

**Hyperinsulinemia sign a danger signal
through the increase of plasma endothelin-1 level in some
cardiovascular risk factors**

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Abstract

Obesity, hypertension, diabetes mellitus and smoking are all well known risk factors for cardiovascular disease. However, the link between these risk factors, plasma insulin and endothelin-1 (ET-1) as well as cardiovascular diseases remains to be undetermined and must be clarified. So, the current work was carried on 120 men. Their ages ranged between 32-64 years with a mean value 59 ± 9.5 . They were classified into 6 groups ;control, obese, hypertensive, uncontrolled, controlled diabetics and smokers. The results of this work showed that plasma C-peptide and insulin were significantly increased in obese, uncontrolled and controlled diabetic groups ($p < 0.05$) compared with the control group. Moreover, plasma insulin was significantly increased in, hypertensive group compared with the control group ($p < 0.005$). In addition, plasma ET-1 was significantly increased in all risky groups compared with the control group ($p < 0.05$). Comparative study of controlled versus uncontrolled diabetic group, plasma C-peptide, insulin and ET-1 were all significantly decreased ($P < 0.05$). On the otherhand , correlation study showed that; plasma insulin was significantly positive correlated with plasma ET-1 in obese ($r = 0.514$ $p < 0.05$), hypertensive ($r = 0.555$ $p < 0.05$), uncontrolled diabetes mellitus ($r = 0.510$ $p < 0.05$) and controlled diabetes mellitus groups ($r = 0.496$ $p < 0.05$) while non-significantly positive correlated with ET-1 in smoking group.

We could conclude that, hyperinsulinemia will sign a danger signal for the increase of plasma ET-1 and subsequent endothelial dysfunction in all risky subjects . So, they are more prone to ischemic heart disease . However, further study was needed using ET-1 antagonists on its receptors which may be of help to abolish or at least to minimize its pathophysiological effects on blood vessels. This is may be benefit for clinical intervention

Introduction

Endothelins ubiquitously produced 21 amino acids peptides that were discovered as endothelial product and may play important roles in cardiovascular physiology and pathophysiology . The main endothelin produced by endothelium is endothelin-1 (ET-1). The vasoconstrictor role of the endothelins may participate in blood pressure elevation and vascular hypertrophy in salt dependent models of hypertension. *(Schiffrin et al., 1997)*

ET-1 acts through smooth muscle ET(A) and ET(B) receptors, which mainly mediate vasoconstriction, and endothelial ET(B) receptors which oppose ET(A) and ET(B)-mediated vasoconstriction by stimulating nitric oxide formation *(Taddei et al., 2000)*.

The endothelium plays a pivotal role in regulating vasomotor tone , vessel permeability ,blood cell extravasations , and antiatherogenic, antithrombogenic and antiadhesive process. Endothelial dysfunction occurs in many physiological and pathological situation that leads to atherosclerosis like advanced age , menopause , high blood pressure , dyslipidemia , diabetes , smoking , elevated homocystinemia and chronic renal failure. The cause of endothelial dysfunction may be related to the presence of radical oxygen species , nitric oxide inhibitors , or increased synthesis or release of endothelin *(Halimi and Lebranchu , 2000)*

Grundy , (2000) described a metabolic syndrome which is characterized by elevated Plasma glucose , plasma lipid disorders

(atherogenic dyslipidemia) , raised blood pressure and a prothrombotic state. One of the most consequence of the metabolic syndrome is the coronary heart disease. Hyperinsulinemia represents a generalized derangement in metabolic processes.

Alterations of plasma endothelin-1 are the key event in the initiation of atherosclerosis . (*Kunz . , 2000*) . ET-1 was reported to be increased in obesity (*Wu et al ., 2000*) , hypertension (*Taddei et al ., 2000*) , diabetes mellitus (*Anwaar et al ., 2000*) ,and smoking (*Tanus – Santos et al 2000*). However, dysfunction of endothelial vasoreactivity contributes to reduced myocardial blood supply and, therefore, might promote myocardial ischemia (*Schachinger and Zeiher, 2000*)

Aim of the work

The aim of the work is to study the effect of some risk factors (obesity, hypertension, diabetes mellitus, and smoking) on plasma C-peptide, insulin and ET-1 as a trial to find any link between plasma insulin and ET-1. Also to clarify their subsequent effect on endothelial function and its relationship to cardiovascular disease.

