# Insulin resistance and plasma triglyceride level are differently related to cardiac hypertrophy and arterial stiffening in hypertensive subjects

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**Objective:** The frequent association between the type 2 diabetes mellitus and cardio-vascular diseases suggests that metabolic factors may contribute to cardio-vascular remodeling. The aim of our study was to examine the relationships between left ventricular posterior wall thickness (LVPWT), pulse wave velocity (PWV), and the metabolic abnormalities of insulin resistance syndrome, in hypertensive patients.

**Methods:** In 227 consecutive hypertensives, we examined the relationships between LVPWT, PWV, and metabolic factors: plasma glucose, insulin, total cholesterol, high density lipoprotein (HDL)-cholesterol, triglycerides levels as well as the homeostasis model assessment of insulin resistance (HOMA). The Pearson correlation coefficient and multiple regression analysis (including age, gender, body mass index, and 24-hour systolic blood pressure) were used as statistical tests.

**Results:** In univariate analysis, glucose, HDL-cholesterol, and triglycerides levels were related to LVPWT ($r = 0.19$, $p < 0.05$; $r = -0.26$, $p < 0.001$; $r = 0.31$, $p < 0.001$, respectively); all metabolic variables, except HDL-cholesterol, correlated to PWV (plasma glucose $r = 0.25$, $p < 0.001$; total cholesterol $r = 0.22$, $p < 0.01$; triglycerides $r = 0.20$, $p < 0.01$; insulin $r = 0.19$, $p < 0.01$; HOMA $r = 0.27$; $p < 0.001$). In the multivariate model, plasma triglycerides remained correlated with LVPWT ($\beta = 0.19$, $p < 0.02$) independently of systolic blood pressure, plasma aldosterone, and normetanephrine. Only HOMA and insulin level remained associated with PWV ($\beta = 0.14$; $\beta = 0.13$ respectively, $p < 0.05$).

**Conclusions:** These data suggest that among typical metabolic abnormalities of insulin resistance syndrome, plasma triglycerides, and insulin as well as degree of insulin resistance may contribute to cardiac hypertrophy and arterial stiffening independently of hemodynamic and hormonal factors.

**Keywords:** cardiac hypertrophy, arterial stiffness, insulin resistance

## Introduction

Approximately 50% of hypertensive patients have an insulin resistance syndrome (Ginsberg 2000). It has been shown that insulin resistance is a risk factor for atherosclerosis and cardiac hypertrophy (Harano et al 1996; Devereux et al 2000). Indeed, cardiac hypertrophy is associated with insulin resistance syndrome even in the absence of hypertension (Lauer et al 1991; Grossman et al 1992; Sundstrom et al 2000a). Moreover, type 2 diabetic hypertensives have an increased left ventricular mass (LVM) when compared to non diabetic subjects, independently of age, sex, body size, and blood pressure (Palmieri et al 2001).

The results of numerous studies concerning the associations between the degree of insulin resistance and the LVM are conflicting (Davis et al 2002; Kumaran et al 2002; Galvan et al 2000; Malmqvist et al 2002). Insulin or insulin sensitivity were not related to left ventricular hypertrophy in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) substudy, Insulin CARotids US Scandinavia (ICARUS) (Olsen et al 2003). In the Framingham Heart Study, a positive relationship was reported between the degree of insulin resistance (by the homeostasis model

assessment—HOMA) and cardiac hypertrophy only in women, but this relation was largely accounted for by obesity (Rutter et al 2003). In contrast, Paolisso et al (1997) has demonstrated that in hypertensive patients insulinemia was significantly related to myocardial wall thickness but not to LVM. Another important marker of insulin resistance syndrome, hypertriglyceridemia, was also proposed as an independent predictor of LVM, but the available data relating triglyceride levels and LVM are often indirect and inconsistent (Guida et al 2001; Sundstrom et al 2000b; Palmieri et al 1999). A Swedish prospective cohort study demonstrated that, in the general population, plasma triglycerides at the age of 50 predicted the prevalence of left ventricular hypertrophy 20 years later, independently of obesity and blood pressure (Sundstrom et al 2000b).

