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INSULIN RESISTANCE AND HYPERESTROGENEMIA AS PARALLEL INDICATORS OF WORSENING HEPATOCELLULAR DYSFUNCTION IN LIVER CIRRHOSIS: CORRELATION WITH CTP AND MELD SCORING

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Abstract

Background: Liver cirrhosis is characterised by progressive hepatocellular dysfunction that disrupts both glucose metabolism and sex hormone homeostasis. Hyperinsulinemia due to insulin resistance and hyperestrogenemia due to impaired hepatic clearance are well-documented in cirrhosis but have not been simultaneously assessed as parallel hormonal indicators of disease progression. The objective of this study was to evaluate serum insulin and serum estradiol levels in cirrhotic patients and correlate them with validated disease severity scoring systems. ***Methods***: A case-control study was conducted at SMS Medical College and Hospitals, Jaipur. Fifty cirrhotic patients (cases) and 50 age- and sex-matched healthy controls were enrolled. Serum insulin and estradiol levels were measured using electrochemiluminescence immunoassay. Disease severity was graded using Child-Turcotte-Pugh (CTP) class and Model for End-Stage Liver Disease (MELD) score. Statistical analysis was performed using SPSS v20 with Spearman's correlation and one-way ANOVA. ***Results***: Elevated serum insulin was found in 58% of cirrhotic patients (mean 46.66±29.90 mU/L vs 12.50±16.31 mU/L in controls; p<0.001). Elevated estradiol was found in 78% of patients (mean 107.24±54.67 pg/ml vs 13.21±12.11 pg/ml; p<0.001). Both parameters showed significant progressive increases across CTP classes: insulin (14.33 → 27.58 → 68.92 mU/L; F=32.95; p=0.00) and estradiol (36.83 → 67.42 → 154.4 pg/ml; F=87.65; p=0.00) from Class A to C. Strong positive correlations were found: estradiol with CTP (r=0.742) and MELD (r=0.769); insulin with CTP (r=0.666) and MELD (r=0.622), all p<0.001. ***Conclusion***: Serum insulin and serum estradiol are significantly elevated in liver cirrhosis and their levels progressively increase with advancing hepatocellular dysfunction. Their strong and independent correlations with CTP and MELD scores establish them as reliable parallel hormonal indicators of disease severity. Combined assessment of these markers should be incorporated in the routine evaluation of cirrhotic patients, as their elevation reflects hepatic metabolic failure and contributes directly to clinical complications including hypogonadism, feminization and type 2 diabetes mellitus.

Keywords: Liver Cirrhosis, Insulin Resistance, Hyperinsulinemia, Hyperestrogenemia, Serum Estradiol, CTP Score, MELD Score, Hepatocellular Dysfunction, Hypogonadism.

INTRODUCTION

Liver cirrhosis is the final common pathway of chronic liver disease and is associated with profound disruptions of hepatic metabolic function. Beyond its well-known complications of portal hypertension, ascites and hepatic encephalopathy, cirrhosis exerts extensive and often underappreciated effects on the endocrine system. The liver is a central organ for hormone synthesis, metabolism and clearance. When cirrhotic injury substantially reduces the functional hepatocyte mass, a cascade of endocrine abnormalities ensues that may develop insidiously and remain clinically occult until advanced disease stages.

Among the most clinically consequential of these hormonal disruptions are hyperinsulinemia and hyperestrogenemia. Insulin resistance is a well-recognised metabolic complication of liver cirrhosis, occurring in an estimated 60-80% of patients with advanced disease and predisposing to the development of type 2 diabetes mellitus (DM) in 21-40% of cirrhotic patients. The liver is responsible for approximately 50% of insulin clearance under fasting conditions via first-pass hepatic

extraction. In cirrhosis, the combination of reduced hepatocyte mass, porto-systemic shunting and peripheral insulin resistance markedly diminishes this clearance, resulting in elevated peripheral insulin levels. Hyperinsulinemia further worsens insulin resistance through receptor downregulation, creating a self-perpetuating cycle of metabolic dysfunction. The development of diabetes in cirrhosis is independently associated with increased risk of complications including bacterial infections, renal impairment and increased mortality.

