DETERMINANTS OF ABNORMAL LIVER FUNCTION TESTS IN DIABETES TYPE 2 PATIENTS IN SUDAN

Hind M. Elmahi¹, AbdElkarim A. Abdrabo *²

¹Department of Clinical Chemistry, Faculty of Medical Laboratory Sciences, Alneelain University-Khartoum-Sudan.
²Department of Clinical Chemistry, Faculty of Medical Laboratory Sciences, Sudan International University-Khartoum-Sudan.

ABSTRACT

Previous data on the evaluation of liver function tests (LFTs) in patients with type 2 diabetes mellitus showed considerable debates, so this study is conducted to evaluate the LFTs in patients with type 2 diabetes mellitus in a group of diabetic patients in Sudan. A cross-sectional study conducted at the diabetic clinic of Jabir Abu-Alez-Khartoum-Sudan, between April 2013 and July 2013, total of (120) type 2 diabetic patients and 85 healthy subjects were selected as controls, LFTs were performed using standard methods. The means of Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), Total Protein, Albumin, and total bilirubin (TB) were significantly higher in patients than in the control (P<0.02), but direct bilirubin (DB) values were not significantly different, (P =0.37). Although the differences were statistically significant, the means of all these LFTs were falling within the normal range. Raised ALT and AST and ALP were noted in 20 % of patients, also raised TB, DB, Total protein and Albumin were noted in 6%, 4%, 10% and 4% respectively. No significant correlation was noted between means of LFTs with duration of diabetes, however, only ALT was found to be significantly positively correlated with duration of diabetes, p.value (0.000). LFTs values in patients with type 2 diabetes mellitus were significantly higher than that of control. 22% of the patients had at least one or more elevated liver enzyme levels. Hence liver function tests are highly recommended for diabetic patients.

Keywords: Type 2 diabetes, Alanine aminotransferase, Aspartate aminotransferase, Alkaline phosphatase, Total Protein, Albumin, and total bilirubin.

INTRODUCTION

Type 2 diabetes is associated with a large number of liver disorders including elevated liver enzymes, fatty liver disease, cirrhosis, hepatocellular carcinoma, and acute liver failure [1]. Liver plays a major role in the regulation of carbohydrate homeostasis. Hepatocellular glycogen accumulation leads to hepatomegaly and liver enzyme abnormalities in poorly controlled diabetes patients. In hyperglycemic states, there will be intracellular glycogen accumulation in the hepatocytes due to increased glycogen synthesis, causing typical biochemical findings of mild to moderately elevated aminotransferases, normal liver synthetic function, with or without mild elevations of ALP. All these biochemical disturbances and hepatomegaly are found to be reversible with good glycemic control [2].

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 [3]. The precise genetic, environmental, and metabolic factors and sequence of events that lead to the underlying insulin resistance [4] hyperinsulinemia might also 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 [5]. Other potential explanations for elevated transaminases in insulin-resistant states include oxidant stress from reactive lipid peroxidation, peroxisomal beta-oxidation, and recruited inflammatory cells [6]. The insulin-resistant state is also characterized

Corresponding Author:- AbdElkarim A. Abdrabo  Email:- abdrabokarim@hotmail.com
by an increase in proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) which may play a role in the pathogenesis of the inflammation in NASH [7,8] thus (TNF-α) interferes with insulin signaling thereby favoring steatosis, is elevated in fatty liver disease [9].

Liver can be affected by steatosis or accumulation of fat, a condition known as non-alcoholic fatty liver disease (NAFLD). It is a well-recognized complication of diabetes with frequency of 40–70% (2). Associated obesity is a confounding variable for fatty liver. The most common clinical finding is hepatomegaly, with normal or only mildly elevated transaminases and normal bilirubin. These changes are not reversible with sustained glucose control [10].

Nonalcoholic fatty liver disease (NAFLD) is the main cause of chronic liver disease associated with diabetes and obesity. It was first reported in 1980’s in obese females with diabetes. Without treatment, compensated steatosis in NAFLD will eventually lead to decompensate steatosis with necroinflammation and fibrosis, i.e. stage of non-alcoholic steatohepatitis (NASH). NASH is a leading cause of end-stage liver disease and also a contributor of cardiovascular disease in type 2 diabetes mellitus [11].

Serum amino transferases such as ALT and AST indicate the concentration of hepatic intracellular enzymes that have leaked into the circulation. These are the markers for hepatocellular injury and are used as primary screening of NASH [12].

A gluconeogenic enzyme whose gene transcription is suppressed by insulin, could indicate an impairment in insulin signaling rather than purely hepatocyte injury [13].

Chronic mild elevations of ALT and AST are seen in type 2 diabetes patients. In a study done in United States by Erbey et al., 2000, reported that the prevalence of elevated ALT among type 2 diabetes is 7.8% compared to 3.8% in those without diabetes [14].

In another study by Salmela et al., 1984, revealed that elevated ALT in diabetes patients was associated with increased BMI and poor glycemic control in multivariate analysis [15].

