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Original Article

LEPTIN AND INSULIN RESISTANCE - MARKERS TO PREDICT MYOCARDIAL INFARCTION ?- A CROSS SECTIONAL STUDY

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Abstract

Introduction: Insulin resistance is known to be a risk factor for ischemic heart disease and myocardial infarction (MI).Leptin may have a role in the pathogenesis of MI. Leptin along with IR may be useful markers to predict MI. Objectives of the study were to find the association between serum leptin levels and insulin resistance in post myocardial infarction patients and also to find out if leptin along with insulin resistance can be used as a marker to predict myocardial infarction.

Methodology: The cross-sectional study was carried out in forty post-MI patients and forty age and gender matched healthy volunteers. Fasting plasma glucose, serum insulin, C-peptide and leptin levels were estimated by ELISA. Insulin resistance models were constructed using suitable formulae. Statistical analysis was carried out by SPSS 20 with suiatable tests.

Results: Serum leptin level was found to be significantly higher ($p<0.0001$) in post-MI group compared to controls. A highly significant hyperinsulinemia ($p<0.0001$) was noted in post-MI patients. Insulin based HOMA IR was also higher in cases. HOMA B Cell, HOMA 1%B Cell & QUICKI were very significantly low ($p<0.0001$) in cases(both insulin and C-peptide based).Correlation study showed that leptin level had a significant negative correlation with QUICKI ($r=-0.246$ & $p= 0.018$). A significant negative correlation ($r= -0.32$, $p= 0.015$) was also seen between leptin and C-Peptide based insulin resistance (HOMA IR-C). A significant positive correlation was observed between HOMA-IR and CK-MB as well as troponin T ($r=0.542$,$p<0.01$ and $r=0.46$ and $p<0.01$ respectively). ROC showed area under the curve (AUC) was found to be 0.667 with a sensitivity and specificity of 74.4% and 66.5% for leptin as a marker for IR

Conclusion: It was concluded in the study that patients showed hyperinsulinemia, hyperleptinemia, elevated IR, a negative association between leptin and insulin sensitivity after MI. Leptin ,along with IR, may be useful in predicting MI.

Keywords: *Leptin, Insulin Resistance, Myocardial Infarction*

Introduction

Insulin resistance (IR) is a heterogenic phenomenon, hyperinsulinaemia and hyperglycaemia being the traditional IR markers [1]. Insulin resistance is known to be a risk factor for ischemic heart disease and myocardial infarction (MI) [2]. IR often manifests in MI and is regarded as an independent predictor of in-hospital mortality, which can provide early risk stratification for recurrent acute coronary events [2,3]. Presently pathogenetic associations between IR and complicated MI are yet to be established.

Leptin and insulin resistance

Leptin is the most abundant hormone produced by adipocytes. Leptin regulates food intake and energy expenditure. Leptin and insulin play key metabolic roles. A majority of the studies suggest that leptin decreases insulin synthesis and secretion by pancreatic beta cells, and increases insulin hepatic extraction.[4-7] As a result, insulin delivery is reduced by leptin.[8]. This so-called adipoinsular axis is part of a leptin-mediated inhibitory feedback on insulin secretion in order to decrease adipogenesis. Leptin also decreases hepatic glucose production, increases insulin sensitivity, and decreases glucagon levels. Insulin, in turn, also plays a role in stimulating leptin production and secretion in the adipose tissue.[7]. leptin is positively correlated with insulin resistance, independently of body weight or adiposity, both in normoglycaemic and in diabetic patients.

Leptin and insulin share common effects in the control of food intake and energy metabolism. In the blood glucose homeostasis, both play important roles. Leptin and insulin directly regulate each other. Leptin inhibits insulin; insulin stimulates leptin synthesis and secretion. Leptin also increases insulin sensitivity, both centrally and peripherally.

A study by Khafaji et al suggested an elevated serum leptin levels after myocardial infarction. It was also suggested that serum leptin level may be a predictor of the left ventricular ejection fraction and the degree of atherosclerosis[9].

Methods

Study setting:

The cross-sectional study was conducted in Central Research Laboratory of K.S.Hegde Medical academy and Department of Medicine, K.S.Hegde Charitable Hospital of Nitte University, Mangaluru, Karnataka, India.

