Excessive Weight Gain and Obesity in Australian Liver Transplant Patients

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ABSTRACT

Aim: To examine the direction and magnitude of weight change post liver transplant in an Australian cohort and investigate whether there are any factors that predict weight change in this group.

Methods: This study was a retrospective case note audit of liver transplant patients. Height and weight measurements were collected pre-transplant, four months post transplant and yearly thereafter. A repeated measures ANOVA was undertaken to determine the direction and magnitude of weight change after transplantation, and multivariate logistic regression was used to examine any pre-transplant risk factors for post transplant obesity. Statistical significance was set at $p<0.05$.

Results: A total of 101/207 eligible patients were included in this study on the basis of the inclusion criteria. These patients underwent orthotopic liver transplantation between March 1996 and December 2008. Due to missing data, the logistic regression analysis and repeated measures ANOVA were only conducted on 88 patients. Mean weight gain after three years was 7.8kg, or 10% of pre-transplant body weight ($p<0.001$). The incidence of obesity increased continually from the time of transplant to seven years post transplant. By year two, 43% of patients were obese, which is almost double the percentage of patients who were obese at the time of transplant (23%). The only statistically significant factor that predicted obesity at three years post transplant was obesity at the time of transplant ($p<0.001$).

Conclusion: Weight gain after orthotopic liver transplantation was significant and occurred most rapidly in the first two years. The most reliable predictor of post transplant obesity was pre-transplant obesity.

Keywords: orthotopic liver transplantation, overweight, obesity, excessive weight gain

INTRODUCTION

Liver disease, in all its forms, is one of the most common diseases of the digestive system, accounting for 1,490 (1%) of all registered deaths in Australia in 2008 [1]. Orthotopic liver transplantation is the primary therapy for end-stage liver disease, and is effective in reducing morbidity and mortality, and improving quality of life [2]. In Australia and New Zealand, the number of procedures per year has steadily increased over past decades and in 2009, 211 new and 17 secondary transplants were performed [3]. Despite the increase, there are still a number of patients in waiting. The most recent statistics indicate that 164 patients were on the waiting list for transplantation at the end of 2009 [3]. Waiting time is dependent upon blood type and can range from approximately 65 days (type AB) to 143 days (type B) [3].

The cost of liver transplantation is substantial, with an estimated $125,000 spent per transplant, not including long-term follow-up [3]. Fortunately, in Australia patient survival rate is relatively high, with an average of 93% at 1 year, 80% at 5 years, and 71.5% at 10 years, so although the cost is considerable there are long-term benefits [4]. However, for patients who are obese, post transplant outcomes are much poorer [5]. A number of studies have found increased morbidity and mortality in obese patients post liver transplant compared to non-obese patients [5-8]. One study in particular reported a mortality rate of 65% in the first 2 years after transplantation in obese patients, and in all cases the cause of death was related to a condition for which obesity is an increased risk factor [5]. According to American data, it is common for post liver transplant patients to experience excessive weight gain, resulting in obesity and other associated co-morbidities [9, 10]. Currently, it is uncertain whether a similar

trend exists in the Australian liver transplant population. Therefore, the first aim of the present study was to investigate the direction and magnitude of weight change post liver transplant in an Australian cohort.

