ORIGINAL ARTICLE

Diabetes Co-existing With Chronic Liver Disease: Clinical Features And Response To Therapy.

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Abstract:

***Background and objectives**: Diabetes mellitus (DM) and chronic liver disease (cirrhosis) may co-exist in the same individual. Diabetes may cause non-alcoholic steatohepatitis with necroinflammatory changes and granuloma formation leading to hepatic fibrosis. Cirrhosis of the liver from alcohol and hepatitis C infection, on the other hand, may give rise to insulin resistance or may result in progressive impairment of insulin secretion leading to DM. We studied the clinical features and response to therapy of diabetic patients with the two conditions to determine if there are differences in the clinical features and effects of the chronic liver disease (CLD) on the management of DM.*

***Methods**: This was a prospective study conducted at the Diabetes Clinic at the Jos University Teaching Hospital (JUTH) over a period of two years. Newly diagnosed diabetics with features of CLD (cirrhosis) were enrolled into the study after obtaining a consent. Age, sex, body mass index (BMI), family history of diabetes were recorded, as well as symptoms and signs of DM or CLD. Serum fasting blood glucose (FBS), prothrombin time ratio (PTR), and serum fasting lipids (serum lipoproteins and serum triglycerides) were measured. Urinalysis was done. The responses to therapy were classified as very rapid, rapid and gradual based on our previous unpublished observations that diabetic patients with CLD responded briskly to antidiabetes therapy.*

***Results:** 26 patients(19 men, and 7 women) were seen with both diseases agreed to participate in the study. This accounted for 8.6% of the diabetic population attending the diabetes clinic .The mean age of the patients was 54.6(9.2)years spanning a range of 34-75 years. Mean BMI was 21.6(6.0)kg/m^2. The mean serum albumin concentration was 25.5(8.5) g/l, mean FBS was 15.5 (3.4) mmol/l and PTR was 1.6 (0.43). Urinalysis showed glycosuriain all patients with only one patient showing trace of ketonuria. Clinical features of DM and CLD were few each. There was a brisk response to insulin therapy so that one needs to be cautious with insulin administration.*

***Conclusion**: Diabetes in patients with CLD has similar but fewer features compared to patients with type2 DM. CLD affects the response to therapy, particularly insulin therapy and calls for caution, as these patients may be sensitive to therapy.*

***Keywords**: Chronic liver disease, diabetes mellitus, clinical features, treatment response.*

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Introduction:

Chronic liver disease (CLD) and DM are prevalent among the patient population of the Jos University Teaching Hospital (JUTH), which is a 500 bed tertiary healthcare centre that serves about nine neighbouring states in Nigeria. These two diseases can co exist, and each disorder can influence the progression of the other Diabetes mellitus can lead to non-alcoholic steatohepatitis with necroinflammation and granuloma formation. The steatohepatitis with the granuloma formation can progress to fibrosis and hepatic disease [1,2].

Chronic liver disease, particularly, cirrhosis of the liver from alcohol or hepatitis C infection leads to glucose intolerance in about 80% of cases [1]. Approximately 20% of patients with glucose intolerance progress to frank diabetes mellitus [1,2]. The glucose intolerance results from insulin resistance in muscle tissues which begins early in the liver disease [3]. This glucose intolerance usually results from an inadequate response of the beta-cells to secrete insulin in sufficient amounts to overcome the defect in insulin action, i.e, insulin resistance [4]. The aetiology of the insulin resistance in these patients with CLD is not well understood . However, it is known that the insulin resistance is not related to the aetiology of the liver disease [1]. The insulin resistance is also not related to the severity of the liver disease nor is it related to the clinical or nutritional status of the patients [2-5].

Patients with insulin resistance can also develop DM as a result of progressive impairment in insulin secretion. The impairment in insulin secretion with the development of hepatic insulin resistance leads to fasting hyperglycaemia [4]. Oral hypoglycaemic agents are used for the control of blood glucose in patients

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without any diabetic complications, while insulin is used in those with complications (e.g., hyperglycaemic emergencies . However, some patients may require insulin therapy for maintenance.

