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Estradiol and Testosterone Levels in Patients Undergoing Partial Hepatectomy:

A Possible Signal for Hepatic Regeneration?

A. FRANCAVILLA, MD, **J.S. GAVALER, PhD**, **L. MAKOWKA, MD, PhD**, **M. BARONE, MD**, **V. MAZZAFERRO, MD**, **G. AMBROSINO, MD**, **S. IWATSUKI, MD**, **F.W. GUGLIELMI, MD**, **A. DILEO, MD**, **A. BALESTRAZZI, MD**, **D.H. VAN THIEL, MD**, **T.E. STARZL**, and **MD. PhD**
Departments of Gastroenterology and Surgery, University of Bari, Bari Italy, Departments of Surgery and Gastroenterology, University of Pittsburgh Health Center, University of Pittsburgh, and Veterans Administration Medical Center, Pittsburgh, Pennsylvania

Abstract

In five adult male patients undergoing a 40–60% partial hepatectomy, serum sex hormone levels before and after hepatic resection were determined. Blood was drawn immediately prior to each surgical procedure and at specified time points postoperatively. Compared to hormone levels found prior to surgery, following major hepatic resection, estradiol levels increase at 24 and 48 hr, while testosterone levels decline, being significantly reduced at 96 and 144 hr, These data demonstrate that adult males who undergo a 40–60% partial hepatectomy experience alterations in their sex hormone levels similar to those observed in male rats following a 70% hepatectomy. These changes in sex hormone levels have been associated in animals with an alteration of the sex hormone receptor status of the liver that is thought to participate in the initiation of the regenerative response. These studies suggest, but do not prove, that in man, as in the case of the rat, sex hormones may participate in the initiation of or at least modulate in part the regenerative response that occurs following a major hepatic resection.

Keywords

steroid hormones; partial hepatectomy; liver regeneration

A variety of hormones have been implicated in the process of hepatic regeneration (1–7). Recently, a relationship between liver cell proliferation, sex hormone levels in serum, and their receptors in hepatic tissue has been demonstrated in rats (8,9). Specifically, serum testosterone levels decrease following a 70% hepatectomy while estrogen levels increase. Simultaneously, the total hepatic content and nuclear retention of estradiol receptors increases. In contrast, both the total and the nuclear androgen receptor content of the liver declines (9). To determine whether similar pertubations in hormone levels occur in man during the hepatic regenerative response that occurs subsequent to a major hepatectomy, the following study was performed.

Address for reprint requests: Dr. Antonio Francavilla, Veterans Administration Hospital, Building 6, Circle Drive, Pittsburgh, Pennsylvania 15240.

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MATERIALS AND METHODS

Patients

Five adult male patients between the ages of 30 and 72 years (mean 54.8 ± 15.8 years) were studied. Each underwent a minimum 50% but less than 75% subtotal hepatic resection. Table 1 summarizes the clinical history, primary diagnosis, and type of hepatectomy performed for each of the individuals studied. Serum was assayed for sex hormone levels immediately prior to (T_0; time zero), and at 7, 24, 48, 72, %, and 144 hr following hepatic resection (8,9). The identical study was performed in three individuals undergoing a cholecystectomy. These individuals served as controls for the effects of a major operative procedure (cholectystectomy), not including a hepatic resection, on the hormone levels assessed.

Hormone Assays

Serum estradiol (E_2) and testosterone (T) levels were determined utilizing ^{125}I solid-phase, direct radioimmunoassay kits obtained from Immuchem Corp., Carson. California. The sensitivities for estradiol and testosterone were 10 pg and 0.2 ng, respectively. The intraassay coefficient of variation (CV) for estradiol was 6.0% and for testosterone, 10.9%. The interassay CV was 11.3% for estradiol and 11.2% for testosterone.

Statistical Analysis

All statistical evaluations were performed utilizing least-squares regression and the Student's *t* test; a value of $P < 0.05$ was considered to be statistically significant. All data are reported as the mean ± standard error of the mean (SEM).

RESULTS

The time courses for the estradiol blood levels in the three cholecystectomized controls and the five individuals having had a partial hepatectomy are shown in Figure 1. In the latter group, estradiol levels began to increase at 7 hr and peaked at 48 hr following the hepatic resection, a time when DNA synthesis and the mitotic index peak in experimental animals subjected to a major hepatic resection. Estradiol levels were increased significantly ($WP < 0.05$) at 24, 48, and 72 hr following hepatic resection, meter the peak of estradiol at 48 hr, the levels of estradiol declined towards preoperative levels. In contrast to these changes following a hepatic resection, no alteration in the serum estradiol levels across time was observed following cholecystectomy.

