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CRYPTOGENIC CIRRHOSIS: METABOLIC LIVER DISEASE DUE TO INSULIN RESISTANCE

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ABSTRACT

OBJECTIVE: *Etiopathogenesis of cryptogenic cirrhosis (CC) is not yet well established. Up to 20% of non-alcoholic fatty liver disease (NAFLD) may progress to cirrhosis, mostly termed as cryptogenic. Insulin resistance and altered metabolic parameters form a major pathogenic link between NAFLD and CC. CC may thus be actually a metabolic liver disease.* ***MATERIALS AND METHODS:*** *Thirty-four patients of CC and 32 patients having cirrhosis due to chronic hepatitis B (Hep B) were assessed in a cross-sectional study in a tertiary hospital for insulin resistance, % β-cell activity, obesity indices, plasma glucose, lipid profiles, and many other parameters.* ***RESULTS:*** *CC patients had higher homeostasis model assessment (HOMA)-IR compared to Hep B group (P = 0.000016). A positive correlation between IR values and Child–Pugh score among CC patients was found ("r" = 0.87; P < 0.00001). Out of 34 CC patients, 15 (44.1%) had obesity contrary to 6 (18.8%) in the control group (P = 0.0022). Differences were observed in subcutaneous fat (P = 0.0022), intra-abdominal fat (P = 0.0055), waist circumference (P = 0.014), and percentage body fat (P = 0.047) between the two groups. Significant differences were observed in the levels of triglyceride, total cholesterol, and very low density lipoprotein (VLDL).* ***CONCLUSION:*** *Most of the CC patients showed significantly higher prevalence of HOMA-IR, obesity indices, and various parameters of "lipotoxicity" and metabolic syndrome, suggesting that CC may be the long-term consequence of a type of "metabolic liver disease." Further studies are required to evaluate the role of therapeutic interventions to enhance insulin sensitivity in such patients.*

Key words: *Cryptogenic cirrhosis, insulin resistance, metabolic syndrome*

INTRODUCTION

Till today, even with advanced diagnostic tools, we are unable to diagnose the etiology of cirrhosis in 5–31% cases,[1,2] which are designated as cryptogenic cirrhosis (CC). Several explanations, e.g. unknown viral

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infections, occult alcohol abuse, burnt-out autoimmune hepatitis, had been proposed as possible causes of CC, but only in few cases.[3]

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of disease that encompasses simple fatty liver, Non-alcoholic steatohepatitis (NASH), and NAFLD-associated cirrhosis, first described in 1980 by Ludwig and colleagues from the Mayo Clinic.[4] 90% of these patients were obese, 25% had hyperlipidemia, and 25% had adult-onset diabetes mellitus. On liver biopsy specimens, the hallmark feature was macrovesicular steatosis with lobular inflammation; fibrosis was present in 70% and cirrhosis in 15% of specimens. NAFLD has been regarded as the hepatic manifestation of metabolic syndrome (MS) which encompasses metabolic and cardiovascular risk factors (abdominal circumference, impaired glucose tolerance, hypertension, dyslipidemia) and predicts diabetes and cardiovascular disease (CVD) better than any of its individual components.[5]

The natural history of NAFLD, though largely unknown, shows evidence of histologic progression in 32–50% of the patients, with development of cirrhosis in up to 20%. Thus, it now seems likely that a substantial proportion of cases of CC represent "burnt-out" NASH.[6]

This MS and NAFLD are closely linked by a common underlying metabolic abnormality: Insulin resistance (IR) leading to multi-organ "lipotoxicity." Dysfunctional fat accounts for a large number of medical disorders including hepatic complications. IR acts as the link between the different components of MS, leading to glucose intolerance, abnormal uric acid metabolism, dyslipidemia, hemodynamic changes, endothelial dysfunction. Likewise, IR and hyperinsulinemia is also the primary pathogenic factor in NAFLD, leading to steatosis by abnormal regulation of free fatty acid (FFA) disposal, e.g. stimulating fatty acid synthesis, down-regulating mitochondrial β-oxidation of FFA, blocking the secretion of triglycerides (TGs), increasing intracellular degradation of very low density lipoprotein (VLDL) and apo B-100, blocking exocytosis of VLDL-containing vesicles, etc.[7-9] On the other hand, excess FFAs contribute to insulin resistance by down-regulating insulin receptor substrate-1 (IRS-1) signaling.[10] Thus, IR, MS, and NAFLD are all interdependent.

