A Study of Hormonal Abnormalities in Chronic Liver Disease

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Abstract

Background: The liver, being involved in multiple metabolic processes, not only impacts the endocrine system normally but also become an inevitable target during the course of endocrine disorders. The effects of this intricate relationship which may be disrupted in CLD can only be addressed by simultaneously studying all hormone profiles in such patients and also their relation to etiology and severity of CLD.

Methods: Serum fasting cortisol, insulin, prolactin, testosterone, estradiol, FSH, LH and thyroid hormones (TSH, free T4 & T3) were measured for any abnormality in 100 randomly selected patients of CLD in a cross sectional observational study and their relation to etiology and severity of CLD (estimated by MELD and CTP score) were studied.

Results: Cortisol, estradiol and insulin levels were significantly higher in alcoholics, the former two also increased with severity of CLD. There was overt hypothyroidism in 19% and subclinical hypothyroidism 43% patients, especially those with chronic hepatitis C and autoimmune hepatitis. Testosterone levels were lower in males. Other hormonal changes were independent of severity or etiology of CLD. Cortisol and insulin levels were significantly higher in diabetics with CLD.

Conclusion: Significant alterations of hormonal profile starting early in the development of CLD of any etiology occur which may need treatment or close follow up. ALD may have worse outcome due to disturbed metabolism of sex hormones, cortisol and insulin. The normal endocrine homeostasis of the body may become disrupted in presence of CLD which may also influence outcome.

Introduction

Among the pleotropic functions of the liver, key ones include its role in regulating energy metabolism, elimination of toxins and byproducts of metabolism, control of infection and maintenance of hormonal balance in the body. Liver is involved both in the biological actions and also in the metabolism of a number of circulating hormones which maintain endocrine homeostasis in the body. Being involved in a myriad of metabolic processes, there are numerous, constant relationships and feedback mechanisms between the liver and all endocrine organs. Hence it becomes an inevitable target during the course of multiple metabolic and endocrine disorders and conversely liver diseases are often associated with hormonal abnormalities.

It is therefore not uncommon for these disorders to coexist in the same individual. In acute liver disease, usually the hormonal abnormalities are reversible with recovery of liver function but in CLD there is failure of the metabolic capacity of the liver leading to derangement of these functions in varying degrees. Examples include the association of NAFLD and chronic hepatitis C with type 2 diabetes mellitus, autoimmune liver disease and hypothyroidism with thyroid disorders, NAFLD (metabolic syndrome) with Cushing syndrome and PCOD, advanced liver failure with hypoadrenalism, sepsis and shock and unexplained elevation of transaminase levels in disorders of thyroid and adrenal glands. In addition multiple drugs (propylthiouracil, chemotherapeutic agents, amiodarone, sex steroids, carbamazepine), toxins (alcohol) and systemic disease (amyloidosis, non-Hodgkin's lymphoma, hemochromatosis) can affect functions of both the liver and the endocrine organs. Alcohol, an important player which affects both the body's neuroendocrine functions and the liver, is often associated with thyroid dysfunction, sex hormone abnormalities, pseudo-Cushing syndrome in addition to the liver dysfunction. Such hormonal abnormalities largely go undetected in the background of CLD which greatly influences patient management and wellbeing. Clinical practice must integrally evaluate the effects of the intricate and tight relationship between the functions of liver and the endocrine system in order to better address all manifestations, complications, and prevent deterioration in function of one or the other organ system[1,2] and this can be addressed by simultaneously measuring all hormone levels in a patient of CLD. Hence the main of our study were to (a) find out the serum level of different hormones in CLD and any abnormalities therein, (b) study the relation of severity of CLD (as determined by CTP[3] and MELD[4] scores) to different hormone levels and (c) find out any association between etiology of CLD and hormone levels. The results of previous Indian studies which have addressed this problem lacks general applicability due to small patient number,[5] profiling only one or two hormones[6,7] or including only male patients.[8]

