# Relationship Between Endothelin-1 Concentration and Metabolic Alterations Typical of the Insulin Resistance Syndrome

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**The purpose of the study was to examine the relationship between the endothelin-1 (ET-1) concentration and the metabolic variables characteristic of the insulin resistance syndrome ([IRS] hyperinsulinemia, insulin resistance, hypertriglyceridemia, low high-density lipoprotein [HDL] cholesterol, visceral obesity, and glycemic abnormalities). The measurement of circulating ET-1 is a well-recognized marker of endothelial atherosclerotic and cardiovascular disease. Two hundred subjects were divided into 3 groups. Group 1 included 50 subjects with impaired glucose tolerance (IGT) or non–insulin-dependent diabetes mellitus (NIDDM) with IRS. Group 2 included 50 subjects with IGT or NIDDM without IRS. Group 3 included 100 normal subjects as controls. ET-1 levels were higher in group 1 versus groups 2 and 3 in women (11.2 ± 0.7 *v* 7.9 ± 0.5 and 6.6 ± 0.4 pg/mL, $P < .01$) and men (10.1 ± 0.6 *v* 6.5 ± 0.8 and 7.2 ± 0.3 pg/mL, $P < .01$). No differences were found between groups 2 and 3. With simple regression analysis, ET-1 levels significantly correlated with insulin, glycosylated hemoglobin, body weight, waist to hip ratio, and triglyceride values. However, with multiple regression analysis, only triglycerides ($P < .009$) and glycosylated hemoglobin ($P < .001$) remained independently correlated with ET-1. In conclusion, this cross-sectional study indicates that glycosylated hemoglobin and triglycerides are independently correlated with ET-1 levels in patients with IRS.**


RECENT STUDIES have shown that endothelin-1 (ET-1), a peptide with potent and characteristically sustained vasoconstrictor actions,[1] is implicated in the proliferation of vascular smooth muscle cells[2] and can determine hypertension and cardiovascular disease.[3] An increase in ET-1 has been described in a variety of pathological conditions including essential hypertension,[4] ischemic heart disease,[5] atherosclerosis,[6] diabetes mellitus,[7] and obesity.[8] In addition, ET-1 actively participates in the infarction size-evolution of the ischemic heart,[9] and the plasma ET-1 level is an independent predictor of 1-year mortality after acute myocardial infarction.[10] Therefore, it is possible to consider the measurement of ET-1 as a marker of endothelial damage and a negative prognostic predictor of cardiovascular disease.[11]

Elevated insulin levels have been previously reported as the most important determinant in the evolution of cardiovascular disease among the cluster of metabolic alterations typical of insulin resistance syndrome (IRS).[12] In a previous study, we reported that subjects with IRS had higher ET-1 levels than normal controls. In addition, we were able to reproduce similar ET-1 levels in normal subjects by a simultaneous and acute increase of insulin and triglyceride levels.[13] The results were interesting but preliminary data obtained in a small number of patients.

The purpose of the present study was to examine the relationships between the ET-1 concentration and the metabolic variables characteristic of IRS in a larger cohort of patients. The study evaluates whether elevated ET-1 levels were already present in subjects with impaired glucose tolerance (IGT) in the absence of overt diabetes and whether a different pattern was present in men and women.

