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Nutritional issues in heart transplant candidates and recipients

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1. ABSTRACT

Heart transplant is the golden standard in the management of end-stage heart failure. Recent studies have pointed out the role of nutritional issues in patients evaluated for heart transplant listing. In particular, extremes in body habitus, cachexia and obesity, have been characterized and identified as independent prognostic factors and clinically relevant target for therapeutic interventions. Effects of such conditions exert a prognostic implication well beyond waiting time up to early post transplant setting. Changes in posttransplant clinical conditions and nutritional status have been recently described in their pattern of presentation and implications on weight gain, reversal of preoperative cachexia and early and late morbidity and mortality. New onset diabetes mellitus and metabolic syndrome have been disclosed as relevant clinical conditions in this setting. Implications for tailoring of immunosuppressive therapy and dietary prescription emerged as main stem of long term recipient management. All this issues have been reviewed focusing on the clinical relevance of this growing body of knowledge and emphasizing the role of a multidisciplinary approach for selection and management of heart transplant recipients.

2. INTRODUCTION

Chronic heart failure (CHF) is a major public health problem in western countries; in fact it is the only cardiovascular condition in which there has not been a substantial decline in both incidence and prevalence over the past twenty years. More, end-stage CHF carries a devastating prognosis, which resembles that of some types of malignant cancer. Indeed about half of the patients die within 4 years of diagnosis (1). Heart transplantation (HTx) remains the gold standard in the treatment of end-stage heart failure. Although patients with severe end-stage disease who undergo heart transplantation may live 10 or 20 years or longer, in the absence of transplantation, life expectancy is often measured in weeks or months. Unfortunately, due to a critical scarcity of available organs for transplantation, in any given year, fewer than 5% of potential beneficiaries undergo HTx. Therefore, achieving maximal benefit from this therapy is predicated on improving patient selection by better understanding the risks and benefits associated with transplanting various groups of heart failure patients.

3. THE RELEVANCE OF NUTRITIONAL STATUS AND THE MAGNITUDE OF THE PROBLEM

In this respect, there is a growing attention to the influence of nutritional status on HTx outcomes. Outcome-analyses focusing on both pretransplant cachexia and obesity have provided mixed results, leaving providers unsure whether donor hearts should be preferentially allocated to patients of normal weight (2-5). From a broader view, current guidelines for the management of CHF provide conflicting directions regarding the prognosis and management of nutritional status, and a growing body of research suggest that clinicians may need to distinguish between weight management strategies for healthy individuals as opposed to those with CHF(6). As to the International Society for Heart and Lung Transplant (ISHLT) guidelines, recently revised listing criteria partially addressed (class II, level of evidence C) the potential for an elevated risk in obese patients neglecting any consideration on pretransplant malnutrition (6). Besides significant differences in the demographics of CHF patients, candidates on the waiting list and of those ultimately transplanted are clearly emerging (7). Aim of this review is to focus on: 1) relevance of nutritional status in end stage heart failure patients evaluated for transplant listing, 2) to determine contemporary practice pattern of listing and organ allocation and 3) to evaluate the effects of body habitus on early and late outcomes as well as on quality of life after the procedure.

4. PROGNOSTIC IMPLICATIONS AND CLINICAL MANAGEMENT OF OBESITY AND CACHEXIA IN END-STAGE CHF

In the general population excess body weight is associated with a significantly increased risk of coronary artery disease, heart failure and death. Nevertheless there is evidence that among patients with CHF excess body weight is paradoxically associated with a decreased risk of adverse outcomes (8-9). This growing body of knowledge is derived from studies that may be partially biased by sample size, target definitions, design and era, in respect to current "state of the art" CHF medical management. In particular definition of body size/composition is a major concern. Indeed, it may be based on percent ideal body weight, body mass index (BMI), weight, cachexia, fluid retention, or albumin. BMI is the usually adopted standard for measuring body weight even though it does not address other major components of body weight (fat mass, lean body mass, fluid and fat distribution). Despite these limitations, as reported in two authoritative reviews, most of the available studies disclosed that among outpatients with stable CHF, higher BMI values are independently associated with a lower risk of death and death due to worsening CHF, such that overweight and obese patients have better survival rates compared with patients at a healthy weight (10-11). These paradoxical observations, which have also been reported in patients with dialysis dependent end-stage renal disease, and those with advanced malignancies and individuals with advanced age, have been referred to as "reverse epidemiology" (12). The mechanisms for this reverse epidemiology are far from clear.