Metabolic factors may also be involved in vascular remodeling, as suggested by the increased arterial stiffness and the higher prevalence of atherosclerosis in type 2 diabetes or in the presence of the metabolic syndrome (Devereux et al 2000; Ferreira et al 2005). In the Atherosclerosis Risk in Communities Study (ARIC) study, arterial stiffness estimated by Young's elastic modulus was associated with glucose, insulin, and triglycerides levels, in type 2 diabetic and in non diabetic subjects as well (Salomaa et al 1995). These results have not been confirmed by van Dijk et al (2003) who found only insulin-mediated glucose uptake positively associated with carotid-femoral pulse wave velocity (PWV) in diabetics.

Evidence presented in ICARUS, a LIFE substudy, has demonstrated that the level of insulin and the degree of insulin resistance were independent predictors of arterial stiffness only in never treated hypertensives (Olsen et al 2000). In hypertensive patients the increased stiffness of the carotid artery was primarily due to the increased level of blood pressure, and aortic PWV was strongly associated with cardiovascular risk (Blacher et al 1999; Bussy et al 2000).

Considering left ventricular mass and PWV as independent cardiovascular risk factors, we previously pointed to the hemodynamic and neuro-hormonal predictors of the left ventricular posterior wall thickness (LVPWT) and PWV in hypertensive patients (Legedz et al 2003). Hypertension is often associated with insulin resistance, and here our working hypothesis for the present investigation was that metabolic variables reflecting insulin resistance are additional and independent determinants of LVPWT and PWV in hypertensive subjects.

## Methods

### Cohort of patients in the study

We studied 227 patients (53.3 ±13.4 years of age; 126 men) (mean ±SD) consecutively referred to a cardiology department for a standardized hypertension work-up because of uncontrolled blood pressure and/or suspicion of secondary hypertension. The history of elevated blood pressure lasted 10 ±9.8 years (mean ±SD). At least 1 week before the hospitalization, current anti-hypertensive treatment was withdrawn and, when deemed mandatory, replaced by a calcium channel blocker and/or a $\pm\alpha_1$-adrenoceptor antagonist.

### Measurements

A 24-hour blood pressure recording was performed in all patients. Measurements were obtained every 15 min during daytime and every 30 min during night-time (Diasys monitor 200RS: Novacor, Rueil-Malmaison, France or Spacelabs device 90207, Redmond, Washington, USA). The average 24-hour measurements of systolic blood pressure was used. M-mode, two-dimensional echocardiography was performed using a VividFive (GE Medical Systems) device equipped with a 2.5 MHz mechanical transducer. Two or three measurements of LVPWT were obtained and averaged for each patient in the partial left lateral supine position, at end-diastole by the leading-edge-to-leading-edge technique. Carotid-femoral PWV, a direct measure of arterial stiffness, was measured by use of the Complior device (Colson, Garges-les-Gonesse, France) as previously described (Asmar et al 1995). An average of 25 measurements have been reported for each patient.

Blood samples for measurements of metabolic variables were obtained in the morning after an overnight recumbency, under fasting conditions. Plasma glucose was analysed by the glucose oxidase method. Plasma cholesterol and triglyceride levels were assayed using an enzymatic procedure (Dade-Behring, Liederbach, Germany). A commercial radioimmunoassay kit was used for measuring plasma immunoreactive insulin level (INS-IRMA BioSource, Camarillo, California, USA). Insulin sensitivity was calculated according to the homeostasis model assessment (HOMA), using the formula (fasting glucose in mmol/L × fasting insulin in μmol/L)/22.5 (Matthews et al 1985).

### Statistical analysis

Values are expressed as means ±SD. Plasma glucose, triglycerides, insulin, and HOMA were log-transformed prior

to statistical analysis because of an asymmetrical distribution. The relationships between LVPWT, PWV, and metabolic variables (plasma glucose, total cholesterol, high density lipoprotein (HDL)-cholesterol, triglycerides and insulin levels, and HOMA) were tested by the Pearson correlation coefficient, then by multiple linear regression analysis. The potential confounding factors: age, gender, body mass index (BMI), and systolic blood pressure (SBP) were included in multivariate model.

Plasma aldosterone and normetanephrine levels, which proved to be significantly associated with LVPWT in an earlier study (Legedz et al 2003), were also included in the multivariate model. A two-sided p value less than 0.05 was considered to indicate statistical significance. The statistical package used was STATISTICA 6.0 (Statsoft Inc, Tulsa).

