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ORIGINAL ARTICLE

Association of insulin resistance, insulin and leptin levels with coronary in-stent restenosis

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Abstract *Background:* In-stent restenosis remains the major limitation of coronary stent implantation. Leptin is a hormone strongly related to insulin resistance (IR). Moreover, insulin resistance and hyperinsulinemia are common in patients with coronary heart disease (CHD), each of the previous metabolic and hormonal factors might be involved in restenosis after stent implantation.
Objective: This study was planned to evaluate the relationship between insulin resistance, insulin, leptin levels and coronary in-stent restenosis after coronary stent implantation in non-diabetic patients with CHD and to determine their value in prediction of restenosis.
Patients and methods: The study included 48 non-diabetic CHD patients with previous successful coronary stent implantation. They were divided into two groups according to the presence of in-stent restenosis on follow-up coronary angiography (6–9 months after stent implantation). The first group was CHD patients with in-stent restenosis which included 20 patients, the second group was CHD patients without restenosis which included 28 patients. All patients were subjected to complete clinical examination including determination of body mass index (BMI), waist to hip ratio (WHR) and laboratory investigations including fasting plasma glucose (FPG), fasting plasma insulin (FP insulin), lipid profile (total cholesterol, HDL-C, LDL-C, TG), glycoselated hemoglobin (HbA1c), plasma leptin, estimation of homeostasis model assessment of IR (HOMA-IR). All subjects were submitted to OGTT with estimation of 2-h post-prandial glucose (2-hPP glucose) and sum post-prandial insulin levels (sum PP insulin). Follow-up coronary angiography was done for all patients with the estimation of minimal luminal diameter (MLD), diameter stenosis % and late lumen loss.

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Results: There was highly significant increase in each of FP insulin, sum PP insulin, HOMA-IR, leptin, diameter stenosis % and late lumen loss ($P < 0.001$) and a highly significant decrease of MLD ($P < 0.001$) in CHD patients with in-stent restenosis when compared to CHD patients without in-stent restenosis. MLD is negatively correlated to each of FP insulin ($r = -0.49$, $P < 0.001$), sum PP insulin ($r = -0.60$, $P < 0.001$) HOMA-IR ($r = -0.63$, $P < 0.001$) and leptin ($r = -0.55$, $P < 0.001$) while late lumen loss was positively correlated to each of FP insulin ($r = 0.98$, $P < 0.001$), sum PP insulin ($r = 0.70$, $P < 0.001$), HOMA-IR ($r = 0.67$, $P < 0.001$) and leptin ($r = 0.72$, $P < 0.001$). Multiple regression analysis revealed that each of FP insulin, sum PP insulin, HOMA-IR and leptin can be considered an independent predictor of in-stent restenosis ($P < 0.001$).
Conclusion: Our study revealed that insulin resistance, fasting and post-prandial hyperinsulinemia and hyperliptinemia are considered predictors of coronary in-stent restenosis. Evaluation of HOMA-IR, insulin levels after standard OGTT and leptin levels are important tools in an attempt to recognize subjects at risk of early restenosis among non-diabetic, CHD patients undergoing percutaneous coronary revascularization and stent implantation.

1. Introduction

Intracoronary stenting is an accepted treatment for coronary artery stenosis or closure after percutaneous transluminal coronary angioplasty.[1] However, in-stent restenosis remains the major limitation of coronary stent implantation.[2] Previous histological studies in human demonstrated that restenosis process is characterized by acute inflammation and early thrombus formation followed by neointimal tissue proliferation in the chronic stage after coronary stent implantation.[3] Another study using serial intravascular ultrasound showed that stents did not recoil and that in-stent restenosis was the result of exaggerated neointimal tissue proliferation.[4]

Insulin resistance is one of the major characteristics of metabolic syndromes related to obesity and obesity associated complications such as type 2 diabetes mellitus, hypercholesterolemia and cardiovascular disease.[5] Insulin resistance with hyperinsulinemia is associated with glucose intolerance, hypertension, obesity and dyslipoproteinemias characterized by hypertriglyceridemias or low high density lipoprotein cholesterol (HDL-C) levels, which are well known risk factors for coronary artery diseases.[6] It has been reported that hyperinsulinemia is an independent risk factor for ischemic heart disease,[7] and induces greater vascular smooth muscle cell (VSMC) proliferation in experimental models.[8]

