



VIEWPOINT

## Nutritional management in renal transplant recipients: A transplant team opportunity to improve graft survival



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Received 17 July 2018; received in revised form 2 January 2019; accepted 2 January 2019

Handling Editor: A. Siani

Available online 12 January 2019

### KEYWORDS

Renal transplantation;  
Nutritional management;  
Chronic kidney disease;  
Dietary adherence

**Abstract** *Aims:* The nutritional management of renal transplant recipients (RTR) represents a complex problem either because the recovery of renal function is not complete and for the appearance of “unavoidable” metabolic side effects of immunosuppressive drugs. Nevertheless, it remains a neglected problem, whereas an appropriate dietary intervention could favorably affect graft survival.

*Data synthesis:* Renal transplantation is associated with steroids and calcineurin inhibitors administration, liberalization of diet after dialysis restrictions, and patients’ better quality of life. These factors predispose, from the first months after surgery, to body weight gain, enhanced post transplant diabetes, hyperlipidemia, metabolic syndrome, with negative consequences on graft outcome. Unfortunately, specific guidelines about this topic and nutritional counseling are scarce; moreover, beyond the low adherence of patients to any dietary plan, there is a dangerous underestimation of the problem by physicians, sometimes with inadequate interventions. A prompt and specific nutritional management of RTR can help prevent or minimize these metabolic alterations, mostly when associated with careful and repeated counseling.

*Conclusions:* A correct nutritional management, possibly tailored to enhance patients’ motivation and adherence, represents the best preventive maneuver to increase patients’ life and probably improve graft survival, at no cost and with no side effects.

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### Introduction

Renal Transplantation represents the best therapeutic option for patients with advanced renal failure or on dialysis, and is associated with improved patients’ survival and a

better quality of life compared to remaining on dialysis [1–3]. After transplantation, many of the metabolic abnormalities that characterize chronic kidney disease (CKD) are greatly reduced following the partial recovery of renal function; nevertheless, the liberalization of dietary restrictions and the unavoidable metabolic side effects of immunosuppressive drugs (like hyperlipidemia or glucose intolerance) determine new nutritional problems that may significantly influence the outcome of the graft. A correct dietary approach can delay the progression of both chronic

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allograft nephropathy and of cardiovascular diseases (CVD), and probably nutritional management remains the best cost-effective, preventive maneuver (together with adherence to drugs) from which the destiny of a graft may benefit.

The aim of the present paper is to encourage transplant caregivers to consider with greater attention nutritional care in renal transplant recipients (RTR), emphasizing that a correct dietary approach may have a positive influence on the graft.

### Data synthesis

Despite the beneficial effects of an adequate nutritional control in any chronic disease are universally accepted, the dietary management often remains a neglected problem for most RTR; indeed, International or National Nephrology Societies guiltily do not have official specific Guidelines, with the CARI-Australian exception [4], with negative consequences, like the absence of shared agreements on important nutritional aspects, and the belief, by physicians, that this is just an ancillary aspect of the global management of RTR. So, information to patients about nutritional care is frequently limited to simplistic advices, focused on healthy living but not supported by strong evidence [5–8].

This attitude is dangerous since, at difference with patients with CKD, RTR require an adequate nutritional management during every step of their new “life”, starting from surgery up to the loss of their graft, with some significant differences with the dietary management of CKD patients.

During the perioperative period, in fact, RTR need to adequately increase their intake of energy (35–40 kcal/kg/day) and of proteins (up to 1.4 g/kg/day) for at least 4 weeks [9], not only to match protein catabolism that follows steroid administration and surgical stress, but also to prevent or cure a pre-existing under-nutrition that may lead to poor wound healing or greater susceptibility to infections [10]. However, early dietary liberalization after the limitations imposed by the dialysis, further supported by increased appetite and improved quality of life, often insinuates in patients' mind the wrong belief that they may indefinitely maintain a “celebratory eating”. Therefore, after these first weeks, it becomes essential to motivate patients to modify their lifestyle to avoid unpleasant metabolic consequences.

