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Study of Insulin Resistance in Normal Obese South Indian Population

V.Varun Raj, G.Pramod, M.Thirupathi, B.Naresh, J.Prashanth and N.Naresh Babu

Medicinal Chemistry Research Laboratories, Vikas College of Pharmacy, Kakatiya University, Warangal, Andhra Pradesh, India

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ABSTRACT

Difficulties in measuring insulin sensitivity prevent the identification of insulin-resistant individuals in the general and obese population. Therefore, we compared fasting insulin, homeostasis model assessment (HOMA), insulin-to-glucose ratio, Bennett index, and a score based on weighted combinations of fasting insulin, BMI, and fasting triglycerides with the euglycemic insulin clamp to determine the most appropriate method for assessing insulin resistance in the obese south Indian population. We measured insulin sensitivity (as the whole body insulin-mediated glucose uptake) and fasting post hepatic insulin delivery rate (IDR) with the use of the euglycemic insulin clamp technique in a large group of obese subjects in the database of the European Group for the Study of Insulin Resistance. Insulin resistance, defined as the lowest decile of insulin sensitivity in the lean subgroup. In the obese with preserved insulin sensitivity, risk for diabetes, cardiovascular risk, and response to treatment may be different than in insulin resistant obesity. As Asian Indians have an increased susceptibility to diabetes and have increased insulin resistance, they are a unique population for carrying out genetic studies. In this Study all the subjects were diagnosed as per the American Diabetes Association criteria based on fasting and post lunch blood glucose levels.

Keywords: Insulin resistance, obesity, obese, blood glucose levels.

INTRODUCTION

Insulin Resistance (IR) is the condition in which normal amounts of insulin are inadequate to produce a normal insulin response from fat, muscle and liver cells. Insulin resistance in fat cells reduces the effects of insulin and results in elevated hydrolysis of stored triglycerides in the absence of measures which either increase insulin sensitivity or which provide additional insulin. Increased mobilization of stored lipids in these cells elevates free fatty acids in the blood plasma. Insulin resistance in muscle cells reduces glucose uptake (and so local storage of glucose as

glycogen), whereas insulin resistance in liver cells results in impaired glycogen synthesis and a failure to suppress glucose production. Elevated blood fatty acid levels (associated with insulin resistance and diabetes mellitus Type 2), reduced muscle glucose uptake, and increased liver glucose production all contribute to elevated blood glucose levels. High plasma levels of insulin and glucose due to insulin resistance are believed to be the origin of metabolic syndrome and type2 diabetes, including its complications. [1-5]

The most common type of insulin resistance is associated with a collection of symptoms known as metabolic syndrome. Insulin resistance can progress to full type2 diabetes. This is often seen when hyperglycemia develops after a meal, when pancreatic β-cells are unable to produce sufficient insulin to maintain normal blood sugar levels (euglycemia). The inability of the β-cells to produce sufficient insulin in a condition of hyperglycemia is what characterizes the transition from insulin resistance to type2 diabetes.Various disease states make the body tissues more resistant to the actions of insulin. Examples include infection (mediated by the cytokine TNFα) and acidosis. Recent research is investigating the roles of adipokines (the cytokines produced by adipose tissue) in insulin resistance. Certain drugs may also be associated with insulin resistance (e.g., glucocorticoids). [6-10]

Insulin itself can lead to insulin resistance; every time a cell is exposed to insulin, the production of GLUT4 (type four glucose receptors) on the cell's membrane is decreased. [11] This leads to a greater need for insulin, which again leads to fewer glucose receptors. Exercise reverses this process in muscle tissue, [12] but if left unchecked, it can spiral into insulin resistance. [13-15]

MATERIALS AND METHODS

The study included 43 non obese subjects, 51 obese subjects were selected from Warangal, Andhra Pradesh, India from January 2009 to March 2009. All subjects are tested individually at Vedasai Diagnostic Centre. Subjects were excluded if they had chronic gastrointestinal diseases associated with mal absorption, chronic pancreatitis, and history of any malignant disease, history of alcohol abuse, kidney and liver failure. All the subjects were diagnosed as per the American Diabetes Association criteria based on fasting and post lunch blood glucose levels.