Hyperestrogenemia in cirrhosis is equally multifactorial. The liver plays a critical role in the conjugation and biliary excretion of oestrogens. In cirrhosis, impaired hepatic clearance of oestrogens leads to their systemic accumulation. Additionally, increased peripheral aromatisation of androgens to oestrogens occurs in the adipose tissue of cachectic cirrhotic patients, and elevated sex hormone-binding globulin (SHBG) reduces free testosterone while leaving bioavailable oestrogen relatively elevated. The clinical consequences of hyperestrogenemia include gynaecomastia, spider angiomata, palmar erythema, testicular atrophy and loss of body hair — the classic stigmata of feminisation in male cirrhotic patients. Concurrent hyperprolactinemia, found in the majority of cirrhotic patients, further inhibits hypothalamic gonadotropin-releasing hormone (GnRH) pulsatility, amplifying hypogonadism. Despite these well-established pathophysiological mechanisms, the simultaneous quantitative assessment of both serum insulin and serum estradiol as parallel hormonal indicators of hepatocellular dysfunction, and their correlation with validated disease severity scores, remains inadequately studied.

The Child-Turcotte-Pugh (CTP) score and the Model for End-Stage Liver Disease (MELD) score are the most widely validated and clinically used systems for grading the severity of liver cirrhosis and predicting short- and medium-term mortality. However, both scoring systems incorporate only hepatic biochemical and clinical parameters and do not capture the hormonal milieu of the patient. If serum insulin and estradiol levels correlate significantly and progressively with CTP and MELD scores, they could serve as supplementary hormonal markers of disease severity with additional clinical relevance beyond conventional scoring.

The present study was therefore designed to systematically evaluate and compare serum insulin and serum estradiol levels in cirrhotic patients versus healthy controls, to characterise their elevation patterns across CTP classes and MELD categories, and to determine their individual and combined correlations with disease severity. A secondary aim was to describe the associated sex hormonal derangements (testosterone, prolactin) in the context of the insulin-estradiol hormonal axis in cirrhosis.

MATERIALS AND METHODS

Study Design and Setting

This was a hospital-based cross-sectional case-control study conducted at the Departments of Biochemistry and Gastroenterology, Sawai Man Singh (SMS) Medical College and Hospitals, Jaipur, India, from December 2017 to December 2020. The study protocol received ethical approval from the Institutional Ethics Committee of Rajasthan University of Health Sciences (RUHS), Jaipur. Written informed consent was obtained from all participants prior to enrollment in accordance with the Declaration of Helsinki.

Participants

The case group comprised 50 consecutive indoor patients with confirmed diagnosis of liver cirrhosis admitted to the Gastroenterology ward. Diagnosis was established based on clinical features (ascites, jaundice, splenomegaly, oesophageal varices, hepatic encephalopathy), biochemical parameters (elevated bilirubin, low albumin, prolonged PT/INR consistent with CTP criteria), and radiological findings (shrunken liver, coarsened echotexture, dilated portal vein, ascites on ultrasonography). Liver biopsy was performed where diagnosis was clinically equivocal. Fifty age- and sex-matched healthy volunteers with no known liver, endocrine or metabolic disease constituted the control group.

Inclusion and Exclusion Criteria

Inclusion criteria for cases: confirmed cirrhosis; age 18-45 years; admission to the Gastroenterology ward. Exclusion criteria: critically ill patients requiring ICU care; hepatocellular carcinoma or other active malignancy; pre-existing diagnosis of diabetes mellitus, thyroid disorder or other endocrine disease; pregnancy; post-organ transplant status; patients on medications known to affect insulin sensitivity (steroids, metformin, insulin) or sex hormone levels (oral contraceptives, androgen deprivation therapy, exogenous oestrogens). These exclusions were applied to ensure that observed hormonal abnormalities were attributable to hepatic dysfunction rather than confounding comorbid conditions.

