

## Adiponectin and Some Inflammatory and Endothelial Markers in Type - 2 Diabetes with and without Cardiovascular Disease

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This study was designed to examine the association between adiponectin and C-reactive protein (CRP), interleukin-6 (IL-6) and endothelin-1, (ET-1) and their possible role in prediction of type-2 diabetes and development of diabetes and macrovascular complications. Forty subjects were studied. They were classified into four equal groups: Control, newly diagnosed type-2 diabetes, diabetics with old myocardial infarction (OMI) and acute myocardial infarction (AMI) groups. They were matched for body mass index (BMI), age, and sex. Adiponectin and IL-6 were determined by ELISA technique, CRP was determined by immunonephelometry and ET-1 was determined by radioimmunoassay. Adiponectin was found to be decreased in newly diagnosed diabetics ( $6.64 \pm 2.3 \mu\text{g} / \text{ml}$ ), OMI ( $4.7 \pm 1.05 \mu\text{g} / \text{ml}$ ) and AMI ( $4.23 \pm 0.73 \mu\text{g} / \text{ml}$ ) when compared to controls ( $9.81 \pm 2.2 \mu\text{g} / \text{ml}$ ), whereas CRP, IL-6 and ET-1 were significantly elevated in AMI ( $18.6 \pm 5.3 \text{mg} / \text{l}$ ,  $12.6 \pm 4.2 \text{pg} / \text{ml}$  and  $36.8 \pm 10.4 \text{fmol} / \text{ml}$ , respectively). The changes were marked in AMI group compared to other diabetic groups. Only adiponectin significantly decreased in newly diagnosed type-2 diabetics, but CRP, IL-6 and ET-1 did not significantly altered in newly diagnosed diabetics ( $4.9 \pm 1.6 \text{mg} / \text{l}$ ,  $6.9 \pm 2.3 \text{pg} / \text{ml}$  and  $22.1 \pm 8.6 \text{fmol} / \text{ml}$ , respectively) compared to control. Adiponectin correlated negatively with CRP, IL-6 and ET-1, BMI and HbA1c, whereas inflammatory and vascular markers correlated positively with each other and with BMI and HbA1c. In conclusions, adiponectin may be implicated in the development of type-2 diabetes and macrovascular complications and can be used as an early predictor of type-2 diabetes. Whereas, none of the inflammatory and vascular markers can predict diabetes, but can be used as markers of acute vascular events and in follow up of these cases. Immunomodulation of adiponectin may help prevention and treatment of type-2 diabetes and its complications.

Chronic inflammation has been postulated to play a role in the pathogenesis of type-2 diabetes (Pickup and Crook 1998). Cross-sectional studies have shown that obesity and insulin resistance are associated with higher levels of markers of inflammation and endothelial function (Visser et al., 1999, Hak et al., 1999, Roytblat et al., 2000, Vozarova et al., 2001 and Weyer et al., 2002). Recent prospective studies have shown a relationship between various inflammatory markers, specifically C-reactive protein (CRP), and interleukin (IL)-6, and the risk of developing type 2 diabetes (Schmidt et al., 1999, Pradhan et al., 2001, Barzilay et al., 2001 and Freeman et al., 2002). Adiponectin is a 244 amino acid adipose-specific protein “adipocyte-derived

hormone” (Nakano et al., 1996) that has been shown to downregulate inflammatory responses (Ouchi et al., 1999 and Yokota et al., 2000), but it also improves glucose tolerance and insulin resistance in mouse models of diabetes (Yamauchi et al., 2001). It is best known for its insulin-sensitizing ability (Clarke et al., 2003). Adiponectin is related to insulin resistance and adiposity in humans (Arita et al., 1999 and Weyer et al., 2001). Recently, it has been shown that adiponectin is protective against later development of diabetes (Lindsay et al., 2002).

Endothelin-1 (ET-1) is a potent vasoconstrictor peptide whose levels are elevated in numerous disease states, including obesity and diabetes. ET-1 has profound effects on adipose tissue metabolism and

alters the release of adipose-derived factors such as leptin, resistin and adiponectin secretion (Clarke et al., 2003). It has been hypothesized that adiponectin might underpin relationships of markers of inflammation, endothelial dysfunction, and obesity and later risk of type-2 diabetes (Lindsay et al., 2002). Therefore this study was carried out to investigate the relationship of adiponectin to some markers of inflammation (CRP and IL-6) and endothelial dysfunction reflected by ET-1 and to assess the relationship of these markers to the pathogenesis of diabetes and macroangiopathy in type-2 diabetes.