## Results

Clinical and demographic characteristics of the patients are presented in Table 1. Sixteen percent of patients were treated for type 2 diabetes and 21% for dyslipidemia. Three percent of patients had angina pectoris and 1.3% presented with peripheral arterial disease of the lower limbs. A history of myocardial infarction was found in 0.9% of subjects and a history of stroke in 10.6%. Smokers of at least 5 cigarettes a day made up 17% of the population. On clinical examination, no signs of significant valvular disease or heart failure were found.

The 24-hour blood pressure reported is a recording of 60–70 measurements for each patient. A qualitatively satisfactory echocardiographic measurement of LVPWT could be obtained in 164 subjects.

In univariate analysis LVPWT was significantly correlated to BMI and SBP ($r = 0.20$, $p < 0.01$; $r = 0.37$, $p < 0.001$, respectively).

A significant correlation was found with plasma glucose, HDL-cholesterol, and triglyceride levels (Table 2). There were no relationships between insulin, total cholesterol or HOMA, and LVPWT. In multivariate analysis, among the variables mentioned above, plasma triglycerides remained independently correlated with LVPWT ($\beta = 0.22$ and $\beta = 0.18$; $p < 0.01$ when glycemia and insulinemia were included in the model, and $\beta = 0.19$; $p < 0.02$ when HOMA was included in the model), even after adjustment for other important factors determining left ventricular wall thickness such as plasma aldosterone and normetanephrine (Table 3). The independent contribution of triglycerides to LVPWT determination was estimated at 19%.

In univariate analysis, PWV which was dependent on age, BMI and SBP ($r = 0.55$, $r = 0.23$ and $r = 0.49$, respectively, with $p < 0.001$ for all), was positively associated with all metabolic variables, except plasma HDL-cholesterol level (Table 2). In multiple regression analysis, only insulin level ($\beta = 0.14$; $p < 0.04$ when total cholesterol level included in the model and $\beta = 0.13$; $p < 0.05$ when HDL-cholesterol include in the model) and HOMA ($\beta = 0.14$, $p < 0.04$ when total or HDL-cholesterol included in the model) remained independent correlates of PWV (Table 3).

**Table I** Clinical characteristics of patients included in the study

| | Number of patients | Mean ±SD |
|---|---|---|
| Age (years) (Men [n, %]) | 227 | 53.3 ± 13.4 (126 [55]) |
| Body mass index (kg/m$^2$) | 227 | 26.8 ± 4.5 |
| Systolic blood pressure (mmHg) | 227 | 155 ± 18.7 |
| Diastolic blood pressure (mmHg) | 227 | 93 ± 12.6 |
| Heart rate (bpm) | 227 | 73 ± 10.2 |
| LVPWT (mm) | 164 | 10.7 ± 2.5 |
| PWV (m/s) | 222 | 12.5 ± 3.5 |
| Total cholesterolemia (mmol/L) | 224 | 5.33 ± 0.97 |
| HDL-cholesterolemia (mmol/L) | 219 | 1.46 ± 0.46 |
| Triglyceridemia (mmol/L) | 223 | 1.23 ± 0.67 |
| Glycemia (mmol/L) | 221 | 5.25 ± 1.13 |
| Insulinemia (mU/L) | 214 | 10.01 ± 5.02 |
| HOMA | 210 | 2.4 ± 1.5 |
| Anti-hypertensive medication (n, %) | 172 (76) | |
| Lipid-lowering medication (n, %) | 47 (21) | |
| Anti-diabetic medication (n, %) | 36 (16) | |

**Note:** The number of subjects available for each measurement is given because, in some cases, measurements could not be obtained.
**Abbreviations:** LVPWT, left ventricular posterior wall thickness; PWV, carotid-femoral pulse wave velocity; HOMA, homeostasis model assessment.

**Table 2** Univariate analysis for the relationships between LVPWT, PWV and metabolic factors

|  | Chol | HDL | Trigly | Gluc | Insulin | HOMA |
|---|---|---|---|---|---|---|
| LVPWT | ns | r = −0.26<br>p < 0.001 | r = 0.31<br>p < 0.001 | r = 0.19<br>p < 0.05 | ns | ns |
| PWV | r = 0.22<br>p < 0.01 | ns | r = 0.20<br>p < 0.01 | r = 0.25<br>p < 0.001 | r = 0.19<br>p < 0.01 | r = 0.27<br>p < 0.001 |

**Abbreviations:** LVPWT, left ventricular posterior wall thickness; PWV, carotid-femoral pulse wave velocity; Gluc, plasma glucose level; Chol, plasma total cholesterol level; HDL, plasma high density lipoprotein-cholesterol level; Trigly, plasma triglycerides level; HOMA, homeostasis model assessment.