Moreover, there is limited research in the area of obesity treatment in this population. Thus far, four case reports have demonstrated positive outcomes from bariatric surgery post liver transplant. For example, one patient lost 25 percent of their pre-transplant body weight within 6 months of undergoing a Roux-en-Y biliary reconstruction and a sleeve gastrectomy [8], one patient lost 39 percent and another 50 percent of their pre-transplant body weight 18 months after undergoing a Roux-en-Y gastric bypass [11]. The latter two patients also experienced normalisation of liver enzymes, lipids and glucose levels and regression of hepatic dysfunction 8-10 months after surgery [11]. Another patient had a BMI of 54kg/m^2 before undergoing a Roux-en-Y gastric bypass and four months after their BMI was 43kg/m^2; in addition, their diabetes and hypertension had resolved [12]. Furthermore, one case report showed that bariatric surgery performed at the same time as liver transplantation also produced positive outcomes [13]. At 6 months following surgery, the patient had lost 45% of their baseline body weight, falling from a BMI of 42kg/m^2 to 34kg/m^2 [13]. In addition, blood glucose levels and blood pressure normalised, venous stasis improved and symptoms from sleep apnoea subsided [13]. In order to determine whether early intervention should be instigated, the second aim of this study was to investigate whether there are any factors that predict weight change in post liver transplant patients. From this knowledge, practitioners may be able to identify at risk patients and intervene early on to manage the problem more proactively.

MATERIALS AND METHODS

A total of 207 patients underwent orthotopic liver transplantation between October 1992 and February 2011, so were considered eligible for the present study. Patients were selected based on the following criteria: successful liver transplantation, recorded height measurement, and weight measurements before transplant, four months after transplant and yearly thereafter for at least 3 years. Data was taken from patient case notes and dietetic patient cards. All data was collected as close to the target dates as possible, and when recording weights the presence of ascites and/or oedema was accounted for. Body Mass Index (BMI) was calculated for each weight recorded.

Other variables were also collected in order to identify predictors of weight change. These included aetiology of liver disease; sex; race; age at liver transplant; marital status; obesity at the time of transplant, which was measured as a BMI greater than or equal to 30kg/m^2; and the presence of type 2 diabetes mellitus and/or hypertension at the time of transplant. All of this information was obtained from the case notes.

Definitions

Overweight and obesity were classified using body mass index, which is weight in kilograms divided by height in meters squared [14]. The categories outlined by the World Health Organisation were used – BMI: 25-29.9kg/m^2 equals overweight, BMI: 30-34.9kg/m^2 equals obese, and BMI: greater than or equal to 35kg/m^2 equals severe obesity [14].

Ascites was defined in accordance to severity: 2kg, 5kg or 14kg were subtracted for slight, moderate or gross fluid retention, respectively [15]. In cases where a dry weight was given, or a weight history, the appropriate number of kilograms was subtracted.

Hypertension was defined as a diastolic blood pressure greater than 90mmHg and/or a systolic blood pressure greater than 140mmHg, or the need for antihypertensive medications [16].

Ethical Considerations

Ethics approval was granted by the Southern Adelaide Flinders Clinical Human Research Ethics Committee. All data were presented as summaries so that no individual patient was able to be identified.

Statistical Analysis

Microsoft Office Excel 2003 was used to document all raw data during the data collection phase. Subsequently, PASW Statistics 2009 (Chicago, Illinois, USA) version 18.0 was used for data analysis. Descriptive statistics were calculated to determine the characteristics of the sample population at the time of liver transplant. Repeated measures analysis of variance (ANOVA) was undertaken to determine the direction and magnitude of weight change after liver transplantation, and multivariate logistic regression was used to explore the impact of potential risk factors on obesity after transplant. All variables were loaded into a multivariate model to begin with and those with $p \geq 0.2$ were eliminated. Univariate logistic regression was then undertaken to determine the individual relationships between each variable and obesity at three

years post transplant. The final multivariate model contained those variables that were most significant in the original multivariate model and the univariate models. Both the logistic regression analysis and repeated measures ANOVA included all patients with full data up to three years post transplant, because this was the time period used in previous research [10] and provided the largest sample size with the data available. The level of statistical significance in this study was $p<0.05$.

