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# Association between Pulse Wave Velocity and the Framingham Risk Score in Patients with different Glucose Metabolism Status

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## Abstract

**Objective:** To investigate the relationship between different glucose metabolism status and Pulse Wave Velocity (PWV)and further explore the relationship between PWV, HOMA-IR and the Framingham risk score of 10-year (FRS).

**Methods:** 105 subjects were divided into three groups: normal glucose tolerance group (G1, n=47); pre-diabetes group (G2, n=32)and type 2 diabetes mellitus (DM) group (G3, n=26)General clinical data and biochemical parameters of each subject were collected. PWV was measured using the Complior SP. FRS was calculated with the lipids excel spreadsheets from Framingham Heart Study homepage. The correlation of different glucose metabolism status, PWV and FRS were analyzed and compared.

**Results:** A positive correlation was found between carotid-to-femoral PWV (cf-PWV) and age, (Systolic Blood Pressure) SBP, 2-hr plasma glucose (2h PG). There is a direct connection between homeostasis model assessment of insulin resistance (HOMA-IR) and HOMA-IR (CP). FRS was difference among three groups. A correlation was found between FRS and cf-PWV, 2h PG, HOMA-IR (CP).

**Conclusion:** HOMA-IR (CP) and cf-PWV are positive correlation with FRS, which is a predictor of cardiovascular disease (CVD). Hence HOMA-IR (CP) and cf-PWV may have a good clinical value for indicating vascular structure and function and further evaluating the 10-year risk of CVD.

**Keywords:** Arterial stiffness; Pulse wave velocity; Insulin resistance; Fasting C-peptide; Framingham risk score

## Introduction

By the end of 2013, diabetes had caused 5.1 million deaths and cost billions for healthcare spending. Without concerted action to prevent diabetes, there will be 592 million people living with the disease in less than 25 years' time [1]. CVD is the major cause of mortality and morbidity in patients with type 2 diabetes. The clinical relevance of this metabolic syndrome is related to its role in the development of vascular disease, including endothelium impair, an increase in arterial stiffness and intima-media thickness. Diabetes mellitus and impaired fasting glucose bring carotid arterioles atherosclerosis and hence draw our attention. PWV can intelligently show the flexible degree of aorta blood vessel, and is the gold standard evaluating atherosclerosis. The research is to investigate the relationship between different glucose metabolism status and PWVand further explore its relationship between PWV, HOMA-IR and FRS. Pre-diabetes has been first described by the WHO in 1980 as impaired glucose tolerance (IGT) [2]. In order to avoid the time-consuming and somewhat cumbersome measurement of 2h PG, the ADA proposed to identify pre-diabetes as impaired fasting glucose (IFG) in 1997, which relies on one fasting measurement only. In 2004, the ADA lowered the cutoff point for IFG from 6.1 to 5.6 mmol/l [3]. IFG and IGT are strongly associated with excess body weight and insulin resistance, which is the central feature of the metabolic syndrome metabolic abnormalities and leads the path to diabetes. The respective prognostic values of IFG and IGT to predict CVD risk are still controversial [4]. So we investigated HOMA-IR instead of different glucose values, which are more rational and perfective, and conform to reality.

The Third Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III) incorporated the FRS for predicting CVD [5]. FRS is to investigate the effects of a large variety of variables, both singly and jointly on the risk of developing the disease. As in all previous publications reporting results in Framingham, the calculator prepared based on a publication by D'Agostino et al. FRS shown is derived on the basis of an equation. It includes the following Risk factors: Sex, Age, systolic blood pressure, treatment for Hypertension, Smoking, Diabetes, HDL and Total Cholesterol. Although FRS is considered a useful tool for quantitative assessment of the risk for CVD in the general populations, the score does not have sufficient power to predict future onset of CVD in type 2 diabetic patients [6-8]. In patients with stable angina, the FRS and flow-mediated dilation are independent predictors of cardiovascular Events [9].

