**TITLE:** The effects of statin on the progression of cardiovascular disease in kidney transplant patients

**1. INTRODUCTION**

The transplant is a widely used renal replacement therapy and has been associated with improved quality of life, lower cost, less morbidity and increased survival rate when compared to dialysis (1-4). Despite the kidney transplant is an effective therapy, the 5-year survival is 90.2% for patients with living donor transplantation and 81.1% for those with cadaver donor (5).

Cardiovascular complications are the leading cause of mortality (6), comprising 30-60% of deaths in this population (6). Acute coronary syndrome is the most common cardiovascular event in transplant, affecting about one in every 100 patient per year (7-10). Studies suggest that coronary heart disease is more aggressive in patients with deficit of renal function, as evidenced by the increased frequency, severity and more rapid progression of atherosclerotic lesions in these patients than in the general population (11).

Coronary calcification was considered a marker of atherosclerosis, were a common finding in patients with chronic kidney disease (CKD) (12,13). Some studies had showed that the extent of calcification is predictive of cardiovascular events and death (14,15). In previous studies of our group, using Multi-slice coronary tomography, it was observed that 79% in hemodialysis patients, 59% in peritoneal dialysis and 56% in conservative treatment (pre-dialysis) had some degree of calcification (16 -18). It is noteworthy that severe calcification, represented by calcium score above 400, were present in respectively 31%, 23% and 22% of patients on hemodialysis, peritoneal dialysis and conservative, indicating a high risk for cardiovascular events.

Few data are available on coronary calcification in patients after renal transplantation (19,20). If on one hand the successful transplant restores kidney function, a fact that may contribute to decrease the occurrence and progression of vascular calcification, on the other hand, these patients often hypertension, diabetes, dyslipidemia, obesity and smoking, known risk factors for atherosclerosis, to which is added the use of immunosuppressive drugs, the presence of inflammation, rejection, graft dysfunction (21,22), infection (23), proteinuria (24), hyperhomocysteinemia (25) and anemia (26), factors that They may also be associated with cardiovascular disease (CVD) in this population.

About these factors, inflammation stands out, which seems to be the main link between the traditional risk factors and non-traditional. The state of chronic inflammation was often observed in patients in different stages of CKD (27), as well as those on dialysis (28). In transplant patients the data are controversial. Some studies have shown a significant decrease in inflammatory markers in the first two months post-transplant in the absence of rejection (29). However, others studies have shown that despite the initial lowering levels of inflammatory markers, especially interleukin-6 and TNF, they are increased 12 months after transplantation (30).

The presence of inflammation has been linked to the loss of the renal graft and CVD (31,32). One possible explanation is that inflammation determines endothelial dysfunction, starting point of atherosclerosis (33). In fact, studies have shown the presence of endothelial dysfunction in kidney transplant patients, even those who had no risk factors for CVD (34). Furthermore, the inflammation decreases the action of lipases with consequent increase of LDL cholesterol (35). It is noteworthy that the oxidation of LDL has been implicated as the main mechanism of atherosclerosis (36).

Dislipidemia é um achado freqüente em pacientes transplantados. Em estudo multicêntrico observou-se que após um ano do transplante, 80 a 90% dos pacientes apresentavam concentrações de colesterol total > 200 mg/dL e 90 a 97% LDL > 100 mg/dL (37,38). As causas de dislipidemia após o transplante estão relacionadas à presença de síndrome nefrótica, disfunção do enxerto ou/e ao uso de hipotensores e imunossupressores principalmente corticoesteróides (39). O uso de tacrolimus tem sido associado à menores concentações dos níveis séricos de colesterol e triglicérides (40,41).

Another risxk factor that may contribute to cardiovascular disease in transplanted patients is the change in bone mineral metabolism. Similar to the dialysis patients, some studies suggest that changes in bone metabolism, especially the decrease in bone mass, are associated with mortality after transplantation (42).

