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BIOCHEMICAL CHANGES OF LIVER ENZYMES AMONG TYPE 2 DIABETIC PATIENTS AT WAD MEDANI, MEDICAL DIABETIC CENTRE – MEDANI CITY - GEZIRA STATE- SUDAN

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ABSTRACT

Objective: The study aimed to evaluate some biochemical changes of the liver enzymes in patients with diabetes mellitus type 2 to measured aspartate aminotransferase, and alanine aminotransferase enzymes. **Methods**: The study was carried out using fifty blood samples collected from Medical Diabetic Center in Medani, between 1. July to September 2018. Samples collected in heparinized tubes and were centrifuged for unhemolyzed serum collection for assessment of liver enzymes, alanine aminotransferase enzymes & aspartate aminotransferase. The principle of ALT was determined by enzymatic kinetic methods using ALT estimation kit (Biosystem). This ALT method was based on transfers the amino group from alanine to 2-Oxoglutarate to form pyruvate and glutamate. **Results**: The study revealed that the fasting blood glucose increased in 43 patients, which represents 86%. Aspartate aminotransferase increased in 4 patients, which represents 8%. Alanine aminotransferase increased in 4 patients, which represents 8%. **Conclusion:** The overall of this study, indicated that the (8) of patients, which represents 16%, had at least some changes of abnormal one or both liver enzymes in type 2 diabetes mellitus in patients on hypoglycemic agents.

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INTRODUCTION

Individuals with type 2 diabetes have a higher incidence of liver function test abnormalities than individuals who do not have diabetes (Dufour *et al.,* 2000). Mild chronic elevations of transaminases often reflect underlying insulin resistance. Elevation of transaminases within three times the upper limits of normal is not a contraindication for starting oral antidiabetic or lipid-modifying therapy. In contrast, antidiabetic agents have generally been shown to decrease alanine aminotransferase levels as tighter blood glucose levels are achieved. The presence of chronic liver disease (CLD) is associated with significant impairment in glucose homeostasis. Glucose intolerance is seen in up to 80% of patients with CLD, and frank diabetes is present in 30–60 % (Dufour and Mihaela *et al*., 2000). Depending on its etiology, chronic liver disease has a significant impact on hepatic glucose metabolism. One of the common causes of chronic liver disease is chronic hepatitis C. Chronic hepatitis C is accompanied by insulin resistance, which causes impaired glucose tolerance.

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Multiple mechanisms have been implicated, including fat accumulation in hepatocytes, increased insulin resistance secondary to increased tumor necrosis factor (TNF)-α, and direct or autoimmune damage to β-cells by the virus (Angulo et al 2007). Liver function tests (LFTs) are commonly used in clinical practice to screen for liver disease, monitor the progression of known disease, and monitor the effects of potentially hepatotoxic drugs. The most common LFTs include the serum aminotransferases, alkaline phosphatase, bilirubin, albumin, and prothrombin time. Aminotransferases, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), measure the concentration of intracellular hepatic enzymes that have leaked into the circulation and serve as a marker of hepatocyte injury. Alkaline phosphatase (AP), γ-glutamyltranspeptidase (GGT), and bilirubin act as markers of biliary function and cholestasis. Albumin and prothrombin reflect liver synthetic function.The aminotransferases AST and ALT are normally < 30-40 units/l. Elevations of aminotransferases greater than eight times the upper limit of normal reflect either acute viral hepatitis, ischemic hepatitis, or drug- or toxin-induced liver injury. Much more common than patients with acute hepatitis, however, are patients with chronic mild elevation of

aminotransferases, or AST and ALT < 250 units/l for > 6 months. Chronic mild elevation of transaminases are frequently found in type 2 diabetic patients. This article will provide a review of the pathology, incidence, causes, and drug therapy related to type 2 diabetic patients with elevated LFTs. The liver helps maintain normal blood glucose concentration in the fasting and postprandial states. Loss of insulin effect on the liver leads to glycogenolysis and an increase in hepatic glucose production. Abnormalities of triglyceride storage and lipolysis in insulin-sensitive tissues such as the liver are an early manifestation of conditions characterized by insulin resistance and are detectable earlier than fasting hyperglycemia. The precise genetic, environmental, and metabolic factors and sequence of events that lead to the underlying insulin resistance, however, is not fully understood (García-Compean *et al*., 2009). In animal models, chronic hyperinsulinemia is found to predispose 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 (Elgouhari *et al*. 2008). 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 simulation of de novo lipogenesis in the liver leads to increased intracellular availability of triglycerides, promoting fatty liver. This also increases VLDL assembly and secretion (García-Compean *et al*., 2009). Thus, hyperinsulinemia might directly lead to hepatic insulin resistance with associated fatty changes.