## Subjects and Methods

Forty subjects were involved in the study, they were classified into four equal groups: Group I, included 10 (5 male and 5 female) apparently healthy volunteers served as control group, their mean age was  $50.0 \pm 2.8$  years. They were selected from those attended a routine health check or hospital staff. Group II, comprised 10 newly diagnosed type-2 diabetes mellitus patients (5 male and 5 female), with mean age  $49.6 \pm 3.3$  years. Type-2 diabetes mellitus was diagnosed according to the criteria of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1997). Group III, involved 10 (5 male and 5 female) type-2 diabetics suffering from acute myocardial infarction (AMI), their mean age was  $52.3 \pm 5.2$  years. AMI was diagnosed by the occurrence of chest pain lasting  $>20$  minutes not relieved by sublingual nitroglycerine, characteristic ECG alterations (elevated ST-segment at least 2mm and/or Q waves) and plasma CPK more than twice the upper limit of normal and LDH elevation (Antiman and Braunwald 1997). Group IV, included 10 (5 male and 5 female) patients suffering from old myocardial infarction (OMI) more than 3 months associated with characteristic ECG changes (Gersh et al., 1997), their mean age was  $51.8 \pm 4.1$  years. Patients were selected from Coronary Intensive Care Unit, Cardiology Department, Zagazig University Hospitals. For all subjects the following measures were carried out: careful history taking, clinical examination, ECG and ultrasonography and routine laboratory investigations e.g. fasting blood glucose levels, liver and renal functions and blood picture. Subjects suffering from any disease known to affect the studied parameters were excluded e.g. rheumatic diseases, chronic liver

disease, renal disorders, malignant diseases, infectious diseases, or heart failure. Also, subjects receiving drugs known to affect the assayed parameters were excluded. Pregnancy and smoking were excluded.

Upon recruitment, all subjects gave informed consent. After fourteen hours fasting, 6 ml blood samples were withdrawn by venipuncture from antecubital vein and aliquoted as follow: One ml blood in disodium-EDTA-containing tubes for determination of HbA1c in the hemolysate of RBCs. One ml blood in disodium-EDTA-containing tubes and 20  $\mu$ l aprotinin/ml (Roche Diagnostic Corporation, Indiana polis, IN, USA) for determination of plasma ET-1, plasma was separated immediately and aliquoted in Eppendorf tubes and kept at  $-70^{\circ}\text{C}$  until time of assay. Three ml blood were collected in anticoagulant-free tubes for determination of TC, HDL-C, LDL-C, TG, CRP, IL-6 and adiponectin. Sera were separated and kept in deep freeze at  $-70^{\circ}\text{C}$  until time of assay. One ml blood was collected in tubes containing fluoride-oxalate mixture for determination of fasting plasma glucose.

## Methods

1- Determination of fasting plasma glucose and serum TG, TC, HDL-C and LDL-C by conventional methods, using kits provided by SPINREACT, S.A.Ctra Sante Coloma, Spain.

2- HbA1c was determined in the hemolysate of packed RBCs by colorimetric method according to Standfer and Eaton (1983).

3- Determination of serum C-reactive protein was carried out by particle-enhanced immuno-nephelometry using the COBAS INTEGRA 400. CRP latex (CRP-Lx) was supplied by Roche, USA (Eda et al., 1998). Human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies and the precipitate was determined turbidimetrically at 552 nm.

4- IL-6 was measured by sandwich enzyme immunoassay (Quantikine High Sensitivity; R&D Systems, Oxon, U.K.) according to Helle et al., (1991).

5- Adiponectin was measured using an sandwich ELISA with an adiponectin-specific antibody, as described previously (Arita et al., 1999), using kits supplied by R&D Systems, Oxon, U.K.

6- Plasma ET-1 was determined by RIA technique (Amersham Corporation Arlington). After acidification, the ET-1 level was measured by means of  $^{125}\text{I}$ -labelled endothelin (Clerico et al., 1994).

