High prevalence of abnormal liver enzymes in South African patients with type 2 diabetes mellitus attending a diabetes clinic

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Abstract

Objective: To determine the prevalence of liver function test abnormalities in South African black and Indian adult patients with type 2 diabetes mellitus attending a tertiary diabetes clinic.

Method: The study was a retrospective chart review of patients with type 2 diabetes attending a diabetes clinic. Recorded data included the past medical and drug history, history of alcohol abuse, anthropometry, lipid profile and liver function tests.

Results: The charts of 313 patients were reviewed. Liver function test abnormalities were found in 146 patients (46.6%). Of these,15 patients had a history of alcohol abuse, or a past medical history that might explain the abnormality, and these patients were excluded from further analysis. Elevations in serum gamma-glutamyl transferase, alkaline phosphatase and alanine transaminase were found in 25.2% (n = 79), 23.3% (n = 73) and 15.3% (n = 48), respectively. Serum total cholesterol, triglycerides and low-density lipoprotein cholesterol were higher in the group with liver function test abnormalities when compared with subjects with normal results. Mean body mass index was similar in the two groups (32.5 vs. 33.2 kg/m^2). Although morbidly obese patients (n = 42) demonstrated the highest frequency of liver enzyme derangements (54.8%), this was not statistically significant.

Conclusion: There is a high prevalence of liver function test abnormalities in this group of patients with type 2 diabetes, and this is particularly so in the morbidly obese subjects. This is comparable with the reported prevalence in the Western world. Lipid abnormalities were more frequent in the group with liver enzyme derangements.

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Objective

Chronic mild elevations of liver enzymes are frequently encountered in type 2 diabetes mellitus.[1-2] Some studies have shown that markers of liver injury can independently predict type 2 diabetes mellitus.[3] The aetiology of liver function test (LFT) derangements in type 2 diabetes mellitus may be quite varied. Non-alcoholic fatty liver disease (NAFLD) is often associated with LFT abnormalities. The reported prevalence of NAFLD in type 2 diabetes mellitus ranges from 30-75% and is almost universally associated with morbidly obese subjects with diabetes.[4-6] Therefore the frequency of such abnormalities in type 2 diabetes mellitus is not at all surprising.

A further contributor to LFT derangements in such patients is drug therapy. Statins are frequently prescribed to reach low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol targets in subjects with type 2 diabetes mellitus. Hepatotoxicity is a known complication of statin therapy, especially in those treated with high doses, and if used in combination with a fibrate. Routine LFT monitoring in this situation is common practice. Oral antidiabetic agents, such as sulphonylureas, thiazolidinediones and alpha-glucosidase inhibitors, may also cause hepatic injury with resultant LFT derangements.[7-10] Deranged liver enzymes, related to poor diabetes control, have also been described.[11] In some of these cases, hepatic glycogenosis has been shown to be the cause.[12]

Also of significance is the high frequency of transaminase abnormalities in obese patients with type 2 diabetes. This probably reflects the strong association between obesity and NAFLD; insulin resistance is the common factor. With the worldwide prevalence of obesity on the rise, the incidence of diabetes is also expected to escalate, and presumably LFT abnormalities will be more commonly encountered in diabetes clinics. Although the prevalence of

LFT abnormalities in type 2 diabetes mellitus has been well documented in Western populations, there is a paucity of data from developing countries and a lack of information from South Africa.[1,2,13,14]

The purpose of this study was to determine the prevalence of asymptomatic LFT abnormalities in South African black (African origin) and Indian patients with type 2 diabetes mellitus, attending a tertiary referral adult diabetes clinic.

Method

The study was a retrospective chart review of patients with type 2 diabetes mellitus attending the diabetes clinic at Inkosi Albert Luthuli Central Hospital (IALCH) in Durban, KwaZulu-Natal. The charts of all the patients attending the clinic between January 2004-October 2007 were reviewed.

