Atherosclerosis After Kidney Transplantation: Changes of Intima-Media Thickness of Carotids During Early Posttransplant Period

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Introduction: The aim of this study was to evaluate atherosclerotic changes in the carotid artery following kidney transplantation.

Materials and Methods: Twenty-six nonsmoker kidney allograft recipients who did not have cardiovascular disease or diabetes mellitus were enrolled in the study. The carotid intima-media thickness (IMT) was measured at 12 points using B-mode ultrasonography. The mean of the measured values was considered as the patient's IMT. We followed the patients and changes in the carotid IMT were evaluated every 2 months up to the 6th posttransplant month.

Results: The mean age of the patients at transplantation was 41.5 ± 11.1 years. The mean baseline IMT was 0.84 ± 0.22 mm. During the follow-up period it reached 0.85 ± 0.22 mm, 0.87 ± 0.23 mm ($P = .01$), and 0.88 ± 0.24 mm ($P = .002$) after 2, 4, and 6 months, respectively. The IMT measures significantly correlated with the age and body mass index. Using the IMT cutoff points of 0.75 mm for stroke and 0.82 mm for MI, we found that 57.7% and 68% of the patients were at the risk of stroke at baseline and 6 months after transplantation ($P < .001$). Also, 46.2 % of the patients were at the risk of MI at baseline that rose to 53.8% at the end of the study ($P < .001$).

Conclusion: Atherosclerosis is an early event after kidney transplantation even in asymptomatic patients and those without major risk factors such as cardiovascular disease, diabetes mellitus, and smoking. Early diagnosis and treatment of atherosclerosis is of utmost importance.

Keywords: kidney transplantation, atherosclerosis, cardiovascular diseases, carotid artery, intima-media thickness

Urol J. 2007;4:105-10.
www.uj.unrc.ir

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Received January 2007
Accepted April 2007

INTRODUCTION

Cardiovascular diseases (CVDs) are the most prevalent causes of morbidity and mortality after kidney transplantation.[1] It is estimated that CVDs are responsible for 40% to 55% of all deaths after kidney transplantation, the majority of which being atherosclerosis and coronary artery disease (CAD).[2] The high prevalence of such diseases is the result of a combination of traditional and transplantation-specific risk factors.[2,3] Like the healthy individuals, many kidney-transplanted patients remain asymptomatic until the heart disease occurs. Therefore, early diagnosis and management of atherosclerosis in these patients is of utmost importance.[4]

While procedures like coronary angiography have good sensitivity and specificity for detecting the atherosclerotic lesions, their complexity, expense, and high rate

of complications make them an inappropriate measure for screening and monitoring the progress of atherosclerotic lesions. Findings about the mirror atherosclerotic changes in the carotid artery along with the process of general atherosclerosis by the high resolution B-mode ultrasound scan have made this noninvasive method a good measure for assessment of asymptomatic atherosclerosis both in general population and end-stage renal disease (ESRD) patients.[5-7] Ultrasonographic measurement of the intima-media thickness (IMT) in the carotid arteries is used as an indicator of coronary atherosclerosis in these populations.[5] This method has a good reproducibility index with acceptable interobserver and intra-observer variabilities.[8,9] There is also a close relation between the morphology of the carotid artery wall and development of CAD.[10,11] In the general population, the risks of the first myocardial infarction (MI) and stroke increase with the IMTs greater than 0.82 mm and 0.75 mm, respectively.[12] It is also found that a progression rate of 0.034 millimeters per year or more in the carotid IMT significantly increases the risk of future cardiovascular events.[12]

Despite a handful of studies that have evaluated the risk of CAD and atherosclerosis by measurement of the carotid IMT in general population and in ESRD patients, there is a lack of evidence on the progression of atherosclerosis after kidney transplantation.[13-16] Information on the course of atherosclerosis after kidney transplantation would be helpful for development of policies for early detection and proper management of CVD and prevention of its life-threatening consequences. The aim of this study was to evaluate atherosclerosis by measurement of the carotid IMT at the time of kidney transplantation and during the first 6 months after the transplantation period.