These diseases (diabetes mellitus and chronic liver disease) are common in the Jos University Teaching Hospital, and we observed that DM in patients with CLD does not frequently present with obesity as do patients with type 2 diabetes. Having conducted a literature search to the best of our ability and finding out that literature is scarce on the topic, we undertook a study of the characteristic clinical features and response to therapy of patients with both conditions in order to know more about DM and CLD co - existing together in the same patients, and to determine if this co-existence has any effects on the management of diabetes mellitus.

Materials and methods:

This study was done based on the observation that some patients with both DM and CLD responded rapidly to insulin therapy.

This prospective study was carried out on consecutive diabetic patients attending the diabetes clinic of the Jos University Teaching Hospital from May 1997 to April 2003. Only patients who connted to the study were enrolled. Diabetic patients were evaluated and examined for features of chronic liver disease, age, body mass index (BMI), sex, family history of diabetes mellitus (DM) symptoms and signs (e.g., leg swelling, abdominal swelling, hyperpigmentation, shrunken or increased liver span, oedema, ascites, jaundice, pubic and axillary hair distribution, etc) suggestive of CLD. These patients also had prothrombin time ratio and serum albumin estimated as these are better indicators of liver dysfunction in compensated liver disease than liver enzymes. These were also more acceptable by patients than liver biopsy. The diabetes was monitored by fasting blood sugar estimation and urinalysis at presentation. The modalities of treatment were either oral hypoglycaemic agents (OHA) or insulin injection. OHA were used for patients that did not have diabetic complications while insulin was used for patients with hyperglycaemic emergencies and those with diabetic complications like diabetic foot ulcer. The responses to therapy were noted as very rapid, rapid or gradual, depending on the time it took to bring the blood glucose level to between 7.8 mmol/l and 8.5mmol/l by the glucose oxidase method of blood sugar estimation. These time frames were classified based on the observations we had earlier noted among our patients with the both conditions.

For **Oral hypoglycaemic** therapy, the following response criteria were used:

very rapid response: blood glucose reached target level within 7 days,

rapid response: blood sugar reached target level within 14 days,

gradual response: blood sugar reached target level within 21 days and more.

For **insulin** therapy, the criteria used were :

very rapid response: blood sugar reached target level within 2 hours or less,

rapid response: blood sugar reached target values within 2 and 3 hours,

gradual response: blood sugar reached target level over 3 hours but within 48 hours.

Patients were monitored closely by the giving of a weekly appointment until their fasting blood sugar levels reached 8 mmol/l, after which they were given longer appointments, as these have become stable . The following investigations were carried out on the patients: serum albumin and lipids, prothrombin time ratio (PTR) and abdominal ultrasound scan to confirm the diagnosis of liver disease. The frequency of fasting blood glucose (FBS) or random blood sugar (for those on admission with hyperglycaemic emergencies) was determined by the individual patient's response to therapy : patients with very rapid and rapid responses had their sugar tested more frequently, until their blood sugar was approximately 8 mmol/l.

The means of variables were compared using the student's t-test. The level of statistical significance was placed at $P<0.05$ of a two- tailed distribution. Relationships were determined using the simple moment correlation co-efficient.

Results:

There were 302 patients seen over the study period .Of these, 26 patients (19 males and 7 females) had both CLD and diabetes mellitus, and this accounted for 8.6% of the diabetic population of the clinic. Of the 26 patients, 21 had liver cirrhosis, 3 had liver cirrhosis with malignant transformation and 2 had chronic hepatitis. The age and sex distribution of these patients is shown on table I.

The clinical characteristics of these patients are summarized table II

Table I: Age and sex distribution of subjects.

Age group (years)	Frequency		Total
	Male	Female	
31-35	1	0	1
36-40	1	0	1
41-45	2	1	3
46-50	2	0	2
51-55	5	3	8
56-60	3	2	5
61-65	3	0	3
66-70	2	0	2
71-75	0	1	1
Total	**19**	**7**	**26**

Table II: Characteristics of patients.

Characteristic	Mean (SD)	Study range
Age (years)	54.6 (9.2)	34-75
BMI (kg/m^2)	21.6(6.0)	14.7- 41.03
Albumin (g/l)	25.5 (8.5)	11 - 48
Mean FBS (mmol/l) at presentation	15.5(3.4)	10.8 - 24.1
Mean PTR	1.6 (0.43)	1.0 - 3.07

BMI, body mass index; FBS,fasting blood sugar; PTR, Prothrombin time ratio.