Aortic PWV is widely used as a marker of arterial stiffness. The aorta (carotid-femoral segment) is the recommended site for determination of arterial stiffness, as carotid-femoral PWV (cf-PWV) best predicts adverse cardiovascular outcomes [10]. And several studies have demonstrated that higher cf-PWV levels are associated with increased risk of CVD and premature death [11-13]. Naoto Katakami1'study suggests that PWV, a non-invasive and user-friendly

method for quantitatively estimating arterial stiffness, can improve the risk prediction of cardiovascular events in asymptomatic type 2 diabetic patients [14]. To our knowledge, previous research has not evaluated whether HOMA-IR might be predictive of CVD risk using the FRS assessment. The aim of this study was to determine if HOMA-IR and PWV were predictive of CVD risk assessed by FRS.

## Materials and Methods

### Patients

105 volunteers were retrospectively studied in our hospital between November 2013 and January 2014. There were 38 male and 67 female. The mean of patients' age was 53 ± 12.45 with the range of 18-76 years old. Normal glucose tolerance group (G1) was fasting blood glucose (FBG)<5.6 mmol/l, 2h PG<7.8 mmol/l and HbA1c<5.7%. None of them had hypertension or diabetes, and their ECGs were quite normal. Pre-diabetes group (G2) was FBG5.6-6.9 mmol/l, 2h PG 7.8-11.0 mmol/l and HbA1c5.7%-6.4%. G3 was the DM group. DM was defined as FBG ≥ 7.0 mmol/l, 2h PG ≥ 11.1 mmol/l, testing of random glucose (defined as any time of day without regard to time since last meal) ≥11.1 mmol/l, which has yet to be replicated, or a current history of anti-diabetic medication. The local research ethics committee approved the study and all participants provided written informed consent.

### Data processing

After an overnight fast of 8 to 12 hours, interested participants underwent a capillary blood glucose test 2h PG after an ingestion of 75 G glucose. For all subjects investigated, fasting venous blood samples were obtained to measure plasma levels of glucose, blood lipid, fasting serum insulin (FIN) and c-peptide (CP, a marker of endogenous insulin secretion). Testing of HbA1c level which did not require fasting was useful both for diagnosis and screening. BMIbody mass indexis a measure of body fat based on height and weight. In each subject, the degree of insulin resistance (HOMA-IR) was calculated with the FIN (μU/ml) × FBG (mmol/l) /22.5 [15]. We call HOMA-IR (CP) when C peptide replaces fasting serum insulin on the HOMA-IR. It shall calculated by the formula HOMA-IR (CP) =1.5+(FBG × CP)/2800.

Arterial stiffness can be assessed non-invasively by measuring PWV. cf-PWV was measured using a 4 MHz continuous wave Doppler ultrasound probe within groups with newly identified age- and sex-matched (Complior SP,Artech-Medical). Two operators blinded to glucose status performed all arterial measurements within a single-site research facility. Participants were fasted and rested supine prior to cf-PWV assessment. Baseline supine brachial artery BP and heart rate (HR) were recorded using the semi-automated oscillometric device prior to subsequent cf-PWV measurements. The cutaneous distance between the site of the femoral pulsation and the sternal notch was repeatedly measured and entered into the device according to manufacturer's instructions. After archiving a minimum of three 10 s continuous waveforms, data were processed using established software and mean cf-PWV was calculated. Cf-PWV was calculated by dividing the measured surface difference by the respective ECG-derived transit time.

The FRS was calculated using available table format [16]. Briefly, total possible scores range from 0 to 25 points; if the total score is <9 points, there is <1% risk of hard CVD (MI or coronary death) in 10 years; a total score of 20 would be associated with 11% CVD risk.

### Statistical Analysis

SPSS (IBM19) was used for statistical analyses. Means+SD and percentages are presented. The inter-group comparison was performed by using single factor, complete randomized analysis of variance. The Spearman's rank correlation coefficient test or Pearson's test was used in showing the associations of the samples. The p value<0.05 was considered statistically significant.