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## SUBJECTS AND METHODS

### *Subjects*

All subjects provided informed consent to participate in the study, and the protocol was approved by the local Ethics Committee. IRS was defined according to Alberti et al,[14] with at least 3 of the following alterations present together with IGT or non–insulin-dependent diabetes mellitus (NIDDM): hyperinsulinemia (>2 SD from the mean of our normal population, ie, >16.3 μU/mL), insulin resistance (homeostasis model assessment [HOMA] index >3.94), hypertriglyceridemia (>1.7 mmol/L), low high-density lipoprotein (HDL) cholesterol (<0.9 mmol/L in men and <1.0 mmol/L in women), visceral obesity (waist to hip ratio in men >0.9 and in women >0.85), and body mass index (BMI) greater than 30 kg/m$^2$. The diagnosis of IGT was made after a standard oral glucose tolerance test ([OGTT] 75 g) according to World Health Organization criteria. Two hundred subjects were studied, divided among 3 groups (Table 1). Group 1 included 50 subjects with IGT (n = 11) or NIDDM (n = 39; mean duration of NIDDM, 7.8 ± 2.3 years) with IRS. Group 2 included 50 subjects with IGT (n = 11) or NIDDM (n = 39; mean disease duration, 8.6 ± 1.7 years) without IRS. Both groups of NIDDM patients were treated with diet alone. NIDDM was also defined by the absence of islet-cell antibody and anti-glutamic acid decarboxylase (anti-GAD) antibodies and a positive intravenous glucagon test. Group 3 included 100 normal subjects. None of the subjects were on chronic medication.

All subjects had normal systolic and diastolic blood pressure, and none had hypertension and/or ischemic heart disease. Their resting electrocardiogram was normal. In diabetic patients, no significant complications were present, except for background retinopathy and microalbuminuria in 28 subjects (16 in group 1 and 12 in group 2). Diabetic complications were defined as proliferative retinopathy as evidenced by fluorangiography, peripheral vascular disease determined by intermittent claudication and Doppler ultrasound echography, and neuropathy evaluated by electromyography. In addition, subjects in the 3 groups were comparable for their history of cigarette-smoking, alcohol intake, and physical activity. Menopause was present in the same percentage of women in the 3 groups (27%, 33%, and 25%, respectively, nonsignificant [NS]). None of them were using estrogen supplements. In fertile women, estradiol-17β levels were similar among the 3 groups (125.0 ± 5.4, 129.0 ± 5.6, and 130 ± 7.8 pmol/L, respectively).

