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Insulin Resistance in Type II Diabetes Mellitus with Liver Cirrhosis

[1]Amal A. Abd El-Fattah, [2]Mohamed I. Hamed, [3]Serag-Eldin A. Sadek and [2]Ahmed S. Abu-Elhana

[1]Department of Biochemistry, Faculty of Pharmacy Benisuif University and Cairo University, Egypt
[2]Department of Clinical Pharmacy, Faculty of Pharmacy, Misr University for Science and Technology, Egypt
[3]Department of Internal Medicine, Faculty of Medicine Misr University for Science and Technology, Egypt

Abstract: Diabetes Mellitus (DM) is a progressive disease characterized by elevation of fasting and post-prandial blood glucose level that may occur due to insulin deficiency, insulin resistance or both. In spite of high prevalence of DM in patients with liver cirrhosis few studies have focused on this association. We investigated the glycemic profile of 61 candidate that were divided into three groups, diabetic group of 21 DM patients, diabetic cirrhotic group of 20 diabetic patients with cirrhosis and control group of 20 healthy volunteers that matches age and sex. The findings of this study revealed that both fasting and post-prandial serum insulin levels of diabetic cirrhotic patients were significantly elevated than those of diabetic non cirrhotic patients ($P < 0.01$). Also positive co-relation between serum Triglyceride (TG) and both serum fasting insulin and blood glucose levels were seen within the diabetic non cirrhotic group. While there was a negative co-relation between serum Low Density Lipo-protein (LDL-C) and serum fasting insulin level of diabetic patients with cirrhosis. These results suggest that insulin resistance may consider as one of the clinical features in diabetic patients with cirrhosis probably related to hepatopathology.

Key words: Insulin Resistance · Liver Cirrhosis · Diabetes Mellitus

INTRODUCTION

One of the most common internal hormonal secretion disorders that affect about 6% of the world's population is diabetes mellitus [1]. Diabetes is a metabolic disorder of carbohydrate, fat and protein, affecting a large number of population in the world [2].Common symptoms of hyperglycemia includes polyuria, polydipsia, polyphagia and unexplained weight loss [3]. Diabetes mellitus is not a single disorder but it is a group of metabolic disorders characterized by chronic hyperglycemia, resulting from defects in insulin secretion, insulin action, or both. Increased thirst, increased urinary output, ketonemia and ketonuria are the common symptoms of diabetes mellitus, which occur due the abnormalities in carbohydrate, fat and protein metabolism that may lead to other diabetic complications [4-6].

There are two main types of diabetes disease, different in etiology, pathology, risk factors, therapy and evolution. Type 1 diabetes occurs when the immune system produces self immunoglobulin against pancreatic beta cells; it typically strikes children and young adults, but it can occur at any age, it`s an autoimmune disease characterized by a local inflammatory reaction in and around islets that is followed by, selective destruction of insulin-secreting cells [7]. Type 2 diabetes mellitus (T2DM) usually begins as insulin resistance and it is quite always associated with risk factors such as older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity and race ethnicity, T2DM accounts for about 90–95% of all diagnosed cases of diabetes [8].

Liver cirrhosis is histologically defined as a diffuse state with replacement of the normal lobular architecture by abnormal nodules and fibrous septa [9]. Chronic hepatitis C and heavy alcohol consumption represent the most common causes of cirrhosis. Other common causes of cirrhosis include hepatitis B, hepatitis D, primary biliary cirrhosis and autoimmune hepatitis [10].

From 17% to 30% of patients who suffer cirrhosis may be clinically diabetic. Diabetes that develops as a complication of cirrhosis is known as "hepatogenous diabetes" (HD) [11].

Corresponding Author: Ahmed S. Abu-Elhana, Department of Clinical Pharmacy,
Faculty of Pharmacy, Misr University for Science and Technology, Egypt.

The natural history of HD is different from that of hereditary T2DM, The treatment of HD is complex due to the presence of liver damage and the hepato-toxicity of oral hypoglycemic drugs frequently prescribed to these patients. Therefore, pharmacological therapy must be closely monitored for the risk of hypoglycemia [12].

