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Review Article

Obesity as predictor of postoperative outcomes in liver transplant candidates: Review of the literature and future perspectives

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ABSTRACT

Background: Current American and European guidelines consider a pre-transplant BMI ≥40 kg/m^2 as a relative contraindication for liver transplantation but this recommendation is graded as uncertain and requires further research. Moreover, conflicting results are reported on the predictive value of BMI 30–39.9 kg/m^2 on post-transplant complication and mortality risk.
Aim: This study analyzed the data of the literature on the effect of all three BMI classes of obesity on postoperative outcomes in liver transplantation.
Materials and methods: A PubMed and Cochrane Library search was conducted from inception to October 2015.
Results: Analysis of the literature demonstrates that discrepancies among studies are mainly either due to limitations of BMI *per se*, the different BMI cut-offs used to select patients with obesity or reference group and the different outcomes considered. Moreover, the evaluation of visceral adipose tissue and the detrimental effect of muscle mass reduction in presence of obesity are never considered.
Conclusions: BMI assessment should be used as a preliminary method to evaluate obesity. Subsequently, the assessment of visceral adipose tissue and muscle mass should complete the preoperative evaluation of liver transplant candidates. This innovative approach could represent a new field of research in liver transplantation.

1. Introduction

Patients with obesity suffer from a large number of medical comorbidities and are at higher risk of postoperative respiratory (pneumonia, atelectasis, pulmonary embolism), cardiac (atrial fibrillation), infectious (nosocomial infections, wound infections) and surgical (wound dehiscence) complications [1–3].

The continuous increase of obesity in the general population translates into an increase in the number of patients with obesity eligible for liver transplantation [4]. In fact, the percentage of liver transplant recipients with obesity increased from 21% to 32% in the periods 1988–1996 and 2001–2011, respectively [5–7]. On the other hand, the prevalence of malnutrition in two large cross sectional studies including 73,538 and 38,194 adult US liver transplant recipients, from 1987 to 2007 and from 2004 to 2011, was only 2.5% [7,8].

Obesity is identified by a body mass index (BMI) ≥30 kg/m^2 [8], but a lower cut-off value (BMI ≥25) has been set in Japan, China and Korea [9–11]. The calculation of BMI was first devised by Adolphe Quetelet in the eighteenth century [12]. Since then, it has been widely used as an anthropometric index because of its easy application. However, the BMI has several limitations. It does not take into account several factors: body composition, *i.e.* the percentage of fat free mass and fat mass of the subjects, gender, age, and consequently, the significantly different percentage of fat mass in men and women and the decrease of fat free mass, namely the muscle mass, in the elderly [13]. Moreover, it does not consider the increase in extracellular fluids, as it occurs in the case of edema or ascites, an aspect particularly important in the case of advanced liver disease.

Finally, it has been proposed that a specific measurement of visceral adipose tissue (VAT) would be more relevant than just BMI for the evaluation of adverse postoperative events related to obesity in patients undergoing general surgery [3,14]. Moreover, obesity might be associated with a decrease of muscle mass, a condition that increases the negative effects of obesity, giving rise

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to the scenario of sarcopenic obesity [15,16]. Sarcopenia is a well characterized syndrome in elderly (namely primary or age-related) defined by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes. A disease-related sarcopenia (secondary sarcopenia) is associated with advanced organ failure (heart, lung, kidney and brain), inflammatory disease, malignancy or endocrine diseases. Only recently, the concept of sarcopenia has been extended to the cirrhotic population, but some considerations including the underlying mechanisms, suggest the need to modify the definition of sarcopenia in this specific setting of patients [17–19].

All these considerations imply that most of the literature assessing obesity on the basis of the mere BMI to predict postoperative outcomes in liver transplant candidates suffers some limitations and does not offer either conclusive results or practical suggestions. In the present review we approached the data of the literature from a new prospective, revisiting the results obtained on the basis of BMI and trying to cover the aspects that were not adequately considered in previous reviews. Finally, new materials that offer more definite conclusions were incorporated.

To achieve the goal of this research, the effect of the three classes of BMI corresponding to the three obesity categories on postoperative outcomes in liver transplantation were analyzed. Then, the predictive value of sarcopenia and visceral adipose tissue, which is currently used to evaluate the postoperative risk related to obesity in general surgery was examined. Finally, the possibility of extending the use of these two parameters to evaluate the postoperative risk in liver transplant recipients with obesity was discussed.

A MEDLINE, PubMed and Cochrane Library search that included studies published up to March 2017 was conducted using the search terms 'body mass index', 'obesity', 'visceral adipose tissue', 'sarcopenia', 'liver transplant*', 'general surgery', 'complication', 'mortality', 'survival', with AND/OR as Boolean connectors. Moreover, further relevant articles were hand-searched using the references of the selected studies.