MATERIALS AND METHODS

Patients and Setting

Between June 2005 and March 2006, we recruited 26 consecutive kidney allograft recipients in a longitudinal study at Shaheed Labbafinejad Medical Center. Candidates for kidney transplantation who consented to participate in the study were enrolled. The Inclusion criteria were an age between 25 and 65 years of age, negative history of CVD (such as MI, coronary bypass surgery, congestive heart disease, etc), stroke, diabetes mellitus (DM), or cigarette smoking and no participation in other clinical studies on evaluation of cardiac diseases. On the other hand, the patients who had one of the followings during the course of the study were excluded: unstable condition of the transplanted kidney (serum creatinine > 3 mg/dL and/or blood urea nitrogen > 50 mg/dL), cyclosporine A intoxication according to the recommended values by International Consensus Statement,[17] a new onset of any severe disease (such as MI, stroke, DM), and administration of antihyperlipidemic agents. The ethics committee of Shaheed Beheshti Medical University on Human Research approved the study and all the participants signed a written consent before enrollment into the study. All patients received kidney transplant from a living donor and were under triple immunosuppressive regimen consisting of cyclosporine microemulsion (Neoral, Novartis), mycophenolate mofetil (Cellcept, Roche), and prednisolone.

Before kidney transplantation, demographic and anthropometric indices (age, sex, height, and weight), past medical history, history of hemodialysis, and disease duration were recorded. After transplantation, we followed each patient every 2 months for a total period of 6 months and the carotid IMT, as well as other routine posttransplantation evaluations, was examined.

Intima-Media Thickness Measurement

We used longitudinal B-mode Doppler ultrasonography (EUB-565, Hitachi Medical, Tokyo, Japan) for evaluation of 12 carotid segments (the near and far walls of the left and right common carotid arteries, carotid bifurcation, and internal carotid artery) in the supine position. For measurement of the carotid IMT, we first identified the carotid arteries by a transverse scan. Then, by a 90° rotation of the probe angle, 2 parallel lines of the lumen–intima interface and the media–adventitia interface were generated. The distance between these 2 lines was determined as the index of the carotid IMT. The maximum carotid thickness was considered as the IMT value for each specific site. We calculated the mean of these 12 IMT values as the carotid IMT for

each patient. All of the examinations were carried out by a single trained ultrasonographist.

Statistical Analyses

We used relative frequencies for qualitative variables and mean ± SD for quantitative variables. Differences between groups were tested using the Wilcoxon signed rank test, Pearson correlation coefficient test, and the chi-square test, as appropriate. For evaluating the correlation of the IMT with other variables, we used the Pearson correlation coefficient. The SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Ill, USA) was used for statistical analyses. A *P* value of less than .05 was considered significant.

RESULTS

There were 20 men (76.9%) and 6 women (23.1 %) with a mean age of 41.5 ± 11.1 year (range, 25 to 62 years) in our study. The mean duration of ESRD was 4.0 ± 2.7 years. Eight patients (30.8%) had no history of dialysis, while 10 (38.5%) had been receiving hemodialysis for less than 1 year and 8 (30.8%) for more than 1 year. The mean body mass index (BMI) was 23.0 ± 3.8 kg/m^2. Four patients (15.4%) were underweight (BMI ≤ 20), 10 (38.5%) had a desirable weight (BMI, 20 to 24.9), 11 (42.3%) were overweight (BMI, 25 to 29.9), and 1 (3.8%) was obese (BMI, 30 to 39.9).