For each subject, demographic details, clinical findings and laboratory results were recorded, including age, gender and duration of diabetes. The past medical history was reviewed to explain abnormal liver enzymes. In particular, a history of alcohol abuse, primary biliary cirrhosis, sclerosing cholangitis, haemochromatosis, congestive cardiac failure, chronic active hepatitis and viral hepatitis was sought. The use of any one of the following drugs was also noted: statins, fibrates, thiazolidinediones, metformin, sulphonyureas and insulin.

Anthropometric data included height and weight for calculation of the body mass index (BMI) [weight (kg)/height (m^2)].[15] Patients were categorised according to the following BMI groups for comparison: normal weight (BMI < 25 kg/m^2), overweight and obese (BMI $\geq$ 25 kg/m^2), obese (BMI $\geq$ 30 kg/m^2) and morbidly obese (BMI $\geq$ 40 kg/m^2).

The following laboratory tests were recorded: liver function tests [serum total protein, albumin, bilirubin, alkaline phosphatase (ALP), alanine transaminase (ALT), gamma-glutamyl transferase (GGT)]; serum lipids (total cholesterol, HDL cholesterol, LDL cholesterol, total triglyceride) and haemoglobin A_{1C} (HbA_{1C}).

Liver enzymes were defined as abnormal if the concentration exceeded the upper limit of normal (ULN) for the reference range. The prevalence of abnormal liver enzymes (ALE) was calculated in the total study group. Patients with a history of alcohol abuse or liver disease, including those with a past medical history, were excluded from further analysis. The remaining group, all of whom had unexplained ALE, were stratified according to gender, ethnicity, BMI category and drug usage.

The severity of ALE was also categorised by the degree of elevation above normal. The ALE severity was compared with the group experiencing any increase in ALE above the upper limit of normal (ULN). The three categories of ALE included:

- Greater than 1.5 times above the ULN (> 1.5 x ULN);
- Between 1-2.5 times the ULN (1-2.5 x ULN); and
- Greater than 3 times the ULN (> 3 x ULN).

The severity of ALE was then assessed and compared across the spectrum of BMI categories.

The Roche/Hitachi Modular® analyser was used to measure liver enzymes. The coefficient of variation for ALP, ALT and GGT assays was 17.5%, 8.6% and 1.8% respectively. Normal reference ranges (IU/L) were as follows: males (ALP 40-129; GGT 8-61; ALT 1-41) and females (ALP 35-104; GGT 5-36; ALT 1-31).

The study was approved by the Nelson R Mandela School of Medicine ethics committee.

Statistical analysis

Categorical variables were compared with the χ^2 test, and Student's two-tailed t-test was used to detect continuous variables. Data are presented as mean ± standard deviation (SD) or as a percentage (%). A p-value < 0.05 was considered significant.

Results

A total of 313 charts were reviewed, of which 98 (31.3%) were those of male patients and 215 (68.9%) were those of female patients. Black and Indian patients represented the largest ethnic groups (38.4% and 55.9%) of the total study group. Table I shows the characteristics of the total study group. The mean age was 57.7 ± 12.5 years, mean diabetes duration 15.7 ± 10.3 years and mean HbA_{1C} 9.2 ± 2.1%.

Liver enzyme levels above ULN were found in 146 patients (46.6%). Of these, 15 patients were excluded from further analysis due to a past medical history that could have explained the abnormality (14 with alcohol abuse, and one with chronic liver disease). Unexplained ALE was found in 131 patients (41.8%).

Of the total group (n = 313), the most frequent ALE was a raised GGT, occurring in 25.2% of patients (n = 79). Derangements in ALP and ALT were noted in 23.3% (n = 73) and 15.3% (n = 48) of patients respectively (Table I). The majority of these derangements were mild, with 22% of patients having ALE > 1.5 times the ULN, 33% with ALE between 1-2.5 times the ULN, 9% with ALE > 2.5 times the ULN, and 6% with ALE > 3 times the ULN.