We suggest that a combined receptor and post receptor defect in insulin action on target cells is certainly an important cause of insulin resistance in cirrhosis of the liver. Insulin resistance may thus depend in part on the following sequence: decreased insulin degradation by the liver may lead to hyperinsulinemia, receptors down-regulation and insulin binding decreases. The question is open to find solution regarding insulin resistance in diabetic patients with liver cirrhosis and recommend a drug protocol.

MATERIALS AND METHODS

This study was designed as a prospective based clinical trial. It was carried out of 61 candidate (41 patients and 20 healthy volunteer) divided into 3 groups. Two groups of chronic type II diabetes mellitus patients, one of them were 20 cirrhotic patients and the other group was 21 type II diabetics without cirrhosis. A third group of non-diabetic healthy volunteers of age and sex matched criteria were used as control. The patients were selected from in-patient and out-patient clinics of Internal Medicine Department, Misr University for Science and Technology teaching hospital.

As Baseline Study, All Patients Were Subjected to the Following:

- Full clinical examinations through history taking (age, sex, diabetes history, other diseases history, drug history, family history and allergy history) and full physical assessment includes routine clinical examinations:
- Estimation of Fasting and postprandial serum glucose level.
- Estimation of serum glycosylated hemoglobin (HbA1c).
- Estimation of fasting and postprandial serum Insulin level.
- Other investigations included:

- Kidney function tests to exclude patients with renal impairment.
- Lipid profile.
- Estimation of albumin and globulin.
- Estimation of liver enzymes to exclude patients with high liver enzymes (patients with high insult to liver).
- Abdominal ultra sound to prove the presence of cirrhosis weather with or without portal hypertension known by estimation of portal vein diameter.

Inclusion Criteria: Patients known to be type II diabetes mellitus treated with oral hypoglycemic drugs for not less than 5 years and patients proved to be liver cirrhotic by ultra sound whatever was the etiology.

Exclusion Criteria: Patients with renal failure (known by estimation of renal function tests), Patients who received insulin at one time on their diabetic state, Patients with tumor of liver malignancy and Patients with any clinical manifestation of malignancy.

Group Classification:

Dm Group: It comprised of 21 diabetic patients; 8 males and 13 female with a mean age of 51 ± 1.5 years.

Dm with Cirrhosis Group: It comprised of 20 diabetic patients with liver cirrhosis; 9 males and 11 females with a mean age of 52 ± 1.5 years.

Control Group: It comprised of 20 non diabetic volunteer; 11 males and 9 females with a mean age of 48.1 ± 1.1 years.

Analysis of data was done by an SPSS program statistical program for social science, Plume *et al*.[13] as follows:

- Description of quantitative variables as mean, standard error (SE).
- Description of qualitative variables as number and percentage.
- Chi-square test was used to compare qualitative variables between groups.
- Unpaired t-test was used to compare quantitative variables, in parametric data); Mann Wittney test in case of non parametric data.
- One way ANOVA (analysis of variance) test was used to compare more than two groups as regard to quantitative variable.
- LSD (Least Significant Difference) of ANOVA was used to show the statistical significance between groups. Kruskall Wallis test was used in case of non parametric data.

- Spearman Correlation co-efficient test was used to rank variables versus each other positively or inversely.
- *P* value > 0.05 : non-significant.
- *P* value <0.05 : significant (a).
- *P*<value < 0.01: highly significant (b).

RESULTS

Demographic Characteristics of Control and Diabetic Patients Involved in the Study: Twenty one diabetic patients, twenty diabetic patients with cirrhosis and twenty healthy control individuals were involved in the study. Nearly equal distribution between males and females occurred in all groups (Table 1, Fig. 1). The average age among the different groups was 48.1±1.1, 51±1.5 and 52±1.5 years for control, DM and DM with cirrhosis respectively (Table 1). All patients had T2DM for a minimum of 5 years with average 7 years, (Table1, Fig 2).