The novelty of this manuscript relies on the original approach used to compare the BMI studies and supports the evaluation of visceral fat and sarcopenia in the transplant setting (it is plausible that data concerning patients with obesity undergoing general surgery might also be applicable to liver transplant recipients). For the first time, we propose a combined assessment of visceral fat and sarcopenia as prognostic factors for postoperative complication and mortality risk in obese liver transplant candidates, which are two parameters easily derivable from the imaging studies expected for preoperative protocols.

2. BMI as prognostic factor

2.1. Post-transplant complication risks

The studies on the influence of pre-operative BMI on postoperative complications in liver transplant recipients are summarized in Table 1, with data from 1987 to 2012 taken into consideration. The first part of the table contains a list of studies that report an increased risk of postoperative complications, while the second part contains a list of studies with opposite results. Only in 4 of these 11 studies recipients with a BMI ≥ or > 40 are compared with recipients with lower BMI; 4 studies adopted a BMI ≥ or > 35 as cut-off but used recipients with BMI < 30 (3 studies) or BMI 18.5–24.9 (one study) as controls; 1 study used a different cut-off for male and female recipients (31.1 and 32.3, respectively) and 2 studies a cut-off >30. Sawyer et al. [20] found a significantly higher number of wound infections in 30 liver transplant recipients with BMI ≥35 (severe obesity) but, at the same time, in these patients they report a total number of complications similar to that found in the 217 patients with a BMI <30 used as reference group. Nair et al. [21] reported significantly higher postoperative complications (respiratory failure and systemic vascular events) in 21 liver transplant recipients with a BMI >32.3 for women and >31.1 for men (severe obesity) as compared to 100 controls with a lower BMI (≤27.8 for women and ≤27.3 for men). Dick et al. [22] analyzed 1447 patients with BMI ≥40 (severe obesity) as compared to 68,172 patients with a BMI 18.5–39.9. In this study, significantly longer periods of hospitalization and use of intensive care unit services following transplantation were observed. Schaeffer et al. [23] found a significantly higher rate of wound infections and dehiscences in 10 liver transplant recipients with a BMI >35 as compared to the 143 controls with a BMI <30. Analysing data retrieved from a prospectively maintained database, including liver transplant recipients, Hakeem et al. [24] observed a longer mean hospital and intensive care unit stay in patients with BMI ≥35 (73 pts.) as compared to patients with normal BMI (646 pts.). Dare et al. [25] described a higher risk of postoperative complications (cardiovascular and respiratory) in 72 liver transplant recipients with a BMI ≥30 as compared to 102 controls (BMI 18.5–29.9). In a recent paper including 12,445 liver transplant recipients, Singhal et al. [26] reported that 416 (3.3%) BMI ≥40 recipients had higher hospital length of stay and were less often discharged as compared to 12,029 BMI <40 controls. By contrast, a study of Braunfeld et al. [27] did not find an increase of intra- and postoperative complications when 40 liver transplant recipients with a BMI >35 were compared to a cohort of 61 time-matched controls (BMI <30). Fujikawa et al. [28] reported that, after liver transplantation, 167 (24%) patients with obesity (BMI range 30–42) had clinical outcomes similar to 533 patients with a BMI <30. Leonard et al. [29] analyzed length of hospital and intensive care unit stay, early and late complications in 704 patients by comparing 22 patients with a BMI >35 plus 10 patients with a BMI >40 versus 672 patients with a BMI ranging from <18.5 to 34.9 without finding any significant differences. However, this was the only study, together with the one from Hillingso et al. [30], which corrected the BMI based on the degree of ascites. Finally, in a single center study on 758 liver transplant recipients, Conzen et al. [31] found no difference among the different BMI categories, including 26 patients with BMI >40, when postoperative complications, hospital and intensive care unit stay were analyzed.

In none of the above-mentioned studies was a different BMI taken into consideration according to gender and ethnicity. Moreover, the presence of sarcopenia was not assessed.

2.2. Post-transplant mortality risk

In the first and second part of Table 1, studies that analyzed not only post-transplant mortality, but also postoperative complications are reported, while in the third part of the table the studies that exclusively analyzed post-transplant mortality are listed. As observed for postoperative complications, conflicting data are also reported on short- and long-term post-transplant mortality in patients with obesity, receiving liver transplantation from 1987 to 2012.

Among the 16 studies analyzed, 7 used a BMI ≥ or > 40 as cut-off for comparison with lower BMI, but in 2 of these studies BMI 19–22 and 20–24.9 were used as controls. Four studies assumed as cut-off a BMI ≥ or > 35 but used recipients with BMI < 30 (3 studies) or BMI 18.5 24.9 (one study) as controls; 1 study used a different cut-off for male and female recipients (31.1 and 32.3, respectively) and 4 studies a cut-off >30.

Five studies reported a significant increase of post-transplant mortality. Sawyer et al. [20] found a significantly higher number of deaths from multi organ failure but a similar overall mortality in the early post-transplant period, and a survival rate at 1 and 3 years, similar to recipients with BMI ≥35 and <30. Nair et al.