The occurrence of cirrhosis from NAFLD is convincingly proved by many investigators,[11,12] which were mostly termed as CC later in life. So, the role of IR and MS behind the pathogenesis of CC needs further evaluation.

MATERIALS AND METHODS

Case selection

A total of 38 patients diagnosed as CC and 37 patients with cirrhosis due to hepatitis B (Hep B) as control who attended the Liver Clinic of Medical College, Kolkata, from July 2009 to April 2010, fulfilled the criteria specified below and were enrolled for the study after obtaining their informed consent. The inclusion criteria were: (1) Patients with cirrhosis documented by clinical, biochemical, radiological, and/or histological evidence. (Clinical evidence: shrunken liver, splenomegaly, caput medusae, ascites, and other signs of liver failure; biochemical evidence: alteration in liver function test, altered albumin:globulin ratio; radiological evidence: shrunken liver with coarse

echotexture in USG, fibrosis documented in fibroscan; histological evidence: bridging fibrosis with nodule formation in biopsy specimens.) (2) Age between 15 and 70 years, of either sex. (3) Etiology of cirrhosis undetermined (cryptogenic) or due to Hep B determined by standard microbiological, biochemical, pathological, radiological, or histological tests.

The following patients were excluded: (1) Patients with cirrhosis other than cryptogenic or with Hep B (HCV, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, hemochromatosis, Wilson's disease, a_1 antitrypsin deficiency, concurrent HIV, any other cause of liver disease). (2) Patients with other known systemic diseases. (3) Patients on any drug that can alter the measured biochemical parameters or insulin secretion/sensitivity.

The study was approved by institute ethical committee.

Clinical and laboratory assessment

The following data were collected from patients through proper history taking, clinical examination, and evaluation of previous medical records: age, sex, physical complaints, previous medications, and treatment history, family history, comorbid illness, complications before or during presentation, presence of jaundice, ascites, spider angioma, encephalopathy, coagulopathy. Biochemical tests were done to measure fasting venous blood sugar, fasting venous blood TG, high density lipoprotein (HDL), low density lipoprotein (LDL), VLDL, fasting venous blood insulin, C-peptide, HbsAg(Hepatitis B surface Antigen), HBV-DNA(Hepatitis B Virus-DNA), anti-HCV antibody, HCV-RNA(Hepatitis C Virus RNA), serum ceruloplasmin, antinuclear factor, LKM-1 antibody, antimitochondrial antibody, serum ferritin, a_1 antitrypsin, complete hemogram, urea, creatinine, liver function test [bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), albumin, globulin]. Chest X-ray, ECG, and USG whole abdomen with Doppler were done routinely in all patients both for diagnosis as well as evaluating for complications and other systemic illness. Elastography of liver and liver biopsy were done in a subset of patients.

β-cell function and insulin sensitivity were assessed by the following indices:[13]

- Insulin sensitivity was assessed by homeostasis model assessment (HOMA) using the equation: HOMA-IR = fasting insulin (μU/ml) × fasting plasma glucose (mg/dl)/405.
- β-cell function was formulated by the equation: HOMA-β (%) = fasting insulin (μU/ml) × 360/fasting plasma glucose (mg/dl) – 63.

Body mass index (BMI) was measured in all in the absence of or after resolution of ascites with treatment. Waist circumference was measured to the nearest 1 cm at the level of the umbilicus (L_4–L_5) and at the end of expiration with the subject upright and his/her hands by the side.[14] Subcutaneous fat was measured as the sum of the four skinfolds (S4S): biceps, triceps, subscapular, and suprailiacal. The skin was pinched at the appropriate sites to raise a double layer of skin and the underlying adipose tissue, but not the muscle. The calipers were then applied 1 cm below and at right angles to the pinch and the reading in millimeters (mm) was taken. The generalized

equation for predicting body density by Jackson and Pollock[15] was used to determine the percentage of body fat and fat density.