Time discrepancy of the competing risk factors, the malnutrition-inflammation complex syndrome and the endotoxin-lipoprotein hypothesis has been singularly or synergistically advocated along with the concept of "reverse causation". A detailed examination of these pathophysiologic pathways is beyond the scope of this review while, strictly linked to the above stated aims, is the clear clinical implication that definitive recommendations concerning weight and weight control for this population are not forthcoming. In recently released guidelines from the European Society of Cardiology it is stated:

"Weight reduction in obese [body mass index (BMI) >30 kg/m2] persons with HF should be considered in order to prevent the progression of HF, decrease symptoms, and improve well-being." (Class of recommendation I, level of evidence)

" In moderate to severe CHF, weight reduction should not routinely be recommended since unintentional weight loss and anorexia are common problems" (class of recommendation IIa, level of evidence C) (5).

Indeed the transition between clinically and body weight stable, ambulatory CHF to cardiac cachexia is not well understood, and the timelines differ widely between patients (13). The pathophysiology and definition of such a wasting syndrome is still underway. New pathophysiologic insights view CHF as a complex catabolic state (14). Mediators implicated in this process are pro-inflammatory cytokines, cathecolamines, cortisol, natriuretic peptides, and heat shock proteins: all in all most of the pathways initially activated to counteract the impairment of myocardial function. Further, several nutritional factors, including alterations in food intake and appetite, an imbalance between anabolic and catabolic factors along with impaired nutrients absorption in the gut have been disclosed as critical steps in the development of cachexia.

As to working definition, it is important to differentiate cachexia from malnutrition and anorexia first because both these clinical conditions are reversible once food is supplied and second because they imply only fat mass consumption with sparing of muscle mass and bone mineral density. Presence of edema may prevent the assessment of weight loss, which stresses the importance to assess changes in body weight in the non edematous state. Current "best" clinical definition is those originally forwarded by Aker and coworkers which suggest: "non-edematous weight loss of >6% of the previous normal weight observed over a period of >6 months"(15).

Once developed cardiac cachexia portends an exceedingly poor prognosis. Indeed, as reported by Lavie and coworkers in a retrospective study of 209 ambulatory patients, the highest percentage of major clinical events (cardiovascular death and urgent transplantation) was found in the sample with the lowest percentage of body surface area (2.0 m^2), BMI (27.7 kg/ m^2), body fat (22.5%), total fat (19.7 kg), and lean body weight (65.5 kg)(10). Davos and coworker comparing outcomes of CHF patients with cachexia with those without found that

unintentional weight loss implied nearly a threefold increase in the likelihood of death (16).

Therapeutic approaches to cardiac cachexia include prevention of weight loss, dietary supplementation and direct pharmacotherapy (appetite stimulants, anabolic steroids and growth hormone). Optimization of medical therapy with extensive usage of angiotensin converting enzymes inhibitors and β-blockers should be emphasized in view of recent data highlighting their role in the prevention or, at least, delay of the wasting syndrome(17-18).

5.PRACTICE PATTERNS OF LISTING AND ORGAN ALLOCATION AND CONTEMPORARY OUTCOMES DURING WAITING

Although obesity is not an absolute contraindication, the transplant community usually considers BMI ≥35 a relative contraindication for HTx. Nevertheless, data from the United Network for Organ Sharing (UNOS) database along with those derived from the Registry of the ISHLT demonstrate that the proportion of patients with BMI ≥30 listed for HTx has significantly increased over the past two decades (7,19). A recent authoritative study by Weiss and colleagues investigated whether obesity affects organ allocation in a cohort of 27,002 HTx candidates included in the UNOS waiting list (1998 to 2007). A potential bias in the selection of obese patients emerged. Mean BMI in study sample was 27.2 with 73% of the patients defined normal or overweight. This data, in the context of >32% of Americans having a BMI≥30 and with the knowledge of obesity as an independent predictor of heart failure, portends for a reluctance to provide obese patients with a transplant candidacy. Once on the waiting list, patient with a BMI≥30 wait twice as long and are 35% less likely to receive a donor graft than patients of normal weight; while patients with BMI ≥35 are 46% less likely to undergo transplantation and wait an average of 200 days longer. Obese patients listed as Status 1 waited 57 days longer than those of normal weight. As to mortality on the waiting list, highest rates were found in patients with normal weight as compared to overweight, obese or extremely obese. When stratified according to status at transplantation, patients with BMI≥35 had the lowest cumulative survival when given a status I priority (6).