Figure 2 shows the time course for the changes in testosterone levels observed in the controls and the subjects who underwent a major partial hepatectomy. In the latter group, serum'testosterone levels declined and were reduced significantly ($P < 0.02$) at 96 and 144 hr following the resection. Moreover, when the testosterone levels were expressed as a percent of the basal levels, a significant correlation between the testosterone level and the time following hepatic resection was evident ($r = 0.401$, $P < 0.05$). In contrast, no relationship between the serum testosterone levels and postoperative time was evident in the cholecystectomized controls.

Figure 3 depicts the estradiol/testosterone ratio across time in the subjects having undergone a major hepatic resection. The highest ratio was obtained at 48 hr when the estradiol levels were maximal and testosterone levels were reduced uniformally. The behavior of this ratio is suggestive of an enhanced peripheral (nongonadal) aromatization of testosterone to estradiol following partial hepatectomy resulting in a net "feminization." In contrast to these changes in the estradiol/testosterone ratio in men following a major hepatic resection, no change in the estradiol/testosterone ratio across time was seen in the cholecystectomized controls (data not shown). A significant correlation between the estimated conversion of testosterone to estradiol,

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as determined by the estradiol/testosterone ratio with the serum estradiol levels ($r = 0.916$, $P < 0.001$), was evident.

DISCUSSION

It has been shown that the mammalian liver contains receptors for both estrogens and androgens and is responsive in terms of a variety of hepatic functions to changes in the plasma sex hormone levels (10–17). Many biochemical functions of the liver are dependent upon steroid hormone action. These include the synthesis of estrogen 2-hydroxylase; the cytosolic amount of the mate estrogen-binding (MEB) protein (18,19); the synthesis and secretion of a wide variety of transport proteins found in plasma, which carry hydrophobic materials such as sex steroid-binding globulin (19,20); the production of important materials found in plasma, such as renin substrate (21,22); and the production and secretion of other proteins such as ceruloplasmin (23), to name but a few.

Recently, it has been reported that serum sex hormone levels and their receptors in the liver undergo extensive alterations following a partial hepatectomy in male rats and that these changes may be related, at least in part, to the subsequent hepatic regenerative response (8,9). Specifically, total hepatic content and the nuclear retention of the estrogen receptor increases following a partial hepatectomy, with the zenith occurring within 48 hr of the partial hepatectomy. Moreover, serum estradiol levels increase and reach a peak level three days after partial hepatic resection. In contrast, serum testosterone levels and the total and nuclear androgen receptor content of liver undergo a parallel decline in male rats following a major hepatic resection. This reduction in plasma testosterone levels and the androgen receptor content of the liver is associated with a loss of the androgen-dependent components of hepatic function characteristic of the adult male rat. Specifically, reductions in the hepatic content of the male estrogen-binding (MEB) protein and estrogen 2-hydroxylase activity have been demonstrated in adult male rat liver following a major hepatic resection (9). It is generally believed that these two cytosolic proteins complement each other to promote rapid binding and metabolism of excess estrogens within the hepatic cytosol of males which might otherwise compromise the sexual integrity of male hepatocellular function. A failure of this process results in a “feminization” of the male liver characterized by increased estrogen receptor activity within the liver (8,9). Moreover, such feminization may either enhance or initiate the hepatic regenerative response observed in rats following a major hepatic resection (8,9).

The data presented here demonstrate that humans who undergo a 40–60% partial hepatectomy experience similar changes in their plasma estradiol and testosterone levels as do rats. Moreover, the data demonstrate that these changes in hormone levels are not a consequence of the trauma of major surgery *per se* as they do not occur in individuals having had a cholecystectomy. Specifically, testosterone levels decline while estradiol levels increase following hepatic resection and are unchanged in men undergoing a cholecystectomy. Because it is ethically impossible to attempt to inhibit the regenerative response in humans, it is impossible to determine whether the changes in hormone levels observed in this study are a consequence of the hepatic resection as an initiating factor for the subsequent regenerative response. The fact that the hormonal changes observed are transient, lasting only 48–72 hr, suggests, but does not prove, that the changes are more apt to be an initiating signal rather than a consequence of a reduction in the functional hepatic mass. Similarly, it would be unethical to serially biopsy the liver of the subjects studied simply to demonstrate that the changes observed in rat liver in terms of the hepatic content of sex hormone receptor activity occur in man; these studies were not done. However, based upon the changes in the serum hormone levels observed in the subjects studied, which are similar to those observed in rats subjected to a 70% partial hepatectomy (8,9), it is not unreasonable to assume that similar changes in the

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receptor status of the liver as observed in animals following a major hepatic resection also occur in man.

