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Increased arterial stiffness in subjects with impaired fasting glucose☆,☆☆

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ABSTRACT

Aims: The present study investigated the association between fasting glucose and arterial stiffness in subjects with normal fasting glucose (NFG) and impaired fasting glucose (IFG).
Methods: The study group consisted of 1043 subjects, including 683 subjects with NFG and 360 subjects with IFG (100 ≤ fasting glucose <126 mg/dL). All subjects were evaluated for glucose, insulin, lipid profiles, high sensitivity C-reactive protein (hs-CRP), malondialdehyde (MDA), 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$) and brachial–ankle pulse wave velocity (ba-PWV).
Results: MDA ($P<0.001$) and ba-PWV ($P<0.001$) in the IFG group were higher than those in the NFG group after adjustment for sex, age, BMI, smoking and drinking, waist, blood pressure, serum lipid profiles. Ba-PWV in the IFG group was still higher than that in the NFG group after further adjustment for hs-CRP, MDA, 8-epi-$PGF_{2\alpha}$ ($P=0.031$). Through multiple linear regression analysis, ba-PWV was found to be independently and positively associated with fasting glucose, age, systolic blood pressure, triglyceride, hs-CRP and insulin and negatively associated with male:female ratio, BMI.
Conclusion: Arterial stiffness was higher in the IFG group than in subjects with NFG even after adjustment for all confounding variables including hs-CRP and oxidative stress markers. In addition, fasting glucose and insulin were positively and independently associated with the ba-PWV in non-diabetic healthy adults.

1. Introduction

It has been suggested that atherosclerotic changes are already evident in subjects with impaired fasting glucose (IFG) as well as in those with diabetes, and risk of cardiovascular disease (CVD) is greater in subjects with IFG than in those with normal fasting glucose (NFG) (Lim, Tai, Tan, Chew, & Tan, 2000; Shaw et al., 2000). These findings indicate that increased fasting glucose can be associated with progression of arterial stiffness, which is considered an early marker of atherosclerosis. Arterial stiffness can be easily and noninvasively assessed by measuring the pulse wave velocity (PWV) (Lehmann, 1999; Munakata, Ito, Nunokawa, & Yoshinaga, 2003). Brachial–ankle PWV (ba-PWV) is an index of central arterial stiffness with a good correlation with the aortic PWV obtained by invasive recording, which has been demonstrated to have a close relationship with carotid–femoral PWV (Tsuchikura et al., 2010; Yamashina et al., 2002). We aimed to investigate the relationship between arterial stiffness and fasting glucose in non-diabetic subjects. We also measured high sensitivity C-reactive protein (hs-CRP) and oxidative stress makers including malondialdehyde (MDA) and 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$).

2. Subjects

One thousand forty-three healthy subjects were recruited at the health promotion center of the National Health Insurance Corporation Ilsan Hospital in Korea between August 2010 and September 2011. NFG was defined as a fasting glucose level <100 mg/dL (5.55 mmol/L), and IFG as a fasting glucose level of 100 to 126 mg/dL (5.55–6.99 mmol/L). Subjects also completed a personal health and medical history questionnaire, which served as a screening tool. Exclusion criteria were previous history of type 2 diabetes, CVD, cancer, abnormal liver or renal function, thyroid or pituitary disease, and use of any medications (anti-hypertensive, lipid lowering, anti-platelets and anti-diabetic etc.). The purpose of the study was

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carefully explained to all participants and their written consent was obtained prior to their participation. The Institutional Review Board of the National Health Insurance Corporation Ilsan Hospital approved the study protocol, which was conducted in accordance with the Helsinki Declaration.

3. Materials and methods

3.1. Anthropometric parameters, blood pressure, and blood collection

Body weight and height of participants who were unclothed and without shoes were measured in the morning. BMI (kg/m^2) was calculated from body height and weight. Waist circumference was measured at the umbilical level with the subjects standing after normal expiration. Blood pressure (BP) was measured in the left arm of seated patients with an automatic blood pressure monitor (TM-2654, A&D, Tokyo, Japan) after a 20-min rest. After a 12-h fast, venous blood specimens were collected in EDTA-treated or untreated tubes. The plasma or serum was then separated and stored at −70 °C until used in further analysis.

3.2. Serum lipid profile and fasting glucose, insulin concentration, and homeostasis model assessment-insulin resistance

Fasting total-cholesterol and triglyceride levels were measured using commercially available kits on a Hitachi 7150 Autoanalyzer (Hitachi Ltd., Tokyo, Japan). After precipitation of apoB-containing lipoproteins with dextran sulfate magnesium, HDL-cholesterol concentrations in the supernatants were enzymatically measured. LDL-cholesterol was estimated indirectly for subjects with serum triglyceride levels <400 mg/dL using the Friedewald formula: LDL-cholesterol = Total-cholesterol − (HDL-cholesterol + [Triglycerides/5]). LDL-cholesterol for subjects with serum triglyceride levels ≥400 mg/dL was measured indirectly. Fasting glucose levels were measured by the glucose oxidase method with a Beckman Glucose Analyzer (Beckman Instruments, Irvine, CA, USA). Insulin levels were measured by radioimmunoassay using commercial kits from Immuno Nucleo Corporation (Stillwater, MN). Insulin resistance (IR) was calculated by the homeostasis model assessment (HOMA) using the following equation: HOMA-IR = [fasting insulin (μIU/mL) × fasting glucose (mmol/L)] /22.5.