During the study period, 1 patient developed ischemic heart disease and was therefore excluded from the study. The remaining 25 patients completed the study. The mean baseline IMT was 0.84 ± 0.22 mm. After two months posttransplantation, it increased to 0.85 ± 0.22 mm which was not significantly higher than the baseline value. This increasing trend continued during the 4th and 6th months and showed a significant increase compared to the baseline IMT (0.87 ± 0.23 mm; *P* = .01 and 0.88 ± 0.24 mm; *P* = .002, respectively; Figure 1). The median IMT changes from baseline value after six months of follow-up was 0.02 mm (first quartile, 0.01 mm; third quartile 0.05 mm).

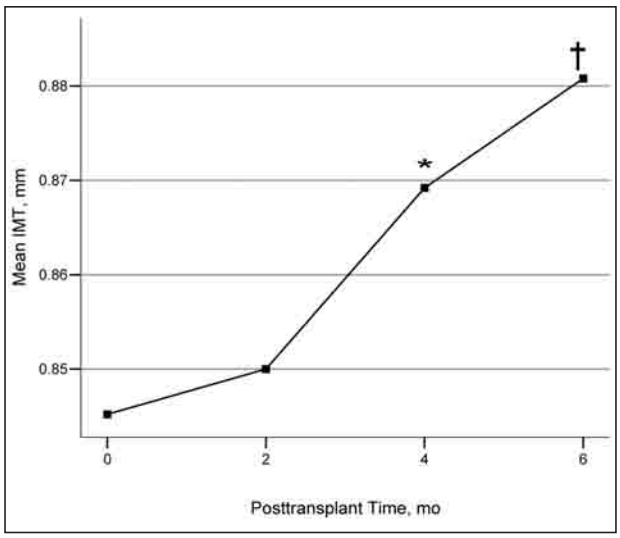

Figure 1. The intima-media thickness (IMT) changes during the 6 posttransplant months.
*P < .05
†P < .01

The patients' age and BMI showed a significant direct correlation with the IMT at different time intervals. This relationship was not observed with the disease duration (Table). In addition, there were not any differences in the IMT values of the patients with regard to their hemodialysis history and gender.

Using the cutoff points for the carotid IMT value defined by previous studies for patients at the risk of MI (IMT > 0.82 mm), stroke (IMT > 0.75 mm), and cardiovascular problems in general (IMT change > 0.034 mm/y), we determined the patients at risk for such events.[12] At baseline, 57.7% of the patients had IMTs greater than 0.75 mm that put them at the risk of stroke. This number reached to 68% six months after the transplantation (*P* < .001). Also, 46.2% of the patients were at the risk of MI at baseline that

Correlation of IMT at Different Times With Clinical and Demographic Factors in Kidney Allograft Recipients*

	IMT			
Factors	**Baseline**	**After 2 Months**	**After 4 Months**	**After 6 Months**
Age	0.59†	0.63†	0.64†	0.63†
BMI	0.34	0.43 ‡	0.46‡	0.45‡
ESRD duration	0.37	0.35	0.30	0.29

*Values are correlation coefficients determined by the Pearson correlation test. IMT indicates intima media thickness; BMI, body mass index; and ESRD, end-stage renal disease.
†P < .01
‡P < .05

