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LIVER ENZYMES AND LIPID PROFILE IN TYPE 2 DIABETES MELLITUS-A CASE CONTROL STUDY

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ABSTRACT

Background: Type 2 diabetes mellitus is associated with dyslipidaemia, dysglycaemia and insulin resistance which among other factors and abnormalities might be responsible for the increased incidence of liver diseases.

Aim: The aim of the study was to evaluate some liver enzymes and correlate them with lipid profile parameters in patients with type 2 diabetes mellitus.

Methodology: The study was randomized cross sectional conducted amongst type 2 diabetic patients attending the endocrinology clinic of Rasheed Shekoni Specialist Hospital, Dutse Jigawa State. One hundred and eighty-nine (189) consecutive type 2 DM patients were recruited and one hundred and twenty-three (123) healthy volunteers served as controls. Biochemical analysis was performed and anthropometry indices were measured and documented. Data analysis was performed using SPSS (Version 20.0) Software with statistical significance at $p \leq 0.05$.

Results: The mean concentration of ALP, AST and TC, LDL-C and ALB was higher in the non- DM controls compared to the DM patients and a statistical significance between the groups for ALP (148.7±62.6 versus 201.9±99.0)($p \leq 0.05$)was observed.

Fasting plasma glucose, TG, ALT, HDL-C and serum protein, were elevated in the diabetic patients compared to the controls and the difference was statistically significant for TG (1.1±0.6±0.9 versus 0.8±0.4) ($p \leq 0.05$).A weak positive correlation was observed between TG and AST ($r = 0.17$, $p \leq 0.05$), TC and AST($r = 0.02$, $p \geq 0.05$), HDL-C and AST($r = 0.19$, $p \leq 0.05$), HDL-C and ALT ($r = 0.12$,$p \geq 0.05$) However, a weak negative correlation exists between TG and ALT, TG and ALP, HDL-C and ALP, LDL-C and AST, LDL-C and ALT, LDL-C and ALP ($r = -0.20$, $p \leq 0.05$), TC and ALT, TC and ALP($r = -0.20$, $p \leq 0.05$) among type 2 DM patients.

Conclusion: Serum transaminases levels even within normal limits can be associated with liver function abnormalities and metabolic liver diseases in type 2 diabetes mellitus patients.

Keywords: Liver enzymes, lipid profile, diabetes mellitus, Jigawa, Nigeria

INTRODUCTION

The liver is an important site for insulin clearance (Michael *et al*., 2000) and it also functions in the regulation of glucose homeostasis, during fasting and post prandial periods (Harris, 2005; Mathur *et al*., 2016). This role is deranged in association with liver enzymes abnormality in type 2 DM and obese individuals (Gulla *et al*., 2011) which makes the liver more vulnerable to diseases in subjects having a metabolic disorder, such as diabetes mellitus (Wild *et al*., 2004).

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Prospective explanations for elevated transaminases in insulin-resistant states include oxidative stress from reactive lipid peroxidation, peroxisomal betaoxidation, increase in proinflammatory cytokines and recruited inflammatory cells which may also contribute to hepatocellular injury (Mathur *et al*., 2016).

Insulin resistance status in type 2 diabetes mellitus patients is responsible for lipid abnormalities (Ginsberg *et al*., 2006)and ALT levels have been associated with decreased hepatic insulin sensitivity (Vozarova *et al.,* 2002), triglyceride (Harris, 2005)and visceral fat accumulation (Song *et al*., 2008). Although, the exact inherent, metabolic factors, environmental and series of events that lead to the underlying insulin resistance is not completely understood (Lewis *et al*., 2002).

Liver function tests are a useful tool, in the evaluation of hepatic dysfunction (Wang *et al.,* 2017) and a relationship has been reported to exist between diabetes and liver injury (Idris *et al*., 2011) mainly due to the fact that obesity, dysglycaemia, dyslipidaemia and elevated liver enzymes are seen more frequently in fatty liver type 2 DM patients than non-fatty liver type 2 DM patients (Atiba *et al*., 2013; Swaminathan *et al.,* 2014).

Alcohol consumption and diet habits have also been reported to have some effects on liver transaminases (Loomba *et al*., 2009; Gulla *et al*., 2011).