A simplified method was used to measure the visceral fat. Single cut was made at the level of L4 vertebra; antero-posterior length was measured from the posterior aspect of the anterior abdominal wall and anterior line of the abdominal aorta excluding the visceras, and transverse length was measured between the inner aspects of lateral abdominal wall excluding the visceras. The average of the two lengths was measured in millimeters and taken as the index of visceral fat. A similar method has been applied in other studies, although transverse diameter and exclusion of viscera was not considered.[16]

Blood pressure was measured in non-dominant arm in sitting posture and the average of three readings was taken.

Statistical analysis

Unpaired Student's *t*-test was used for normally distributed variables and chi-square test was used for nominal categorical variables. $P < 0.05$ was taken as significant. Spearman's rank correlation coefficient was used where applicable.

RESULTS

Presence of comorbid illness led to exclusion of four patients in the CC group and five patients in the Hep B group. The data were analyzed for 34 CC patients and 32 Hep B patients.

Baseline clinical profile of cases and controls [Table 1]

Thirty-four CC patients (M/F = 20/14) and 32 Hep B patients (M/F = 19/13) were included in our study. Mean ages of the two groups were 50.74 years and 50.17 years, respectively. Child–Pugh score was matched in the two groups: 35.3% versus 34.4% (Child–Pugh A), 41.2% versus 37.5% (Child–Pugh B), and 23.5% versus 28.1% (Child–Pugh C). Among the various features of hepatocellular dysfunction and portal hypertension, jaundice was present in approximately one-third of the patients in each group, ascites in 82.4% (CC) versus 68.8% (Hep B) (although the difference was not significant), and varices were present in 88.2% (CC) versus 90.6% (Hep B). Grade III varices were most common in CC group, whereas Grade IV varices were common in controls. The complications of cirrhosis that were documented in our patients during the course of disease since diagnosis included encephalopathy in 20.6% of CC and 15.6% of Hep B patients, and hepatorenal syndrome in 11.8% of CC and 12.5% of Hep B patients. None of these differences were significant. However, a significantly higher occurrence of cardiac diastolic dysfunction was observed in CC patients (52.9% vs. 12.5%; P = 0.000496).

Baseline biochemical profile of the cases and controls [Table 2]

The biochemical parameters in the two groups, including bilirubin, ALT, AST, ALP, albumin, globulin, A: G ratio, hemoglobin, WBC count, urea, creatinine, international normalized ratio (INR), and ferritin, were all comparable without any significant difference.

Comparison of metabolic parameters between cases and controls [Table 3]

In our study group, BMI was 25.39 ± 3.76 in the CC group compared to 22.65 ± 3.74 in the Hep B group ($P = 0.0057$). Obesity

Table 1: Clinical profile of the patients included in the study

	Clyptogenic cirrhosis		*Hepatitis B cirrhosis*		*P value*
n= sample size	34		32		
Age	50.74		50.17		0.846090302
M:F	20:14		19:13		
Child A	12	35.3%	11	34.4%	.938*
Child B	14	41.2%	12	37.5%	.76*
Child C	8	23.5%	9	28.1%	.67*
Jaundice	11	32.4%	10	31.3%	.92*
Spider Angioma	9	26.5%	9	28.1%	.88*
Ascites	28	82.4%	22	68.8%	.197*
Varices	30	88.2%	29	90.6%	.753*
Grade I	4	11.8%	4	12.5%	
Grade II	8	23.5%	6	18.8%	
Grade III	10	29.4%	9	28.1%	
Grade IV	8	23.5%	10	31.3%	
Hepato Renal Syn	4	11.8%	4	12.5%	.927*
Diastolic dysfunction	18	52.9%	4	12.5%	.000496*
Encephalopathy	7	20.6%	5	15.6%	.6*
Grade I	2	5.9%	1	3.1%	
Grade II	1	2.9%	1	3.1%	
Grade III	2	5.9%	1	3.1%	
Grade IV	2	5.9%	2	6.3%	
MAP	95.89 ± 6.58		93.62 ± 5.97		0.193558702