Subjects and methods

The study had comprised 120 male subjects. Their ages ranged between 32-64 years (mean value ; 59 ± 9.5 years) . They were selected from outpatient clinic of internal medicine , Benha university hospital. all subjects were categorized into the following groups :

1. **Control group**; comprised 20 healthy, non-obese , normotensives , normoglycemics , and non- smokers

2. **Obese group**; comprised 20 subjects with body mass index (BMI) > 30 . They were , normotensives , normoglycemics and non- smokers
3. **Hypertensive group**; comprised 20 patients. They were non-obese, normoglycemics , and non-smokers.
4. **Diabetic group**; comprised 40 non-insulin dependent diabetic patients. They were subclassified into uncontrolled (20 patients) and controlled (20 patients) diabetics. These patients were non-obese , normotensives and non-smokers.
5. **Smoker group**; comprised 20 subjects who were chronic heavy smokers. They were non-obese , normotensives and normoglycemics.

Exclusion criteria :

1. Insulin-dependent diabetics (IDD)
2. Non- Insulin-dependent diabetics receiving insulin .
3. Patients with past history of ischemic heart disease (IHD)
4. Mild to moderate smokers.

All subjects included in the study were subjected to the following :

1. Full history and clinical examination including:
 - A. Body mass index (BMI) = $\text{weight (Kg)} / \text{height (m}^2\text{)}$ as an index of obesity (*Garrow ,1990*)
 - B. WHO-ISH classification of blood pressure. mean arterial pressure (MAP) = $\text{diastolic pressure} + 1/3 (\text{systolic} - \text{diastolic pressure})$ (Ganong , 1991)
 - C. Chronic heavy cigarette smokers who were smoking more than 20 cigarettes for more 5 continuous years (*WHO , 1996*).

2. Sampling:

About 7.0 cc venous blood was taken from our subjects after fasting more than 12 hours . Another sample (2.0 cc) was taken 2 hours postprandial on an ethylene diamine tetra- acetic acid (EDTA) powder , then

centrifuged. The plasma separated was used for determination of postprandial glucose level to assure the diabetic condition.

All fasting samples were divided into 2 parts . The first part (5.0 cc) was taken on an EDTA powder for determination of glycosylated hemoglobin (HBA1c) (*Gonen and Rubenstein , 1978*). The remaining blood was centrifuged. Part of the plasma separated was used for routine estimation of :

1. Fasting plasma glucose (*Trinder , 1969*)
2. Total plasma cholesterol (*Watson , 1960*)
3. Plasma triglycerides (*Scheletter and Nussel , 1975*)
4. Plasma HDL and LDL (*Friedewald, 1972*)
5. Plasma AST and ALT (*Reitman and Frankel , 1957*)
6. Plasma creatinine (*Henry ,1974*)

The other part of the plasma was kept frozen at – 80 °C for determination of :

1. C- peptide by radioimmunoassay (*Bonser and Garcia-Webb, 1984*)
2. Insulin by radioimmunoassay (*Kuzuya et al ., 1977*)

The 2nd part (2.0 cc) was transferred into polypropylene tube containing 2.0 mg of EDTA powder (mg/ml) and aprotonin (2000 KIU/ml) ,then centrifuged in a cooling centrifuge at 1.600 xg for 15 minutes at 0 °C. The plasma separated was kept frozen at – 80 °C for determination of endothelin-1 by ELISA (*Porstrnann and Kiessig , 1992*).

Data analysis

The results of this work were tabulated and statistically analyzed using student (t-test) and correlation coefficient (r) .p values <0.05 were considered significant while p values >0.05 were insignificant (*Budneck , 1987*)

Results and discussion

Table (1): mean values and \pm SD of age , body mass index(BMI) , mean arterial pressure(MAP),fasting plasma glucose(FPG),postprandial plasma glucose(PPG) and glycosylated hemoglobin(HBA1c) in all studied groups compared with the control group

