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ORIGINAL ARTICLE

Weight gain and obesity after liver transplantation

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Summary

Excessive weight gain is common after liver transplantation and frequently leads to obesity. This has been attributed to immunosuppression. The aim of the present study was to assess the extent of weight gain and the risk factors for weight gain after liver transplantation. Height and estimated dry weight were collected prospectively in consecutive adult liver-transplant patients, transplanted between January 1996 and October 2001. A total of 597 patients (45% female, median age of 50 years; range 16–73) was studied. Eighty-six percentage was transplanted for chronic liver disease. The median weight gain at 1 and 3 years was 5.1 and 9.5 kg above dry weight pretransplant. By 1 and 3 years, 24% and 31% had become obese (defined as a body mass index (BMI) >30 kg/m^2). There was no significant difference in weight gain between the sexes, those who were obese before transplantation or those who received corticosteroids for >3 months. Weight gain was significantly greater ($P < 0.05$) in patients aged >50 years and those transplanted for chronic liver disease compared with fulminant liver failure. A pretransplant BMI >30 was a strong indicator that the patient would still have a BMI >30 at 3 years. There was no effect of the type of immunosuppression on weight gain. Obesity is common in the liver transplant population, but it seems to be unrelated to any specific immunosuppressive drug. The greatest weight gain occurs after the first 6 months and intervention with dietary advice at this point could be implemented to minimize the long-term morbidity and mortality risks associated with obesity.

Introduction

Improved survival after liver transplantation and the increasing numbers of liver transplants performed have meant that increasingly the long-term consequences of liver transplantation are becoming more evident. These include obesity, hyperlipidaemia, diabetes mellitus, renal dysfunction, hypertension and bone disease [1].

Cardiovascular complications arising post-transplant are an important cause of morbidity and mortality. Cardiovascular disease is the third most common cause of death in those recipients surviving the first year and accounts for up to 14% of deaths [2]. Johnston estimated that the excess incidence of ischaemic heart disease events and mortality is 7.9% over 10 years, but concluded that this was probably an underestimate of the increased risk [3]. Others, however, have reported that the incidence of cardiovascular disease in patients surviving 5 years is similar to the general population [4].

Weight gain after liver transplantation has been widely reported with about two-thirds of patients becoming obese soon after transplant [5]. There is much debate as to the cause of this weight gain, but several factors, including immunosuppressive drugs and a return of normal diet and appetite have been suggested. The aim of this study was to establish the nature and extent of any weight gain in the postliver transplant population and determine the contribution of these factors.

Methods

This prospective study was carried out using data collated by the Liver Unit at Queen Elizabeth Hospital on consecutive adult liver transplant patients between January

1996 and October 2001. Those who required a re-graft, were excluded.

Dry patient weight was assessed pretransplant, and 3 months, 6 months, 1 year, 2 years and 3 years post-transplantation. Where dry weight could not be calculated, an estimate of the weight was made where the amount of fluid in the ascites was estimated by measuring girth. Previous studies in our unit (Johnson *et al.*, unpublished observations) have shown an excellent correlation between estimated and measured dry weight, $P < 0.01$, $r = 0.95$. Dry weight was calculated as measured weight less estimated weight of ascites and oedema. For ascites, the weight was taken either from the volume removed at paracentesis or assumption from the degree of ascites (minimal 2.2 kg, moderate 6.0 kg and severe 14.0 kg) and the degree of peripheral oedema (mild 1.0 kg, moderate 5.0 kg and severe 10.0 kg) according to Wicks and Madden in A Practical Guide to Nutrition in Liver Disease, 1994, Liver Interest Group of the British Dietetic Association.

Obesity was classified using the World Health Organization (WHO) classification of obesity, which uses the body mass index (BMI) of patients, as calculated by weight (kg) divided by height (metres) squared. Underweight is defined as BMI <20 kg/m^2, overweight as BMI 25–30 kg/m^2, obese as BMI 30–40 kg/m^2 and morbidly obese as BMI >40 kg/m^2.