### Statistical analysis

The data were represented as mean  $\pm$  SD. "F" test was used to compare parameters in all groups. A paired "t" test was used to compare measurements and levels of markers of inflammation and endothelial dysfunction between case groups and control subjects. Correlation coefficient was used to determine relationship between adiponectin and inflammatory and endothelial markers. All statistical analyses were performed using the Statistical Package for Social Science program (SPSS) for Windows, version 7.5.1; SPSS, Chicago (Norusis 1997).

### Results

Clinical and biochemical criteria of all groups were shown in table 1 and 2. A significantly higher CRP levels were found in AMI group ( $t=7.966$ ,  $p<0.001$ ) and old MI group ( $t=3.706$ ,  $p<0.01$ ) compared to control group. Similar results were obtained when the CRP levels in AMI and old MI was compared with levels in newly diagnosed type-2 diabetes ( $t=7.825$ ,  $p<0.001$  and  $t=3.437$ ,  $p<0.01$ , respectively) and when AMI was compared with old MI ( $t=5.287$ ,  $p<0.001$ ). No significant difference of ET-1 between newly diagnosed type-2 diabetes and control ( $t=0.525$ ,  $p>0.05$ ), table 2.

With respect to IL-6, significantly higher levels were found in AMI compared to control group ( $t=4.936$ ,  $p<0.001$ ) and old MI

( $t=3.258$ ,  $p<0.01$ ). No significant difference of IL-6 between newly diagnosed type-2 diabetes and: control ( $t=1.689$ ,  $p>0.05$ ), AMI ( $t=1.981$ ,  $p>0.05$ ) and old MI ( $t=0.436$ ,  $p>0.05$ ), table 2.

Adiponectin levels were significantly lower in newly diagnosed type-2 diabetes ( $t=3.249$ ,  $p<0.01$ ), AMI group ( $t=5.178$ ,  $p<0.001$ ) and old MI group ( $t=5.907$ ,  $p<0.001$ ) compared to control group. Similarly, adiponectin levels were significantly lower in AMI as compared to the levels in newly diagnosed type-2 diabetes ( $t=2.713$ ,  $p<0.05$ ). No significant difference of adiponectin between old MI when compared with both newly diagnosed type-2 diabetes ( $t=1.992$ ,  $p>0.05$ ) and AMI ( $t=0.652$ ,  $p>0.05$ ), table 2.

A significantly higher ET-1 levels were found in AMI group ( $t=4.242$ ,  $p<0.001$ ) and old MI group ( $t=3.972$ ,  $p<0.001$ ) compared to control group. Similar results were obtained when the ET-1 levels in AMI and old MI was compared with levels in newly diagnosed type-2 diabetes ( $t=3.445$ ,  $p<0.01$  and  $t=2.825$ ,  $p<0.05$  respectively). No significant difference of ET-1 between newly diagnosed type-2 diabetes and control ( $t=0.693$ ,  $p>0.05$ ) and between acute and old MI ( $t=1.547$ ,  $p>0.05$ ), table 2.

Table 1. Characteristics of patients with Type-2 DM, acute myocardial infarction (AMI), old myocardial infarction (OMI) and control subjects.

	Control	Type-2 DM	AMI	Old MI
N (F/M)	10 (5/5)	10 (5/5)	10 (5/5)	10 (5/5)
Age (years)	50.05 $\pm$ 3.5	48.6 $\pm$ 3.8	48.4 $\pm$ 3.9	50.5 $\pm$ 3.8
Duration (year)			6.1 $\pm$ 2.6	9.7 $\pm$ 1.8
BMI (kg/m <sup>2</sup> )	30.5 $\pm$ 2.3	30.7 $\pm$ 3.7	30.1 $\pm$ 2.6	31.0 $\pm$ 1.7
FPG (mg/dl)	75.3 $\pm$ 4.6	205.3 $\pm$ 24.4	195.7 $\pm$ 10.6	215.6 $\pm$ 22.4*
HbA <sub>1c</sub> (%)	4.9 $\pm$ 0.2	12.4 $\pm$ 2.0	12.0 $\pm$ 2.3	11.5 $\pm$ 1.6*
TC (mg/dl)	167.2 $\pm$ 7.8	178.7 $\pm$ 12.5	192.6 $\pm$ 15.4	188.4 $\pm$ 14.3*
TG (mg/dl)	130.5 $\pm$ 7.8	138.3 $\pm$ 10.4	150.8 $\pm$ 8.2	145.6 $\pm$ 10.5*
HDL-C (mg/dl)	53.6 $\pm$ 6.4	43.2 $\pm$ 5.4	38.2 $\pm$ 4.3	41.6 $\pm$ 5.6*
LDL-C (mg/dl)	105.2 $\pm$ 3.8	122.4 $\pm$ 6.7	145.6 $\pm$ 8.9	128.6 $\pm$ 7.4*

