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Profiles of Liver Function Tests among Type 2 Diabetic Patients Who are Receiving Different Anti-Diabetic Drugs Attending Tikur Anbessa Specialized Hospitals

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Abstract

Background: Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia with disturbances of carbohydrates, fat and protein metabolism resulting from insufficient insulin secretion, defects in insulin secretion, insulin action, or both. Individuals with type 2 diabetes have a higher incidence of liver function abnormalities. The objective of this study was to investigate profile of liver function tests among type 2 diabetic patients who are receiving different anti-diabetic drugs attending Tikur Anbessa Specialized Hospital.

Methods: Hospital based cross-sectional study was conducted on 70 type 2 diabetic patients who are receiving different anti-diabetic drugs and 35 type 2 diabetic patients who do not receive any medication were recruited for this study. The blood was taken at the fasting period and liver enzymes, Total Protein (TP), Albumin (AL), Total Bilirubin (TB), Fasting Blood Sugar (FBS), lipid profiles and Body Mass Index (BMI) were carried out in all patients and control group following the standard procedures.

Results: Mean values of Alkaline Phosphatase (ALP), Albumin (AL), TP and FBS were significantly higher in type 2 diabetic patients receiving different anti-diabetic drugs than in control group. In contrast, mean value of Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) among study group were lower than control group. Mean values of TC and LDL were lower in study group than in the control group. The mean value differences between the study group and control of TB, TG and HDL were statistically not significant. There are no significant differences of liver enzymes, TP, AL, TB, and lipid profiles in different patients who were on different anti-diabetic drugs. But mean value of liver enzymes and lipid profiles were slightly lowered in patients receiving mono therapy of insulin and metformin than insulin plus metformin, whereas BMI and FBS were lowered in their combination therapy receiving group. Similarly mean value of FBS, ALT, TC, HDL, LDL and lipid profiles were lowered in patients receiving mono therapy of glibenclamide and metformin than glibenclamide plus metformin combination therapy receiving group, while BMI and TB were increased in patients receiving mono therapy of metformin and glibenclamide.

Conclusion and recommendation: The anti-diabetic drugs were found to have an effect in lowering liver enzymes and lipid profiles in type 2 diabetic patients. The different biochemical parameters tested were more or less similar in different groups of individuals who were on different anti-diabetic drugs of mono therapy or combination therapy.

Keywords: LFT; Alkaline phosphatase; Lipid profile; Aminotransferases (ALT & AST)

Introduction

Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia with disturbances of carbohydrates, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. Glucose is an important regulator of various pancreatic β-cell processes, including insulin biosynthesis and release. Glucose, over short intervals, stimulates insulin biosynthesis at the level of translation. Glucose thus becomes the final common pathway for the transport of almost all carbohydrates to tissue cells. Normally, rates of glucose influx into the circulation and those of glucose efflux out of the circulation into tissues other than the brain are co-ordinately regulated largely by the plasma glucose lowering hormone, insulin, and the plasma glucose raising hormones, glucagon and epinephrine. Thus systemic glucose balance is maintained, hypoglycaemia as well as hyperglycemia is prevented, and a continuous supply of glucose to the brain is ensured [1-3].

Type 2 diabetes is present in the range of 85-95% of all diabetes cases in high-income countries. In Ethiopia it has been reported as number of cases of diabetes to be estimated about 1.9 million in 2013. Individuals with type 2 diabetes have a higher incidence of liver function test abnormalities than non-diabetics. Mild chronic elevations of transaminases often reflect underlying insulin resistance. The excess free fatty acid found in the insulin-resistant states is directly toxic to hepatocytes. Putative mechanisms include liver cell membrane disruption at high concentration of fatty acids, mitochondrial dysfunction, toxin formation, and activation and inhibition of key steps in hepatic metabolism. Several oral hypoglycemic such as sulphonylureas, biguanide, meglitinides, pioglitazone and

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α-glucosidase inhibitors drugs are used at present for treatment of type 2 diabetes mellitus [4-8].

There is a link between liver function abnormality progression and type 2 diabetic mellitus. The cause of such liver function abnormality may varies; such as NALD, alcohol, viral infection and etc. The severity of type 2 diabetes and severity of liver function abnormality influence the therapy. So patients receiving different anti-diabetic drugs may improve this abnormality [9-13].

Lebovitz et al. [14-15] have reported that there was no difference in the incidence of liver abnormalities in patients treated with rosiglitazone, placebo, metformin, or a sulfonylurea in trials involving 5,000 patients.

Rivellese et al. [16] found that insulin therapy compared with glibenclamide is associated with greater decreases in plasma triglyceride, very low density lipoprotein, increases in the high density lipoprotein and no change in low density lipoprotein.

Studies have shown that diabetes mellitus is a progressive disorder which cannot be effectively managed with drug mono therapy. Regardless of drug management, the pancreatic beta-cells in type 2 diabetic patients continue to deteriorate leading to worsening glycemic control and consequent requirement for multiple therapies or exogenous insulin [17].

In Ethiopia, no study was undertaken to examine the extent of compliance and adherence to progression of liver function tests among T2DM patients who are receiving different anti-diabetic drugs. For that reason, this study was undertaken to fill this gap in the literature. The present study is expected to investigate the causative link of liver function abnormality progression in T2DM patients who are receiving different anti diabetic drug regimen at Tikur Anbessa Specialized Hospital [18-25].