These data support, but do not prove, the hypothesis that the process of “feminization” that occurs following a partial hepatectomy may be a general biological event that is not species-dependent and may contribute at least in part to triggering the subsequent hepatic regenerative response. As noted above, however, a direct cause-and-effect relationship between the alterations in hormone levels observed, the activity of their receptors in the liver, and the subsequent regenerative response cannot be demonstrated but appears likely.

It is of some interest to note that the process of “feminization” following partial hepatectomy (9) interferes with the expression of the epidermal growth factor receptor on hepatocyte plasma membranes and suggests a role for estrogens or “feminization” in the regenerative response following injury manifested by the mammalian liver.

As an extension of these studies, it is important to note that, until now, only androgens have been used in attempts to ameliorate the course of experimentally induced or clinical hepatic injury (24–26). Since recent data (8,9) demonstrate that androgens are unlikely to directly influence the regenerative response of the liver, other mechanisms, particularly the use of estrogens, may have to be considered to explain the apparent beneficial effect of androgen treatment in the few situations where sex steroids have been shown to cause a hepatic regenerative effect. Specifically, the data reported here suggest that after a partial hepatectomy in man, there is an increase in the nongonadal aromatization of androgens such as testosterone to estradiol that accounts for the observed increase in serum estradiol levels. This change, in turn, induces a state of hepatic “feminization” that appears to be important in the initiation of the subsequent regenerative response. In this regard, it is important to note that in cases where androgens have been shown to be useful, the androgens may have acted following their own conversion to an estrogen.

Acknowledgments

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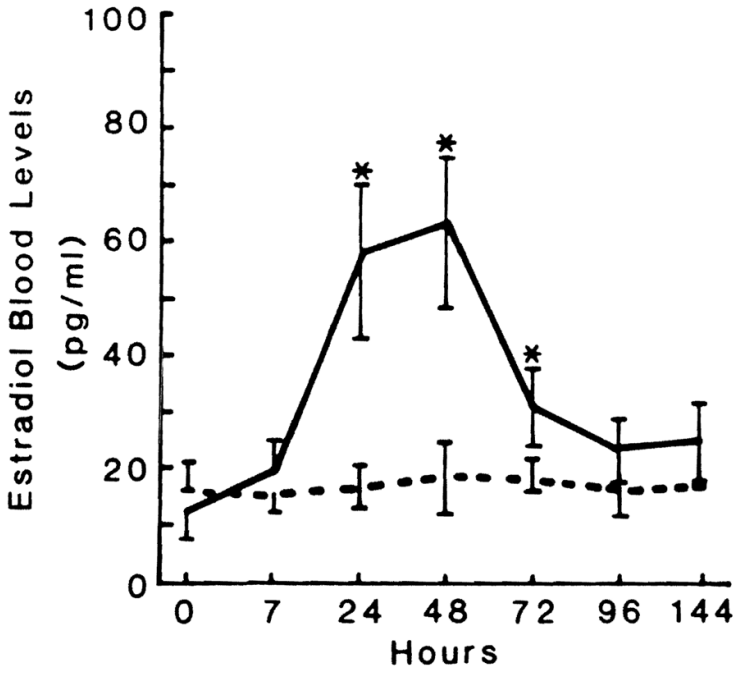

Fig 1.

Time course of estradiol blood levels in controls (---) and patients who have had a partial hepatectomy (—). Estradiol levels are expressed as the mean ± SEM. The asterisks indicate values that are significantly greater than the baseline level ($P < 0.05$).