Assessment of Disease Severity

Disease severity was quantified using two internationally validated scoring systems. The Child-Turcotte-Pugh (CTP) score was calculated on five parameters: serum bilirubin, serum albumin, prothrombin time, presence and grade of ascites and presence and grade of hepatic encephalopathy. Scores of 5-6, 7-9 and 10-15 were classified as Class A (well-compensated),

Class B (significant functional compromise) and Class C (decompensated), respectively. The Model for End-Stage Liver Disease (MELD) score was calculated using the validated formula incorporating serum creatinine, total bilirubin and INR. MELD scores were dichotomised as <15 (lower risk) and ≥15 (higher risk) for comparative analyses.

Sample Collection and Hormonal Assays

Venous blood was collected after an overnight fast (minimum 8 hours) from the antecubital vein in appropriate vacutainer tubes. Samples were processed on the day of collection. Liver function tests (serum bilirubin, albumin, AST, ALT, GGT, ALP) were measured on the Beckman Coulter AU-680 auto-analyser using IFCC-approved enzymatic methods. Serum insulin was measured using the Siemens ADVIA Centaur XPT electrochemiluminescence immunoassay (ECLIA) platform. Reference range for fasting serum insulin: 2.6 - 24.9 mU/L. Insulin resistance was assessed by the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) where applicable. Serum estradiol (E2) was measured using the ADVIA Centaur competitive chemiluminescent immunoassay. Reference range for adult males: <39.8 pg/ml; for females: varies by menstrual phase (follicular 12.4-233 pg/ml; ovulation 40-200 pg/ml). Additional sex hormonal parameters including serum total testosterone (reference: 241-827 ng/dl in males) and serum prolactin (reference: 1.9-25 ng/ml) were also measured to characterise the broader HPG axis disruption.

Statistical Analysis

Data were expressed as Mean ± Standard Deviation (SD). Differences between case and control group means were assessed using the unpaired Student's t-test for continuous variables. Categorical variables were analysed by Chi-square test or Fischer's exact test as appropriate. Differences in serum insulin and estradiol levels across CTP classes A, B and C were assessed by one-way analysis of variance (ANOVA) with F-statistic. Post-hoc multiple comparisons were performed using the Bonferroni correction. Spearman's rank-order correlation coefficient (r) was used to evaluate the relationship between hormonal levels and CTP score, MELD score, and other continuous variables. Statistical significance was defined as $p < 0.05$. All analyses were conducted using IBM SPSS Statistics Version 20.

RESULTS

Demographic and Clinical Characteristics

Fifty cirrhotic patients and 50 healthy controls were enrolled. The mean age of the case group was 40.98 ± 5.05 years (range 28-55 years), with males constituting the majority, consistent with the male predominance of alcoholic liver disease. The most common aetiology of cirrhosis was chronic ethanol use (64%), followed by hepatitis B virus infection (HBV; 20%), hepatitis C virus infection (HCV; 8%), and autoimmune hepatitis (4%). A combined ethanol and HBV aetiology was identified in 4% of patients.

Ascites was the most prevalent presenting feature (86%), followed by oliguria (76%), abdominal pain (30%), gastrointestinal bleeding (26%) and hepatic encephalopathy (22%). Mean BMI was significantly lower in cases (21.16 ± 2.18 kg/m²) compared to controls (27.86 ± 3.07 kg/m²), reflecting the muscle wasting and malnutrition characteristic of advanced cirrhosis. Serum albumin was severely low in cases (2.03 ± 0.37 g/dl vs 3.70 ± 0.35 g/dl; p<0.001) and PT/INR was markedly elevated (2.06 ± 0.70 vs 1.12 ± 0.14; p<0.001). CTP classification: Class A 12% (n=6), Class B 40% (n=20), Class C 48% (n=24). Mean MELD score was 23.30 ± 6.40, with 88% of patients having MELD ≥15.