Data on prognostic implications of small BMI are fewer. A recent report from Berlin Herzzentrum analyzed whether lower body surface area of adult patients affects their prognosis after listing. Adult candidates for de novo HTx, who were newly listed by Eurotransplant without ventricular assist device (VAD) support between 2000 and 2009 (n=545), were studied. The patients were divided into two groups: group S (n=272): BSA<1.9563m^2 and group L (n=273): BSA≥1.9563m^2. Most female patients (82/84, 97.6%) belonged to group S. Among all these patients, 286 progressed to critically ill status, that is, they were listed in urgent status or received a VAD. Actuarial survival rates were studied in each group. Results: Overall survival rates after listing for HTx in group S were comparable to those in group L (43.0% vs 43.7% for 7-year survival, p=0.95). However, 1-year survival rate on waiting list after progression to critically ill status in group S (58.0%, n=135) and that of female patients in group S (55.8%, n=33) were significantly lower than those in group L (67.3%, n=151, all were men; p=0.042 and p=0.044, respectively). After multivariate Cox analysis, BSA<1.9563m^2 (hazard ratio 2.120, p=0.0019), serum creatinine (hazard ratio 1.202, p=0.033), obesity defined as body mass index ≥30kgm^{-2} (hazard ratio 2.043, p=0.0096) and primary use of VAD (hazard ratio 3.243, p<0.0001) were identified as independent risk factors for mortality on waiting list after progression to critically ill status. One-year survival rate on waiting list after VAD implantation in group S (44.4%, n=65) and that of female patients in group S (38.1%, n=14) were significantly lower than those in group L (63.0%, n=78, all were men; p=0.020 and p=0.012, respectively). Author concluded that HTx candidates with lower BSA, including most women, had worse prognosis on waiting list after progression to critically ill status, especially after VAD implantation. Given that most of HTx are nowadays performed in critical status, the clinical relevance of this observation is crucial (20).

Similar findings derive from a recent analysis of the UNOS database: when compared with normal weight recipients, survival on the waiting list was significantly worse in those underweight (19).

6. BMI AND MORBIDITY AND MORTALITY AFTER HEART TRANSPLANT

Studies examining the effects of BMI on posttransplant morbidity and mortality in solid organ transplantations disclosed a clear U-shaped relationship with recipients at the extremes experiencing the worst outcomes (21-22). Data from heart transplant recipients are still limited and often conflicting (2,3). An authoritative study by Russo and co-workers brought new evidences analyzing 19,593 adult recipients transplanted January 1 1995 and December 31 2005. Recipients were stratified by BMI at the time of transplantation: BMI <18.5 (underweight), 18.5 to 24.99 (normal weight), 25 to 29.99 (overweight), 30 to 34.99 (obesity class I), and >35 (obesity class II/III). The primary outcome measure was post-transplant survival. Secondary outcomes were in-hospital morbidity, including the incidence of stroke, infection and need for dialysis during the transplant hospitalization; posttransplant cardiovascular comorbidities, including hypertension, hyperlipidemia, and stroke; and the long-term complications of transplantation, including new onset diabetes mellitus, transplant coronary artery disease, posttransplantation chronic dialysis, severe infection, and severe rejection. Risk-adjusted median survival in the underweight, normal weight, overweight, obesity I, and obesity II/III groups was 8.31, 10.20, 10.03, 9.51, and 9.05 years, respectively. In multivariate Cox proportional hazards regression, BMI in the overweight and obesity I ranges were not associated with significantly diminished survival. However, BMI in the underweight and obesity II/III ranges were associated with diminished posttransplant survival. This diminished survival in the underweight group resulted from excess morbidity in the

first year posttransplantation. In particular such recipients had an increased risk of infection during the transplant hospitalisation. However, with correction of their heart failure and subsequent reversal of their cachectic state, their risk of death, along with the mean BMI, normalized after the initial posttransplant period and such sample did not experience and elevated risk of any long-term complication of transplantation or posttransplant cardiovascular comorbidity. Notably among the entire study population, 15.3% of recipients with a BMI <18.5 (n = 287) in the first year posttransplant died ($P < 0.001$) compared with 4.37% of recipients with BMI > 18.5 (n=15,123). Diminished survival in obesity II/III resulted instead from long-term events. Indeed, incidence of posttransplant cardiovascular comorbidities (hyperlipidemia and hypertension) as well as incidence of all long term complications of transplantation increased as BMI increased. The relationship between the comorbidities associated with obesity, including hypertension, hyperlipidemia, and type II diabetes, and cardiac, vascular, and kidney disease confirmed previously described data on obesity in general population (24).