\*F test,  $p<0.001$

Table 2. Comparison of inflammatory and endothelial markers between patients with Type-2 DM, acute myocardial infarction (AMI), old myocardial infarction (OMI) and control subjects

Parameter	Control	Type-2 DM	AMI	Old MI
CRP (mg/l)	4.5±1.8	4.9±1.6	18.6±5.3	8.5±2.9*
IL-6 (pg/ml)	5.2±2.2	6.9±2.3	12.6±4.2	7.4±2.8*
Adiponectin (µg/ml)	9.81±2.2	6.64± 2.3	4.23±0.73	4.7±1.05*
ET-1 (fmol/ml)	19.6±7.5	22.1±8.6	36.8±10.4	31.1±5.25*

\*F test, p<0.001

Adiponectin was negatively correlated with CRP (r = -0.368, P<0.05), IL-6 (r = -0.54, P<0.05), ET-1 (r = -0.473, P<0.05), BMI (r = -0.356, p<0.05), fasting plasma glucose (r = -0.427, p<0.05) and HbA1c (r = -0.562, p<0.05). Conversely, ET-1 was positively correlated with CRP (r = 0.505, P<0.05), IL-6 (r = 0.468, P<0.05), BMI (r = 0.391, p<0.05), fasting plasma glucose (r = 0.525, p<0.05)

and HbA1c (r = 0.432, p<0.05). Also, IL-6 was positively correlated with CRP (r = 0.476, P<0.05), BMI (r = 0.641, p<0.05), fasting plasma glucose (r = 0.376, p<0.05) and HbA1c (r = 0.354, p<0.05). CRP was positively correlated with BMI (r = 0.313, p<0.05), fasting plasma glucose (r = 0.532, p<0.05) and HbA1c (r = 0.612, p<0.05), table 3, Fig 1, 2, 3 and 4.

Table 3. Correlations between adiponectin, IL-6, ET-1, CRP, and other parameters.

	Adiponectin		ET-1		IL-6		CRP	
	r	p	R	P	r	p	r	P
BMI	-0.356	<0.05	0.391	<0.05	0.641	<0.05	0.313	<0.05
F. Bl. Glucose	-0.427	<0.05	0.525	<0.05	0.376	<0.05	0.532	<0.05
HbA1c	-0.562	<0.05	0.432	<0.05	0.354	<0.05	0.612	<0.05
CRP	-0.368	<0.05	0.505	<0.05	0.476	<0.05		
IL-6	-0.54	<0.05	0.468	<0.05				
ET-1	-0.473	<0.05						

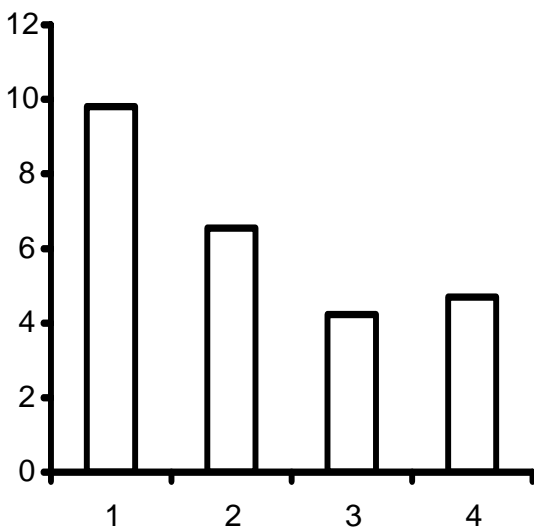


Figure 1. Adiponectin level (µg/ml) in 1- control, 2- newly diagnosed diabetics, 3-AMI and 4- old MI.