Table 1: Baseline Demographic and Biochemical Profile

Parameter	Cases (n=50)	Controls (n=50)
Mean Age (years)	40.98 ± 5.05	40.28 ± 2.9
BMI (kg/m²)	21.16 ± 2.18	27.86 ± 3.07
Serum Albumin (g/dl)	2.03 ± 0.37	3.70 ± 0.35
Total Bilirubin (mg/dl)	3.54 ± 2.42	1.00 ± 0.40
PT/INR	2.06 ± 0.70	1.12 ± 0.14
AST (IU/L)	110.10 ± 36.59	41.54 ± 12.49
CTP Class A/B/C	12% / 40% / 48%	N/A
MELD Score (mean)	23.30 ± 6.40	N/A

All p values <0.001 for comparison of continuous variables between cases and controls

Serum Insulin Levels and Insulin Resistance

Serum insulin levels were significantly elevated in cirrhotic patients compared to healthy controls. The mean fasting serum insulin in cases was 46.66 ± 29.90 mU/L versus 12.50 ± 16.31 mU/L in controls (p<0.001). Elevated serum insulin (above the upper reference limit of 24.9 mU/L) was found in 58% of cirrhotic patients, compared to 18% of controls (p<0.001).

Progressive and significant elevation of serum insulin was observed across CTP classes: Class A: 14.33 ± 2.16 mU/L; Class B: 27.58 ± 23.61 mU/L; Class C: 68.92 ± 18.46 mU/L (ANOVA F = 32.95; p = 0.00). Post-hoc analysis confirmed statistically significant differences between all pairwise class comparisons (A vs B: p<0.05; A vs C: p<0.001; B vs C: p<0.001). MELD stratification demonstrated that patients with MELD ≥15 had significantly higher serum insulin (51.07 ± 29.2 mU/L) than those with MELD <15 (14.33 ± 2.16 mU/L; p = 0.003). Spearman's correlation confirmed a strong positive correlation of serum insulin with CTP score (r = 0.666; p<0.001) and MELD score (r = 0.622; p<0.001).

Serum Estradiol Levels and Hyperestrogenemia

Serum estradiol levels were markedly elevated in cirrhotic patients. The mean serum estradiol in cases was 107.24 ± 54.67 pg/ml compared to 13.21 ± 12.11 pg/ml in controls (p<0.001). Elevated serum estradiol (above the upper reference range for the predominant male study group) was found in 78% of cirrhotic patients versus 12% of controls (p<0.001).

Across CTP classes, serum estradiol showed the most dramatic progressive increase of any hormonal parameter studied: Class A: 36.83 ± 22.14 pg/ml; Class B: 67.42 ± 28.62 pg/ml; Class C: 154.4 ± 23.95 pg/ml (ANOVA F = 87.65; p = 0.00). This represented a 4.2-fold increase from Class A to Class C. MELD stratification confirmed that patients with MELD ≥15 had significantly higher estradiol levels (116.84 ± 50.62 pg/ml) compared to those with MELD <15 (36.83 ± 20.21 pg/ml; p = 0.0004). Spearman's correlation of estradiol with disease severity yielded the second strongest positive correlation among all hormonal parameters: r = 0.742 with CTP score and r = 0.769 with MELD score (both p<0.001).