Leptin is an adipokine hormone which was shown to be strongly correlated with body mass index (BMI), fat accumulation and insulin resistance,[9] insulin resistant individuals were shown to have higher leptin concentrations than those who are insulin sensitive, and independent of body fat mass.[10] In addition leptin has been recognized as an independent risk factor for coronary heart disease.[11] Previous studies have demonstrated different direct effects of leptin on vascular and inflammatory cells responsible for promoting atherothrombosis, particularly; it activates multiple signal transduction pathways in human monocytes and vascular cells.[12] Leptin receptors are expressed in human atherosclerotic lesions.[13] Furthermore, the prothrombotic effects of leptin might be mediated by platelet leptin receptors.[14] Moreover, leptin is emerged as a metabolic hormone that contributes to the regulation of vascular biology and it modulates endothelial nitric oxide (NO) synthesis.[15]

This study was planned to evaluate the relationship between insulin resistance, insulin levels, leptin levels and coronary in-stent restenosis after successful coronary stenting in non-diabetic patients with coronary heart disease, and to determine their value in prediction of restenosis.

2. Patients and methods

This study was carried out in the Departments of Internal Medicine, Cardiology and Clinical Pathology, Faculty of Medicine, Zagazig University. The study was conducted from January 2008 to December 2009.

The study included 48 non-diabetic patients (39 males and 9 females) with coronary heart disease (CHD) who came due to recurrence of symptoms (chest pain) 6–9 months after successful elective placement of intracoronary bare-metal stents. All patients were subjected to 12 lead ECG, stress ECG and follow-up coronary angiographic study to evaluate the cause of recurrent chest pain. The patients were classified according to the presence of intracoronary stent restenosis (defined as recurrence of stenosis by $>50\%$ reduction in the diameter of the stented coronary segment) into two groups:

1. CHD patients with in-stent restenosis: It included 20 patients (16 males and 4 females) with a mean age of 51.75 ± 3.7 years, stenosis severity % at a follow-up of 72.25 ± 5.98 and minimal luminal diameter (MLD) at a follow-up of 0.95 ± 0.28 mm.
2. CHD patients without in-stent restenosis: It included 28 patients (23 males and 5 females) with a mean age of 50.85 ± 3.4 years, stenosis severity % at a follow-up of 19.6 ± 3.1 and MLD at a follow-up of 2.59 ± 0.4 mm.

All the patients included in the study were not diabetic (FPG < 100 mg/dl) but on performing oral glucose tolerance test (OGTT) 23 patients were shown to have impaired glucose tolerance (IGT) (2-h postload glucose 140–199 mg/dl) and (25 patients) had normal glucose tolerance (NGT) (2-h postload glucose < 140 mg/dl), but all patients had normal fasting plasma glucose levels < 100 ng/dl.

The levels of normal FPG, IGT, NGT are according to the American Diabetic Association (ADA).[16]

All patients gave informed consent to participate in the study.

All the subjects were submitted to full clinical assessment including history taking and through clinical examination

Table 1 Demographic and clinical data of the studied groups.

	CHD patients with in-stent restenosis (n = 20)	CHD patients without in-stent restenosis (n = 28)	P
Age (year)	51.75 ± 3.7	50.85 ± 3.4	0.39
Male/female	16 (80%)/4 (20%)	23 (82%)/5 (18%)	0.89
BMI (kg/m^2)	29.4 ± 1.2	29.3 ± 1.16	0.61
WHR	0.97 ± 0.02	0.96 ± 0.025	0.07
S.B.P (mmHg)	127.4 ± 9.0	124.8 ± 13.0	0.45
D.B.P (mmHg)	82.3 ± 6.0	79.7 ± 9.9	0.29
Hypertension, n (%)	8 (40%)	12 (42.9%)	0.84
IGT, n (%)	10 (50%)	13 (46.4%)	0.8
Dyslipidemia, n (%)	11 (55%)	14 (50%)	0.73
Oral antiplatelet drugs, n (%)	8 (40%)	12 (42.9%)	0.84
Hypolipidemic drugs (statins), n (%)	11 (55)	14 (50%)	0.73

Table 2 Comparison of the laboratory parameters in the studied groups.