Fasting Insulin Levels:
A fasting serum insulin level of greater than the upper limit of normal for the assay used (approximately 60pmol/L) is considered evidence of insulin resistance.

Glucose tolerance testing (GTT):
During a glucose tolerance test, which may be used to diagnose diabetes mellitus, a fasted patient takes a 75 gram oral dose of glucose. Blood glucose levels are then measured over the following 2 hours.

Interpretation is based on WHO guidelines. After 2 hours a Glycemia lessthan 7.8 mmol/L is considered normal, a glycaemia of between 7.8 to 11.0 is considered as Impaired Glucose Tolerance (IGT) and a glycaemia of greater than or equal to 11.1 is considered Diabetes Mellitus.

An OGTT can be normal or mildly abnormal in simple insulin resistance. Often, there are raised glucose levels in the early measurements, reflecting the loss of a postprandial (after the meal) peak in insulin production. Extension of the testing (for several more hours) may reveal a hypoglycemic "dip," which is a result of an overshoot in insulin production after the failure of the physiologic postprandial insulin response.

Biochemical Parameters

TC, HDL-C and TG were quantified using kits obtained from Biosystems S.A., Barcelona, (Spain). Clinical history was obtained from all patients including age, sex, drugs, smoking, and alcohol consumption, level of physical exercise, previous history of diabetes, coronary heart disease and peripheral vascular disease. Family history of diabetes was also ascertained. Following exclusion criteria were used in this study: hypothyroidism, liver, kidney or heart failure and neoplasm. Informed written consent was taken from the selected patients. After 12 hours of overnight fast, each participant's weight, height and blood pressure were measured and recorded. Blood samples were collected into the in dry tubes with EDTA. Plasma was separated immediately by centrifugation at 4000 rpm for a period of 10 minutes. Fasting blood glucose was assessed by absorbance method (Diagnostic- Merck). Fasting insulin was assessed by ELISA (Diagnostic-Automation). Fasting triglyceride levels were measured enzymatically by colorimetric test (LABKIT). Four indirect methods used for the assessment of IR (Insulin Resistance) were calculated using the equations mentioned below.

HOMA = insulin (mU/m) x [glucose (mmol/L)/22.5]
QUICKI = 1/ (log insulin+log glycemia in mg/dL)
HOMA-IR = FI in mU/l or µU/ml X FPG in mg/dl / 405

The insulin sensitivity index or QUICKI defined as 1/ [log (I0) + log (G0)], where I0 is fasting insulin and G0 is fasting glucose, was also calculated for each subject.

Table: 1. Descriptive Data of the subjects in the study

PARAMETER	NORMAL SUBJECTS	OBESE SUBJECTS	P-VALUE
SEX (M/F)	52/0	44/0	NA
AGE (Y)	49.09 ± 5.60	48.31 ± 5.78	0.5059
BMI (Wt/Ht*Ht)	24.23 ± 0.62	28.89 ± 3.41	0.0001
FBS (mg/dl)	82.44 ± 6.34	102.41 ± 13.36	0.0001
INSULIN (mU/L)	18.10 ± 5.72	13.29 ± 4.33	0.0001
PLBS (mg/dl)	131.24 ± 16.13	149.05 ± 38.29	0.003
HBAIC (%)	5.95 ± 1.00	6.51 ± 1.68	0.047
TC (mg/dl)	146.48 ± 14.38	166.72 ± 38.30	0.0006
HDL (mg/dl)	48.83 ± 6.02	50.45 ± 7.78	0.2561
TRYGLYCERIDES (mg/dl)	130.39 ± 23.58	133.42 ± 20.05	0.5044
LDL (mg/dl)	70.26 ± 14.60	90.65 ± 33.24	0.0001
CREATININE	0.96 ± 0.11	0.97 ± 0.11	0.6813
HOMA-IR (FBS*Insulin/405)	3.68 ± 1.21	3.30 ± 1.04	0.09
INSULIN SENSITIVITY (1/(log(G0)+log(I0))	0.31 ± 0.02	0.33 ± 0.04	0.1502

All the data were expressed as Mean ± S.D, significant difference of the groups were analysed by using Student t-test (unpaired), p-value less than the 0.05 were considered as statistically significant.