Table II shows a comparison between the group with unexplained ALE (n = 131) and the group without ALE (n = 167). The prevalence of abnormal liver enzymes above

Table I: Characteristics of the total study group (n = 313)

Variable[a]	
Gender (male:female) [n (%)]	98:215 (31.3:68.9)
Ethnicity [n (%)]	
Black	120 (38.3)
Indian	175 (55.9)
White	13 (4.1)
Coloured	5 (1.6)
Age (in years)	57.7 ± 12.5
Diabetes duration (in years)	15.7 ± 10.3
BMI (kg/m^2)[b]	32.5 ± 7.1
HbA_{1c} (%)[c]	9.2 ± 2.1
Drug history [n (%)]	
Fibrate	10 (3.2)
Statin	200 (63.6)
Thiazolidinedione	1 (0.3)
Sulphonylurea	137 (43.7)
Metformin	178 (56.8)
Insulin	211 (67.4)
Serum lipid (mmol/l)	
Total cholesterol	4.9 ± 1.3
Total triglyceride	2.3 ± 2.2
HDL[d] cholesterol	1.3 ± 0.4
LDL[e] cholesterol	2.6 ± 0.9
Serum LFT[f] variables (IU/L)	
Alkaline phosphatase	93.9 ± 30.4
Gamma-glutamyl transferase	45.9 ± 59.9
Alanine transaminase	29.4 ± 30.9
Unexplained serum ALE[g] [n (%)]	131 (41.8)
Elevated serum liver enzymes [n (%)]	
Alkaline phosphatase	73 (23.3)
Gamma-glutamyl transferase	79 (25.2)
Alanine transaminase	48 (15.3)

[a] = values expressed as means (standard deviation) or n (%)
[b] = body mass index
[c] = haemoglobin A_{1c}
[d] = high-density lipoprotein
[e] = low-density lipoprotein
[f] = liver function test
[g] = abnormal liver enzymes

Table II: Comparison between type 2 diabetes patients with normal (n = 167) and unexplained abnormal liver enzymes (n = 131)

Variable[a]	Normal liver enzymes (n = 167)	Abnormal liver enzymes (n =131)
Age (in years)	58.0 ± 12.8	57.3 ± 12.3
Gender [n (%)]		
Male	59 (35.3)	26 (19.8)
Female	108 (64.7)	105 (80.2)
Ethnicity [n (%)]		
African	71 (42.5)	49 (37.4)
Indian	87 (52.1)	75 (57.3)
White	7 (4.2)	6 (4.6)
Coloured	2 (1.2)	3 (2.3)
BMI[b] category [n (%)]		
Normal weight	22 (13.2)	12 (9.2)
Overweight and obese	145 (86.8)	119 (90.8)
Obese	103 (61.7)	85 (64.9)
Morbidly obese	19 (11.4)	23 (17.6)
Diabetes duration (in years)	15.76 ± 11.0	15.35 ± 9.1
HbA_{1c}[c] (%)	9.06 ± 2.05	9.30 ± 2.06
Lipid profile (mmol/l)		
Total cholesterol	4.6 ± 1.0	5.2 ± 1.4
Total triglyceride	1.9 ± 1.1	2.8 ± 2.8[d]
HDL[e] cholesterol	1.3 ± 0.3	1.4 ± 0.4
LDL[f] cholesterol	2.4 ± 0.8	2.8 ± 1.0[d]
Liver enzymes (IU/L)		
Alkaline phosphatase	80.7 ± 16.3	109 ± 35.9
Gamma-glutamyl transferase	22.8 ± 9.5	72.7 ± 82.5
Alanine transaminase	20.2 ± 7.1	40.1 ± 44.1

[a] = values expressed as means (standard deviation) or n (%)
[b] = body mass index
[c] = haemoglobin A_{1c}
[d] = p-value < 0.05
[e] = high-density lipoprotein
[f] = low-density lipoprotein

the ULN was similar between genders and the different ethnic groups. Patients with ALE had significantly higher mean serum total triglycerides and LDL-cholesterol (p-value < 0.05). No difference was observed between the two groups with regard to age, duration of diabetes, HbA_{1C} and other lipid levels.