**Table 1. Clinical and Metabolic Characteristics of the Subjects**

| Characteristic | Women | | | Men | | |
|---|---|---|---|---|---|---|
| | Group 1 (n = 21) | Group 2 (n = 28) | Group 3 (n = 51) | Group 1 (n = 29) | Group 2 (n = 22) | Group 3 (n = 49) |
| NIDDM patients (n) | 15 | 21 | | 25 | 18 | |
| IGT patients (n) | 6 | 7 | | 5 | 4 | |
| Age (yr) | 47.9 ± 1.2 | 48.6 ± 1.8 | 48.9 ± 1.2 | 51.4 ± 1.7 | 52.2 ± 2.1 | 53.1 ± 1.0 |
| Weight (kg) | 72.4 ± 1.8* | 64.0 ± 2.1 | 62.5 ± 1.3 | 80.1 ± 1.8* | 72.4 ± 2.3 | 72.0 ± 1.0 |
| BMI (kg/m$^2$) | 28.5 ± 0.5* | 25.7 ± 0.9 | 25.0 ± 0.5 | 27.2 ± 0.6* | 25.1 ± 0.6 | 24.6 ± 0.4 |
| Waist to hip ratio | 0.93 ± 0.02* | 0.96 ± 0.01 | 0.85 ± 0.01 | 1.00 ± 0.01* | 0.94 ± 0.01 | 0.91 ± 0.01 |
| Blood pressure (mm Hg) | | | | | | |
| Systolic | 140 ± 2* | 132 ± 2 | 129 ± 2 | 138 ± 2 | 130 ± 2 | 128 ± 2 |
| Diastolic | 89 ± 2* | 80 ± 1 | 81 ± 1 | 86 ± 1 | 82 ± 1 | 80 ± 1 |
| Glucose (mmol/L) | | | | | | |
| Basal | 8.2 ± 0.6† | 8.1 ± 0.5† | 5.7 ± 0.1 | 9.1 ± 0.7† | 8.5 ± 0.6† | 5.6 ± 0.1 |
| 2 h after OGTT‡ | 9.5 ± 0.5† | 9.8 ± 0.5† | 6.2 ± 0.2 | 10.2 ± 1.0† | 9.6 ± 0.7† | 6.0 ± 0.2 |
| Insulin (μU/mL) | | | | | | |
| Basal | 16.6 ± 1.0* | 6.0 ± 0.4† | 5.7 ± 0.4 | 11.8 ± 1.0* | 7.1 ± 0.6 | 7.4 ± 0.5 |
| 2 h after OGTT‡ | 114.0 ± 19.0* | 37.8 ± 7.6 | 32.3 ± 3.5 | 73.9 ± 16.8† | 67.8 ± 27.5† | 36.0 ± 4.2 |
| Glycosylated hemoglobin (%) | 6.9 ± 0.3† | 7.3 ± 0.2† | 5.2 ± 0.1 | 7.1 ± 0.2† | 7.1 ± 0.3† | 5.2 ± 0.1 |
| Triglycerides (mmol/L) | 3.8 ± 0.5* | 1.3 ± 0.1 | 1.1 ± 0.1 | 4.2 ± 0.6* | 1.3 ± 0.1 | 1.1 ± 0.1 |
| Cholesterol (mmol/L) | 6.2 ± 0.4 | 5.9 ± 0.3 | 5.8 ± 0.2 | 5.9 ± 0.2 | 5.3 ± 0.3 | 5.6 ± 0.2 |
| HDL cholesterol (mmol/L) | 1.2 ± 0.1* | 1.4 ± 0.1 | 1.5 ± 0.1 | 1.1 ± 0.7 | 1.2 ± 0.1 | 1.2 ± 0.1 |
| HOMA index | 6.1 ± 0.6* | 2.1 ± 0.2 | 1.5 ± 0.1 | 4.7 ± 0.5* | 2.5 ± 0.2 | 1.9 ± 0.1 |
| Creatinine (mg/dL) | 0.75 ± 0.05 | 0.83 ± 0.05 | 0.83 ± 0.03 | 0.91 ± 0.04 | 1.03 ± 0.04 | 0.96 ± 0.02 |

NOTE. Group 1, subjects with IGT or NIDDM associated with IRS; group 2, subjects with IGT or NIDDM without IRS; group 3, normal subjects.
*$P < .05$ *v* groups 2 and 3.
†$P < .05$ *v* group 3.
‡Nondiabetic subjects.

*Protocol and Laboratory Methods*

Samples for all hormonal and metabolic variables were obtained after the subjects rested at least 15 minutes in the supine position in the morning after an overnight fast. Blood pressure was taken in the recumbent position after 10 minutes of rest, using a random-zero sphygmomanometer. Insulin resistance was calculated from fasting blood glucose and insulin levels using the HOMA mathematical model proposed by Matthews et al,[15] and currently used in epidemiological studies.[16]

Plasma glucose, serum triglyceride, and serum total and HDL cholesterol levels were measured using automated enzymatic spectrophotometric techniques adapted to a Cobas Fara II instrument (Roche, Basel, Switzerland). Serum insulin levels were measured with a Microparticle Enzyme Immunoassay (IMX; Abbott Laboratories, Chicago, IL) in which the lowest insulin sensitivity was 1 μU/mL. The cross-reactivity of this kit with proinsulin was less than 2%. ET-1 samples were measured with a commercial radioimmunoassay kit (Du Pont de Nemours, Boston, MA) as previously reported.[13]

*Statistical Analysis*

Results are expressed as the mean ± SEM. Comparisons among groups were performed using 1-way ANOVA followed by the Scheffe F test when appropriate. Simple and multiple regression analysis was performed with ET-1 as the dependent variable and all other parameters as independent variables. Triglyceride levels were logarithmically transformed to correct for skewness, and these variables were then back-transformed to their natural units for presentation in the tables.

