Cardiac and vascular changes with kidney transplantation

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ABSTRACT

Cardiovascular event rates are high in patients with chronic kidney disease (CKD), increasing with deteriorating kidney function, highest in CKD patients on dialysis, and improve with kidney transplantation (KTx). The cardiovascular events in CKD patients such as myocardial infarction and heart failure are related to abnormalities of vascular and cardiac structure and function. Many studies have investigated the structural and functional abnormalities of the heart and blood vessels in CKD, and the changes that occur with KTx, but the evidence is often sparse and occasionally contradictory. We have reviewed the available evidence and identified areas where more research is required to improve the understanding and mechanisms of these changes. There is enough evidence demonstrating improvement of left ventricular hypertrophy, except in children, and sufficient evidence of improvement of left ventricular function, with KTx. There is reasonable evidence of improvement in vascular function and stiffness. However, the evidence for improvement of vascular structure and atherosclerosis is insufficient. Further studies are necessary to establish the changes in vascular structure, and to understand the mechanisms of vascular and cardiac changes, following KTx.

Key words: Ejection fraction, endothelial function, kidney transplantation, left ventricular hypertrophy, pulse wave velocity

Introduction

Cardiovascular changes related to chronic kidney disease (CKD) are common and a major cause of morbidity and mortality.[1] Large population-based studies have demonstrated a high incidence of cardiovascular events in the CKD patients, increasing with deteriorating renal function, with the highest rates in patients on dialysis.[2-5]

Kidney transplantation (KTx) is associated with improvements in mortality due to cardiovascular events, namely myocardial infarction.[6,7] However, the risk is still high compared to the general population.[8]

The pathological changes in cardiac and vascular, structure and function in CKD are relatively well known, however, there is evidence that improvements occur following KTx and thus, may explain the reduced cardiovascular event rates in the transplanted population.[1,8]

The aim of this review is to summarize the changes in cardiac and vascular, structure, and function, with KTx, from the available evidence.

Methods

A literature search was conducted on PubMed using a generic search as well as a MESH term search involving the following prospective study, renal transplantation, CKD, echocardiography, left ventricular hypertrophy (LVH), left ventricular function, cardiac systolic function, cardiac diastolic function, pulse wave analysis, carotid intima-media thickness (CIMT), vascular endothelium, flow-mediated dilatation (FMD), endothelial function, endothelial dysfunction, endothelium, endothelial

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dependent dilatation, augmentation index (AIx), atherosclerosis, and arteriosclerosis.

The search results were then analyzed in order to select the prospective studies that explored any cardiac and vascular, structure and function, changes before and after renal transplantation.

Cardiac changes with kidney transplantation

Structure

There is ample evidence that the cardiac hypertrophy associated with CKD improves with KTx. Various echocardiographic studies have demonstrated such improvements in LVH with KTx. Table 1 lists the prospective studies of LVH in CKD patients undergoing KTx.

The total numbers of patients included in the review of cardiac structural changes were 612 of which there were 63 children and 549 adults. The average ages spanned 8 ± 5 years in children to 47 ± 12 years in adults. The largest study was conducted by Rigatto *et al*. consisting of a prospective analysis of 143 patients and the smallest sample size was of 13 patients in three studies.[9,13,17,20]

In 11 out of the 15 studies, a significant reduction of mean LV mass index (LVMI) was noted after transplantation. The remaining four studies showed changes in LVH prevalence and LVMI but the differences were not significant.[12,14,16] The greatest improvement in LVMI was noted by Himelman *et al*., with an average decrease of 55 g/m^2 in 36 patients ($P < 0.001$).[18]

The change in LVMI was noted through a range of follow-up intervals after transplantation: As early as 3.2 ± 2.8 months and as late as 4 years postoperatively. Interestingly, in one long-term follow-up study, significant LVMI regression was observed only in the first 2 years after KTx and noted to plateau and stop

Table 1: Summary of studies showing changes in cardiac structure before and after KTx