Study subjects:

Forty patients diagnosed with ST elevation MI were recruited in to the study. The diagnosis wasbased on clinical, electrocardiographic (ECG), echocardiographic and biochemical characteristics of MI (2007 National Cardiology Society Guidelines). MI patients within 24 hours from the onset of infarction were included.

Exclusion criteria: subjects with the history of type 2 diabetes mellitus , anaemia, renal or hepatic insufficiency, cancers, worsening of infectious or inflammatory diseases, and autoimmune conditions. Informed consent will be taken from patients. Institutional ethics committee approval was taken before starting the study.

Controls: Age and gender matched apparently healthy volunteers

Two milliliters of venous blood sample was drawn in plain tubes from the recruited patients for biochemical analysis after obtaining written informed consent from patients' bystanders.Samples will be centrifuged at 3000 rpm for 15 minutes.

Laboratory Investigations:

Fasting plasma glucose was estimated using automated chemistry analyzer, serum insulin,C-peptide and leptin levels were assayed using ELISA. Insulin resistance was calculated by homeostasis model assessment (HOMA) for insulin as well as C-petide as epicted in table 1.

Statistical analysis

The statistical analysis was carried out with SPSS 20. Catergorical data was expressed as percentages and continuous data wasexpressed as mean ± standard deviation (SD). Comparison of leptin, Insulin, C peptide levels and various Insulin Resistance models was done using Mann Whitney U test. Spearmann's correlation was used to find the correlation between leptin and various Insulin resistance models. Receiver operating characteristic curve was used to find the usefulness of leptin as a marker of MI. Chi-square test was done to find the association between leptin and Insulin Resistance. Odd's ratio was calculated to assess the risk of MI in patients with elevated leptin levels.

Results

Cases had a mean CK-MB levels of 42.29±5.23 U/L and 356.47±41.89 pg/ml.Serum leptin level was found to be significantly higher (p<0.0001) in post-MI group compared to controls (Figure 1). A highly significant hyperinsulinemia (p<0.0001) was noted in post-MI patients. Insulin based HOMA IR was also higher in cases (p<0.01).

HOMA B Cell, HOMA 1%B Cell & QUICKI were very significantly low (p<0.0001) in cases (fig 2).

C-peptide levels were significantly lower in cases (p=0.022) as compared to controls. Insulin resistance models based on C peptide also were calculated. HOMA-IR C was insignificantly higher in cases. HOMA B cell-C, HOMA 1% B Cell-C as well as C peptide IR (CIR) were significantly lower in cases (p<0.0001 & p=0.002) respectively as compared to controls(fig 3).

Correlation study showed that leptin level had a significant negative correlation with QUICKI (r=-0.246 & p= 0.018). A significant negative correlation (r= -0.32, p= 0.015) was also seen between leptin and C-Peptide based insulin resistance (HOMA IR-C). There was no significant correlation seen between leptin and other insulin resistance models. A significant positive correlation was observed between HOMA-IR and CK-MB as well as troponin T (r=0.542 ,p<0.01 and r=0.46 and p<0.01 respectively).

On analyzing ROC, area under the curve (AUC) was found to be 0.667 with a sensitivity and specificity of 74.4% and 66.5% for leptin as a marker for IR(fig 4).

ROC was constructed between leptin and HOMA IR, considering HOMA-IR >2.4 as insulin resistance. AUC was 0.52, sensitivity of 56.4% & specificity of 50% (fig 5).

An odd's ratio of 1.87 was obtained which suggests that the risk of T2DM is 1.87 times higher in subjects with elevated PON1 levels. Chi-square showed a significant association (p= 0.0001) between MI and leptin levels.

Discussion

It is evident from our results that hyperleptinemia,hyperinsulinemia, elevated HOMA-IR (insulin based),lowered C-peptide,lowered HOMA B Cell, HOMA 1%B Cell & QUICKI (both insulin and C-peptide based),lowered QUICKI were noted in post-MI patients.These findings are suggestive of insulin resistance playing a major role in the pathogenesis in MI patients. This finding is supported by a significant positive association between cardiac markers,CK-MB ,troponinT and HOMA-IR.

Our findings are supported by the results by Soderberg et al, who suggested that leptin is a risk factor for MI [10].The study reported an elevated leptin levels in patients with MI. Pathogenetic causes of coronary heart disease includes a cluster of risk factors like insulin resistance syndrome or Syndrome X [11.12]. Since the insulin resistance syndrome is associated with obesity, which is accompanied by high leptin levels ,leptin may be important for the development of the insulin resistance syndrome and its sequelae [13].