Immunosuppression: patients were started on combination therapy with a calcineurin inhibitor, azathioprine and corticosteroids (usually prednisone 20 mg/day and discontinued, where possible at 3 months). A prolonged course of steroids was defined as one lasting longer than 3 months after transplantation.

To assess the hypothesis that the observed weight gain resulted from a regain in body weight, which was previously lost as a result of a chronic disease process, a number of markers were identified. The mid-arm muscle circumference (MAMC) below the 25th centile was used as a proxy for nutritional impairment [6].

Statistical methods

SPSS (Inc., Chicago, Illinois, USA) for Windows version 11.5 was used.

Results

Patients

Among the 628 patients (54.5% male) who were eligible for the study, 31 (17 male, 14 female) were excluded, as they had required re-grafting, leaving 597 patients (45% male) for the study. Of these, 85 (14%) patients were transplanted for fulminant liver failure and 512 (86%) for chronic liver disease. The median age at transplant was 50 years (range 16–73). Of these, 332 (56%) had ascites at the time of transplant but in nine (1.5%), the presence of ascites was not recorded. The median follow up was 35.2 months (range 0–77.9) and 21.9% died during the study period. Three hundred and thirty-two (55.6%) of the included patients had ascites, 256 (42.9%) had no ascites and in nine (1.5%) patients the presence of ascites was unrecorded. Of those with ascites, 164 had their dry weight estimated, equivalent to 27.5% of the study population.

Identification and timing of patients at weight gain and obesity

The weight gain and change in BMI in all patients is shown in Tables 1 and 2. Overall, there was an initial weight loss, followed by a steady increase during the first 3 years after liver transplantation. The most rapid weight gain occurred within the first year after liver transplantation. Almost one-third of the patients became obese by 3 years after transplantation. There was no significant difference in weight gain or the incidence of obesity between men and women ($P < 0.05$). Those aged >50 years had gained more weight by 2 years than younger patients ($P < 0.05$), but there was no significant difference by 3 years ($P > 0.05$).

Regain of weight loss or excessive weight gain?

Overall, 31% of patients became obese and 67% became overweight or obese by 3 years, compared with only 13%

Table 1. Weight gain after liver transplantation.

Weight gain after transplantation (kg)	Median	Minimum	Maximum	25th centile	75th centile
At 3 months	−0.8	−29.9	35.9	−6.7	4.4
At 6 months	1.8	−25.0	43.0	−4.7	7.0
At 1 year	5.1	−24.2	31.2	−0.3	11.4
At 2 years	8.2	−26.6	46.0	1.8	15.6
At 3 years	9.5	−14.5	40.6	2.8	16.4

Table 2. Body mass index (BMI) following transplantation.

	BMI value			
Classification	Underweight (<20 kg/m^2)	Optimal (20–25 kg/m^2)	Overweight (20–25 kg/m^2)	Obese (>30 kg/m^2)
At transplant	63 (10.6%)	263 (44.2%)	194 (32.6%)	75 (12.6%)
At 3 months	59 (12.3%)	236 (49.4%)	136 (28.5%)	47 (9.8%)
At 6 months	47 (10.5%)	184 (41.2)	151 (33.8%)	65 (14.5%)
At 1 year	30 (7.5%)	140 (34.9%)	136 (33.9%)	95 (23.7%)
At 2 years	21 (6.5%)	98 (30.4%)	109 (33.9%)	94 (29.2%)
At 3 years	17 (6.9%)	65 (26.2%)	90 (36.3%)	76 (30.6%)

and 45%, respectively, at the time of transplant. A total of 313 (52%) patients had pretransplant MAMC data recorded in their dietetic notes; 46.3% were below the 25th centile. The nutritionally impaired group were not significantly more likely to gain more weight ($P > 0.05$). The obese population lost significantly more weight ($P < 0.05$) than the nonobese in the first 6 months, but by 1 year there was no statistical difference in the weight gain between these two groups (Fig. 1, Table 3). Of those who were not obese at transplantation, 15.5% became obese at 1 year after transplantation and 26.3% at 3 years (Table 4).

Patients transplanted for fulminant liver failure initially lost more weight after transplantation in the first 6 months and then gained less weight by 3 years post-transplantation than those with chronic liver disease ($P < 0.05$) (Table 5).

