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# ASSOCIATION BETWEEN IRISIN AND GAMMA GLUTAMYL TRANSFERASE IN NORMAL AND TYPE 2 DIABETICS

Biochemistry

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## ABSTRACT

The aim of study was to evaluate and compare serum Irisin and Gamma Glutamyl Transferase (GGT) activity in type 2 diabetic patient (T2D) and in normal individual. In this case control study, age and sex matched 100 diagnosed cases of type 2 diabetes mellitus were compared with 100 healthy participants at Jawaharlal Nehru Medical College & Associated Group of Hospitals, Ajmer (Rajasthan). Levels of GGT were significantly higher (28.8 ± 8.0 vs 48.0 ± 10.7 IU/Lt.) and levels of Irisin were lower (214.9 ± 28.4 vs 202.2 ± 10.5 ng/ml) in T2D patients (P value < 0.001). GGT was found to be negatively correlated with Irisin (r = -0.946) in T2D patients and positively correlated with Irisin (r = 0.810) in healthy controls. In our study we found myokine Irisin level decreasing gradually with the progression of T2D and increase in GGT level in diabetics in response to oxidative stress.

## KEYWORDS

Irisin, Gamma Glutamyl Transferase, oxidative stress

## INTRODUCTION

Obesity is a worldwide health burden, accompanied by a number of comorbidities including glucose intolerance, insulin resistance and type 2 diabetes. So, Biomarker like Irisin and GGT were studied in T2D for early diagnosis and treatment.

Irisin, is an exercise-mediated myokine which regulates energy metabolism by inducing browning of white adipose tissue and thus dissipates chemical energy in the form of heat. Bostrom et al.,( 2012) revealed that exercise stimulates PPAR-γ co-activator-1α (PGC-1α), which in turn upregulates its downstream target fibronectin type III domain containing 5 (FNDC5), thereafter the C-terminus is cleaved and the remaining 112 aminoacid peptide is referred to as Irisin. Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance (Moreno-Navarrete JM et al., 2013). Several studies were held out to investigate Irisin's role in glucose and fatty acid metabolism leading to great expectations surrounding "Irisinemia" as new concept in the prediction of metabolic disorders (Sanchis-Gomar F et al.,2013).

Serum gamma-glutamyl transferase (GGT) is an ectoplasmic enzyme responsible for the extracellular catabolism of glutathione, which is synthesized in epithelial cells of the intrahepatic duct (Whitfield JB, 2001). GGT has an important role in glutathione homeostasis by initiating the breakdown of extracellular glutathione and turnover of vascular glutathione (Lieberman MW et al., 1995). Considering the antioxidant activity of glutathione, increased level of GGT may be linked to greater oxidative stress. Increased oxidative stress has been implicated in insulin resistance by promoting β cell dysfunction and reducing insulin action (Blaha M et al., 2006). Therefore, serum GGT activity could reflect several different processes relevant to diabetes pathogenesis.

## MATERIAL AND METHODS

In this case control study, we have studied age and sex matched 100 cases of Type 2 Diabetes Mellitus disease and 100 normal participants from OPD and medicine wards of J.L.N. Medical College and Associated Group of Hospitals, Ajmer, Rajasthan during the period of May 2016 to September 2017. Both the cases and controls were within age range of 20-60 years and were explained about the study in detail, following which an informed written consent was taken regarding permission for inclusion in the study. T2D was diagnosed when a patient fulfilled the criteria of the American Diabetes Association. Exclusion criteria were type 1 diabetes, abnormal renal and liver function test, smokers and alcoholics, malignant neoplasm, Triglycerides (TG) > 400mg/dl and insulin treatment.

Venous blood samples were collected after 10-12 hr overnight fasting and serum were obtained. Glucose, total cholesterol and TG were measured by means of enzymatic assays, and HDLc concentrations were determined using a direct method. LDL and VLDL were calculated from the friedwald's formula. Serum Insulin were measured by an enzymatic luminescence technique. Insulin Resistance was calculated by homeostasis model assessment (HOMA-IR = fasting insulin (μU/ml) x fasting glucose (mg/dl) / 405. Serum Irisin concentration were measured using a commercial ELISA kit (Phoenix Pharmaceuticals,USA) and GGT was estimated by carboxy substrate enzymatic method on Fully Auto Analyzer-Randox RX imola at Biochemistry Central Laboratory, J.L.N. Medical College & Associated Group of Hospitals, Ajmer.