Insulin is reported to enhance leptin-induced NO release by potentiating leptin-stimulated phosphorylation of Akt and endothelial NO synthase. This is responsible for the possibility of cross talk between insulin and leptin signalling [14]. On the contrary, leptin does not alter mesenteric blood flow in conscious rats treated with NO synthase inhibitors or α-adrenergic blockers, despite increased sympathetic activity [15].The findings of the study conclude that leptin alters the NO-dependent vascular reactivity of resistance vessels. Systemic leptin administration does not attenuate vasoconstriction caused by sympathetic nerve stimulation, suggesting that direct vasodilator actions of leptin may be insufficient to oppose sympathetically mediated vasoconstriction [16]. Thus, although leptin may possess beneficial NO-dependent vasodilator actions, the net effects of leptin on vascular function in vivo are still unclear and may depend on the presence or absence of other metabolic and cardiovascular pathophysiology.

Leptin increases insulin sensitivity in rats and may improve vascular responses to insulin in states of insulin resistance [17]. Leptin secretion by adipocytes is stimulated by insulin, and plasma leptin significantly correlates with plasma insulin [18]. By contrast, under some conditions, leptin negatively regulates insulin signalling and glucose uptake [19, 20].

Leptin increases free fatty acid oxidation in isolated mouse soleus muscle by 42%, whereas insulin decreases this by 40%. When both hormones are administered, leptin attenuates both the antioxidative and lipogenic effects of insulin by 50% [21]. Leptin attenuates the antioxidative, lipogenic actions of insulin on muscle free fatty acid metabolism via a peripheral mechanism, whereas the effects of leptin in modulating insulin-stimulated glucose disposal appear to occur via a central mechanism [22]. Recombinant mouse leptin inhibits glycogen synthesis in soleus muscle of *ob*/*ob* mice in the presence of insulin [23]. By contrast, leptin increases glycogen synthesis in cultured C2C12 muscle cells [24].

Important peripheral actions of leptin include inhibition of insulin biosynthesis and secretion in pancreatic *β*-cells. In turn, insulin stimulates leptin secretion from adipose tissue, establishing a hormonal regulatory feedback loop, the so-called adipoinsular axis. Multiple signal transduction pathways are involved in leptin signalling in pancreatic *β*-cells. In most overweight individuals, physiological regulation of body weight by leptin seems to be disturbed, representing "leptin resistance." This leptin resistance at the level of the pancreatic *β*-cell may contribute to dysregulation of the adipoinsular axis and contribute to development of hyperinsulinemia and manifest type 2 diabetes mellitus in overweight patients [25].

Leptin may potentiate pressor effects of hyperinsulinemia in insulin-resistant states. Therefore, interactions between Ang II and insulin with leptin may have deleterious cardiovascular effects in the setting of obesity.
Leptin contributes to atherogenicity in every possible way,by affecting endothelial functions,smooth muscle proliferation, potentiating inflammatory markers,predisposing to dyslipidemia and oxidative stress.It also thrombogenic iin nature.Several human studies suggest that leptin contributes to endothelial dysfunction or damage in some pathological states[26,27].
However the role of leptin in regulating endothelial function in humans remains controversial and may depend on the context of cardiovascular pathophysiology that is present or absent. Leptin stimulates lipoprotein lipase secretion in cultured human and murine macrophages. Leptin increases accumulation of cholesterol esters in foam cells, especially at high glucose concentrations[28].
Leptin potentiates secretion of tumor necrosis factor and interleukins 2 and 6, increases generation and accumulation of reactive oxygen species, and enhances expression of monocyte chemoattractant protein-1[29]. Leptin stimulates production of proinflammatory cytokines and enhances production of Th1-type cytokines[30].In endothelial cells, leptin stimulates transforming growth factor-*β* synthesis[31].
The ability of leptin to promote proinflammatory signaling through cytokines and growth factors may contribute to endothelial dysfunction, atherosclerosis, and insulin resistance in hyperleptinemic states. Leptin stimulates migration and proliferation of vascular smooth muscle cells and expression of matrix metalloproteinase-2 in human aorta in vitro[32].
Leptin may increase oxidative stress through multiple mechanisms. In bovine aortic endothelial cells, leptin increases formation of reactive oxygen species in a process coupled with increased fatty acid oxidation and activation of protein kinase A[29].In rats, chronic induction of hyperleptinemia decreases paraoxonase 1 activity.

