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Somatomedin C (IGF I) plasma levels after orthotopic liver transplantation (OLT) in end-stage cirrhotic patients

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Insulin-like growth factors [IGF I and II or somatomedins (SMS)] are polypeptides chemically and biologically correlated with insulin. The main source of synthetic activity and secretion is the liver, although many other tissues have been demonstrated to synthesize SMS [5]. In the circulation, they are not present in a free form, but are mostly bound to a specific carrier protein independently synthesized in the liver. Hepatic or extrahepatic storage organs have not been demonstrated; the half life of the SMS–binding protein complex is between 3 and 4 [1]. Synthesis of SMS is regulated by GH, insulin, thyroxine and nutrition (caloric and protein intake, and nitrogen balance). The role of corticosteroids is still a matter of debate: in patients treated with steroids SMS blood levels have been shown to be within normal limits, while biological activity has been demonstrated to be significantly reduced by SMS inhibitors, probably induced by corticosteroid therapy [2].

The biological properties of SMS are related to their structural homology with insulin, and can be summarized as follows [5]:

A. Insulin-like activity (glucose oxidation, lipogenesis, glycogen synthesis, inhibition of lipolysis and glycogenolysis)
B. Sulphation activity (incorporation of sulphate and leucine into glycosaminglycans of the cartilage)
C. Stimulation of fibroblast multiplication
D. Amplification of other hormone activities (GH)
E. Complementary anabolic activity with insulin.

Low levels of SMS have been demonstrated in hypopituitarism (secondary) or in other diseases independent of GH reduced secretion (primary) such as malnutrition, malabsorption, acute or chronic liver failure and uraemia [2]. Negative nitrogen balance, hypocaloric and/or low protein diets are usually correlated with low levels of SMS. Recently, Schalch et al. reported on the role of orthotopic liver transplantation (OLT) in normalizing SMS blood levels in a group of end-stage liver diseased patients [3].

This preliminary paper deals with changes in IGF-I plasma levels (somatomedin C) in a group of patients affected by end-stage liver cirrhosis before and after OLT.

Key words: Liver transplantation – Somatomedin

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Patients and methods

Ten patients (eight male, two female) suffering from end-stage postnecrotic cirrhosis and candidates for OLT comprised the study population. Mean age was 42 ± 11 years. Child's classification was B in six and C four patients.

Standard surgical and anaesthetic techniques and a venovenous bypass during the anhepatic phase were used in all the recipients.

Standard immunosuppression included 1 g Solumedrol after reperfusion of the liver and, in the postoperative period, rapidly tapered steroids, RATG (2 mg/kg body weight) for the first 8–10 days, azathioprine (1.5 mg/kg body weight) and cyclosporine.

From day 2 after OLT, nutritional intake included 30 kcal/kg per day and 0.25 g nitrogen/kg body weight. An RIA method (Nichols Institute, San Juan, Calif.) was used to measure IGF-I: normal values in our laboratory are between 0.7 and 2.2 U/ml. Arterial blood samples were drawn from 4 to 6 h before induction of anaesthesia (baseline) and on days 1, 3, 5, 8, 10, 15 and 18 after OLT. The blood samples were stored and retrospectively analysed. Data are reported as mean ± SD. Student's *t*-test was used to compare the means. Linear regression analysis was applied to paired data of daily SMS blood levels, daily dosage of steroids, daily caloric intake, daily nitrogen balance, prothrombin time (expressed as percent of normal) and daily bile flow to calculate correlation coefficients. $P \leq 0.05$ was considered significant.