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 (Mann *et al.,* 1922).Other potential explanations for elevated transaminases in insulin-resistant states include oxidant stress from reactive lipid peroxidation, peroxisomal beta-oxidation, and recruited inflammatory cells. The insulin-resistant state is also characterized by an increase in proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), which may also contribute to hepatocellular injury. In preliminary studies, an increased frequency of specific TNF-α-promoter polymorphism was found in nonalcoholic steatohepatitis (NASH) patients, suggesting a possible genetic link or predisposition to fatty liver found in insulin-resistant states (Mann *et al.,* 1923). The above theories all attribute elevated transaminases to direct hepatocyte injury. It is also hypothesized that elevation in ALT, a gluconeogenic enzyme whose gene transcription is suppressed by insulin, could indicate an impairment in insulin signaling rather than purely hepatocyte injury (Bjornstorp and Sjostrom, 1978).GGT is a nonspecific marker that is known to rise in patients with type 2 diabetes. In epidemiological studies, it has a positive association with alcohol intake, cigarette smoking, coronary heart disease, BMI, systolic blood pressure, serum triglyceride, heart rate, uric acid, and hematocrit. It has an inverse association with physical activity level (Katz *et al.,* 1983). Because GGT increases in diabetes, and increases as BMI increases, it has been proposed as another marker of insulin resistance. To determine whether elevated GGT could predict the development of type 2 diabetes, a prospective cohort study of 7,458 nondiabetic men aged 40-59 years was conducted for 12 years (Karem *et al.,*1994). Mean serum GGT at the start of the study was significantly higher in the 194 men who developed type 2 diabetes than in the rest of the cohort who did not develop diabetes (20.9 vs. 15.3 units/l, $P< 0.0001$). The association was independent of serum glucose and BMI. However, when GGT was added to a model for predicting the development of type 2 diabetes, it did not improve the power of BMI and glucose for predicting the development of type 2 diabetes (McGilvery *et al.,* 1979) found elevated ALT in nondiabetic Swedish men to be a risk factor for type 2 diabetes, independent of obesity, body fat distribution, plasma glucose, lipid, AST, bilirubin concentrations, and family history of diabetes. With similar results (Scofield *et al*., 1985). Followed 451 non - diabetic Pima Indians for an average of 6.9 years to determine whether hepatic enzyme elevations could be linked to the development of type 2 diabetes. At baseline, ALT, AST, and GGT were related to percent body fat. After adjustment for age, sex, body fat, whole body insulin sensitivity, and acute insulin response, only elevated ALT at baseline was associated with an increase in hepatic glucose output. Prospectively, increasing ALT concentrations were associated with a decline in hepatic insulin sensitivity and risk of type 2 diabetes.

MATERIALS AND METHODS

The study was carried out using fifty blood samples collected from Medical Diabetic Center in Medani, between 1. July to 29 August 2013. Samples collected in heparinized tubes and were centrifuged for unhemolyzed serum collection for assessment of liver enzymes, ALT & AST. The principle of ALT was determined by enzymetic kinetic methods using AlT estimation kit (Biosystem). This ALT method was based on transfers the amino group from alanine to 2- Oxoglutarate to form pyruvate and glutamate. The pyruvate enters alactate dehydrogenase catalyzed reaction with NADH to produce lactate and NAD+. The decreased in absorbance due to consumption of NADH is measured at 340 nm and was proportional to the Alt activity in the sample:

$$\text{Alanine + 2- Oxoglutarate} \xrightarrow[\text{LDH}]{} \text{Pyruvate + Glutamate}$$

$$\text{Pyruvate + NADH+H+} \longrightarrow \text{L. Lactate+ NAD+}$$

The kit contents, two reagents A and B. The composition of reagent A: Tris 150 mmol/L, lactate dehydrogenase >1350 U/L, pH 7.3. Reagent B composed of: NADH 1.3 mmol/L, 2-oxoglutarate 75 mmol/L, Sodium hydroxide 148 mmol/L, sodium azide 9.5 g/L. Procedure: to 50 µL of sample, 1.0 mL of working reagent (4 ml reagent A + 1 ml reagent B was added to the mixture, after 1 minute record initial absorbance and 1 minute intervals thereafter for 3 minutes and then after that calculate the difference between consecutive absorbances, and the average absorbance difference per minute.