Post-transplant bone disease is a complex situation and dependent on the pre-transplant renal osteodystrophy (43). Factors such as the partial re-stabilization of renal function and chronic administration of drugs that negatively influence on bone metabolism, especially corticosteroids, are the main causes of non-maintenance of post transplant osteodystrophy. Indeed, we observed a decrease of bone mass in post-transplant patients using glucocorticoids (44-46), data about another immunosuppressors are limited, but the use of tacrolimus are also appears to be associated with bone demineralization (47).

Another factor to consider is obesity, as transplant patients tend to gain weight (48,49). The increase of visceral fat has been associated with increased risk of CVD in the general population (50). This consequence may be related to the release of adipokines by adipose tissue (51). However the role of visceral fat in the CVD has not yet been proven in kidney transplant patients.

Some studies have shown that the use of statins in patients with CKD decreases cholesterol concentrations (52), and possibly attenuating endothelial dysfunction by its anti-inflammatory properties (53).

Despite not having been demonstrated increased survival of diabetic patients on dialysis with statin use (54), the ALERT study proved the effectiveness of these drugs in lowering cholesterol levels and the occurrence of cardiovascular events in transplant patients (55.56 ).

In summary, kidney transplant can control several factors related to the onset and progression of vascular calcification, moreover, it is also associated with several potentially modifiable atherogenic factors, such as dyslipidemia and inflammation. The use of statins can lead to a decrease in the progression of vascular calcification after renal transplantation with consequent improvement in survival in this population.

**2. OBJECTIVES**

. 2.1 PRIMARY:

\* Evaluate the role of statins on the progression of cardiovascular disease in patients undergoing kidney transplantation

2.2 SECUNDARY:

* Identify the factors that contribute to the development or progression of cardiovascular disease in post kidney transplant
* To evaluate the relationship between cardiovascular disease and inflammation, bone metabolism, nutritional status and renal function
* To assess the effects of statins in post transplant renal function
* Analyze the effects of statins on cardiovascular events

**3. METODOLOGY**

Prospective, randomized, controlled, including patients with recent donor-vivo kidney transplant and regularly followed in the post-transplant clinic in Oswaldo Ramos, UNIFESP Foundation.

Number of selected patients: 150

Number of patients randomized: approximately 120

Patients will be randomized 1: 1 in statins and control groups.

Follow-up period: 12 months

**POPULATION:**

The selection will include patients in the immediate post-kidney transplant.

1. ***Inclusion criteria:***

* Use of calcineurin inhibitor as immunosuppressive treatment throughout the study selection periodhomem ou mulher com 18 a 65 anos
* Recent Postoperative renal (1-2 months)
* Estimated clearance of creatinine greater than 30 ml / min

2. ***Exclusion criteria:***

* patients with a formal indication for statin or fibrate
* patients with prescription of statin and fibrate within 3 months prior to transplantation
* cardiovascular event in the three months before renal transplantation
* patients with CHF functional class III or IV
* patients with severe hepatic impairment (Child C)

**LABORATORY EVALUATION:**

A whole blood sample will be collected fasting at baseline, 6 and 12 months for dosage: blood count, urea, creatinine, glucose, ALT, CPK, cholesterol, LDL, HDL and VLDL, triglycerides, blood level of tacrolimus or cyclosporine.

The same whole blood sample collected in fasting at baseline and after 12° months also be used for determination of: albumin, C-reactive protein, interleukin 6, venous blood gases, ionized calcium, phosphorus, alkaline phosphatase, PTH and 1, 25 (OH) 2 vitamin D.

It will be collected fasting at baseline, 6 and 12 months a urine sample to conduct examination of urine I.

Renal function is evaluated by formula CKD-EPI.

**CARDIOVASCULAR PARAMETERS:**

Cardiovascular parameters will be evaluated by echocardiography, multi-slicecoronary **tomography** scan and evaluation of pulse wave velocity.

