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Research Article

# Correlation Between the Levels of Circulating Adipokines, the Adiponectin/Resistin Index, with Circulating Adhesion Molecules in Normotensive Type-2 Diabetic Patients

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## Abstract

**Background:** Hypoadiponectinemia and hyperresistinemia are associated with endothelial dysfunction. Endothelial dysfunction is a common feature in type-2 diabetic patients and is associated with inflammation.

**Objective:** To evaluate the correlation between adipokine levels, with soluble adhesion molecules in normotensive type-2 diabetic patients.

**Methods:** Serum levels of adiponectin, resistin, VCAM-1, ICAM-1 and E-selectin were measured by ELISA in 30 type-2 diabetic normotensive patients. The relationship between adipokine levels and the adiponectin/resistin index with the circulating adhesion molecules levels were assessed by the Pearson correlation coefficient test.

**Results:** We did not find correlation between soluble adhesion molecules with resistin nor with adiponectin levels. However we found a significantly correlation between ICAM and the adiponectin/resistin index ($R = 0.428$, $p < 0.023$).

**Conclusion:** Our results shown that the adiponectin/resistin index seems to be more strongly associated with inflammation than adipokine levels, and may be used as a reliable marker of endothelial dysfunction in type-2 diabetic normotensive patients.

***Keywords:*** *Adiponectin; Resistin; Adiponectin/Resistin Index; Soluble Adhesion Molecules; Type 2 Diabetes*

## Introduction

Endothelial dysfunction is a common feature in diabetes mellitus and leads to atherosclerosis, the major cause of death in subjects with diabetes [1].

Adiponectin and resistin were first described as adipocyte-secreted hormones (adipokines) that modulate insulin action; both hypoadiponectinemia and hyperresistinemia are associated with the coexistence of type-2 diabetes [2]. Hypoadiponectinemia has been reported as a risk factor for the development of cardiovascular disease [3], whereas in humans, resistin is involved in the pathways that lead to atherosclerosis [4]. We have shown that adiponectin/resistin index (ARI) has a strong correlation with the carotid intima-media thickness (CIMT) [5].

Leukocytes are unable to adhere to normally functioning arterial endothelium; however, in the setting of endothelial dysfunction, the bioavailability of nitric oxide is reduced, resulting in the activation of nuclear factor κB (NFκB). NFκB increases systemic concentrations of soluble forms of adhesion molecules (SAM). Circulating levels of SAM are thought to reflect increased endothelial cell surface expression and high serum levels of SAM are markers of endothelial dysfunction. We have shown that SAMs are associated with the development of the atherosclerotic plaque, perhaps by facilitating the attachment and migration of leukocytes into the arterial wall [6].

The aim of this study was to evaluate if there is a correlation between the circulating levels of adipokines, the adiponectin/resistin index, with circulating adhesion molecules levels in normotensive type-2 diabetic patients.

## Materials and Methods

A total of 30 normotensive patients with type-2 diabetes mellitus (> 12 months), who were thiazolidinedione-naive, statin-naive and ACE/ARB-naïve, were included in this study. The diagnosis of type-2 diabetes was performed according to the American Diabetes Association criteria [7].

In all of them, VCAM-1, ICAM-1 and E-selectin circulating levels were measured in duplicate by commercial ELISA kits (R and D Systems, Minneapolis, MN). All venous samples were collected in the morning after a 12-h overnight fast. Intra-assay precision (precision within an assay) was 3.1 for VCAM-1, 4.1 for ICAM-1, and 3.8 for E-selectin, whereas inter-assay precision (precision between assays) was 7 for VCAM-1, 7.3 for E-selectin and 7.4 for ICAM-1. Also, fasting glycaemia (glycose oxidase) and HbA1c were measured from those samples.

Also, adiponectin and resistin circulating levels were measured in duplicate by commercial ELISA kits (R&D Systems, Minneapolis, MN). All venous samples were collected in the morning after a 12-h overnight fast. Also, fasting glycaemia (glucose oxidase) and HbA1c were measured from those samples. Intra-assay coefficient of variability (CV) for adiponectin was 3.4%, and inter-assay CV was 5.8%. Whereas intra-assay CV for resistin was 5.5%, and inter-assay CV was 9.2%.

The ARI was estimated using the following formula (1+log10 Resistin-log10 adiponectin), as described by Lau [5].

Patients with any of the following diagnoses were excluded from the study: Decompensated diabetes mellitus (fasting blood glucose > 250 mg/dl); heart, hepatic, or renal failure; evidence of valvular heart disease; heart block or cardiac arrhythmia; acute coronary syndrome or cerebrovascular disease six months before the study's initiation; autoimmune disease; pregnancy; urinary tract infection; fever; or a history of alcohol abuse and/or psychotropic drugs.

### Statistical Analysis

Data are presented as the mean ± standard deviation. The relationship between the levels of adipokines and SAMs was assessed by the Pearson correlation coefficient test.