Indeed, when possible, a nutritional program should start when the patients enter the waiting list: this may help them to face transplantation in the best conditions. Malnourished patients, in fact, show increased risks of CV events or death after transplantation [11], and need to gain weight before transplantation. Moderately obese patients, conversely, may benefit from dietary restrictions before surgery, since they tend to gain more weight than patients with a normal BMI after transplantation [12]. Probably, a normal or even slightly increased BMI (24–28.7 kg/m<sup>2</sup>) at time of surgery [13,14] could positively influence the global outcome of the graft, and make easier the

prevention of the metabolic alterations that follow transplantation which, once established, difficulty recover [15].

The most important metabolic repercussions, in fact, occur during the first year after transplantation. Different studies [16–20] describe a significant body weight gain early after transplantation (range: 10%–35%) in a consistent percentage of patients (42–61%), and this represents an obvious risk factor for alterations of lipid profile and for development of new-onset diabetes and of metabolic syndrome [21–23], that contribute to negative outcomes like graft loss or CV events [24–26]. El-Agroudy et al. followed 650 RTR with normal BMI (>18.5 and < 25 kg/m<sup>2</sup>) at transplant; after 6 months, 188 (29%) became overweight, and 86 (13%) frankly obese: these latter patients had significantly more hypertension, diabetes and vascular complications than normoweight patients and were more likely to die due to CVD, while infections remained the main cause of death in normo- and overweight patients [27].

Obviously, the patients are not the sole responsible for this.

A small study by Stanfill et al. reports the personal thoughts expressed by RTR on why they gained weight: the most prevalent reasons included steroid-induced hyperphagia, enjoyment of a non-restricted diet after dialysis, as well as lack of information regarding nutrition [28]. These answers certainly unmask the responsibilities of RTR for the scarce control of their dietary intakes, but also evidence some faults of physicians who often do not provide their patients satisfying information.

Indeed, data of interventional studies to prevent weight gain in early transplantation are old and scarce [18,29–33], and also the composition of the prescribed diets remains somehow speculative: a small, non randomized study clearly shows that an adequate energy restriction after the perioperative period (30% of estimated energy expenditure) may effectively prevent an uncontrolled weight gain [31]. Moreover, if a high protein intake (>1.4 g/kg Ideal BW/day) is recommended in the perioperative period to reverse negative nitrogen balance and to increase muscle mass, there is no clear evidence about protein requirements in stable RTR [9,34]; the goal is to optimize the nutritional status while avoiding an unnecessary protein load to a solitary kidney: it could be reasonably defined by 0.75 (females) and 0.84 (males) g/BW/day, irrespective of renal function [9].

What seems essential, however, is a careful and constant counseling to persuade our patients to follow the dietary plan [30]. Studies in the general population have shown that interventions addressing nutrition and physical activity promote weight loss in obese patients [35]. Indeed, and quite surprisingly, a recent randomized trial on RTR recruited during the first month after transplantation failed to demonstrate that the intensive dietary counseling and the increased physical exercise significantly influenced weight gain, compared to standard care, during the first year after transplantation [36]. There is to consider, however, that average weight gain of those patients was modest (4.6% in 6 months), and that “standard

care” consisted of 4 dietary visits per year (with a 97% attendance!), a “standard” difficult to guarantee, although potentially cost-effective. In fact, according to a recent estimate in patients with CKD [37], to offer 5 dietary counseling visits/year to patients with stage 3b CKD in USA would demand that 26% of the entire registered dietitian working force be exclusively dedicated to these patients! A new randomized, controlled trial to prevent weight gain after renal transplantation through physical exercise and/or diet is ongoing in Dutch patients and, hopefully, will offer new important information on this topic [38].