Author	Number of patients	Modality	Changes in LVH	Age (years)	Mean follow-up
Becker-Cohen *et al*.[9]	13 children	Echo	LVMI decreased from 45.4±12.6 g/m^2 to 34.9±10.4 g/m^2 LVH prevalence decreased from 54% to 8% (P=0.03) after KTx	7.9±4.9	17.2±6.3 months after KTx
Keven *et al*.[10]	28	Echo	LVMI decreased from 132±38 to 119±32 g/m^2 (P=0.02)	34±9	12 months after KTx
Mitsnefes *et al*.[11]	29 children	Echo	LVMI decreased from 43.9±17.8 g/m^2 to 39.3±12.0 g/m^2, however, the change was not significant, P=0.19), no significant difference was noted in the prevalence of LVH (52% pretransplant and 56% posttransplant, respectively)	15.4±5.1	1.9±1.6 year mean difference between pre and post-KTx echo
Alvares *et al*.[12]	21 children	Echo	The LVMI decreased from 139 g/m^2 to 104 g/m^2, representing a 21% reduction of the initial value, but this reduction was not of statistically significant	11.8±2.6	30.2±15 months after KTx
Rigatto *et al*.[13]	143	Echo	LVMI fell from 161 g/m^2 at 1-year to 146 g/m^2 (P=0.009) g/m^2 after 2 years. No further regression was seen in years 3 and 4	35±2	1, 2, 3 and 4 years post-KTx
McGregor *et al*.[14]	20	Echo	No significant change in LVMI or EDD. ESD improved in 60% of patients (median 3.3 vs. 3. 7 cm; P=0.031)	38.3 (range 18.7-64.5)	4 months after KTx
Parfrey *et al*.[15]	102	Echo	In the 41% (n=41) with concentric LVH before transplantation, the LVMI improved from 158±39 g/m^2 to 132±39 g/m^2. In 32% with LV dilatation, LVMI fell from 166±55 g/m^2 to 135±37 g/m^2	37±12	47±23 months after KTx
Hüting[16]	24	Echo	LVH (71 vs. 67%; P=NS) LV muscle mass (332±104 vs. 329±94 g; P=NS)	47±12	Echo performed immediately before and 41±30 months after RT
Torres *et al*.[17]	13	Echo	The LVMI (g/m^2) reduced progressively, from 243±82 to 190±38 at the end of the study (P<0.05)	33±10	12 months after KTx
Himelman *et al*.[18]	36	Echo	LVM by echocardiography decreased from 237±66 to 182±47 g (P<0.001), a decrease of 23%	40±13	1.5±1.4 years after KTx
Vaidya *et al*.[19]	105	Echo	Of the 105 patients, 57 had significant LVM regression (mean difference −37.2±31.3 g/m^2) and 48 had no significant regression (mean difference 15.7±17.1 g/m^2)	54	1.7 years after KTx
Ikäheimo *et al*.[20]	13	Echo	LV posterior wall thickness decreased by 1.1±1.7 mm (P<0.05) and LVM decreased by 54.2±43.3 g/m^2 (P<0.001)	31 (range 20-50)	Average of 4.5 months before KTx and 9 months after KTx
Cueto-Garcia *et al*.[21]	18	Echo	LVM decreased from 286.6±64.4 to 182.7±55.7 g P<0.0005 after KTx	28.8	31.16±23.59 weeks after KTx
Dudziak *et al*.[22]	23	Echo	LVMI decreased (from 126.4±18.0 g/m^2 to 104.6±15.9 g/m^2, P<0.05). The incidence of LVH decreased from 70% to 40% (P<0.05)	43.3±10.9	3.2±2.8 months after KTx
Ferreira *et al*.[23]	24	Echo	LVH, incidence decreased from 75% before transplantation to 52.1% at 12 months after transplantation (P=0.125)	33.5±10.0	12 months after KTx

LV: Left ventricular, LVH: Left ventricular hypertrophy, LVMI: Left ventricular mass index, LVM: Left ventricular mass, ESD: End systolic diameter, EDD: End-diastolic diameter, KTx: Kidney transplantation, NS: Not significant, RT: Renal transplantation

beyond this time frame.[13] However, whether this trend is reflective of the general transplanted population and reproducible, remains to be seen. A major drawback of this study was that at 4 years posttransplantation, only 18 out of the 143 initial patients were available for follow-up echocardiograms.[13] Further long-term follow-up studies are, therefore, required in order to establish the potential course of LVH, years after transplantation.