3.3. Serum hs-CRP, plasma MDA, and Urinary 8-epi-$PGF_{2\alpha}$ levels

Serum hs-CRP levels were measured with an Express Plus™ auto-analyzer (Chiron Diagnostics Co., Walpole, MA) using a commercially available, high-sensitivity CRP-Latex(II) X2 kit (Seiken Laboratories Ltd., Tokyo, Japan). Plasma MDA was measured from thiobarbituric acid-reactive substances (TBARS Assay Kit, Zepto-Metrix Co., Buffalo, NY). Urine was collected in polyethylene bottles containing 1% butylated hydroxytoluene after a 12-h fast. The bottles were immediately covered with aluminum foil and stored at −70 °C until further analysis. The compound 8-epi-$PGF_{2\alpha}$ was measured using an enzyme immunoassay (BIOXYTECH urinary 8-epi-$PGF_{2\alpha}^{TM}$ Assay kit, OXIS International Inc., Portland, OR, USA). Urinary creatinine levels were determined using the alkaline picrate (Jaffe) reaction.

3.4. Brachial–ankle pulse wave velocity (ba-PWV) and pulse pressure

ba-PWV and pulse pressure were measured using an automatic waveform analyzer (model VP-1000; Nippon Colin Ltd., Komaki, Japan) using a previously described method (Kim et al., 2010). The average ba-PWV from both left and right sides was used for analysis.

3.5. Data analysis

Statistical analyses were performed using SPSS version 12.0 for Windows (SPSS Inc., Chicago, IL, USA). We determined whether each

Table 1
Clinical and biochemical characteristics.

	Subjects with NFG (n = 683)	Subjects with IFG (n = 360)	*P*	P^a	P^b	P^c	P^d
Male / Female (%)	72.9 / 27.1	73.1 / 26.9	0.961	-	-	-	-
Age (year)	46.6 ± 0.37	46.9 ± 0.53	0.587	-	-	-	-
BMI (kg/m^2)	24.1 ± 0.08	24.8 ± 0.15	<0.001	-	-	-	-
Alcohol drinker, n (%)	497 (72.8)	287 (79.7)	0.013	-	-	-	-
Cigarette smoker, n (%)	210 (30.7)	111 (30.8)	0.977	-	-	-	-
Waist (cm)	84.3 ± 0.22	85.9 ± 0.39	<0.001	0.195	-	-	-
SBP (mmHg)	118.4 ± 0.52	124.2 ± 0.74	<0.001	<0.001	-	-	-
DBP (mmHg)	72.4 ± 0.40	76.3 ± 0.59	<0.001	<0.001	-	-	-
TG (mg/dL)*	107.6 ± 2.30	136.1 ± 4.24	<0.001	<0.001	-	-	-
Total-cholesterol (mg/dL)*	191.5 ± 1.20	194.3 ± 1.79	0.268	0.721	0.231	-	-
HDL-cholesterol (mg/dL)*	52.8 ± 0.57	50.9 ± 0.76	0.029	0.042	0.159	-	-
LDL-cholesterol (mg/dL)*	117.4 ± 1.18	117.0 ± 1.74	0.543	0.303	0.417	-	-
hs-CRP (mg/L)*	0.98 ± 0.05	1.49 ± 0.15	<0.001	0.003	0.026	0.035	-
MDA (nmol/mL)*	8.64 ± 0.10	9.62 ± 0.15	<0.001	<0.001	<0.001	<0.001	-
$PGF_{2\alpha}$ (pg/mg creatinine)*	1343.4 ± 18.7	1423.4 ± 28.7	0.023	0.014	0.099	0.103	-
Waist hip ratio	0.90 ± 0.00	0.91 ± 0.00	0.001	0.078	0.464	0.644	0.287
Pulse pressure (bpm)*	63.6 ± 0.36	67.0 ± 0.57	<0.001	<0.001	<0.001	<0.001	0.008
ba-PWV (cm/s)*	1309.3 ± 6.91	1389.8 ± 12.8	<0.001	<0.001	<0.001	<0.001	0.031
Glucose (mg/dL)*	88.6 ± 0.28	105.7 ± 0.28	<0.001	<0.001	<0.001	<0.001	<0.001
Insulin (μIU/mL)*	8.24 ± 0.12	9.93 ± 0.23	<0.001	<0.001	<0.001	<0.001	<0.001
HOMA-IR*,**	1.81 ± 0.03	2.60 ± 0.06	<0.001	<0.001	<0.001	<0.001	<0.001

Means ± S.E.
NFG, normal fasting glucose; IFG, impaired fasting glucose; BMI, body Mass Index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; hs-CRP, high sensitivity C-reactive protein; MDA, malondialdehyde; $PGF_{2\alpha}$, urinary8-epi-$PGF_{2\alpha}$; ba-PWV, brachial–ankle pulse wave velocity.
Tested by independent t-test or general linear model with the adjustment.
p: unadjusted.
p^a: adjusted for sex, age, BMI, and alcohol consumption.
p^b: adjusted for sex, age, BMI, alcohol consumption, cigarette smoking, waist, SBP, DBP, and TG.
P^c: adjusted for sex, age, BMI, alcohol consumption, cigarette smoking, waist, SBP, DBP, TG, Total-cholesterol, HDL-cholesterol, and LDL-cholesterol.
P^d: adjusted for sex, age, BMI, alcohol consumption, cigarette smoking, waist, SBP, DBP, TG, Total-cholesterol, HDL-cholesterol, LDL-cholesterol, hs-CRP, MDA, and $PGF_{2\alpha}$.
* Tested bylogarithmic transformation.
** HOMA-IR = {fasting insulin (μIU/mL) × fasting glucose (mmol/L)}/22.5.