfavorable effects on arterial stiffness. Moreover, because PWV is a strong determinant of cardiovascular mortality and because fasting glucose and 2-hour glucose in OGTT remained as independent determinants of PWV in multivariable models, the current findings highlight the importance of glucose tolerance measurements in the risk evaluation of the middle-aged population.

The data available on the association between glucose metabolism disorders and cardiac function are limited and, to a degree, also controversial, particularly with reference to SV. Previous echocardiography studies suggest abnormalities in the cardiac structure and function of subjects with abnormal glucose tolerance [16-19,31], even without a difference in SI between the NGT, IGT, and DM2 groups [18]. However, Heckbert et al [20] found a decreased SV in subjects with diabetes as detected by cardiac magnetic resonance imaging. The present study shows a trend for decreasing cardiac function, measured by SI, with the deterioration of glucose tolerance. Decreased SI was found in both the IFG and the IGT groups as compared with the NGT group, but the difference between DM2 and NGT groups was not statistically significant. The mechanism of these adverse alterations in cardiac function is not completely understood; but it may involve myocardial cell injury and interstitial fibrosis [32], as well as slow coronary flow [33] and alterations in intracellular calcium homeostasis leading to depressed contractility [34]. On the other hand, in addition to a direct influence of deteriorating glucose tolerance on SI, increased arterial load caused by increased stiffness and SVR could be responsible for the lower SI in subjects with a glucose metabolism disorder. In concert with previous reports, [18,27], we observed no difference in HR, CO, or CI between study groups. Although many cardiovascular risk factors were univariately associated with SI, only HDL cholesterol, HR, BMI, and DBP were independent determinants of SI in multivariable models. Similar findings have been reported previously [20], but the mechanisms underlying these observations are less known and require further study.

Previous studies have shown higher mean levels of SVR and total peripheral resistance in subjects with IGT or DM2 as compared with healthy subjects, although these differences have not been statistically significant [18,35]. To the best of our knowledge, this is the first study to report a trend for increasing SVRI with the deterioration of glucose tolerance. In pairwise comparisons, SVRI was increased in subjects with IGT and DM2 when compared with subjects with NGT; but there was no statistically significant difference between subjects with IFG and NGT. Moreover, SVRI was higher in the IGT and DM2 groups than the IFG group. Previously, subjects with IGT have been shown to be more insulin resistant than subjects with IFG [36]; and this may also partially explain our findings. Interestingly, 2-hour glucose and insulin in OGTT were independently associated with SVRI, whereas fasting glucose and 2-hour glucose in OGTT were independent determinants of increased PWV. These findings highlight the fact that SVRI and PWV are clearly diverse vascular phenotypes with potentially different mechanisms behind elevation of them in glucose metabolism disorders. The pathophysiologic mechanism behind these observations is not clear based on the present findings. However, it is known that subjects with IFG, IGT, or DM2 have impaired endothelial function [37]; and this might have a role in increased SVR. In addition, it has been suggested that endothelial dysfunction causes decreased blood flow to skeletal muscles, which in turn could contribute to insulin resistance [38]. Furthermore, in hypertensive and obese subjects, impairment of insulin-mediated vasodilation may contribute to the increase in peripheral resistance [39]. It has been also shown that flow-mediated endothelium-dependent vasodilatation is rapidly reduced after glucose loading in subjects with DM2 and even in subjects with NGT or IGT whose fasting glucose levels are within normal limits [40]. Thus, it is tempting to speculate that prolonged and repeated exposure to postprandial hyperglycemia may play an important role in the development of atherosclerosis and alterations of systemic hemodynamics, even in those who have normal fasting plasma glucose levels, and that these pathophysiologic mechanisms may influence SVRI and PWV differentially. Clearly, the pathophysiologic bases underlying our observations, particularly whether there

are any alternative or additional factors responsible for increasing SVR in subjects with a glucose metabolism disorder, deserve further investigation.

In the present analysis, traditional cardiovascular risk factors explained only 15.7% of the variation in SI and 11.2% to 12.9% of the variation in SVRI. Previously, the proportion of the total variability of SV explained by the sociodemographic variables, height, and the cardiovascular risk factors (including also alcohol intake and exercise per week) has been shown to be roughly one third [20]. In addition, several other variables, such as genetic factors (heritable factors explaining 50%-60% of variance in systemic hemodynamics [41]) strongly explain variance in systemic hemodynamics. In the current study, we were not able to include all these potential explanators in the analysis; and this might lower the degree of explanation of variance in SI. One plausible factor explaining variance of SVRI could be HR variability because diabetic subjects have been shown to have higher sympathetic tone [42]. Therefore, associations of HR variability and SVRI on subjects with impaired glucose metabolism should be assessed in future studies.

There were some limitations in the present study. Our data were cross-sectional, and the causality of the observed associations could therefore not be assessed. Moreover, the study cohort was ethnically homogenous, limiting the generalization of the results to white Europeans only. The strengths of the present study include the fact that we used a population-based cohort and indexed hemodynamic parameters (SI, SVRI, and CI, which reduce the influence of body size to measurement results), improving the comparability of the present findings to those of previous studies and allowing a more direct evaluation of the associations of risk factors with systemic hemodynamics.

In conclusion, our results show that there is a trend for increasing SVR and arterial stiffness as well as decreasing cardiac pump function with the worsening of glucose tolerance status. Understanding the wide alterations in systemic hemodynamics and cardiovascular function caused by deteriorating glucose tolerance may lead to secondary preventive strategies to reduce cardiovascular disease and mortality.

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