The reduction in LVMI was predominantly significant for adults' post-KTx. Although an average reduction in LVMI did occur in the studies focusing on children, in 2 out of the 3 studies, this change was not significant.[9,11,12] This questions whether differences exist in the way hearts in children respond physiologically to the effects of a kidney transplant compared to adults.

It is unclear from the studies whether varying ages of adults influences the degree of change in LVMI. The study by Vaidya *et al*., explored 105 patients with a mean age of 54 years and showed a regression of 37.2 ± 31.3 g/m^2 ($P < 0.05$) in 57 patients after transplantation.[19] In contrast, patients in the study by Ikäheimo *et al*. had a mean age of 31 years and showed a reduction of 54.2 ± 43.3 g/m^2 in 13 patients ($P < 0.001$).[20] This could possibly indicate that with the exclusion of children and adolescent ages, the younger a CKD patient has a kidney transplant, the more the potential regression of the LVMI and LVH. These observations suggest more research is necessary to compare the LVMI change in younger versus older adults. The encouraging point, however, is that some degree of LVMI regression did occur irrespective of adult age.

Contrary to the above, rather than age, the length of follow-up time after transplantation may determine the degree of LVMI regression. McGregor *et al*. analyzed follow-up scans at an average of 4 months after KTx and found no significant difference between pretransplant and posttransplant LVMI.[16] However, Parfrey *et al*. analyzed patients with an average of 47 ± 23 months after transplantation and found that the LVMI improved from 166 ± 55 g/m^2 to 135 ± 37 g/m^2.[17] Another research avenue that could be explored is whether the more LVH one has at baseline is associated with greater regression post-KTx.

Function

There is reasonable evidence that shows improvement of cardiac function with KTx. Table 2 displays the prospective studies in adults and children demonstrating this change.

Similar to LVMI, most studies demonstrate significant improvement in both systolic and diastolic function in CKD patients following KTx.

There were 11 studies to our knowledge that described such changes following KTx. These comprised a total of 423 patients, including 29 children and 394 adults. The largest study was conducted by Parfrey *et al*. in whom 102 patients had their cardiac function assessed before and after KTx.[15] In comparison, the smallest study was undertaken by Sahagún-Sánchez *et al*. with 13 patients.[27]

A significant increase in LV ejection fraction (LVEF) posttransplantation was noted in 7 of the 11 studies. In addition, one study also demonstrated improvement in stroke volume.[16] There were four studies that showed a significant improvement in the fractional shortening after KTx.[11,14,15,27] Similarly, diastolic function had also been shown to improve following transplantation in four studies.[24,26,27,29]

The largest increase in systolic function was noted by Casas-Aparicio *et al*. who found that LVEF of the entire group of 35 patients had increased from 52% to 64% ($P < 0.001$) by 12 months after KTx.[26] In contrast, a study by Chammas *et al*., reported no significant change in LVEF in 32 patients at 28 ± 8 months post-KTx: The preoperative EF being 64% ± 5% and postoperative EF at 65% ± 4%.[28] Interestingly, however, in this same study by Chammas *et al*., there was also differing data on the diastolic function when compared with other studies. The group observed that a total of 6 patients out of 32 (19%) had diastolic dysfunction pretransplant, which decreased to five patients posttransplant. However, at 28 ± 8 months follow-up, diastolic dysfunction had increased to 7 out of 32 patients (22%).[28] Though the study suggests an improvement in diastolic function in the short-term with some deterioration long-term, overall data suggest an improvement in cardiac function. Of the two studies with the longest follow-ups, Hüting and Parfrey *et al*., showed significant improvements in LVEF of 5% and fractional shortening of 12%, respectively, 41–47 months after KTx.[15,16]

Unlike the observation with cardiac structural changes, no difference was noted in cardiac function between studies conducted on children compared to those done on adults when assessing cardiac function, thus, indicating a general improvement across all ages.

