# Elevated Liver Enzymes as a Predictor for Development of Type 2 Diabetes Mellitus

**Thesis**

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# Abstract

The aim of this study is to study the relation between elevated liver enzymes and type 2 diabetes mellitus and whether or not could be a predictor for development of type 2 diabetes. This study was conducted on 85 subjects divided into 4 groups, group (A) (control group) 17 subjects not obese, diabetic or had a history or laboratory evidence of liver disease, group (B) 28 subjects obese, not diabetics and had not liver disease, group (C) 20 subjects obese, not diabetic, but had elevated liver enzymes, group (D) 20 subjects obese, type 2 diabetics and had no history of liver disease. All the groups subjected to the following investigations, fasting and postprandial plasma glucose, fasting serum insulin, plasma lipid profile, plasma hepatic enzymes AST, ALT and GGT and abdominal ultrasonography. The present study demonstrated that there is an independent association between hepatic steatosis and both hyperinsulinemia and insulin resistance after adjustment for both BMI and W/H ratio. Non-diabetic NAFLD patients have a significant positive correlation between elevated AST, ALT and the level of fasting serum insulin, insulin resistance, serum triglyceride level and BMI and a significant negative correlation to high density lipoprotein cholesterol level. We demonstrated also that, there is a non-significant correlation between elevated GGT level and all the previous variables. Also, we demonstrated that patients who receive insulin sensitizers have a more improving lipid profile and a lower serum insulin level.



**Key Words**:

- Insulin resistance.
- Non-alcoholic fatty liver disease.
- Type 2 diabetes.
- Liver enzymes.

Dedicated to

My

***Family***

# List of Abbreviations

| | |
|---|---|
| ADP | : Adenosine diphosphate |
| AIR | : Acute insulin response |
| ALKP | : Alkaline phosphatase |
| ALT | : Alanine transaminase |
| AMPK | : AMP-activated protein kinase |
| AST | : Aspartate transaminase |
| ATP | : Adenosine triphosphate |
| AUC | : Area under the curve |
| β-cell | : Beta-cell |
| BG | : Blood glucose concentration |
| BMI | : Body mass index |
| CRP | : C-reactive protein |
| CT | : Computed tomography |
| CYP | : Cytochrome peroxidase |
| DM | : Diabetes mellitus |
| eNOS | : Endothelial nitric oxide synthase |
| FFAs | : Free fatty acids |
| FSIGTT | : Frequently sampled intravenous glucose tolerance test |
| GGT | : Gamma glutamyl transferase |
| GLUT-4 | : Glucose transporter-4 |
| 8-hdG | : 8-hydroxy-2 deoxy-guanosine |
| HDL | : High density lipoprotein |
| HGO | : Human glucose output |
| HO | : Heme oxygenase |
| HOMA | : Homeostasis model assessment |
| HOMA-IR | : Homeostasis model assessment of insulin resistance |
| 2HPPG | : Two-hours postprandial plasma glucose |
| IFG | : Impaired fasting glucose |
| IGT | : Impaired glucose tolerance |
| IL | : Interleukin |
| IMCL | : Intramyocellular lipid |
| iNOS | : Inducible nitric oxide synthase |
| IR | : Insulin resistance |

| | |
|---|---|
| IRI | : Immunoreactive insulin concentration |
| IRS | : Insulin receptor substrate |
| ISI | : Insulin sensitivity index |
| ITT | : Insulin tolerance test |
| LDL | : Low density lipoprotein |
| LCACoA | : Long chain acyl Co-A ester |
| LCPUFAs | : Long chain polyunsaturated fatty acids |
| MAP kinase | : Mitogen activated protein-kinase |
| MRI | : Magnatic resonance imaging |
| MTP | : Microsomal triglyceride transfere protein |
| NAFLD | : Non-alcoholic fatty liver disease |
| NASH | : Non-alcoholic steatohepatitis |
| NO | : Nitric oxide |
| OGIS | : Oral glucose insulin sensitivity |
| OGTT | : Oral glucose tolerance test |
| PCOS | : Polycystic ovary syndrome |
| PI3K | : Phosphatidylinositol-3-kinase |
| PPAR-γ | : Peroxisome proliferator-activated receptor-gamma |
| QUICKI | : Quantitative insulin sensitivity check index |
| RIA | : Radioimmunoassay |
| ROS | : Reactive oxygen species |
| SAHS | : San Antonio Heart Study |
| Si | : Insulin sensitivity index |
| SOCS | : Suppressors of cytokine signaling |
| SREBP | : Sterol regulatory element binding protein |
| SS | : Steady state |
| STAT | : Single transducer and activator of transcription |
| TG | : Triglyceride |
| TNF-α | : Tumour-necrosis factor-alpha |
| VLDL | : Very low density lipoprotein |
| WC | : Waist circumference |

