Influence of cholestatic jaundice on the weight variance in an experimental model

Influência da icterícia colestática na variação ponderal em modelo experimental

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A B S T R A C T

Objective: To evaluate the influence of cholestatic jaundice in weight variation. **Methods**: We used 64 adult rats divided into six groups: F1 (n = 6): normal females; F2 (n = 6): laparotomy females; F3 (n = 20): jaundiced females; M1 (n = 6): normal males; M2 (n = 6): laparotomy males; M3 (n = 20): jaundiced males. Jaundice was obtained by ligation and section of the biliopancreatic duct. The animal weights were recorded weekly for seven weeks. On the 14th day of the experiment, bilirubin and gonadal hormones were assessed. After the seventh week a histological study of the liver was performed. **Results**: The animals in groups F3 and M3 showed elevated bilirubin and decreased body mass when compared to the other groups. The weight differences were significant from the fourth week on amongst females and from the fifth in males. In Jaundiced animals there was increased estradiol and decreased progesterone and testosterone. Perivenular septa and periportal fibrosis, cholangitis and bile duct hyperplasia occurred in the liver of jaundiced rats. No animal showed cirrhosis. **Conclusion**: There was decrease in murine body weight in the presence of cholestatic jaundice in both genders.

Key words: Cholestasis. Jaundice. Hyperbilirubinemia. Gonadal hormones. Rats.

INTRODUCTION

Jaundice is the clinical manifestation of many liver and non-liver diseases, reflecting disruptions in production, metabolism and excretion of bilirubin. Its organic repercussions may be followed by serious sequelae[1]. While there are discussions about possible effects of hyperbilirubinemia in body metabolism, there are still studies that examine the impact of liver disease on body weight [2-5]. Zaina et al., In 2004, studied 219 candidates to liver transplant of both genders and observed that patients with cholestatic diseases were more malnourished when compared to patients with non-cholestatic diseases[6]. Other authors also suggested interaction between hepatic metabolism and body mass[7-9].

Studies that relate to liver weight change are complex[3]. Many factors are involved in the pathogenesis of this interaction, including control of feeding behavior, fat storage mechanisms, regulation of energy intake and energy expenditure, as well as hormonal, genetic and psychological influences[10]. Given the possibility of distinct liver characteristics between genders of the same species and the close relationship between the metabolism of sex steroids and liver function, body mass should be considered when studying cholestatic jaundice[1,4,11].

Diseases such as primary biliary cirrhosis, cholelithiasis and autoimmune hepatic diseases occur more in women, alcoholic cirrhosis being more common in men [12,13]. Furthermore, the impact of alcoholism in women results in higher hepatic damage and increases even further the possibility of developing cirrhosis[1]. Similarly, previous studies from the same research line of this work have reported delayed emptying of the gallbladder in perimenopausal women[14,15]. In this sense, the interaction of sex hormones seems to influence the hepatobiliary functions[12-15].

The relationship between sex steroids and weight variation has been postulated by several authors[16-21]. It is known that from the third decade of life the body starts declining functional abilities, especially in women after menopause, who tend to increase in body fat and decrease in basal metabolism. As a result, women show weight gain[12]. At menopause, there is addition of 800g body weight each

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year. Szabo et al., In 2000, reported weight gain in ovariectomized female cats[17]; the same was observed by Melton et al. in thesame year[18]. With the discovery of leptin, a hormone regulator of obesity, we question its possible interaction with the metabolism of bilirubin[22-24]. In previous studies in line with our research on jaundice[14,15,25,26] and sex hormones[24.27-31], there was correlation between sex hormones and hyperbilirubinemia.

Given the importance of risk factors caused by hyperbilirubinemia and their relations to body weight, the present study aimed to evaluate the influence of cholestatic jaundice in weight variation.

METHODS

This work was performed in accordance with the recommendations of the International Protection of Animals and the Brazilian Code of Animal Experimentation (1988) and was approved by the Department of Surgery, Faculty of Medicine, Federal University of Minas Gerais (UFMG) and the Ethics Committee of Experimental Research at UFMG under number 092/04.

We studied 64 rats Wistar (*Rattus norvegicus*), 32 females and 32 males, with three months of age. The distribution of animals was done randomly, for both females and males, in six groups: F1 (n = 6): normal females; F2 (n = 6): laparotomy females; F3 (n = 20): jaundiced females; M1 (n = 6): normal males; M2 (n = 6): laparotomy males; M3 (n = 20): jaundiced males.