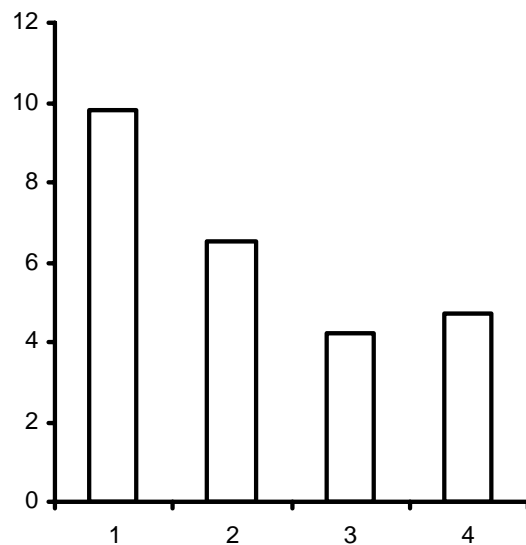
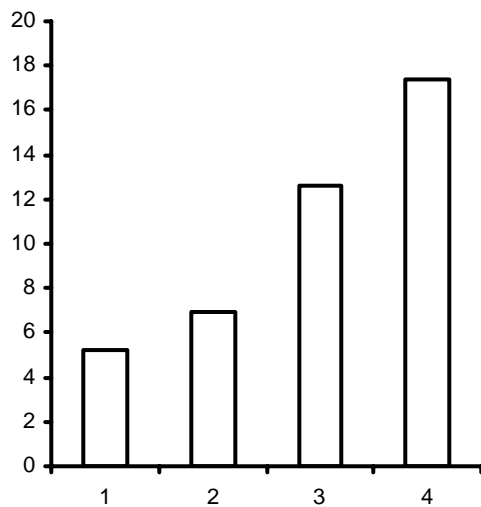
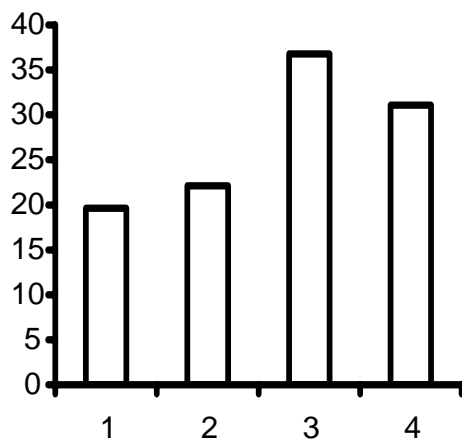


Figure 2. C-reactive protein level (µg/ml) in 1- control, 2- newly diagnosed diabetics, 3-AMI and 4- old MI.



**Figure 3.** IL-6 levels ( $\mu\text{g/ml}$ ) in 1- control, 2- newly diagnosed diabetics, 3-AMI and 4- old MI.



**Figure 4.** Et-1 levels ( $\mu\text{g/ml}$ ) in 1- control, 2- newly diagnosed diabetics, 3-AMI and 4- old MI.

## Discussion

In this study, adiponectin was decreased in diabetics with and without complications compared to control group, whereas CRP, IL-6 and ET-1 were significantly elevated in diabetic group with AMI as compared to control group, in newly diagnosed type-2 diabetes, the three parameters were similar to those of control. Only adiponectin is significantly altered in newly diagnosed type-2 diabetics compared to control. CRP and IL-

6 were significantly decreased in old MI compared to AMI and ET-1 was significantly higher in diabetics with macrovascular complications than newly diagnosed diabetics. Adiponectin was negatively correlated with CRP, IL-6, ET-1 fasting plasma glucose, HbA1c and BMI. A significant positive correlation was found between ET-1, CRP and IL-6.