Methods

100 patients of CLD aged 18 – 70 years who attended the liver clinic or were admitted indoor in this hospital from January 2014 to December 2016 were included in this cross sectional observational study by random selection from computerized random numbers. CLD was diagnosed on the basis of clinical (presence of ascites, encephalopathy, variceal bleed, splenomegaly or history of previous such complaints), biochemical (deranged liver function or prothrombin time), serologic (positivity of HBsAg, Anti HCV or autoimmune markers), ultrasonological (small liver

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Table 1: Numerical distribution of sex, age and severity scores according to etiology

Etiology	Sex		Age in years			MELD score		CTP class		
	Male	Female	<40	40-60	>60	<15	>15	A	B	C
Alcohol (35%)	35	0	11	22	2	3	32	2	6	27
Hepatitis B (24%)	12	12	8	13	3	16	8	15	5	4
NAFLD (20%)	9	11	0	10	10	11	9	9	4	7
Hepatitis C (17%)	7	10	6	8	3	4	13	4	7	6
Auto-immune (4%)	0	4	0	4	0	3	1	3	1	0
Total (100%)	63	37	25	57	18	37	63	33	23	44

NAFLD = Non alcoholic fatty liver disease, CTP = Child Turcotte Pugh, MELD = Mayo End stage Liver Disease

Table 3: Level of different hormones according to CTP class

Hormones	CTP class			F-test
	A	B	C	
Cortisol	8.68±6.83	13.83±11.21	19.39±10.13	F = 12.16 p=0.001*
Insulin	29.65±7.51	33.38±17.89	36.53±15.34	F = 2.46 p=0.11
LH	35.59±5.95	30.32±7.36	31.51±6.24	F = 2.34 p=0.13
FSH	21.45±9.76	15.75± 6.64	11.19±7.45	F = 4.35 p=0.016*
Prolactin	51.05±14.13	52.26±13.92	53.75±15.21	F = 0.32 p=0.72
Testosterone	0.65±0.27	0.75±0.28	0.75±0.41	F = 0.92 p=0.40
Estradiol	148.36±73.72	176.06±54.83	232.63±37.65	F = 4.87 p=0.04*
TSH	12.16±17.84	19.38±23.62	9.78±14.65	F = 2.15 p=0.12
FT3	1.39±0.61	1.53±0.65	1.57±0.68	F = 0.72 p=0.48
FT4	1.49±0.27	1.51±0.30	1.52±0.28	F = 0.12 p=0.88

Hormone levels expressed as mean ± standard deviation, CTP = Child Turcotte Pugh

Table 2: Overall view of hormonal abnormalities

Hormones	Normal	Low	High	Overall levels
Cortisol N = 6.2-19.4 mcg/dl	50 7.7 ± 1.33	14 4.37 ± 0.78	36 23.04 ± 7.59*	14.58 ± 10.47
Insulin N=2.6-24.9 microIU/ml	32 20.36 ± 4.68	00	68 38.44 ± 13.89*	32.65 ± 14.39
TSH N=0.27-4.2 microIU/ml	38 3.12 ± 0.86	00	43 (5.63 ± 1.12)*1 19(46.57 ± 18.62)*2	12.26 ± 5.62
FT4 N=0.93-1.7 ng/ml	63 1.24 ± 0.4	19 0.86 ± 0.62	18 2.52 ± 0.35*	1.51 ± 0.28
FT3 N=1.5-4.1 pg/ml	63 2.87 ± 0.66	37 0.86 ± 0.16*	00	1.49 ± 0.65
FSH (Male) N=1.5-12.4 mIU/ml	16 8.52 ± 2.03	00	47 23.45 ± 8.25*	17.58 ± 8.47
FSH (Female) N=1.8-21.5 mIU/ml, 25.8-134.8 mIU/ml®	33 11.45 ± 3.65	4 [all post menopausal] 15.25 ± 3.33	00	11.09 ± 3.37
LH(Male) N=1.7-8.6 mIU/ml	00	00	63 (20.23 ± 0.35)	20.23 ± 0.35
LH (Female) N=2.4-95.6 mIU/ml 7.7-58.5 mIU/ml®	37 40.67 ± 12.6	00	00	40.67 ± 12.6
Testosterone (Male) N=2.8-8 ng/ml	02 2.42 ± 0.72	61 0.69 ± 0.31	00	0.70 ± 0.27
Testosterone(Female) N=0.06-0.82 ng/ml	20 0.49 ± 0.13	00	17 0.94 ± 0.07	0.39 ± 0.74
Estradiol (Male) N=7.63-42.6 pg/ml	02	00	61* Median 150 (45.2 - 550)	225.1 ± 151.14
Estradiol (Female) N=12.5-248.3 pg/ml, 5 - 54.7 pg/ml®	27 127.3 ± 72.5	00	10* 264.2 ± 9.47	166.31 ± 44.7
Prolactin(Male) N=4.5-21.4 ng/ml	00	00	63 42.31 ± 13.21	42.31 ± 13.21
Prolactin (Female) N=6-30 ng/ml	01	00	36 48.21 ± 14.11	48.24 ± 14.14