Calculations: The ALT/GPT concentration in the sample is calculated using the following general formula:

$$\Delta A/\min \times \frac{Vt \times 10}{\epsilon \times I \times Vs} = U/L$$

The molar sorbance (£) of NADH at 340 nm is 6300, the lightpath (I) is 1 cm, the total reaction volume (Vt) is 1.05 at 37°C and 1.1 at 30°C, the sample volume (Vs) is 0.05 at 37°C and 0.1 at 30°C, and 1 U/L are 0.0166 µkat/L. The following

formulas are deduced for calculation of the catalytic concentration:

	37°C	30°C
ΔA/m	×3333 = U/L × 5555 = µ kat/ L	× 1746 = U/L ×29.1 = µkat / L

The assay of AST based on catalyzes the tranmission of as partate and alpha- oxoglutarate, forming glutamate and oxalacetate. The oxalacetate was then reduced to L-malate dehydrogenase, while the NADH was simultaneously converted to NAD+.

The decreased in absorbance due to consumption of NADH was measured at 340 nm, by means of the malate dehydrogenase (MDH) coupled reaction. Reference value = 40 U/L

RESULTS

The study revealed the fasting blood glucose was increased in 86% (43) (Fig 1), aspartate aminotransferase was increased in 8% (4) Fig 2 and alanine aminotransferase was increased in 8% (4) patients Fig 3. Alanine aminotransferase and aspartate aminotransferase were both significantly raised in patient with DM type 2 on oral hypoglycemic agents'(Fig 4).