	CHD patients with in-stent restenosis (n = 20)	CHD patients without in-stent restenosis (n = 28)	P
F. glucose (mg/dl)	92.9 ± 6.1	92.0 ± 5.3	0.6
2-hPP glucose (mg/dl)	145 ± 30.1	143.0 ± 29.4	0.82
F insulin (μU/ml)	12.57 ± 1.17	8.2 ± 1.2	< 0.001*
Sum PP insulin (μU/ml)	204.7 ± 26.5	135.9 ± 23.1	< 0.001*
HbA1c	5.5 ± 0.2	5.4 ± 0.26	0.1
HOMA-IR	2.9 ± 0.44	1.88 ± 0.37	< 0.001*
Total cholesterol (mg/dl)	189.3 ± 25.6	187.1 ± 27.7	0.78
HDL-C (mg/dl)	55 ± 6.5	56.1 ± 7.3	0.7
LDL-C (mg/dl)	110.55 ± 18.9	107.75 ± 21.4	0.63
TG (mg/dl)	121.75 ± 14.9	117.3 ± 17.7	0.33
Leptin (ng/ml)	10.54 ± 1.63	6.6 ± 1.0	< 0.001*

* P is significant.

Table 3 Comparison of the angiographic parameters before and after stent implantation and at follow-up in the studied groups.

	CHD patients with in-stent restenosis (n = 20)	CHD patients without in-stent restenosis (n = 28)	P
MLD (mm)			
Before stent implantation	0.74 ± 0.28	0.76 ± 0.29	0.83
After stent implantation	2.85 ± 0.43	2.88 ± 0.41	0.78
At follow-up	0.95 ± 0.28	2.59 ± 0.4	< 0.001*
Late lumen loss (mm)	1.9 ± 0.17	0.29 ± 0.14	< 0.001*
Diameter stenosis %			
Before stent implantation	83.7 ± 6.8	82.1 ± 6.75	0.43
After stent implantation	15.55 ± 3.44	14.86 ± 3.25	0.48
At follow-up	72.25 ± 5.98	19.6 ± 3.1	< 0.001*
Number of stents			
One stent, n (%)	14 (70%)	20 (71.4%)	0.91
Two stents, n (%)	6 (30%)	8 (28.6%)	0.91

* P is significant.

including blood pressure measurement, assessment of body mass index (BMI) [weight (kg)/high (m^2)] and waist to hip ratio (WHR) [waist circumference (cm)/hip circumference (cm)].

Laboratory measurements: Blood samples were collected from all subjects after overnight fasting (12 h) for the following investigations:

Fasting plasma glucose (FPG), 2-h post-prandial blood glucose (2-hPPG) levels, total cholesterol (T. cholesterol), high density lipoprotein cholesterol (HDL-C), triglyceride (TG) were assessed by using an ADVIA 1650 auto analyzer (Siemens Medical Solutions Diagnostic, USA).

Low density lipoprotein cholesterol (LDL-C) was estimated with the equation of Friedewald et al.[17]

Table 4 Correlation study of mean MLD at follow-up and some parameters of the study.

	MLD	
	All patients (n = 48)	
	r	P
F insulin (μU/ml)	−0.49	< 0.001*
Sum PP insulin (μU/ml)	−0.6	< 0.001*
HOMA-IR	−0.63	< 0.001*
Leptin (ng/ml)	−0.55	< 0.001*

* P is significant.

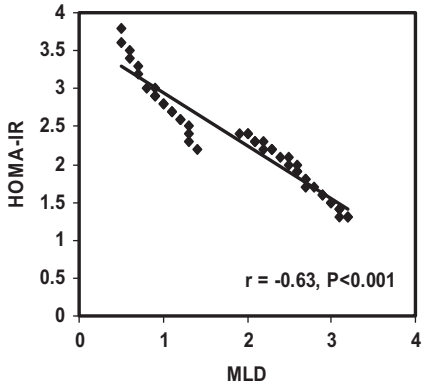

Fig. 1 Correlation between MLD and HOMA-IR.