MAP = Mean arterial pressure, *P* value < 0.05 taken as significant

Table 2: Biochemical profile of the patients included in the study

	Cryptogenic cirrhosis	*Hepatitis B cirrhosis*	*P value*
Ceruloplasmin mg/dl	30.63±12.74	23.86±6.73	0.192733933
Urea (mg/dl)	39.83±11.67	33.71±14.99	0.345715768
Creatinine (ng/ml)	1±16	1.02±35	0551473944
Hemoglobin (gm/dl)	10.6±1.34	11.3±1.69	0.102944232
Total WBC count	5500±1958.74	7612.5±2166.61	0.274072308
Bilirubin (mg/dl)	2.8±1.32	3.11±3.83	0.637245378
SGPT (U/L)	55.93±32.9	58.16±18.3	0.738442385
SGOT (U/L)	56.33±26.99	61.34±26.56	0.50088
ALP (U/L)	347.33±96.62	319.46±81.25	0.338064574
Albumin (gm/dl)	3.23±.41	3.17±.62	0.548885058
Globulin (gm/dl)	3.63±.34	3.88±.75	0.123602712
A:G Ratio	.95±.36	.85±.27	0.249070253
Ferritin (ng/ml)	104.14±36.58	88.9±22.77	0.080078072
INR	1.43±.26	1.44±.27	0.870107656

SGPT = Serum glutamic pyruvic transaminase, SGOT = Serum glutamic oxaloacetic transaminase, ALP = Alkaline phosphatase, A:G Ratio = Albumin: Globulin ratio, INR = International normalised ratio, *P* value < 0.05 taken as significant

in India is presently defined as BMI ≥ 25, and 15 (44.1%) out of 34 CC patients were obese. However, none of them had morbid obesity (BMI ≥ 40). In the control group, only 6 (18.8%) had obesity. This difference was corroborated by significant difference

Table 3: Comparison of major risk factors for NAFLD in patients with cryptogenic cirrhosis versus cirrhosis due to hepatitis B

	Cryptogenic cirrhosis	*Hepatitis B cirrhosis*	*P value*
WC (cm)	80.48±5.01	77±5.68	0.013878
BMI	25.39±3.76	22.65±3.74	0.005535
S/C Fat (Mm)	24.13±12.93	14.92±6.04	0.002212
Intra-abd. Fat (cm)	4.65±1.23	3.3±.75	0.005459
% fat	24.91±6.79	9.47±4.31	0.047
Fat density	1.1±.014	1.1 ±.015	0.656591
Fasting Insulin (μU/ml)	8.76±5.77	5.47 ± 3.21	0.00004
HOMA-IR %	2.12±1.57	.74±.47	0.000016
%B (β cell activity)	92.70%	60.19%	<.0001
FBS (mg/dl)	118.38±44.07	102.63±23.03	0.001638
Triglyceride (mg/dl)	122.54±55.54	84.13±29.94	0.001021
Total Cholesterol (mg/dl)	143.34±27.1	122.38±35.95	0.010391
HDL-C (mg/dl)	34.38±12.74	32.22±10.22	0.453577
LDL-C (mg/dl)	93±12.46	75.09±31.74	0.126377
VLDL (mg/dl)	24.41±9.26	16.63±5.59	0.00016

WC = Waist circumference, BMI = Body mass index, S/C = Subcutaneous, Intra-abd = Intra- abdominal, HOMA-IR = Homeostasis model assessment insulin resistance, FBS = Fasting blood sugar, LDL-C = Low density lipoprotein cholesterol, VLDL-C = Very low density lipoprotein, HDL-C = High density lipoprotein cholesterol, *P* value < 0.05 taken as significant

in subcutaneous fat (*P* = 0.0022), intra-abdominal fat thickness (*P* = 0.0055), and waist circumference (*P* = 0.014). Using the generalized equation of Jackson and Pollock for predicting body fat density, 15% body fat was calculated and found to be significantly high in the CC group **(**24.91 ± 6.79 vs**.** 9.62 ± 4.42; *P* = 0.047). However, fat density was similar in the two groups.

Insulin metabolism was assessed by HOMA 2 Calculator (downloaded version). HOMA-IR in CC patients was 2.12 ± 1.57 compared to 0.74 ± 0.47 in the Hep B group [Figure 1], which was also statistically significant (*P* = 0.000016). There was a higher fasting insulin (8.76 ± 5.77 vs. 5.47 ± 3.21 μIU/ml; *P* = 0.00004) and higher fasting plasma glucose (118.38 ± 44.07 vs. 102.63 ± 23.03 g/dl; *P* = 0.0016) in the CC patients. 87.82% pancreatic β-cell activity was observed in the CC patients in contrast to 60.19% in the control group (*P* < 0.0001).