## RESULTS

Baseline characteristics of the 3 groups appear in Table 1. Men and women with IRS (group 1) had significantly higher body weight, BMI, waist to hip ratio, systolic and diastolic blood pressure, HOMA index, fasting insulin, and triglycerides compared with groups 2 and 3. On the contrary, the body weight, BMI, waist to hip ratio, systolic and diastolic blood pressure, HOMA index, fasting insulin, triglycerides, cholesterol, and HDL cholesterol were similar in groups 2 and 3, suggesting that the 2 groups only differed by plasma glucose levels.

ET-1 levels were higher in group 1 versus groups 2 and 3 in women (11.2 ± 0.7 *v* 7.9 ± 0.5 and 6.6 ± 0.4 pg/mL, $P < .01$; NS between group 1 and group 2) and men (10.1 ± 0.6 *v* 6.5 ± 0.8 and 7.2 ± 0.3 pg/mL, $P < .01$; NS between group 1 and group 2) (Fig 1). A significant increase of ET-1 was still present in subjects with IRS when considering only subjects with IGT in groups 1 and 2 (9.32 ± 1.24 *v* 5.46 ± 0.61 pg/mL, $P < .02$). A simple regression analysis was performed after grouping all study subjects, with ET-1 as the dependent variable and the other parameters as independent variables. ET-1 levels were positively correlated with all variables present in IRS such as insulin (slope = 0.190, $P < .0001$), HOMA index (slope = 0.536, $P < .0001$), triglycerides (slope = 1.987, $P < .0001$), body weight (slope = 0.060, $P < .004$), BMI (slope = 0.155, $P < .02$), and waist to hip ratio (slope = 10.26, $P < .02$). In addition, ET-1 levels were significantly correlated with systolic (slope = 0.070, $P < .0002$) and diastolic (slope = 0.099, $P < .002$) blood pressure, glucose (slope = 0.330, $P < .0001$), and glycosylated hemoglobin (slope = 0.810, $P < .0001$) (Fig 2).

A multiple regression analysis to assess the independent effect of gender, group, and all other variables on ET-1 was also performed. Triglyceride and glycosylated hemoglobin levels

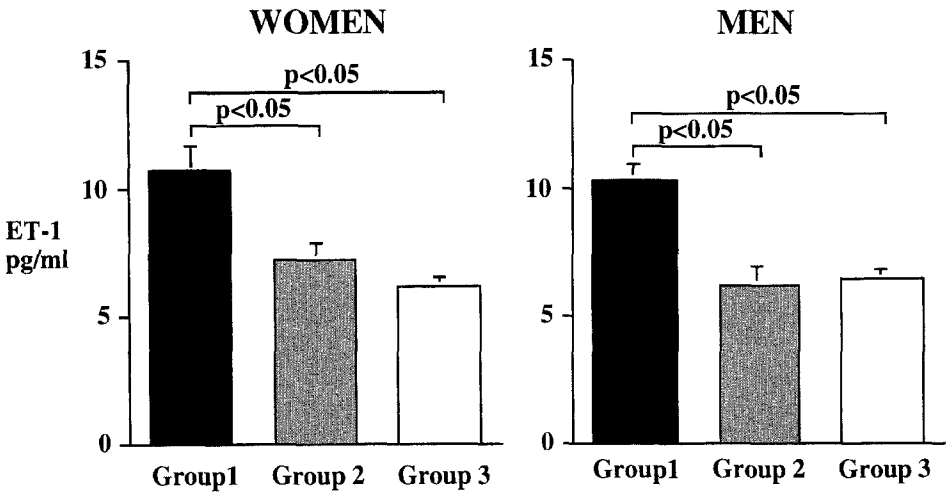


**Fig 1. ET-1 levels in the 3 study groups. Group 1, subjects with IGT or NIDDM associated with IRS; group 2, subjects with IGT or NIDDM without IRS; group 3, normal subjects.**

remained independently correlated with ET-1 ($\beta = 1.141$, $P < .009$ and $\beta = 0.843$, $P < .001$, respectively). In addition, ET-1 levels were also independently correlated with group status ($\beta = -0.677$, $P < .05$) as expected (Table 2). Adjusted mean ET-1 levels in the 3 groups were 9.29 ± 0.62, 7.24 ± 0.42, and 7.56 ± 0.44 pg/mL, respectively ($P < .05$ for group 1 *v* groups 2 and 3).