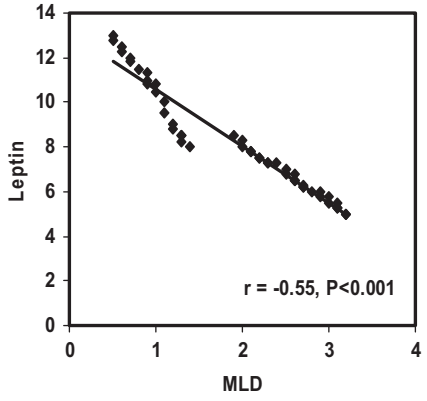

Fig. 2 Correlation between MLD and leptin.

Fasting and post-prandial insulin concentrations were measured by chemiluminescence immunoassay using an imulite analyzer (DPC, New York, USA) kit provided from diagnostic products co-operation (Los Angeles, CA, USA). This assay is a solid phase, two-site chemiluminescent methods immunometric assay. The unlabeled antigen binds to the immobilized antibody and is measured (in terms of quantity) after the labeled antibody is added.

Glycoselated hemoglobin (HbA1c) was estimated by ion exchange resin chromatography using Stanbio Glycohemoglobin.

After 12 h overnight fast, an oral glucose tolerance test (OGTT) was made for all patients by giving a 75 g oral glucose load, then blood samples were drawn from all patients after 1 and 2 h of assessment of 1-h post-prandial insulin (1-hPP insulin) and 2-h post-prandial insulin (2-hPP insulin) concentrations and also 2-h post-prandial blood glucose (2-hPP glucose) levels were evaluated.

The sum of 1-hPP insulin and 2-hPP insulin (sum PP insulin) was calculated and taken as a measure of post-prandial insulin concentrations.

Serum leptin was measured using a DRG® leptin (sandwich) ELISA kit (Ruo, USA). The microtiter wells are coated with monoclonal antibody directed toward a unique antigenic site on a leptin molecule. An aliquot of patient sample containing endogenous leptin is incubated in the coated well with a specific rabbit anti-leptin antibody. A sandwich complex is formed. After incubation, the unbound material is washed off and an antirabbit peroxidase conjugate is added for detection of the bound leptin. After addition of the substrate solution, the intensity of the color developed is proportional to the concentration of leptin in the patient sample.

Insulin resistance (IR) was calculated with the formula of homeostasis model assessment of IR (HOMA-IR) using the following equation: HOMA-IR = fasting plasma insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5, the median insulin resistance in normal subjects assessed by HOMA in a study made by Matthews et al. was 1.21, 1.45, 1.96 in stressed fasting samples, 1.3 in overnight basal samples and 2.0 in morning basal samples.[18]

2.1. Coronary angiography

Coronary angiography was performed through transfemoral approach using the Seldinger technique.[19] Coronary angiography was performed at baseline, immediately after stenting and 6–9 months after stenting to detect in-stent restenosis in patients presented with recurrence of chest pain. All patients were subjected to coronary angiography to evaluate the cause of recurrence of symptoms.

The following parameters were assessed in the stented coronary segment: minimal luminal diameter (MLD) and percentage of diameter stenosis and they were taken before and after stent implantation and at follow-up. Also late lumen loss (MLD after stent implantation minus MLD at follow-up) was assessed.

2.2. Procedure of stent implantation

All patients in the study received 600 mg clopidogrel the day before the procedure and another 75 mg at the day of the procedure and 10,000 units of unfractionated heparin at the procedure. Angioplasty stent implantation was performed

Table 5 Correlation study between late loss of coronary lumen in the stented coronary segment and some parameters of the study.

	Late loss	
	All patients (n = 48)	
	r	P
F insulin (μU/ml)	0.98	< 0.001*
Sum PP insulin (μU/ml)	0.7	< 0.001*
HOMA-IR	0.67	< 0.001*
Leptin (ng/ml)	0.72	< 0.001*

* P is significant.