High prevalence of liver function test abnormalities also reported in other study done in South Africa by Paruk IM et al., 2011, in South African patients with type 2 diabetes mellitus attending a diabetes clinic [16].

In another study done in Myanmar by Han Ni et al, reported elevated ALT and AST are the markers for associated non-alcoholic fatty liver disease in diabetes patients [17].

Sudan (and most of Africa) is believed to have one of the highest mortality rates for a non-infectious disease. One study indicated that 10% of adult patient deaths in hospitals were caused by diabetes [18]. The current prevalence of diabetes in Sudan is unknown although the very initial study estimated the prevalence by 3.4% [19] and with no doubt the risk of morbidity due to this disease is increasing, especially in the urban areas. Therefore, the comprehensive study of the diabetes mellitus and its impact is needed to be undertaken. The present study was aimed to evaluate the liver function in Sudanese patients with long standing diabetes type 2 compared to non-diabetic control group.

MATERIALS AND METHODS

This study was a hospital based cross sectional descriptive study conducted at the diabetic clinic (Jabir Abu-Alez) in Khartoum-Sudan, between April 2013 and July 2013. A total of 120 subjects with diabetic type 2 and 85 apparently healthy subject were selected as control for the study. For each subject, demographic details, clinical findings and laboratory results were recorded on a questionnaire sheet, including age, gender and duration of diabetes.

Clinical assessment of the study group was done by a medical doctor and they were not suffering from any other disorder. Patients who were in treatment which might affect liver function tests were excluded.

Venous blood (5.0 ml) was drawn from each volunteer in this study using a disposable plastic syringe. The samples were then analyzed for total protein, albumin, bilirubin, ALT, AST, and ALP, by automated chemistry analyzer (Mindray BS-200).

Statistical analysis

Statistical evaluation was performed using the Microsoft Office Excel (Microsoft Office Excel for windows; 2007) and SPSS (SPSS for windows version 19). Student T-test was used to assess significant difference in the means of LFT’s. Correlations between LFT and duration of disease were assessed using bivariate correlations. P < 0.05 was considered statistically significant.

RESULTS

The study covered 205 subjects in Khartoum state-Sudan, 120 patients, 50 male (41.6%) and 70 female (56.4%) with type 2 diabetes mellitus, with average age of (51±8.13) years, ranging between 37 and 74 years and duration of the disease between 1.0 to 24 years. Other 85 apparently healthy subject’s volunteers with average age of (45±5.7) years, ranging between 30 and 62 years as control group.

All LFT measurements of patients were significantly increased when compared with LFT’s of control group, except direct bilirubin in which insignificantly different was observed (P =0.37), (M±SD =0.168±0.145 mg/dl) in patients and (M±SD=0.168±0.10 mg/dl) in controls. As illustrated in table (1).

Liver enzymes (ALT, AST, ALP) measurements of patients were ALT (M±SD=23.26±17.66), AST

(M±SD=34.91±15.80), ALP (M±SD=110.45±43.14), and control ALT (M±SD=15.58±4.69), AST (M±SD=25.01±5.15), ALP (M±SD=88.31±16.75), (P=0.000).

As shown in table (2) there is significant but direct correlation between ALT enzyme and duration of diabetes mellitus (r= 0.433, p=0.000), while there is insignificant correlation between serum AST and ALP level with duration of diabetes (r=0.148, p=0.133) and (r=0.133, p=0.138), respectively.

### Table 1. Means of liver function tests in studied group

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients No 120 (Mean±SD)</th>
<th>Control No 85 (Mean±SD)</th>
<th>P. value</th>
<th>Laboratory reference range</th>
<th>% of patients outside the reference range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT in U/L</td>
<td>23±17</td>
<td>15±4.0</td>
<td>0.000</td>
<td>0 - 40</td>
<td>20%</td>
</tr>
<tr>
<td>AST in U/L</td>
<td>34±15</td>
<td>25±5.0</td>
<td>0.000</td>
<td>0 - 40</td>
<td>20%</td>
</tr>
<tr>
<td>ALP in U/L</td>
<td>110±43</td>
<td>88±16</td>
<td>0.000</td>
<td>30 - 120</td>
<td>20%</td>
</tr>
<tr>
<td>T.Protein in g/dl</td>
<td>8.06±0.59</td>
<td>7.50±0.35</td>
<td>0.000</td>
<td>6.0 - 8.3</td>
<td>10%</td>
</tr>
<tr>
<td>Albumin in g/dl</td>
<td>4.37±0.41</td>
<td>4.14±0.42</td>
<td>0.020</td>
<td>3.5 - 5.6</td>
<td>4%</td>
</tr>
<tr>
<td>Total Bilirubin in mg/dl</td>
<td>0.45±0.40</td>
<td>0.27±0.10</td>
<td>0.016</td>
<td>0.1 - 1.0</td>
<td>6%</td>
</tr>
<tr>
<td>Direct Bilirubin in mg/dl</td>
<td>0.16±1.14</td>
<td>0.16±0.10</td>
<td>0.016</td>
<td>0 - 0.3</td>
<td>4%</td>
</tr>
</tbody>
</table>