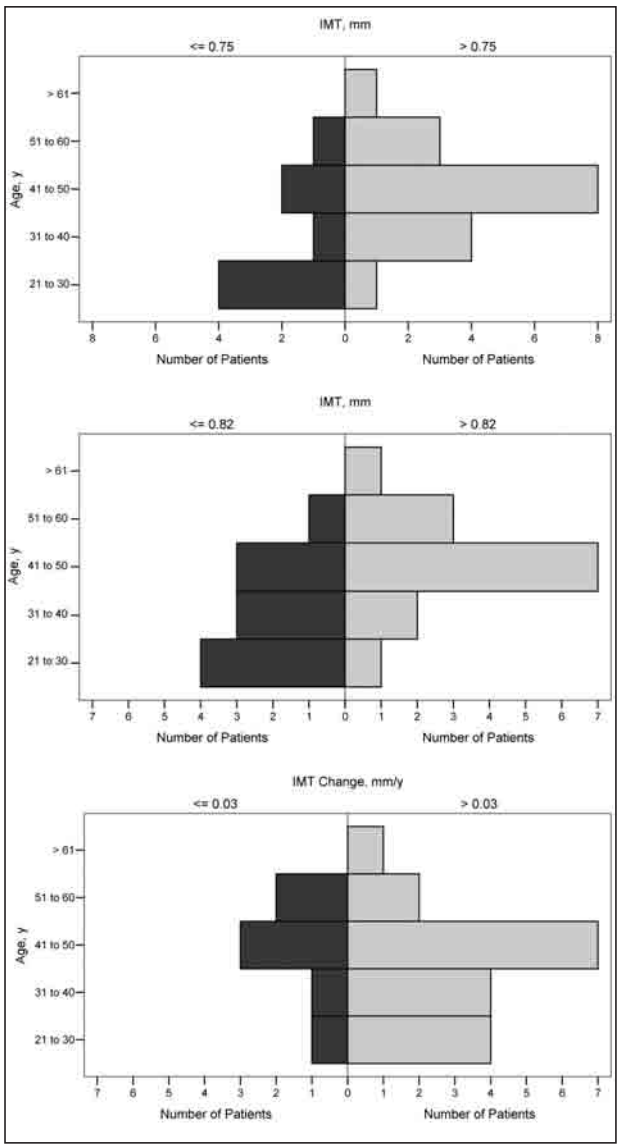

Figure 2. Distribution of the patients at the risk of stroke (IMT > 0.75 mm), MI (IMT > 0.82 mm), and cardiovascular problems in general (IMT change > 0.03 mm/y) based on the age groups. IMT indicates intima-media thickness.

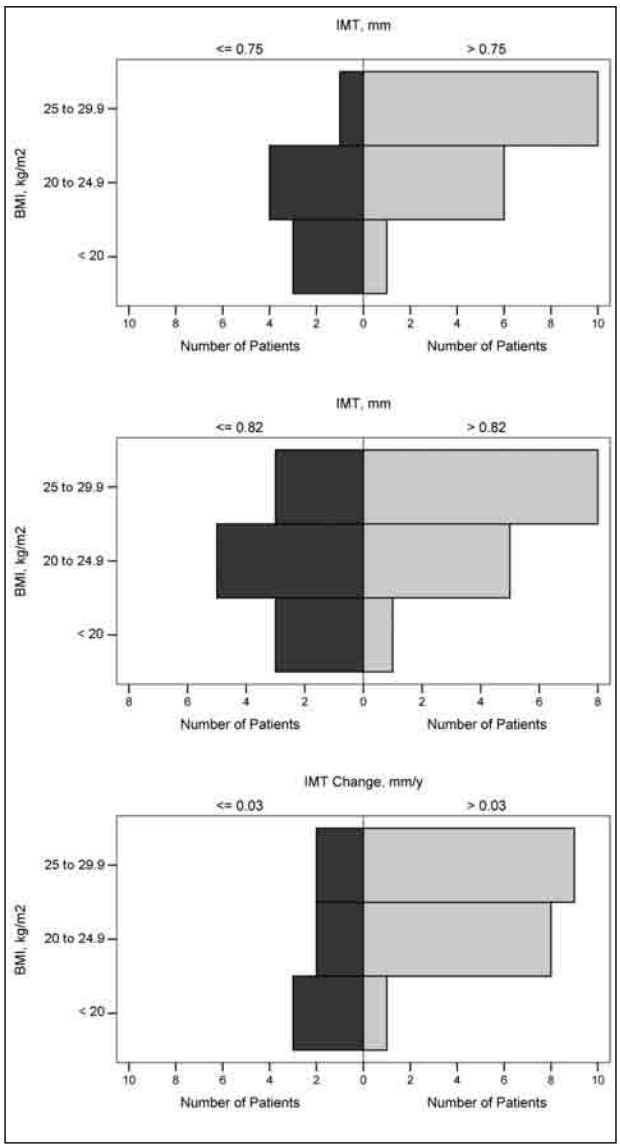

Figure 3. Distribution of the patients at the risk of stroke (IMT > 0.75 mm), MI (IMT > 0.82 mm), and cardiovascular problems in general (IMT change > 0.03 mm/y) based on The BMI categories. IMT indicates intima-media thickness and BMI, body mass index.