Statistical analysis were conducted using SPSS 22.0 software. Pearson's correlation coefficients were employed to explore the association between Irisin, GGT and other biochemical parameters. Differences were considered significant when $p < 0.05$.

## RESULTS AND OBSERVATION

In this study 100 T2D patients were compared with 100 healthy controls (70 male & 30 female)

**Table 1 :-**
**Clinical and metabolic characteristics of healthy controls and T2D patients.**

| parameter | Healthy controls | T2D patients | P - value |
|---|---|---|---|
| Age (years) | 46.89 ± 4.91 | 47.2 ± 4.68 | <0.001 |
| BMI (kg/m²) | 26.9 ± 2.87 | 30.0 ± 0.89 | =0.040 |
| SBP (mm Hg) | 130.0 ± 18.0 | 146 ± 19.0 | <0.001 |
| DBP (mm Hg) | 82.0 ± 11.0 | 78.0 ± 10.0 | 0.031 |
| Glucose (mg/dl) | 82.6 ± 11.3 | 120.2 ± 17.7 | <0.001 |
| Insulin (μIU/ml) | 10.8 ± 2.1 | 14.0 ± 1.5 | <0.001 |
| TC (mg/dl) | 153.7 ± 35.8 | 170.7 ± 16.3 | <0.001 |
| TG (mg/dl) | 102.2 ± 37.0 | 173.2± 44.8 | <0.001 |
| VLDL (mg/dl) | 20.4 ± 7.4 | 34.6 ± 9.0 | <0.001 |
| LDLc (mg/dl) | 95.4 ± 30.1 | 101.5± 12.3 | =0.062 |
| HDLc (mg/dl) | 37.8 ± 10.3 | 34.6 ± 9.3 | =0.022 |
| HOMA-IR | 2.18 ± 0.39 | 4.17 ± 0.89 | <0.001 |
| Irisin (ng/ml) | 214.9 ± 28.4 | 202.2 ± 10.5 | <0.001 |
| GGT (IU/Lt) | 28.8 ± 8.0 | 48.0± 10.7 | <0.001 |

SBP: Systolic blood pressure, DBP: diastolic blood pressure, TC: total cholesterol, TG : triglycerides, LDLc: LDL cholesterol, HOMA-IR:

homeostasis model assessment insulin resistance. *Data are expressed as mean ± SD or median (25th-75th percentile).

SBP, glucose, Insulin, HOMA-IR was found to be higher in T2D patients than controls (p <0.001). High TC, TG (p <0.001) and low HDLc (p =0.022) in T2D patients is shown in Table1.

GGT was higher (28.8 ± 8.0 vs 48.0 ± 10.7 IU/Lt.) and Irisin was lower (214.9 ± 28.4 vs 202.2 ± 10.5 ng/ml) among T2D patients (p <0.001). Among cases as serum GGT level increases, serum Irisin level decreases and correlation coefficient is strongly negative (-0.946). In controls as serum GGT level increases serum Irisin level also increases and correlation coefficient (r) is strongly positive (0.810).