RESULTS

Patients

Of the 207 patients eligible for this study, data was collected for 101 patients on the basis of the inclusion criteria. These patients were transplanted between March 1996 and December 2008. Due to missing data, the logistic regression analysis and repeated measures ANOVA were only conducted on 88 patients, equating to 87% of patients included in the study and 43% of those who were eligible. For the majority of patients, pre-transplant weight was recorded two weeks to one month prior to transplant. For five patients, the only pre-transplant weight available was recorded greater than five months prior to transplant. The mean BMI of the patients studied was 26.4kg/m^2 before transplantation and 23% were obese (See Table 1). Almost half of the patients were aged 50 years or over at the time of transplant and 68.3% were male. A total of 59 (58%) patients had ascites at the time of transplant, 36 had no ascites and for six the presence of ascites was not recorded. Table 1 further describes patient characteristics at the time of liver transplantation.

Weight change post transplant

Figure 1 illustrates the mean weight at different time points before and after liver transplantation. For comparison, figure 2 depicts the same sequence for BMI. The mean weight gain from before liver transplant to three years after was 7.8kg, or 10% of pre-transplant body weight. This weight change was statistically significant, as indicated by the results of the repeated measures ANOVA ($p<0.001$). In particular, weight gain in the second and third year after transplant (7.5kg and 7.9kg, respectively) was statistically significant when compared to pre-transplant weight, according to the Bonferroni post-hoc analysis ($p<0.001$).

In regards to obesity, the incidence increased continually from before transplant to seven years post transplant. By year two, 43% of patients were obese, which is almost double the percentage of patients who were obese at the time of transplant (23%). At four years, 46% (31/67) of patients were obese. The rate dropped to 41% (22/54) at five years, and then increased to 51% (18/35) at seven years post transplant.

Pre-transplant factors predicting post transplant obesity

Multivariate logistic regression and univariate logistic regression were undertaken and variables with $p\leq0.2$ were noted and entered into a final multivariate model. Table 2 depicts the variables that were most significant. The only statistically significant factor that predicted the prevalence of obesity at three years post liver transplant was obesity at the time of transplant (RR:61.75 (95% CI:6.91-552.05); $p<0.001$). For those aged 40-49 years at the time of liver transplant, the likelihood of becoming obese after three years was four times greater than those younger and three times greater than those older. Married patients and those with type 2 diabetes were more likely to be

obese after three years compared to unmarried patients and non-diabetics respectively, but these results were not statistically significant (p=0.18 and p=0.38, respectively). Patients whose liver disease was caused by hepatitis were three times more likely to become obese after transplant compared to those who had alcohol-related liver disease. Compared to this same group, it was less likely for those whose liver disease was caused by cancer, genetics or was cholestatic to become obese after transplant. The results related to aetiology were not significant, as indicated in Table 2.

DISCUSSION

The results of the present study clearly demonstrate a significant increase in weight after liver transplantation. After three years, patients gained an average of 7.8kg, which is approximately 10% of their pre-transplant body weight. The most rapid weight gain occurred within the first two years after transplantation, and this is consistent with the findings of six other studies [9, 10, 17-20]. There was a distinct trend in weight change post liver transplant, with an initial loss of weight in the first four months, followed by a steady increase in the subsequent three years, and then weight appeared to plateau until seven years (Figure 1). The rate of obesity increased by almost 50% two years after transplant, with 23% obese at the time of transplant and 43% two years post transplant. Once again, similar trends in weight change and obesity were seen in two other studies [10, 17].

The average BMI at time of transplant and three years after was 26.4kg/m^2 and 29.2kg/m^2, respectively. Very similar findings were seen in a much larger study with a mean BMI of 24.8kg/m^2 at the time of transplant (n=774) and mean BMI of

28.6kg/m^2 three years post transplant (n=203) [10]. This similarity indicates that even though the sample size of the present study was quite small, the trend discovered may accurately represent that of the larger liver transplantation population.

Current international literature indicates that obesity is common after liver transplantation [8, 10-12]. Consequently, there are now a number of American case reports on liver transplant patients who have undergone bariatric surgery during or after liver transplantation. To date, gastric banding, Roux-en-Y biliary reconstruction with a sleeve gastrecomy, and laparoscopic Roux-en-Y gastric bypasses have been undertaken on liver transplant patients all with successful outcomes of weight loss and normalisation of metabolic complications, as referred to previously [8, 11-13].