## Results

Table 1 displays the sample characteristics. Correlation analysis showed there was relationship between cf-PWV and groups while the factors of age is excluded (r=0.22, p=0.037). A positive correlation was found between cf-PWV and age (r=0.51, p=0.000), SBP (r=0.26, p=0.014), carotid-radial pulse wave velocity (cr-PWV) (r=0.45, p=0.000), 2h PG (r=0.23, p=0.05), FIN/CP (r=-0.28, p=0.028). Cr-PWV was associated with sex (r=0.23, p=0.028), TC (r=-0.32, p=0.03) and HDL-C (r=-0.32, p=0.02), but the association between cr-PWV and TC disappeared after HDL-C was eliminated. While excluding relevant affecting causes, there is still significant difference between cf-PWV and cr-PWV (r=0.55, p=0.000). Whereas no statistic difference was found in insulin and CP among three groups, HOMA-IR and HOMA-IR (CP) are very different (Table 1). It is highly likely that there are direct connection between HOMA-IR (CP) and HOMA-IR (r=0.86, p=0.000), BMI (r=0.336, p=0.007), TG (r=0.355, p=0.001), HDL-C (r=-0.272, p=0.009). FRS was difference among three groups (Table 2). A correlation was found between FRS and cf-PWV(r=0.43, p=0.000), 2h PG (r=0.3, p=0.06), FIN/CP (r=-0.25, p=0.033), HOMA-IR (CP) (r=0.23, p=0.029).

| Variables | G1 (n=47) | G2 (n=32) | G3 (n=26) | P value |
|---|---|---|---|---|
| Gender (Male%) | 15 (31.9) | 14 (43.8) | 9 (34.6) | 0.551 |
| Age (yr) | 51.43 ± 14.00 | 58.38 ± 6.98 | 49.31 ± 12.95 | 0.01 |
| Smoking (%) | 3 (6.4) | 4 (12.5) | 5 (19.2) | 0.253 |
| SBP (mmHg) | 124.87 ± 12.59 | 126.25 ± 14.04 | 127.50 ± 16.25 | 0.737 |
| BMI (kg/m$^2$) | 24.07 ± 3.16 | 25.16 ± 3.06 | 23.76 ± 3.9 | 0.238 |
| FBG (mmol/l) | 4.77 ± 0.40 | 5.32 ± 0.72 | 10.01 ± 3.69 | 0 |

| | | | | |
|---|---|---|---|---|
| 2 hPG (mmol/l) | 6.00 ± 0.92 | 8.12 ± 1.55 | 14.19 ± 6.48 | 0 |
| TG (mmol/L) | 1.31 ± 0.77 | 1.51 ± 0.59 | 1.8 ± 1.18 | 0.07 |
| TC (mmol/L) | 4.52 ± 0.76 | 4.89 ± 0.86 | 4.89 ± 0.96 | 0.097 |
| LDL-C (mmol/L) | 2.84 ± 0.68 | 3.09 ± 0.66 | 3.21 ± 0.75 | 0.082 |
| HDL- (mmol/L) | 1.07 ± 0.20 | 1.12 ± 0.37 | 1.06 ± 0.26 | 0.637 |
| crPWV (m/s) | 8.87 ± 1.50 | 8.94 ± 1.01 | 9.14 ± 1.03 | 0.713 |
| cfPWV (m/s) | 7.62 ± 1.39 | 8.08 ± 1.35 | 8.25 ± 2.01 | 0.258 |
| HbA1c | 5.37 ± 0.26 | 5.88 ± 0.31 | 9.76 ± 3.90 | 0 |
| FIN (μU/l) | 9.89 ± 5.27 | 7.58 ± 3.23 | 12.57 ± 13.32 | 0.102 |
| CP (ng/ml) | 2.51 ± 0.80 | 2.43 ± 0.98 | 2.42 ± 1.49 | 0.914 |
| FIN/ Cp (μU/ng) | 3.80 ± 1.05 | 3.18 ± 0.67 | 3.32 ± 1.66 | 0.074 |
| HOMA-IR (CP) | 3.71 ± 0.69 | 3.96 ± 1.40 | 6.14 ± 3.29 | 0 |
| HOMA-IR | 2.08 ± 1.07 | 1.81 ± 1.00 | 5.85 ± 6.08 | 0 |