Of the drugs commonly utilised in the management of type 2 diabetes mellitus, only fibrate use was associated with ALE prevalence (Table III). Bezafibrate was prescribed to 3.2% (n = 10) of the total study group and all 10 patients (100%) had ALE above the upper limit of normal. However, these derangements were mild (< 2.5 times the ULN). Patients on bezafibrate had higher serum total triglycerides and total cholesterol when compared to those who were not receiving this therapy (triglycerides 8.54 ±7.1 mmol/l vs. 2.1 ±1.4 mmol/l, p-value < 0.05; total cholesterol 6.39 ±1.8 mmol/l vs. 4.8 ±1.2 mmol/l, p-value < 0.05).

There was an increase in the prevalence of ALE above the ULN with higher BMI. Rates in the normal weight, overweight and obese, obese and morbidly obese BMI groups were 42%, 47%,46% and 55% respectively. However, the difference was not statistically significant (Figure 1).

The prevalence of ALE in the different BMI categories was examined with regard to severity of derangements. There was a non-significant rise in the prevalence of ALE with increasing BMI category noted with ALE ≤ 2.5 times

Table III: Prevalence of abnormal liver enzymes (ALE) according to drugs prescribed in patients with type 2 diabetes (n = 313)

	n (%)			
	Receiving drug therapy of total with ALE[a]		Not receiving drug therapy of total with ALE[a]	
Fibrates[b]	10 (3.2)	10 (100.0)	303 (96.8)	136 (44.8)
Statin	200 (63.8)	92 (46.0)	113 (36.1)	54 (47.7)
TZD[c]	1 (0.3)	1 (100)	312 (99.7)	145 (46.5)
SU[d]	137 (43.8)	67 (48.9)	176 (56.2)	79 (44.9)
Metformin	178 (56.9)	78 (43.8)	135 (43.1)	68 (50.4)
Insulin	211 (67.4)	102 (48.3)	102 (32.6)	44 (43.1)

[a] = abnormal liver enzymes
[b] = p-value <0.05 (patients with ALE compared to total group receiving drug therapy)
[c] = thiazolidinediones
[d] = suphonylurea

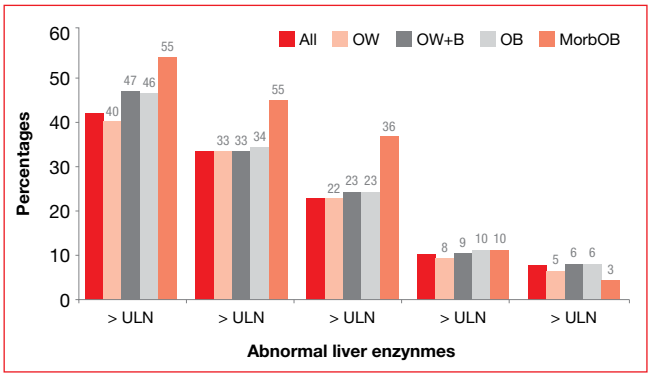

Figure 1: Body mass index and severity of abnormal liver enzymes in patients with type 2 diabetes mellitus
ULN: upper limit of normal
BMI category (kg/m^2): OW 25-30; OW+OB ≥ 25; OB ≥ 30; morbid OB ≥ 40

the ULN. (Figure 1).The prevalence of ALE between 1-2.5 times the ULN in the overweight, obese and morbidly obese groups, was 33%, 34% and 45%, respectively. This trend was not observed with more severe abnormalities (above 2.5 times the ULN). The prevalence of ALE above 2.5 times the ULN in the overweight, obese and morbidly obese groups was 8%, 10% and 10% respectively.

Discussion

This study, of predominantly South African black and Indian patients with type 2 diabetes mellitus, has shown a high prevalence (42%) of unexplained ALE, a finding similar to the reported prevalence in Western populations.