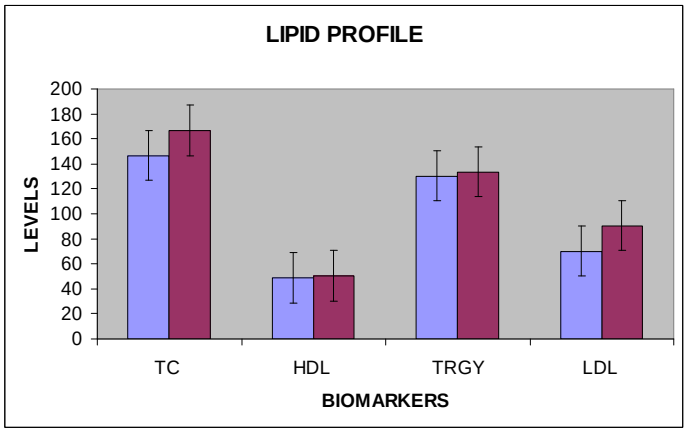

Fig.1

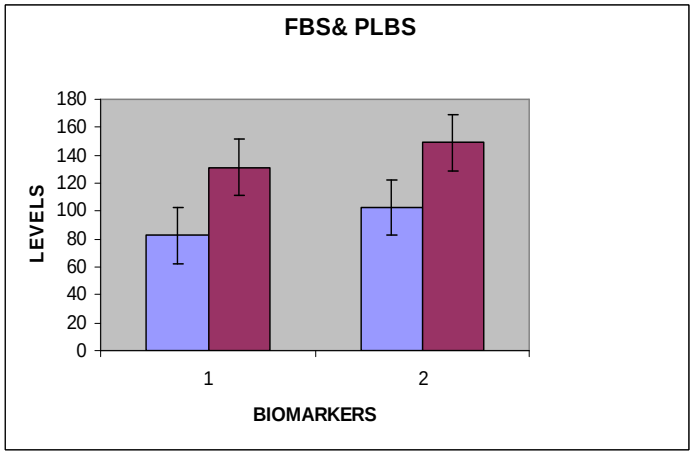

Fig.2

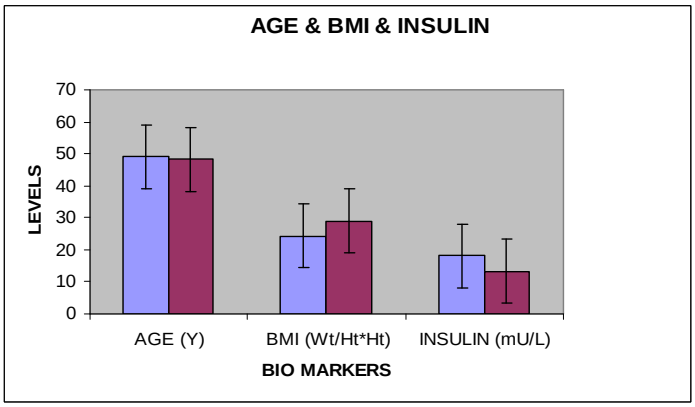

Fig.3

Raised TG (≥ 175 mg %) and/or low HDL- cholesterol (<39 mg %) or treatment. IFG, glucose ≥ 110 and <126 and IGT, glucose ≥ 140 mg% <200 mg%. HOMA ≥ 3.16 was considered as cut off for insulin resistance.