The clinical bottom line is as follows: 1) since prognostic relevance of end-stage CHF associated cachexia affects also early post transplant survival every effort should be spent in preventing and treating such complication. Development of tailored perioperative management strategies is mandatory to expand the benefit of transplantation in this recipient subset. 2) Listing patients with BMI> 35 should be thoroughly evaluated since it implies significantly increased morbidity and mortality over the long term.

7. CHANGES IN BMI OVER TIME AND THEIR PROGNOSTIC IMPLICATIONS

In the aforementioned study by Russo and co-workers, the mean BMI in the underweight group at 1 year posttransplantation increased moving within the normal weight. The mean BMI remained in the normal weight range through posttransplant year 10. The mean BMI in the overweight, obesity I, and obesity II/III groups remained relatively unchanged over the follow-up period (19). Pattern of BMI changes were described in details also by a prospective study from the German Heart Institute (25). After stratifying patients according to the pre-HTx BMI, authors disclosed that a significant early postoperative weight loss, followed by a substantial stability was common in normal or obese subsets. Reversibility of cardiac cachexia was achieved by the underweight patients who gained weight significantly and continuously, and most of them reached a normal BMI within two years after the procedure. The complete termination of the neuroendocrine and metabolic disorders leading to cachexia seems to be determined by the increased cardiac function. Such an anabolic process was elegantly described by Grady who disclosed that adequate visceral protein stores may be found in only 66% of heart transplant candidates but in nearly 100% of recipients (26). In a study from Williams (27) data about the magnitude and timeline of weight changes after heart transplantation were evaluated in comparison with data of Kidney Transplantation to better understand the phenomenon. Data showed a significant change in weight that was consistent at all time points. There was an average decrease in weight of approximately 1 kg at 1-month post-HTx ($p < 0.001$), whereas there was significant weight gain at all other time points. Beyond the first month after HTx, patients began to gain weight, which resulted in a mean increase of approximately 8 kg at 6 months, and approximately 10 kg at 12 months post-transplant. By the 12-month post-transplant time point HTx patients gained 10.3 ± 10.6 kg ($p<0.001$). Weight gain in HTx patients was significantly greater at Months 4, 5, 6 and 12 compared to Kidney transplant patients. A large study by the Cardiac Transplant Research Database described changes in BMI from before HTx to 5 years after the procedure, identified risk factors for BMI increase at 1 year post transplant and determined whether postoperative BMI is prognostically relevant in terms of morbidity and mortality. Such study concluded that the number of obese patients increased significantly from immediately before the procedure to 5 years later (17% vs38%) and that increased BMI at 1 year explained 56% of this variance. Several risk factors for weight gain were disclosed such as: pre-HTx BMI, younger age at transplantation, black race, non-ischemic etiology of heart disease, Status I and non-use of mycophenolate mofetil. Posttransplant cachexia and obesity implied a trend toward poorer clinical outcomes (28). All in all, the analysis of available literature prevents a clear definition of the prognostic implications of postoperative BMI changes. Early postoperative weight loss after the procedure, though usual in normal and obese patients, when marked significantly portends a poor survival (25,28). It is unknown whether this pattern reflects a direct causation or is rather a marker of risk. Postoperative obesity seems also to imply a poorer survival, maybe through the development of new onset post transplant diabetes and the metabolic syndrome, but the evidences are conflicting (28-30). Maybe the definition of obesity through BMI instead of waist circumference adopted in most of the available studies prevents any definitive conclusion. Indeed while excess of intra-abdominal fat is the proved major determinant of the metabolic syndrome increased BMI may be the reflection of both obesity and volume overload (28,31). The clinical bottom line is that transplantation effectively cures preoperative cachexia and usually implies weight gain. Knowledge of demographic and clinical predictors of increased postoperative BMI is useful to identify patients at increased risk. Weight loss programs should be implemented and tailored on the individual patient.

8. NEW-ONSET DIABETES AND THE METABOLIC SYNDROME

New-onset diabetes mellitus (NODM) is an increasingly recognized complication of solid-organ transplantation, although its importance has been greatly underestimated due to a long-standing lack of a consensus definition of the condition and a bias in study design intended to define its incidence (shortness of follow-up)(32). Homogeneously with the data reported in the kidney and liver recipients' settings, the incidence in heart transplant recipients is as high as 32% at 5 years (33).