In addition to this, no major variation or influence was seen objectively from the time of follow-up on systolic and diastolic function. Sharma *et al*. 2014 found that LVEF improved in 60 patients

Table 2: Summary of studies showing changes in cardiac function before and after kidney transplantation

Author	Number of patients	Modality	Change in function	Age (years)	Follow-up
Souza *et al*.[24]	40	Echo	A reduction in LV diastolic diameter (52.23 mm-49.95 mm, *P*=0.021) Mean E/e' decreased in the 3rd and 6th months after KTx, when compared to baseline (8.13 and 7.85 vs. 9.79, *P*<0.05) EF increased from the 1st month after KTx compared to baseline (69.72% vs. 65.68%, *P*<0.05) Prevalence of diastolic dysfunction decreased 43% during the evaluated period	31.6±12.7	6 months after KTx
Sharma *et al*.[25]	60	Echo	LVEF (%) improved from 55.0±9.4 to 63.6±8.9 (*P*<0.001)	40.3±13.0	3 months after KTx
Casas-Aparicio *et al*.[26]	35	Echo	LVEF increased from 52% to 64% (*P*<0.001) by 12 months after KTx Echocardiograms normalized 1-year after transplant in 8 (66.7%) of the patients with diastolic dysfunction and 9 (56.2%) with systolic dysfunction Diastolic dysfunction persisted in 5 patients (31.2%)	40±14	Echo performed before and 1-year after KTx
Sahagún-Sánchez *et al*.[27]	13	Echo	LV fractional shortening and EF increased 3 months after transplant Only 2 patients showed diastolic dysfunction at the end of the study (reduction from 6 patients)	33.64±10.13	Before and 3 months after KTx
Mitsnefes *et al*.[11]	29 children	Echo	LV shortening fraction (%) increased from 37.10±8.3 to 41.8±7.0 (*P*=0.03)	15.4±5.1	6 months after KTx
Chammas *et al*.[28]	32	Echo	The EF was 64±5% preoperative, 63±5% at day 15 and 65±4% at 28±8 months postoperative (*P*=NS) Diastolic function: 6 patients (19%) had a diastolic dysfunction pretransplant versus 5 (16%) at day 15 postoperative and 7 (22%) at 28±8 months later	33.8±9.7	28±8 months after KTx
Omran *et al*.[29]	50	Echo	EF and stroke volume after KT increased, however, the LVED volume, LVES volume, LVESD, and LVEDD decreased	33.9±11.7	Before and 3 months after KTx
McGregor *et al*.[14]	20	Echo	Fractional shortening improved in 67% of patients (0.33 vs. 0.29; *P*=0.001)	38.3 (range 18.7-64.5)	4 months after KTx
Parfrey *et al*.[15]	102	Echo	Fractional shortening increased from 21.5±4.6% to 33.5±5.6% in the 12 patients with systolic dysfunction	37±12	47±23 months after KTx
Hüting[16]	24	Echo	LVEF increased from 58±10% to 63±12% (*P*<0.02) Stroke volume improved from 98±26 ml to 118±25 ml (*P*<0.02)	47±12	Echo performed immediately before and 41±30 months after RT
Cueto-Garcia *et al*.[21]	18	Echo	EF slope increased from 75.60±25 to 81.50±26.70 mm/s LVEF - 62.8±14.1 to 58.1±15.7 (NS)	28.8	31.16±23.59 weeks after KTx

LV: Left ventricular, LVEF: Left ventricular ejection fraction, LVED: Left ventricular end diastolic volume, LVES: Left ventricular end systolic volume, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, KTx: Kidney transplantation, SV: Stroke volume, EF: Ejection fraction, NS: Not significant, RT: Renal transplantation

from 55% ± 9% to 64% ± 9% ($P < 0.001$) just 3 months after KTx.[25] In comparison, Hüting, who followed up patients at a mean time of 41 ± 30 months after renal transplantation, found that the LVEF increased from 58% ± 10% to 63% ± 12% ($P < 0.02$).[16] In fact, the degree of pre- to post-KTx improvement in LVEF was actually slightly smaller in patients who had echocardiograms after a longer follow-up period. Although this could be attributed to a number of factors such as hypertension and cardiac fibrosis due to immunosuppressive medications it needs further exploration with more careful research.