Statistical analysis

All variables were expressed as means ± SD. Group differences of continuous variables were compared using unpaired student's t-test. Relationships between variables were determined by

Pearson's correlation coefficient. For all analyses, a *P* value < 0.05 was considered to be statistically significant. All analyses were performed using Graph Pad Prism 4 software.

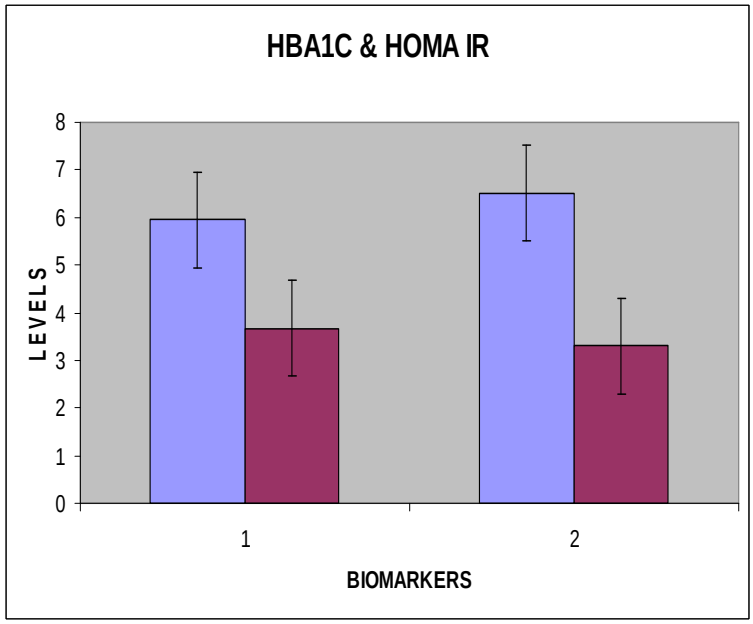

Fig.4

RESULTS AND DISCUSSION

Anthropometric and biochemical characteristics of the study subjects are shown in Table-5. Treated type-II diabetes patients were had significantly higher fasting and post lunch blood glucose (*P*<0.0001, *P*<0.0001), glcosylated hemoglobin (P=0.010), high sensitive C-reactive protein (P=0.005) and insulin resistance (HOMA-IR) (0.0108) and not significantly higher fasting serum insulin, c-peptide and abnormal lipid profile than nondiabetic subjects. Interestingly, insulin sensitivity expressed as HOMA-S (0.0114) and serum IGF-I concentrations were significantly lower in treated type-II diabetes patients when compared to the normal subjects (*P*=0.043).

Univariate correlations between serum IGF-I concentrations and established components of the insulin resistance syndrome were assessed for the study subjects and are shown in the Table-2. In normal subjects serum IGF-I concentrations were negatively correlated with age, BMI, Hs-CRP, c-peptide, total lipid profile and insulin sensitivity expressed as HOMA-S but HbA1c, glucose, insulin and insulin resistance (HOMA-IR) were positively correlated. In treated type-II diabetic patients serum IGF-I concentrations were negatively correlated with age, glucose, HbA1c, Hs-CRP, insulin, c-peptide, total lipid profile and insulin resistance expressed as HOMA-IR but positively correlated with HDL cholesterol and insulin sensitivity expressed as HOMA-S.

Correlations for HOMA-S with these metabolic variables in normal subjects were negatively correlated with glucose, HbA1c, insulin, c-peptide, total lipid profile, insulin resistance expressed as HOMA-IR and IGF-I but positively correlated with age, BMI, and Hs-CRP. HOMA-S was negatively correlated with age, BMI, glucose, Hs-CRP, insulin, c-peptide,

triglycerides, LDL, VLDL cholesterol and insulin resistance (HOMA-IR). In contrast, it was positively correlated with HbA1c, HDL, total cholesterol and serum IGF-I in treated patients.