The animals in groups F1 and M1 were not operated. The animals from F2 and M2 underwent laparotomy followed by closure. Hyperbilirubinemia was induced in the animals of groups M3 and F3 by means of ligation and section of the biliopancreatic duct. All procedures followed aseptic and antiseptic techniques. The date on which the surgical procedures were performed was considered the beginning of the experiment.

Operations were conducted in the animals of groups F2, M2, M3 and F3 under general anesthesia with ketamine hydrochloride (90mg/kg) and xylazine (10mg/kg), both intraperitoneally[32]. In animals from F2 and M2 groups a 3cm-length laparotomy was held from the xiphoid process, the abdominal organs were manipulated, followed by wall closure in two planes, with polyglactin 4-0. The animals in groups F3 and M3 underwent the same procedures described for groups F2 and M2 plus ligation of the biliopancreatic duct with 5-0 silk thread and its section, an inch of the duodenum.

Throughout the monitoring period, the animals were placed in individual cages with free access to water and proper chow. To evaluate the effectiveness of the surgical procedure of groups M3 and F3, the skin and mucosal surfaces of animals were assessed for clinical jaundice, and there was also choluria and fecal hipocholia researches.

The variation in weight of each group was comparatively studied over a period of seven weeks. Each animal was weighed weekly, by the same observer, on a precision balance, with a maximum load for 1000g and sensitivity of 0.1g. The initial weight of animals from F2, F3, M2 and M3 was measured soon after surgery. The non-operated animals, groups F1 and M1, were also weighed on the same day of surgery. The final weight was noted on the 49th day of the experiment.

Blood collection was performed in all animals on the 14th day of the experiment. With the animal anesthetized and in supine position, we dissected the right femoral vein and collected 1ml of blood with an aluminum foil-coated tube to protect from light. After hemostasis by compression at the collection site, a 4-0 nylon suture was performed. The collected blood samples were centrifuged at 4000rpm for 10 minutes and subjected to colorimetric examination of bilirubins[33]. We also dosed estradiol and progesterone in females and testosterone in males by the method of immunofluorimetry[34].

After seven weeks, all animals were anesthetized with double dose of ketamine. A wide laparotomy was performed and, after careful study of the abdominal cavity, hypovolemic shock was caused by section of the inferior vena cava to induce death. We removed two fragments of liver tissue for histopathological study.

All results were initially tested for normality with Kolmogorov-Smirnov test[35]. To compare the measurements of bilirubin between different groups, we used the nonparametric Kruskal-Wallis test followed by Dunn's multiple comparison. Comparisons of estradiol, progesterone and testosterone, as well as weekly body weights, between different groups were carried out with analysis of variance (unimodal ANOVA) followed by Tukey-Kramer multiple comparison test. All results were considered significant for a probability of less than 5% significance ($p < 0.05$).

RESULTS

All animals that underwent ligation and section of the biliopancreatic duct became jaundiced, with yellow pigmentation of the skin and mucosa, and dark urine and fecal hipocholia. There were differences between groups in values of bilirubin ($p < 0.0001$). Serum total bilirubin was higher in animals undergoing biliopancreatic duct ligation, groups F3 and M3, than in other groups ($p < 0.01$). This increase was primarily due to the direct fraction. There was no difference in bilirubin between females and males. Table 1 shows the values of serum bilirubin in all groups.

Serum levels of sex steroids were different between groups ($p < 0.0001$). In F3 there was increased estradiol and reduction of progesterone when compared to the other female groups ($p < 0.001$). The animals of group M3 showed reduced total testosterone when compared to

groups M1 and M2 (p <0.001). Table 2 shows serum hormone values in all groups.

At necropsy, the abdominal cavity of the animals without biliopancreatic duct ligation, M1, M2, F1 and F2, showed no apparent morphological changes. In jaundiced animals (M3 and F3), we found hepatomegaly and diffuse yellow-green pigmentation in the abdominal organs. In no animal from groups M1, F1, F2 and M2 changes were observed in liver histological architecture, both in males as in females. However, liver histology was changed in all animals that were submitted to biliopancreatic duct ligation. There were biliary stasis, dilation and hyperplasia of intrahepatic bile ducts, inflammatory infiltrate with a predominance of intra and periductal polymorphonuclears (cholangitis). Septal fibrosis was observed in some animals, but none of them had liver cirrhosis.

The initial body weight of females in all three groups was similar (p = 0.1004), the same occurring in males (p = 0.0908). The average weight of the groups showed differences between females from the fourth week, and among males, from the fifth week, due to reduced mass weight of jaundiced rats (p <0.05). Table 3 shows the weight weekly change of all groups for seven weeks. Initial and final body weight average of all animals is shown in Figure 1.