Effect of DM with Cirrhosis on Glycemic Profile: Diabetes mellitus did not cause any significant change in either the fasting or2 Hours Post-Prandial (2HPP) serum insulin levels when compared with normal control individuals (Table 2, Fig. 3). On the other hand, patients with DM and cirrhosis showed a highly significant increase (p<0.01) in both fasting and 2HPP serum insulin levels (Table 2, Fig. 3). Both fasting and 2HPP blood glucose levels were highly significantly elevated when compared with control values in both diabetic and diabetic cirrhotic patients (p<0.01), (Table 2, Fig. 4). Similarly glycated hemoglobin (HBA1c) was highly significantly elevated in both diabetic and diabetic patients with cirrhosis ($p<0.01$), (Table 2, Fig. 5).

Effect of DM with Cirrhosis on Glycemic Profile: Serum concentrations of both fasting and 2HPP insulin of diabetic patients with cirrhosis were highly significantly elevated (p<0.01) when compared with patients of DM without cirrhosis (Table 3, Fig. 6). Similarly fasting glucose level of DM patients was significantly increased (p<0.05) when compared with corresponding diabetic cirrhotic patients (Table 3, Fig. 7).

Correlation Between Glycemic Profile and Lab Data of Control, Dm and Dm with Cirrhosis Groups: There was no statistical significant correlation (p>0.05) between glycemic profile and other variables among control group (Table 4), However a significant Positive correlation (p<0.05) between serum TG and both fasting serum insulin and fasting blood glucose levels had been showed among DM group (Table 4, Figure 9). Similarly there was a significant Positive correlation (p<0.05) between Blood Urea Nitrogen (BUN) and Glycosylated Hemoglobin (HBA1c) among DM group (Table 4, Fig. 10).

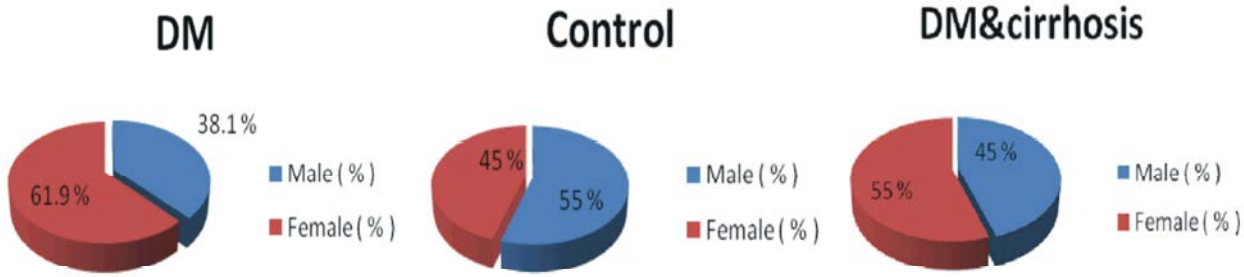

Fig1: Distribution of Males and Females among tested group.

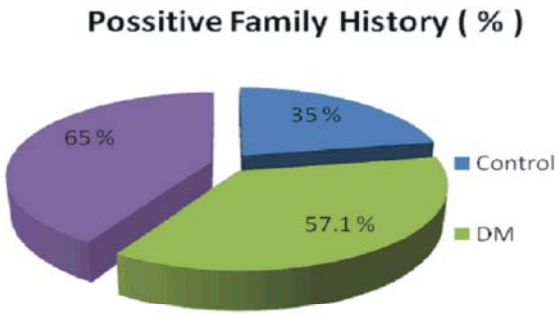

Fig. 2: Positive family history of Diabetes Mellitus among tested groups.