The finding that low adiponectin level is associated with increased risk of diabetes and inversely correlated with BMI and HbA1c has been previously published (Arita et al., 1999, Weyer et al., 2001, Krakoff et al., 2003, Spranger et al., 2003 and Fumeron et al., 2004). Adiponectin has anti-inflammatory and insulin-sensitizing properties and protect against future development of type-2 diabetes. Subjects with lower adiponectin concentrations are at greater risk of developing diabetes, it is considered an independent predictive factor in diabetes (Bayes et al., 2004). Early onset of type-2 diabetes is genetically associated with, the adipocyte-derived peptide, adiponectin. The adiponectin gene is located on chromosome 3q27, where a type-2 diabetes susceptibility locus has been mapped and this may explain the association of adiponectin and the onset of type-2 diabetes. Adiponectin gene polymorphisms have been associated with BMI, insulin sensitivity, and type-2 diabetes as well as adiponectin levels (Fumeron et al., 2004 and Gibson and Froguel 2004). In addition to its role in development of diabetes, plasma adiponectin levels in diabetic patients with coronary artery disease (CAD) are lower than in patients with CAD alone. It is speculated that people who have very low plasma adiponectin levels may be at increased risk of developing both diabetes and CAD (Chan et al., 2004). The role of adiponectin in pathogenesis of macrovascular complications is confirmed in the present study, since its levels were significantly lower in AMI patients than non-complicated diabetics.

Fasshauer et al., (2004) suggested that the role of adiponectin as a vasoprotective anti-inflammatory is mediated by interfering with various atherogenic processes and its deficiency is linked to insulin resistance (IR) and CAD.

In the present study, we extend this observation by assessment of both the correlation of adiponectin to markers of inflammation and endothelial function and the relationship between these markers and onset of diabetes. Despite strong correlations between many of these markers and the metabolic measurements at baseline, only adiponectin was significantly related to the development of type 2 diabetes. Other inflammatory markers, most notably CRP and IL-6, were not related to onset of diabetes. These findings agree with those reported by Krakoff et al., (2003) and Gibson and Froguel (2004).

Our results provide further evidence that adiponectin concentrations correlate with markers of inflammation and endothelial dysfunction. This finding is in agreement with Ouchi et al., (2003) who suggested that inflammatory and vascular markers including CRP, IL-6, and ET-1 are generally associated with subclinical inflammation. In vitro, adiponectin modulates the immune system in several ways. Adiponectin is structurally similar to TNF-alpha (Shapiro and Scherer 1998) and inhibits TNF-alpha production by macrophages (Yokota et al., 2000). Adiponectin also inhibits the expression of adhesion molecules in cultured endothelial cells (Ouchi et al., 1999) acting via necrosis factor-alphaB signaling pathways (Ouchi et al., 2002), a pathway crucial to inflammatory response (Barnes et al., 1997). Thus, the inverse correlations of adiponectin with inflammatory markers observed in the present study support the idea that adiponectin is associated with anti-inflammatory activity.

The other markers in this study were intercorrelated, with strong relationships of

CRP, IL-6 and the endothelial marker, ET-1. CRP and IL-6 were positively associated with BMI, and coefficients were similar to those in other studies (Yudkin et al., 1999, Festa et al., 2000 and Krakoff et al., 2003). The concentrations of CRP and IL-6, a characteristic inflammatory markers, were high-normal at diagnosis and did not change later on without diabetic complications and correlated, at diagnosis, with BMI, IR and poor glycemic control "HbA1c" (Scholin et al., 2004). Glycemic control improves the IR and lower the levels of related inflammatory markers (Gao et al., 2004). There is a possibility that IR and risk of cardiovascular disease are linked and represent common consequences of low-grade inflammation reflected by IL-6 and CRP (Yudkin et al., 2004). Higher serum CRP concentrations, but not IL-6 were shown in subjects with impaired glucose tolerance support the hypothesis that acute-phase reaction (CRP), but not the pro-inflammatory cytokine-induced systemic inflammation is an early metabolic defect prior to onset of type 2 diabetes (Choi et al., 2004). Thus, the inflammatory markers are not predictive of the onset of type-2 diabetes, although the subclinical inflammation can't be ruled out. In contrast, these markers are powerful predictor of cardiovascular events confirmed by marked elevation in AMI and their decrease in old MI cases. A number of explanations for the relationship of markers of inflammation with diabetes and macrovascular complications have been proposed. C-reactive protein actively participate in the development of atherosclerosis via marked and sustained increase in native LDL uptake by macrophages and endothelial cells by enhanced expression of Lectin-like oxidized low-density lipoprotein "oxLDL" receptor-1 (LOX-1) a newly identified endothelial receptor for oxLDL that plays a pivotal role in oxLDL-induced endothelial dysfunction. CRP effects are mediated, in part, by increased

secretion of the potent endothelium-derived vasoactive factor, ET-1, and the inflammatory cytokine, IL-6. The proatherosclerotic and proinflammatory effects of CRP are attenuated by mixed ET (A/B) receptor antagonism and IL-6 inhibition (Verma et al., 2002 and Li et al., 2004). Also, activation of the inhibitor ( $\kappa$ ) kinase  $\beta$  (IKK $\beta$ ) pathway by inflammation has been found to influence IR in mouse models (Yuan et al., 2001) and via other pathways perhaps mediated via TNF-alpha (Hotamisligil 1999).