According to the Obesity Surgery Society of Australia and New Zealand, the criteria for bariatric surgery includes one or more of the following: BMI greater than 40kg/m^2 or greater than 35kg/m^2 with co-morbidities such as diabetes, hypertension and/or sleep apnoea; a history of weight loss attempts; aged between 18-65; and the capacity to understand the commitment and risks of surgery [21]. On this basis, the results of the present study indicate that whilst there is a problem with significant weight gain after transplantation, it may not be to the extent of requiring bariatric surgery. The mean BMI of patients appeared to plateau at a BMI of 29-30kg/m^2, which is under the cut-off for bariatric surgery in Australia. A more suitable strategy may be to begin counselling patients immediately after transplantation regarding the high risk of obesity, and the lifestyle, dietary and behaviour modifications that are required to avoid this, and continue frequent follow up appointments over the next 1-2 years. The evidence from this study and previous research [17] suggest that patients begin to gain

weight around four to six months after transplant and then gain weight rapidly over the subsequent two years; therefore, beginning counselling early and maintaining regular appointments thereafter may help avoid or lessen excessive weight gain.

This study found that obesity at the time of transplantation statistically significantly increased the risk of obesity after transplantation ($p<0.001$). Whilst other factors such as age, aetiology of liver disease, marital status and type 2 diabetes did have an effect on the incidence of obesity after transplant, none of these results were statistically significant. Similar to the present study, Palmer et al. found that obesity prior to transplant predicted obesity after transplant ($p<0.005$) [9]. In addition, Everhart et al. found that increased pre-transplant BMI, increased donor BMI and being married were all significantly associated with obesity two years after transplant ($p=0.0001$, $p=0.03$ and $p=0.02$, respectively) [10]. Similar to the results of this study, another study found that older persons had a higher risk of obesity compared to younger persons and patients diagnosed with hepatitis had the highest incidence of obesity, though in both studies these results were not statistically significant [10]. Everhart's findings in regards to marital status were consistent with that of the present study and the general population; married individuals appear to have a higher incidence of obesity compared to individuals who are not married [10, 22-24].

The differing results and lack of significant findings in the present study may have been attributed to the small sample size, which was one of the primary limitations of this study. Unfortunately, because of the inclusion criteria, more than half of the eligible patients were unable to be included. Furthermore, there were a number of patients with missing data, but due to time constraints, a time censored model was

unable to be used for analysis, so all patients with missing data had to be excluded. Although the number of patients in this study was relatively small, the median sample size in the current literature is 93 patients. Therefore, the present study is still comparable to others in the field.

Another limitation of the present study was the probable inaccuracy of weight measurements. First of all, there was no consistent method of how patients were weighed – clothed or unclothed, fasted or not, hydrated or not, type of scales used. Therefore, the measurements recorded in the case notes likely contained some degree of error. Furthermore, for patients with ascites, dry weight may not have been accurately estimated, because in some cases the degree of ascites was recorded as symbols, such as '+' or '++' and in other cases as words, such as 'gross' or 'severe', 'moderate' or 'slight'. Descriptions were inconsistent and therefore may have been interpreted inaccurately. In addition, in some cases the closest pre-transplant weight, which was used for the baseline weight, was recorded several months prior, in which time weight could have changed markedly. Finally, in some cases there was no information regarding ascites and/or oedema, so error may have been introduced in these cases.

In conclusion, weight gain after orthotopic liver transplantation was significant and occurred most rapidly in the first two years. Moreover, the most reliable predictor of post transplant obesity was pre-transplant obesity. Whilst obesity is common amongst liver transplant patients, it does not appear to be extensive enough for surgical intervention. Rather, early patient counselling regarding the high incidence and risk of obesity post transplant and the dietary, lifestyle and behavioural modifications

required to avoid this, in addition to frequent follow ups over the first 1-2 years may be most beneficial. Future research investigating the reasons why patients gain weight, including any effects of immunosuppressant medications, will add to the present findings and assist in the attempt to improve current outcomes.