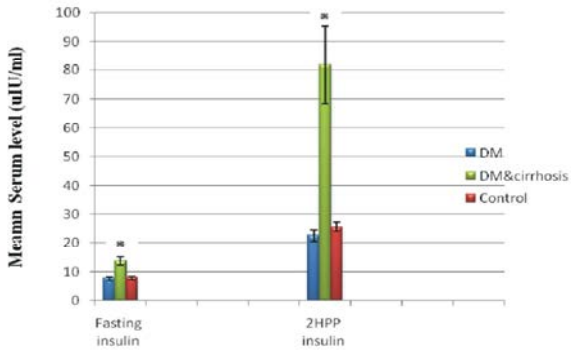

Fig. 3: Schematic presentation of Control, DM and DM & cirrhosis groups as regard to Serum insulin level. * Significant with control

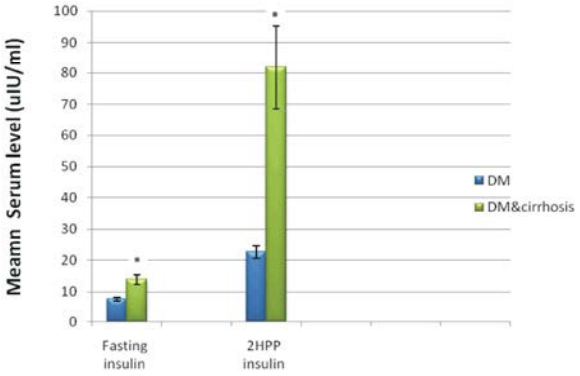

Fig. 6: Serum insulin level of DM and DM & cirrhosis groups involved in the study. *significant change

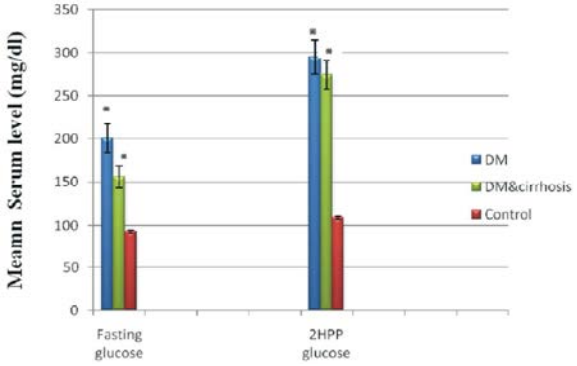

Fig. 4: Schematic presentation of Control, DM and DM&cirrhosis groups as regard to Serum glucose level. *significant with control

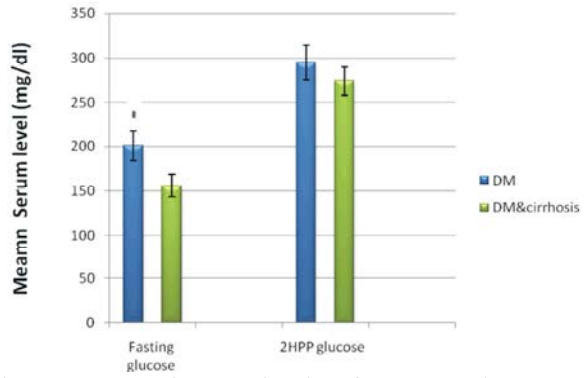

Fig. 7: Serum glucose level of DM and DM & cirrhosis groups involved in the study. *significant change

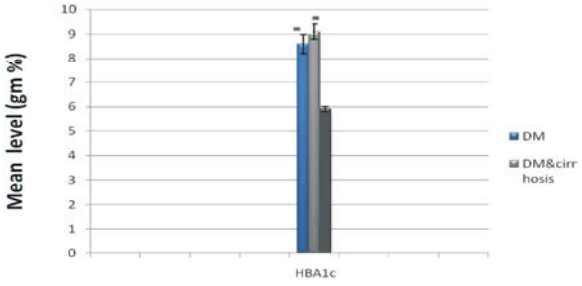

Fig. 5: Schematic presentation of Control, DM and DM&cirrhosis groups as regard to glycosylated hemoglobin percent. significant with control

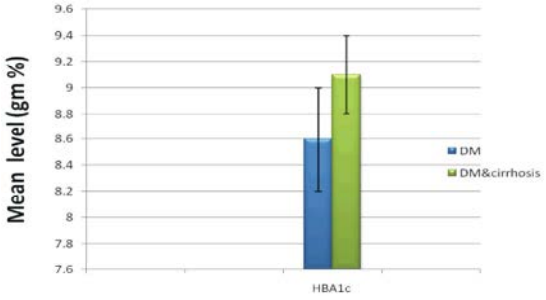

Fig. 8: Glycosylated hemoglobin of DM and DM & cirrhosis groups involved in the study.