*Significant at $p < 0.05$, [1]Subclinical hypothyroidism, [2]Overt hypothyroidism, N = normal serum hormone levels. Whole numbers indicate number of patients in each category. Hormone levels expressed as mean ± standard deviation, ® Indicate normal hormone level in post menopausal women

size and coarse echotexture, irregular surface, splenomegaly and features of portal hypertension) and endoscopic (esophageal or gastric varices, portal hypertensive gastropathy) criteria with/without histology. Alcohol etiology was confirmed from history of alcohol intake elicited from patient or family members/friends and CAGE questionnaire. Viral hepatitis was confirmed by presence of HBV DNA or HCV RNA in serum. The patients who were excluded were those : (1) who had undergone liver transplant, (2) who had undergone surgical interventions for CLD (TIPSS, shunt surgeries), (3) with congenital or juvenile endocrine diseases, (4) who had undergone endocrine surgeries, (5) already on any hormone therapy, antiparkinson drugs, carbamazepine, amiodarone or had previous/current interferon therapy (6) suffering from other major systemic disease like cancer, HIV, amyloidosis, active drug abuse, major neuropsychiatric illness and advanced cardiopulmonary disease.

Morning fasting blood samples were collected for complete hemogram, fasting blood sugar, lipid profile, liver and renal function tests, prothrombin time, serum iron, total iron binding capacity and ferritin, serological tests like anti HCV, HBsAg, HIV, antinuclear antibody, anti smooth muscle antibody, liver kidney microsomal antibody, antimitochondrial antibody, thyroperoxidase antibody (in those with high TSH) and serum ceruloplasmin. Body mass index and post prandial blood sugar were also measured. CTP and MELD scores were calculated from the required parameters. A MELD score of 15 was taken as dividing line between mild and severe disease.

Hormones studied : Serum cortisol, insulin, prolactin, testosterone, estradiol, FSH, LH and thyroid hormones (TSH, FT4 & FT3) were estimated from the morning fasting blood sample in the Pathology Department of this hospital using Electrochemiluminescence immune assay by machine ECYSIS1010 / Coba E 410 and their normal values used were as per lab standards.

Low FT4 with raised TSH was defined as primary hypothyroidism, normal FT4 with raised TSH as subclinical hypothyroidism and low FT3 or FT4 with normal TSH as sick euthyroid syndrome. Gonadal failure was defined as primary when LH and FSH were higher or secondary when they were lower than upper limits of normal associated with lower testosterone levels in males or amenorrhea in females.

Statistics

The minimum sample size needed for this cross sectional observational study in a population of CLD patients (based on an estimated 50% prevalence of hormonal abnormalities in CLD population[5] with 10% precision) was ascertained to be 100. Continuous variables were expressed as mean ± standard deviation and categorical variables as proportions (%). Students