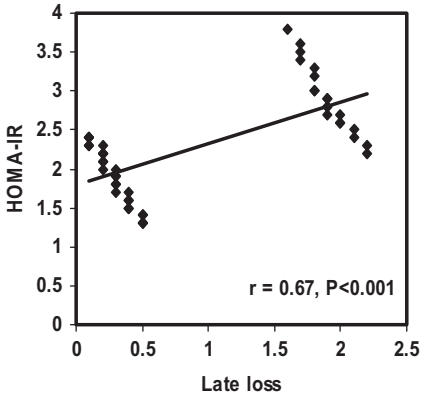

Fig. 3 Correlation between late loss and HOMA-IR.

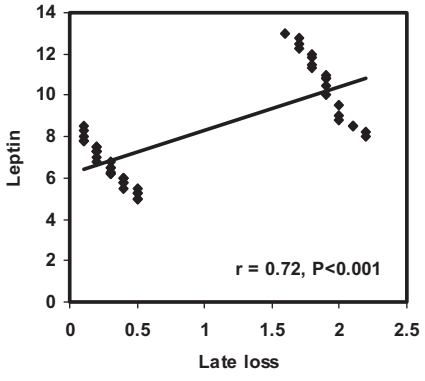

Fig. 4 Correlation between late loss and leptin.

according to the standard clinical practice through femoral approach either by direct stenting or after predilatation according to the criteria of each individual lesion. All patients who underwent coronary angiography were instructed to receive clopidogrel 75 mg in addition to acetylsalicylic acid daily for one year.

2.3. Statistical analysis

Results were entered, checked and analyzed using SPSS version 15.0 (statistical package for social science, SPSS Inc., Chicago, USA). Continuous variables were expressed as means ± standard deviation (SD). Dichotomous, discrete or categorical variables were expressed as percent. The unpaired Student's t test was used for comparison of means of the continuous variables to evaluate differences between the two groups. The chi-square (χ^2) test was used to compare categorical variables. The correlation between variables was done using Pearson's correlation coefficient. Logistic multiple regression analysis was used to determine the predictors of restenosis. Differences were considered to be statistically significant when the P values were < 0.05.

3. Results

Table 1 demographic and clinical data of the studied groups, age and male/female ratio were comparable and did not significantly differ in CHD patients with in-stent restenosis as compared to CHD patients without in-stent restenosis, also there was no statistical significant difference between the two groups as regard to BMI, WHR, SBP, DBP and percentage of patients who had hypertension, IGT and dyslipidemia. The percentage of patients taking oral antiplatelet drugs, antihypertensive drugs and hypolipidemic drugs were comparable in both groups ($P > 0.05$).

There was a highly significant increase in mean values of FP insulin (12.57 ± 1.17 versus 8.2 ± 1.2, $P < 0.001$), sum PP insulin (204.7 ± 26.5 versus 135.9 ± 23.1, $P < 0.001$), HOMA-IR (2.9 ± 0.44 versus 1.88 ± 0.37, $P < 0.001$) and leptin (10.54 ± 1.63 versus 6.6 ± 1.0, $P < 0.001$) in CHD patients with in-stent restenosis when compared to CHD patients without in-stent restenosis but there was no significant difference between both groups in F glucose, 2-hPP glucose, HbA1c, T. cholesterol, HDL-C, LDL-C and TG ($P > 0.05$) (Table 2).

MLD at follow-up was significantly lower in CHD patients with in-stent restenosis when compared to CHD patients without in-stent restenosis (0.95 ± 0.28 versus 2.59 ± 0.4, $P < 0.001$) while diameter stenosis% at follow-up and late lumen loss were significantly higher in patients with restenosis when compared to patients without restenosis [(72.25 ± 5.98 versus 19.6 ± 3.1, $P < 0.001$), (1.9 ± 0.17 versus 0.29 ± 0.14, $P < 0.001$), respectively], whereas there

Table 6 Multiple regression analysis for predictors of in-stent restenosis.