Vascular changes in structure and function with kidney transplantation

Structure

There have been a very limited number of prospective studies exploring changes in vascular structure in patients with CKD undergoing KTx. These are listed in Table 3.

The CIMT, which is a reliable marker of atherosclerosis, was prospectively examined in two studies only. The total numbers of patients were 78 adults and follow-up intervals ranged from 3 months to 12 months posttransplant. Only one study showed a significant reduction in CIMT after KTx.

Caglar assessed CIMT in 42 patients before and 3 months after KTx. CIMT decreased from 8.52 ± 0.96 mm pretransplant to 5.96 ± 0.63 mm posttransplant ($P < 0.001$).[37] In contrast, Zoungas *et al*. assessed CIMT in 36 patients before and 12 months after KTx.[32] No significant difference in CIMT was noted between before, 0.76 ± 0.11 mm, and after, 0.75 ± 0.14 mm, transplantation. Lima *et al*. assessed CIMT in 22 patients,

Table 3: Summary of studies showing changes in vascular structure (CIMT) and function (PWV and AIx) before and after kidney transplantation

Author	Number of patients	Age group	Measurement	Changes in endothelial function	Mean age (years)	Follow-up
Kaur *et al*.[30]	23	Adults	PWV, AIx, and central pulse pressure	PWV (m/s) - Decreased from 8.65±2.02 to 8.06±2.54 (NS) AIx % - Decreased from 27.7±11.3 to 13.8±12.4 (P<0.05) Pulse pressure (mmHg) - Decreased from 41.7±13.9 to 30.1±9.8 (P<0.05)	35.9±9.3	6 months follow-up after KTx
Hornum *et al*.[31]	40	Adults	PWV, AIx	AIx was reduced from 27% (17-33) to 14% (7-25) (P=0.01) PWV was similar in the Tx group, uremic controls and healthy controls and no significant change after Tx	38±13	12 months after KTx
Keven *et al*.[10]	28	Adults	PWV	PWV (m/s) - Decreased from 7.76±1.8 to 6.16±1.6 (P<0.0001)	34±9	1-year after KTx
Zoungas *et al*.[32]	36	Adults	PWV. CIMT, AIx	CIMT - Decreased from 0.76±0.11 to 0.75±0.14 mm, P=0.28 PWV - Decreased from 9.6±2.6 to 8.8±2.2 m/s, P=0.007 AIx - Decreased from 24.3±13.4 to 15.9±11.4%, (P=0.003)	46±11	12 months follow-up after KTx
Covic *et al*.[33]	20	Adults	PWV, AIx	AIx - Decreased from 25.1±7.8% to 15.9±7.0% (P<0.0001) PWV - Decreased from 7.19±1.88 m/s to 6.59±1.62 m/sec (P<0.05)	41.8	3 months follow-up after KTx
Hotta *et al*.[34]	58	Adults	PWV	PWV (m/s) - Decreased from 15.9±4.5 to 14.3±2.6 (P<0.01)	40.5±12.3	6 months follow-up after KTx
Kovács *et al*.[35]	17	Adults	PWV, AIx	PWV (m/s) - Decreased from 13.36±3.07 to 8.25±1.93 (P=0.0075) AIx (%) - Decreased from 41.97±11.88 to 21.96±11.98 (P=0.013)	46.16±12.19	Before surgery and 17 days after KTx
Aoun *et al*.[36]	15	Children	PWV, AIx	PWV (m/s) - Increased from 6.1±1.3 m/s to 6.5±1.4 m/s (NS) AIx (%) - Decreased from 6.93±11.41% versus 0.53±17.05 (NS)	11.1±4.8	6 months follow-up after KTx
Caglar *et al*.[37]	42	Adults	CIMT	CIMT - Decreased from 8.52±0.96 to 5.96±0.63 (P<0.001)	25.2±6.1	3 months follow-up after KTx

PWV: Pulse wave velocity, AIx: Augmentation index, CIMT: Carotid intima-media thickness, KTx: Kidney transplantation, NS: Not significant

12–20 weeks following KTx and found that CIMT fell from 0.79 ± 0.02 mm to 0.68 ± 0.03 mm ($P < 0.01$).[38] Although the study by Lima shows a significant reduction in CIMT, the baseline measurement was taken 2–3 weeks after KTx in contrast to the other two studies in which the measurement was taken before the transplant.

