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ORIGINAL ARTICLE

Carotid intima-media thickness in kidney transplant recipients

Rizna Abdul Cader [a,*], Noor Izyani Zakaria [a], Yazmin Yaacob [b], Shamsul Azhar Shah [c]

[a] Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia
[b] Department of Radiology, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia
[c] Department of Public Health, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia

KEYWORDS
ADMA;
cardiovascular risk;
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hs-CRP;
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Abstract *Background/Purpose:* Cardiovascular disease is the leading cause of mortality among kidney transplant recipients. Carotid intima-media thickness (CIMT) of the common carotid artery is a surrogate marker for early atherosclerosis. We wanted to compare the prevalence of increased CIMT among kidney transplant recipients with matched controls and its association with clinical and laboratory parameters.
Methods: A comparative cross-sectional study involving kidney transplant recipients and controls matched for age, sex, chronic kidney disease staging, and cardiovascular risks was used. CIMT measurements were done using carotid ultrasound and considered increased if $>75^{th}$ percentile matched for age- and sex-matched normal controls. Standard laboratory investigations, high sensitivity C-reactive protein, and asymmetric diamethylarginine were analyzed.
Results: Thirty-six kidney transplant recipients (25 men, 11 women) with a median age of 41 years [interquartile range (IQR), 38–52 years] and 36 matched controls with a median age of 44 years (IQR, 37–53 years) were enrolled. There were no demographic differences between the two groups. Kidney transplant recipients had a significantly increased CIMT, 0.8 mm (IQR, 0.6–0.9) compared to matched-controls 0.55 mm (IQR, 0.5–0.7, $p = 0.001$). Two thirds of kidney transplant recipients had increased CIMT, which was associated with a higher low density lipoprotein (LDL) ($p = 0.022$) and higher hemoglobin ($p = 0.006$). Smoking status ($p = 0.058$) and male gender ($p = 0.073$) had a trend towards significance to increased CIMT. Multiple linear stepwise regression demonstrated both age and hemoglobin were independent predictors of CIMT ($p < 0.001$). We found no relationship between high sensitivity C-reactive protein and asymmetric diamethylarginine with CIMT.

* Corresponding author. Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, Cheras, 56000 Kuala Lumpur, Malaysia.
E-mail address: rizna_c@hotmail.com (R.A. Cader).

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Conclusion: CIMT among our kidney transplant recipients was significantly higher compared to controls thereby increasing their cardiovascular risk.
背景: 心血管疾病是腎臟移植接受者的主要死因,總頸動脈的內膜中膜厚度 (CIMT) 則是早期動脈粥樣硬化的替代性指標。在本研究中,我們比較了 CIMT 增厚於腎臟移植接受者與匹配對照組之間的盛行率,並調查了 CIMT 與臨床及實驗室參數之間的關聯。
方法: 這是一項橫斷式比較性研究,涉及的對象包括腎臟移植接受者、及與其匹配 (年齡、性別、慢性腎病分期及心血管風險) 的對照者。CIMT 以頸動脈超音波測量,增厚的定義為對應年齡性別匹配正常對照組之 $> 75^{th}$ 百分位數。其他測量項目除了標準實驗室參數外,亦包括高敏感度 C-reactive protein (hs-CRP) 及 asymmetric diamethylarginine (ADMA)。
結果: 分析對象包括 36 位年齡中位數 41 歲 (38,52) 之腎臟移植接受者 (25 男、11 女) 及 36 位年齡中位數 44 歲 (37,53) 之匹配對照者,兩組間的人口學特徵並無不同。腎臟移植接受者之 CIMT 為 0.8 mm (0.6,0.9 mm),明顯高於匹配對照者之 0.55 mm (0.5,0.7 mm) ($p = 0.001$)。腎臟移植接受者之間,3 分之 2 呈現 CIMT 增厚的情形,較厚的 CIMT 與較高的低密度脂蛋白 ($p = 0.022$) 及較高的血色素 ($p = 0.006$) 有關。吸煙狀況 ($p = 0.058$) 及男性性別 ($p = 0.073$) 亦有傾向與 CIMT 增厚有關。多變項線性逐步迴歸分析顯示,年齡及血色素均是CIMT的獨立預測因子 ($p < 0.001$)。對於 CIMT 與 hs-CRP 或 ADMA 數值之間,我們並未發現明顯的關係。
結論: 在本研究的腎臟移植接受者中,CIMT 明顯高於對照組,因此具較高的心血管風險。