Results

IGF-I plasma levels before OLT were very low (0.6 ± 0.4 U/ml). In six patients mean blood levels were 0.34 ± 0.12 (range 0.22–0.44) U/ml, while in the remaining four patients the levels were within the normal range

Table 1. Means ± SD of somatomedin (SMS) blood levels, prothrombin time (PT) and bile flow during the studied period

	SMS (*U*/ml)	PT (%)	Bile flow (ml/day
baseline	0.6 ± 0.4	50 ± 11	160 ± 189
Day 1	0.9 ± 0.4	61 ± 22	210 ± 166
Day 3	1 ± 0.5*	71 ± 23	180 ± 170
Day 5	1.4 ± 0.9*	71 ± 18*	240 ± 190
Day 7	1.7 ± 0.9**	81 ± 15***	300 ± 175
Day 8	2 ± 0.9**	84 ± 13***	365 ± 100
Day 10	2.2 ± 0.8***	85 ± 25***	430 ± 50
Day 15	1.7 ± 0.8**	81 ± 17***	
Day 18	2.4 ± 1.5***	86 ± 16***	

* $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$ vs baseline

(0.8 ± 0.4 U/ml). This profile closely reflected preoperative hepatic function tests which defined Child–Pugh scores for each patient.

Compared with preoperative values (baseline), IGF-I blood levels began to rise significantly 5 days after OLT ($P \leq 0.05$ vs baseline), and peaked on the 8th day ($P \leq 0.01$ vs baseline). All the patients had normal IGF-I blood levels 15 days after OLT ($P \leq 0.01$ vs baseline). At follow-up 1 month later normal SMS blood levels were found in three patients.

The rise in IGF-I blood levels was found to be independent of standard immunosuppressive steroid therapy, dietary intake, insulin supplementation and nitrogen balance. A direct correlation was found between the rate of rise in SMS blood levels and prothrombin time ($r = 0.94$, $P \leq 0.001$) from the first day after OLT and bile flow ($r = 0.94$, $P \leq 0.005$).

Discussion

Chronic liver diseases are usually associated with decreased levels of SMS, the synthesis of which, is markedly reduced in end-stage hepatic failure. These changes have been demonstrated to be closely correlated with the severity of the liver pathology [4]. In a recent report by Schalch et al. [3], OLT restored normal levels of IGF-I in patients affected by acute or chronic hepatic failure, indicating a possible role of liver transplantation in curing growth retardation in children suffering from chronic hepatic diseases.

In our series of adult patients affected by end-stage postnecrotic cirrhosis admitted to OLT and all with successful transplants, IGF-I blood levels were restored to normal levels within a few days after surgery, giving further confirmation to the data reported by Schalch. Rapid restoration of SMS seems to be related to the very early recovery of synthetic capacity of the newly grafted liver, as demonstrated by the close correlation with prothrombin time.

Fresh frozen plasma (FFP) has been demonstrated to be virtually IGF-I free (personal, unpublished observation). Since in the early postoperative period FFP is often liberally administered, PT values could be influenced by FFP supplementation, while IGF-I levels should specifically reflect the synthetic capacity of the transplanted liver.

Nutritional intake, exogenous insulin administration and positive nitrogen balance, together with GH and thyroxine, have been demonstrated to promote hepatic synthesis and secretion of IGF-I, while malnutrition, malabsorbtion and negative nitrogen balance have been reported to be accompanied by a reduced level of IGF-I [2]. In our series of patients the increase and normalization in IGF-I blood levels were present in spite of the negative nitrogen balance recorded during the first 5 days after OLT, thus reinforcing the central role played by the restored synthetic capacities of the new liver.

Steroid therapy has been reported to interfere with IGF-I: 66% decreased activity was observed in renal transplanted patients while on steroids [2]. Inhibitors of IGF-I activity were demonstrated to double during steroid therapy, while IGF-I circulating levels were found to be unchanged. The authors stated that steroid therapy was able to induce circulating inhibitors, while IGF-I synthesis was not altered. Since in our study only IGF-I plasma blood levels were measured, the only conclusion we can draw is that the rapidly tapered steroid therapy administered to our patients did not influence either IGF-I synthesis or secretion.

In conclusion IGF-I plasma levels were rapidly restored to normal levels in end-stage cirrhotic patients a few days after OLT. The measurement of IGF-I plasma levels could represent a specific and sensitive indicator of the synthetic capacities of the newly grafted liver. Further studies are needed to define the IGF-I profile during primary non-function and rejection and the possible correlations with the compromised function. In this case retrospective analysis, as performed in this study, is the major drawback.

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