Table 4: Level of different hormones according to MELD score

Level of hormones	MELD Score		t-test
	≤15 (n=37)	>15 (n=63)	
Cortisol	9.40±7.64	17.62±10.76	t=4.07;p=0.001*
Insulin	29.25±12.97	34.65±15.02	t=1.82;p=0.07
LH	33.47±5.72	31.58± 6.38	t=1.75;p=0.08
FSH	21.48 ± 8.36	13.33± 6.85	t=3.72;p=0.001*
Prolactin	51.37±14.32	53.19±14.64	t=0.60;p=0.54
Testosterone	0.66±0.27	0.76±0.37	t=1.43;p=0.15
Estradiol	137.25±133.66	187.42±170.34	t=1.34;p=0.09
TSH	11.45±16.97	13.56±19.11	t=0.55;p=0.583
FT3	1.44±0.61	1.54±0.68	t=0.73;p=0.46
FT4	1.49±0.28	1.53±0.29	t=0.67;p=0.50

Hormone levels expressed as mean ± standard deviation, MELD = Mayo End stage Liver Disease

t-test and χ^2 test were used to test the significant difference between means and proportions respectively. Intergroup comparison of hormonal levels was done using one way analysis of variance followed by *post hoc* Tukey's Test taking Critical Difference at 5% level of significance to compare the mean values. P <0.05 was considered significant. All statistical analyses were performed with help of Epi Info (TM) 3.5.3.

Ethical clearance for the study was obtained from the institutional ethics committee and informed consent was obtained from all participating patients and their families regarding obtaining information. All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results

The results are summarised in Tables 1-6. As per BMI (Asia-Pacific criteria), 22% patients were underweight (BMI<18.5), 74% had normal weight (BMI 18.5–22.9), 4% were overweight (BMI 23–24.9) but none were obese (BMI ≥25).

Average cortisol level was within normal range but increased significantly with severity (by both CTP class and MELD score) of CLD. Highest levels were found in ALD compared to other etiologies (34/36 = 94.4%) and this was present in all CTP classes. It was also higher in diabetics (n=62, mean 18.68 ± 10.47 mcg/dl) compared to non diabetics (n=38, mean 7.88 ± 6.20 mcg/dl, p = 0.0001). Some patients (n=14), mostly in the viral hepatitis group (13/14 = 92.8%) and in CTP class C, had low cortisol level.

Overall fasting insulin levels were higher than normal independent of the severity or etiology of CLD. Significantly higher levels were observed in 34% of alcohol, 20% of viral hepatitis and 14% of NAFLD related CLD. It was significantly higher in the diabetics (35.72 + 15.35 mIU/ml) though above normal in the non diabetics also (27.63 + 11.39 mIU/ml, p = 0.0006). Numerically highest insulin levels were observed in the ALD group.

There were interesting results of the thyroid function tests. Overall TSH levels were slightly above normal range due to the 19% patients of overt hypothyroidism (16% in viral hepatitis, 3% in autoimmune hepatitis group) and 43% of subclinical hypothyroidism (16% in alcohol, 18% in viral hepatitis and 9% in NAFLD related CLD group). Sick euthyroid syndrome was present in 18% patients (11% in alcohol and 7% in NAFLD related CLD). TSH levels were significantly higher in hepatitis C related and autoimmune CLD compared to other etiologies paralleled by the overall low FT3 levels in hepatitis C patients. Normal FT4 level were observed overall as also among the various etiologies and severity groups of CLD except the 18% sick euthyroid patients. Low FT3 was observed in 37% compared to low FT4 in 19% patients (p<0.05). Overall TSH, FT4 and FT3 levels were independent of severity of CLD (by both the CTP class and MELD score) but a subgroup analysis among different etiologies by CTP class revealed significantly lower levels in chronic hepatitis C patients in all CTP classes. 2 (2.7%) patients, both with autoimmune CLD, had anti thyroperoxidase antibodies.

Overall FSH levels were above normal in males (74.6% had high levels) but normal in females (89.2% had normal levels), independent of etiology in both sexes but decreased significantly with increasing severity (by both the CTP class and MELD score). Subgroup analysis among CTP class showed this trend to be significant in the alcohol related CLD group only.

LH levels were higher in all males but normal in all females without any relation to etiology and severity of CLD.

Overall testosterone levels were lower than normal in males (97% had low levels) but normal in females (46% had slightly high levels) and these changes were independent of the etiology or severity of CLD in both sexes.