When the sample was restricted to these patients with a measurable LVPWT, similar trends were observed with regard to the relationships between PWV and HOMA (r = 0.21, p < 0.01 in univariate analysis and p = 0.06 in multivariate model). The correlation between PWV and plasma insulin level in this cohort (ie, in patients with measurable LVPWT), was still significant in univariate analysis (r = 0.17, p < 0.05) but not in multivariate model (p = 0.17).

## Discussion

In the present study we showed that plasma triglyceride levels but not insulin resistance was associated with left ventricular wall thickness independently of hemodynamic and neuro-hormonal factors in hypertensive subjects. In contrast, insulinemia and the degree of insulin resistance were associated with an impairment of arterial elasticity in addition to age and SBP.

Evidence from previous studies that were carried out in different types of populations (general population, hypertensives, diabetics, subjects at high cardiovascular risk) are inconsistent. Most of these investigations did not find any relationship between glycemia, insulinemia or degree of insulin resistance, and left ventricular mass (Malmqvist et al 2002; Olsen et al 2003; Rutter et al 2003). In contrast, lipid variables as total cholesterol, HDL-cholesterol or triglyceride levels were more frequently associated with cardiac remodeling. In the study of Schillaci et al (2001) an inverse correlation was found between HDL-cholesterol and LVM in untreated hypertensive subjects while triglyceride level showed a positive association with LVM only in univariate analysis.

An increase in plasma triglyceride level is frequently associated with concomitant decrease in HDL-cholesterol in the insulin resistance syndrome, and can represent a marker of metabolic alterations (Guida et al 2001). In our present study, even though both HDL-cholesterol and triglycerides level are related to left ventricular wall thickness in univariate analysis, only triglycerides are strongly correlated with left ventricular mass independently of other classical confounders

**Table 3** Multivariate analysis for the relationships between LVPWT, PWV and metabolic factors

|  | $R^2$ | Age | Sex | BMI | SBP | Aldo | Nadr | Gluc | Chol | Trigly | Insul |
|---|---|---|---|---|---|---|---|---|---|---|---|
| LVPWT | 0.40 | ns | ns | ns | p < 0.01<br>β = 0.24 | p < 0.01<br>β = 0.23 | p < 0.001<br>β = 0.31 | ns | ns | p < 0.01<br>β = 0.22 | ns |
| PWV | 0.47 | p < 0.001<br>β = 0.44 | ns | ns | p < 0.001<br>β = 0.39 | ns | ns | ns | ns | ns | p < 0.04<br>β = 0.14 |

|  | $R^2$ | Age | sex | BMI | SBP | Aldo | Nadr | Gluc | HDL | Trigly | Insul |
|---|---|---|---|---|---|---|---|---|---|---|---|
| LVPWT | 0.40 | ns | ns | ns | p < 0.01<br>β = 0.23 | p < 0.01<br>β = 0.21 | p < 0.001<br>β = 0.33 | ns | ns | p < 0.01<br>β = 0.18 | ns |
| PWV | 0.44 | p < 0.001<br>β = 0.44 | ns | ns | p < 0.001<br>β = 0.37 | ns | ns | ns | ns | ns | p < 0.05<br>β = 0.13 |

|  | $R^2$ | Age | sex | BMI | SBP | Aldo | Nadr | HDL | Trigly | HOMA |  |
|---|---|---|---|---|---|---|---|---|---|---|---|
| LVPWT | 0.40 | ns | ns | ns | p < 0.01<br>β = 0.23 | p < 0.01<br>β = 0.21 | p < 0.001<br>β = 0.32 | ns | p < 0.02<br>β = 0.19 | ns |  |
| PWV | 0.44 | p < 0.001<br>β = 0.43 | ns | ns | p < 0.001<br>β = 0.37 | ns | ns | ns | ns | p < 0.04<br>β = 0.14 |  |