Circulating ET-1 is a well-recognized marker of endothelial atherosclerotic and cardiovascular disease (Piatti et al., 2000). Increased levels of ET-1 are associated with metabolic variables indicating more pronounced endothelial injury with diabetes (Seligman et al., 2000 and Pontiroli et al., 2004). Hyperendothelinaemia is associated with various IR states and inhibits in a tissue- and time-dependent manner the insulin-stimulated glucose uptake (Idris et al., 2001). Taylor (2001) reported that there is compelling evidence for endothelial dysfunction in diabetics that associated with blunting of the potent endothelium-derived, NO, vasodilator and increased production of the vasoconstrictor, ET-1. Moreover, ET-1 inhibits NO production this effect is abolished by ET (A-receptor) blockade (Mather et al., 2002). These effects contribute to the microvascular and macrovascular complications in diabetes and accelerate the atherosclerotic process. Protein kinase-C is thought to be activated in diabetes and is implicated in promoting proatherogenic mechanisms including enhanced ET-1 expression or inhibiting antiatherogenic mechanisms (Pontiroli et al., 2004).

The expression of adiponectin is downregulated in diabetics and associated cardiovascular insults may be mediated by IR and ET-1, since adiponectin secretion, from 3T3-L1 adipocytes, significantly increased 1h following insulin or ET-1 treatment,

respectively. Pretreatment with ET-1 for 24h significantly inhibited the ability of insulin or ET-1 to acutely stimulate adiponectin secretion. The specific ET (A) receptor antagonist, BQ-610 (1 microM), significantly inhibited ET-1-stimulated adiponectin secretion. Although ET-1 acutely stimulates adiponectin secretion through the ET (A) receptor, chronic exposure to ET-1 dramatically decreases the stimulatory effect of insulin and ET-1 on adiponectin secretion. Thus, vascular factors such as ET-1 may play a role in the regulation of adiponectin secretion and whole body energy metabolism (Clarke et al., 2003). This finding may explain why adiponectin is negatively correlated with ET-1 and the increase of ET-1 is associated with decrease of adiponectin particularly with macrovascular complications. There is an association between IR states and vascular dysfunction involves the expanding repertoire of adipocyte-derived hormones. Of these, particular interest has been focused on adiponectin, which has both vascular and metabolic actions, and may contribute importantly to the connection between metabolism and vascular function. Since, insulin can directly stimulate the action of nitric oxide synthase, thus macrovascular complications in type-2 diabetes may be also attributed to TNF-alpha-induced IR that associated with impaired endothelium-dependent vasodilation and, specifically, with impaired insulin-stimulated vasodilation. IR-associated reductions in nitric oxide availability due to increases in oxidative stress, reduced availability of tetrahydrobiopterin and excess levels of asymmetrical dimethylarginine. An excess of the vasoconstrictor endothelin, may result directly from hyperinsulinemia and/or indirectly due to a loss of the suppressive effects of nitric oxide on endothelin production and action (Lteif and Mather 2004). Thus, several mechanisms link insulin resistance, the metabolic syndrome and

vascular disease. Epidemiological associations are now well established between insulin resistance, the metabolic syndrome and worsened cardiovascular outcomes (Krakoff et al., 2003). The significant decrease of inflammatory and vascular markers in AMI compared to old MI indicate that these markers are associated with both acute inflammatory process as well as severe vascular injury.

In conclusions, in newly diagnosed type-2 diabetic subjects matched for BMI, none of the inflammatory or vascular markers can predict diabetes, but can be used as markers of acute vascular events and in follow up of these cases. Conversely, adiponectin can be used as early predictor of thype-2 diabetes. Also, adiponectin may be the link between type-2 diabetes, inflammatory reactions and macrovascular complications associated with diabetes. Immunomodulating protocols for adiponectin can help in prevention as well as treatment of type-2 diabetes.

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