Overall estradiol levels were higher than normal in males (97% had high levels) but normal in females (73% had normal levels). Among those with high levels, males had much higher levels than females. It was independent of etiology in females but in males levels were significantly higher in ALD compared to other etiologies. Overall levels were significantly higher in patients belonging to CTP class B and C of ALD compared to other etiologies.

By etiology primary hypogonadism was present in 27% of alcohol, 13% of viral hepatitis and 7% of NAFLD related CLD and all were males. There was no case of secondary hypogonadism or PCOS.

Prolactin levels were elevated in all 99% patients independent of etiology or severity of CLD.

Thus overall 85% patients had altered hormonal levels excluding prolactin [34/35 (97%) in alcohol, 34/41 (83%) in viral hepatitis, 14/20 (70%) in NAFLD group and 3/4 (75%) in autoimmune related CLD group]. 21% had four, 46% had three, 16% had two and 2% had one hormone abnormality.

Discussion

Thus our study shows that overt or subclinical hormonal abnormalities are present in a large number of CLD patients. The only other Indian study which evaluated multiple hormones in 30 CLD patients of only alcohol and viral etiology found 50% prevalence of occult endocrine abnormalities.[5] Other studies from India have found relation of hormonal alteration with CTP class as our study.[6,8]

Most studies evaluating the relation

Table 5: Hormone level in different CTP class according to etiology of CLD

Hormone		CTP class			Row p	Column p
	Etiology	A	B	C		
FT3	Alcohol	0.63±0.51	1.65±0.65	1.60±0.71	ns	ns
	Hepatitis B	1.51±0.62	1.54±0.22	1.52±0.71		
	NAFLD	1.64±0.56	1.90±0.52	1.96±0.44		
	Hepatitis C	1.89±0.08	1.06±0.50	1.01±0.55		
	AIH	1.22±0.68	0.67±0.01			
FT4	Alcohol	1.65±0.11	1.44±0.41	1.49±0.33	ns	ns
	Hepatitis B	1.36±0.35	1.53±0.36	1.34±0.30		
	NAFLD	1.65±0.10	1.45±0.43	1.70±0.03		
	Hepatitis C	1.60±0.04	1.59±0.11	1.65±0.06		
	AIH	1.47±0.25	1.57±0.01			
TSH	Alcohol	4.82±0.15	4.84±0.52	4.83±0.79	ns	P< .05 for Hepatitis C vs all others in A,B and C class
	Hepatitis B	4.43±0.42	4.62±1.41	4.69±0.33		
	NASFLD	5.25±1.92	7.20±2.86	5.14±0.95		
	Hepatitis C	51.71±21.41	47.18±24.72	40.93±22.27		
	AIH	23.81±18.50	34.21±0.01			
Estradiol	Alcohol	128.01±38.64	146.41±47.37	205.36±68.07	ns	P< .05 for alcohol vs hepatitis B & C in class B & C
	Hepatitis B	116.89±71.76	124.36±40.63	176.36±53.54		
	NAFLD	117.60±64.84	138.99±54.21	182.37±67.32		
	Hepatitis C	131.23±58.35	126.79±64.44	162.84±68.47		
	AIH	96.64±52.88	137.62±0.01			
Testosterone	Alcohol	0.67±0.01	0.75±0.38	0.73±.0.42	ns	ns
	Hepatitis B	0.66±0.33	0.64±0.28	0.74±0.22		
	NAFLD	0.64±0.20	0.80±0.26	0.94±0.56		
	Hepatitis C	0.82±0.32	0.81±0.25	0.68±0.28		
	AIH	0.48±0.16	0.92±0.01			
Prolactin	Alcohol	67.91±3.82	63.96±9.46	57.97±14.54	ns	ns
	Hepatitis B	45.50±16.19	45.91±12.01	43.19±12.15		
	NAFLD	55.50±16.19	53.06±13.23	58.24±13.04		
	Hepatitis C	43.84±12.73	48.20±15.30	45.21±5.79		
	AIH	49.28±16.58	39.11±0.01			
FSH	Alcohol	21.36±6.41	15.27±6.38	11.08±3.35	P<.05 for alcohol in A,B,C	ns
	Hepatitis B	20.30±8.53	16.38±3.41	14.16±5.34		
	NAFLD	20.88±8.65	17.34±2.50	12.43±4.16		
	Hepatitis C	21.64±6.14	18.61±4.31	14.83±3.04		
	AIH	20.38±3.56	18.14±0.01			
LH	Alcohol	25.16±5.46	23.84±5.22	26.10±2.45	ns	
	Hepatitis B	31.73±4.26	28.51±3.65	28.02±5.12		
	NAFLD	32.02±5.73	31.04±4.81	27.72±5.65		
	Hepatitis C	30.91±6.20	29.07±5.47	30.26±4.16		
	AIH	32.34±3.86	32.21±0.01			
Insulin	Alcohol	37.21±4.24	38.20±7.70	39.57±15.87	ns	ns
	Hepatitis B	28.74±6.51	39.50±17.34	33.89±12.86		
	NAFLD	30.20±3.91	42.36±33.32	28.24±4.02		
	Hepatitis C	27.89±9.49	23.88±4.21	27.72±5.96		
	AIH	22.28±5.76	14.61±0.01			
Cortisol	Alcohol	30.66±2.05	29.64±4.14	26.03±5.78	ns	P< .05 for alcohol vs all others in A,B and C class
	Hepatitis B	5.80±3.14	6.17±1.95	9.14±4.25		
	NAFLD	10.73±3.60	14.79±10.51	10.21±3.31		
	Hepatitis C	7.73±3.65	6.60±3.53	7.06±3.47		
	AIH	3.58±0.35	4.11±0.01			