However, the correlations between serum IGF-I concentrations and established components of the insulin resistance syndrome including Hs-CRP, total and LDL cholesterol were significant in normal subjects but age and insulin sensitivity were significant in treated patients. The correlations between serum insulin sensitivity calculated from HOMA-S and serum insulin and insulin resistance estimated from HOMA-IR were statistically significant in normal subjects but age, HDL cholesterol and serum IGF-I were significant in treated patients. The significant correlations of serum IGF-I and HOMA-S with all established components of insulin resistance syndrome were shown.

CORRELATION DIAGRAMS
NORMAL SUBJECTS (Fig.5-9)

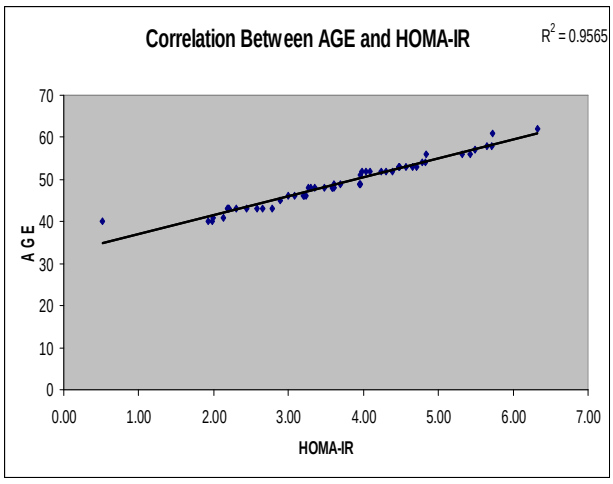

Fig.5

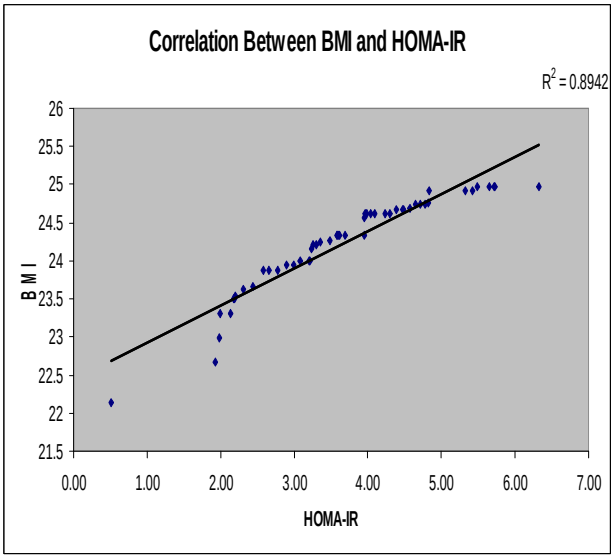

Fig.6

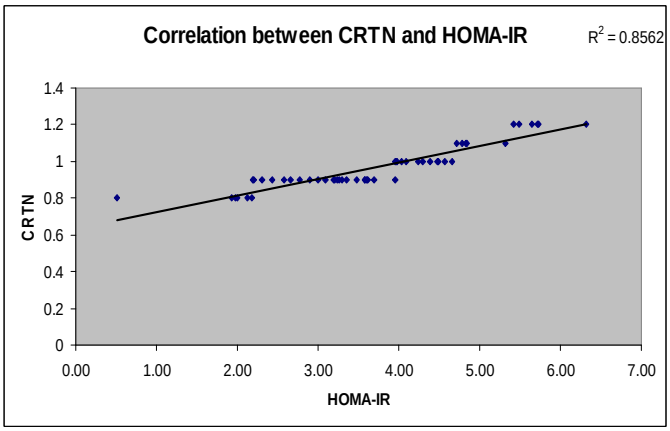

Fig.7

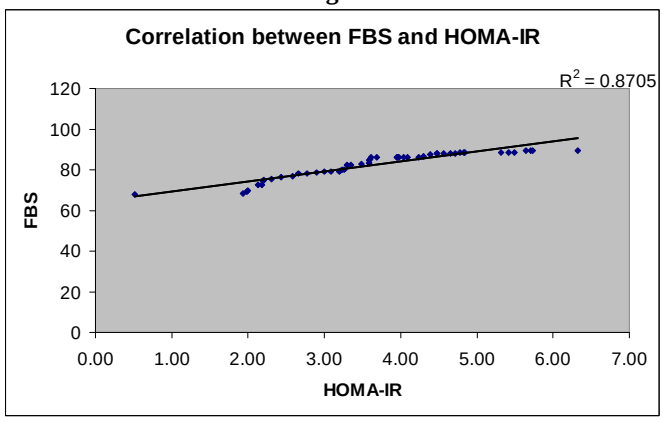