Methods and Subjects

The study setting

An institutional based cross sectional study was conducted in Tikur Anbessa Specialized Hospital and control patients were recruited from Federal Referral Police Hospital, Addis Ababa; because, the patients who visited TASH were already on advanced stages of medications. Hence newer patients who were to be recruited without medications were not available. Therefore, recruitment of patients before the start of any medications was done at Federal Referral Police Hospital, Addis Ababa. The numbers of patients attending diabetic clinic in Tikur Anbessa Specialized Hospital during study period were 850 while patients visiting Federal Referral Police Hospital were 1250. The data were collected from January 2015 to March 2015 [26-36].

Population

The source of population was diabetic patients who were attending diabetic clinic at Tikure Anbessa Specialized Hospital and Federal Referral police Hospital in Addis Ababa. The study population consisted of 70 type 2 diabetic patients who are receiving different anti-diabetic drugs and 35 diabetic patients who did not started any medication. Hence a total of 105 diabetic patients were considered in the study [37-50].

Inclusion and exclusion criteria

Patients of age greater than 18 years (both sexes) who are diabetic patients receiving different anti-diabetic drugs attending Tikur Anbessa Specialized Hospital and T2DM patients from the Federal Referral Police Hospital who had not started taking any medications included as a control group in this study. Patients who had any clinical evidence of cirrhosis or other causes of chronic liver disease, diagnosed type 1 diabetic patients, pregnant and lactating mothers, children less than 18 years of age, type 2 diabetic patients who used HIV drugs and patients drinking alcohol greater than twice a week were excluded from this study.

Sample size determination and sampling technique

The sample sizes were estimated by using a single proportion formula and calculated as follows.

- P: Assumed the highest population proportion prevalence of diabetes mellitus in Ethiopian adults 4.36% [5],
- 5% marginal error (d) to get sample size,
- Confidence Interval (CI) of 95%.

$$n = \frac{Z^2 pq}{d^2};$$

n=Sample size; p=Proportion of DM=0.0436; d=Margin of error=0.05; q=1-p=1-0.0436=0.9564; Z=1.96 at 95% Confidence Interval (CI).

$$n = \frac{(1.96)2 \times 0.0436 \times 0.9564}{0.05 \times 0.05} = \frac{0.160191}{0.0025} = 64.0764 = 64$$

To avoid non-response rate 10% is added. So the total sample was 70.

Simple random sampling technique was applied among type 2 diabetic patients who have been attending Tikure Anbessa specialized hospital for medication. To select patients for the study, two options were assigned (number one and number two) and Nurses who collected the sample were instructed. The patient who had been calling number one and then volunteered to participate in the study was selected. Those patients who have been calling number one but did not volunteer to participate in the study and those calling number two were excluded. To recruit patients for control sampling, which was carried out at the Federal Referral Police Hospital, selection was made from the patients who reported at the hospital during the study period. Patients whose fasting blood glucose levels were >115 mg/dl were selected. 70 patients were recruited for study group and 35 patients were recruited for control group, in the ratio of 2:1 [51-60].

Data analysis

Collected quantitative data was coded, entered to computer, processed, edited, and analyzed using EPI-INFO and SPSS (20th version) and expressed at 95% confidence interval and the p-value were considered significant at $p<0.05$. Then data computed using appropriate statistical methods (mean, standard deviation, p-value, F test statistic value and one-way ANOVA) and the results were presented using tables and figures. Clinical and laboratory data were expressed as the mean ± standard error of mean (SE). Differences in the means between the studies group and control group were evaluated by independent samples t-test and chi (χ^2) tests.

Correlations were evaluated by the Pearson correlation test. The data collected during the current study were recorded and analyzed statistically to determine the significance of different parameters by using SPSS package for windows version 20.0 [61-65].

Data quality assurance

The data quality starts with the sample collection. The sample

Variable	Patients with anti-diabetic drugs (n=70)	Patients without anti-diabetic drug (n=35)	*p-value*
Age (years)			
Mean ± SD	55.10 ± 10.227	52.17 ± 11.833	**0.192**
Range	34–76	28–78	
Sex distribution			
Males	30 (42.9%)	19 (54.3%)	**0.268**
Females	40 (57.1%)	16 (45.7%)	
Duration of diabetes (years)			
Mean ±	12.33 ± 8.018	0 (0)	**-**
SD	1–40	-	
Range	-	-	
BMI (Kg/m^2)			
Underweight	1 (1.4%)	1 (2.9%)	**0.199**
Normal	26 (37.1%)	15 (42.9%)	
Overweight	30 (42.9%)	15 (42.9%)	
Obese	13 (18.6%)	4 (11.4%)	
Alcohol intake status			
	6 (8.6%)	10 (28.6%)	**0.007**
	64 (91.4%)	25 (71.4%)	
Drinker	-	-	
Non-drinker	-	-	
Treatment			
Insulin injection	34 (48.6%)	0 (0)	**-**
Insulin+metformin	5 (7.1%)	0 (0)	
Glibenclamide	5 (7.1%) 24 (34.3%)	0 (0) 0 (0)	
Gibenclamide+ metformin	2 (2.9%)	0 (0)	
Metformin	-	-	

Table 1: Demographic and clinical characteristics of type 2 diabetic patients who are receiving different anti-diabetic drugs and diabetic patients who don't receive any medication (Controls). The mean values of liver enzyme (ALT, ALP) and FBS, lipid profile (TC, TG, HDL, LDL) were lower in type 2 diabetic patients receiving metformin group than insulin receiving group. The mean value of BMI, TP, AST, AL, and TB among insulin group is lower than metformin group; but not statistically significant at the *p* value <0.05 by using independent-t test analysis.

had been taken in aseptic techniques and collected with considering proper procedure. The kit had been made free from contamination and kits were checked for consistency. Collected results were checked for completeness on daily basis by the immediate supervisor. Attention in data insertion to software on computer. The completed result was rechecked repeatedly to maintain the quality of data [66-70].

