Article

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GENTON GRAF, Laurence, *et al*.

Abstract

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Reference

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SMALL INTESTINE

Four year nutritional follow up after living related small bowel transplantation between monozygotic twins

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While small bowel transplantation (SBTX) may allow parenteral nutrition independence in the case of short bowel syndrome, its effects on body composition and growth are unclear. For the first time, a paediatric living related SBTX was performed between monozygotic twins. This case report describes their four year nutritional follow up. The 13 year old recipient and his healthy brother underwent measurements of body composition by 50 kHz bioimpedance analysis and bone mineral density of the femoral neck and total femur by dual energy *x* ray absorptiometry. Xylose tests and measurements of faecal fat evaluated gut absorption. All tests were performed before and after SBTX. Body weight increased from 34.7 to 51.9 kg in the recipient and from 45.0 to 53.2 kg in the donor within four years. The recipient caught up with the height and fat free mass of his brother within two years. Fat mass, and total femur and femoral neck densities are still lower in the recipient than in the donor four years after SBTX (–1.2 kg, –0.087 g/cm^2, –0.035 g/cm^2). The xylose test of the recipient was still abnormally low after four years (1.37 mmol/l) and faecal fat was high until two years after SBTX (March 2001: 12 g/24 h). The donor always showed normal xylose tests and faecal fat, except for one episode of high faecal fatty acids about 10 months after SBTX. SBTX improved the nutritional state and growth of the graft recipient although body composition, femoral bone mineral densities, and intestinal absorption had not completely normalised after four years.

Short bowel syndrome is associated with malabsorption and requires lifelong parenteral nutrition (PN). However, PN alters quality of life and is associated with line infections, thrombosis, liver dysfunction and, in children, failure to thrive.[1] In case of major intestinal failure and PN related complications, small bowel transplantation (SBTX) represents the last therapeutic option.

Twenty one living related SBTX have been described.[2] Three living related SBTX were carried out between monozygotic twins and therefore did not necessitate immunosuppressive therapy. In the first case, a 31 year old adult underwent SBTX for a desmoid tumour of the small bowel mesentery. On the fourth postoperative day, he presented a culture negative sepsis-like syndrome but this was the only complication. Thirty one days after surgery, he tolerated a soft diet. One year after surgery, he showed stable weight, regular diet without gastric complaints, and 2–6 bowel movements per day. Serum levels of albumin, transferrin, vitamin B12, and haemoglobin indices were within the normal range. Gastric emptying was normal but intestinal transit time was shortened. The donor was released from hospital five days after SBTX. No measurements of body composition were performed.[3 4] In the second case, a 40 year old man underwent SBTX after intestinal resection for superior mesenteric thrombosis. Three weeks after SBTX, he began to eat and drink normally and gradually gained weight. No adverse events were reported for the recipient or the donor. Tests of gut absorption and measurements of body composition were not described.[5] The third living related SBTX between monozygotic twins, and the first ever in children, was performed at the Geneva University Hospital.[6] Their four year nutritional follow up is presented below.

CASE REPORT

A 13 year old boy underwent extensive intestinal resection in December 1997 after appendicectomy complicated by internal midgut volvulus. An anastomosis was performed between the third duodenum and the mid part of the transverse colon. On 20 March 1998, the boy was referred to our centre because of debilitating diarrhoea, failure to thrive, and an anamnestic 14 kg weight loss despite PN support. On 30 April 1998, he underwent SBTX and received a 160 cm long small bowel graft, consisting only of ileum, from his healthy identical twin. A skin graft, performed prior to SBTX, was not rejected. Thus no immunosuppression was administered to the recipient after SBTX. Both boys stayed at Geneva University Hospital until 22 June 1998 and had careful follow up every six months. The evolution of the recipient's nutritional state was evaluated using the donor as control. The proposal was accepted by the ethics committee of the University Hospital of Geneva, Switzerland, the two boys and their parents.