Increased age, non-white race, increased BMI, presence of ischemic heart disease, recipient CMV positivity, and tobacco use have been recently reported as specific heart recipient predisposing factors (34). Definition of pathogenesis of transplant-associated hyperglycemia is well beyond the scope of this review and has been recently described in an authoritative paper by Bloom and Cracow (35). As reported by these two authors hyperglycemia results from imbalance between pancreatic beta cell insulin production and the insulin required to effectively regulating fasting glucose production and post-prandial glucose disposal. Restoration of renal and hepatic insulin metabolism, postoperative obesity and weight gain and immunosuppressive medications are the transplant specific factors that interplay with the baseline metabolic milieu of predisposed individuals in the genesis of NODM. Those transplant specific factors may be amenable of ample modification in recipients at high risk of developing NODM, and actually have been addressed in ad-hoc consensus guidelines (36). Diabetogenic potential of immunosuppressive medication is extensively described elsewhere (32,35,36). What is important to stress here, for the sake of this report's clarity and completeness, is that calcineurin inhibitors, glucocorticoids and proliferation signal inhibitors not only impair glucose metabolism but also lipids metabolism along with arterial pressure control and renal function. Such evil interplay synergistically enhance the effect of each given derangement and their inherent physiopathologic interconnections and may explain the conflicting evidences emerging from the literature on the net clinical effect of any single posttransplant metabolic condition. Taking in mind these considerations is not surprising that the precise impact on NODM on the outcome of heart transplant has not been ruled out. Correlation with the development of CAV is indeed still unclear (32,35).

Strictly linked to new-onset diabetes is the metabolic syndrome (MS), which is a multiplex risk factor for cardiovascular disease (31,37) that clusters in the same subject, linked by insulin resistance. The syndrome develops through interplay of obesity and metabolic susceptibility (37). From a clinical standpoint, components of the metabolic syndrome include atherogenic dyslipidemia, elevated blood pressure, elevated glucose, a prothrombotic state, and a proinflammatory state. The National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines, proposed that the finding of any three of five components (abdominal obesity, elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol, elevated blood pressure, and elevated glucose), which can be easily recognized, are sufficient for the diagnosis in clinical practice. Commonly accepted definitions were used for each component (38). A recent Spanish study assessed the prevalence of this syndrome in the heart transplant setting. The main findings of this analysis were that MS was highly prevalent (42.3%) and abdominal obesity was the leading cause of this clustering. Etiology of heart failure (ischemic heart disease), time since surgical procedure and severe impairment of renal function were the major determinants of MS, reflecting the impact of immunosuppressive therapy and the change in habits of life and dietary patterns (39). A non significant association between MS and chronic allograft vasculopathy was reported by the authors. A significant correlation between MS and CAV as detected by intimal thickening at intracoronary ultrasound was instead disclosed by an authoritative study by Valentine and coworkers. These metabolic abnormalities significantly predicted also the development of coronary artery stenosis and death during the subsequent follow-up (30). Relevance of clustering of metabolic derangements on morbidity (major cardiac events) and CAV was also been confirmed in the more recent reports by Kobashigawa and by Biadi (40-41).

Again the clinical bottom line is that evaluation of individual patient clinical status and risk profile is fundamental in the postoperative management as to the choice of immunosuppressive regimen and development of tailored dietary prescriptions. Available consensus guidelines for the treatment of NODM help guide patient management from listing to early and long term posttransplant course. Definition of the metabolic syndrome is useful in helping clinicians to stratify patients according to the risk of developing major cardiovascular events and to identify specific therapeutic strategies and targets.

9.PERSPECTIVES

Nutritional issues are main stem for the prognosis of heart transplant candidates and recipients. Available epidemiologic, physio-pathologic and pharmacologic knowledge should prompt transplant care giver in tailoring medical, dietary and immunosuppressive prescriptions to the risk profile, clinical status and setting (pretransplant, early or late posttransplant phase) of the individual patient in order to maximize survival and quality of life . More insights are needed on several pathogenetic patterns such as those of cardiac cachexia, cardiac allograft vasculopathy, metabolic syndrome, renal impairment and long term systemic inflammatory response to transplantation induced metabolic derangements. From a therapeutic stand point optimisation and development of new immunosuppressive regimen together with knowledge of inherent long term sequelae is paramount. Definition of optimal medical therapy and development of new drugs for the treatment of post transplant hypertension, diabetes and metabolic syndrome is warranted.

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