Ethical consideration

Ethical clearance was obtained from Research and Ethical Committee of the Department of Biochemistry, School of Medicine, College of Health Sciences, and Addis Ababa University after full review was conducted meeting no. DRERC 04/14 attended by the research committee and give approval with protocol number of M.Sc. Thesis 06/14. Structured Questionnaire (attached as Appendix) and consent form was prepared with detailed explanation of objectives, risks, and benefits to the study subject and the confidentiality of responses were given to participants. Data were collected after obtaining informed consent and agreement from the patients under study. Sample collection was performed by trained health professionals following ethical steps and procedures [71-75].

Method of data collection and analysis

Data was collected by well trained Nurses. Data collection form was designed to record sex, age, weight, height, BMI, alcohol intake status, and medical history of each patient. Portable mechanical analog scales were used to measure height and weight, respectively.

Blood collection

Five ml of venous blood were drawn from each volunteer patient using a disposable plastic syringe. The blood was poured in a test tube and then centrifuged after it clotted. Serum was kept at -80°C in the refrigerator till used. AST, ALT, ALP, TB, TC, TG, HDL and FBS were measured by (Human gesellschaft for biochemical and diagnostic mbh-Germany). TP and albumin measured by (Linear chemicals S.L, Spain) according to the manufacturer's procedures [74-75].

Body Mass Index (BMI)

Body Mass Index is a useful clinical calculation to diagnose obesity because it is correlated with total body fat and is relatively unaffected by height. It is most often used to diagnose obesity, but it is equally applicable to defining those who are underweight. There are some limitations to the BMI since it will overestimate body fat in persons who are very muscular and underestimate body fat in persons who have lost muscle mass, such as the elderly [76].

Results

A total of 70 patients diagnosed with type 2 diabetic mellitus and 35 diabetic individuals who do not receive any medication as control group were randomly selected. The average age of diabetic patients on medication was 55.10 ± 10.227 years, ranging between 34 and 76 years. The average age of diabetic patients who do not receive any medication was 52.17 ± 11.8 years, ranging from 28 to 78. For diabetic patients on medication, the mean duration of diabetes was 12.3 ± 8.0, ranging from 1 to 40 years. Body mass index (BMI) was <18 kg/m^2; in 1 patients (1.4%); 26 patients (37.1%) had a BMI between 18 and 25 kg/m^2; 30 patients (42.9%) had a BMI between 25 and 30 kg/ m^2; 13 patients (18.6%) with BMI>30 kg/m^2. For diabetic who don't receive

Parameters	Type of drugs	Mean ± SD	
	Metformin (n=2)	Insulin (n=34)	*P-value*
BMI (Kg/m^2)	29.6 ± 0.28	27.9 ± 4.9	**0.630**
FBS (mg/dl)	133 ± 7.1	219.3 ± 0.9	**0.146**
AST (U/l)	24 ± 2.83	20.38 ± 6.0	**0.408**
ALT (U/l)	15 ± 2.83	16.88 ± 8.88	**0.769**
ALP (U/l)	194.5 ± 57.3	252.6 ± 90.9	**0.382**
TP (g/dl)	8.15 ± 0.35	7.46 ± 0.65	**0.146**
AL (g/dl)	5.1 ± 0.42	4.5 ± 0.56	**0.156**
TB (mg/dl)	0.63 ± 0.30	0.57 ± 0.15	**0.650**
TC (mg/dl)	148 ± 60.81	182.1 ± 36.5	**0.219**
TG (mg/dl)	112 ± 32.53	167.3 ± 81.5	**0.350**
HDL (mg/d)	41.5 ± 6.36	47.62 ± 9.62	**0.380**
LDL (mg/dl)	84 ± 48.08	104.4 ± 34.6	**0.429**

Table 2: Biochemical characteristics of patients who were receiving metformin and insulin. The difference mean values of liver enzymes (AST, ALT, and ALP), TP, AL, lipid profile (TC, HDL and TG), BMI and FBS were not significant between type 2 diabetic patients receiving insulin and glibenclamide group. However there is an increase in the levels of AST, ALT, TP, AL and TG level in glibenclamide treated patients than insulin treated ones. On the contrary, FBS, TC, TB and HDL levels were increased in insulin treated patients but mean value of LDL in glibenclamide receiving group was lower than insulin receiving group significantly using independent-t test analysis.