ns= not significant, AIH = Autoimmune hepatitis, NAFLD = non alcoholic fatty liver disease, CTP = Child Turcotte Pugh

of cortisol to CLD show normal serum cortisol levels with a blunted response to release trigger (insulin induced hypoglycaemia, corticotrophin) which may be inversely related to severity of CLD.[9] The activity of the enzyme 11 beta-hydroxysteroid dehydrogenase, found predominantly in liver and kidney and responsible for the shuttling of active plasma cortisol to cortisone is decreased in CLD causing increase in plasma cortisol along with its half-life in the face of decreased production. However, in ALD morning plasma cortisol is elevated[10] due to continuing normal secretion in the face of impaired metabolism. Our study shows similar results with normal levels in 50%, but high levels in 36% of which 34% have ALD. Also the levels increased with severity by MELD and CTP class and this was mostly related to ALD group. Terminal adrenal failure in a proportion of patients due to exhaustion, especially those in intensive care with sepsis, may cause low levels.[9,11] This may be the reason that some of our patients (14%) had low cortisol level.

T4 is a prohormone and T3 is the biologically active form. The liver plays an important role in maintaining thyroid hormone homeostasis by converting T4 to T3 (accounting for 80% of the T3 produced daily). Most studies show that CLD produce changes that result in the sick euthyroid syndrome due to decreased conversion of T4 to T3. However, most patients are euthyroid and have no clinical signs of hypothyroidism.[12] Our study shows that though 18% have sick euthyroid syndrome and 43% have subclinical hypothyroidism, there is overt hypothyroidism needing treatment in 19% patients all of whom had hepatitis C related and autoimmune CLD. Another Indian study reports an incidence of 6.4% subclinical hypothyroidism and 2.1% overt hypothyroidism in CLD.[6] Other studies have shown higher prevalence (13%) and risk (odds 2.9 -3.1) of hypothyroidism and other thyroid abnormalities in chronic hepatitis C.[12-14] We excluded patients who received interferon therapy so this was not the cause of abnormalities in any of our patients. Autoimmune liver diseases are also associated with thyroiditis and Grave's disease as present in 2 of our patients. Two studies have addressed the relationship of severity of CLD to hormone levels,[8,15] both reporting lower FT3 levels with increasing severity with no difference in TSH and FT4 levels. In our study though there was no relation of overall TSH, FT3 or FT4 levels to severity, higher TSH (but not FT3 or FT4) levels were found in hepatitis C related CLD compared to other etiologies in all CTP classes. Thus it appears that clinical hypothyroidism is more prevalent in hepatitis C related CLD but alteration in hormone levels