Table 1. **Patient characteristics at time of liver transplant**

	Frequency n (%)
All	101
Sex	
Male	69 (68.3)
Female	32 (31.7)
Race	
Caucasian	88 (87.1)
Other (incl. Asian, Australian Aboriginal, Other)	13 (12.9)
Age at LT (years)	
18-39	13 (12.8)
40-49	27 (26.7)
≥50	48 (47.5)
Married	
Yes	69 (68.3)
No	32 (31.7)
T2D at time of LT	
Yes	37 (36.6)
No	64 (63.4)
HTN at time of LT	
Yes	30 (29.7)
No	71 (70.3)
Obesity at time of LT	
Yes	23 (22.8)
No	78 (77.2)

Abbreviations: LT, Liver transplantation; T2D, Type 2 diabetes; HTN, Hypertension

Table 2. **Potential pre-transplantation risk factors for obesity[(a)] 3 years after liver transplantation**

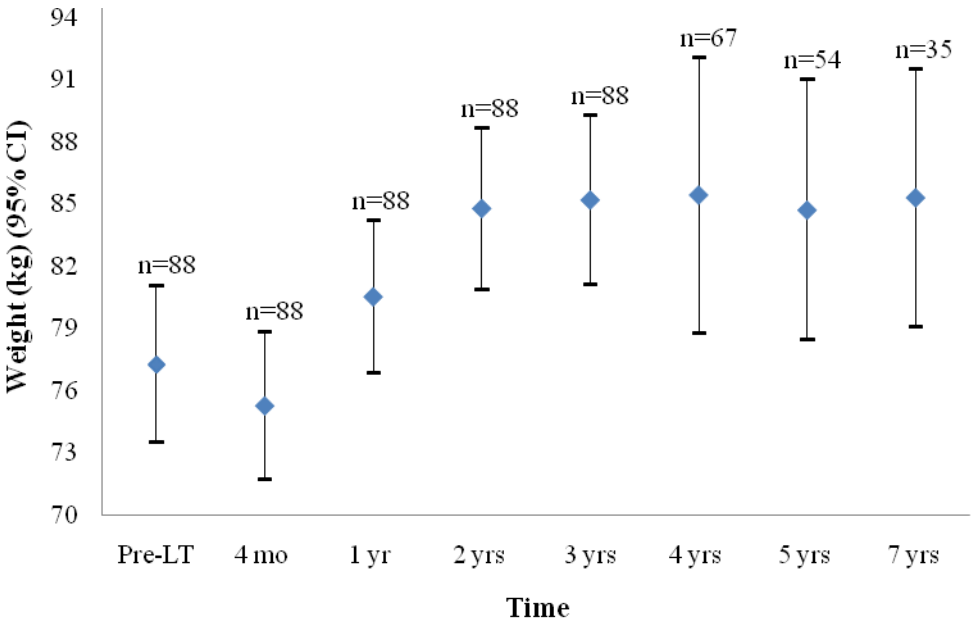
	N	Relative Risk (95% CI)	*P*
All	88		
Married			
No	30	1.00	
Yes	58	2.48 (0.66-9.25)	0.18
Obesity at time of LT			
No	69	1.00	
Yes	19	61.75 (6.91-552.05)*	<0.001
Age (years)			
18-39	13	1.00	0.25
40-49	27	4.18 (0.77-22.81)	0.10
≥50	48	1.19 (0.34-4.15)	0.79
T2D at time of LT			
No	56	1.00	
Yes	32	1.68 (0.53-5.37)	0.38
Aetiology			
Alcohol Related	24	1.00	0.15
Hepatitis	32	3.02 (0.70-13.10)	0.14
Other (incl. Cancer, Genetic, Cholestatic, Unknown Origin)	32	0.80 (0.21-2.98)	0.73

