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EDITORIAL

Effects of exercise in renal transplant recipients

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Abstract

Even after a successful renal transplantation, the renal transplant recipients (RTRs) keeps on suffering the consequences of the uremic sickness. Cardiovascular risk, work capacity, and quality of life do not improve according to expectations since biological and psychological problems are not completely solved by pharmacological treatment. Furthermore, post-transplant treatment, per se, induces additional problems (i.e., side effects of drugs). It becomes, indeed, very important to insert "non-pharmacological" therapies able to reverse this trend. Exercise may represent an important contribution in the solution of this problem. In fact, many studies have demonstrated, in the last two decades, that physical training is able both, to improve graft function, work capacity and quality of life, and to reduce cardiovascular risk. In conclusion, if the analysis of the available data suggests that an appropriate dose of physical training represent a useful, safe and non-pharmacologic contribution to RTR treatment, it becomes a kidney transplantologist responsibility to introduce exercise in the current therapy of RTRs.

Key words: Renal transplantation; Exercise; Working capacity; Quality of life; Cardiovascular risk; Renal function; Immunology

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BACKGROUND

Uremic patients' survival is conditioned by an increased cardiovascular risk. In spite of the decline of its incidence rate in the general population during the last three decades, cardiovascular events remain the major cause of death in nephropathic patients[1,2] with a mortality 10 to 20 higher than in the general population[3,4]. In 1998 the National Kidney Foundation Task Force in Cardiovascular Disease recommended to consider uremic patients as a group with very high risk for cardiovascular events[1]. The main cause of this raised risk is the accelerated atherosclerosis, which is now considered to be the expression of an inflammatory process[5,6]: pro-inflammatory cytokines are secreted by immune cells within the atherosclerotic plaque. These include interleukin (IL)-1, IL-2, IL-6, IL-8, IL-12, IL-10, tumor-necrosis factor, interferon-γ and platelet-derived growth factor[7]. The accelerated atherosclerosis is the most important late complication for all organ recipients too[8,9]. Over the years, various risk factors have been associated with the manifestation of atherosclerosis. Among these, elevated levels of plasma cholesterol (LDL in particular) are recognized as a major risk factor as well as hypertension, diabetes mellitus, smoking[10] and sedentary life style[11]. An increasing amount of data demonstrates that uremia,

per se, represents an inflammatory condition and that this inflammation remains unaffected by transplantation[12]. Also in nephropathic patients cardiovascular events are strictly related to inflammation[13,14] and they represent the main cause of death not only in predialysis[15] and in replacement therapy patients[16,17], but also in renal transplant recipients (RTRs)[12]. The immunosuppressive treatment itself contributes to increase cardiovascular complications in RTRs through the induction of hypertension and dislipidemia[18,19]. Moreover, it is important to consider that the tendency to sedentary lifestyle is favoured by both the depression and the reduced quality of life that affect not only dialysed patients[20,21] but also patients after a successful renal transplantation[22].

GOAL

On the basis of the above considerations, the question that arises is the following: Is it possible to reduce cardiovascular risk and to influence graft survival of RTRs other than pharmacologically? In our opinion physical activity could play an important role in this subset of patients. In fact, many studies have demonstrated that physical training is able to improve several factors involved in the increased cardiovascular risk of RTRs and may contribute to save renal function. In this review we will examine the existing evidences with respect to these topics.

EVIDENCE BASED RESULTS

Glomerular filtration rate

Greater physical activity is a statistically significant predictor of improved graft function over a 1-year period. The authors believe that physical activity leads to improved cardiovascular function, which, probably, improves perfusion and oxygen delivery to the kidney graft[23].

Arterial pressure

Exercise reduces the need for pharmacological therapy of hypertension both in lung[24] and kidney transplanted patients[22].

Homocysteine

It is a factor related to an higher prevalence of cardiovascular disease and poorer outcome[25-29]. It remains higher in RTRs with respect to general population but an exercise program may significantly decrease the levels of this aminoacid[30].

Work capacity

Patients with advanced chronic kidney disease have lower cardiorespiratory fitness (CF)[31,32] that remains reduced by 30% after transplantation in comparison with age and gender matched control subjects[33]. CF expresses the maximum capacity of aerobic activity. It is measured through the evaluation of the peak oxygen uptake (VO_2) obtained by expired gas analysis. It is important to note that CF is a well-validated predictor of cardiovascular outcome both in individuals with underlying cardiovascular disease and in normal individuals[34]. Exercise improves CF in RTRs[22,35-37]. The mechanisms behind this reduced work capacity are not known, but it could be simply due to the reduced activity level before transplantation[38]. Exercise enhances muscle strength too[37,39], while it does not modify the body composition (BC), evaluated through dual-energy X-ray absorptiometry[22,37]. The lack of difference in the BC is due to the fact that exercise alone is ineffective for weight loss, unless a careful dietary management is adopted[40].

Effects of exercise among elderly RTRs

Despite best practices, older patients are at increased risk for early graft loss and death[41]. It has been demonstrated that pre-transplant inactivity is a negative predictor of overall patients and graft survival in this subset of patients[42].