RESULTS AND DISCUSSION

Nutritional support and resting energy expenditure

On the first three days of hospitalisation, the recipient received a daily PN of 1680 kcal (90 g amino acids, 75 g triglycerides, 250 g glucose; Nutriflex, B Braun, Crissier, Switzerland). This calorie supply was well tolerated but suboptimal for renutrition as indirect calorimetry (Deltatrac II; Datex Engström, Kuopio, Finland) showed a resting energy expenditure (REE) of 1600 kcal. Thus from day –36 to –2 before SBTX, calorie intake was increased to 2190 kcal/day (121 g amino acids, 100 g triglycerides, 320 g glucose; Nutriflex) with micronutrients, as recommended. After SBTX, from day 4 to 15, the recipient received 2190 kcal of PN, which was decreased to a 1680 kcal solution, as enteral nutrition was initiated (per day: 500 kcal; 23 g protein, 12 g lipids, 75 g carbohydrates; Survimed OPD, Fresenius Kabi, Bad Homburg, Germany). Enteral nutrition was stopped 21 days after SBTX when the recipient began to eat. PN was reduced to 1200 kcal on day 29, 1000 kcal on day 32, and finally stopped on the 34th day after SBTX because of infectious thrombosis of the central catheter. A right jugular thrombectomy was performed on the

Abbreviations: PN, parenteral nutrition; SBTX, small bowel transplantation; REE, resting energy expenditure; FM, fat mass; FFM, fat free mass; BMD, bone mineral density; BMC, bone mineral content.

Table 1 Evolution of resting energy expenditure measured by indirect calorimetry in the recipient and donor

	Day	Height (cm)	RQ	REE (kcal/24 h) Total	REE (kcal/24 h) Per kg body weight	REE (kcal/24 h) Per kg FFM
	Recipient					
	−38	156.0	0.94	1600	46	69
SBTX	−1	156.0	0.99	1460	38	55
	8	156.0	0.95	1470	39	59
	40	157.5	0.82	1360	35	55
	56	158.0	0.83	1270	33	48
	167	161.0	0.82	1390	36	44
	320	165.0	0.84	1520	36	43
	557	166.5	0.80	1670	37	45
	691	169.0	0.83	1740	34	—
	1026	171.0	0.78	1530	32	37
	1487	173.0	0.89	1740	34	39
SBTX	Donor					
	167	163.5	0.83	1500	32	37
	320	166.0	0.86	1380	29	38
	557	167.0	0.88	1390	29	38
	691	169.0	0.85	1860	34	—
	1026	169.3	0.84	1390	25	41
	1487	171.0	0.92	1430	27	32

RQ, respiratory quotient; FFM, fat free mass; SBTX, small bowel transplantation (30 April 1998, day 0); REE, resting energy expenditure.

36th day after SBTX. The donor did not receive any nutritional support before or after SBTX.

When expressed per kg/body weight or kg/fat free mass, the recipient showed a trend towards a higher REE before than after SBTX (table 1). Compared with his brother, the recipient tended to have a higher REE after SBTX. We hypothesise that he was catching up with the height of his brother and thus had more important secretion of androgens and growth hormone, which in turn increased REE.[7] However, the difference in REE between both brothers decreased with time.

Anthropometry and body composition

From hospital admission to SBTX, the weight of the recipient increased from 34.7 to 38.5 kg while that of the donor remained stable at 45 kg (fig 1). Immediately after SBTX, the weight of the recipient increased to 39.6 kg, probably because of water retention. At the time of discharge, 53 days after SBTX, the weights of the recipient and donor were 37.4 kg and 42.9 kg, respectively. The latest medical follow up, which occurred in May 2002, demonstrated that the recipient had not yet caught up with the weight of his brother. However, he caught up in height, mainly during the first nine months after SBTX. Indeed, while he was 3 cm shorter than his twin in March 1998, he was 2 cm taller in May 2002 (fig 1).