Parameters	Type of drugs	Mean ± SD	
	Insulin (n=34)	Glibenclamide (n=5)	*P-value*
BMI (Kg/m^2)	27.9 ± 4.9	27.3 ± 3.1	**0.787**
FBS (mg/dl)	219.3 ± 0.9	171 ± 41.29	**0.202**
AST (U/l)	20.38 ± 6.0	30.4 ± 11.96	**0.053**
ALT (U/l)	16.88 ± 8.88	26.4 ± 25.12	**0.099**
ALP (U/l)	252.6 ± 90.9	250.4 ± 103.2	**0.960**
TP (g/dl)	7.46 ± 0.65	7.8 ± 0.70	**0.252**
AL (g/dl)	4.5 ± 0.56	4.8 ± 0.35	**0.272**
TB (mg/dl)	0.57 ± 0.15	0.56 ± 0.15	**0.849**
TC (mg/dl)	182.1 ± 36.5	156.4 ± 49.35	**0.167**
TG (mg/dl)	167.3 ± 81.5	210.8 ± 148.2	**0.325**
HDL (mg/d)	47.62 ± 9.62	38.8 ± 16.28	**0.089**
LDL (mg/dl)	104.4 ± 34.6	67 ± 16.38	**0.024**

Table 3: Biochemical characteristics of patients who were receiving insulin and glibenclamide. The difference in mean values of liver enzymes (AST, ALT and ALP), TP, AL, lipid profile (TC, HDL, LDL and TG) BMI and FBS were not statistically significant between type 2 diabetic patients receiving metformin and glibenclamide group at P value <0.05 by using independent- t test analysis. However there was increment in liver enzymes, FBS, TC, and TG levels but decrease in TP, AL, HDL and LDL in glibenclamide receiving group than metformin receiving group.

any medication controls, 1 (2.9%) had BMI <18 kg/m^2, 15 (42.9%) had a BMI between 18 and 25 kg/m^2, 15 (42.9%) had a BMI between 25 and 30 kg/m^2, and 4 (11.4%) had a BMI>30 kg/m^2. 43 (61.5%) of patients are overweight or obese. The percentages of patients taking different anti diabetic drugs were different within the study group 34 (48.6%) patients received insulin, 24 (34.3%) received metformin & glibenclamide, 5 (7.1%) received insulin & metformin, 2 (2.9%) received metformin and 5 (7.1%) received glibenclamide (Table 1) [77-79].

Discussion

In present study the mean values of liver enzymes (ALT and ALP) were higher in type 2 diabetic patients receiving insulin group than metformin group, On the contrary, mean value of AST and TB were higher in metformin receiving group than insulin receiving group [80-82]. The present results were in disagreement with the result reported by Swislocki and North found that metformin increase ALP, ALT and AST without any change in bilirubin. It may be due to differences in the background of patients in both situations (environment, genetic) and sample size [82]. Similarly other study reported by Al-Mola and Ahmed [79] showed ALP and ALT were higher ($p<0.05$) in metformin treated diabetics. At the same time AST and bilirubin did not show any changes. In contrast, Desilets et al. [82] showed elevation of bilirubin in diabetic patient treated by metformin. However, this elevation in bilirubin returned to normal level after metformin was withdrawn. The difference in mean values of liver enzymes was not significant between type 2 diabetic patients receiving insulin and glibenclamide groups. However there is an increase in the levels of liver enzymes, AL and TP in Glibenclamide treated patients than in insulin treated one. On contrary, FBS were higher in insulin receiving group than glibenclamide receiving group. This could be due to an inject-able of insulin which lead to non-compliance of patients [83-86].

In present study the TC level was significantly lowered in insulin treated patients than the group receiving combination therapy insulin plus metformin. The TG and LDL levels were also the reduced, but not to `statistically significant level. On the contrary HDL was increased in insulin alone receiver group. Similar results were reported by Mullugeta et al. [17] in which the patients on insulin therapy appeared to have slightly lower cholesterol levels but addition of metformin to the management protocol resulted in a significant improvement in the serum cholesterol. Addition of metformin not only decreased the total cholesterol levels but also had a positive effect on the distribution of cholesterol between HDL (increase) and LDL lipoproteins (decrease). The results were in agreement with the combined therapy with metformin plus bedtime insulin injections that showed beneficial effects on decreasing levels of LDL [86]. But mean values of lipid profiles (TC, LDL and TG) were higher among patients receiving combination therapy of insulin plus metformin than those receiving metformin plus glibenclamide receiving group but not statistically

Parameters	Type of drugs	Mean ± SD	
	Metformin (n=2)	Glibenclamide (n=5)	*P-value*
BMI (Kg/m^2)	29.6 ± 0.28	27.3 ± 3.1	**0.367**
FBS (mg/dl)	133 ± 7.1	171 ± 41.29	**0.275**
AST (U/l)	24 ± 2.83	30.4 ± 11.96	**0.763**
ALT (U/l)	15 ± 2.83	26.4 ± 25.12	**0.570**
ALP (U/l)	194.5 ± 57.3	250.4 ± 103.2	**0.517**
TP (g/dl)	8.15 ± 0.35	7.8 ± 0.70	**0.569**
AL (g/dl)	5.1 ± 0.42	4.8 ± 0.35	**0.376**
TB (mg/dl)	0.63 ± 0.30	0.56 ± 0.15	**0.696**
TC (mg/dl)	148 ± 60.81	156.4 ± 49.35	**0.854**
TG (mg/dl)	112 ± 32.53	210.8 ± 148.2	**0.416**
HDL (mg/d)	41.5 ± 6.36	38.8 ± 16.28	**0.836**
LDL (mg/dl)	84 ± 48.08	67 ± 16.38	**0.470**