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# Introduction and Aim of the Work

# INTRODUCTION

Type 2 diabetes is the condition most obviously linked to insulin resistance. Compensatory hyperinsulinemia helps to maintain euglycemia-often for decades before overt diabetes develops. Eventually, the B-cells of the pancreas are unable to overcome insulin resistance through hypersecretion. Glucose level rise and diagnosis of diabetes can be made **(Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2001)**.

The only way that insulin-resistant persons can prevent the development of type 2 diabetes is by secreting the increased amount of insulin that is necessary to compensate for the resistance to insulin action. The greater the magnitude of muscle and adipose tissue insulin resistance, the more insulin must be secreted to maintain normal or near-normal glucose tolerance. Although compensatory hyperinsulinemia may prevent the development of fasting hyperglycemia in insulin-resistant individuals, the price paid is the untoward physiologic effects of increased circulating insulin concentrations on tissues that retain normal insulin sensitivity **(Reaven, 2005)**.

Metabolic syndrome has been coined to indicate a cluster of diseases, strictly correlated with each other, having insulin resistance

and carrying a high risk of cardiovascular disease **(Hu et al., 2004)**. It includes insulin resistance and compensatory hyperinsulinemia, glucose intolerance, hypertension, and dyslipidemia. Several other components have subsequently been added, including obesity and especially abdominal obesity, microalbuminuria, abnormalities in fibrinolysis and coagulation and the presence of small dense atherogenic LDL particles **(Goutham, 2001)**. Multiple authors have proposed that hepatic steatosis and non-alcoholic steatohepatitis (NASH) are included as clinical features in the metabolic disorders of insulin resistance **(Pagano et al., 2002)**.

Type 2 diabetes is frequently observed in association with fatty liver. At autopsy, liver fat is found in about one third of non-obese type 2 diabetics. As a group, patients who have fatty liver-as indicated by ultrasonographic scan-are more likely to exhibit glucose intolerance and elevated baseline insulin levels than those with normal livers **(Neuschwander-Tetri, 2001)**.

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease observed in the clinical practice of hepatology. The coexistence of metabolic syndrome in these cohort of patients has made insulin resistance central to the pathogenesis of these disorders. The subsequent fate of steatotic hepatocytes depends on the capacity of additional factors such as adipocytokines to induce inflammatory

response. This latter process is responsible for producing the phenotype of non-alcoholic steatohepatitis (NASH). Irrespective of the process by which this phenotypic response occurs, it is now universally accepted that in the absence of insulin resistance the spectrum of changes associated with (NAFLD) does not develop **(Choudhury and Sanyal, 2005)**.

It is of interest to determine the role of NAFLD in the early stages of the etiology of metabolic syndrome and prospective association with the development of type 2 diabetes **(Nakanishi et al., 2004)**. However, direct measurements of liver fat require ultrasound, CT scan or proton spectroscopy **(Liangpunsakul et al., 2005)** and assessment of liver biopsy is important in the diagnosis and management of NALFD **(Hubscer, 2004)**, such techniques are unlikely to be recommended for this purpose in routine clinical practice **(Liangpunsakul et al., 2005)**.

Fortunately, circulating concentrations of a number of variables appear to give insight into the extent of liver fat accumulation. Among these are GGT, ALT and AST, of these three, ALT is the most specific marker of liver pathology and appears to be the best marker for liver fat accumulation **(Tükkainen et al., 2003)**. NASH patients typically have serum aminotransferase levels that range from normal to 5 folds the upper limit of normal. In the absence of cirrhosis, patients with NASH almost invariably have ALT levels that are greater than AST levels **(Sorbi et al., 1999)**.