Hence, the convincing evidence is, therefore, lacking for vascular structural changes following KTx. There have, however, been various observational studies showing lower CIMT measurements in the kidney transplant population when compared to the CKD dialysis population.[39-41] Thus, more carefully planned prospective studies are necessary to explore the changes in vascular atherosclerosis with KTx.

Function

Arterial stiffness

The techniques used to measure arterial stiffness include measurement of arterial pulse wave velocity (PWV) and AIx. There have been a few studies that prospectively analyzed the effects of KTx on PWV in CKD patients [Table 3].

Our literature search found eight studies that prospectively assessed PWV before and after KTx. These studies encompassed a total of 237 patients of which 15 were children, and the remaining were 222 adults. The average age ranged from 11 ± 5 years in children to 46 ± 12 years in adults.

There were six studies that analyzed the AIx before and after KTx. These included a total of 151 patients, of which there were 15 children and 136 adults. Five out of these six studies showed a significant decrease in AIx post-KTx.[30-33,35,36]

Seven studies showed a reduction in post-KTx PWV when compared to pretransplantation. However, five of these demonstrated a significant difference.[10,32-35] Of the remaining two studies, both showed nonsignificant changes but one study actually showed an average increase in PWV after KTx.[31,36]

The largest reduction in PWV post-KTx was observed by Kovács *et al*., who showed an average decrease of 5.1 m/s in 17 patients.[35] Kovács also showed a significant reduction of 48% in AIx posttransplantation from 42% ± 12% to 22% ± 12% ($P < 0.05$). Interestingly, this was also the study with the smallest patient size. Even more strikingly, this change was seen just 17 days after the transplantation. In contrast, the study with the longest follow-up time by Zoungas *et al*., showed a reduction in

PWV of only 1.2 m/s, ($P = 0.007$) and a 33% reduction in AIx in 36 patients, 12 months after KTx.[32] In addition, the largest study by Hotta *et al*., conducted on 58 patients showed a reduction in PWV of 1.6 m/s ($P < 0.01$) at a follow-up period 6 months post-KTx.[34]

Only one of the seven studies looking at PWV involves children and when comparing this to the adult studies, a difference was noted. This study on 15 children, conducted by Aoun *et al*., observed an increase in PWV of 0.5 m/s after KTx; however, it was not found not to be significant. In addition, the change in AIx posttransplant was also not noted to be significant.[36] In contrast, every study on adults found a reduction in PWV posttransplantation. Due to lack of prospective PWV studies on children, we are unable to comment on whether really there is a difference between the changes in PWV in adults compared to children following KTx. This is, therefore, a potential for further research.

Endothelial function

Endothelial function assessment includes measuring endothelial dependent dilation either from analyzing brachial artery FMD or following angiography with acetylcholine infusion. Measurement of endothelial function has also be assessed by nitroglycerin induced dilatation (NID) and endothelial progenitor cell migration (EPC).

There is increasing evidence to show that the endothelial function improves following renal transplantation. Table 4 summarizes the changes in endothelial function in CKD patients following KTx.

There were eight studies found during the literature search that spanned across the years 2003–2014. In total, 383 patients were assessed, of which all were adults. The age range of patients varied from 25 ± 6 years to 40 ± 3 years. Follow-up intervals ranged from 14 days to 12 months after KTx. Out of the eight studies, seven assessed endothelial dependent dilation: Six with FMD and one with acetylcholine administration. The remaining study assessed endothelial function by analyzing EPC migration to mature endothelial cells. NID was assessed alongside five of the six FMD studies. The largest study was conducted by Yilmaz *et al*., who assessed a cohort of 161 patients.[42] In contrast, the smallest sample study was conducted by Passauer *et al*., in which eight patients were assessed.[45]