Liver enzyme anomalies and hepatomegallyare results of accrual of hepatocellular glycogen in poorly managed diabetes patients**.** In the hepatocytes, accumulation of intracellular glycogen is largely owed to increased synthesis which results in hyperglycemic states causing characteristic biochemical findings of normal liver synthetic function, mild to moderately elevated aminotransferases devoid of mild elevations of alkaline phosphatase (Ni *et al*., 2012).

Individuals with type 2 diabetes have increased prevalence of LFT abnormalities than individuals who do not have diabetes (Neuschwander-Tetri, 2003; Harris, 2005). The diabetes dyslipidaemia is initiated by the elevation of triglyceride rich very low-density lipoprotein from hepatic over production (Taskinen, 2003; Adiels *et al*., 2006) and for this reason, abnormalities of triglyceride storage and lipolysis in insulin-sensitive tissue such as the liver serves as a predictor of conditions characterized by insulin resistance and is detectable earlier than fasting hyperglycaemia (Lewis *et al*., 2002).

MATERIALS AND METHODS

Study Population and Design

The study population comprised one hundred and eighty-nine(189) type 2 diabetic patients attending the endocrinology clinic of Rasheed Shekoni Specialist Hospital, Dutse Jigawa StateNorth-western Nigeria recruited in a cross-sectional pattern using simple random sampling method while one hundred and twenty-three age and sex matched apparently healthy volunteers enrolled served as controls. Informed consent was obtained from all participants and relevant information was obtained using a standardized structured interviewer-based questionnaire and anthropometric indices were measured and documented.

Laboratory Procedures

Under aseptic conditions 5 ml of venous blood sample was collected, using appropriate sample bottles and transferred to the laboratory for analysis. After centrifugation, the harvested sera were stored in clean sterile containers at -20^{o}C prior to use after centrifugation. Biochemical parameters measured were: fasting plasma glucose (Trinder, 1999), total cholesterol (Allain *et al*., 1974), high density lipoprotein-cholesterol (Gerald *et al*., 1992), low density lipoprotein-cholesterol (Friedwald *et al*., 1972), triglycerides (McGowan *et al*., 1983). Serum protein,albumin, alanine transaminase, aspartate transaminase and alkaline phosphatasewere assayed using Agappe and Randox test kits on Selectra pro-S chemistry analyzer (EliTech Clinical Systems).

Statistical Analysis

Data were analyzed using SPSS (version 20.0). Quantitative data was expressed in mean±SD. Unpaired t-test was used for comparison between the groups and Pearson's correlation was used to find the correlation between the liver enzymes and lipid profile parameters. $p \leq 0.05$ was considered as statistically significant.

Ethical Approval

Ethical clearance for the study was obtained from the Ethics and Review Committee of Rasheed Shekoni Specialist Hospital, DutseJigawa State.

RESULTS

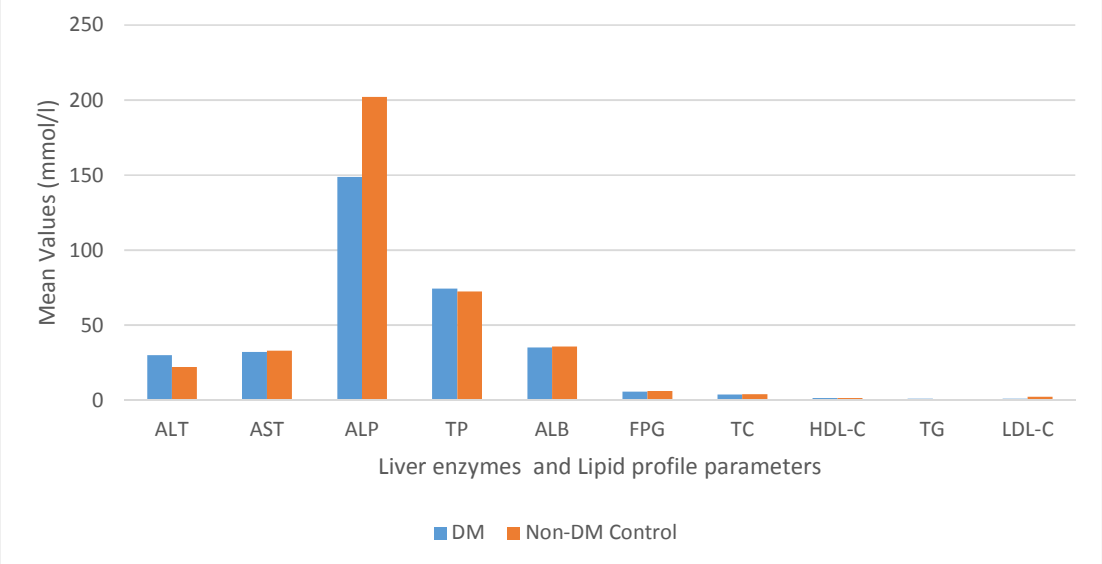
Figure 1.0 Bar chart showing the pattern of the biochemical parameters in the type 2 DM patients and non-DM controls.