**Table 1:** Clinical characteristics of the participants by glucose exposure levels.

| Variable | G1 (n=47) | G2 (n=32) | G3 (n=26) | p value |
|---|---|---|---|---|
| Age (year) | 51.43 ± 14.00 | 58.38 ± 6.98 | 49.31 ± 12.95 | 0.01 |
| Sex (% males) | 15 (31.9) | 14 (43.8) | 9 (34.6) | 0.551 |
| Active smoking (%) | 3 (6.4) | 4 (12.5) | 5 (19.2) | 0.253 |
| SBP (mmHg) | 124.87 ± 12.59 | 126.25 ± 14.04 | 127.50 ± 16.25 | 0.737 |
| TC (mmol/L) | 4.52 ± 0.76 | 4.89 ± 0.86 | 4.89 ± 0.96 | 0.097 |
| HDL-C (mmol/L) | 1.07 ± 0.20 | 1.12 ± 0.37 | 1.06 ± 0.26 | 0.637 |
| FRS% (M) | 6.3 | 10.55 | 13.1 | 0.003 |

**Table 2:** Framingham risk score of the participants by glucose exposure levels.

## Discussion

Diabetes is a leading cause of early death, heart disease, stroke, kidney disease, and blindness. Insulin resistance has an important role in pathogenesis of a number of human disorders, including type 2 diabetes mellitus, obesity, hypertension, and dyslipidemia, as extensively discussed by Matthews et al. [17]. As we all know, low HOMA-IR values indicate high insulin sensitivity, whereas high HOMA-IR values indicate low insulin sensitivity. The statistics show a high correlation between HOMA-IR and HOMA-IR (CP). A positive correlation was found between HOMA-IR (CP), the body mass index and triglyceride (TG). A negative correlation was also evident between HOMA-IR (CP) and HDL-C.

Nakamura's research suggests that increased HOMA-IR predicted subsequent cardiovascular events in non-diabetic Japanese men. Webb's research showed that fasting glucose concentration, 2h PG and HOMA-IR were independently related to cf-PWV after adjustment for age, sex, mean arterial pressure, heart rate, body mass index, renal function and antihypertensive medication. LILAC study showed, in elderly community-dwelling people, arterial stiffness measured by means of PWV predicted the occurrence of cardiovascular death beyond the prediction provided by age, gender, blood pressure and cognitive functions. The early detection of risk by chronomics allows the timely institution of prophylactic measures, thereby shifting the focus from rehabilitation to pre-habilitation medicine, as a public service to several Japanese towns. While in our study, after eliminating the effects of age, the research showed that cf-PWV differed distinctively from these three groups and it was correlative with 2h PG.

At the same time, this study shows that there are strong correlation between cf-PWV and age, systolic pressure and FIN/CP. HOMA-IR (CP) among the three groups did differ significantly (P0.05). These findings provide further evidence for increased cardiovascular risk associated with pre-diabetes and further stress the need for early screening and management of pre-diabetes. FRS was significantly correlative with 2h PG, HOMA-IR (CP) and FIN/CP and well correlated with cf-PWV. Namely, HOMA-IR (CP) and cf-PWV are positive correlation with FRS, which is predictor of cardiovascular disease. The FRS of three groups are of statistical significance and it was significantly correlative with HOMA-IR (CP) this may mean that

long-term high blood glucose levels did predict FRS. That is to say, cf-PWV has a good clinical value for indicating vascular structure and function, HOMA-IR (CP) and cf-PWV can further evaluate the 10-year risk of CVD.

## Conclusions

HOMA-IR (CP) and cf-PWV are not the same of different glucose metabolism status participants and they have good clinical values for indicating vascular structure and function. Higher blood glucose levels do predict FRS. In short, HOMA-IR (CP) and cf-PWV can be indicators for evaluating the 10-year risk of CVD.

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