Exercise and immunology of kidney transplantation

An 8-wk aerobic exercise program enhances T-helper cell count, CD4+ to CD8+ ratio, natural killer cells activity and IgG and IgM levels without causing graft dysfunction in the short term[35].

Moreover, it has been widely demonstrated that IL-6 plays a significant role in the progression of mesangial proliferative glomerulonephritis[43] and that it is an important risk factor with respect to the relapse of IgA nephropathy in transplanted kidney[44]. Furthermore, IL-6 amplifies the inflammatory cascade also by promoting the development of Th17 and the synthesis of IL17 from naive T cells (along with TGFb1 and IL21), whereas the maturation of memory Th17[45] and IL17 induces the synthesis of IL6 by myoblasts thus creating a vicious cycle[46]. San Segundo *et al*[47] and Afzali *et al*[48] demonstrated that IL-17 serum levels were augmented in graft dysfunction (compared with end stage renal disease patients) and, in agreement with Afzali *et al*[48], hypothesized that an imbalance between T(H)17 and Tregs enhances immune inflammation among renal transplant patients. In addition, since elevated levels of Il-6 represent a trigger factor of inflammation, they may significantly contribute to the cardiovascular risk of RTRs. Increased basal levels of this cytokine have been measured in RTRs[49].

Castaneda *et al*[50] demonstrated that exercise reduces the levels of IL-6 in uremic patients and we recently showed that this happens in RTRs too[22].

It is interesting to note that IL-6 increase is actually indicated both as the effect of an overtraining syndrome[51] and as one of the main factors able to induce an "underperformance syndrome"[52]. In fact, during strenuous exercise, IL-6 increases[53] by greater amounts than any other cytokine[54-56]: an increment registered in behavioral changes during physical as well as psychological stress[57]. In agreement with Castaneda *et al*[50] our data[22] seem to demonstrate that there is a difference in the IL-6 production depending on the dose of physical training. This can lead to the conclusion that, if strenu-

ous exercise increases IL-6 production, a well regulated level of exercise will produce the opposite result (i.e., a reduction of IL-6 levels). The "appropriate level" of exercise, indicated in several studies regarding the effects of exercise in RTRs, consists of a 30-45 min/session of aerobic exercise (walking or cycling) three or more times per week[22,23,30,35,37,42,58]. Therefore data suggest that while the strong exercise is detrimental, the moderate exercise (appropriate level) is of great benefit because it improves, as shown by our experimental *in vivo* in RTR study[22], the physical strength while decreasing IL6 levels, thus clearly indicating that the net biological effect is overwhelmingly positive.

Anxiety and depression

The quality of life and the psychological status are impaired in patients on maintenance dialysis[20,21]. The most common psychological and psychosocial problems are depression, anxiety and social withdrawal[59-61]. Anxiety and depression are common in RTRs too[62] and contribute to increase cardiovascular risk[63,64].

We have recently demonstrated that physical activity is able to reduce anxiety and depression in RTRs[22].

Why kidney transplanted patients show low rates of exercise ?

Zhong *et al*[65] got to the bottom of this question: these authors believe it depends on the fear of injuring the transplanted graft[66,67], and/or on the transplant professionals' silence about the benefits of exercise[66]. The cause can sometimes be the protective attitude of the family members and friends[35]. Moreover, patients of diverse ethnic and cultural backgrounds may place differential values on exercise and self-care[68,69] or this lack of importance given to physical training can be the consequence of the absence of structural support[65].

CONCLUSION

For patients affected by end-stage renal disease, renal transplant represents a dramatic improvement of quality of life: the freedom from the dialytic treatment might be considered the starting of a second life. Nevertheless, also following a successful renal transplant, several previously taken drugs (i.e., antihypertensive drugs, allopurinol, statins), can't be stopped, whereas new treatments (i.e., immunosuppressive drugs), have to be started thus increasing per se the cardiovascular risk of RTRs (through drug-induced hypertension and dislipidemia). This massive drug administration and the need for a strict medical follow-up may justify both the persistence of depression and the interest in "non-pharmacological" therapies, which can improve psychical and physical health of RTRs.

The analysis of the available data allows to state that an appropriate dose of physical training is a useful, safe and non-pharmacological contribution to RTRs treatment through the reduction of the of the risks of cardiovascular disease, the improvement of the biology of transplantation, the increase of energetic metabolism, and allows for a better quality of life in these subtype of patients. The studies analysed in this review do not distinguish among different subgroups, such as different "age groups", of RTRs with respect to different physical exercise programs[22,23,30,35,37,42,58]. This non-distinction is a further confirmation that, regardless of the type, physical activity can always yield remarkable health benefits. Despite the positive effects of physical activity, most RTRs do not exercise adequately according to the routine practice recommended by the Surgeon General (3 times per week)[70].

It is now the moment to fill this gap, it is now the moment that kidney transplantologists consider exercise not as a luxury accessory, but as integral part in the complex treatment of RTRs

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