Fig.8

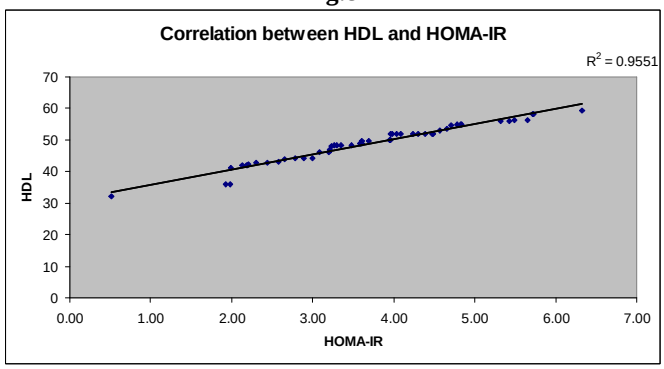

Fig.9

Serum IGF-I levels were positively correlated with insulin sensitivity and HDL cholesterol and negatively correlated with all components of insulin resistance syndrome. These relations of HOMA-S were similar in degree and directions to those observed with serum IGF-I levels. Furthermore, low levels of serum IGF-I were significantly related with the metabolic syndrome according to the WHO. However, our findings are consistent with the animal studies demonstrating low insulin sensitivity in mice with liver specific deletion of the IGF-I gene that is reversed by treatment with recombinant human IGF-I. Raised blood pressure and slightly enhanced plasma insulin concentrations have been reported in mice with a mutant IGF-I allele causing a marked decrease in circulating IGF-I levels.

OBESE SUBJECT DIAGRAMS: (Fig.10-14)