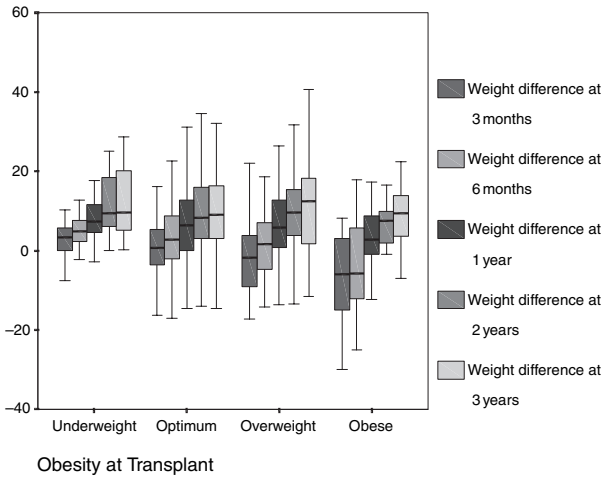

Figure 1 Weight gain (in kg) by pretransplant body mass index grouping.

Role of immunosuppression in weight gain

Corticosteroids

One hundred and seventy-five patients (35%) were treated with corticosteroids for more than 3 months. There was no difference in weight gain between those who did and did not receive corticosteroids for more or less than 3 months.

Tacrolimus and cyclosporin

Two hundred and eleven patients were treated with tacrolimus, of whom four were changed to cyclosporin; 311 were treated with cyclosporin, of whom 67 were switched to tacrolimus. Patients treated with cyclosporin were more likely to have gained more weight by 1 year post-transplant ($P < 0.05$), but by 2 years there was no

Table 3. Weight gain (in kg) by pretransplant body mass index (BMI) grouping.

BMI at transplant	Weight difference	Median	Minimum	Maximum	25th centile	75th centile
BMI <20 (underweight)	At 3 months	3.7	−9.8	17.4	−0.1	7.8
	At 6 months	5.3	−9.1	19.1	0.9	8.3
	At 1 year	7.3	−8.7	24.5	3.9	12.3
	At 2 years	11.1	−1.2	25.8	6.7	20.4
	At 3 years	9.7	−2.9	28.6	4.7	17.5
BMI 20–25 (optimum BMI)	At 3 months	0.2	−19.1	35.9	−4.1	4.4
	At 6 months	2.2	−21.2	43.0	−2.6	7.25
	At 1 year	4.5	−21.2	31.2	−0.5	11.0
	At 2 years	7.2	−20.3	46.0	0.4	14.0
	At 3 years	8.8	−14.5	37.1	1.2	14.6
BMI 25–30 (overweight)	At 3 months	−3.1	−24.7	22.0	−10.5	2.4
	At 6 months	0.0	−22.0	18.7	−6.4	6.2
	At 1 year	4.6	−20.30	26.8	−1.0	11.6
	At 2 years	9.6	−26.6	37.6	0.6	15.6
	At 3 years	11.7	−11.6	40.6	1.4	17.8
BMI <30 (nonobese)	At 3 months	−0.3	−24.7	35.9	−6.37	4.4
	At 6 months	2.3	−22.0	43.0	−3.68	7.0
	At 1 year	5.4	−21.2	31.2	0.0	11.5
	At 2 years	8.2	−26.6	46	2.0	15.7
	At 3 years	9.5	−14.5	10.6	2.7	16.5
BMI >30 (obese)	At 3 months	−4.1	−29.9	11.6	−12.2	2.6
	At 6 months	−1.0	−25.0	17.9	−18.1	6.7
	At 1 year	2.9	−24.1	28	−2.9	9.9
	At 2 years	7.3	−16.3	39.6	0.0	14.5
	At 3 years	9.4	−6.9	38	3.4	14.8

Table 4. Incidence of obesity in those who were nonobese [body mass index (BMI) 30 kg/m^2] at transplant.