Three patients (2 males, one female) had a family history of type 2 diabetes, three patients (2 males, one female) had a body mass index of over 30kg/m^2(i.e., they were obese). There were no statistically significant differences in the mean age and BMI of the female and the male patients therefore these were merged and discussed together as patients and not as separate groups. The clinical features of these patients at presentation are shown on Table III.

Other clinical features were seen in these patients but not as frequent as those cited above; these included breathlessness, blurred vision, dizziness, vomiting, dryness of the throat, palmar erythema and loss of sensations in the feet of a glove and stocking distribution. Each was observed in only one patient.

The lipid profile of most of these patients were within normal laboratory limits. The mean total serum cholesterol was 3.76 (1.37) mmol/l, with a range between 1.6 to 7.4mmol/l. Only two (2) patients had hypercholesterolaemia; one was obese and had a BMI of 34.2kg/m^2 while the other had a normal BMI of 23.1kg/m^2. The mean serum high density lipoprotein cholesterol was 2.16 (0.81) mmol/l, with a range between 0.6 to 4.3 mmol/l. The mean (SD) serum triglyceride level was 1.58 (2.1) mmol/l with a range between 0.52 to 11.5mmol/l. Three of the patients had hypertriglyceridaemia but these had BMI values that were less than 25kg/m^2. These same patients exhibited a gradual response to oral hypoglycaemic agents but a rapid response to insulin therapy.

Table III: Clinical Features of Patients.

Feature	*Frequency (%)*
Symptoms	
Polyuria	22 (84.6)
Polydipsia	18(69.2)
Weight loss	18(69.2)
Body weakness	10 (38.5)
Nocturia	5 (19.2)
Leg swelling	5 (19.2)
Diarrhoea	2 (7.7)
Polyphagia	2 (7.7)
Signs	
Decreased liver span	19 (73.1)
Hyperpigmentation	11 (42.3)
Pedal oedema	7 (26.9)
Increased liver span	7(26.9)
Wasting	6(23.1)
Obesity	3(11.5)
Jaundice	2(7.7)
Loss of axillary hair	2(7.7)
Ascites	2 (7.7)

There were four patients who presented with severe hyperglycaemia and 2 others who developed severe hyperglycaemia while on insulin therapy. The same two patients that developed the hyperglycaemia on insulin therapy, had various infections; one had diabetic foot ulcer while the other had a chest infection. No patient with hyperglycaemia was seen in coma. The response to insulin therapy was brisk in all patients, and this is shown on Table IV.

Table IV: Response of patients to treatment

Insulin (severe hyperglycaemia)	
Very rapid (within 2 hours)	3(11.5)
Rapid (within 3 hours)	3(11.5)
Gradual (within 21 days and over)	1(3.9)
Insulin (severe hyperglycaemia)	
Very rapid (within 2 hours)	3(11.5)
Rapid (within 3 hours)	3(11.5)

In the insulin- treated diabetic patients, insulin decreased the blood sugar concentration to the target level of about 8 mmol/l within 48 hours while those receiving oral hypoglycaemic agents had the sugar level controlled by 21 days.

Correlation between parameters were determined using the Pearson's moment correlation coefficient. These were between fasting blood glucose (FBS) and prothrombin time ratio (PTR), FBS and duration for which target blood glucose was achieved, PTR and duration for which target blood glucose was achieved, serum albumin and duration for which target blood glucose was achieved, and, age and duration for which target blood glucose was achieved. These relationships between the parameters were not significant.

Discussion

The purpose of this study was to determine the clinical features and response to treatment of diabetics with chronic liver disease. This was a prospective study that was based on observations made at the diabetes clinic of JUTH.

There were several findings but the main findings were that: there was a paucity of clinical features of DM in these patients. However, each patient had at least one symptom of diabetes. The majority of the patients had mild decompensation of the CLD, and therefore, few of the patients presented with leg and abdominal swelling. These patients also exhibited few signs of DM but signs of CLD were present in many patients. The treatment response to insulin therapy was more brisk than that of observed insulin therapy in diabetics without CLD. The mean BMI was within normal limits; however, 46.2% of the patients were underweight. Correlations between parameters were mainly positive but statistically insignificant.