### Table 2. Correlation between liver function tests and duration of D.M

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Statistics</th>
<th>Person correlation</th>
<th>Significance (P.value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>Person correlation</td>
<td>0.433</td>
<td>0.000</td>
</tr>
<tr>
<td>AST</td>
<td>Person correlation</td>
<td>0.148</td>
<td>0.133</td>
</tr>
<tr>
<td>ALP</td>
<td>Person correlation</td>
<td>0.133</td>
<td>0.138</td>
</tr>
<tr>
<td>Total Protein</td>
<td>Person correlation</td>
<td>0.619</td>
<td>0.072</td>
</tr>
<tr>
<td>Albumin</td>
<td>Person correlation</td>
<td>0.692</td>
<td>0.057</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>Person correlation</td>
<td>0.429</td>
<td>0.114</td>
</tr>
<tr>
<td>Direct Bilirubin</td>
<td>Person correlation</td>
<td>0.852</td>
<td>0.027</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Type 2 diabetes patients have been reported to be associated with higher incidence of abnormal liver function tests (LFT) compared to the individuals without diabetes, elevated ALT being the most common abnormality [2]. In this study, although the differences were statistically significant, the means of ALT, AST, GGT, total protein, and albumin were within the normal values in 120 patients of abnormal liver function tests; (51%) of patients have at least one abnormal LFT, and (24%) of patients had at least two abnormal LFT, abnormal liver enzymes shown (15%) of patients had elevated ALT, (25%) of patients had elevated AST, (22%) of patients had elevated ALP, and the present of patients outside the reference range in ALT, AST and ALP enzymes is (20%) for each, and (10%) for T.Protein this is in agreement with recent study in Sudan, where 50 diabetes patients and 30 normal control subjects were tested for liver function, the means of ALT, AST, γGT, total protein and albumin were reported to be significantly higher among diabetes compared to the control. However, the mean values were within the normal range [20]. Also agree with Salmela et al who studied the liver function tests of 175 diabetic patients without chronic liver disease, 57% were found to have at least one abnormal LFT, 27% had at least two abnormal LFTs. However, these increases in liver function values were rarely more than two times of the upper limit of normal [15].

Similar finding was also present in a study by Foster et al, showed elevation of ALP and γGT in 11 and 10 patients respectively, but the rise was not more than two times upper limit of normal value, in which the means of ALT, AST, ALP, γGT, bilirubin and albumin of 60 study subjects with diabetes were within the reference range [16]. In UK cohort study of 959 diabetic patients over four year period, 15.7% had raised ALT, 10.4% had elevated alkaline phosphatase whereas only 3.9% had hyperbilirubinaemia [21]. Another study of 60 well controlled diabetic outpatients showed elevation of alkaline phosphatase and γGT in 11 and 10 patients
respectively, but the rise was not more than two times upper limit of normal value [22]. Likewise in recent study in 2012 Maynmar, found the means of ALT, AST, ALP, γGT, bilirubin and prothrombin time were within normal range among 81 diabetes patients. Raised ALT and AST were noted in 18.5% and 14.8% respectively. 4.9% had high bilirubin and prolonged prothrombin time [17]. Our results also agree with Nannipieri et al, in a study carried out in Mexico city, he stated that an elevated serum ALT level is greater among persons with type 2 diabetes, those who are overweight or obese, men and those who consume more than three drinks per day [23]. Meltzer and Everhart previously noted a greater prevalence of abnormal ALT levels among Mexican American with diabetes [24].

REFERENCES
2. Chatila R, West AB. Hepatomegaly and abnormal liver tests due to glycogenosis in adults with diabetes, Medicine, 75(6), 1996, 327-33.
19. Ahmed AM, Ahmed NH Diabetes mellitus in Sudan, the size of the problem and the possibilities of efficient care, 18, 2001, 324-327.

CONCLUSION
In conclusion, values of the liver function tests in patients with type 2 diabetes mellitus were significantly higher than that of control, 22% of the patients had at least one or more elevated liver enzyme levels. Hence liver function tests are highly recommended for diabetic patients.

ACKNOWLEDGEMENT
We thank all the study participants, all members of staff at the faculty of medical laboratory sciences-Alneelain University for their help and support, and colleagues at Laboratory and Research Unit (LRU) – Jabir Abu-alezz for excellent technical assistance in conducting the LFT analyses.
21. Sherif Gonem, Alan Wall, Parijat De Prevalence of abnormal liver function tests in patients with diabetes mellitus, 
22. Foster KJ, Dewbury K, Griffith AH, Price CP, Wright R Liver Disease in Patients with Diabetes Mellitus, Postgraduate 
metabolic syndrome, and incident diabetes, the Mexico City Diabetes Study, Diabetes Care, 28, 2005, 1757–1762.
24. Meltzer AA, Everhart JE Association between diabetes and elevated serum alanine aminotransferase activity among 