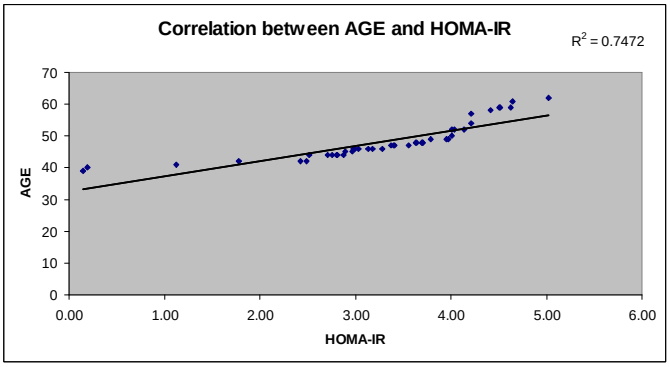

Fig.10

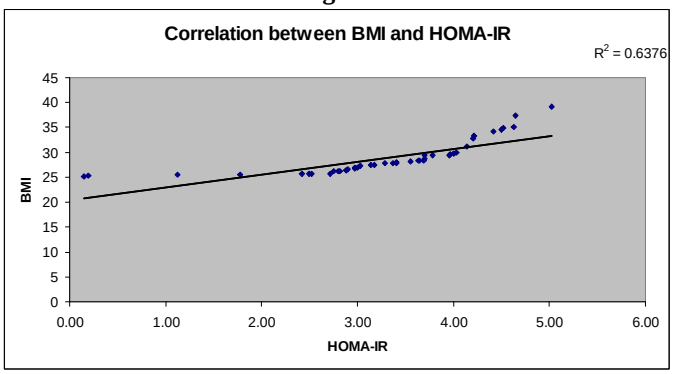

Fig.11

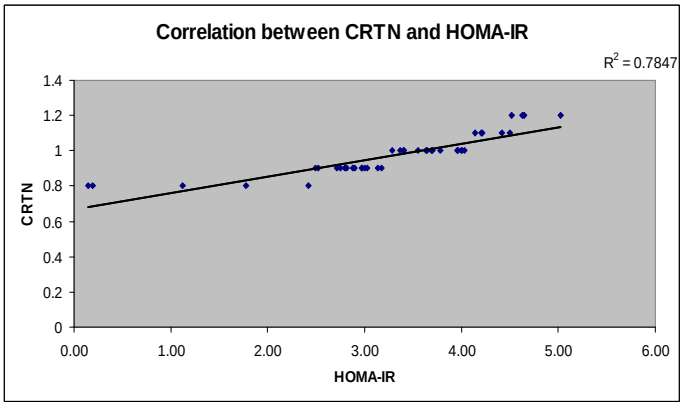

Fig.12

The present investigation was limited by the fact that the analyses were based on total IGF-I rather than the biologically active free IGF-I. Moreover, the analyses of total IGF-I is very high, it is also possible that the nutritional and genetic factors might influence the actual levels of circulating IGF-I. In this regard, a polymorphism in the promoter region of the IGF-I gene was associated with low levels of IGF-I and increased risk of type-II diabetes mellitus. In addition to this, IGF-I binding proteins (IGFBPs) were not measured which play an important role in regulating the bioavailability of IGF-I. Among IGFBPs, IGFBP-3 is very important since it binds more than 95% of IGF-I in blood circulation.