Table 2: Serum Insulin and Estradiol Levels Across CTP Classes and MELD Groups

Group	Serum Insulin (mU/L)	Serum Estradiol (pg/ml)	p-value (ANOVA)
CTP Class A (n=6)	14.33 ± 2.16	36.83 ± 22.14	Reference
CTP Class B (n=20)	27.58 ± 23.61	67.42 ± 28.62	<0.05
CTP Class C (n=24)	68.92 ± 18.46	154.4 ± 23.95	<0.001
MELD <15 (n=6)	14.33 ± 2.16	36.83 ± 20.21	Reference
MELD ≥15 (n=44)	51.07 ± 29.2	116.84 ± 50.62	<0.001
Controls (n=50)	12.50 ± 16.31	13.21 ± 12.11	<0.001 vs cases

F-statistic for ANOVA: Insulin F=32.95 (p=0.00); Estradiol F=87.65 (p=0.00)

Associated Sex Hormonal Derangements

Consistent with the hyperestrogenemic state, serum testosterone was low in 80% of cirrhotic patients (mean 48.79 ± 69.25 ng/dl vs 78.02 ± 21.88 ng/dl in controls; p = 0.005). Serum prolactin was elevated in 94% of patients (mean 66.58 ± 28.30 ng/ml vs 13.47 ± 17.16 ng/ml in controls; p<0.001). The triad of hyperestrogenemia, hypertestosteronemia and hyperprolactinemia was clinically manifested as gynaecomastia and loss of secondary sexual characteristics in the majority of decompensated (CTP Class C) male patients.

Table 3: Spearman Correlation of Hormonal Parameters with CTP and MELD Scores

Parameter	r (CTP)	p (CTP)	r (MELD)	p (MELD)
Serum Estradiol	+0.742	<0.001	+0.769	<0.001
Serum Insulin	+0.666	<0.001	+0.622	<0.001
Serum Prolactin	+0.198	0.167 (NS)	+0.201	0.162 (NS)
Serum Testosterone	-0.287	0.043 (sig.)	-0.263	0.065 (NS)
Vitamin D3	-0.803	<0.001	-0.816	<0.001
IGF-1	-0.382	0.006	-0.372	0.008

NS = Not Significant; sig. = Significant (p<0.05); r = Spearman's rank correlation coefficient

DISCUSSION

The present study demonstrates that hyperinsulinemia and hyperestrogenemia occur in parallel in patients with liver cirrhosis and that both hormonal disturbances escalate progressively with worsening hepatocellular dysfunction as measured by CTP class and MELD score. These findings provide a quantitative hormonal basis for understanding two of the most clinically recognisable but metabolically underinvestigated aspects of cirrhosis.

Insulin resistance in liver cirrhosis has been attributed to a complex interplay of mechanisms. The liver under normal conditions extracts approximately 50% of portal insulin during first-pass circulation. In cirrhosis, porto-systemic shunting,

which was present in virtually all decompensated patients in our series (88% had oesophageal varices of grade 2 or above), bypasses this hepatic extraction mechanism, directly elevating peripheral insulin levels. Additionally, the reduced viable hepatocyte mass impairs hepatic insulin receptor signalling, and chronic elevation of counter-regulatory hormones such as glucagon and cortisol in cirrhosis further exacerbates peripheral insulin resistance. Our finding of serum insulin of 68.92 mU/L in CTP Class C patients — nearly five times the upper reference limit — is consistent with the severe insulin resistance documented by Petrides and DeFronzo (1989) in advanced cirrhosis. Similarly, Del Gaudio et al. (2005) demonstrated that insulin resistance in cirrhosis predicts the development of clinically overt diabetes and is associated with worse survival outcomes.

Hyperestrogenemia in our cohort showed the most dramatic progressive increase across CTP classes of any hormonal parameter studied, with a 4.2-fold elevation from Class A to Class C. This finding underscores the fundamental role of the liver in oestrogen metabolism. The liver conjugates oestrogens (primarily to glucuronides and sulphates) and excretes them via bile. As cirrhosis advances, this conjugation capacity is progressively lost, allowing unconjugated oestrogens to accumulate. Simultaneously, increased activity of peripheral aromatase in the skin, adipose tissue and muscle of cachectic cirrhotic patients enhances the conversion of androgens (androstenedione and testosterone) to oestrogens (oestrone and estradiol), further compounding hyperestrogenemia. Our data are in accordance with findings by Van Thiel and Lester (1979), who first systematically characterised the feminisation syndrome in male alcoholic cirrhotic patients, and with more recent studies by Mathurin et al. (2002) who documented a direct correlation between oestrogen levels and Child-Pugh score in alcoholic cirrhosis.