Leptin seems to promote both atherogenesis and and insulin resistance. By contrast, in other contexts, leptin may have anti-atherogenic and insulin-sensitizing effects. These opposing actions of leptin are maintained in balance under healthy conditions. In pathological conditions such as obesity, the balance of leptin actions may shift to stimulate vascular inflammation, oxidative stress, and vascular smooth muscle hypertrophy. These actions may contribute to the pathogenesis of hypertension, atherosclerosis, left ventricular hypertrophy, and type 2 diabetes mellitus. Several clinical studies demonstrate that hyperleptinemia predicts acute cardiovascular events, restenosis after coronary injury, and cerebral stroke independent of traditional risk factors [33]. By contrast, some data indicate that leptin may protect against atherosclerosis in specific animal models

[26]. Indeed, low plasma leptin predicts cardiovascular mortality.

Leptin may potentiate the pressor effects of hyperinsulinemia in insulin-resistant states. Therefore, interactions between Ang II and insulin with leptin under insulin-resistant conditions may have deleterious cardiovascular effects in obesity. Positive and independent associations between leptin and insulin resistance suggest a role for leptin in the metabolic syndrome [34]. However, human studies specifically examining the interactions between cardiovascular actions of insulin and leptin in normal and pathological states are lacking.

Conclusion

It was concluded from the study that patients showed hyperinsulinemia, hyperleptinemia, elevated IR, a negative association between leptin and insulin sensitivity after MI. Leptin ,along with IR, may be useful in predicting MI.The association of leptin levels as well as with insulin resistance may help in understanding the pathogenesis of MI and related complications. Leptin along with IR may be used as an alternative marker in predicting the risk of myocardial infarction.

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Table 1. Insulin resistance Models

HOMA -IR	(fasting glucose x fasting insulin)/22.5 ; insulin expressed in µU/L, glucose in mmol/l.
HOMA B cell	20x insulin / (Fasting blood glucose -3) ; FBS in mmol/l
HOMA B 1%	20x Insulin/ Fasting Plasma Glucose- 3.5 ; FBS in mmol/l
QUICKI	1/ (log G+ log I)
C-peptide insulin resistance, CIR	20/ (Glucose X C-Peptide) ; glucose and C-peptide in mmol/L