Differences were observed in lipid profile, with significantly high levels of TG (122.54 ± 55.54 vs. 84.13 ± 29.94 mg/dl; *P* = 0.001), total cholesterol (143.34 ± 27.1 vs. 122.38 ± 35.95 mg/dl; *P* = 0.01), and VLDL (24.41 ± 9.26 vs. 16.63 ± 5.59 mg/dl; *P* = 0.0001) levels. LDL-c level was also higher (*P* = 0.126). HDL-c levels were equal in the two groups.

An important observation in our study was a positive correlation between HOMA-IR values and Child–Pugh score among CC patients, which was statistically highly significant (correlation coefficient "*r*" = 0.87; *P* < 0.00001) [Figure 2]. However, no such correlation was observed in the Hep B group. Mean arterial pressure was 95.89 ± 6.58 mm Hg in the CC

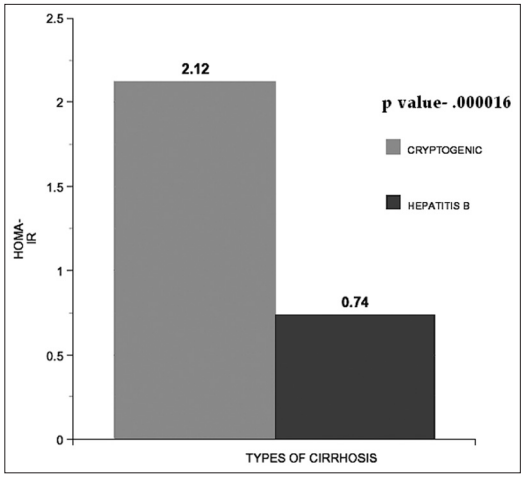

Figure 1: Bar diagram to show the relative insulin resistance between two groups of our patients

group and 93.62 ± 5.97 mm Hg in the Hep B group ($P = 0.194$).

DISCUSSION

CC, yet a gray area, accounts for a substantial proportion of liver-related morbidity. NAFLD has been proposed as one of the important etiologies for CC.

NAFLD represents the hepatic manifestation of MS and is a direct consequence of IR. The natural history of IR begins in childhood, from the interplay of genetic and environmental factors. Genetic factors include several molecular pathways in energy homeostasis, lipid metabolism, insulin receptor signaling pathway, cytokines, hormone-binding proteins including those that are serine protease inhibitors (SERPINS), and other protease regulators that are responsible for the development of IR, obesity, or lipodystrophy [e.g. uncoupling proteins, leptin-proopiomelanocortin (POMC), ghrelin-neuropeptide Y (NPY), mutations in insulin receptors, development of insulin

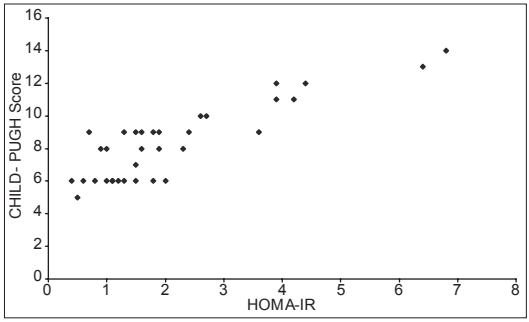

Figure 2: Scatter diagram to show the strong correlation between HOMA-IR and Child–Pugh score (correlation coefficient "*r*" = 0.87; $P < 0.00001$)

receptor autoantibodies, and defects in plasma cell membrane glycoprotein-1 and glucose transporter 4 (GLUT4), adiponectin, resistin, peroxisomal proliferator-activated receptor-γ (PPAR γ), PPARα, etc.].[17]

To understand the pathogenesis of CC in a better way, we thought of studying the prevalence of IR, impaired glucose tolerance, dyslipidemia, obesity, visceral fat, and hypertension in patients with CC and comparing with the control group of patients having cirrhosis due to Hep B. A significantly higher incidence of metabolic alterations (after excluding all possible confounding factors) in CC patients would suggest the likely possibility that cirrhosis in them had actually evolved from NAFLD as a consequence of IR. Cirrhosis cases due to other common etiologies, e.g. alcoholism, hepatitis C, were excluded from the study as metabolic alterations are known to be associated with these conditions itself, even without cirrhois.[18] Although few studies reported IR in Hep B patients, other recent studies have not been able to substantiate it.[19,20]

We also searched for any significant correlation between IR and various other evaluated parameters of MS.