DISCUSSION

The relationship between hyperbilirubinemia and weight variation has been studied in some works, which show conflicting results due to the complexity and variety of assessment methods adopted[7-9,23]. Several factors interact in weight gain, such as heredity, eating habits, physical exercise, sedentary lifestyle, psychiatric disorders, among others[10,24]. In this study, we sought to eliminate interference. All animals, males and females, had similar initial ages and weights, received the same kind and quantity of nutrition and remained allocated in individual cages. Thus, the biliopancreatic duct ligation became the most important variable.

In this study, the albino rats choice was based on their anatomy and physiology of the liver and viability of the surgical procedure without requiring special material. Another advantage of this model is the similarity with the research line related to cholestatic jaundice[14,15,25,26]. The random allocation of animals in groups aimed homogenisation of the sample[35]. Considering that liver disease may evolve differently depending on gender, it was considered pertinent to assess the presence of induced jaundice in males and females[1].

Table 1 - Serum direct, indirect and total bilirubins (mean ± standard deviation of the mean) from animals in all groups, obtained on the 14th day of the experiment.

Groups	Serum Bilirubin (mg/dl)		
	Direct Bilirubin	Indirect Bilirubin	Total Bilirubin
F1	0.1 ± 0.05	0.2 ± 0.08	0.3 ± 0.13
F2	0.1 ± 0.05	0.2 ± 0.10	0.3 ± 0.10
F3	4.6 ± 1.83	3.1 ± 1.25	7.7 ± 2.14*
M1	0.1 ± 0.04	0.2 ± 0.1	0.3 ± 0.13
M2	0.1 ± 0.05	0.2 ± 0.08	0.3 ± 0.12
M3	4.9 ± 1.52	3.2 ± 0.84	8.0 ± 1.64**

*F1 (n = 6) - normal females; F2 (n = 6) - females subjected only to laparotomy; F3 (n = 20) - jaundiced females; M1 (n = 6) - normal males, M2 (n = 6) - males submitted only to laparotomy; M3 (n = 20) - jaundiced males. * Difference between the group F3 and the groups F1 and F2, through the multiple comparison test of Dunn, significant at p <0.01**. Difference between group M3 and groups M1 and M2, through the multiple comparison test of Dunn, significant at p <0.01.*

Table 2 - Serum hormones (mean ± standard deviation of the mean) from all animals, harvested on the 14th day of the experiment.

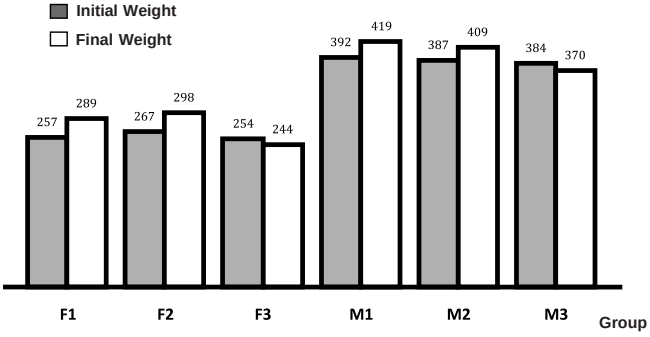
Hormones (pg/ml)	Females			Males		
	F1	F2	F3	M1	M2	M3
Estradiol	24.80 ± 5.84	23.17 ± 6.32	65.93 ± 17.78*	–	–	–
Progesterone	19800 ± 3150	18600 ± 2110	10200 ± 2380*	–	–	–
Total Testosterone	–	–	–	3.86 ± 1.47	4.05 ± 1.32	1.15 ±0.45**

*F1 (n = 6) - normal females; F2 (n = 6) - females subjected only to laparotomy; F3 (n = 20) - jaundiced females; M1 (n = 6) - normal males, M2 (n = 6) - males submitted only to laparotomy; M3 (n = 20) - jaundiced males. * Difference between the group F3 and the groups F1 and F2, through the multiple comparison test of Tukey-Kramer, significant at p <0.001**. Difference between group M3 and groups M1 and M2, through the multiple comparison test of Tukey-Kramer, significant at p <0.001.*

Table 3 - Body Weight (mean ± standard deviation of the mean) of animals from all groups, observed weekly for seven weeks.