Introduction

Kidney transplantation not only improves quality of life in end-stage renal disease patients but also gives them a long-term survival advantage by reducing their mortality risk compared to maintenance dialysis.[1] Cardiovascular disease (CVD) is a major cause of morbidity and mortality in kidney transplant (KTx) recipients and death from CVD is the commonest cause of graft loss.[2] Although KTx recipients have a lower risk of fatal and nonfatal cardiovascular events compared to dialysis patients, their risk is much higher than the general population.[3] In addition to the traditional risk factors, nontraditional risk factors that contribute to CVD in KTx recipients include reduced kidney function post-transplantation, longer dialysis duration prior to transplantation, episodes of graft rejection, the effect of immunosuppressive drugs, hyperhomocysteinemia, and elevated levels of lipoprotein(a), C-reactive protein (CRP), interleukin-6, and asymmetric dimethylarginine (ADMA).[4–7] Accurate risk stratification of these patients will allow targeted interventions to prevent or limit adverse outcomes.

Atherosclerotic structural changes as detected by high-resolution B-mode ultrasound precede clinical findings by several decades. Endothelial dysfunction has been shown to be predictive of future cardiovascular events.[8] Although kidney function improves, endothelial dysfunction persists after transplantation and the true mechanism is still poorly understood.[9] Carotid intima-media thickness (CIMT) of the common carotid artery is a surrogate marker used to predict early atherosclerosis.[9,10] The prevalence of subclinical atherosclerosis measured by CIMT is greater in KTx recipients compared to the general healthy population.[3] Endothelial dysfunction and ongoing chronic inflammation due to multiple risk factors including immunosuppressive therapy play an important role towards premature subclinical atherosclerosis in KTx recipients.[11]

Previous studies have compared KTx recipients with healthy controls. Therefore, in our study we selected a control group who are not only matched for age but also CVD risk factors such as hypertension, diabetes mellitus, and staging of chronic kidney disease. We wanted to compare CIMT between KTx recipients and non-KTx matched controls and determine the factors influencing the CIMT in KTx recipients.

Methods

This was a comparative cross sectional study involving KTx recipients at Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Kuala Lumpur, Malaysia, from January 2014 to August 2014. The study was approved by the UKMMC Ethics and Research Committee (Study Code FF-2014-022). All KTx recipients attending the nephrology outpatient clinic at our institution were screened. KTx recipients $>$ 6 months post-transplantation, aged $\geq$ 18 years and on stable triple immunosuppressive therapy for $>$ 6 months were included. We excluded patients with documented CVD (ischemic heart disease, stroke, peripheral artery disease) and any patients who were pregnant. The matched control group was selected from volunteers matched for age, sex, chronic kidney disease staging, underlying hypertension, and diabetes mellitus from nephrology and medical clinics in UKMMC. We excluded controls who were either pregnant, had documented CVD, or were on any immunosuppressive therapy.

After obtaining informed consent, history regarding previous cardiovascular events (defined as any coronary event such as myocardial infarction, angioplasty or coronary artery bypass surgery, and cerebrovascular accident) were obtained from patients' medical records. Baseline blood investigations for hemoglobin level, renal profile, fasting blood sugar, glycated hemoglobin, and fasting lipid profile were collected from both groups of patients. High-sensitivity CRP (hs-CRP) and ADMA were collected only in KTx recipients.

In addition to a mean of two seated blood pressure (BP) readings, ambulatory BP monitoring was carried out in KTx recipients using the BPRO machine (model T6400; Healthstats, London, UK). BP readings were taken at 15-minute