Table 4: Biochemical characteristics of patients who were receiving metformin and glibenclamide. Both, insulin and insulin plus metformin treated patients are overweight but the latter had a lower blood glucose level than the former. Serum liver enzyme levels were lower in the insulin treated groups than those receiving combination therapies but difference was not statistically significant except AST. The TC level was significantly lowered in insulin treated patients than the group receiving combination therapy. The TG, TP, TB, and LDL cholesterol levels were also the same reduced but not to a statistically significant level.

significant. In contrast, the mean value of HDL was lower in insulin plus metformin group. Even though it was not statistically significant as shown in Tables 2 and 3, mean values of lipid profile (TC, TG, HDL and LDL) were higher in type 2 diabetic patients receiving insulin group than metformin group. This could be due to non-compliance of patients. The present work is not in agreement with the reported values of insulin therapy by Keidan et al. [86] that showed LDL and TC levels were static but HDL levels were elevated. It was found that insulin therapy do not beneficially affect lipid levels leading to a reduction in triglyceride levels. Metformin was found to be effective in reducing insulin resistance and several studies were undertaken to assess its effects on Total Cholesterol (TC), Triglycerides (TG), and HDL-Cholesterol (HDL-C) levels. The literature shows various contradictory results about the influence of metformin on lipid profile. Some studies reported reduction only in TC levels, while others reported reduction of TC and TG levels with an increase of HDL-C [80]. Santana et al. [80] have shown that treatment with metformin increased HDL level while serum total cholesterol levels were reduced and this is not in conformity with the present work. But, some similarities exist with decreased values of LDL. Mean value of TG, LDL, TC and HDL were lower in insulin alone receiver group than combination of metformin plus glibenclamide receiver group but not significant. The present work is not in agreement with the study which reported the combination of bedtime insulin plus daytime sulphonylureas. They showed similar lipid effects to those seen with insulin therapy alone.

The decrease in triglyceride, increase in HDL levels and LDL levels being constant with insulin therapy denotes dyslipidemia and shows similarities in insulin treated group with that of sulphonylurea treated groups [87]. Another result also reported by Mullugeta et al. [17] in which the patients on insulin therapy showed LDL higher than glibenclamide plus metformin therapy. The mean values of TC, TG and HDL levels were decreased in insulin treated patients than glibenclamide treated group but not statistically significant. On the contrary, value of LDL in insulin receiver group is higher than glibenclamide group which was statistically significant as shown in Table 4. Mullugeta et al. [17] reported similar results in which higher total cholesterol concentrations in the patients taking glibenclamide only. But, the present work is not in agreement with their report lowered LDL and HDL in glibenclamide received group than insulin group. The present results also in agreement with the study reported by Rivellese et al. [16] that showed insulin therapy compared with glibenclamide is associated with decreases in plasma triglyceride, but not in agreement with their report on the increased level of high density lipoprotein in insulin therapy and no change in low density lipoprotein. It could be suggested that non-compliance of the patients with reference to insulin therapy.

Even though it was not statistically significant, it was shown in the present work that mean value of BMI, in group taking metformin was higher than those groups taking other drugs but the FBS was better controlled in the group taking metformin. The present study do not support the concept that the metformin treatment avoids weight gain in diabetic patients that emphasized the advantageous and uniqueness of metformin in avoiding the weight gain associated with other pharmacological treatments of type 2 diabetics. This may be due to the number of population in this study group. Avile's-Santa et al. [83] reported a 0.5 kg weight gain in subjects taking insulin plus metformin. The insulin plus placebo subjects in their study gained an average of 3.2 kg. Although metformin has anorexic properties, the precise reason metformin treated diabetic patients do not gain weight is still unclear.

The difference in mean values of TC and TG were lower in metformin therapy than glibenclamide where as HDL and LDL was higher in metformin receiver group but not statistically significant (Tables 5-11). Similar result was reported by Al-neaimy [77] which showed an improvement in all lipid profile parameters by metformin therapy, but the improvement did not reach statistical significance, it could be due to non-compliance and the number of patients included in this study, while in the group that received the glibenclamide therapy, there were improvement in the lipid profile, and specially a significant reduction in TC, and LDL-C which disagreed with our result. The present study was in agreement with the reported result by Mughal et al. [84] that showed total cholesterol, triglycerides, low-density lipoprotein and very low density lipoprotein did not change significantly during glibenclamide therapy.

