

# Hypothalamic-pituitary-gonadal function in men with liver cirrhosis before and after liver transplantation

## *Função do eixo hipotálamo-hipófise-gonadal em homens cirróticos antes e após o transplante hepático*

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### A B S T R A C T

**Objective:** To evaluate the influence of end-stage liver disease and orthotopic liver transplantation in the pituitary function and hormone metabolism before and after liver transplantation. **Methods:** In a prospective study, serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) and prolactin (PRL) of 30 male patients with cirrhosis were determined two to four hours before and six months after liver transplantation. The results were compared according to the Model for End-stage Liver Disease (MELD). **Results:** male patients with liver cirrhosis have hypogonadism. FSH was normal, but inappropriately low due to androgen failure; E2 and PRL, on their turn, were high. After liver transplantation, FSH and LH levels increased ( $p < 0.05$ ), whereas E2 and PRL normalized ( $p < 0.05$ ). The MELD score did not influence changes in FSH, PRL and LH, however, the more severe the cirrhosis was, the more significant was the normalization of E2 ( $p = 0.01$ ). **Conclusion:** Patients with cirrhosis and male hypogonadism have inappropriately normal levels of FSH and LH, associated with an increase in E2 and LRP. After liver transplantation, FSH and LH increased, while E2 and PRL returned to normal. Changes in E2 levels were most pronounced in patients with MELD  $> 18$ . The severity of cirrhosis had no influence on FSH, PRL and LH.

**Key words:** Liver Transplantation, Liver Cirrhosis, Pituitary Gland, Hypogonadism.

### INTRODUCTION

Patients with end-stage liver disease have several endocrine dysfunctions, which include alterations in the functioning of the hypothalamic-pituitary-gonadal axis and the serum levels of sex hormones<sup>1-4</sup>. Testicular atrophy, decrease in libido, impotence, oligospermia, infertility, loss of body hair, reduction of prostate size, gynecomastia, vascular spiders, gynecoid distribution of fat and palm erythema are often found in cirrhotic men<sup>5-10</sup>. These findings are more pronounced in patients with alcoholic cirrhosis due to the direct harmful effect of ethanol to the testicles. The pathophysiology of hypogonadism in patients with advanced liver disease is complex and controversial.

Few studies have evaluated the dysfunction of the hypothalamic-pituitary-gonadal axis in men with cirrhosis before and after orthotopic liver transplantation (OLT). The correlation between changes in serum levels of sex hormones and the MELD score (Model for End-stage Liver Disease) has not yet been studied.

The aim of this study was to evaluate the influence of terminal liver disease and OLT in the pituitary function and hormone metabolism by measurement of serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) and prolactin (PRL) before and after liver transplantation.

### METHODS

Between August 2008 and April 2011, 93 liver transplants were performed at the Clinics Hospital of the Federal University of Paraná. The study included all male patients who did not present any of the following exclusion criteria: patients submitted to living-donor transplantation, re-transplantation, multivisceral transplantation, domino transplant and split liver transplant. Five patients who died were also excluded. In total, 30 men were selected and prospectively followed.

We used the Child-Pugh and MELD scores to determine the severity of liver disease. Among those

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included in the study, three patients (12%) were Child-Pugh class A, 6 (24%) class B, and 16 (64%) class C. The MELD ranged from 10 to 30 points, averaging  $17.7 \pm 4.2$  (95% CI 16.1-19.2). We did not consider the additional scores for cirrhotic patients with associated hepatocellular carcinoma. To evaluate the relationship between the severity of liver disease and the variation in the levels of sex hormones, we divided the study subjects into two groups, based on MELD classification, 17 patients with MELD <18, and 13 with MELD  $\geq$  18.

The mean age was  $51.4 \pm 7.6$  years. The main causes of cirrhosis were infection with hepatitis C and alcohol abuse (Table 1). All patients with alcoholic cirrhosis were abstinent for more than six months prior to OLT.

After liver transplantation, all patients underwent the same standard protocol of immunosuppressive therapy, consisting of cyclosporine or tacrolimus, mycophenolate mofetil and corticoids.

We collected peripheral blood samples two to four hours before induction of anesthesia and six months after liver transplantation, with determination of levels of FSH, LH, E2 and PRL through commercial immunoassay kits. We also measured total bilirubin, prothrombin and

creatinine by routine biochemical tests for determining the MELD score on the day of transplantation.

The study protocol was in accordance with guidelines of the Helsinki Declaration of 1975, and was approved by the Ethics Committee of the Clinics Hospital of the Federal University of Paraná, Brazil (CAAE: 0159.0.208.000-08, CEP Registration: 1712.129/2008-07). All patients signed an informed consent form to participate in the study.

### Statistical Analysis

The measures of central tendency and dispersion are expressed as means and standard deviation (mean  $\pm$  SD) for symmetrically distributed, continuous variables, and as median, minimum and maximum values for the ones with asymmetric distribution.