All eight studies showed some degree of improvement in endothelial function. In five out of six studies assessing FMD and three out of the five studies assessing NID, significant improvements were observed following KTx. In addition, the one study looking at endothelial dependent dilation via acetylcholine administration also showed a significant improvement after KTx.[45] Finally, KTx was also found to increase EPC migration by approximately two-fold.[43]

One of the biggest changes in FMD was observed by Sharma *et al*., in which 60 Indian patients were assessed before and 3 months after KTx.[25] The study showed an improvement in FMD from 9.1% to 15.7% following KTx. In addition, impaired FMD, defined as FMD <4.5%, was present in 26.8% of CKD patients pretransplant and 3.3% of patients posttransplant.[25] Thus, indicating that KTx can reverse endothelial dysfunction in CKD patients. Interestingly, however, there was no significant improvement in NID in the cohort of 60 patients posttransplantation. In contrast, the opposite was observed in a study by Hornum *et al*. in which both FMD and NID were assessed in 40 hemodialysis patients. The study found that NID improved significantly from 11% to 18% posttransplant; however, no significant difference was noted in the FMD.[31] Reasons for the variations in observations are difficult to explain but could be due to varied sample sizes and differences in patient characteristics.

Comparatively, the study by Yilmaz *et al*. was conducted on a larger sample of 161 chronic hemodialysis patients receiving KTx. At 6 months posttransplant, there was a significant improvement of 1.4% in FMD from 5.2% ± 0.8% to 6.6% ± 0.8% ($P < 0.001$) as well as a significant improvement of 0.6% in NID from 11.9% ± 0.9% to 12.5% ± 0.7% ($P < 0.001$).[42] In addition to improved vascular function, this study also showed a parallel improvement in the FGF23, serum phosphorus, and 25 (OH) Vitamin D levels. Thus, highlighting a potential link between improvement of CKD-mineral bone disease and reduction in cardiovascular risk.[42]

The study with the shortest follow-up time was conducted by Kocak *et al*., who assessed FMD in 30 patients 3 days before and 14 days after KTx. The study found a 57% improvement in FMD, from 6.7% to 10.5%, posttransplantation ($P < 0.001$).[46] In comparison, Oflaz *et al*. followed up patients both at 6 months and 12 months after KTx. The study found that FMD improved from baseline (5.6%) at both 6 months (8.3%) and continued to improve at 12 months (12.1%).[44] Hence, a total improvement of 116% posttransplantation. This indicates that KTx potentially result in a sustained improvement in FMD and thus, improve atherosclerosis in long-term, which needs further research.

Table 4: Summary of changes in endothelial function before and after kidney transplantation

Author	Number of patients	Modality of assessing EF	Changes in endothelial function	Age (years)	Follow-up
Sharma *et al*.[25]	60	FMD, NMD	There was 72% increase in FMD following RT (9.1-15.7%, *P*<0.001) while mean NMD was unchanged. Following RT, only 3.3% had impaired FMD of <4.5%	40.3±13.0	3 months after KTx
Yilmaz *et al*.[42]	161	FMD, NMD	FMD increased by 27% after transplantation from 5.2±0.8% to 6.6±0.8% (*P*<0.001) NMD improved from 11.9±0.9% to 12.5±0.7% after KTx (*P*<0.001)	(Living Tx, *n*=115) 31±9 (cadaveric Tx, *n*=46) 32±9	Before Tx and 6 months after KTx
Hornum *et al*.[31]	40	FMD, NID	NID increased from 11% (7-16) to 18% (12-23) (*P*=0.0005)	38±13	12 months after KTx
Herbrig *et al*.[43]	20	EPC migration to mature endothelial cells	KTx increased the migration of EPC to approximately two-fold. Adhesion to fibronectin and to collagen type IV was significantly increased after KTx. An improved adhesion rate of EPC to mature EC was observed	45.5±2.9	12 months after KTx
Oflaz *et al*.[44]	22	FMD	EDD prior to transplantation was significantly lower when compared with EDD measured at the 6th and 12th months after KTx (EDD pretransplantation: 5.6±3.7%, EDD at the 6th month of KTx: 8.3±2.3% and EDD at the 12th month of KTx: 12.1±3.6%, *P*<0.001). EDD measurements of the 12th month were found significantly higher than those of the 6th month (*P*<0.001)	33.9±11.6	12 months after KTx
Passauer *et al*.[45]	8	EDD measured by venous occlusion, plethysmography, and Ach administration	The response to Ach in HD patients improved after Tx, and this change was significant for low-dose Ach (*P*<0.05)	39±6	12-24 months after KTx
Kocak *et al*.[46]	30	FMD and NID	FMD values significantly improved after KTx (6.69±3.1% vs. 10.50±3.0%, *P*<0.001) in HD patients	38±6	3 days before and 14 days after KTx
Caglar *et al*.[37]	42	FMD, NID, hs-CRP	FMD 4.44±0.71-6.87±0.84 (*P*<0.001) NID 10.11±0.90-11.54±0.65 (*P*<0.001) hs-CRP 33.02±12.99-4.09±1.54 (*P*<0.001)	25.2±6.1	Follow-up 90 days after KTx