	B ± S.E.	P
F insulin	0.41 ± 0.02	< 0.001*
Sum PP insulin	0.02 ± 0.003	< 0.001*
HOMA-IR	1.5 ± 0.15	< 0.001*
Leptin	0.3 ± 0.03	< 0.001*

* P is significant.

was no significant difference between the two groups as regard to MLD and diameter stenosis % before and after stent implantation ($P > 0.05$) (Table 3).

There was a highly significant negative correlation between MLD at follow-up and each of FP insulin ($r = -0.49$, $P < 0.001$), sum PP insulin ($r = -0.6$, $P < 0.001$), HOMA-IR ($r = -0.63$, $P < 0.001$) and leptin ($r = -0.55$, $P < 0.001$) (Table 4, Figs. 1 and 2), whereas a positive correlation was found between late lumen loss and each of FP insulin ($r = 0.98$, $P < 0.001$), sum PP insulin ($r = 0.70$, $P < 0.001$). HOMA-IR ($r = 0.67$, $P < 0.001$) and leptin ($r = 0.72$, $P < 0.001$) (Table 5, Figs. 3 and 4). Multiple regression analysis revealed that each of FP insulin, sum PP insulin, HOMA-IR and leptin can be considered as an independent predictor of in-stent restenosis ($P < 0.001$) (Table 6).

4. Discussion

In-stent restenosis constitutes a significant clinical problem after coronary stent implantation and continues to limit the long term success of the procedure. In this study we tried to evaluate the relationship between insulin resistance, insulin levels, leptin levels and in-stent coronary restenosis in non-diabetic patients with CHD. Insulin resistance is a state in which peripheral tissues have decreased sensitivity to insulin leading to increased circulating insulin levels to maintain euglycemia. So, hyperinsulinemia is secondary to insulin resistance. Hyperinsulinemia in non-diabetic individuals may be a marker for a cluster of metabolic abnormalities including hypertension, dysplipidemia and impaired insulin mediate glucose uptake (impaired glucose tolerance),[6] the later is a metabolic state in which hyperinsulinemia is associated with normal fasting blood glucose and is considered a risk factor of cardiovascular disease,[20] HOMA-IR is the parameter that expresses insulin resistance, our study revealed a highly significant increase in HOMA-IR in CHD patients with in-stent restenosis as compared to CHD patients without in-stent restenosis (2.9 ± 0.44 versus 1.88 ± 0.37, $P < 0.001$) this indicates that patients with restenosis are more insulin resistant than patients without restenosis, also our results revealed a negative correlation between HOMA-IR and MLD at follow-up and a positive correlation between HOMA-IR and late lumen loss. Our results were supported by those obtained by Piatti et al.[21] who found that patients with CHD and restenosis after a stenting procedure were markedly insulin resistant and that insulin resistance is an independent predictor of early restenosis after coronary stenting, also Nishio et al.[22] had suggested that the cutoff value of HOMA-IR for restenosis after coronary stenting is 2.0 and that insulin resistance is associated with the increase in late lumen loss of stented coronary segment, and MLD at follow-up was significantly decreased in insulin resistant group of CHD patients. Moreover, Lima-Filho et al.[23] concluded that insulin resistance with HOMA-IR < 2.06 decreased the risk of restenosis. Some studies which were made to evaluate the effect of metabolic syndrome (including IR) on the risk of restenosis in drug eluting stents (DESs) implanted recipients has shown that metabolic syndrome did not increase restenosis rates after DESs implantation and that the recent advent of DESs has significantly reduced the incidence of restenosis compared with bare-metal stents, both in non-diabetic and in diabetic patients.[24]