Results from the multivariate logistic regression

Abbreviations: CI, Confidence Interval; LT, Liver transplantation; T2D, Type 2 diabetes

[(a)]Obesity defined as BMI≥30kg/m^2

*Statistically significant at $P<0.05$



*An ANOVA was only completed for the first 3 years post transplant due to sample size restrictions

Figure 1. **Mean Body Weight before and after Liver Transplantation**

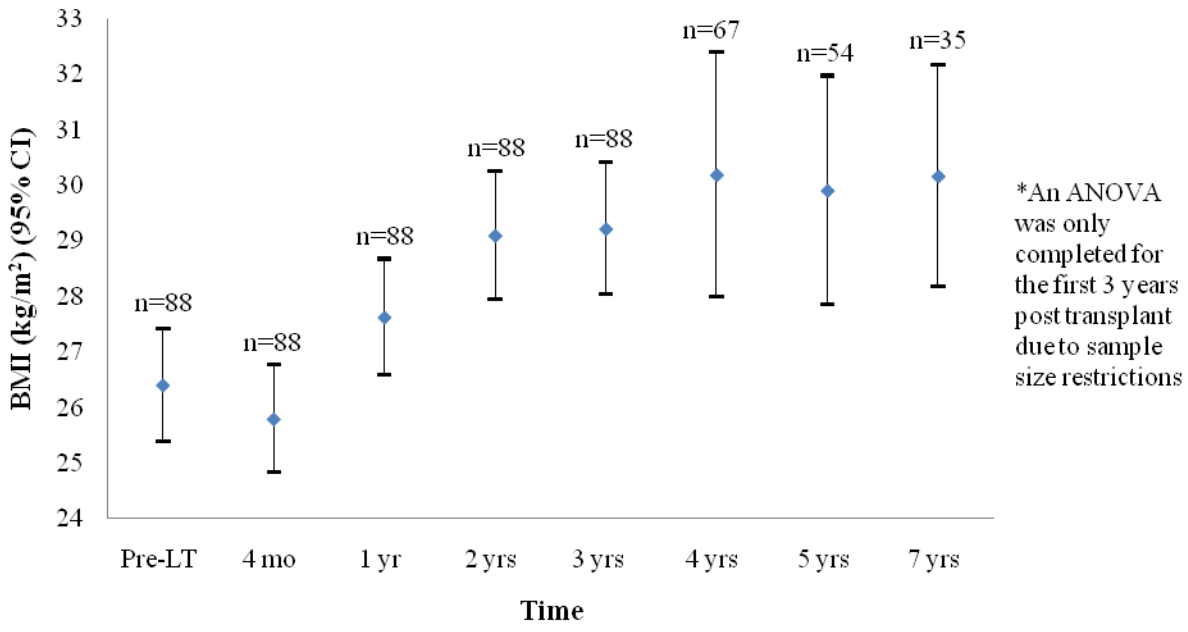


Figure 2. **Mean Body Mass Index before and after Liver Transplantation**

REFERENCES

1. **Diseases of the digestive system** [http://www.abs.gov.au/ausstats/abs@.nsf/Products/5B4583E4556F5C36CA2576F600123861]
2. Sutocky JB, S: **End stage liver disease (ESLD): Morbidity, Mortality, and Transplantation**. In. Edited by Services H. California; 2005.
3. ANZLT: **Australia and New Zealand Liver Transplant Registry 21st Report**. In. Edited by Lynch S, Balderson, GA. Brisbane; 2009.
4. ANLTU: **Liver Transplantation at Australian National Liver Transplantation Unit**. In. Sydney; 2010.
5. Hillingso JG, Wettergren A, Hyoudo M, Kirkegaard P: **Obesity increases mortality in liver transplantation--the Danish experience**. *Transpl Int* 2005, **18**(11):1231-1235.
6. Nair S, Cohen DB, Cohen C, Tan H, Maley W, Thuluvath PJ: **Postoperative morbidity, mortality, costs, and long-term survival in severely obese patients undergoing orthotopic liver transplantation**. *Am J Gastroenterol* 2001, **96**(3):842-845.
7. Nair S, Verma S, Thuluvath PJ: **Obesity and its effect on survival in patients undergoing orthotopic liver transplantation in the United States**. *Hepatology* 2002, **35**(1):105-109.
8. Butte JM, Devaud N, Jarufe NP, Boza C, Perez G, Torres J, Perez-Ayuso RM, Arrese M, Martinez J: **Sleeve gastrectomy as treatment for severe obesity after orthotopic liver transplantation**. *Obes Surg* 2007, **17**(11):1517-1519.
9. Palmer M, Schaffner F, Thung SN: **Excessive weight gain after liver transplantation**. *Transplantation* 1991, **51**(4):797-800.
10. Everhart J, Lombardero, M, Lake, JR, Wiesner, RH, Zetterman, RK & Hoofnagle, JH **Weight change and obesity after liver transplantation: incidence and risk factors**. *Liver Transplantation and Surgery* 1998, **4**(4):285-296.