Table 1.0 shows the mean activity of the transaminases (ALT, AST), alkaline phosphatase (ALP) and other biochemical parameters assayed. Alkaline phosphatase activity, total cholesterol, low density lipoprotein-cholesterol, albumin and AST concentrations were increased in the non-DM controls compared to the DM patients and a statistical significance between the groups for ALP was observed ($p \leq 0.05$). Triglycerides, ALT, HDL-C, fasting plasma glucose and serum protein, were elevated in the diabetic patients compared to the controls and the difference was statistically significant for TG ($p \leq 0.05$).

Table 2.0 shows the mean values for the waist and hip circumference using independent t-test for the male and female gender in diabetic and non-DM control subjects.

Table 3.0 shows the Pearson's correlation between liver enzymes and lipid profile parameters in the diabetic patients with a weak positive correlation observed between TG and AST ($r = 0.17$, $p \leq 0.05$), TC and AST ($r = 0.02$, $p \geq 0.05$), HDL-C and AST ($r = 0.19$, $p \leq 0.05$), HDL-C and ALT ($r = 0.12$, $p \geq 0.05$). However, a weak negative correlation exists between TG and ALT, TG and ALP, HDL-C and ALP, LDL-C and AST, LDL-C and ALT, LDL-C and ALP ($r = -0.20$, $p \leq 0.05$), TC and ALT, TC and ALP ($r = -0.20$, $p \leq 0.05$).

Table 4.0: shows the Pearson's correlation between liver enzymes and anthropometric indices in type 2 DM patients with a weak positive correlation observed between AST and SBP($r = 0.05$, $p \geq 0.05$), ALT and BMI($r = 0.10$, $p \geq 0.05$), ALP and WC($r = 0.00$, $p \geq 0.05$), ALP and HC ($r = 0.01$, $p \geq 0.05$).



Key: AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline phosphatase, FPG: fasting plasma glucose, TC: total cholesterol, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, TG: triglycerides, TP: total protein, ALB: albumin

Table 1: Comparison of biochemical parameters between type 2 DM and non-DM controls
p- value is significant at ≤ 0.05

Parameters	Diabetic	Control	P-value
ALT(IU/L)	30.0±21.9	22.2±19.4	0.38
AST (IU/L)	32.2±21.6	32.9±20.1	0.86
ALP (IU/L)	148.7±62.6	201.9±99.0	0.00*
TP(g/l)	74.4±14.5	72.5±14.4	0.45
ALB(g/l)	35.2±5.4	35.9±6.6	0.51
FPG (mmol/l)	6.2±2.2	5.8±2.2	0.23
TC (mmol/l)	3.9±0.1	4.0±7.1	0.48
HDL-C (mmol/l)	1.5±0.5	1.4±0.4	0.69
TG (mmol/l)	1.1±0.6	0.8±0.4	0.01*
LDL-C (mmol/l)	1.1±0.9	2.2±1.1	0.15

Key: AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline Phosphatase, FPG: fasting plasma glucose, TC: total cholesterol, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, TG: triglycerides, TP: total protein, ALB: albumin

Table 2: Comparison of Waist and Hip circumference using independent t-test between type 2 DM and non-DM controls