The mean values of lipid profile were lower in metformin alone therapy than metformin plus glibenclamide combination therapy but not statistically significant. Mean value of LDL and TC in combination drug of metformin plus glibenclamide receiver group was significantly higher than glibenclamide alone receiver group. The mean difference of HDL and TG were not significant; however, mean value of TG was higher in glibenclamide alone receiver group. This may be due to duration of follow up. Similarly, results reported by Garber et al. [85] showed that patients administered with glibenclamide plus metformin tablets had increase in HDL and LDL levels than patients receiving

Parameters	Type of drugs	Mean ± SD	
	Insulin (n=34)	Insulin & metformin (n=5)	*P value*
BMI (Kg/m^2)	27.9 ± 4.9	26.3 ± 4.2	**0.487**
FBS (mg/dl)	219.3 ± 0.9	160.4 ± 43.9	**0.123**
AST (U/l)	20.38 ± 6.0	27.4 ± 10.71	**0.035**
ALT (U/l)	16.88 ± 8.88	22 ± 14.98	**0.279**
ALP (U/l)	252.6 ± 90.9	269.4 ± 27.3	**0.686**
TP (g/dl)	7.46 ± 0.65	7.58 ± 0.52	**0.686**
AL (g/dl)	4.5 ± 0.56	4.6 ± 0.71	**0.745**
TB (mg/dl)	0.57 ± 0.15	0.59 ± 0.12	**0.761**
TC (mg/dl)	182.1 ± 36.5	218.2 ± 37.24	**0.047**
TG (mg/dl)	167.3 ± 81.5	197.4 ± 104.5	**0.460**
HDL (mg/d)	47.62 ± 9.62	44.2 ± 16.21	**0.502**
LDL (mg/dl)	104.4 ± 34.6	129 ± 41	**0.156**

Table 5: Biochemical characteristics of patients who were receiving insulin and insulin plus metformin. The mean values of liver enzymes (AST, ALT) and AL were significantly higher in type 2 diabetic patients receiving combination drug of glibenclamide plus metformin receiving group than insulin receiving group. In contrast mean value of BMI, among insulin receiving group is higher than glibenclamide plus metformin receiving group and statistically significant. Other than ALP and FBS, Mean value of TP, TB, TG, LDL, TC, HDL and LDL were lower in insulin receiving group but not significant. By using independent- t test analysis.

Parameters	Type of drugs	Mean ± SD	
	Insulin (n=34)	Metformin& glibenclamide (n=24)	*P value*
BMI (Kg/m^2)	27.9 ± 4.9	24.7 ± 3.5	**0.007**
FBS (mg/dl)	219.3 ± 0.9	197.3 ± 61.6	**0.269**
AST (U/l)	20.38 ± 6.0	26.92 ± 13.61	**0.016**
ALT (U/l)	16.88 ± 8.88	28.67 ± 19.89	**0.003**
ALP (U/l)	252.6 ± 90.9	244.5 ± 90.1	**0.737**
TP (g/dl)	7.46 ± 0.65	7.78 ± 0.76	**0.083**
AL (g/dl)	4.5 ± 0.56	4.9 ± 0.62	**0.016**
TB (mg/dl)	0.57 ± 0.15	0.61 ± 0.16	**0.364**
TC (mg/dl)	182.1 ± 36.5	200 ± 34.45	**0.065**
TG (mg/dl)	167.3 ± 81.5	193 ± 86.71	**0.254**
HDL (mg/d)	47.62 ± 9.62	48.63 ± 11.61	**0.719**
LDL(mg/dl)	104.4 ± 34.6	113.1 ± 43.17	**0.399**

Table 6: Biochemical characteristics of patients who were receiving insulin and metformin plus glibenclamide.Even though, mean values difference of liver and lipid profiles were not statistically significant between type 2 diabetic patients receiving metformin group and combination drug of metformin plus glibenclamide group, liver enzymes, lipid profiles and FBS were lowered in the group taking metformin than those taking metformin plus glibenclamide but TP, TB and AL were higher in metformin receiving group. With regards to BMI, the group taking combination drug had a mean value in the normal range but the metformin taking group was obese

Parameters	Type of drugs	Mean ± SD	
	Metformin (n=2)	Metformin & glibenclamid (n=24)	*P value*
BMI (Kg/m^2)	29.6 ± 0.28	24.7 ± 3.5	**0.063**
FBS (mg/dl)	133 ± 7.1	197.3 ± 61.6	**0.160**
AST (U/l)	24 ± 2.83	26.92 ± 13.61	**0.769**
ALT (U/l)	15 ± 2.83	28.67 ± 19.89	**0.350**
ALP (U/l)	194.5 ± 57.3	244.5 ± 90.1	**0.453**
TP (g/dl)	8.15 ± 0.35	7.78 ± 0.76	**0.510**
AL (g/dl)	5.1 ± 0.42	4.9 ± 0.62	**0.660**
TB (mg/dl)	0.63 ± 0.30	0.61 ± 0.16	**0.909**
TC (mg/dl)	148 ± 60.81	200 ± 34.45	**0.061**
TG (mg/dl)	112 ± 32.53	193 ± 86.71	**0.208**
HDL (mg/d)	41.5 ± 6.36	48.63 ± 11.61	**0.406**
LDL (mg/dl)	84 ± 48.08	113.1 ± 43.17	**0.371**

Table 7: Biochemical characteristics of patients who were receiving metformin and metformin plus glibenclamide. As presented in Table 9, mean values difference of liver enzymes (AST, ALT and ALP), TP, AL, lipid profiles (TC, HDL, LDL and TG), BMI and FBS were not statistically significant between type 2 diabetic patients receiving metformin group and combination drug of metformin plus insulin. But serum liver enzyme and lipid profile were higher in combination receiver than mono therapy receiver group.

