The effect of obesity and Insulin Resistance on Liver Enzymes in Type2 Diabetes Mellitus

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Abstract:

Diabetes mellitus (DM) has been defined as a clinical syndrome that is characterized by abnormal carbohydrate metabolism. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction, and failure of different organs, especially the liver. This study was conducted to assess the effect of obesity and insulin resistance on liver enzymes in diabetic Iraqi patients.

A comparative study of (90) Iraqi adults divided to three subgroup (30) obese, (30) nonobese diabetic patients and (30) person had used as control. The analysis included Liver enzyme ALP, ALT, AST, GGT, Fasting Plasma Glucose (FBG), Lipid Profile, Hemoglobin A1C, insulin and homeostasis model assessment of insulin resistance (HOMA IR) were measured. Subjects were excluded from this study if they had liver disease, alcohol intake, medications for lowering lipid, insulin treatment, pregnant women and women taking contraceptive pills.

The study shows significantly higher of liver enzymes level (gamma glutamyl transpeptidase (GGT), alkaline phosphatase, Aspartate Amino Transferase, Alanine Transaminase) in obese diabetic patients compared with non-obese diabetic patients and control subject and HOMA IR showed significantly higher in obese diabetic patients compared with non-obese with diabetic patients and control (P < 0.05). The lipids level showed significantly higher in obese diabetic patients compared with non-obese diabetic patients and control. The HbA1c level showed significantly higher in obese diabetic patients compared with control and there is a positive correlation between insulin and HOMA IR, ALP in obeses diabetic patients while there was negative correlation between ALT and cholesterol in obese group and with HbA1c in control group. The liver enzymes level (alkaline phosphatase, alanine transaminase, aspartate transaminase gama glutaminase transferase) is significantly higher in obese diabetic patients than non-obese diabetic patients and control group, also there was positive correlation between ALP and HOMA IR while there was negative correlation between ALT and cholesterol in obese group and with HbA1c in control group.

**Key words:** Type 2 diabetes, Alanine aminotransferase, Aspartate aminotransferase, Alkaline phosphatase, Gama Glutamyl Transaminase, HOMA IR, Insulin resistance.

Introduction:

Diabetes mellitus (DM) has been defined as a clinical syndrome that is characterized by abnormal carbohydrate metabolism. It is also
associated with altered regulation of fat and protein metabolism. According to American Diabetes Association (ADA), DM has been defined as a group of metabolic diseases characterized by hyperglycemia resulting from defect in insulin secretion, insulin action or both. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction, and failure of different organs, especially the liver. Insulin resistance is a decreased ability in cells, tissues (especially skeletal muscle, adipose tissue, liver, or the whole body) response to normal levels of exogenous or endogenous insulin. Thus insulin resistance has been implicated in the pathogenesis of the metabolic syndrome[1].

Insulin resistance predisposes to metabolic syndrome and type 2 diabetes and may represent a risk factor for liver disease independently of these conditions[2,3]. The liver plays a major role in the regulation of carbohydrate metabolism, as it uses glucose as a fuel, it has the capability to store glucose as glycogen and also synthesize glucose from non-carbohydrate sources. This key function of liver makes it vulnerable to diseases in objects with metabolic disorders, particularly diabetes. Increased activities of liver enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT) and γ-glutamyltranspeptidase (GGT) are indicators of hepatocellular injury. Increased activity of these markers is associated with insulin resistance, metabolic syndrome, and type 2 diabetes[4]. However, most of these studies were performed in Western countries, and the two studies from Japan and Korea were not community-based. An association exists between diabetes and liver injury. Liver pathology among diabetics is similar to that of alcoholic liver disease, including Fatty liver (steatosis), steatohepatitis, fibrosis, and cirrhosis[5].

Elevated serum activity of the two aminotransferases, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), is the most frequently measured indicator of liver disease and occurs in diabetics more frequently than in the general population. The same spectrum of liver injury and enzyme changes in diabetes has also been described among overweight individuals without diabetes. Whether an association of liver disease with diabetes is independent of confounding factors, such as overweight and alcohol consumption is unknown[6]. Nearly 70 to 80% of the diabetic subjects have been reported to have hepatic fat accumulation, referred to as nonalcoholic fatty liver (NAFL)[7]. NAFL leads to nonalcoholic steatohepatitis (NASH), a progressive nonalcoholic fatty liver (NAFL) was first reported in 1980’s in obese females with diabetes. There is renewed interest recently because of the increased prevalence of NAFL in diabetes and as it has been shown to be a predisposing factor for insulin resistance and hyperinsulinemia[8].