Parameters Groups	Age (Y)	BMI (Kg/m ²)	MAP (mmHg)	FPG (mg/dl)	2h PPG (mg/dl)	HBA1c (%)
Control group (n=20)	47.85 \pm 8.6	24.63 \pm 1.67	91.00 \pm 4.37	80.55 \pm 5.81	129.5 \pm 7.59	7.33 \pm 0.462
Obese group(n=20)	48.95 \pm 8.9 N.S	33.04 \pm 1.7 p<0.05	84.9 \pm 4.1 N.S	87.15 \pm 7.15 N.S	131.5 \pm 6.68 N.S	7.22 \pm 0.435 N.S
Hypertensive group (n=200)	50.8 \pm 6.9 N.S	24.87 \pm 1.3 N.S	111.6 \pm 5.25 p<0.05	84.55 \pm 5.03 N.S	127.15 \pm 6.25 N.S	7.30 \pm 0.443 N.S
Uncontrolled D.M group (n=20)	49.15 \pm 6.9 N.S	26.5 \pm 1.38 N.S	92.62 \pm 4.46 N.S	214.65 \pm 13.4 p<0.05	344.00 \pm 29.7 p<0.05	18.53 \pm 2.933 p<0.05
Controlled D.M group (n=20)	50.55 \pm 8.3 N.S	25.5 \pm 1.33 N.S	86.6 \pm 4.15 N.S	116.5 \pm 11.84 p<0.05 p1<0.05	181.25 \pm 7.71 <0.05 p1<0.05	8.71 \pm 1.667 p<0.05 p1<0.05
Smoking group (n=20)	47.45 \pm 8.1 N.S	24.3 \pm 1.26 N.S	88.4 \pm 4.24 N.S	81.25 \pm 7.56 N.S	127.45 \pm 5.18 N.S	7.54 \pm 0.406 N.S

p : probability versus control

p1 : probability versus uncontrolled D..M

N.S : non-significant (p>0.05)

p<0.05 : significant

Table (2): mean values and \pm SD of plasma C-peptide, insulin and endothelin-1 (ET-1) in all studied groups compared with the control group

Biochemical parameters Groups	Plasma C-peptide (μ IU/ml)	Plasma insulin (μ IU/ml)	Plasma endothelin-1 (μ IU/ml)
Control group (n=20)	1.76 \pm 0.123	21.6 \pm 1.16	3.10 \pm 1.60
Obese group (n=20)	2.05 \pm 0.303 p<0.05	23.4 \pm 1.39 p<0.05	5.85 \pm 2.19 p<0.05
Hypertensive group (n=20)	1.75 \pm 0.12 NS	22.9 \pm 1.97 p<0.005	6.60 \pm 2.19 p<0.05
Uncontrolled D.M group (n=20)	2.33 \pm 0.474 p<0.05	24.36 \pm 2.05 p<0.05	9.90 \pm 3.25 p<0.05
Controlled D.M group (n=20)	1.82 \pm 0.123 N.S p1<0.05	23.03 \pm 1.55 p<0.05 p1<0.05	6.15 \pm 2.7 p<0.05 p1<0.05
Smoking group (n=20)	1.72 \pm 0.215 N.S	21.63 \pm 1.17 N.S	6.25 \pm 2.53 p<0.05

p : probability versus control .

p1: probability versus uncontrolled D.M.

N.S : non-significant (p>0.05).

p<0.05 : significant.

Table (3): correlation coefficient (r) between plasma insulin and BMI , MAP,HBA1c , plasma cholesterol, C-peptide and ET-1 in all studied groups

Parameters Groups	BMI (kg/m ²) "r"	MAP (mmHg) "r"	HBA1c (%) "r"	Plasma cholesterol (mg/dl) "r"	Plasma C- peptide (μIU/ml) "r"	Plasma ET-1 (μIU/ml) "r"
Obese group (n=20)	0.639 p<0.002	0.018 N.S	0.212 N.S	0.559 p<0.05	0.195 N.S	0.514 p<0.05
Hypertensive group (n=20)	0.377 N.S	0.525 p<0.05	0.269 N.S	0.503 p<0.05	0.294 N.S	0.555 p<0.05
Uncontrolled D.M group (n=20)	0.613 p<0.05	0.293 N.S	0.475 p<0.05	0.648 p<0.05	0.465 p<0.05	0.510 p<0.05
Controlled D.M group (n=20)	0.233 N.S	0.320 N.S	0.591 p<0.05	0.528 p<0.05	0.571 p<0.05	0.496 p<0.05
Smoking group (n=20)	0.160 N.S	0.283 N.S	0.211 N.S	0.473 p<0.05	0.011 N.S	0.357 N.S

N.S : non-significant (p>0.05).
p<0.05 : significant .