Body composition was assessed by bioelectric impedance (50 kHz, 0.8 Amp; Nutriguard, Data Input, Frankfurt, Germany).[8] At hospital admission, the recipient had 10.6 kg fat free mass (FFM) and 2.5 kg fat mass (FM) less than his twin (fig 1). During the month before SBTX, the recipient increased his FFM from 23.1 to 26.5 kg as a result of efficient PN support while maintaining his FM. In contrast, the donor lost 4.6 kg of FFM and gained 4.6 kg of FM, probably due to relative immobility for one month. Indeed, the donor never left his inactive brother alone and therefore was certainly more sedentary than usual. After SBTX, both boys increased their FFM and the recipient succeeded in catching up with the FFM of his brother by September 1999. FM (kg) remained stable after SBTX in the recipient because the energy was not stored as fat but most likely used to catch up with height. In contrast, FM of the donor, which tended to increase during the first three years after SBTX, finally decreased last year. This may be explained by the recent start of soccer practice. However, FM of the donor always exceeded that of the recipient after SBTX.

Bone mineral density and bone mineral content

Bone mineral densities (BMD) and contents (BMC) were measured by dual energy *x* ray absorptiometry (QDR 4500;

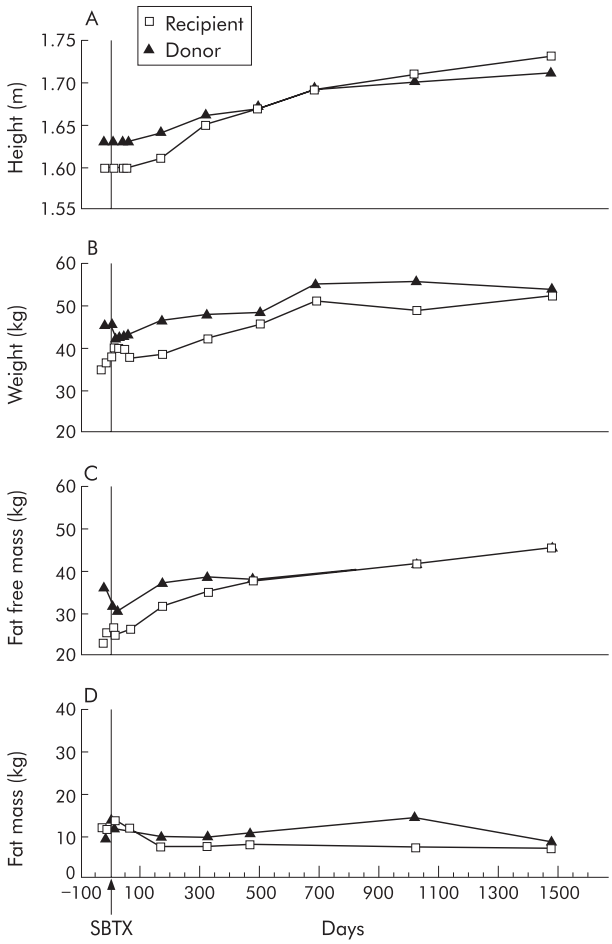

Figure 1 Evolution of height (A), weight (B), fat free mass (C), and fat mass (D), using 50 kHz bioelectric impedance analysis of the small bowel recipient and donor, before and after small bowel transplantation (SBTX). The arrow indicates the time of SBTX.