The study was conducted with the approval of the Research and Medical Ethics Committee of our hospital, in accordance with the Helsinki declaration. Participants provided informed, written consent before their inclusion in the study protocol.

## Results

Baseline patient characteristics are depicted in table 1.

| | |
|---|---|
| Age | 58 ± 10.2 |
| Gender (M/F) | 13/17 |
| Glycemia (mmol/L) | 7.51 ± 1.39 |
| Hb A1c | 6 ± 0.4 |
| Low Density Lipoproteins (mmol/L) | 3.32 ± 0.83 |
| Triglycerides (mmol/L) | 2.04 ± 0.26 |
| Body Mass Index (Kg/m$^2$) | 30.4 ± 5.1 |
| Blood pressure (mm Hg) | 124 ± 9 / 74 ± 4 |
| History of type-2 diabetes | 8.48 years |

***Table 1:*** *Basal Characteristic of Patients.*

Circulating levels of SAM were: VCAM-1, 824.3 ± 99 ng/ml; ICAM-1, 277.6 ± 46 ng/ml; and E-selectin, 68.4 ± 13 ng/ml.

Resistin levels were 16.7 ng/ml, and adiponectin levels 7.5 µg/ml.

We were unable to demonstrate any relationship between SAMs and adiponectin levels (VCAM r = -0.12, ICAM r = -0.05, e selectin r = -0.06. $p > 0.05$), nor with resistin (ICAM r = 0.19, e-selectin r = 0.1, VCAM r = 0.21 $p > 0.05$).

We did not find correlation between the ARI with VCAM (r = 0.11, nor with e-selectin r = 0.17, $p > 0.05$), However, we found a significantly correlation between the ARI with ICAM-1 (r = 0.428, $p = 0.023$), figure 1.

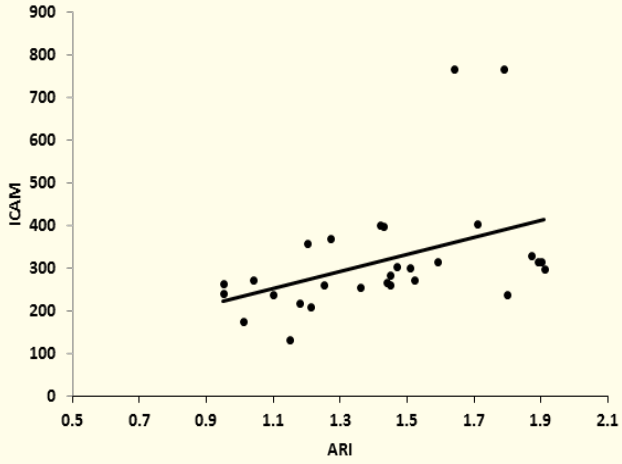


***Figure 1:*** *Correlation between the adiponectin/resistin index and ICAM levels.*

## Discussion

In this study, the ARI significantly correlated with serum ICAM levels in type-2 diabetic patients, whereas no significant association was observed for adiponectin and resistin. Interestingly, we have previously found that both, the ARI and circulating ICAM levels correlated with the CIMT in type-2 diabetic patients [5,6]. It is important to remark that our patients were thiazolidinedione-naive, statin-naïve and ACE/ARB-naïve. All of these drugs have been shown to reduce circulating levels of SAM and modify circulating adipokines [5,6].

Several studies had shown an inverse relation between adiponectin and the development of inflammation and vascular damage [3], this fact explain the inverse (although non-significantly) association between adiponectin and circulating SAMs levels.

Resistin has not only been associated with insulin resistance and metabolic syndrome, this adipokine impairs endothelial function and has proinflammatory effects, and is involved in atherosclerosis and cardiovascular disease too [4]. Due to Its effects on inflammation, it is expected that the levels of resistin correlate with circulating SAM levels, although in our study that correlation did not reached significance.

The ARI was described by Lau as a marker more strongly associated with the metabolic syndrome components than the adipokines levels, as adiponectin is reported in micrograms and resistin in nanograms, the formula uses logarithms for normalization [8].

Resistin has proinflammatory actions and adiponectin anti-inflammatory properties; changes in the relative proportion of both adipokines might effect distinct inflammatory manifestations than would adiponectin or resistin alone. Then, it is reasonable that the ARI, which include information about the circulating levels of both adipokines, may be a more sensitive and reliable marker of inflammation than the values of resistin or adiponectin alone. Our results appeared to support this idea. Interestingly the ARI -which is associated with atherosclerosis [5] correlated only with ICAM, which is also associated with atherosclerosis [6], this finding requires further studies.

## Conclusion

In conclusion, our results suggest that the ARI may be a clinical marker associated with vascular inflammation in normotensive type-2 diabetic patients; ARI seems to be more strongly associated with inflammation than adipokine levels alone.

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