	TYPE 2 DM				CONTROL			
Variable	n	Mean ± SD	f value	p value	n	Mean ± SD	f value	P value
WC(cm) Males	81	92.28±13.17	0.67	0.41	54	83.75±12.53	5.28	0.02
WC(cm) Females	108	89.88±12.14			69	79.01±20.17		
HC(cm) Males	81	96.65±10.72	0.07	0.79	54	93.85±11.66	0.77	0.38
HC(cm) Females	108	94.03±10.26			69	91.00±17.30		

p- value is significant at ≤ 0.05
Key: WC: Waist Circumference, HC: Hip Circumference

Table 3: Correlation between lipid profile and liver enzymes in type 2 DM patients
p- value is significant at ≤ 0.05

		AST	ALT	ALP
SBP	r	0.05	-0.07	-0.05
	p	0.48	0.46	0.50
DBP	r	-0.05	-0.02	-0.02
	p	0.46	0.75	0.77
WC	r	-0.07	-0.02	0.00
	p	0.35	0.75	0.99
HC	r	-0.11	-0.04	0.01
	p	0.15	0.60	0.93
BMI	r	-0.65	0.10	-0.02
	p	0.38	0.17	0.75

Key: AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline Phosphatase, TC: total cholesterol, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, TG: triglycerides

Table 4: Correlation between liver enzymes and anthropometric indices in type 2 DM patients

		AST	ALT	ALP
TG	r	0.17	-0.01	-0.12
	p	0.02*	0.87	0.99
TC	r	0.02	-0.08	-0.20
	p	075	0.31	0.01*
HDL-C	r	0.19	0.12	-0.02
	p	0.01*	0.11	0.79
LDL-C	r	-0.13	-0.01	-0.20
	p	0.09	0.87	0.01*

p- value is significant at ≤ 0.05
Key: AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline Phosphatase, WC: Waist Circumference, HC: Hip Circumference, BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure.

DISCUSSION

The liver plays an important role in the regulation of carbohydrate homeostasis with its most common pathology been steatosis, manifested in a condition known as non-alcoholic fatty liver disease (Ni *et al*. 2012). NAFLD is the main cause of chronicliver disease associated with diabetes and obesity (Kenneth, 2009) and may be considered the hepatic component of T2DM as seen in metabolic syndrome (Angulo, 2002; Mathur *et al*. 2016).

Type 2 diabetes mellitus is a complex heterogeneous group of metabolic conditions characterized by increased levels of blood glucose due to impairment in insulin action and/or insulin secretion (Lin and Sun, 2010) and a link has been established between liver function abnormality progression and type 2 diabetic mellitus (Brun *et al*. 2000; Trombetta *et al*. 2005; Balaji *et al*. 2013; Choudhary and Vyas, 2015).

The findings of our study include increased concentrations of ALP, AST, TC, ALB and LDL-C while ALT, serum protein, HDL-C, TG levels were decreased although within normal limits amongst the controls. The outline of the results obtained is not unconnected to the likely potential increase in the prevalence of metabolic syndrome among the general population due to the possible association of the findings with components of metabolic syndrome such as dyslipidaemia and hyperglycaemia observed amongst the non-DM controls (Nam *et al*. 2007; Villegas *et al*. 2011).

In this study, triglycerides, ALT, HDL-C and serum protein, were elevated in the diabetic patients compared to the controls and the difference was statistically significant for TG ($p \leq 0.05$). Significantly elevated triglyceride levels observed among the T2DM patients in the present study is similar to the findings of Swaminathan *et al.* 2014; Wang *et al*. 2016; Kashinakunti *et al*. 2017 who reported that hypertriglyceridaemia in association with mildly elevated liver enzymes among T2DM patients serves a risk marker for NAFLD. Increased HDL-C levels observed among T2DM patients in this study is in line with the study of Wang *et al*. 2016 but contrary to the findings of Atiba*et al*. 2013; Kashinakunti et al. 2017 who reported decreased HDL-C levels among T2DM patients compared to non-DM controls owing to its cardio protective role in insulin resistant states.

The finding of increased serum albumin levels amongst controls in our study is in line with Idris *et al*. 2011 likewise the decreased serum protein levels among the controls is contradicted by the same study. Low density lipoprotein-cholesterol levels were found to be within normal limits for both T2DM patients and controls in our study although decreased levels were observed in the T2DM patients compared to the non-DM controls which may be due to the effect of medications administered to the diabetic patients.