Parameters	Type of drugs	Mean ± SD	
	Metformin (n=2)	Insulin & metformin (n=5)	*P value*
BMI (Kg/m^2)	29.6 ± 0.28	26.3 ± 4.2	**0.336**
FBS (mg/dl)	133 ± 7.1	160.4 ± 43.9	**0.440**
AST (U/l)	24 ± 2.83	27.4 ± 10.71	**0.692**
ALT (U/l)	15 ± 2.83	22 ± 14.98	**0.560**
ALP (U/l)	194.5 ± 57.3	269.4 ± 27.3	**0.053**
TP (g/dl)	8.15 ± 0.35	7.58 ± 0.52	**0.225**
AL (g/dl)	5.1 ± 0.42	4.6 ± 0.71	**0.411**
TB (mg/dl)	0.63 ± 0.30	0.59 ± 0.12	**0.837**
TC (mg/dl)	148 ± 60.81	218.2 ± 37.24	**0.108**
TG (mg/dl)	112 ± 32.53	197.4 ± 104.5	**0.330**
HDL (mg/d)	41.5 ± 6.36	44.2 ± 16.21	**0.836**
LDL (mg/dl)	84 ± 48.08	129 ± 41	**0.262**

Table 8: Biochemical characteristics of patients who were receiving metformin and insulin plus metformin. The Mean values of ALT, TP, AL, TB, and HDL, BMI were lower in combination drug of metformin plus glibenclamide receiving group than insulin plus metformin receiving group, while AST, ALP, TC, LDL, TG and FBS were lowered in insulin plus metformin receiving group but not significant by using independent- t test analysis.

Parameters	Type of drugs	Mean ± SD	
	Insulin & metformin (n=5)	Metformin & glibenclamid (n=24)	*P value*
BMI (Kg/m^2)	26.3 ± 4.2	24.7 ± 3.5	**0.369**
FBS (mg/dl)	160.4 ± 43.9	197.3 ± 61.6	**0.216**
AST (U/l)	27.4 ± 10.71	26.92 ± 13.61	**0.940**
ALT (U/l)	22 ± 14.98	28.67 ± 19.89	**0.487**
ALP (U/l)	269.4 ± 27.3	244.5 ± 90.1	**0.549**
TP (g/dl)	7.58 ± 0.52	7.78 ± 0.76	**0.575**
AL (g/dl)	4.6 ± 0.71	4.9 ± 0.62	**0.346**
TB (mg/dl)	0.59 ± 0.12	0.61 ± 0.16	**0.830**
TC (mg/dl)	218.2 ± 37.24	200 ± 34.45	**0.298**
TG (mg/dl)	197.4 ± 104.5	193 ± 86.71	**0.920**
HDL (mg/d)	44.2 ± 16.21	48.63 ± 11.61	**0.470**
LDL (mg/dl)	129 ± 41	113.1 ± 43.17	**0.458**

Table 9: Biochemical characteristics of patients who were receiving insulin plus metformin and metformin plus glibenclamide.The difference mean values of AST, ALP, TP, TG and BMI were lower in combination of metformin plus glibenclamide receiving group than glibenclamide receiving group but not statistically significant. But mean value of LDL and TC in combination of drug metformin plus glibenclamide receiving group were significantly higher than glibenclamide receiving group by using independent- t test analysis.

Parameters	Type of drugs	Mean ± SD	
	Metformin & glibenclamide (n=24)	Glibenclamide (n=5)	*P value*
BMI (Kg/m^2)	24.7 ± 3.5	27.3 ± 3.1	**0.130**
FBS (mg/dl)	197.3 ± 61.6	171 ± 41.29	**0.370**
AST (U/l)	26.92 ± 13.61	30.4 ± 11.96	**0.667**
ALT(U/l)	28.67 ± 19.89	26.4 ± 25.12	**0.826**
ALP(U/l)	244.5 ± 90.1	250.4 ± 103.2	**0.897**
TP (g/dl)	7.78 ± 0.76	7.8 ± 0.70	**0.922**
AL (g/dl)	4.9 ± 0.62	4.8 ± 0.35	**0.733**
TB (mg/dl)	0.61 ± 0.16	0.56 ± 0.15	**0.516**
TC (mg/dl)	200 ± 34.45	156.4 ± 49.35	**0.024**
TG (mg/dl)	193 ± 86.71	210.8 ± 148.2	**0.715**
HDL (mg/d)	48.63 ± 11.61	38.8 ± 16.28	**0.119**
LDL (mg/dl)	113.1 ± 43.17	67 ± 16.38	**0.028**

Table 10: Biochemical characteristics of patients who were receiving metformin plus glibenclamide and glibenclamide.The mean values of ALP, AL, TP and FBS were significantly higher in type 2 diabetic patients receiving anti-diabetic drug than in diabetic patients who don't receive any drug control group. In contrast, mean value of liver enzymes (AST, ALT) among study group were significantly lower than control grouped. Mean values of lipid profiles (TC, LDL) were significantly lower in type 2 diabetic patients receiving anti-diabetic drug than in the control group. Mean value of TB, TG and HDL were statistically not significant by using independent- t test analysis.