Table 6: Hormone levels in various etiologies of CLD

Etiology	Cortisol	Insulin	TSH	FT4	FT3
Alcohol	26.91±5.56* (1,0,34)	37.93±22.02 (1,0,34)	4.82±0.72 (19,0,16)	1.48±0.33 (28,0,7)	1.55±0.71 (19,16,0)
Hepatitis B	6.43±4.68 (18,5,1)	26.53±8.16 (10,0,14)	4.51±0.68 (7,0,17)	1.39±0.34 (22,1,1)	1.62±0.59 (19,5,0)
Hepatitis C	7.02±3.33 (9,8,0)	29.80±5.86 (11,0,6)	46.03±22.01* (0,0,17)	1.61±0.08* (2,15,0)	0.97±0.44* (4,13,0)
NAFLD	11.36±5.42 (18,1,1)	32.09±7.57 (6,0,14)	5.61±1.96 (11,0,9)	1.46±0.20 (11,0,9)	1.80±0.51 (18,2,0)
Autoimmune	3.71±0.39 (4,0,0)	30.81±4.99 (4,0,0)	26.41±15.97* (1,0,3)	1.49±0.21 (0,3,1)	1.08±0.62 (3,1,0)
Significance	F = 88.66 p=0.0001	F = 2.43 p=0.062	F = 66.80 p=0.0001	F = 2.57 p=0.04	F = 5.32 p=0.0007

Etiology	LH (male)	LH (female)	FSH (male)	FSH (female)	Testosterone (male)	Testosterone (female)	Estradiol (male)	Estradiol (female)	Prolactin (male)	Prolactin (female)
Alcohol	19.25±4.77 (0,0,35)	0	20.02±7.83 (8,0,27)	0	0.72±0.39 1,34,0)	0	300.37±172.54* (0,0,35)	0	41.51±14.34 (0,0,35)	0
Hepatitis B	19.23±1.67 (0,0,12)	40.7±5.36 (12,0,0)	17.57±10.8 (4,0,8)	11.67±5.84 (12,0,0)	0.74±0.32 (0,12,0)	0.58±0.25 (8,0,4)	99.10±57.66 (0,0,12)	161.69±92.7 (9,0,3)	39.42±15.71 (0,0,12)	47.33±13.62 (1,0,11)
Hepatitis C	18.98±3.68 (0,0,9)	35.9±6.54 (10,0,0)	18.32±5.09 (2,0,5)	12.65±5.63 (10,0,0)	0.67±0.30 (0,7,0)	0.83±0.23 (4,0,6)	101.65±67.59 (1,0,6)	146.55±98. 24(6,0,4)	45.36±11.54 (0,0,7)	47.47±13.88 (0,0,10)
NAFLD	20.78±4.78 (0,0,7)	42.35±5.86 (11,0,0)	23.27±9.60 (2,0,7)	10.77±3.43 (7,4,0)	0.83±0.52 (1,8,0)	0.73±0.21 (5,0,6)	197.07±193.05 (1,0,8)	177.01±61.36 (11,0,0)	46.98±11.48 (0,0,9)	50.72±15.09 (0,0,11)
Autoimmune	0	39.7±3.47 (4,0,0)	0	11.73±6.47 (4,0,0)	0	0.59±0.25) (3,0,1)	0	163.88±56.52 (1,0,3)	0	46.73±14.45 (0,0,4)
Significance	F = 2.39 p=0.06	F = 2.50 p=0.08	F = 2.51 p=0.06	F = 1.66 p=0.19	F = 0.24 p=0.86	F = 2.28 p=0.09	F = 7.19 p=0.0001	F = 0.06 p=0.98	F = 2.90 p=0.06	F = 1.67 p=0.19

*Significantly higher than rest which are comparable. Hormone levels expressed as mean + standard deviation. (Number in parentheses indicate number of patients with normal, low and high hormone levels respectively)

are mostly subclinical in others and these patients must be followed up for later development of overt disease.