11. Duchini A, Brunson ME: **Roux-en-Y gastric bypass for recurrent nonalcoholic steatohepatitis in liver transplant recipients with morbid obesity**. *Transplantation* 2001, **72**(1):156-159.
12. Tichansky DS, Madan AK: **Laparoscopic Roux-en-Y gastric bypass is safe and feasible after orthotopic liver transplantation**. *Obes Surg* 2005, **15**(10):1481-1486.
13. Campsen J, Zimmerman M, Shoen J, Wachs M, Bak T, Mandell MS, Kam I: **Adjustable Gastric Banding in a Morbidly Obese Patient During Liver Transplantation**. *Obes Surg* 2008, **18**(12):1625-1627.
14. WHO: **Report of WHO Expert Committee on Physical status: the use of interpretation of anthropometry**. In. Geneva; 1995.
15. Wicks CM, A: **A practical guide to nutrition in liver disease**, 2 edn: British Dietetic Association; 1994.
16. Mahan LE-S, S: **Krause's Food and Nutrition Therapy**: Elsevier Saunders; 2008.
17. Richards J, Grunson, B, Johnson, J & Neuberger, J: **Weight gain and obesity after liver transplantation**. *Transplant International* 2005, **18**:461-466.

18. Stegall MD, Everson G, Schroter G, Bilir B, Karrer F, Kam I: **Metabolic complications after liver transplantation. Diabetes, hypercholesterolemia, hypertension, and obesity**. *Transplantation* 1995, **60**(9):1057-1060.
19. Mor E, Facklam, D, Hasse, J, Sheiner, P, Emre, A, Schwartz, M: **Weight gain and lipid profile changes in liver transplant recipients: long term results of the American FK506 multicentre study**. *Transplant Proceedings* 1995, **27**:1126.
20. Canzanello V, Schwartz, L, Taler, SJ, Textor, SC, Wiesner, RH, Porayko, MK & Krom, RAF: **Evolution of cardiovascular risk after liver transplantation: a comparison of cyclosporine A and Tacrolimus (FK506)**. *Liver Transplantation and Surgery* 1997, **3**(1):1-9.
21. **Are You A Candidate?** [http://www.ossanz.com.au/candidate.asp]
22. Sobal J, Rauschenbach B, Frongillo EA: **Marital status changes and body weight changes: a US longitudinal analysis**. *Soc Sci Med* 2003, **56**(7):1543-1555.
23. Sobal J, Rauschenbach BS, Frongillo EA: **Marital-Status, Fatness and Obesity**. *Soc Sci Med* 1992, **35**(7):915-923.
24. Lipowicz A, Gronkiewicz S, Malina RM: **Body mass index, overweight and obesity in married and never married men and women in Poland**. *Am J Hum Biol* 2002, **14**(4):468-475.