Weeks	Females			Males		
	F1	F2	F3	M1	M2	M3
Initial weight	257 ± 20	267 ± 14	254 ± 17	392 ± 15	387 ± 18	384 ± 12
1ª	264 ± 22	264 ± 17	252 ± 20	397 ± 19	385 ± 23	381 ± 18
2ª	271 ± 19	272 ± 19	259 ± 19	404 ± 18	389 ± 25	386 ± 20
3ª	276 ± 18	278 ± 18	264 ± 18	409 ± 18	395 ± 20	389 ± 21
4ª	280 ± 17	284 ± 20	262 ± 20*	413 ± 17	398 ± 18	385 ± 22
5ª	283 ± 20	290 ± 15	256 ± 22*	415 ± 14	402 ± 17	379 ± 20**
6ª	286 ± 19	295 ± 19	251 ± 19*	417 ± 18	406 ± 21	376 ± 21**
7ª	289 ± 21	298 ± 18	244 ± 21*	419 ± 16	409 ± 21	370 ± 23**

*F1 (n = 6) - normal females; F2 (n = 6) - females subjected only to laparotomy; F3 (n = 20) - jaundiced females; M1 (n = 6) - normal males, M2 (n = 6) - males submitted only to laparotomy; M3 (n = 20) - jaundiced males. * Difference between the group F3 and the groups F1 and F2, through the multiple comparison test of Tukey, significant at p <0.05.** Difference between group M3 and groups M1 and M2, through the multiple comparison test of Tukey, significant at p <0.05.*



*F1 (n = 6) - normal females; F2 (n = 6) - females subjected only to laparotomy; F3 (n = 20) - jaundiced females; M1 (n = 6) - normal males, M2 (n = 6) - males submitted only to laparotomy; M3 (n = 20) - jaundiced males. * Difference between the group F3 and the groups F1 and F2, through the multiple comparison test of Tukey, significant at p <0.05.** Difference between group M3 and groups M1 and M2, through the multiple comparison test of Tukey, significant at p <0.05.*

Figure 1 - *Body weight all the groups (g average), assessed on day 1 (initial) and in the 7th week (final) of the experiment.*

The time of 14 days between blood collection and surgical procedures aimed at verifying the increase in serum bilirubin and their possible relationships with the systemic metabolism, sex steroids and mass weight of jaundiced rats. For the assessment of bilirubin, blood collection under protection from light and immediate processing of samples were based on studies that observed false results due to changes in this pigment by photosensitivity and cryopreservation[33,36].

The ligation and section of the biliopancreatic duct caused cholestasis and hyperbilirubinemia, predominantly of the direct fraction, but some mice showed values of indirect bilirubin higher than the direct fraction, due to hepatocyte impairment by cholestasis[4,5].

Cholestatic jaundice evolved similarly in both genders, given that there was no difference between the values of bilirubin between males and females. In such cases, the rate of progression of the disease and its prognosis could be determined by the intrinsic characteristics of the individual, such as age, nutrition and immune status[1-5]. In the present work, the fact that some animals showed higher levels of bilirubin could also justify this hypothesis.

The literature suggests possible interactions between sex hormones and body weight[16-21]. In this study, the elevation of estradiol and serum progesterone decline in females undergoing biliopancreatic duct ligation may suggest a relationship between hyperbilirubinemia and the pituitary-gonadal axis. In previous work from the same research line, we observed a decrease of progesterone in jaundiced female rats, with decreased corpora lutea and elevation of serum estradiol. Another possibility is the injury of hepatocytes through the action of bilirubin, raising serum estradiol [37]. It is common for men with liver disease to present high estradiol and high incidence of gynecomastia[1].

In males, the reduction of serum testosterone occurred in the presence of biliopancreatic duct ligation, suggesting interaction between hyperbilirubinemia and testicular function. Excess bilirubin pervades Leydig cells and there is reduction in testosterone production.

In this study, the weight difference became significant after the fourth week of the experiment. All animals that underwent biliopancreatic duct ligation had reduced weight mass, accompanied by greater apparent weakness. The reduction in body weight of both males and females after biliopancreatic duct ligation may be directly related to hyperbilirubinemia. It is known that jaundiced patients with advanced liver disease lose weight not only due to the disease itself, but also by low food intake[1-5]. In the literature, there are reports of weight loss

in the presence of cholestatic liver[6-9]. Mabuchi et al. observed that cholestatic jaundice triggered intense murine tissue catabolism, decreasing not only body weight, but also bone density[8]. A year later, Isaksson et al. also found that obstructive jaundice by biliopancreatic duct ligation in rats caused cachexia, reducing their body weights[9].

All operated animals had reduced weight gain in the first postoperative week. It is known that surgical trauma can trigger catabolic effects to the body, reducing weight[24]. In the following weeks, the animals submitted only to laparotomy recovered from the surgical trauma and gained weight, similar to the non-operated.