The estimated difference of continuous variables with normal distribution were analyzed by parametric tests, Student's t test for dependent samples, and ANOVA for repeated measures, while for asymmetric distribution variables we employed the non-parametric Wilcoxon and Friedman ANOVA tests. We applied the McNemar test in the study of the behavior of biochemical and hormonal variables according to the reference values, evaluating the categories' variations: normal, below and above the reference value, before and after liver transplantation. The results were considered statistically significant when  $p < 0.05$ .

**Table 1** - Clinical and Demographic Characteristics of patients.

Features	Patients	
Number	30	
Age (in years)		
Mean $\pm$ Sd	51.4 $\pm$	7.6
Variation	25 -	64
IC 95%	48.6 -	54.3
Gender (male/female)	30/0	
Etiology of cirrhosis	N	(%)
HCV infection	10	(33.33)
Alcohol abuse	8	(26.67)
NASH	3	(10.0)
HBV infection	2	(6.67)
Hemochromatosis	2	(6.67)
Other	5	(16.67)
Associated Hepatocarcinoma	4	(13.33)

CI = confidence interval; SD = standard deviation; HCV = hepatitis C virus; HBV = hepatitis B virus; NASH = Nonalcoholic Steatohepatitis.

**Table 2** - Serum levels of FSH, LH, PRL and EE.

Hormone	Reference	Pre-OLT		Post-OLT		p
FSH	1.5 - 12.4 mIU/mL	8.1	(0.7 - 73.0)	13.4	(2.2 - 92.5)	0.002
HL	1.7 - 8.6 mIU/mL	4.6	(1.3 - 34.0)	9.9	(2.9 - 82.2)	< 0.001
E2	< 43 pg/mL	54.7	(26.0 - 466.0)	33.5	(15.5 - 314.0)	0.001
PRL	2.0 - 15.2 ng/mL	16.5	(4.8 - 68.1)	8.4	(3.2 - 29.0)	< 0.001

OLT = Orthotopic Liver Transplantation; FSH = Follicle Stimulating Hormone; HL = Luteinizing Hormone; E2 = Estradiol; PRL = Prolactin.

## RESULTS

The FSH and LH levels were within normal limits and increased, respectively, from 8.1 mIU/ml to 13.4 mIU/ml ( $p = 0.002$ ) and from 4.6 mIU/mL to 9.9 mIU/ml ( $p < 0.001$ ) after OLT. Estradiol was initially high, and returned to normal after liver transplantation ( $p = 0.001$ ). Prolactin levels were also elevated preoperatively. After OLT its levels decreased to normal ( $p < 0.001$ ) (Table 2).

The multivariate analysis based on generalized linear models showed no influence of age on the date of transplantation or the etiology of cirrhosis in the hormonal changes observed.

In both MELD groups we observed a rise in serum FSH values before and after OLT ( $p = 0.004$ ), but without significant difference ( $p = 0.89$ ) (Figure 1). There

was an increase in HL in the MELD group  $< 18$  ( $p = 0.01$ ), while there was no change in the MELD group  $\geq 18$  ( $p = 0.26$ ). Nor was there a significant difference between groups ( $p = 0.89$ ) (Figure 2). There was a drop in estradiol values after OLT both in the group with MELD  $< 18$  ( $p = 0.05$ ) and in the one with MELD  $\geq 18$  ( $p = 0.005$ ), being more pronounced in the group with MELD  $\geq 18$  ( $p = 0.006$ ) (Figure 3). There was a reduction in serum prolactin levels in the MELD group  $< 18$  ( $p = 0.03$ ) and MELD  $\geq 18$  ( $p = 0.005$ ), with no statistically significant difference ( $p = 0.07$ ) (Figure 4).

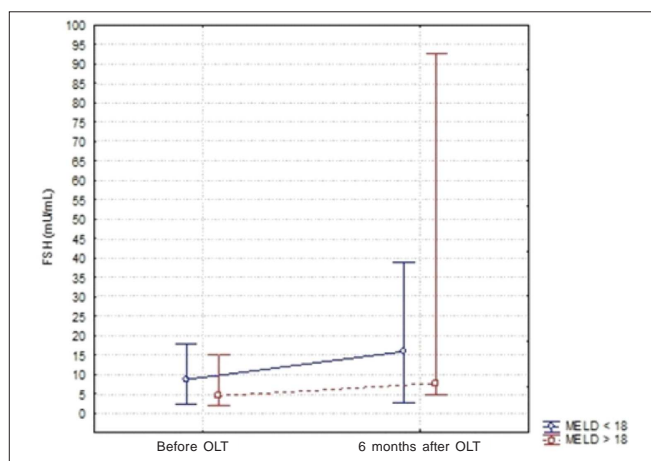
## DISCUSSION

Male patients with cirrhosis have a number of changes in the regulation of their sex hormones, resulting