Also a significant negative correlation ($p<0.05$) was seen between LDL-C and fasting serum insulin levels within DM group (Table 4, Fig. 11).

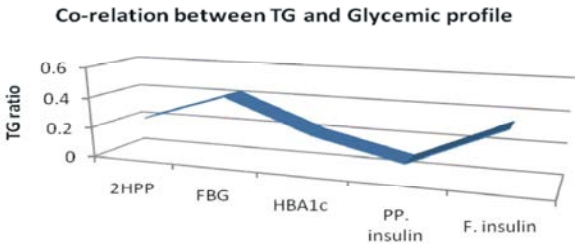

Fig. 9: Correlation between TG and glycemic profile among DM group

DISCUSSION

An association between diabetes mellitus (DM) and liver cirrhosis was first described by Bohan [14] and

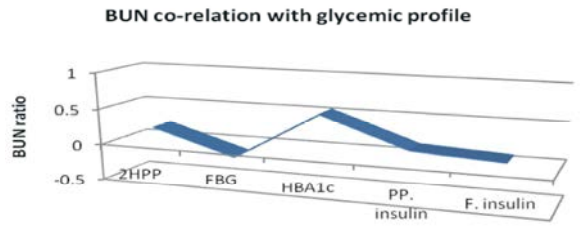

Fig. 10: Correlation between BUN and glycemic profile among DM group.

Table 1: Demographic characteristics of control, diabetic patients and diabetic patients with cirrhosis involved in the study.

Variables	Controls N=20	DM &cirrhosis N=20	P
Age (year)	48.1+1.1	52+1.5	>0.05 NS
Gender*			
Male	11(55%)	9(45%)	>0.05
Female	9(45%)	11(55%)	NS
Family history*	7(35%)	13(65%)	>0.05 NS

*using Chi-square test

Table 2: Glycemic profile of diabetic and diabetic patients with cirrhosis versus control.

Variable	Control N=20	DM & cirrhosis N=20
Fasting insulin (uIU/ml)	7.9+0.6	13.8+1.5 (b)
2HPP insulin (uIU/ml)	25.7+1.5	81.8+13.4 (b)
Fasting glucose (mg/dl)	93+1.5	156+12.5 (b)
2HPP glucose (mg/dl)	109+2	274+16.3 (b)
HBA1c (%)	5.9+0.1	9.1+0.3 (b)

(b): p<0.01(highly significant change with control)

Table 3: Glycemic profile of diabetic patients versus diabetic patients with cirrhosis.

Variables	DM N=21	DM &cirrhosis N=20
Fasting insulin (uIU/ml)	7.6+0.6	13.8+1.5(b)
PP insulin (uIU/ml)	22.6+2.1	81.8+13.4(b)
Fasting glucose (mg/dl)	201+16.8	156+12.5(a)
2HPP glucose (mg/dl)	295+20	274+16.3
HBA1c (%)	8.6+0.4	9.1+0.3

(a) p<0.05 (significant changes between the 2 groups)

(b) p<0.01 (highly significant changes between the 2 groups)

named as hepatogenous diabetes by Megyesi *et al*. [15], in which 57% of cirrhotic patients showed increased insulin resistance. Various pathogenetic factors are involved in development of the insulin resistance, serum insulin levels are higher in diabetic patients with chronic liver disease than those in patients with life style-related diabetes mellitus [16]

Insulin resistance in liver cirrhosis may depend on either reduced sensitivity (receptor defect) and/or reduced response to insulin (post-receptor defect), hyperinsulinism (in both the fasting subject and after oral glucose loading) may be attributable to liver cell damage resulting in reduced insulin uptake [17]. Insulin resistance may thus depend in part on the following sequence: decreased insulin degradation by the liver which leads to hyperinsulinemia, down-regulation and insulin binding decrease [18].