CLD is itself a state of peripheral insulin resistance (apart from NAFLD etiology where insulin resistance is present much before development of CLD) so high fasting insulin levels are normally expected.[16] This is mostly related to decreased insulin metabolism, insulin resistance in liver and muscle, insulin secretory abnormalities, portasystemic shunt and disturbances in glucose metabolism. Our study shows raised levels in 68% patients independant of the severity or etiology of CLD (especially NAFLD) but levels were also significantly more in diabetics compared to non diabetics with CLD.[17,18] The reason why levels were highest in ALD is unclear but may be related to insulin signalling abnormalities.[19] Other endocrine derangements are also associated with NAFLD related CLD (via metabolic syndrome) e.g. thyroid hormone (hypothyroidism), sex hormone (PCOS), cortisol (Cushing syndrome) and growth hormone. Their interaction in regulating lipid and glucose metabolism in the normal liver may become disordered in cirrhotic liver.

Primary hypogonadism was present in 47% patients in our study similar to 41.7% reported in another Indian study.[6] The relationship of plasma sex hormone levels to CLD is complex. In addition to normal sex difference in serum level, there is variation according to time in menstrual cycle and after menopause in women. The gonadotrophins also have different release and feedback control mechanism among the sexes, regulation being tighter for LH than FSH by GnRH and sex hormones. In addition GnRH integrates cues from stress, sex steroids, glucocorticoids, nutritional and metabolic status, prolactin and endorphins to controls gonadotropin secretion. It is well known that CLD causes feminisation and hypogonadism in men with amenorrhoea and infertility in women due to low testosterone with high oestrogen and prolactin levels. The changes are more pronounced in alcoholics. Our study show similar results. Portocaval shunts in CLD increase systemic estrogen level along with its low peripheral conversion to testosterone more profoundly in males where it is needed physiologically. Because testosterone controls LH and FSH levels in males, their levels increase due to loss of feedback. In females the same function is controlled mainly by estradiol so levels of LH and FSH are not much disturbed as estrogen level remains normal. The actual effect of sex hormone changes in CLD is dependant on estrogen/androgen ratio (which is usually increased in cirrhotic patients) rather than purely on individual levels. Several factors may contribute to these changes including elevated prolactin levels (via its effect on dopamine).

Estrogen levels were significantly higher in ALD compared to other etiologies and increased significantly with worsening liver function as has also been shown before.[20,21] That it was higher in males compared to females is possibly due to bias introduced by only male ALD patients.

Alcohol has its own direct effects e.g. toxic effect on Leydig cells, disruption of the hypothalamic–pituitary–gonadal axis mostly via hyperprolactinemia (and its effect on dopamine in brain) which decreases the response of LH to GnRH, increased activity of aromatase which increase circulating estrogen levels from aromatization of androstendione.[20,22]

Prolactin plays a physiological role in breast development and lactation and its level and action is intertwined with that of sex hormones, especially oestrogen. When produced in excess it may lead to amenorrhea and sterility commonly found in CLD. Our study show increased prolactin levels in all but one patient and this may be due to high oestrogen levels as well as the effect of CLD (and alcohol) on its controller dopamine in brain. High prolactin levels in CLD has been shown in other Indian studies[7] but our study

did not show relation to severity.

Thus our study shows significant alterations of hormonal profile in CLD. Most hormonal abnormalities (except cortisol, sex hormones) are independant of severity of CLD which indicate that they start early in the development of CLD of any etiology. Alcohol especially disturbs the metabolism of sex hormones, cortisol and insulin in addition to causing CLD that may worsen the outcome. The normal interplay of different hormones in endocrine homeostasis of the body may become disrupted in presence of CLD which may also influence outcome.

Abbreviations

CLD = chronic liver disease, ALD = Alcohol related CLD, NAFLD = non alcoholic fatty liver disease, PCOD = polycystic ovary disease, CTP = Child Turcotte Pugh, MELD = Mayo End stage Liver Disease, TIPSS = transjugular intrahepatic portasystemic shunt, FSH = follicle stimulating hormone, LH = leutinizing hormone, TSH = thyroid stimulating hormone, FT4 = free T4, FT3 = freeT3, BMI = body mass index, GnRH = gonadotrophin releasing hormone,

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