Figure 1. Comparison of leptin levels in cases and controls

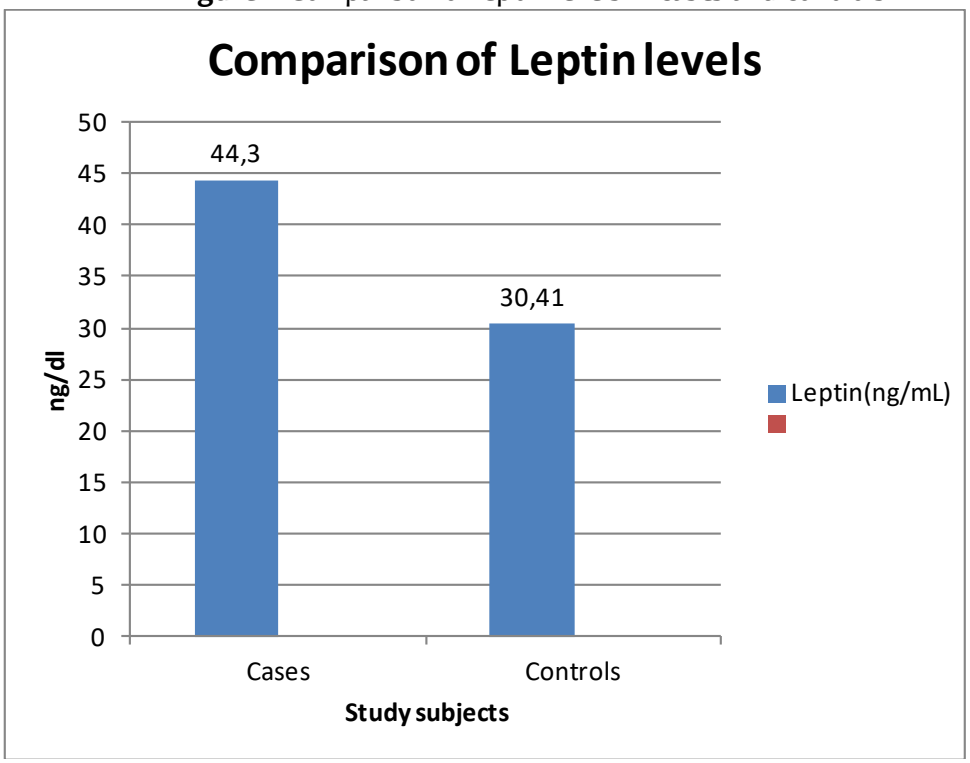

Figure 2. Comparison of Insulin Based IR models

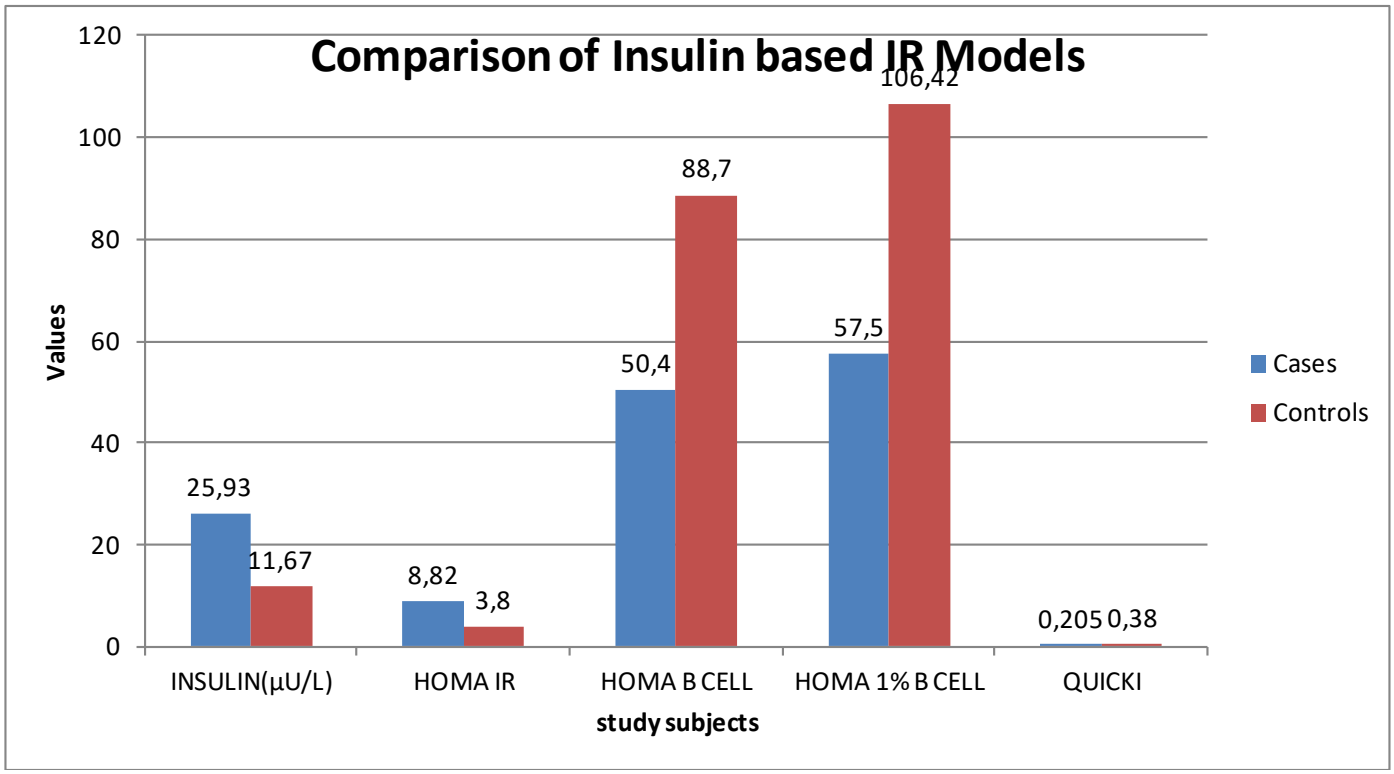