Table 4: Co-relation between Glycemic profile and different variables and characteristics involved in the study within the tested groups.

	Control group					DM group					DM with cirrhosis				
Variables	F. insulin	PP. insulin	HBA1c	FBG	2HPP	F. insulin	PP. insulin	HBA1c	FBG	2HPP	F. insulin	PP. insulin	HBA1c	FBG	2HPP
Age	0.15	-0.15	0.2	0.29	0.03	0.11	-0.09	0.23	0.29	0.16	0.11	-0.17	0.26	0.22	0.26
Fasting insulin	0.27	0.07	0.14	0.36	0.13	0.08	0.06	0.11	0.08	0.13	0.07	0.02	0.13	0.06	0.23
PP insulin	-0.16	-0.13	0.18	-0.11	-0.11	0.12	-0.11	0.17	0.11	-0.11	0.19	-0.1	0.18	0.19	-0.31
Fasting glucose	0.2	0.18	-0.19	0.14	0.19	0.07	0.19	-0.11	0.19	0.18	0.22	0.11	-0.1	0.13	0.1
2HPP glucose	0.13	0.15	0.11	-0.02	-0.2	0.14	0.18	0.19	0.03	-0.2	0.18	0.13	0.12	0.02	-0.1
HBA1c	0.12	-0.1	-0.06	-0.12	0.04	0.16	-0.07	-0.08	-0.17	0.19	0.12	-0.17	-0.04	-0.18	0.14
LDL	-0.1	0.02	0.23	0.16	0.25	0.22	0.04	0.16	0.18	0.24	-0.50*	0.02	0.26	0.19	0.2
HDL	0.11	0.17	0.2	0.2	0.22	0.12	0.11	0.22	0.23	0.27	0.18	0.1	0.29	0.23	0.26
Cholesterol	0.05	0.26	0.12	0.32	0.11	0.09	0.22	0.17	0.18	0.17	0.02	0.2	0.12	0.12	0.13
TG	0.18	0.05	0.26	0.03	0.18	0.35*	0.09	0.22	0.43*	0.25	0.15	0.02	0.2	0.13	0.15
PT	0.21	0.04	0.12	0.22	-0.19	0.06	0.04	0.07	0.08	-0.14	0.01	0.01	0.02	0.28	-0.12
PTT	0.12	0.18	0.14	0.2	0.11	0.14	0.17	0.16	0.06	0.18	0.13	0.1	0.13	0.26	0.12
INR	0.11	-0.11	0.29	0.14	0.16	0.13	-0.04	0.27	0.14	0.18	0.17	-0.14	0.2	0.16	0.1
AST	-0.09	0.11	0.17	0.28	0.16	0.04	0.19	0.17	0.24	0.17	0.02	0.13	0.18	0.24	0.18
ALT	0.18	-0.18	-0.25	0.04	0.22	0.06	-0.14	-0.13	0.18	0.29	0.28	-0.19	-0.15	0.14	0.2
Platelets	0.16	0.04	0.2	0.28	0.14	0.12	0.011	0.17	0.06	0.24	0.12	0.01	0.1	0.08	0.14
Albumin	0.01	0.2	0.11	0.07	-0.06	0.06	0.22	0.02	0.18	-0.08	0.09	0.23	0.17	0.28	-0.08
Globulin	-0.09	0.11	0.19	-0.22	0.1	-0.12	0.19	0.19	-0.27	0.18	-0.11	0.15	0.18	-0.07	0.11
A/G	0.01	-0.18	-0.03	0.1	0.15	0.09	-0.16	-0.04	0.19	0.15	0.02	-0.16	-0.04	0.19	0.13
Total protein	0.15	0.14	0.12	-0.04	-0.2	0.07	0.18	0.07	-0.03	-0.17	0.17	0.19	0.22	-0.04	-0.27
Direct bilirubin	0.27	0.2	0.18	-0.1	0.23	0.02	0.2	0.18	-0.3	0.08	0.22	0.23	0.17	-0.2	0.28
Total bilirubin	-0.15	0.14	-0.21	0.15	0.18	-0.23	0.17	-0.22	0.16	0.19	-0.25	0.11	-0.24	0.14	0.15
Creatinin	0.07	0.27	-0.01	0.17	0.19	0.17	0.18	-0.28	0.09	0.29	0.27	0.28	-0.21	0.19	0.19
Urea	0.22	-0.12	0.14	-0.26	0.28	0.04	-0.14	0.3	-0.08	0.23	0.24	-0.17	0.1	-0.28	0.2
BUN	0.23	0.18	0.2	-0.12	0.13	0.09	0.15	0.55*	-0.12	0.22	0.29	0.19	0.25	-0.22	0.12