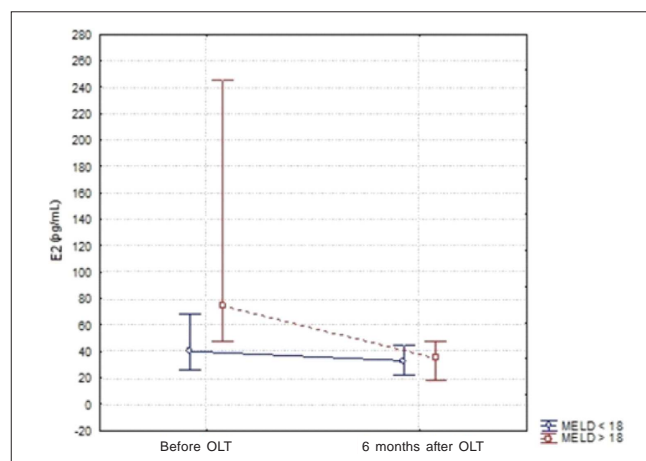
in hypogonadism and feminization. End-stage liver disease causes dysfunction in the hypothalamic-pituitary-gonadal axis and hormonal peripheral metabolism<sup>1,2,11,12</sup>, resulting in a significant deterioration in quality of life<sup>3-10</sup>.

Our prospective study showed that cirrhotic men have significant alterations in the pituitary regulatory functions, and that these disorders are completely reversed after liver transplantation.

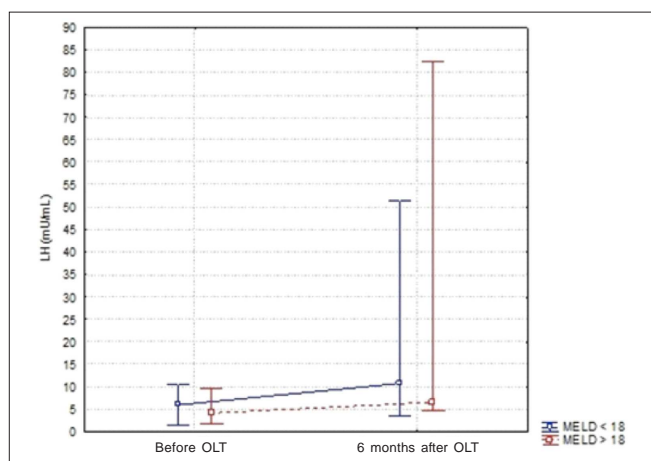
The FSH and HL were at levels within their reference values, and increased after OLT<sup>13</sup>. These data confirm the results of previous studies. However, it is important to note that serum levels of these hormones were inappropriately low, given the androgen failure evidenced in these patients<sup>7,14,15</sup>. In fact, one would expect them to suffer a compensatory increase due to low serum testosterone levels. Our results showed that six months after transplantation the values of FSH and HL showed a



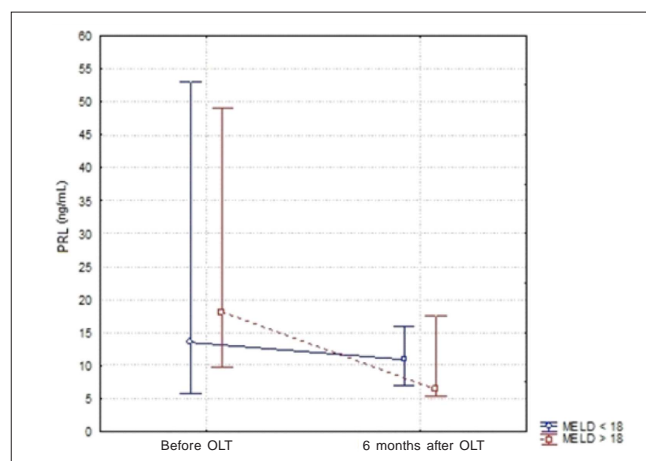
**Figure 1** - Orthotopic liver transplantation (OLT); follicle stimulating hormone (FSH). Increased serum FSH levels in both groups MELD  $< 18$  and MELD  $\geq 18$  ( $p = 0.04$ ), with no difference between them ( $p = 0.89$ ).



**Figure 3** - Orthotopic Liver Transplantation (OLT); estradiol (E2). Reduction in E2 levels in groups MELD  $< 18$  ( $p = 0.05$ ) and MELD score  $\geq 18$  ( $p = 0.005$ ), more pronounced in the MELD group  $\geq 18$  ( $p = 0.01$ ).



**Figure 2** - Orthotopic liver transplantation (OLT); luteinizing hormone (LH). Increases in serum LH levels in the MELD group  $< 18$  ( $p = 0.01$ ), not observed in the MELD group  $\geq 18$  ( $p = 0.26$ ), with no difference between them ( $p = 0.89$ ).