Rioux *et al.*, comparing rats undergoing only laparotomy with others submitted to biliopancreatic duct ligation, found decreased food intake during the first 24 hours after surgery in the laparotomy group. However, the jaundiced animals continued without eating properly, reaching cachexia[7]. Although we attempted to assess the amount of food consumed by the rats to justify the weight change, this data could not be reliably achieved. As we did not used metabolic cages, we could not quantify losses by the animal waste. It is clear, however, that the weight variation of the animals was a few grams, representing less than one gram per day, with no significant difference between them. Thus, the research was conducted on a weekly basis. Between the sixth and seventh week, non-jaundiced animals had lower body weight, tending to stabilize. Moreover, because of the risk of death of jaundiced rats due to cachexia, the study was stopped after seven weeks.

Besides hyperbilirubinemia, one could still think that sex steroids would likely influence murine body weight[16,17,18]. In previous work in the same line of investigation, it was observed that young adult female rats submitted to oophorectomy had increased body weight in relation to the only laparotomized ones, with weight gain from the ninth week of castration on[24]. The elevation of estradiol in jaundiced rats may also have contributed to the weight reduction in our study. This finding was also raised by other authors. Guyard et al reported that estrogen increases energy consumption and, consequently, decreases body weight[37]. Chu *et al.* found greater weight gain in oophorectomized animals[38]. Moreover, according to Geary *et al.* oophorectomized rats treated with estradiol gain less weight[6], while animals receiving progesterone gain even less[6].

Estrogen reduces serum leptin and inhibits food intake, decreasing body weight[22]. By being able to keep body fat distribution, its deficiency increases the visceral fat deposit, with increased waist-hip ratio, androids features. Tommaselli *et al.* revealed an action of estrogen in decreasing leptin brain receptors and consequent weight reduction[23].

According to some studies, the decline in serum testosterone observed in jaundiced males could also change the weight mass[19-21,39]. Brodsky *et al.* studyed patients with hypogonadism and Snyder *et al.*, the elderly, both groups reporting a decrease in fat mass after testosterone replacement therapy[19,21]. Katznelson *et al.* observed that the decrease in serum testosterone levels may cause increased body mass, mainly by deposition of fat tissue, rather than muscle tissue[20]. Nevertheless, there are studies that failed to show such an association[39].

The pathological changes of the present study were consistent with the expectations. In the presence of the cholestatic processes, there is liver histoarchitecture disorganization, with formation of fibrosis septa, hypertrophy and hyperplasia of bile ducts, and cholangitis[1,26]. The absence of cirrhosis was important for the interpretation of the results, as if I were present, its metabolic effects would be more complex than the systemic effects of isolated hyperbilirubinemia. Perhaps a longer follow-up could have rendered transformation of the cholestatic liver to cirrhosis[4].

Based on the data of the present study, we can conclude that hyperbilirubinemia induced by biliopancreatic duct ligation reduced the murine body mass in both genders.

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R E S U M O

Objetivo: *Avaliar a influência da icterícia colestática na variação ponderal.* ***Métodos:*** *Foram utilizados 64 ratos adultos, distribuídos em seis grupos: F1 (n=6) - fêmeas normais, F2 (n=6) - fêmeas laparotomizadas, F3 (n=20) - fêmeas ictéricas, M1 (n=6) - machos normais, M2 (n=6) - machos laparotomizados, M3 (n=20) - machos ictéricos. A icterícia foi obtida com ligadura e secção do ducto biliopancreático. Os pesos dos animais foram registrados semanalmente, durante sete semanas. No 14º dia de experimento, dosaram-se as bilirrubinas séricas e os hormônios gonadais. Após a sétima semana, realizou-se estudo histológico do fígado.* ***Resultados:*** *Os animais dos grupos F3 e M3 apresentaram bilirrubinas elevadas e diminuição da massa corpórea, quando comparados com os demais grupos. As diferenças ponderais foram significativas a partir da quarta semana entre as fêmeas e da quinta semana entre os machos. Nos animais ictéricos houve aumento do estradiol e diminuição da progesterona e da testosterona total. Septos de fibroses perivenular e periportal, colangite e hiperplasia de ductos biliares ocorreram no fígado dos animais ictéricos. Nenhum animal apresentou cirrose.* ***Conclusão****: Ocorreu redução do peso corpóreo murino em presença de icterícia colestática em ambos os sexos.*

Descritores: *Colestase. Icterícia. Hiperbilirrubinemia. Hormônios gonadais. Peso corpóreo Ratos.*

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