This study was performed to estimate the glycemic profile (serum insulin, blood glucose levels in both fasting and 2HPP samples and HbA1c %) of both diabetic patients with or without cirrhosis to evaluate absence or presence of insulin resistance in diabetic patients with cirrhosis.

In this study, occurrence of insulin resistance was found in diabetic patients with cirrhosis through estimation of both fasting and 2HPP serum insulin levels. Marked insulin resistance secondary to liver disease, as reduced with insulin hepatic extraction was confirmed and agrees with findings of some investigators [19-22].

Although there were slight difference between serum insulin levels of diabetic and cirrhotic diabetic patients, it wasn`t considered to be statistically significant, The results of this study were disagreed with Kurszynska [23] who indicated that insulin levels were increased in cirrhotic patients without diabetes but on the contrary of those with diabetes.

On the other hand it has been noticed in this study that, the serum fasting and 2-hours post-prandial insulin levels of diabetic group were slightly reduced than those of normal individual. This may be due to defects in insulin secretion including abnormalities in pulsatility and kinetics, quantitative and qualitative abnormalities of insulin, cell loss progressing with time. These findings are in harmony with those of some investigators [24, 25]. Results of the present study showed that, hyperglycemia in diabetic non cirrhotic patients were associated with hyperinsulinemia. This hyperglycemia necessitates drug therapy to control blood glucose level and measures to reduce diabetic complications.

Regarding blood glucose levels, results of the current study revealed that fasting and 2 hour post prandial serum glucose levels of both diabetic with or without cirrhosis were significantly higher than those of control individuals. Serum glucose level elevation could be attributed either to poor pancreatic insulin secretion or reduction in insulin receptor sensitivity. This finding is consistent with results of other research workers [26, 27].

Plasma haemoglobin A1c (HbA1c) reflects mean ambient fasting and postprandial glycaemia over a 2–3 months period. HbA1c is formed by the slow irreversible, non-enzymatic glycation of valine and lysine residues in the haemoglobin molecule. HbA1C is a reliable test for characterizing dysglycemia as it is easier to be performed than an oral glucose tolerance test and it is independent of patient prandial status. According O'Sullivan *et al.* [28], elevated HbA1c levels (>7%) are associated with a higher incidence of micro-vascular and macro-vascular complications in patients with diabetes mellitus.

In support with this conclusion [29] reported that a reduction in plasma HbA1c levels below 6.5 %, leads to a lower incidence of microvascular complications in both type 1 and type 2 diabetes mellitus.

Finding of the present study also indicted that although the 2 hour post prandial serum glucose levels of diabetic patients with cirrhosis was slightly decreased than those of non cirrhotic diabetics patients and fasting serum glucose levels of cirrhotic diabetic patients were significantly decreased than those of non cirrhotic diabetic patients. Paradoxically the glycosylated hemoglobin (HbA1C) of diabetic cirrhotic patients was slightly elevated than those of non cirrhotic diabetic patients.