When resources are scarce, it is crucial to constantly encourage patients to accept the dietary prescription since non-adherence to therapies or diets in RTR is high [39,40], comparable to that of CKD patients [41]. A good dietary compliance in the first post-transplant year is associated (mostly in male patients) with a significant weight loss (−11%) and significantly lower plasma levels of cholesterol (−33%) and glucose (−17%), at difference with non-adherent control patients [18]; moreover, despite the dietary restrictions, adherent patients maintained an adequate nutritional status, with constant fat-free mass and body cell mass [18].

Unfortunately, despite our efforts to promote the weight reduction, several patients with a long transplant vintage continue to maintain a BMI in the overweight or obese range: a recent cross-sectional observation in RTR from our Unit (7.5 ± 5.0 years after transplantation) has shown that 29% of patients had a BMI ranging between 25 and 30, and 19% were obese, with a BMI >30; these latter patients also showed elevated levels of inflammatory markers and high prevalence of multidrug regimens, with potentially harmful drug–food interactions [42]. The most striking data, however, was that *all* the patients of the study, including those with a BMI <25, had energy, protein and fat intakes higher than CKD guidelines recommendations [42]; this suggests the need of a greater attention by physicians in recalling nutritional needs to our patients. Some years ago, Strejic described his experience of presenting a review of dietary suggestions to a group of RTR whose time from transplant ranged from 3 months to 10 years. Most patients described how important was for them to hear such information again, since reinforcing these concepts helped them increase their knowledge and retention of the matter, and definitely “... (they) found this opportunity very useful in managing their diets and health ...” [43]. Although no study has shown a better graft outcome due to dietary adherence, it is important to recall periodically nutritional principles to our patients, and to provide more intensive intervention when deemed necessary.

If it seems clear that all RTR should benefit from dietary attention immediately after transplantation, problems arise when resources are scarce and we can address our attention only to a limited number of patients. Some Authors suggest that surveillance efforts should be primarily devoted to compliant patients, i.e. those showing favourable trends in weight and metabolic control, and in visit attendance [37]. All the patients, indeed, deserve

our attention, and it is important to distinguish among non-compliant patients those who have specific barriers to overcome: they mostly need our help, leaving to “resistant” patients suggestions facilitating self-management, like dietary treatment apps [44] or simple dietary tips.

We have recently shown, in a prospective and randomized trial in CKD patients, that 6 easy-to-follow tips may satisfactorily substitute a standard dietary plan when dietitians are not available, and are well accepted by non-adherent patients with excellent results in terms of nutritional intakes and of metabolic results [45]; some of these tips (reported in Table 1) could be easily suggested to all patients, as well as those available on the web [46,47].

After the early phases of transplantation, nutritional management is mostly influenced by the side effects of immunosuppressive drugs. Balanced and “healthy-heart” diets are necessary to maintain the optimal protein intake, the desirable body weight, and to attenuate the dangerous adverse effects of anti-rejection agents. This “maintenance” phase should be characterized by a careful evaluation of energy requirements, in most cases consisting in a slight reduction of the caloric intake (≤30 kcal/kg Ideal BW/day), and a better control of protein intake, which should be constantly maintained around 0.75–0.84 g/kg BW/day [9].

Obese RTR must reduce caloric consumption to levels less than energy expenditure, and probably need an individualized and intensive treatment plan that encompasses the nutritional requirements of the transplant population. Since the evidence of specific diets for weight loss in these patients is scant, one reasonable approach is to start with 25 kcal/kg BW/day [48].

No difference exists with CKD patients in carbohydrates management, even in presence of post-transplant new onset diabetes, which should continue to represent the 50% of energy intake, with the obvious recommendation to use carbohydrates at low glycemic index, integrated by an adequate intake of foods rich in wholegrain and fibers (>25 g/day) [49].