Table (4): correlation coefficient (r) between plasma ET-1 and BMI , HBA1c, plasma cholesterol and C-peptide in all studied group

Parameters Groups	BMI (kg/m ²) "r"	MAP (mmHg) "r"	HBA1c (%) "r"	Plasma cholesterol (mg/dl) "r"	Plasma C-peptide (μIU/ml) "r"
Obese group (n=20)	0.579 p<0.05	0.371 N.S	0.322 N.S	0.502 p<0.05	0.395 N.S
Hypertensive group (n=20)	0.088 N.S	0.746 p<0.05	0.296 N.S	0.576 p<0.05	0.394 N.S
Uncontrolled D.M group (n=20)	0.449 p<0.05	0.100 N.S	0.675 p<0.05	0.468 p<0.05	0.600 p<0.05
controlled D.M group (n=20)	0.094 N.S	0.056 N.S	0.716 p<0.05	0.478 p<0.05	0.571 p<0.05
Smoking group (n=20)	0.027 N.S	0.034 N.S	0.210 N.S	0.657 p<0.05	0.034 N.S

N.S : non significant.
p<0.05 : significant.

Analysis of the results obtained in obese group showed a significant increase of plasma C-peptide , insulin and ET-1 ($p<0.05$) compared with the control group (Table 2) .

Moreover, plasma insulin showed a significant positive correlation with BMI ($r = 0.639$ $p<0.002$) plasma cholesterol ($r=0.559$ $p<0.05$) and plasma ET-1 ($r=0.514$ $p<0.05$) while, non-significant positive correlation was shown with MAP , HBA1c, and plasma C-peptide (Table 3) .

Also, there was significant positive correlation between plasma ET-1 , BMI ($r=0.579$ $p<0.05$),and plasma cholesterol ($r = 0.502$ $p<0.05$) while there was non-significant positive correlation with mean arterial pressure (MAP), glycosylated haemoglobin (HBA1C) and C-peptide (Table 4) .

The hyperinsulinemia seen in our obese group had been explained through the reports of *Holden et al ., (1997)* ; *Winkler et al ., (1999)* and *Hotamisligil , (2000)*. *Holden et al ., (1997)* summerized the main action of TNF-alpha. It inhibits the activity of a number of key enzymes involved in energy metabolism and major histocompatibility (MHC) class-1 molecule expression. These enzymes include: protein-tyrosine kinase (PTK-ase) and protein-tyrosine phosphatase (PTP-ase) which involved in energy metabolism, cell proliferation and stimulation of the MHC class-1 molecule pathway . Of primary importance is the inhibiting effect of TNF-alpha on PTK-ase, since this induce insulin resistance. Also,*Winkler et al ., (1999)* concluded that tumour necrosis factor (TNF)-Alpha may be one of the factors contributing to insulin resistance and vascular dysfunction in patients with android obesity. Additionally, *Hotamisligil , (2000)* reported that, the genetic absence of TNF- alpha signaling in obesity of experimental animals showed : (i) significantly improves insulin receptor signaling capacity and consequently insulin

sensitivity ; (ii) prevents brown adipose tissue atrophy and beta 3-adrenoreceptor deficiency and improves thermo-adaptive responses (iii) decreases the elevated plasminogen activator inhibitor (PAI)-1 and tumour necrosis factor (TNF) - Beta production and (iv) lowers hyperlipidemia and hyperleptinemia. Hence, abnormal TNF-alpha action in adipocytes disturbs many aspects of metabolic homeostasis in obesity . However, visceral obesity seems to be the main driving factors by mean of the increased production of free fatty acids whose activity , in turn , might interfere with the action of insulin (*Bosello & Zomboni , 2000*)

Wu et al., (2000) reported a link between hyperinsulinemia and endothelin – A (ETA) receptor expression and vasoconstriction in the aorta of obese Zucker rat . They concluded that elevated insulin level have been linked to increased endothelin receptor expression. So , hyperinsulinaemia upregulates endothelin receptors to endothelin-1 in the model of obesity & hypertension .