Current approaches to assessing glycemia rely on self-monitoring of blood glucose levels (SMBG) and measurement of HbA1c value. Since HbA1c percent is a measure of average glycemia for 2-3 months, it does not reflect acute glucose fluctuations and is poorly correlated with PPG excursions and dietary status, so it is considered more reliable in evaluating diabetic patients. Accordingly it`s preferable to depend on the estimation of HbA1c as a measure for glycemia rather than estimation of fasting and post-prandial glucose level [30].

Moreover, fasting serum glucose levels of diabetic non cirrhotic patients differ statistically from those diabetic cirrhotic patients. It` s note worthy that the serum fasting glucose levels of diabetic cirrhotic patients were significantly lesser than those of non cirrhotic, these results were in harmony with Vidal *et al*. [31] but were not in accordance with Kurszynska [23] which indicated that the blood glucose level of diabetic cirrhotic patients was higher than those of diabetic patients without cirrhosis.

There is a lack of information on sex-dependent differences in glycemic profile and control in elderly patients with T2DM. However, few studies have indicated that female patients are at higher risk of not achieving recommended glycosylated hemoglobin (HbA1c) levels than male patients [32, 33] the present study showed that there is no statistical significant difference between HbA1C levels in males and in females, although female patient levels of HBA1c were slightly less than those of males, a finding which is in agreement with that of Kamenov *et al.* [34].

Gender variance in body composition may be due sex hormone difference. It seems that female sex has a favorable effect on insulin sensitivity, despite women having higher adiposity relative to men [35]. The decrease in insulin sensitivity with menopause and subsequent improvement with estrogen replacement, suggest that estrogen may play a role in the insulin sensitivity observed in women. Moreover, complete lack of estrogen synthesis or activity in men is associated with insulin resistance. However, the present study showed that there are no significant differences in glycemic profile (blood glucose, serum insulin and glycosylated hemoglobin levels) between males and females within the same group (control, diabetic and cirrhotic diabetic groups). However for the post-prandial insulin levels, only in non cirrhotic diabetic group the insulin levels were significantly elevated in females than in males, an observation which is in agreement with those of other investigators [36, 37].

The relationship between all tested biochemical markers and glycemic profile (fasting and 2HPP serum insulin, glucose and HBA1C levels) were evaluated. Regarding non cirrhotic diabetic patient group, the present study indicated that there is a significant positive co-relation between serum triglyceride levels and both fasting serum insulin and glucose levels, these results may be explained by previous studies revealing disturbance in glycolysis associated with lipolysis in DM patients, in addition to the nutritional implications may considered a significant factor [38, 39].

The dys-regulation of lipid and lipoprotein profile in hyperglycaemic states may be attributed to insulin resistance, pathophysiological status of type 2 diabetes and abdominal obesity. Those appear to cause hyperinsulinemia, enhanced hepatic gluconeogenesis and glucose output, in addition to lipolysis suppression in adipose tissue leading to a high free fatty acid flux and increased hepatic secretion of very low density lipoprotein (VLDL) with consequent hypertriglyceridemia and reduced levels of HDL-C [40].

The present study estimated also that there is a significant positive co-relation between blood urea nitrogen and HbA1C levels that may be due to oxidative stress conditions associated with uncontrolled diabetes which may aggravate diabetic complications specially nephropathy, a findings that is in accordance with results of Yamagishi [41].

This study also indicated that there is a significant negative co-relation between fasting serum insulin and low density lipoprotein (LDL-C) levels, this finding is in accordance with that of Ogita [42], which explained that insulin is a key modulator of LDL-C metabolism, The possible reason for insulin decreases LDL-C is that insulin may up-regulates lipoprotein lipase and reduced larger particles of very-low-density lipoprotein (VLDL), in addition to increasing the rate of LDL-C clearance.

CONCLUSION

Insulin resistance was showed in diabetic patients with liver cirrhosis that was confirmed by elevation of serum insulin level when compared with diabetic non cirrhotic patients.

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