In these patients, these symptoms of complications were also used as the diagnostic features of DM since DM can present in some individuals with complication . However, there was no patient without one or the other of the symptoms or some complications. This is different from our previous study (6) on the clinical presentation of diabetes, which showed that about 20% of type 2 diabetics do not have symptoms at presentation. This difference may be as a result of the different aetiology of DM in type 2 DM and DM-associated liver disease. Other features of diabetes such as body weakness, nocturia, diarrhoea and polyphagia were seen, but were infrequently reported as part of the presenting complaints

Leg swelling was prominent among the symptoms seen at presentation suggesting the presence of decompensated Chronic Liver Disease, and it was this symptom that suggested the presence of CLD. Abdominal swelling was not recorded in any of the patients, suggesting that these patients did not have much fluid retention , because they had mild decompensation.

Physical signs were those suggestive of CLD as diabetes in general, has few signs. Decreased liver span was seen in 4 out of 5 patients because these were cirrhotics. The decreased liver span was closely followed by hyperpigmentation of face and patchy hyperpigmentation of the palms and soles of the feet. These were the commonest of the signs of CLD seen. The other signs of CLD such as leuconychia , gynaecomastia in the male, spider naevi, palmer erythema were not observed frequently and a patient may just have one sign of CLD before confirmation by investigations. In other words, there was a paucity of signs of CLD . Ascites was seen in 2 patients who also had bilateral pitting pedal oedema. The fluid retention seen in these patients resulted mainly from hypoalbuminaemia seen in CLD.

Serum albumin was low and dependent on the degree of liver damage, i.e, those patients with markedly reduced liver span had much lower albumin. It was observed that those with low serum albumin had fluid retention. PTR level also depended on the degree of liver damage. The serum lipids were mainly within the reference range for age and sex except for those that were obese or underweight. This finding is similar to that found by Jarikre, et al in Lagos Nigeria [10].

The treatment of these patients with CLD associated DM calls for caution especially with insulin therapy as they responded briskly to therapy with insulin. These patients were not in hyperosmolar state as they were not severely dehydrated and their serum osmolality was within the normal range although in the normal level. Insulin was administered in severe hyperglycaemia (>33mmol/l). Within 2 hours of insulin therapy, the glucose level dropped to between 7.8 to 8.5mmol/l. In general, insulin therapy in patients with associated CLD calls for caution as these patients can develop hypoglycaemia rapidly on this treatment. Therapy with oral hypoglycaemic agents (OHA) affects or changes glucose level less rapidly but these agents can not be used in severe hyperglycaemic states.

OHA give gentle and smooth diabetic responses within the first 2 weeks of therapy during which time the blood glucose levels are lowered to the target level of between 7.8 to 8.5mmol/l.

The mean age of these patients was 54.6(9.2) years.This is similar to the mean age of onset of type 2 diabetes mellitus. However, other features peculiar to type 2 diabetes in these patients, like obesity, which is common in type 2 DM were less frequent. Obesity was seen in only 2 patients, and one of them had hyperlipidaemia. The hyperlipidaemia may have resulted from poor diabetic control. No patient had known family history of diabetes mellitus suggesting that this type of diabetes is different from type 2 DM.

The mean BMI of these patients was within normal limits although 46.2% were underweight (BMI < 18kg/m^2) This finding may be due to the fact that chronic liver disease gives rise to malnutrition or undernutrition [1]. This feature was more noticeable in patients without fluid retention, while those with fluid retention may weigh more because of the accumulated fluid in form of ascites and/or dependent oedema.

Conclusion

Clinical features of diabetes in these patients were similar to those of diabetes in the general population but were fewer. Patients may have one symptom or sign of either disease. DM, usually diagnosed from biochemical analysis will become the focus of therapy, making the CLD not to be recognized early. Clinicians should therefore, have a high index of suspicion of CLD when managing diabetes that responds urgently to therapy as that will help in the dosage of antidiabetic drugs. The CLD seem to influence the response of the DM to therapy especially insulin therapy in severe hyperglycaemic emergencies.

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