**Figure 4** - Liver Transplantation Orthotopic (OLT); prolactin (PRL). Reduction in levels of PRL in the MELD groups  $< 18$  ( $p = 0.03$ ) and  $\geq 18$  ( $p = 0.005$ ), with no difference between them ( $p = 0.07$ ).

significant increase, suggesting that the liver disease had a direct influence on this abnormality, which is consistent with the available literature on the subject<sup>3,12,13,16</sup>.

The exact cause of this central dysfunction has not been clearly elucidated. It is speculated that liver cirrhosis alone can cause a malfunction of the hypothalamic-pituitary-gonadal axis<sup>1,3,10</sup>. Furthermore, high circulating levels of estradiol and prolactin also contribute to hypogonadism<sup>2,3</sup>, either by regulatory suppression or by direct inhibition of the testicular function<sup>10</sup>. The results also showed that both the PRL and E2 were at levels above normal in patients with end-stage liver disease, with normalization after OLT, in line with previous studies<sup>1,17,18</sup>. The increase in serum levels of E2 is primarily due to increased peripheral conversion of androgens into estrogens and reduction in liver clearing function<sup>5,7</sup>. Portal hypertension can lead to a diversion of blood flow from the liver to peripheral tissues, resulting in a further increase in the conversion of steroids into estrogens<sup>8</sup>. Although some studies<sup>2,19,20</sup> have established a correlation between increased PRL in cirrhosis and hyperestrogenemia, the mechanism that leads to hyperprolactinemia is not yet clear.

Another important finding of our study is the correction between these hormonal changes and the MELD score at the time of transplantation. It was found that the

severity of liver disease has no influence on changes in FSH, LH and PRL ( $p = 0.89$ ,  $p = 0.89$  and  $p = 0.07$ , respectively) after OLT. This may be due to the limited number of patients included in this analysis.

However, E2 values decreased after liver transplantation in direct proportion with the worst liver function ( $p = 0.01$ ). Furthermore, the higher the value of MELD at the time of OLT, the more significant the normalization of estradiol ( $p = 0.006$ ).

Finally, after the evaluation of the impact of liver transplantation in the hypothalamic-pituitary-gonadal dysfunction in male cirrhotic patients, we observed that all hormone levels are normal six months after transplantation. This conclusion is consistent with the literature<sup>3,7,10,13,16-18</sup>. Seehofer *et al*, after a five-year follow-up of their patients, found that this improvement is persistent<sup>12</sup>.

The present study demonstrated that male patients with end-stage liver disease have inappropriately low levels of FSH and LH due to androgenic failure, and elevated serum E2 and PRL. After liver transplantation, FSH and LH values increased, while E2 and PRL returned to normal. Changes in estradiol are more pronounced in patients with higher MELD (MELD e" 18). Changes of FSH, PRL and LH did not vary according to the severity of liver disease.

## R E S U M O

**Objetivo:** avaliar a influência da doença hepática terminal e do transplante hepático ortotópico na função hipofisária e no metabolismo hormonal através da aferição dos níveis séricos dos hormônios folículo estimulante (FSH), hormônio luteinizante (HL), estradiol (E2) e prolactina (PRL) antes e após o transplante hepático. **Métodos:** em um estudo prospectivo, níveis séricos dos hormônios folículo estimulante (FSH), hormônio luteinizante (HL), estradiol (E2) e prolactina (PRL) de 30 paciente masculinos com cirrose foram determinados duas a quatro horas antes e seis meses após o transplante hepático. Os resultados foram comparados de acordo com o Model for End-stage Liver Disease (MELD). **Resultados:** pacientes masculinos com cirrose hepática apresentam hipogonadismo. O FSH encontravam-se normais, porém inapropriadamente baixos devido à falência androgênica; já o E2 e o PRL estavam elevados. Após o transplante hepático, os níveis de FSH e HL aumentaram ( $p < 0,05$ ), enquanto o E2 e o PRL normalizaram ( $p < 0,05$ ). O MELD não influenciou as alterações no FSH, HL ou PRL, todavia, quanto mais grave a cirrose, mais significante foi a normalização do E2 ( $p=0,01$ ). **Conclusão:** pacientes masculinos com cirrose e hipogonadismo apresentam níveis inapropriadamente normais de FSH e HL, associados com elevação do E2 e PRL. Após o transplante hepático, FSH e HL aumentaram, enquanto E2 e PRL retornaram aos valores normais. As alterações nos níveis de E2 foram mais pronunciadas em pacientes com MELD > 18. A gravidade da cirrose não teve influência no FSH, HL e PRL.

**Descritores:** Transplante de Fígado, Cirrose Hepática, Hipófise, Hipogonadismo.

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