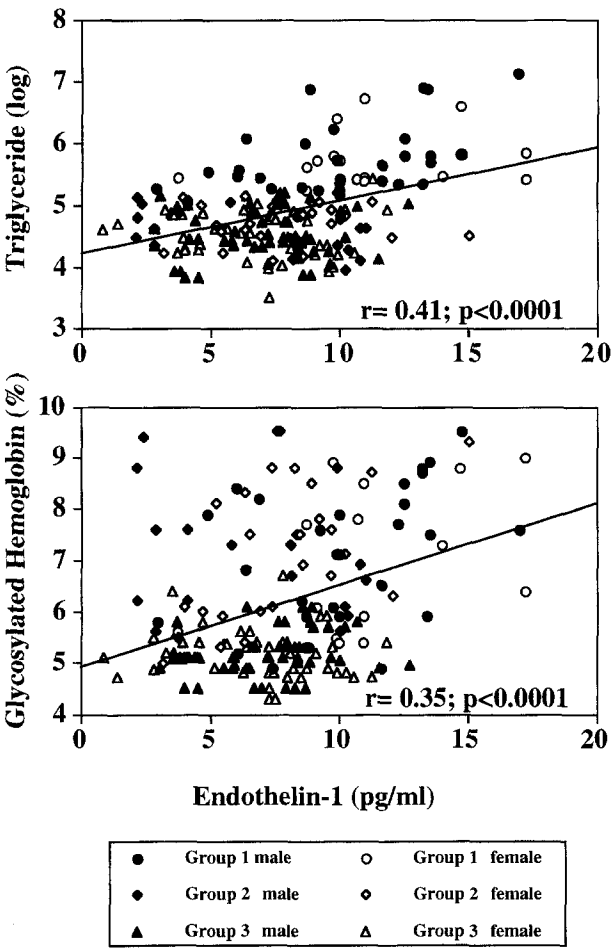


**Fig 2. Relationship between ET-1 and triglyceride (logarithmically transformed) and between ET-1 and glycosylated hemoglobin levels.**

## DISCUSSION

The present study confirms in a large group of subjects that ET-1 levels are increased in IRS. Moreover, there are some novel aspects that need to be underlined. First of all, in the group with IRS, ET-1 levels were 5% higher in women than in men, while the opposite trend was found in the group of normal controls, in whom ET-1 levels were 10% lower in women than in men, as previously published.[17] These data could partly explain why diabetic women show the well-recognized loss of protection against coronary disease.[18] This result may be especially meaningful since the majority of cardiovascular events occur in NIDDM women around age 50,[19] when they show a 4-fold increase in the risk of coronary heart disease as compared with the 2-fold increased risk in men with NIDDM. Moreover, higher ET-1 concentrations were found in subjects with IGT and IRS but not in subjects with IGT in the absence of IRS. This is a very interesting result, since overt diabetes was