Further proof for the association of liver disease with diabetes comes from the insulin resistance atherosclerosis study (IRAS), which showed that liver function markers like the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are predictors of incident diabetes[9]. Presently there are not much therapeutic options for nonalcoholic fatty liver except correction of obesity with hypocaloric diets and physical exercise and controlling hyperglycemia with diet, insulin, or oral hypoglycemic agents[10]. Sudan (and most of Africa) is believed to have one of the highest mortality rates for a non infectious
The current prevalence of diabetes in Sudan is unknown although the very initial study estimated the prevalence by 3.4%[12]. 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[13].

The aims of study:
1- Studying the effect of obesity on liver enzymes in type2 diabetes mellitus patient.
2- The study role of complicating glucose and lipid metabolism in type 2 diabetic subjects.

Materials and Methods:
This study was carried out in Center for Endocrinology and Diabetes (ALKindy Hospital) in Baghdad-Iraq, between April 2013 and July 2013. The study included (90) patients(42men and 48women) age range is(23-76)year ,the patients have been divided to three subgroup(1)obese with diabetic (30) patients(12 men and 18 women ) were obese , group(2) non-obese with diabetic 30patients (14men and 16women ) ,group(3) control (30)patients (16men and 14 women) healthy people. Subjects were excluded from this study if they had liver disease, alcohol intake, medications for lowering lipid, insulin treatment, pregnant women and women taking contraceptive pills.

The following biochemical investigations have been studied for their fasting plasma glucose, lipidprofile ,HbA1C ,serum liver enzymes (ALP, AST, ALT, GGT), serum insulin. From each patient,10 ml of blood were obtained by vein puncture, using a 10 ml disposable syringes between (8.30 and 11.00 A.M) after (12-14) hours fasting . The blood sample was divided into two parts ; 2 & 8 ml. the first parts of blood was dispensed in a tube containing Ethylene Diamine Tetraacetic Acid (EDTA),this blood mixed gently and used for HbA1c estimation, While the second parts was dispensed in a plain tube and left for around an hour to clot at room temperature (24 °C), and then separated by centrifuge at (3000 rpm) for (10 min) to collect serum and used for liver enzymes estimation , also analysis included Fasting Plasma Glucose (FBG) , Lipid Profile and insulin. The instruments used in the study and their suppliers in biochemistry lab was Abbot (USA). Kits used in our study were: insulin kits (Demeditec,Germany), Glycated hemoglobin kit(Infopia ,Korea),liver enzymes (Abbot , USA)kits.

Statistical Analysis
Statistical analysis was performed using SPSS-21(Statistical Packages for Social Sciences- version 21) and Microsoft Office Excel (Microsoft Office Excel for windows; 2003). Data were analyzed by using One Way Analysis of Variance (ANOVA). Student T-test was used to assess significant difference among means. Proportions were compared by chi-square. Correlations between parameters were assessed using bivariate correlations. P < 0.05 was considered statistically significant

Result:
Data in table analysis is showed that there is a significant differences in the mean of ALP level between obese diabetic patients(76.88±22.61) U/L and non-obese diabetic patients (70.10±19.82) U/L diabetic patients compared with control group (69.20±20.60) U/L(P<0.05) .on the other hand there is a significant defferences in the mean of ALP level
between non-obese diabetic patients and control groups. Our results show that there is no significant differences in the mean of AST,ALT,GGT level between obese (25.23±8.08) (29.52±12.79) (31.00±15.06) U/L and non-obese (25.11±7.59) (72.70±9.49) (27.26±15.65) U/L diabetic patients compared with control group (22.26±6.62) (20.30±12.31) U/L (P<0.05).on the other hand there is a significant defferences in the mean of AST,ALT level between each other groups and control group, The means of serum GGT level in obese diabetic patients and non-obese diabetic patients were significantly (P < 0.05) higher than control (20.43±9.99)U/L ,as shown in (table1). Our results show the positive correlation between AST in obese diabetic patients (r=0.662**)at the 0.01 level and with ALT in control group(r= 0.828**)at the 0.01 level ,as shown in (table2). There is a positive correlation between ALP in obese and non – obese diabetic patients ( r = 0.612**) (r=0.548**) at 0.01 level , as shown in (table3).There is a significant strong positive correlation between AST and ALT in obese, non-obese diabetic patients and control group(r=0.589**) (r=0.529**) (r=0.740**)respectively at 0.01 level ,also there is positive correlation with GGT in control group (r=0.662**)at 0.01 level ,as shown in( table4) . There is positive correlation between ALT and cholesterol in non- obese diabetic(r= 0.495**)at 0.01 level ,also there is strong positive correlation with AST in all groups (r=0.589**) (r=0.529**) (r=0.740**) respectively at 0.01 level , there is strong positive correlation with GGT in control group (r=0.828**), while there was negative correlation between ALT and cholesterol in obese diabetic patients and with HbA1c in control group as shown in (table5), strong positive correlation between HOMA IR and FBS in obese diabetic patients ( r =0.662**)and non obese diabetic patients (r=0.568**)at the 0.01 level ,also is significant positive correlation between HOMA IR and insulin in obese diabetic patients( r = 0.690**) at the 0.01 level ,as shown in( table6).