Table 2 Evolution of plasma parameters and absorption tests in the recipient and donor

	Day	C reactive protein (mg/l)	Total protein (g/l)	Albumin (g/l)	AP (U/l)	γ-GT (U/l)	Total bilirubin (μmol/l)	Xylose 2 h after intake (mmol/l)	Faecal fatty acids (g/24 h)
	Recipient								
	–40	17.1	69	37.5	44		13	0.03	11.0
	–24	—	69	33.5	—	—	—	—	—
	–15	12.8	67	34.2	218	312	11	—	—
SBTX	–3	—	68	—	297	273	37	—	—
	7	—	63	37.4	102	72	12	—	—
	15	—	—	—	—	—	—	0.56	6.0
	22	—	77	35.4	227	132	9	1.08	—
	46	—	63	38.1	92	18	7	—	
	60	<5.0	51	26.3	129	12	6		—
	79	—	—	—	—	—	—	—	21.4
	170	<5.0	56	26.5	218	11	9	1.20	2.6
	319	<5.0	68	41.9	226	5	11	6.20	6.2
	496	<5.0	73	44.6	211	11	25	2.06	—
	689	6.0	68	—	133	10	8	4.23	12.1
	1025	<5.0	67	—	96	8	16	1.16	6.7
	1487	<5.0	69	44.0	62	10	13	1.37	2.0
	Donor								
SBTX	–24	—	88	48.7	315	15	11	—	—
	19	—	—	—	—	—	—	—	1.0
	170	<5.0	83	46.2	260	12	6	3.86	3.8
	319	<5.0	80	46.5	177	12	11	2.69	13.2
	496	—	—	45.0	—	—	—	2.92	6.4
	689	8.0	72	—	108	13	9	—	6.4
	1025	—	70	—	84	19	10	2.79	2.2
	1487	<5.0	71	42.0	60	13	10	3.20	—

AP, alkaline phosphatase; γ-GT, gamma glutamyltransferase; SBTX, small bowel transplantation (30 April 1998, day 0).

Hologic Inc, Waltham, Massachusetts, USA). At hospital admission, the future recipient showed a lower BMD of the total femur and femoral neck than the donor (0.785 and 0.727 *v* 0.865 and 0.785 g/cm^2), probably due to vitamin D and calcium malabsorption. Total BMC was similar between the twins.

Six months after SBTX, BMD of the total femur and femoral neck were reduced by 11.3% and 11.0% in the recipient and by only 3.9% and 2.9%, respectively, in the donor. Immobilisation and anticoagulation with heparin may explain the reduction in BMD in both boys at an age where we would expect an increase because of growth.[9 10] The more important reduction in BMD in the recipient than in the donor may have resulted from a less favourable ratio of absorption to intake, from the infectious thrombus which necessitated a right jugular thrombectomy and therefore led to immobilisation or, less likely, from reduced physical mobilisation due to dependence on PN. Total BMC remained stable in the donor but decreased in the recipient (−8.3%). The reductions in BMD and BMC in the recipient are likely a result of impaired intestinal function.

Between six and 49 months after SBTX, total femur and femoral neck BMD increased by 9.3% and 2.4%, respectively, in the donor and by 17.8% and 15.3%, respectively, in the recipient, and attained values before SBTX. The rise in BMD in the recipient may have resulted from higher adrenal androgen secretion.[11] Total BMC increased in both brothers as a result of growth (+26.4% in the recipient, +39.5% in the donor). Thus during this period of time, the recipient showed an increase in both BMC and BMD while the donor increased BMC but only slightly BMD. As BMD is expressed in g/cm^2, we deduced that the bone surface area increased more in the donor than in the recipient. Possibly, longitudinal bone growth prevailed in the recipient while longitudinal and transverse bone growth occurred in the donor.

Table 3 Evolution of plasma vitamins in the recipient and donor

	Day	Retinol (μmol/l) [N: 1.5–4.0]	Tocopherol (μmol/1) [N: 10–50]	Folates (nmol/1) [N: 6.6–35.4]	Cyanocobalamin (pmol/1) [N: 135–700]	25-hydroxyvitamin-D_3 (nmol/1) [N: 20–90]
	Recipient					
SBTX	–40	1.0	16	2.8	416	—
	53	—	—	17.5	217	—
	60	—	—	16.4	140	133
	166	2.0	13	1.7	187	60
	174	2.0	10	5.3	209	37
	319	2.0	11	14.3	301	54
	466	2.0	15	16.1	248	62
	689	2.2	12	14.2	261	73
	1025	1.9	11	22.1	385	36
	1487	2.0	12	18.1	430	51
SBTX	Donor					
	166	2.0	17	16.5	215	41
	319	2.0	15	>45	237	39
	466	3.0	21	33	212	61
	689	2.9	20	25.8	244	42
	1487	2.0	15	25.4	235	53

SBTX, small bowel transplantation (30 April 1998, day 0).