The simultaneous occurrence of hyperinsulinemia and hyperestrogenemia is not coincidental — both reflect the degree of residual hepatocellular function. The strongest positive correlations with CTP and MELD score among all parameters studied were found for serum estradiol ($r = 0.742$ and 0.769 respectively), second only to the negative correlation of Vitamin D3. These two hormonal markers therefore add quantitative hormonal data to supplement the clinical and biochemical parameters already incorporated in CTP and MELD scoring. Their combined measurement could serve as an easily accessible, blood-based hormonal severity index for cirrhosis management.

The associated hormonal findings further contextualise the insulin-estradiol axis in cirrhosis. Serum testosterone was low in 80% of patients, consistent with reduced Leydig cell function (suppressed by hyperprolactinemia and hyperestrogenemia), reduced LH secretion, and direct toxic effects of ethanol on the testes in alcoholic cirrhosis. Prolactin was elevated in 94% of patients, driven by the inhibition of dopamine release in the CNS by false neurotransmitters (phenyl ethanolamine, octopamine) generated by the failing liver and by hyperestrogenemia itself (which directly stimulates lactotroph secretion). The resultant clinical triad of hyperestrogenemia, hypertestosteronemia and hyperprolactinemia represents the hormonal fingerprint of decompensated cirrhosis and contributes directly to its most visible clinical stigmata: spider naevi, palmar erythema, gynaecomastia and testicular atrophy.

From a clinical management standpoint, these findings have direct implications. First, all cirrhotic patients should have fasting serum insulin measured at the time of diagnosis and at each assessment, as the degree of insulin elevation predicts the trajectory toward overt type 2 DM and the need for insulin-sensitising or glycaemic management strategies. Second, serum estradiol measurement provides objective hormonal evidence of the feminisation syndrome and its severity, which correlates with disease stage. Third, the strong correlation of both parameters with MELD score suggests that their serial measurement may serve as a useful, non-invasive adjunct to track disease progression between formal reassessments. Monitoring estradiol and insulin levels alongside conventional biochemical markers could facilitate earlier identification of disease decompensation.

Limitations of the present study include the cross-sectional design, which precludes determination of temporal causality between hormonal elevation and clinical decompensation. The sample was predominantly male (consistent with the alcoholic aetiology in 64% of patients), which limits the generalisability of estradiol reference ranges to female patients with cirrhosis. HOMA-IR could not be calculated in all patients due to incomplete fasting glucose data in a subset. Future prospective studies should include longitudinal follow-up of insulin and estradiol levels following interventions such as transjugular intrahepatic portosystemic shunt (TIPS) insertion, or liver transplantation, to determine whether reversal of these hormonal abnormalities tracks with improvement in hepatocellular function.

CONCLUSION

Serum insulin and serum estradiol are significantly and progressively elevated in patients with liver cirrhosis, with both parameters tracking closely with the degree of hepatocellular dysfunction as quantified by CTP class and MELD score. Serum estradiol showed the strongest positive correlation with disease severity among all hormonal parameters studied, and serum insulin showed the second strongest. The combined elevation of both markers reflects the parallel failure of hepatic insulin clearance and hepatic oestrogen conjugation as cirrhosis advances. Their assessment provides a clinically

meaningful, quantitative hormonal index of disease severity that complements conventional biochemical scoring. All cirrhotic patients should undergo routine measurement of fasting serum insulin and serum estradiol as part of their endocrine evaluation. Their progressive elevation should be viewed not merely as a clinical curiosity but as a direct hormonal marker of advancing hepatocellular failure warranting active clinical monitoring and management.

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