**Table1: the mean of the studied parameters of obese, non – obese diabetic patients and control groups.**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Obese diabetic group</th>
<th>Non-obese diabetic group</th>
<th>control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP</td>
<td>76.88±22.61</td>
<td>70.10±19.82</td>
<td>69.20±20.60</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>AST</td>
<td>25.23±8.08</td>
<td>25.11±7.59</td>
<td>22.26±6.62</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ALT</td>
<td>29.52±12.79</td>
<td>72.70±9.49</td>
<td>20.30±12.31</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>GGT</td>
<td>31.00±15.06</td>
<td>27.26±15.65</td>
<td>20.43±9.99</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HOMA IR</td>
<td>9.41±11.23</td>
<td>5.64±4.01</td>
<td>1.04±0.61</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Data in table analysis is showed that there is a significant differences in the mean of ALP level between obese diabetic patients(76.88±22.61) U/L and non-obese diabetic patients (70.10±19.82) U/L diabetic patients compared with control group (69.20±20.60) U/L(P<0.05) .on the other hand there is a significant defferences in the mean of ALP level between non-obese diabetic patients and control groups. Our results show that there is no significant differences in the mean of AST,ALT,GGT level between obese (25.23±8.08) (29.52±12.79) (31.00±15.06) U/L and non-obese (25.11±7.59) (72.70±9.49) (27.26±15.65) U/L diabetic patients compared with control group (22.26±6.62) (20.30±12.31) U/L
Our results show the positive correlation between GGT in obese diabetic patients (r=0.662**) at the 0.01 level and with ALT in control group (r=0.828**) at the 0.01 level, as shown in (table2). There is a positive correlation between GGT and insulin in obese and non-obese diabetic group (r=0.383*) (r=0.368*) respectively at 0.05 level.

There is a positive correlation between ALP and FBS in obese and non-obese diabetic patients (r=0.612**) (r=0.548**) at 0.01 level, positive correlation between ALP and VLDL, HbA1c, HOMA IR (r=0.386*) (r=0.446*) (r=0.398*) as shown in (table3)

| Table4: the correlation between AST with the pointed in obese, non obese diabetic and control groups. |
|-------------------------------|----------------|-----------------|------------------|----------------|
| Parameters                  | Obese diabetic group | Non-obese diabetic group | control group | P value |
| ALT                         | (r=0.589**)          | (r=0.529**)        | -               | 0.001    |
| GGT                         | -                    | -                 | (r=0.662**)     | 0.000    |

There is a significant strong positive correlation between AST and ALT in obese, non-obese diabetic patients and control group (r=0.589**) (r=0.529**) (r=0.740**) respectively at 0.01 level, also there is positive correlation with GGT in control group (r=0.662**) at 0.01 level, as shown in (table4)

| Table5: the correlation between ALT with the pointed in obese, non obese diabetic and control groups |
|-------------------------------|----------------|-----------------|------------------|----------------|
| Parameters                  | Obese diabetic group | Non-obese diabetic group | control group | P value |
| Cholesterol                 | (r=0.406*)         | (r=0.495*)        | -               | 0.049    |
| AST                         | (r=0.589*)          | (r=0.529*)        | (r=0.740*)      | 0.001    |
| GGT                         | -                    | -                 | (r=0.838*)      | 0.000    |
| HbA1C                       | -                    | -                 | (r=0.393*)      | 0.032    |

while there was negative correlation between ALT and cholesterol in obese diabetic patients and with HbA1c in control group as shown in (table5),

| Table6: the correlation between HOMA IR with the pointed in obese, non obese diabetic and control groups |
|-------------------------------|----------------|-----------------|------------------|----------------|
| Parameters                  | Obese diabetic group | Non-obese diabetic group | control group | P value |
| FBS                         | (r=0.662**)       | (r=0.568*)       | -               | 0.001    |
| Insulin                     | (r=0.690*)        | (r=0.399*)       | -               | 0.000    |
| ALP                         | (r=0.387*)        | (r=0.398*)       | -               | 0.03     |

strong positive correlation between HOMA IR and FBS in obese diabetic patients (r=0.662**) and non obese diabetic patients (r=0.568**) at the 0.01 level, also is significant positive correlation between HOMA IR and
insulin in obese diabetic patients (r = 0.690**) at the 0.01 level, as shown in Table 6.