rose to 53.8 % at the end of the study ($P < .001$). In the case of IMT changes, 72% of the patients had IMT changes more than 0.02 mm in the period of 6 months. Categorizing patients based on the age (Figure 2) and BMI (Figure 3) showed that the older patients or those with a higher BMI were at a higher risk of developing MI, stroke, or CVD.

DISCUSSION

Our findings showed that the carotid IMT increased over a short time in kidney transplant recipients. The increase rate was so high and in the 4th posttransplant month, it reached a level significantly higher than the baseline. Finding that 6 months after transplantation, 68% of the patients are at the risk of stroke and 54% are at the risk of developing MI confirms the results of previous studies about the high prevalence of CVD in kidney allograft recipients.[1,3] In other studies, Jogestrand and colleagues and Suwelack and colleagues evaluated the characteristics of the carotid artery after kidney transplantation. They found that during a short-time period after kidney transplantation, the carotid atherosclerosis markers are significantly increased compared to those of the healthy individuals.[18,19]

Several studies have evaluated the cause of such a great prevalence of CVD after kidney transplantation. By improving the uremic state, platelet activity, endothelial dysfunction, and microinflammation after kidney transplantation, it is expected that the rate of cardiovascular events be decreased.[20-22] However, a combination of traditional risk factors such as smoking, hypertension, DM, physical inactivity, and anemia along with transplantation-specific risk factors like immunosuppressive drugs (especially cyclosporine A) and new-onset DM seem to overcome the beneficial effects of kidney transplantation on cardiovascular risk factors.[23-25]

There are some kinds of controversies over the role of BMI in kidney allograft recipents' survival. Johnson and associates reported that there was no difference in the short-term and long-term patient and graft survival rates between the obese and nonobese patients.[26] This is while some more studies have reported decreased patient and graft survivals mainly due to CVD.[27,28] Our findings about the correlation of higher carotid IMT values and high relative frequency of patients at the risk of stroke and MI with BMI supports the findings of other studies about the harmful effects of increased BMI both in general population and kidney transplanted patients. Age was another factor which was related to the carotid IMT in our series, in line with the findings of other studies about the progression of atherosclerosis and cardiovascular events in normal population, ESRD patients, and kidney transplanted patients.[29-31]

Other studies have found that longer duration of dialysis and male gender are related to increased carotid IMT[32-34]; however, our results failed to show any association of gender or duration of the previous dialysis with the progression of atherosclerosis in the carotids. We believe that the small sample size of our study is the main cause of such differences.

It is not clear whether the transplantation per se or other comorbid conditions are the cause of such progress in atherosclerosis. The complexity of the situation makes it difficult to isolate a single cause. Further studies with longer follow-up periods are required to pinpoint on the issue. The value of our study lies in the use of a valid and powerful tool—carotid IMT measurement—for evaluation of atherosclerotic changes in kidney transplanted patients. By excluding the patients with a history of CVD, DM, and smoking, we were able to assess the progression of atherosclerosis in the absence of these major confounders. All the participants except one finished the study and it adds to the power of our work. One weakness of our study is the small sample size. Future studies with longer duration and larger sample sizes focusing on the effect of treatment modalities on atherosclerosis markers would be of great usefulness.

CONCLUSION

We observed that atherosclerosis is an early event after kidney transplantation. Special attention should be paid to the older patients and those with CVD risk factors such as a high BMI. Early treatment and preventive measures could be useful in increasing the patient and graft survivals.

CONFLICT OF INTEREST

None declared.

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