FMD: Flow-mediated dilatation, NMD: Nitroglycerin mediated dilatation, NID: Nitroglycerin induced dilatation, EPC: Endothelial progenitor cell, EDD: Endothelial dependent dilatation, Ach: Acetylcholine, hs-CRP: High sensitivity C-reactive protein, KTx: Kidney transplantation, EF: Ejection fraction, RT: Renal transplantation, EC: Endothelial cell, HD: Hemodialysis

An interesting question is whether there is a difference in endothelial function between the preemptive and dialysis patients, post-KTx. Sharma *et al*. found that CKD patients with GFR of <15 had poorer average FMD (8.8%) compared with those patients who had a GFR of 15–60 ml/min/1.73 m^2 (12.9%).[25] Potential research could, therefore, help identify whether KTx has a more beneficial effect on endothelial function in predialysis versus dialysis patients.

Finally, no prospective studies assessing endothelial function in children were found during our literature search. This is another area for further research in order to establish the effect of KTx on endothelial function in children.

Risk factors and pathophysiology

The heightened cardiovascular event rates in the CKD population have been predominantly attributed to atheromatous and nonatheromatous vascular disease. Traditional risk factors, though frequently present do not fully explain this increased risk in the CKD population. Interestingly, the nontraditional risk factors such as inflammation, oxidative stress, abnormalities of calcium, phosphate and PTH balance, as well as Vitamin D deficiency and anemia are increasingly being recognized as causes of the high cardiovascular event rates.[47]

The vascular changes related to the improvement in uremic milieu are not very well known, however, may be attributed to improvements in the inflammatory profile. Inflammation contributes to chronic dysregulation of nitric oxide in vascular smooth muscle, and hence, results in endothelial dysfunction; the consequence of which is vessels being at risk of becoming proatherogenic.[48,49] Down regulation of inflammatory pathways and intercellular adhesion molecules responsible for the endothelium-leukocyte interaction, could contribute to the improved nitric oxide generation and endothelial function following KTx.

LVH is caused by inflammation, fibrosis, and increased afterload. In addition, anemia and fluid overload results in left ventricular dilation with LVH and the resulting structural abnormalities contribute to both systolic and diastolic dysfunction.[50] A large proportion of the studies discussed in this review show regression of LVH and improvement of cardiac function following KTx. More recent research has found a relationship between endothelial dysfunction and LVH.[51] We propose that improvement in LVH may be related to improvement in endothelial dysfunction.

Conclusion

There is substantial evidence to show that KTx results in a reduction in LVH. There is some evidence to suggest an improvement of cardiac function in CKD patients following KTx. There is a lack of prospective research assessing the effect of KTx on vascular structure, especially CIMT. There is increasing evidence describing the improvement of endothelial function in CKD patients following KTx in adults; however, further research is required in children.

This review highlights the changes in cardiovascular structure and function following KTx; however, further research is necessary to establish the vascular changes, as well as to investigate the mechanisms behind these changes.

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Conflicts of interest
There are no conflicts of interest.

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