**Abbreviations:** LVPWT, left ventricular posterior wall thickness; PWV, carotid-femoral pulse wave velocity; BMI, body mass index; SBP, systolic blood pressure; Aldo, plasma aldosterone level; Nadr, plasma metanoradrenaline level; Gluc, plasma glucose level; Chol, total plasma cholesterol level; HDL, plasma high density lipoprotein-cholesterol level; Trigly, plasma triglycerides level; HOMA, homeostasis model assessment, β, regression coefficient β evaluating the relative contribution of each predictive variable.

in multivariate analysis. These data are in agreement with results of the Sundstrom et al (2000b) longitudinal study spanning 20 years that highlighted the triglyceride level as predictor of left ventricular hypertrophy. Taken together, there is a good deal of evidence suggesting that plasma lipids are a possible link between metabolic alterations and cardiac hypertrophy. Indeed, it was demonstrated that genetic defects or pharmacological inhibition of several energy production pathways cause hypertrophic forms of cardiomyopathy (Kelly 2002). For example, fasting or pharmacological inhibition of fatty acids oxidation leads to myocardial lipid accumulation and cardiac hypertrophy in rats and in peroxisome proliferator-activated receptor α (PPARα)-null mice (Campbell et al 2002). The PPARα, a major regulator of fatty acid oxidation, may be a link between myocardial lipid metabolism and hypertrophy. PPARα activity and gene expression decrease in the pressure overloaded heart in rodent models (Sack et al 1996; Barger et al 2000). These experimental data suggest an association between a reduction in the PPARα-mediated control of myocardial lipid metabolism, an intracellular triglyceride accumulation, and the pathological cardiac hypertrophic response.

A decrease in cardiac PPARα activity is conceivable in human hypertension favoring intracellular triglyceride accumulation and hypertrophic response. The metabolic perturbations of insulin resistance syndrome leading to hypertriglyceridemia may aggravate this process. This hypothesis opens the way for a new approach to prevention or treatment of cardiac hypertrophy, and it can be speculated that fibrates, PPARα activators, and hypotriglyceridemic drugs, may be beneficial.

In the present study, we also demonstrated that, unlike LVPWT, arterial stiffness was associated with all metabolic factors in univariate analysis. After adjustment for age, sex, BMI, and SBP, only plasma fasting insulin level and the degree of insulin resistance were correlated with PWV. Other factors such as plasma glucose, total cholesterol and triglycerides levels being strongly related to age and/or BMI did not appear as significant correlates with PWV in multivariate analysis. Currently, only age and SPB are considered as independent determinants of arterial stiffness (Amar et al 2001; Mackey et al 2002). The present study pointed to the weak but significantly independent participation of insulin level and degree of insulin resistance in arterial stiffness determination. This is in agreement with data of ICARUS, a LIFE sub-study, undertaken in similar population of hypertensive subjects (Olsen et al 2000). These results are consistent with the fact that (1) type 2 diabetes is

an important risk factor for atherosclerotic diseases and (2) even strict glycemic control in type 2 diabetics does not improve cardiovascular mortality due to macroangiopathy (UKPDS Group 1998). In contrast, an improvement in glucose tolerance with angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor antagonists, results in reduction of cardiovascular risk in hypertensive and/or diabetic subjects (HOPE Study Investigators 2000) as well as in decrease in arterial stiffness (LIFE study). These results also suggest that in our hypertensive, only moderately insulino-resistant (HOMA = 2.4) patients, the degree of insulin resistance could influence arterial stiffening. Thus, an improvement of insulin resistance state and a decrease in plasma insulin level may be very important for the reduction of arterial stiffening, in addition to blood pressure control, even in non diabetic hypertensives.

At the cellular and molecular levels, our results are supported by the fact that insulin has demonstrated proliferative effects on cultured vascular smooth muscle cells; it also enhances lipid synthesis and low density lipoprotein binding to these cells as well as connective tissue synthesis in arterial wall (Stout 1992; Bouguerra et al 2001).

Accordingly, these data suggest that among typical metabolic abnormalities of insulin resistance syndrome, plasma triglycerides and insulin may contribute to the increased cardiovascular risk, and could represent targets for prevention and/or treatment of cardiac hypertrophy and arterial stiffening, in hypertensive subjects. The dissociation between triglyceride on one hand, and insulin and insulin resistance on the other hand, as possible determinants of cardiac hypertrophy and vascular stiffening may also help in individualizing therapeutic approaches in hypertensive patients.

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