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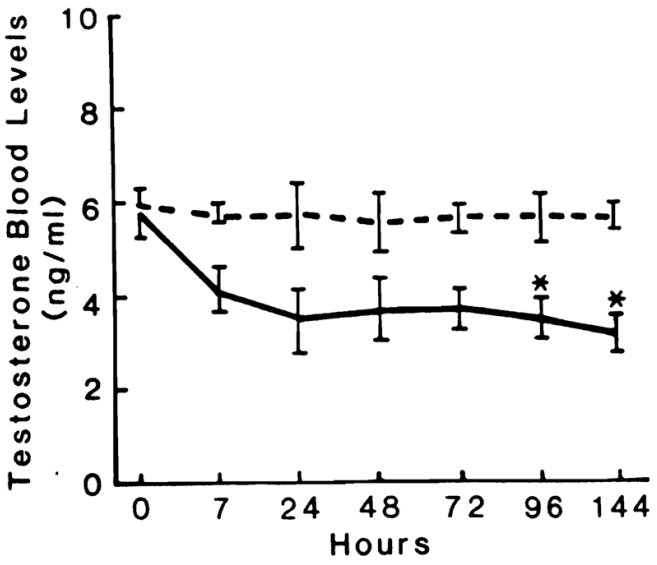

Fig 2.

Time course of testosterone blood levels in controls (---) and patients who have had a partial hepatectomy (—) Testosterone levels are expressed as the mean ± SEM. The asterisks indicate values that are significantly less than the baseline level ($P < 0.02$).

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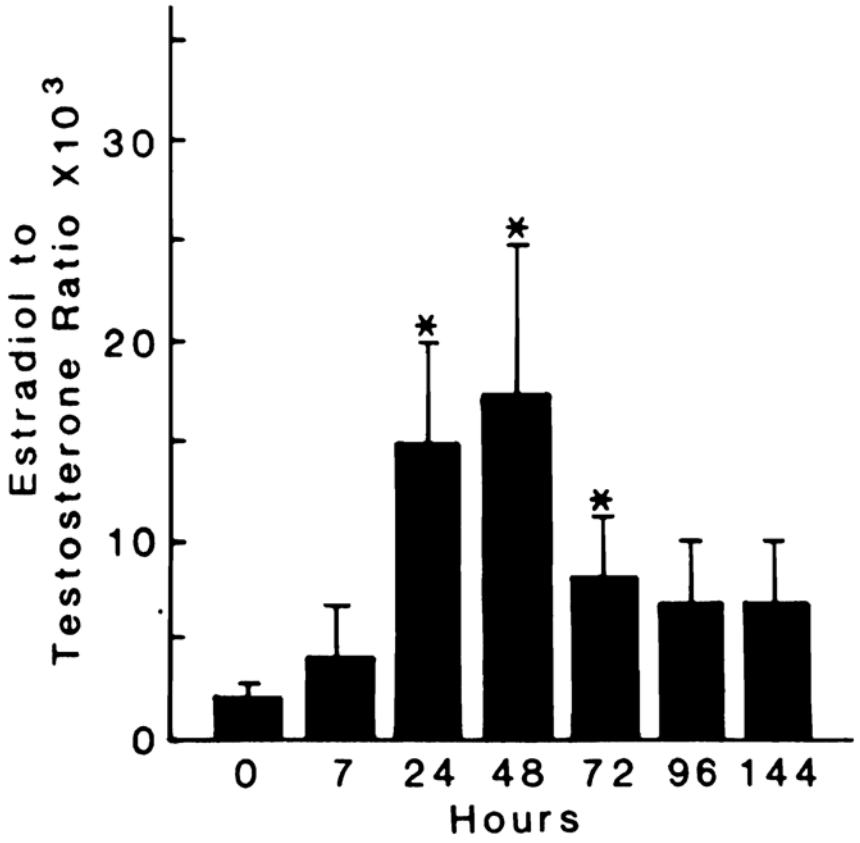

Fig 3.

Pattern of the calculated estradiol/testosterone ratio following partial hepatectomy in man. The values are expressed as he mean ± SEM. The asterisks indicate values that are statistially greater than the baseline ($P < 0.05$).

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TABLE 1

PATIENT INFORMATION

Patient number	Age (years)	Diagnosis	Associated diseases	Type of hepatectomy	Degree of liver Resection* (%)
1	72	Metastatic colorectal tumor	No	Right trisegmentectomy	75
2	51	Metastatic colon tumor	Ulcerative colitis	Left lobectomy	40
3	58	Metastatic rectal tumor	Hepatitis	Right lobectomy	60
4	30	Multiple stones within right intrahepatic bile ducts	No	Right lobectomy	60
5	63	Metastatic colon tumor	No	Right trisegmentectomy	75

* The quantity of liver removed is expressed as a percent of total liver volume determined by preoperative assessment of liver volume and mass of the resected specimen.