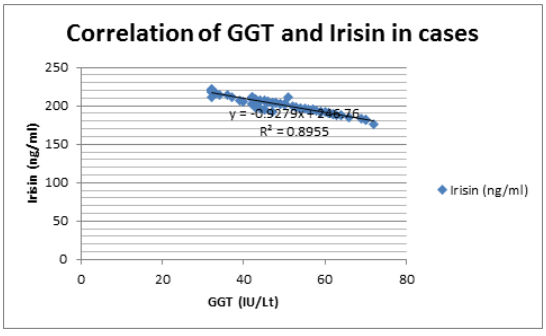


**Figure 1:-** Shows the correlation between GGT and Irisin in T2D patients.

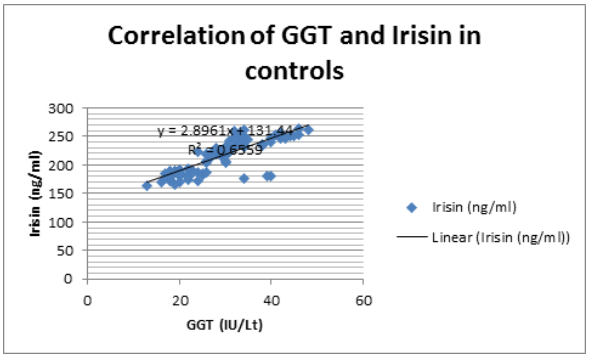


**Figure 2:-** Shows the correlation between GGT and Irisin in Healthy controls.

## DISCUSSION

Our main finding was that Irisin level is lower and GGT level is higher in T2D than control (p <0.001). We also found inverse correlation between these parameters in T2D patients.

In accordance with our findings, other studies have reported decreased Irisin (Choi YK et al., 2013; Liu JJ et al., 2013) and increased GGT (Andre P et al., 2006; Cho NH et al., 2007) levels in T2D patients. As Irisin is a myokine secreted in response to PGC-1α activation. Studies suggest that PGC-1α is important for mitochondrial homeostasis for it regulates mitochondrial biogenesis and oxidative metabolism. Evans JL et al., (2003) also found that mitochondrial function also plays a role in insulin resistance. This can be because of obesity associated lower brown or beige adipocyte in human adipose tissue. Furthermore, expression and activity of PGC-1α are lower in patients with Type 2 diabetes mellitus.

The liver helps maintain normal blood glucose concentration. Loss of insulin effect on the liver leads to glycogenolysis and an increase in hepatic glucose production. Chronic hyperinsulinemia predisposes the liver to relative resistance to insulin. This is characterized by a failure of insulin to signal an increase in insulin receptor substrate-2. Upregulation of sterol regulatory element-binding protein 1c (SREBP-1c) also occurs, leading to increased lipogenesis. Despite down-regulation of the insulin receptor substrate-2- mediated insulin signaling pathway in insulin-resistant states, the up-regulation of SREBP-1c and subsequent stimulation of de novo lipogenesis in the liver leads to increased intracellular availability of triglycerides, promoting fatty liver. This also increases VLDL assembly and secretion. The association of high levels of GGT with obesity is due to obesity related hepatic steatosis and that hepatic steatosis leads to hepatic insulin resistance. The excess in free fatty acids found in the insulin-resistant state is known to be directly toxic to hepatocytes. Putative mechanisms include cell membrane disruption at high concentration, mitochondrial dysfunction, toxin formation, and activation and inhibition of key steps in the regulation of metabolism. Our study were similar to studies done by Forlani G et al. (2008) & Pery IJ et al.(1998).

We also found increased cholesterol & Triglyceride ( p <0.001) with decreased HDL( p= 0.022) in T2D patients similar to study of Sadika et al.,(1987) which may be due to increased hepatic triglyceride lipase activity.

### Limitations of Study

First, our sample size was relatively small, and the age range of subjects was relatively limited.

Second, T2D patients taking antihypertensive therapy during the study period.

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NIL

## CONFLICTS OF INTEREST

We have no competing interests.

## FUNDING

NIL

## CONCLUSIONS AND FUTURE STUDY

It is thus concluded from our study that Obesity leads to high HOMA-IR, dyslipidemia and metabolic derrangements. Serum Irisin level is decreased in type II diabetic patients and increased in healthy controls. Irisin is a myokine decreasing gradually with the progression of glucose intolerance and type II diabetes mellitus. Seum GGT also significantly increases in T2D than healthy controls. Irisin is negatively correlated with GGT in T2D but positively correlated in healthy controls.

Thus our study shows that measurement of biomarker like Irisin and GGT in T2D patients may be helpful in assessing the risk of diabetes.

Further studies need to be conducted on this matter to prove the usefulness and constraints in using serum Irisin and GGT as biomarker in the progression of type 2 diabetes.

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