Our results revealed a highly significant increase in F insulin and sum PP insulin (as a measure of post-prandial insulin concentrations) in CHD patients with in-stent restenosis and that both F insulin and sum PP insulin levels were negatively correlated with MLD at follow-up, whereas they were positively correlated with late lumen loss of the coronary stent. Piatti et al.[21] had reported that both CHD patient groups (with and without restenosis) were hyperinsulinemic after glucose load, but insulin levels were markedly higher in patients with restenosis. Moreover, Radke et al.[25] demonstrated that fasting plasma insulin levels serves as a valuable predictor of restenosis after coronary stent implantation and patients with high fasting insulin levels (> 8 μU/ml) were characterized by a smaller reference diameter of coronary vessels and developed a significantly higher late lumen loss. Moreover, Takagi et al.[26] and Babalik et al.[27] have shown that the sum of immunoreactive insulin (post-prandial hyperinsulinemia) during an OGTT was the best predictor of increased neointimal tissue proliferation and was a strong predictor of restenosis at six month follow-up after coronary stenting. Takagi et al.[28] also reported that the neointimal index measured by intracoronary ultrasound six months after coronary stenting was correlated with fasting and post glucose load insulin levels. Also, follow-up studies using intracoronary ultrasound showed that there was a decrease of in-stent neointimal tissue proliferation and intimal index measured by intracoronary ultrasound by almost 50% in patients with IGT by improving insulin sensitivity after six months therapy using thiazolidinediones, pioglitazone or rosiglitazone.[29–31]

The vascular effects of insulin are rather complex. Some of its vascular effects are protective and induced through activation of phosphatidyl inositol 3 kinase (PI3 K), production of cGMP[32] and endothelial nitric oxide (NO).[33] NO in turn can inhibit neointimal hyperplasia which is dependent upon migration and proliferation of vascular smooth muscle cells (VSMCs) and also it can attenuate binding of inflammatory cells to vascular wall, inhibit thrombosis by reducing platelet adhesion and aggregation and maintain vascular relaxation.[34,35] Insulin has other vascular effects which is hazardous, and occurs through stimulation of mitogen activated protein kinase (MAPK) signaling pathway, which in turn stimulates VSMCs proliferation and migration, stimulates other vascular growth factors production and increases endothelin-1 (a vasoconstrictor agent) production.[33] During the state of insulin resistance, insulin signaling via PI3 K is decreased, whereas the MAPK remains intact.[36]

Our findings revealed that plasma leptin levels were significantly increased in CHD patients with in-stent restenosis when compared with CHD patients without in-stent restenosis, also leptin was negatively correlated with MLD at follow-up and positively correlated with late lumen, loss, our findings were supported by those obtained from Piatti et al.[21] who revealed that leptin levels are increased in non-diabetic patients with restenosis after stenting and Nishio et al.[22] found that concentrations of leptin in the insulin resistant group were higher than those in the non-insulin resistant group. Recently, Galluccio et al.[37] found that impaired leptin/adiponectin ratio and hyperinsulinemia were reported in patients with in-stent restenosis. Leptin is a hormone related to fat metabolism and IR, it has been recognized as an independent risk factor for coronary heart disease and promotes vascular remodeling and neointimal tissue proliferation by induction of proliferation, differentiation of VSMCs. Multiple regression analysis in our study revealed that each of insulin

resistance, fasting and post-prandial hyperinsulinemia and hyperleptinemia can be considered as a predictor of coronary in-stent restenosis, so it is important to determine HOMA-IR, fasting and PP hyperinsulinemia after an OGTT, and leptin levels for non-diabetic CHD patients undergoing stent implantation to take a primary preventive strategies to decrease rate of restenosis after stenting, from the therapeutic point of view the group of CHD patients with insulin resistance, hyperinsulinemia and hyperleptinemia should be considered a high risk group and many measures should be taken to decrease insulin resistance such as weight reduction which will be also beneficial in decreasing leptin levels, and also giving such patients insulin sensitizers (pioglitazones, rosiglitazone) to improve insulin sensitivity and decrease hyperinsulinemia. Moreover the stents which are implanted in this group of patients should be eluted with antiproliferative drugs which are effective in restenosis prevention.

5. Conclusion

The present study revealed that fasting and sum PP insulin levels, HOMA-IR and leptin levels were significantly increased in CHD patients with in-stent restenosis and each of them was negatively correlated with MLD at follow-up and positively correlated to late lumen loss, our study, also suggests that insulin resistance, fasting and post-prandial hyperinsulinemia and hyperleptinemia are considered predictors of coronary in-stent restenosis and evaluation of HOMA-IR, insulin levels after standard OGTT and leptin levels are important tools in an attempt to recognize subjects at a risk of early restenosis among non-diabetic, CHD patients undergoing percutaneous coronary revascularization and stent implantation.

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