	Underweight	Optimum	Overweight	Obese
At transplant	12.1%	50.6%	37.3%	0%
At 3 months	14.0%	55.1%	27.8%	3.1%
At 6 months	12.0%	46.8%	34.3%	6.9%
At 1 year	8.2%	39.4%	36.9%	15.5%
At 2 years	7.2%	33.1%	36.5%	23.2%
At 3 years	7.3%	28.0%	38.4%	26.3%

Table 5. Weight gain in patients transplanted for fulminant liver failure and chronic liver disease.

Fulminant versus chronic	Time after transplant	Median	Minimum	Maximum	25th Centile	75th centile
Fulminant	3 months	−5.1	−22.6	15.7	−9.6	0.4
($n = 85$;	6 months	−4.1	−24.7	20.0	−9.95	1.8
14.2%)	1 year	−0.7	−21.2	26.2	−8.2	4.5
	2 years	1.7	−20.3	32.0	−6.7	9.1
	3 years	4.5	−14.5	31.9	−5.8	9.0
Chronic	3 months	0.2	−29.9	35.9	−6.1	4.7
($n = 512$;	6 months	2.8	−25.0	43.0	−3.3	7.2
85.8%)	1 year	5.9	−24.1	31.2	0.4	11.9
	2 years	9.0	−26.6	46	3.0	16.3
	3 years	10.7	−12.8	40.6	3.6	17.3

Table 6. Weight gain in patients on tacrolimus only versus cyclosporin only.

	Weight difference	Median	Maximum	Minimum	25th Centile	75th Centile
Cyclosporin	At 3 months	−.05	23.60	−25.10	−5.85	4.83
	At 6 months	2.60	25.90	−25.00	−2.40	7.90
	At 1 year	6.20	31.20	−21.20	.70	11.80
	At 2 years	8.80	46.00	−26.60	2.10	16.43
	At 3 years	10.20	40.60	−14.50	3.25	17.15
Tacrolimus	At 3 months	−1.40	35.90	−25.90	−6.80	3.90
	At 6 months	.50	43.00	−24.70	−5.65	5.70
	At 1 year	3.95	26.80	−24.10	−2.02	9.20
	At 2 years	7.20	34.70	−18.00	.60	12.10
	At 3 years	9.10	27.70	−7.90	1.90	14.90

significant difference in the observed weight gain ($P > 0.05$) (Table 6).

Discussion

Patients gained approximately 5 kg within 1 year and almost 10 kg by 3 years after liver transplantation, with approximately 30% becoming obese. This is a similar rate to that quoted in a number of other studies. There was no significant difference in weight gain between the sexes, but older patients (as in the general population) were at an increased risk of gaining more weight. We have not studied other factors that might be associated with excess weight gain such as socio-economic class, family history or occupation. We were not able to study in greater detail the extent of weight gain because of fat rather than an increase in muscle mass. There are many theories about why patients gain weight after liver transplantation and become obese. These include the regaining of weight loss as a result of malnutrition and chronic disease, and weight gain as a result of immunosuppression and overeating.

Not all liver allograft recipients gained weight and, of those who gained weight, the extent of weight gain varied (Table 7). Overall, by 1 year 5.7% and by 3 years 15.7% had gained more than 30% of their original pretransplantation weight. In both cases, this represented an excessive weight gain with 91.3% (52.2%) and 97.4% (64.1%) becoming overweight (obese). In contrast. at 1 and 3 years, 10% and 5.6% had lost weight by more than 10%. There was no significant difference found in weight gain in these patients between the sexes, in those taking prolonged courses of steroids, on different immunosuppression regimen, between age groups or between fulminant and chronic aetiology. This population, in particular, would be likely to benefit mostly from aggressive management of their weight gain with dietetic input in order to minimize the long-term morbidity and mortality associated with obesity.

Patients regained the weight that was lost pretransplant; this weight loss occurs for several reasons including decreased food intake because of anorexia, nausea and vomiting and sometimes dietary advice. This is most profound in patients with chronic disease and especially those with alcohol-related liver disease. Problems such as malabsorption and maldigestion further have an impact on the effectiveness of intake. Metabolism may also be disturbed because of altered liver function. Hypermetabolic states frequently exist in patients with chronic liver disease.