Despite the relevant incidence of hyperlipidemia, dietary fat should still represent about 30% of total energy, with 8–10% of such energy from n-6 polyunsaturated fat (PUFA) and mostly from n-3 polyunsaturated fats from plant and marine sources; approximately 20% of fat should

**Table 1** Some tips to suggest to renal transplant recipients (adapted from the 6-tip Diet for CKD patients, Ref. [43]).

1. Do not add salt at table and for cooking
2. Avoid: any kind of salami, sausages, cheese and dairy products or canned food
3. Limit bread and noodles
4. Meat, fish and eggs, as main course, are allowed once a day in the usual quantity
5. 4–5 servings/day of fruits or vegetables are suggested
6. Once or twice a week the main course may be of noodles with legumes instead of the second course, with fruit and vegetables

derive from monounsaturated fat and <10% from saturated and trans fatty acids. Unfortunately, Western diets are characterized by a high intake of saturated fats and of n-6 PUFA compared to n-3 PUFA that results in a high n-6/n-3 ratio, which predisposes to inflammation. Also this attitude deserves more attention: we have recently shown, in fact, that a diet rich in n-3 PUFA, beyond a significant lowering of both cholesterol and triglycerides plasma concentrations, decreased the levels of several inflammation biomarkers (IL-6, CRP, ferritin) and also reduced proteinuria, an independent risk factor for CVD, all-cause mortality and chronic allograft dysfunction [50]. This diet consists of many palatable, easily available, and cheap fresh foods (like salmon, sardines, herrings, oranges, strawberries, bananas, artichokes, mushrooms, cauliflower, pumpkin), but requires the intervention of a dietitian to explain how to correctly manage these nutrients. The data of this latter study are particularly intriguing since hyperlipidemia, described in almost 80% of RTR, may adversely affect the outcome of the graft [51,52] and requires the use of statins that may have unpleasant side effects, may interfere with calcineurin inhibitor metabolism, and represents an additional cost for the Public Health System.

Although average dietary sodium intake in RTR may be below the level of general population [53], it is far above 90 mmol/day, the target recommended by K-DIGO guidelines for CKD patients [54]. High salt intake is an established risk factor for hypertension also in RTR [53], and can result in decreased graft survival and left ventricular hypertrophy, an independent risk factor for heart failure and death in RTR [55,56]. Therefore, restriction of dietary sodium chloride to a maximum of 5 g/day for an adult, should be a priority not only to combat hypertension but also to reduce proteinuria, which decreases during low-salt diets probably following BP reduction [57]. It seems important, therefore, to test also urinary sodium and protein excretion to evaluate patients' adherence to our prescription.

Although beyond the aim of this paper, it seems very important that RTR may associate nutritional intervention with lifestyle changes to improve their physical functioning, depressed by the reduced muscle mass, the sensation of fatigue and the lack of motivation. Physical activity, in fact, declines during chronic renal failure and reaches its nadir at end stage renal disease, mostly on dialysis. Appropriate exercise should be strongly encouraged to all RTR, to avoid sarcopenia, which can easily occur after long lasting dietary restrictions and to improve the noxious effects of CNI and steroids on insulin synthesis and its peripheral resistance. As previously mentioned, while the importance of physical activity is widely recognized in general population, its effects in RTR have been inconclusive [58–61]. Nevertheless, we strongly believe that to improve muscle mass with controlled physical activity may promote an anabolic state, characterized by an optimal use of energy and proteins, with potential positive implications on cardiovascular burden and on patients' quality of life.

## Conclusions

In conclusion, we believe that all Transplant Caregivers should remember that the nutritional management is an important determinant of clinical outcomes in RTR and should become a cornerstone to improve patients' quality of life and, hopefully, the outcome of their grafts. When feasible, a "tailored and dynamic" approach should be used in any single patient, possibly starting from the pre-transplant period, to get appreciable metabolic results and beneficial effects on graft outcome. No drug can offer our patients these possibilities with no side effects and, mostly, at no additional costs!

## Conflicts of interest

All the authors have no competing interest to declare.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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