**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[14,15,16]. The highly accelerated incidence of type 2 diabetes has been fuelled by a tremendous increase in obesity worldwide, resulting from excess calorie intake and lack of physical exercise. Such a highly anabolic state of the body results in an accumulation of fat in both (normal) adipose tissue and (abnormal) locations in the liver, visceral fat depots and muscle, also named ectopic fat accumulation. Thus, when the energy intake exceeds the storage capacity of adipose tissue, this leads to an energy overflow to ectopic sites[17,18,19].

Ectopic fat accumulation in the liver can have several negative effects on the normal metabolic functions of the liver. Currently, Non-alcoholic fatty liver disease (NAFLD) is considered by some authors to be the hepatic component of the metabolic syndrome[20,21].

In the majority of cases, NAFLD causes asymptomatic elevation of liver enzyme levels including alanine aminotransferase (ALT), aspartate aminotransferase and glutamyl transferase AST [22]. These findings stress the need for methods to detect (and treat) NAFLD at an early stage. Our results indicated that the means of serum ALT level in patients obese with T2DM and non-obese were not differ significantly. But both groups differ significantly (P < 0.05) as compared with control group. This result agree with Chan et al[23] and [24]. They found that there is elevated ALT level with BMI, another study in India by [25] showed that serum ALT level is greater among type 2 diabetes, overweight or obese. The elevated ALT level is most closely related to liver fat accumulation, and our results disagree with the study in Saudi Arabia by [26] who found the ALT and AST did not show a significant difference, whereas GGT and ALP enzymes were significantly higher in obese than non-obese subjects. Consequently ALT has been used as a marker of NAFLD[27,28].

The large impact of NAFLD on patient survival was recently emphasized in a study showing that NAFLD accompanied by elevated liver enzymes is associated with a clinically significant risk of developing end-stage liver disease, resulting in a lower survival in patients with Nonalcoholic steatohepatitis (NASH), which is a common, often “silent” liver disease. It resembles alcoholic liver disease, but occurs in people who drink little or no alcohol. The major feature in NASH is fat in the liver, along with inflammation and damage[29]. Most people with NASH feel well and are not aware that they have a liver problem. Nevertheless, NASH can be severe and can lead to cirrhosis, in which the liver is permanently damaged and scarred and no longer able to work properly. Furthermore, [30]. Reported that most patients with NAFLD will develop diabetes or impaired glucose tolerance in the long term and that progression of liver fibrosis is associated with more severe insulin resistance and weight gain.

Our results indicated that the means of serum AST level in patients obese with and non-obese were not differ significantly. But the both groups were differ significantly (P<0.05) as compared with control group. These results agree with [31], who found were significantly elevated AST level.
in obese diabetic patients compared with control, and disagree with another study by [32] who confirmed the non significant difference in AST level between obese patients and controls. Our results shows that there is a significant differences (P<0.05) in the mean of ALP levels between obese group and each of non-obese and control groups, on the other hand the difference between obese and non-obese groups was not significant, these results are consistent with results obtained by Foster et al[33], and [34],who showed that; the most frequently encountered abnormalities with type 2 diabetes mellitus, is GGT and ALP, rather than ALT. On the other hand the results of the present study were disagree with [32] who showed the elevated AST rather than ALP in patients with type 2 diabetes mellitus. Our results shows significant (P< 0.05) differences between each means of serum GGT level in obese and non-obese as compared with control. Similar results were reported by [35] who postulated that possible mechanisms by which GGT is a marker for increased risk of type 2 diabetes include the following: (a) elevated serum GGT could indicate excess fat deposits in the liver, which may cause hepatic insulin resistance and increase the risk of type 2 diabetes by contributing to systemic insulin resistance; (b) increased GGT is a marker for oxidative stress; and (c) increased GGT may be the expression of inflammation. [36] in India reported that GGT was a significant predictor of insulin resistance independently of weight, BMI, or percentage of fat. Numerous studies have found that GGT is not just a marker of alcohol consumption, but is an independent predictor of many diseases, including cardiovascular diseases, type 2 diabetes, inflammation, and, possibly, underlying oxidative stress [37]. Many studies have reported an increased risk of type 2 diabetes with increased levels of GGT. [38] prospectively studied a group of 4,088 healthy, male Korean workers and found a strong response relationship between serum GGT levels at baseline and incident type 2 diabetes after 4 years of follow up. This relationship was observed even in nondrinkers. [39] found that increased serum GGT increased the risk of incidence of metabolic syndrome and type 2 diabetes in 3,000 middle aged Japanese male office workers. [40]evaluated 20,158 Finnish subjects of both genders, aged 25-64, in a prospective cohort study and found that higher serum GGT was directly associated with an increased risk of type 2 diabetes. [41] evaluated liver enzymes (AST, ALT, ALP, and GGT) in 1441 middle-aged (35-64 yrs) male and female participants in the population-based Mexico City Diabetes Study and at 7-year follow-up to determine the incidence of type 2 diabetes. They stated that only increased GGT is an independent of type 2 diabetes. They theorized that GGT elevation may reflect increased hepatic insulin resistance or oxidative stress [42, 43, 44, 45].