Our results in obese group, were in agreement with *Halawa & Mazurek, (1997) , Ferri et al., (1997) , Muller-Wieland et al. (1998) and Grundy (2000)*.

The data in our hypertensive group showed that , plasma C-peptide was non-significantly increased while plasma insulin and ET-1 were significantly increased ($p < 0.05$) when compared with the control group (Table 2) .

Moreover, correlation study showed that plasma insulin was significantly positive correlated with MAP ($r = 0.525$ $p < 0.05$) plasma cholesterol ($r=0.503$ $p < 0.05$) and plasma ET-1 ($r=0.555$ $p < 0.05$) while non- significantly positive correlated with BMI, HbA1c, and C-peptide (Table 3) .

Also, plasma ET-1 was significantly positive correlated with MAP ($r=0.746$ $p < 0.05$) and plasma cholesterol ($r = 0.576$ $p < 0.05$) but non-

significantly positive correlated with BMI, HBA1c, and C-peptide (Table 4) .

The hyperinsulinaemia in our hypertensive group may be explained by *Shimamoto, (2000)* who reported that leptin may play a role in the pathophysiology of insulin – resistance hypertension. Leptin is a recently discovered hormone produced by an a dipocyte-specific ob gene, that contributes to the regulation of energy balance by informing the hypothalamus of the amount of adipose tissue in the body . As a result, the hypothalamus adjusts food intake , thermogenesis, and energy expenditure appropriately. It was clarified that ob gene expression and plasma leptin level in humans were highly correlated with the body mass index , insulin sensitivity and blood pressure.

The resultant hyperinsulinemia were considered to raise blood pressure through, firstly , sympathetic nervous system activation. Secondly , renal sodium retention. Thirdly, renin-angiotensin system stimulation and finally , intracellular calcium accumulation in vascular smooth muscle (*Shimamoto , 2000*).

Also, insulin could directly stimulate leptin production independently of its effect on adiposity (*Suga et al.,2000*) . Consequently, leptin has been shown to increase heart rate and blood pressure through stimulation of cardiac sympathetic nervous system activity (*Paolisso et al., 1999*) .

Beside the role of leptin in the pathophysiology of insulin-resistant hypertension (*Shimamoto , 2000*) , and over expression of ET-1 receptor and increased their sensitivity to ET-1 due to hyperinsulinemia(*Wu et al., 2000*), the resultant hypertension may be due to imbalance between ET-1 and nitric oxide. Both ET-1 and nitric oxide play a crucial role in the cardiovascular physiology and an alteration of these systems could be a promoter of or be associated with most cardiovascular diseases. In

hypertensive patients, nitric oxide availability is impaired because of the production of cyclooxygenase – derived vasoconstrictor substances which mediate the vasoconstrictor response to ET-1 . Also , the vasoconstrictor activity of ET-1 may be related to a reduced ET(B) receptor – mediated nitric oxide activation. These peculiar aspects of the role of ET-1 in essential hypertension could have pathophysiological relevance (*Taddei et al., 2000*) .

Our findings in hypertensive group, were in accordance with *Ferri et al., (1997)*, *Minami et al., (1997)* , *Neri et al. (1997)* , *Mangiafico et al., (1998)* , *Hopfner et al., (1998)* , *Shimamoto (2000)* and *Taddei et al., (2000)*.

The current results of diabetic group (Table 2) showed that plasma C-peptide , insulin and ET-1 were significantly increased in uncontrolled diabetic group when compared with the control group. ($p < 0.05$) . Also , plasma insulin and ET-1 were significantly increased in controlled diabetic group when compared with the control group ($p < 0.05$) . Meanwhile, plasma C-peptide was not significantly increased in controlled diabetic group compared with the control group. Comparative study of controlled versus uncontrolled diabetic group , our results showed that plasma C-peptide, insulin & ET-1 were significantly decreased ($p < 0.05$) .