Although deranged LFTs in type 2 diabetes mellitus have been reported for over two decades, these are limited to a few reports emanating mainly from Western countries, with little or no data available from African countries, including South Africa. In an earlier study, which included 175 unselected Finnish patients with type 1 and type 2 diabetes, Salmela et al reported that the prevalence of ALE was 57%.[1] Recent studies have confirmed the high prevalence of ALE in patients with type 2 diabetes mellitus, with rates ranging from 15-30%.[13-14]

In patients with asymptomatic ALE, NAFLD was the most common diagnosis when detailed investigations were conducted, accounting for 64-90% of cases.[18-20] Although the aetiology of ALE in patients with type 2 diabetes mellitus may be varied, the most common cause is assumed to be NAFLD. In general, the prevalence of NAFLD has been shown to be high in patients with type 2 diabetes mellitus, and is almost universal in morbidly obese subjects with type 2 diabetes mellitus.[4-6]

In this study, the most frequently encountered abnormalities were those of GGT and ALP, rather than ALT abnormalities. The few available reports have highlighted ALP as the most frequent abnormality in subjects with type 2 diabetes mellitus and ALE.[1,13] However, this is not a universal finding and transaminase abnormalities have been shown to be the most common abnormality in some studies.[14] Higher transaminases would be more suggestive that NAFLD is the probable cause in such patients. However, since a recent history of alcohol intake was not available, the possibility that this may have contributed to the higher prevalence of ALP and GGT abnormalities in the present study cannot be excluded.

Lipid abnormalities were more frequently encountered in patients with ALE when compared to patients with normal liver enzymes. The two abnormalities that were associated with ALE included a higher serum total triglyceride and LDL cholesterol. Considering that hepatic steatosis is common in patients with type 2 diabetes mellitus, it is of interest that hepatic steatosis has been shown to influence both the severity and composition of dyslipidaemia.[16] Toledo et al demonstrated that hepatic steatosis, as detected by computed tomography, predicted more severe dyslipidaemia in men and women with type 2 diabetes mellitus. In the present study, pooling patients with ALE from a group of subjects with type 2 diabetes mellitus may have resulted in a higher proportion of patients with NAFLD being selected. Hence, the higher frequency of lipid abnormalities in the ALE group in the present study would be compatible with the findings of Toledo and colleagues.

Forlani et al have previously shown that elevated triglycerides and fibrate treatment were independently associated with a high ALT.[13] An unusually high frequency of ALE among patients on fibrate therapy was also observed in this small group of patients. Of importance is that all the derangements were mild, drawing attention away from drug-induced hepatotoxicity as the likely culprit, and implicating an alternate aetiology.

In terms of the severity of ALE recorded in this study, the majority of liver enzyme derangements were mild, between 1-2.5 times the ULN. More severe derangements were less frequent, and only 9% and 6% of the total study group had ALE above 2.5 times and 3 times the ULN respectively. Since most studies have not reported on the severity of ALE, the exact implications of this finding are not known. However, it may be inferred that, in this study, the cause of the ALE is less likely due to drug-induced hepatotoxicity or viral hepatitis, where one would expect more severe derangements, in particular, the transaminases.[21-22] Although the full spectrum of liver enzyme abnormalities may be observed with NAFLD, mild derangements, such as that noted in this study, are more frequently encountered with hepatic steatosis.

Previous reports have documented a higher prevalence of ALE with increasing BMI category.[1,13,17] The likely explanation for this observation is a rising prevalence of NAFLD with increasing BMI. In this study, there was a trend toward a rise in prevalence of ALE with increasing BMI category, but this was only noted for mild derangements, and not for the more severe abnormalities (ALE > 2.5 times and > 3 times the ULN). This trend may be explained by the lower probability of severe derangements in liver function being attributable to NAFLD. More severe derangements in liver function are more likely to be due to factors other than NAFLD, and therefore unrelated to BMI.

Conclusion

In conclusion, the results of this study are in accordance with previously reported high prevalence rates of ALE in patients with type 2 diabetes mellitus in other populations. Although there are currently no consensus guidelines or recommendations regarding LFT screening in patients with type 2 diabetes mellitus, these findings lend support to the practice of routine liver function monitoring in subjects with type 2 diabetes mellitus. Furthermore, the high prevalence of severe derangements also highlights the importance of performing LFTs in these otherwise asymptomatic patients, as they may harbour potentially treatable co-morbid illnesses. Many of these patients would require further laboratory, radiological and histological investigation. Therefore, if LFT screening is to be adopted, it would be incumbent on the physician to ensure that abnormal findings are appropriately investigated, or that the patient be timeously referred to a tertiary institution with the necessary facilities.

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