Table 4 Evolution of plasma minerals in the recipient and donor

	Day	Serum Fe (μmol/l) [N: 8–33]	Iron binding capacity (μmol/l) [N: 41–83]	Serum ferritin (μg/1) [N: 26–417]	Serum Mg (mmol/l) [N: 0.65–1.05]	Serum Ca (mmol/l) [N: 2.2–2.5]	Serum P (mmol/l) [N: 0.8–1.5]
	Recipient						
SBTX	–40	9	37	177	0.98	2.38	—
	11	7	82	—	0.89	2.45	1.92
	18	5	88	—	0.83	2.45	1.79
	25	5	82	51	0.76	2.47	1.88
	33	4	74	—	0.66	2.30	1.65
	41	10	80	—	0.73	2.38	—
	46	4	62	116	0.68	2.21	1.70
	53	5	58	68	0.82	2.22	1.72
	60	5	58	20	0.58	2.16	1.80
	174	13	70	23	0.68	2.23	1.65
	319	10	57	26	0.73	2.3	1.81
	406	18	67	57	0.72	2.34	1.74
	689	8	65	43	0.81	2.24	1.36
	1025	19	60	57	0.75	2.26	1.48
	1487	17	61	38	0.74	2.28	1.56
	Donor						
SBTX	–21	12	74	27	0.77	2.47	1.74
	167	9	77	13	0.8	2.6	1.54
	319	13	54	24	0.77	2.4	1.42
	406	10	59	43	—	—	—
	689	13	60	47	0.79	2.33	1.29
	1025	—	—	—	0.81	2.33	1.38
	1487	14	54	60	0.78	2.31	1.39

SBTX, small bowel transplantation (30 April 1998, day 0).

Laboratory tests

Before SBTX, the recipient showed high C reactive protein levels, possibly due to anaemia secondary to folate deficiency, and elevated liver function tests as a result of prolonged PN (day −3: aspartate aminotransferase 78 U/l, alanine aminotransferase 154 U/l), as shown in table 2. These values normalised after SBTX. Gut absorption was evaluated by xylose tests and measurements of faecal fat (table 2). In the recipient, plasma D-xylose, measured two hours after intake of 25 g of D-xylose, was still abnormally low after four years (1.37 mmol/l) and faecal fat was high until two years after SBTX (March 2001: 12 g/24 h). Plasma levels of calcium and phosphate were always within the normal range in the recipient. The donor always showed laboratory tests within the normal range except for one episode of high faecal fatty acids about 10 months after SBTX.

Plasma tocopherol and cyanocobalamin were within the normal range before and after SBTX (table 3). Plasma retinol and folates were below the normal range before SBTX (1.0 μmol/l and 2.8 nmol/l, respectively), probably as a consequence of malabsorption, but normalised immediately after SBTX. However, plasma folates were low again six months after SBTX (1.7 and 5.3 nmol/l) while the recipient was on a regular diet, and normalised definitively after nine months. The donor always showed vitamin values within the normal range. Mineral status is shown in table 4.

CONCLUSION

Following the first paediatric living related SBTX between monozygotic twins, the graft recipient became independent of PN, gained weight, and caught up with the height and fat free mass of his brother within three years. However, he still showed lower body fat mass and femoral bone mineral densities than his brother as of March 2001. Laboratory markers indicating malabsorption had not completely normalised four years after SBTX. This is the first time that the effect of SBTX on growth was observed without the confounding effect of immunosuppressive drugs.

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