Correlation study, showed that, plasma insulin was significantly positive correlated with HBA1c ($r = 0.475$ $p < 0.05$) , $r = 0.591$ $p < 0.05$), plasma cholesterol ($r = 0.648$ $p < 0.05$, $r = 0.528$ $p < 0.05$) , C- peptide ($r = 0.465$ $p < 0.05$, $r = 0.571$ $p < 0.05$) , and ET-1 ($r = 0.510$ $p < 0.05$ $r = 0.496$ $p < 0.05$) in both uncontrolled & controlled diabetic groups, respectively . Also , plasma insulin was significantly positive correlated with BMI ($r = 0.613$ $p < 0.05$) in uncontrolled diabetic group while non-

significantly positive correlated with BMI in controlled diabetic group , and MAP in both uncontrolled and controlled diabetic groups (Table 3) .

Moreover, plasma ET-1 was significantly positive correlated with HBA1c ($r = 0.765$ $p < 0.05$, $r = 0.716$ $p < 0.05$) , plasma cholesterol, ($r = 0.468$ $p < 0.05$) $r = 0.478$ $p < 0.05$) plasma C- peptide ($r = 0.60$ $p < 0.05$; $r = 0.571$ $p < 0.05$) in uncontrolled and controlled diabetic groups, respectively. Also , plasma ET-1 was significantly positive correlated with BMI ($r = 0.449$ $p < 0.05$) in uncontrolled diabetic group. Meanwhile, ET-1 has non-significant positive correlation with BMI in controlled diabetic group , and MAP in both uncontrolled and controlled diabetic groups (Table 4) .

Type 2 diabetes is characterised by both impaired insulin secretion and insulin resistance but their relative contribution to the development of hyperglycemia may differ due to heterogeneity of the disease (*Groop* , 2000) . Although our diabetic patients had hyperinsulinemia which was contradictory to the explanation of *Groop* , (2000) , who reported that ; in patients with manifest diabetes, chronic hyperglycemia can result in deterioration of insulin sensitivity & secretion (glucotoxicity) , which is aggravated by elevated free fatty acids (FFA) (lipotoxicity) . On the other hand, *Boden* ,(1999) recorded that plasma FFA are one important link between obesity , insulin resistance and type 2 diabetes . Thus, the elevated plasma FFA inhibit insulin- induced glucose uptake into muscle. Also , plasma FFA increase gluconeogenesis which enhance endogenous glucose production as well as increase insulin secretion which decrease endogenous glucose production . So , the elevated plasma FFA are responsible for oversecretion of insulin and subsequent hyperinsulinemia . It seems to be a compensatory mechanism for FFA- induced insulin resistance.

Moreover, the significant increase of plasma ET-1 in diabetic patient could be explained by *Quehenberger et al., (2000)*. In vitro study, incubation of bovine aortic endothelial cells with erythrocytes from patients with type 2 diabetes induced an increase in ET-1 production. The effect of erythrocytes on ET-1 synthesis was dependent on glycemic control . Carboxymethyl lysine (CML) – containing protein isolated from patients erythrocytes induced ET-1 production. Also advanced glycation end product (AGEs) induced ET-1 mRNA transcription. They concluded that ET-1 transcription is controlled by the AGE-inducible redox-sensitive transcription factor called nuclear factor – kappaB.

Our results in diabetic group, were compatible with the findings of *Hopfner et al., (1998)* , *Winkler et al., (1998)* , *Perfetto et al. (1997)* , *De-Mattia et al., (1998)* and *Migdalidis et al., (2000)*.

Finally, smoking group showed that plasma C-peptide and insulin were non-significantly increased (Table 2) while plasma ET-1 was significantly increased ($p < 0.05$) compared with the control group .

Moreover , plasma insulin revealed a positive significant correlation with plasma cholesterol ($r = 0.473$ $p < 0.05$) while there was non-significant positive correlation with BMI, MAP , HbA1c , plasma C-peptide and ET-1 (Table 3) .

In addition, plasma ET-1 showed a significant positive correlation with plasma cholesterol ($r = 0.657$ $p < 0.05$) , while there was non-significant positive correlation with BMI, MAP , HbA1c, and plasma C-peptide (Table 4) .

It seems possible to assume that nicotine exhibited a tendency to accelerate arterial intimal hyperplasia, the longer exposure to nicotine or a higher dose of the agent or both through enhanced improvement of endothelium – derived relaxing factor (NO) production and enhanced increase in ET-1 production in the vessel wall (*Hamasaki et al., 1997*) .