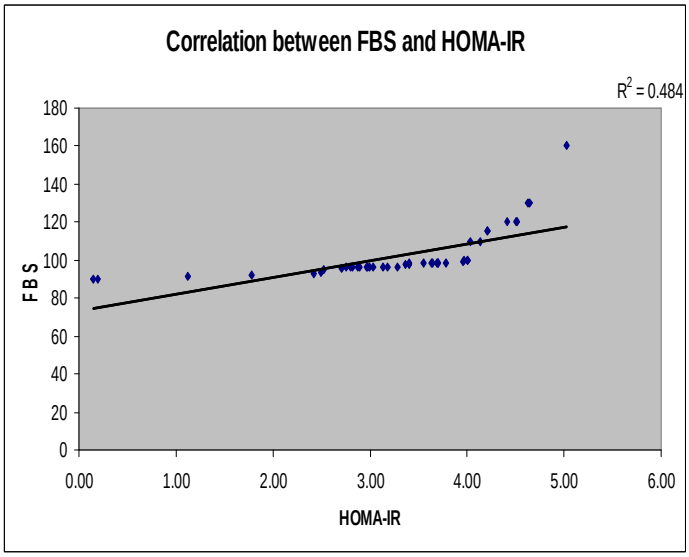

Fig.13

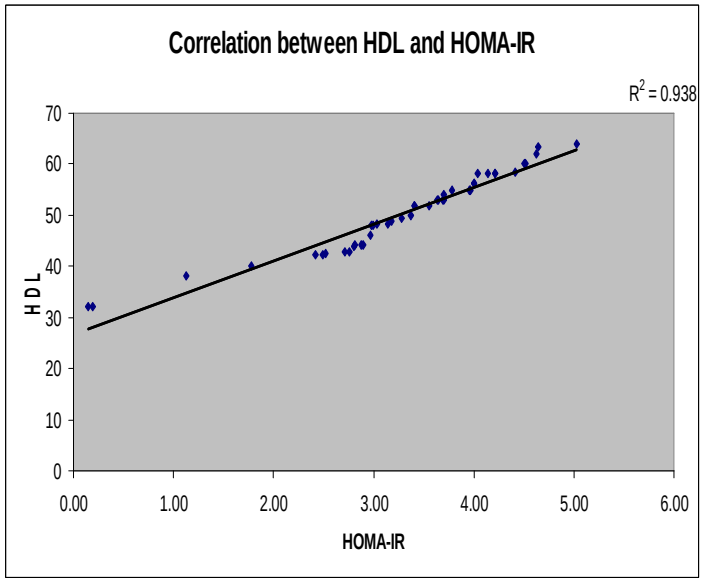

Fig.14

IGF-I has hypoglycemic effects and enhances insulin sensitivity in both experimental and human subjects it is due to its type-1 receptors and / or hybrid insulin / IGF-I receptors. However, it is not clear how low IGF-I levels may induce insulin insensitivity. The insulin receptors are widely distributed in human tissues and behave as IGF-I homo receptor rather than insulin homo receptor or some intermediate of the two receptors. It has been proposed that the hybrid insulin/IGF-I receptors would reduce insulin sensitivity in target tissues of insulin action leading to insulin resistance. Because of this fact, in patients with insulinoma, a condition characterized by marked hyperinsulinemia, down regulation of insulin receptors induced by elevated plasma insulin was associated with increased abundance of hybrid insulin/IGF-I receptors.

Most of the circulating IGF-I is derived from its synthesis in the liver, regulated by growth hormone, insulin and nutritional intake. Low levels of circulating IGF-I may be because of

inadequate negative feedback at the level of the hypothalamus and / or pituitary thus resulting in growth hormone hypersecretion and a decrease in insulin sensitivity. In support of this possibility, it has been shown that mice with liver specific deletion of the IGF-I gene exhibited elevated GH levels, which were associated with insulin resistance and impaired activation of early signaling events in response to insulin. It has been demonstrated that blocking of GH action in mice with liver specific deletion of the IGF-I gene by crossing them with mice over expressing a mutant form of GH, which prevents GH activation of its receptor, resulting improved insulin sensitivity. Considering these results together, it was suggested that GH hypersecretion may be a major determinant of insulin resistance in subjects with low plasma IGF-I concentrations.

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REFERENCES

[1] McGarry J, J Diabetes., **2001,** 51, 1, 7–18.
[2] J R Flores, Riveros, *J. Diabetics*, **1993**, 90, 512-516.
[3] Paul S. MacLean, *Biochemical and Biophysical Research Communications***, 2002,** 2, 409.
[4] DeFronzo R, Tobin J, Andres R, *Am J Physiol*, **1979**, 237, 3, 1487–95.
[5] Pham, T; Cornea A; Blick KE; Jenkins A, The *American Journal of the Medical Sciences*., **2007**, 333, 6, 333–339.
[6] Jeff Unger, Solinas Giovanni, Emergency Medicine *Cell Metabolism*, **2007**, 6, 386–397.
[7] Chiu KC, Chu A, Go VL, *American Journal of Clinical Nutrition*. **2004**, 79**,** 5, 820-825.
[8] J Hong1, R R Smith, A E Harvey, *International Journal of Obesity.*, **2009**, 33, 197–203.
[9] Boden G, Sargrad K, Homko C, Mozzoli M, Stein TP, Annals of Internal Medicine., **2005,** 142, 6, 403-411.
[10] Bramnert M, Segerlantz M, Laurila E, Daugaard JR, *Journal Of Clinical Endocrinology & Metabolism*., **2003**, 88, 4, 1455–1463.
[11] Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, *New England Journal of Medicine*, **2002**, 346, 6, 393–403.
[12] Lovejoy, JC, Current *Diabetes Reports.*, **2002**, 2, 5, 435–440.
[13] Fukuchi S, *Experimental Biology and Medicine*. **2004**, 229**,** 6, 486–493.
[14] Storlien LH, *J.Diabetologica*. **1996**, 39, 6, 621–631.
[15] Harinantenaina L, Chemical & *Pharmaceutical Bulletin* **2006**, 54, 7, 1017–21.