Figure 3. Comparison of C-peptide Based IR Models

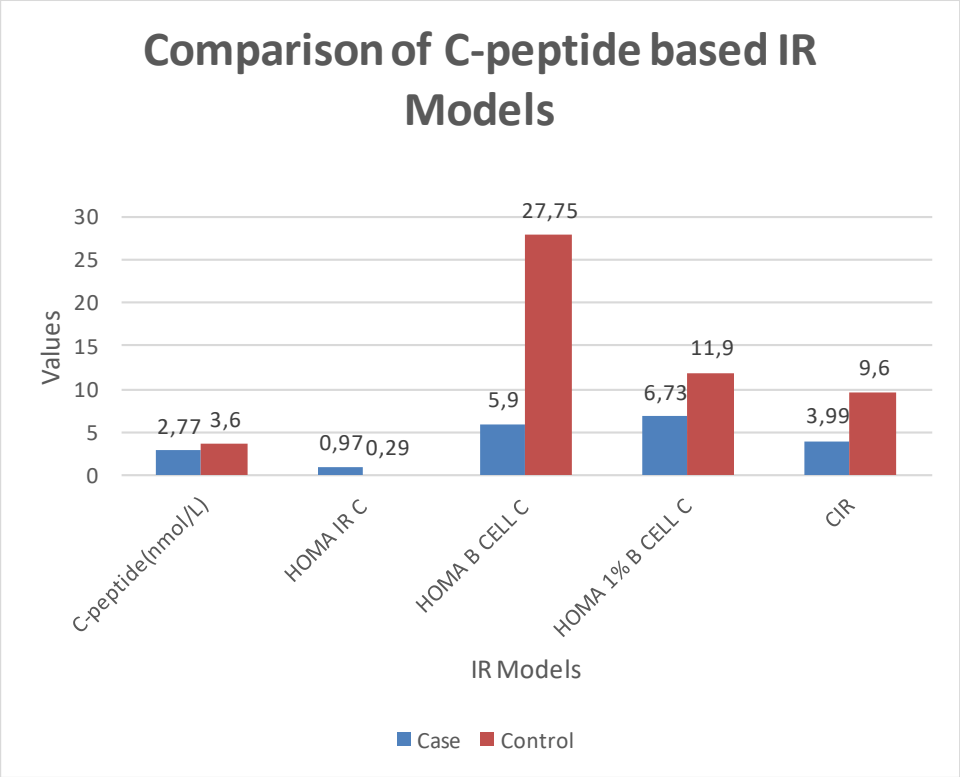

Figure 4. ROC for Leptin as a marker for MI

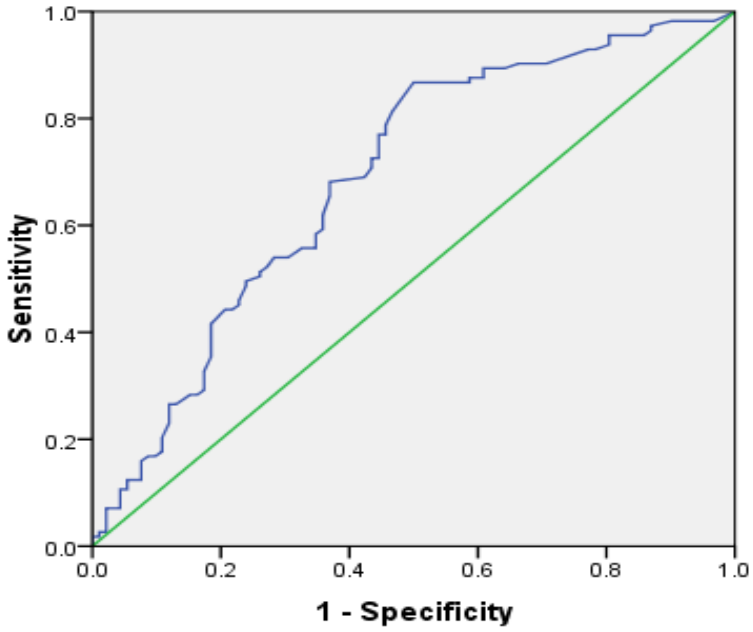

Figure 5. ROC for Leptin as a marker for IR