Before transplantation, patients are often encouraged to eat a high calorie diet as they are in a hypermetabolic state and may not adapt their diet after transplantation to take into account their reduced metabolic needs. Hence, after transplantation they gain excessive amounts of weight and become overweight and obese. The loss of afferent and efferent pathways between the liver and the hypothalamus, and therefore, the liver's role in metabolic homeostasis may delay postprandial satiety and hence directly influence the overeating observed. No conclusive data to date have been able to establish whether this does have an effect on food intake, body weight or meal

Table 7. Percentage weight change.

Percentage weight change	3 months	6 months	1 year	2 years	3 years
−100% to −30%	1 (0.2%)	0 (0%)	1 (0.2%)	0 (0%)	0 (0%)
−30% to −20%	23 (4.8%)	15 (2.9%)	10 (2.5%)	8 (8.5%)	1 (0.4%)
−20% to −10%	88 (18.4%)	63 (14.1%)	30 (7.5%)	20 (6.3%)	13 (5.2%)
−10% to 10%	294 (61.5%)	257 (57.6%)	194 (48.4%)	108 (34.1%)	80 (32.3%)
10–20%	56 (11.7%)	88 (19.7%)	98 (24.4%)	86 (27.1%)	69 (27.8%)
20–30%	12 (2.5%)	15 (3.4%)	45 (11.2%)	45 (14.2%)	46 (18.5%)
30–100%	4 (0.8%)	10 (2.2%)	23 (5.7%)	50 (15.8%)	39 (15.7%)
Total	478	448	401	317	248

patterns [7–9]. Patients generally eat more because of improved psychological well-being and so their appetite may improve, possibly to the extent of overeating.

In this study, we have not evaluated the metabolic consequences of this rise in obesity, from an initial pretransplant obese level of 12.6%. By 3 years, more than 30% patients were obese which is greater than that seen in the overall UK population, as the incidence of obesity in the UK is between 20.3–21.3% across all age groups older than 16 in both sexes [10]. Previous studies from our unit looking at the prevalence of and risk factors for developing diabetes post-transplant have found that older age and use of tacrolimus were the significant risk factors. Obesity (BMI >30) was associated with the onset of diabetes, but this was not statistically significant (Perrin and Gunson, unpublished observation). However, this population is probably not representative of the liver transplant population as a whole and ideally patients should also be matched for other characteristics including socioeconomic class. The weight gain post-transplant is excessive and not purely a regain of weight lost previously through chronic illness. Patients transplanted for fulminant liver failure gained significantly less weight than those transplanted for chronic liver disease, consistent with the theory of regaining lost weight. In order to have a complete picture of the nutritional state of the patients included in the study, it would have been preferable to have a more comprehensive dietetic assessment of the patients, allowing more accurate interpretation of the type of weight gained by patients, i.e. muscle versus fat. Along with the MAMC, dry weight and BMI, other useful data would include estimations of the lean body weight, bioelectrical impedence analysis and nutrition intake and exercise charting.

Weight gain after liver transplantation was found to be independent of commonly used immunosuppressive regimens. Corticosteroids were discontinued in nearly two-thirds of the patients by 3 months and a prolonged course was found not to cause a significant difference in weight gain. It is widely thought that the hyperphagic effects of steroids after liver transplant may be the prime cause of weight gain [11]. However, some series note that weight gain continues despite tapering down the steroid dose [12]. It has been reported that relatively low doses of prednisolone daily (such as 5 mg daily) do not cause metabolic complications such as obesity [13].

Several studies have observed that there is a decreased incidence of obesity after liver transplantation in patients taking tacrolimus compared with those on cyclosporin [14]. However, in this study cyclosporin was found to cause increased weight gain compared with tacrolimus only in the first year after transplantation, but not in the long term.

It is reasonable to counsel patients in advance of and after their liver transplantation about the risks of excessive weight gain and possible lifestyle changes that may need to be made in an attempt to avoid the risks of obesity. This advice would be the most beneficial within the first year after transplantation, the time of the most rapid weight gain.

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