## Cardiovascular events will be recorded during the study through suggestive history, myocardial necrosis markers, ECG, echocardiography, myocardial scintigraphy and / or coronary coronary angiography.

## *Echocardiogram*

All patients underwent echocardiography at baseline and after 12 months of study entry. These exams will consist of evaluations with M-mode, two-dimensional and Doppler using Philips HDI 5000 (Philips Electronics, Netherlands). All analyzes will be carried out in accordance with the recommendations of the American Society of Echocardiography.

***Coronary tomography***

Coronary tomography will be held in Brazil Diagnostic Center with LightSpeed Pro16 equipment (GE Healthcare, Milwaukee, USA) at baseline and after 12 months of study entry. The calculation of calcium score is based on formulas that use volume measurements, density and area of the lesions, and expressed in units Agatston modified.

***Pulse wave velocity***

At baseline, 6 and 12 months will be obtained pulse wave velocities of the carotid and femoral arteries by a Complior®SP equipment (Artech Medical, Pantin, France) and analyzed by appropriate software.

***clinical variables***

Acute rejection was can defined as an acute deterioration of renal function, which is associated with specific pathological changes of the graft.

Chronic allograft nephropathy is a diagnosis suggested by the clinical picture which usually corresponds to a slow and gradual increase in serum creatinine, appearance / increase in proteinuria and worsening of blood pressure control. Usually a biopsy of the graft is performed and provides the degree and staging of renal impairment.

Cardiovascular disease wera defined as a spectrum of diseases ranging coronary heart disease, cardiomyopathy, heart valve disease, arrhythmia, cerebrovascular disease or peripheral vascular disease. Some or all of these entities can coexist or advancing in sequence over time.

Waist circumference is the most reliable anthropometric index of intra-abdominal fat. It is the measurement of the circumference of the abdomen in the middle of the distance between the iliac crest and the lower costal margin. It is recommended that this value be below 94 cm in men and 80 cm in women.

Body mass index (BMI) is used to estimate normal weight, overweight, obesity or malnutrition in the individual. It is obtained by dividing weight by height squared. Values between 25 kg / m² and 29.9 kg / m² define overweight and values above 30 kg / m² define obesity.

**4. TRATMENT**

Rosuvastatin is administered at a dose of 10mg once daily in the corresponding group.

All patients will be treated with immunosuppressive agents according to pre-established by the Foundation Osvaldo Ramos and adjusted the dose according to blood level of tacrolimus protocols.

Hypertensive patients was treated with calcium channel blockers, beta-blockers, converting enzyme inhibitors, diuretics and other hypotensive classes, according to the blood pressure control.

         Patients with hemoglobin less than 11 g / dL, receive recombinant human erythropoietin, after being away another cause of anemia and verified iron stores. The iron deficient patients (ferritin <100 ng / mL and / or transferrin saturation <20%) will receive intravenous iron supplementation (Noripurum 200mg / month).

Patients with hyperphosphatemia (P> 4,6mg / dl) will make use of binders in accordance with the recommendations of DOKQI / ASN.

**5. CRONOGRAMA DO ESTUDO**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Selection | Baseline  (1-2 months) | 6 o. months | 12 o. months |
| **informed consent** | X |  |  |  |
| **Criteria inclusion / exclusion** | X |  |  |  |
| **history** |  | X | X | X |
| **physical examination** |  | X | X | X |
| **cardiovascular events** |  | X | X | X |
| **Waist circumference and BMI** |  | X | X | X |
| **Laboratory examination** |  |  |  |  |
| Venous blood gases, Cai, P, AF, PTH, 1,25OHVitD, inflammatory markers, urine I |  | X |  | X |
| Blood count, cholesterol, kidney function, tacrolimus or cyclosporine, blood glucose, ALT, CPK |  | X | X | X |
| **Echocardiogram** |  | X |  | X |
| **Coronary tomography** |  | X |  | X |
| **Pulse wave velocity** |  | X | X | X |
| **Adverse events** |  |  | X | X |

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