Conclusion:
The following factors could be conducted:-
1. The liver enzymes of(alkaline phosphatase, alanine transaminase, aspartate transaminase gama glutaminase transferase) is higher significantly in obese diabetic patients than non–obese diabetic patients and control group.
2. Insulin resistance has been found to be significantly higher in obese than non-obese diabetic patients and control.
3. The HbA1c has been found to be significantly higher in obese than non-obese diabetic patients and control. The result shows positive correlated between HOMA IR and BMI with Insulin level in obese diabetic patients.

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دراسة تأثير السمنة ومقاومة الإنسولين على أنزيمات الكبد في مرضى السكري النوع الثاني

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الخلاصة:

يعتبر داء السكري النوع الثاني مرض متأثر بشكل أكبر من احتمال إصابته في الغير مصابين بمرض السكري. في علوم النبات، ظهر ارتفاع متوسط أنزيمات الكبد يكون متورطاً مع زيادة مؤشر كلفة الجسم، ومقاومة الجس للانسولين نتيجة اعتلال الدهون بالدم والالتهابات. المجموعة التي تأتي إلى زيادة الأصابات بأمراض الكبد التي تسبب احتقاناً حول.

دراسة تأثير السمنة على أنزيمات الكبد في مرضى السكري النوع الثاني. دور أدنى الدين والدهون وتعويض الكالوز في مرضى السكري النوع الثاني. علاقة تأثير السمنة على أنزيمات الكبد ومستوى الدهون في مرضى السكري النوع الثاني ضمت deux من النوع الثاني من الأطفال والمكور مع عدد متوازي 30-60 سنة. المجموعة الأولى وتم (30) مريضاً بداء السكري علاوة على السمنة، والمجموعة الثانية (30) مريضاً أصحاء. وقد تم أجراء الفحوصات المخبرية التالية: أنزيمات الكبد (انقسام الكلازيم فوسفتيز) ومستوى الأنسولين. في الدم، في مرضى السكري، مرضى الكبد والسكير التراكمي، تسبب القياس الوزن والطول وضغط الدم. أنزيمات الكبد (فوسفتيز القاعدي وانقسام الامين) وأمراض أمين ونساء إسمنتات ترانس أمين. كلا كولوتامي السكري (فوسفتيز) كانت مرتفعة في الأشخاص المصابين بالسمنة والسكير نوع 2 مقارنة بالأشخاص الذين لا يعانون من السمنة، وهم مصابين بالسكير نوع 2، والأشخاص الأصحاء أيضاً. إن مستوى مقاومة الإنسولين تأثير إشراقة وانزيمات بداء السكري النوع الثاني؛ مثاً، بالإضافة إلى افضلية الأشخاص الذين لا يعانون من السمنة ومصابين بداء السكري النوع الثاني. كانت مرتفعة عند الأشخاص الذين يعانون السمنة، والأشخاص الذين يعانون من السمنة. الايضاً إن مستوى الكبد والدم كان مرتفع مستواه في مرضى السكري، من الأشخاص الذين يعانون من السمنة، والأشخاص الأصحاء، أيضاً، إن مستوى السكري التراكمي كان مرتفع مستواه، من الأشخاص الذين يعانون من السمنة، والأشخاص الأصحاء، أيضاً، إن مستوى السكري التراكمي كان مرتفع مستواه في مرضى السكري. 

الكلمات المفتاحية: مرض السكري النوع الثاني، الأنسولين، فوسفتيز، ترانس أمين، الكلازيم FFA، انقسام الكبد، البقريات، مقاومة الإنسولين.