In our study, we found that CC patients, when compared with an age-, sex-, and Child–Pugh score-matched control population of cirrhosis due to Hep B, had a significantly higher degree of IR. In our study, HOMA-IR method was used to measure IR, which is a validated method in both diabetics and non-diabetics in a study by Bonara *et al.* and in other studies.[21,22] HOMA-IR score of ≥ 1 implies insulin sensitivity of less than 100%, and hence implies IR. However, although a HOMA score of 1.0 is ideal, the study of Bonora *et al.*[21] found a mean HOMA-IR score of 2.06 ± 0.14 in the normal non-diabetic population. A value greater than 2.0 was taken as the cutoff to represent IR.[23] Although the Western population shows a higher normal range of HOMA-IR values (≥ 4 or higher), Asian Indian population shows lower normal levels, as indicated by various researches in this field.[24-26] HOMA-IR in CC patients was 2.12 ± 1.57 compared to 0.74 ± 0.47 in the Hep B group, which was also statistically significant (P = 0.000016). Considering HOMA-IR of 2 as the cutoff, 11 (32.35%) in the CC group versus 1 (3.33%) in the Hep B group had IR above the cutoff.

This IR was the cumulative result of a higher fasting insulin (P = 0.00004) and higher fasting plasma glucose (P = 0.0016) in CC patients compared to Hep B group. No such difference was observed in HOMA-IR between males and females (P = 0.81).

Similar trends were observed in the lipid profile, with significantly high levels of TG (P = 0.001), total cholesterol (P = 0.01), and VLDL (P = 0.0001). LDL-c level was higher than that of controls (P = 0.126). HDL-c levels were similar in the two groups.

An important observation in our study was a positive correlation (correlation coefficient "r" = 0.87) between HOMA-IR values and Child–Pugh score among CC patients, which was statistically highly significant (P < 0.00001). However, no such correlation was observed in the Hep B group. Weak positive correlation was also observed between HOMA-IR and fasting blood sugar, BMI, and waist circumference. Such a positive correlation was hardly observed before and this may bear important prognostic and therapeutic implications in CC patients.

Thus, this study corroborates similar results obtained in few other studies as well as yields certain new aspects. In 2006, Kojima *et al.* from Japan[27] conducted a study where it was convincingly shown that obesity (BMI = 25 kg/m^2), diabetes mellitus, hypertriglyceridemia, and HOMA-IR were significantly higher and the visceral fat area was larger in the CC patients than in the controls. In 2008, the prevalence of MS, obesity, and type 2 diabetes mellitus (T2DM) was found to be significantly higher in a group of Mexican Mestizo patients with CC, compared with patients having cirrhosis secondary to other causes.[28] Significant results were also obtained by Stephen *et al.* earlier in 2003.[29]

Although it is generally unclear whether a primarily genetically encoded state of IR and/or satiety disorder appears first, IR results in hyperinsulinism and precocious development of NAFLD which develop cirrhosis in the long run. IR leads to multi-organ "lipotoxicity." Insulin hypersecretion leads to increased FFA synthesis, especially in the liver and adipose tissue. A compensatory increase in glucose oxidation and increased malonyl

coenzyme A (CoA) signaling divert FFAs away from β-oxidation to compensatory increases in long-chain CoA and TG synthesis in the liver. TG in the blood is a marker of intracellular hepatic long chain CoA accumulation and increased VLDL synthesis. Normally appetite can be suppressed by both leptin and insulin; however, diets high in fat stimulate the appetite directly. The liver, in turn, becomes insensitive to compensatory leptin signaling to increase β-oxidation, which is blocked in IR because of high levels of malonyl CoA. Elevated levels of malonyl CoA block FA β-oxidation, leading to TG accumulation in muscle and liver, with impaired serine phosphorylation of IRS-1, decreased GLUT4 translocation, and thereby decreased glucose oxidation. In the islets, these events lead to activation of caspases and increased ceramide levels inducing apoptosis of β-cells. Type 2 diabetes thus results when there is insufficient insulin secretion to counter preexisting IR. Similarly, IR and hyperinsulinemia is the primary pathogenic factor in NAFLD, leading to steatosis by abnormal regulation of FFA disposal by several mechanisms.[7-9] FFAs, in turn, contribute to IR by down-regulating IRS-1 signaling.[10] Thus, IR, MS, and NAFLD are all interdependent.