Mild to chronic elevations of AST have been linked to dyslipidaemia, type 2 DM risk, liver dysfunction and metabolic syndrome (Idris *et al*. 2011; Atiba *et al*. 2013; Swaminathan *et al*, 2014; Wang *et al*. 2016) which is in line with the findings observed in our study of mildly AST levels within normal limits among T2DM patients and controls.

Alkaline phosphatase levels although within normal reference limits observed among the non-DM controls in our study is in concordance with the studies of Shimizu *et al*. 2013; Wang *et al*. 2016 who reported that increased ALP levels in the general population was associated with increased risk of T2DM and metabolic syndrome. Shao *et al*. 2010; Johnson *et al*. 2005 and Mathur *et al*. 2016also reported altered ALP activities among T2DM patients as an independent risk factor for increased hepatic insulin resistance or oxidative stress.

On the other hand, Cheung *et al*. 2013 reported bone-specific ALP to be more significantly related to metabolic syndrome than the tissue nonspecific alkaline phosphatase. Likewise, Kashinakunti *et al*. 2017 reported insignificant increased levels of ALP among T2DM subjects compared to controls while Idris *et al.* 2011; Atiba *et al.* 2013 reported significant elevation in ALP levels among T2DM patients compared to controls.

The findings of mildly elevated ALT levels within normal limits in both T2DM patients and non-DM controls in our study is in line with the studies Marchesini *et al*. 2001; Prati *et al*. 2002;Mofrad *etal.* 2003; Kim *et al*. 2004; Angelico *et al*. 2005 who reported that normal ALT levels does not rule out the existence of liver disease mainly because NAFLD is considered to be associated with metabolic disorders, including obesity, hypertension, hyperglycemia, and dyslipidaemia, which are components of the metabolic syndrome.

Studies by Idris *et al*. 2011; Ni *et al*. 2012 and Chen *et al*. 2016have also reported ALT levels within normal limits to be linked with metabolic syndrome. Significantly elevated ALT levels have also been implicated in type 2 DM risk and its increased prevalence as seen in studies like Idris *et al*. 2011;Atiba *et al*. 2013; Ni *et al*. 2012; Mathur *et al*. 2016; Wang *et al*. 2016;Wang *et al*. 2017.

It is also hypothesized that elevated ALT, a gluconeogenic enzyme whose gene transcription is suppressed by insulin, could indicate impairment in insulin signalling rather than purely hepatocyte injury (Atiba *et al*., 2013).

The correlation between liver enzymes and lipid profile parameters in the diabetic patients in our study showed a positive correlation between TG and AST, TC and AST, HDL-C and AST which is in line with the study of Chen *et al*. 2016; Kashinakunti *et al*. 2017 but contrary to the findings of Atiba *et al*. 2013; Swaminathan *et al*. 2014.

Negative correlations between TC and ALP, LDL-C and ALP was observed in our study which is contrary to the findings of Atiba *et al*. 2013; Kashinakunti *et al*. 2017 who reported a significant positive correlation in their respective studies which explains the dyslipidemia and liver enzyme abnormalities observed in T2DM patients.

Waist and hip circumferences for both genders were within normal limits in our study, this may be due to the fact that interpretation of waist and hip circumference despite being simple and requiring no equipment might not be accurate due to interferences from operator reliance (Tomizawa *et al*., 2014).

Limitation of the study include the inability to measure □-glutamyl transferase which is a reliable marker for hepatic fat accumulation thereby leading to hepatic insulin resistance and eventually resulting in type 2 diabetes mellitus associated liver disorders. Our major constraint was the small sample size, which might not give a good representation of the general population and the inability of the study participants to undergo liver biopsy.

CONCLUSION

Serum levels of liver transaminases even within normal limits can be related to liver function abnormalities in type 2 diabetes mellitus. The routine screening of type 2 diabetic patients for lipid profile and liver dysfunction may be important and updated normal limits for AST and ALT could help identify the ideal diagnostic cutoff standards for liver enzymes that can be generally associated with liver diseases in this group of patients.

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