Moreover, *Adachi et al., (2000)* investigated the effects of cigarette smoking on the tissue mRNA expression of ET-1 level by reverse transcriptase polymerase chain reaction (RT-PCR) followed by southern blot analysis . They suggested that cigarette smoking could cause cardiovascular and pulmonary diseases by modulating ET-1 mRNA expression in tissues .

These data were in accordance with that obtained by *Hamasaki et al., (1997)* , *Gambaro et al., (1998)* , *Ylikorkala et al., (1998)* and *Tanus – Santos et al., (2000)* .

We could conclude that, hyperinsulinemia will sign a danger signal for the increase of plasma ET-1 and subsequent endothelial dysfunction in all risky subjects . So, they are more prone to ischemic heart disease . However, further study was needed using ET-1 antagonists on its receptors which may be of help to abolish or at least to minimize its pathophysiological effects on blood vessels. This is may be benefit for clinical intervention

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الملخص العربي

زيادة مستوى الإنسيولين بالبلازما يعطى إشارة خطيرة من خلال زيادة مستوى الإندوثيلين -

1 بالبلازما فى بعض العوامل الخطرة للقلب والأوعية الدموية

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من المعروف أن السمنة وضغط الدم المرتفع والبول السكرى والتدخين من العوامل الخطرة التى تؤثر على القلب والأوعية الدموية . وما زال الارتباط بين هذه العوامل الخطرة من ناحية ومستوى الإنسيولين والإندوثيلين - 1 بالبلازما من ناحية أخرى يحتاج الى توضيح . لذلك أجريت هذه الدراسة على مائة من المرضى الرجال وعشرين رجلا من الأصحاء كمجموعة ضابطة ، تتراوح أعمارهم من 32 الى 64 عاما . هؤلاء المرضى تم تقسيمهم

الى 5 مجموعات وهى ومجموعة مرضى السمنة وضغط الدم المرتفع والبوال السكرى الغير منضبط والمنضبط والمدخنين .

كانت نتيجة البحث وجود زيادة ذات قيمة إحصائية فى سى- بيتيد بمرضى السمنة والبوال السكرى المنضبط والغير منضبط بينما أن مستوى الإنسيولين بالبلازما قد زادت قيمته زيادة إحصائية فى مرضى السمنة وضغط الدم المرتفع والبوال السكرى المنضبط والغير منضبط وذلك عند مقارنتهم بالمجموعة الضابطة. على الجانب الآخر ، وجد أن هناك زيادة ذات دلالة إحصائية فى مستوى الإندوتلين -1 بالبلازما فى كل المجموعات الخطرة عند مقارنتهم أيضا بالمجموعة الضابطة . وعند عمل دراسة مقارنة بين مرضى البوال السكرى الغير منضبط والمنضبط وجد أن هناك نقص ذات دلالة إحصائية فى مستوى سى- بيتيد و الإنسيولين والإندوتلين -1 بالبلازما. أيضا وجد أن هناك علاقة طردية بين مستوى الإنسيولين ومستوى الإندوتلين -1 بالبلازما وأنها ذات دلالة إحصائية وذلك بمرضى السمنة وضغط الدم المرتفع والبوال السكرى المنضبط والغير منضبط بينما لا يوجد لهذه العلاقة دلالة ذات قيمة إحصائية فى المدخنين .

نستنتج من هذا البحث أن زيادة مستوى الإنسيولين بالبلازما يمكن أن يعطى إشارة خطيرة إلى هناك زيادة فى مستوى الإندوتلين -1 بالبلازما وبالتالي إلى اضطراب فى وظائف الطبقة الطلائية الداخلية المبطنة للأوعية الدموية وذلك فى جميع المجموعات الخطرة ولذلك فهم أكثر عرضة للإصابة بقصور الدورة الدموية للقلب. كما يوصى هذا البحث بعمل دراسة أخرى باستخدام مضادات الإندوتلين -1 على المستقبلات الحسية الخاصة بالإندوتلين وهذا مكن أن يكون ذا فائدة إكلينيكية عن طريق تقليل تأثير هذه المادة على الأوعية الدموية وبخاصة تلك التى تغذى عضلة القلب.