The confounding effect of cirrhosis on causing hyperinsulinemia (by impaired hepatic insulin clearance) was eliminated by a normal C-peptide: insulin ratio.[30,31] C-peptide and insulin are secreted in equimolar amounts, and unlike insulin, C-peptide is not significantly cleared by the liver. Thus, C-peptide: insulin ratio allows to differentiate between hyperinsulinemia due to impaired insulin degradation (low ratio) and insulin hypersecretion (normal ratio).

Obese patients represent a heterogeneous subgroup of metabolic and phenotypical expressions of IR, whereas individuals with the same BMI can have different degrees of IR and metabolic (insulin) compensation. However, most individuals with BMIs more than 35–40 kg/m^2 have IR. In our study group, the BMI was 25.39 ± 3.76 in CC group compared to 22.65 ± 3.74 in Hep B group (P = 0.0057). Obesity in India is presently defined as BMI ≥ 25 and 15 (44.1%) out of 34 CC patients had obesity. However, none of them had morbid obesity (BMI ≥ 40). In the control group, only 6 (18.8%) had obesity. This difference was corroborated by significant difference in subcutaneous fat (P = 0.046), intra-abdominal fat thickness (P = 0.0055), and waist circumference (P = 0.014) between the two groups. Using the generalized equation of Jackson and Pollock for predicting body fat density, % body fat was calculated and found to be significantly high in the CC group (P = 0.047). However, fat density was similar in the two groups.

Out of the 34 patients in the CC group, 6 patients (17.6%) were lean and non-diabetic, but had IR (considering HOMA-IR of 2 as the cutoff). The presence of IR in these subjects strongly speaks in favor of hereditability of IR and why lean non-diabetic individuals may still develop NASH and cirrhosis. Also, it is important to note that IR individuals who can compensate by hyperinsulinemia may escape diabetes, but are still prone to other complications, such as early atherosclerosis, progression of obesity (especially central type), acanthosis nigricans, increased skin tags, hypertension, dyslipidemia, hypercoagulation, polycystic ovarian syndrome, fatty liver

infiltration, focal segmental glomerulosclerosis, and an increased cancer rate as well.[32] Thus, IR is not benign even when diabetes does not develop.

Liver biopsy done in a subset of patients revealed different stages of cirrhosis with features suggestive of NASH (macrovescicular steatosis, ballooning hepatocyte degeneration, Mallory's hyaline) in some of the CC patients.

Another incidental finding from this study was a significantly higher proportion of cardiac diastolic dysfunction among CC patients (P = 0.000496). Since MS can be associated with diastolic dysfunction, this finding seems to be relevant in our group of patients.[33,34]

With this background, presence of significant IR, excessive dysfunctional fat accumulation, and metabolic alterations (that may lead to lipotoxicity and MS) in most cases of CC would suggest that these patients had an altered metabolic state from a much earlier age, which led to MS and NAFLD, and over a long course of time have progressed to CC. This altered metabolic milieu in them persists even when cirrhosis has developed and may thus be a potential area to treat. Any possible correlation between IR and other evaluated parameters in our study may also provide important clues for categorization, prognostication, and management. IR may thus prove to be a mandatory diagnostic tool in the evaluation of cirrhosis patients and may have important therapeutic implications.

In summary, although there may be some diversities that indicate more than one cause of CC, our findings suggest that IR plays a substantial role in most patients with CC. Thus, HOMA-IR measurement should be considered as part of routine evaluation in CC patients. Moreover, a significant positive correlation between HOMA-IR and Child–Pugh score suggests that HOMA-IR can be used as a useful tool to prognosticate and monitor response to therapy. The findings of our study may bear important therapeutic implications in the management of CC.

To conclude, may we be permitted to reclassify a good proportion of CC patients under a new entity, "Metabolic Liver Disease due to Insulin Resistance?"

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