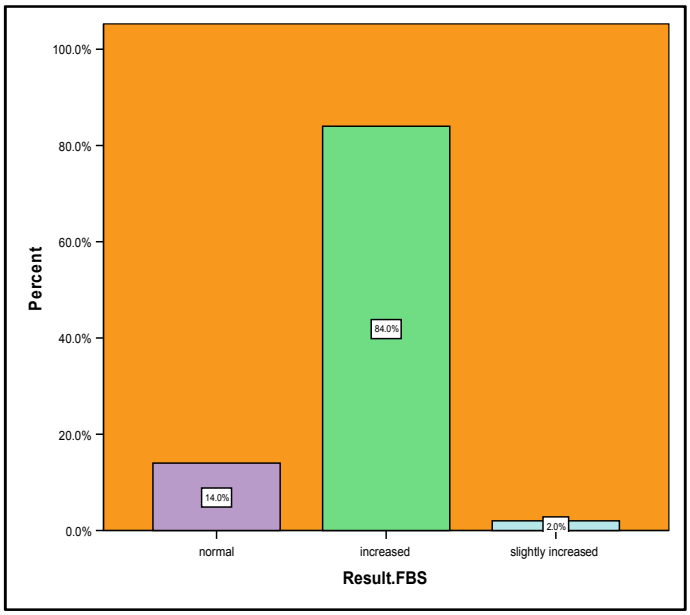

Figure 1. Shows the percentage of fasting blood glucose

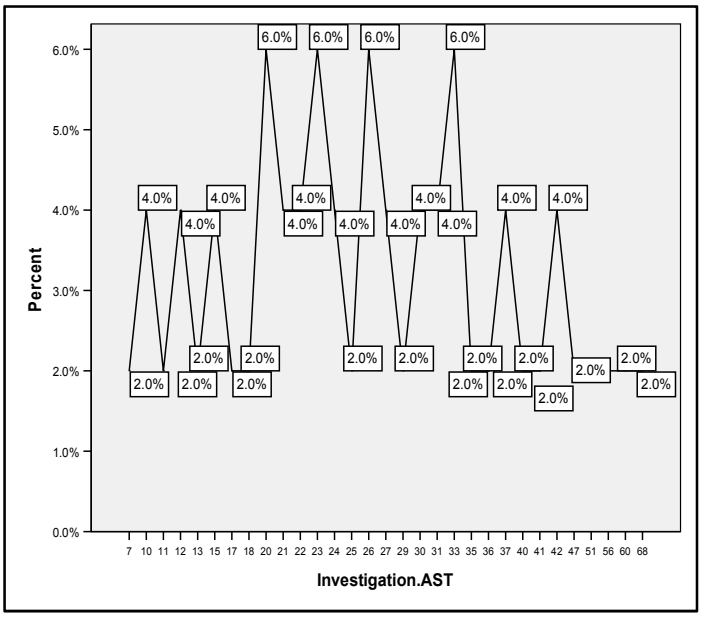

Figure 2. Shows the percentage of aspartate aminotransferase

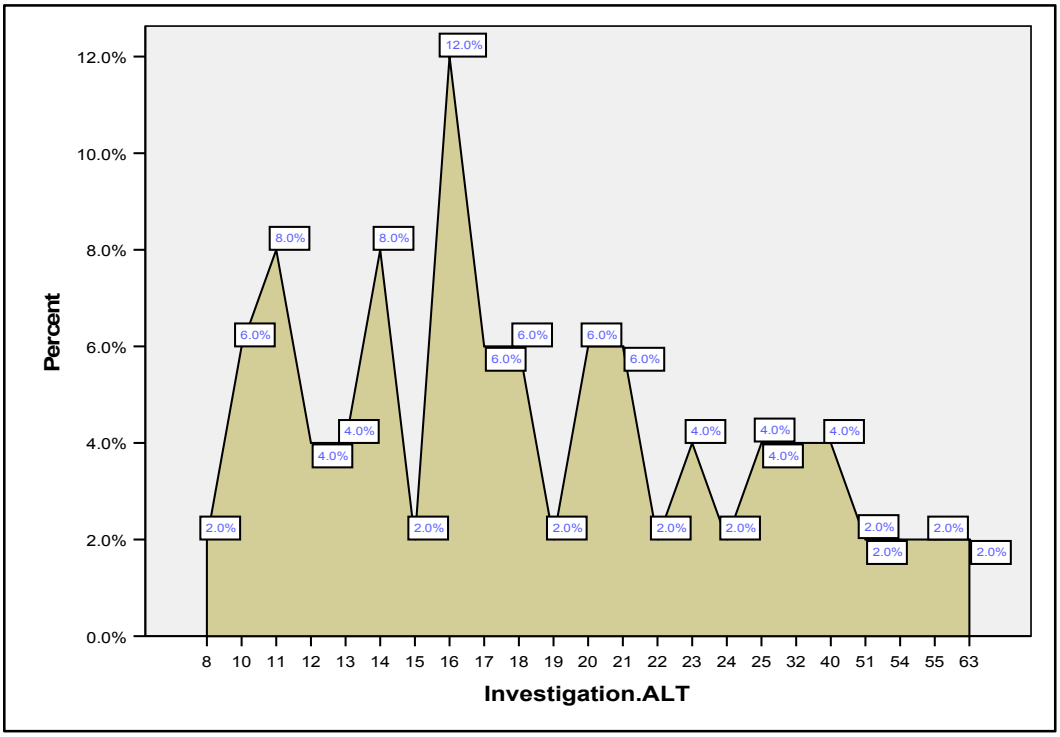

Figure 3. Shows the percentage of ALT

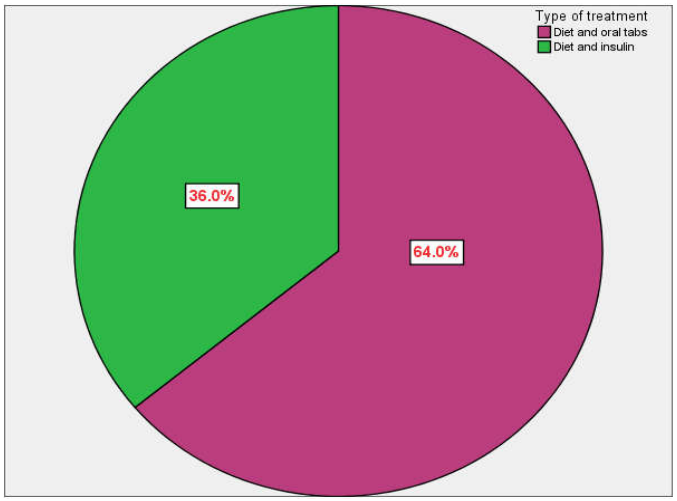

Figure 4. Shows types of treatment in diabetic patients

DISCUSSION

The study revealed the fasting blood glucose was increased in 86% (43) of cases, aspartate aminotransferase was increased in 8% (4) cases and alanine aminotransferase was increased in 8% of (4) patients. The study shows that the prevalence of elevated of ALT and AST were equally higher in type 2 diabetes mellitus, in patients on hypoglycemic agents. Further studies investigating the causes and the pathogenesis of this elevation of the liver enzymes in diabetic patients may reveal the actual reasons for the elevation and suggest appropriate early intervention.

Conclusion

The overall of this study, indicated that the (8) of patients, which represents 16%, had at least some changes of abnormal one or both liver enzymes in type 2 diabetes mellitus in patients on hypoglycemic agents.

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