**Table 2. Multiple Regression Analysis With ET-1 as the Dependent Variable**

| Variable | β Coefficient | F Ratio | Probability (P<) |
|---|---|---|---|
| Gender | −0.736 | 1.436 | .232 |
| Group | −0.677 | 3.872 | .05 |
| Age | −0.010 | 0.146 | .703 |
| Body weight | 0.052 | 2.024 | .157 |
| BMI | −0.091 | 0.715 | .399 |
| Systolic blood pressure | 0.016 | 0.558 | .456 |
| Diastolic blood pressure | 0.023 | 0.364 | .547 |
| Waist to hip ratio | 4.291 | 1.481 | .225 |
| Log serum triglycerides | 1.141 | 6.930 | .009 |
| Serum insulin | −0.156 | 1.794 | .182 |
| HOMA index | 0.518 | 2.717 | .101 |
| Plasma glucose | −0.211 | 1.355 | .246 |
| Glycosylated hemoglobin | 0.843 | 11.619 | .001 |
| Serum cholesterol | −0.007 | 1.914 | .168 |
| Serum HDL cholesterol | 0.021 | 2.380 | .125 |
| Creatinine | −0.657 | 0.367 | .545 |

not necessary for the increase of ET-1 levels. However, more studies are needed to draw definitive conclusions.

Another novel aspect of the study is that a strong relationship between triglycerides and ET-1 was maintained in our sample independently of HDL cholesterol and total cholesterol levels. For many years, hypertriglyceridemia was considered a marker of cardiovascular disease only in certain subjects such as women[19,20] and patients with NIDDM.[21] The association between triglycerides, independently of HDL cholesterol levels, and definite cardiovascular disease such as myocardial infarction or angina was found in some studies[19] but not in others, in which the simultaneous association of high triglycerides and low HDL cholesterol was necessary to predict cardiovascular risk.[22] This apparent discrepancy is probably related to the fact that it is difficult to match for the duration and degree of cardiovascular disease in different populations and, when cardiovascular disease is established, some factors may have lost their primary pathogenic significance. In this respect, our study is of particular significance, since we tried to define independent predictors of endothelial damage in patients with IRS but without a history of overt cardiovascular disease.

The mechanism by which high triglyceride levels could interfere with the production of endothelial factors is not completely elucidated, although it is well known that intermediate-density lipoprotein remnants may be atherogenic.[23] In addition, hypertriglyceridemia increases monocyte binding to endothelial cells,[24] and purified very–low-density lipoprotein (VLDL) from hypertriglyceridemic patients stimulates plasminogen activator inhibitor 1 release by endothelial cells.[25] Both of these effects are considered early events in the development of atherosclerotic lesions. However, further studies are necessary to better understand the real effect of triglycerides on endothelial cells. The use of glycosylated hemoglobin, an index of long-term glycemic control, as an independent predictor of ET-1 levels is in agreement with previous studies in which hyperglycemia was related to an alteration in endothelial function.[26] In Fig 2, $r$ values of .41 and .35 are reported for the correlation between ET-1 and triglyceride and glycosylated hemoglobin. These relatively weak correlations are probably related to the relatively small sample size of the groups. More extensive epidemiological studies are mandatory to define the biological significance of our results.

We found that insulin levels and insulin resistance are significantly correlated with ET-1 levels, although we did not find that insulin was an independent variable in increasing ET-1. This result does not reduce the importance of insulin in the evolution of cardiovascular disease in the cluster of metabolic alterations of IRS.[13] Taking all of the results together, it is possible to speculate that in subjects with IRS, hyperinsulinemia increases free fatty acid availability and hepatic VLDL-triglyceride secretion, inducing hypertriglyceridemia, which may further decrease insulin sensitivity[27] and increase the production of endothelial factors such as ET-1, which probably adversely affect the evolution of cardiovascular disease.

In conclusion, our data suggest that in subjects with IRS, it is important not only to decrease insulin resistance and blood glucose but also to normalize all other components of the syndrome, such as triglyceride levels, in order to decrease ET-1. With this in mind, therapeutic strategies to increase insulin sensitivity and to normalize lipid metabolism, as well as strategies focused on each separately, can offer benefits in our struggle to reduce atherosclerotic and cardiovascular disease in patients with IRS. In this context, large trials aimed at evaluating the cause-and-effect relationship between the ET-1 level and the metabolic variables typical of IRS and the prognostic impact of increased ET-1 in these patients should be implemented.

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