Parameters	Patients with anti-diabetic drug (n= 70)	Patients without anti-diabetic drug (n=35)	P value	95% CI
FBS	201.643 ± 71.390	132.743 ± 31.432	**<0.001**	(43.79–94.01)
AST (U/l)	23.943 ± 11.853	35 ± 17.009	**<0.001**	(-16.711)–(-5.404)
ALT (U/l)	22.186 ± 16.557	38.23 ± 18.052	**<0.001**	(-23.049)–(-9.036)
ALP (U/l)	249.19 ± 86.59	183.543 ± 65.362	**<0.001**	(32.71–98.57)
TP (g/dl)	7.623 ± 0.688	7.169 ± 1.056	**0.009**	(0.115–0.79)
AL (g/dl)	4.687 ± 0.598	4.28 ± 0.782	**0.004**	(0.135–0.68)
TB (mg/dl)	0.587 ± 0.155	0.529 ± 0.249	**0.149**	(-0.021)–(0.136)
TC (mg/dl)	188.014 ± 39.515	209.800 ± 52.246	**0.032**	(-36.2)–(-1.7)
TG (mg/dl)	179.77 ± 89.269	167.857 ± 79.286	**0.505**	(-23.44)–(47.27)
HDL (mg/dl)	46.814 ± 11.306	44.26 ± 11.016	**0.255**	(-1.95)–(7.26)
LDL (mg/dl)	105.914 ± 39.026	129.06 ± 42.846	**0.007**	(-39.7)–(-6.59)

Table 11: Mean values of the biochemical parameters in type 2 diabetic patients who are receiving anti-diabetic drugs and control group.Variables (factors) which affect the dependent variables (LFTs) were age, BMI and Diabetic Duration (DD). However, these factors had no significant strong correlation with most of the LFTs and lipid profile (liver biomarkers). But, there was significant moderate negative correlation between: ALT and DD (r= - 0.389, *p* <0.001); AST and DD (r= -0.338, *P* <0.001).

mono therapy of Glibenclamide or metformin. This reported value was not in agreement with the present data in which mean value of TG was higher in glibenclamide mono therapy.

Our results have emphasized variables (factors) which may assume to affect the dependent variables (LFTs) like age, BMI and Diabetic Duration (DD). However, these factors had no significant strong correlation with most of the LFTs and lipid profiles (liver biomarkers). But, there was significant moderate negative correlation between: ALT and DD (r=-0.389, p<0.001), AST and DD (r=-0.338, P<0.001). Similar findings were reported in the study by Belay et al. [1] in which Variables which may assume to affect the dependent variables (LFTs and lipid profiles) were like waist to hip ratio (WHR), age, BMI and Diabetic Duration (DD). However, these factors had no strong correlation with most of the LFTs and lipid profile (liver biomarkers). Contrary to this situation, Ni et al. [7] found a significant positive correlation between ALT and BMI (r=0.555, p-value <0.001). Similarly, AST significantly increased with BMI showing significant positive correlation (r=0.431, p-value <0.001).

The mean values of ALP, TP, AL and FBS were significantly higher in type 2 diabetic patients receiving anti-diabetic drug than in diabetic patients who don't receive any drug (control group). Which was disagreeing with findings reported in a study by Patra et al. [8] in which the distribution level of alkaline phosphatases were greater in patients without drug group? This could be due to duration of diabetes in study group and most of the individuals in control group were pre-diabetics.

The mean value of liver enzymes (AST, ALT) among study group was significantly lower than control group at the p value <0.05. Similar findings were reported in a study by Patra et al. [8] in which the mean values of AST and ALT among patients with drugs were lower than patients without drugs. Mean values of lipid profiles (TC, LDL) were significantly lower in type 2 diabetic patients receiving anti-diabetic drug than in the control group (P<0.05). Mean value concentrations of TG and HDL were statistically not significant at the p value<0.05. In the present study, there was no significant difference among the distribution of TB levels between the two groups of population. But the average bilirubin level in 'patients without drugs' group is less than the patients with drugs' group (0.587 compared to 0.529; p>0.05). This result disagree with the finding reported in the study by Patra et al. [8] in which the mean values of TB level in patients without drugs' group is greater than the patients with drugs' group that were not significant.

Conclusion

This work confirms that anti-diabetic drugs were found to have an effect in lowering liver enzymes and lipid profiles in type 2 diabetic patients. The effects were found to be prominent in patients who were consuming drugs in comparison with groups of individuals who were not taking any medications. However, in patients tested in the present study, it has been observed that the effects of anti-diabetic drugs did not reduce levels of total protein, albumin and alkaline phosphatase. Many different biochemical parameters tested were more or less statistically similar in different groups of individuals who were on different anti-diabetic drugs.

Limitations and Recommendations of the study

The limitations in the present study include: Small study population, lack of histopathological studies on the liver, and sequential pathological and anatomical studies on liver functions during the drug regimen could not be undertaken.

- Also, this short cross- sectional study could not follow up the patients, who were taking anti-diabetic drugs for long duration of biochemical and enzymatic progression due to limitation of money and time.

- The patient's compliance to the drugs and the regimen of treatment could not be ascertained.

The following recommendations are forwarded

- Further study is needed with large sample size to investigate effects of anti-diabetic drugs on liver functions among T2DM in our country.

- More studies are needed which include techniques such as histopathological, pathological and anatomical parameters to understand more specific effects of the drugs.

- More studies are needed with follow up on patients, in order to understand the progressive biochemical changes within the duration of drug regimens.

- Overestimation level of adherence to diabetic drugs is to be avoided and to monitor the process of strict drug compliance by the patients during treatment because they may breakup participating in the study.

- In future, interventions are urgently needed to improve adherence to anti-diabetic drugs in the study area.

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