



## Ultrastructural examination of left internal mammary artery under electron microscopy in patients with chronic kidney disease who underwent coronary bypass surgery

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### ABSTRACT

**Aim:** To investigate the vascular damage of internal mammary artery graft with electron microscope secondary to chronic renal failure transmission in patients who underwent coronary artery bypass grafting surgery.

**Method:** A total of 30 patients (10 patients with chronic renal failure and 20 patients without chronic renal failure) who underwent coronary artery bypass graft surgery were included in this prospective study. Left internal mammary artery graft was harvested as conventional fashion with no touch technique. Samples were prepared and then examined with the transmission electron microscope. Every arterial sample was individually examined ultrastructurally, and the changes were recorded. Then the samples of the control group and chronic renal failure group were compared.

**Results:** There were no significant differences between chronic renal failure group and the control group in terms of demographics, comorbidities, intraoperative data and postoperative outcomes, and the groups were statistically similar ( $p < 0.05$ ). Moreover, no statistically significance was detected in terms of structure and ultrastructure between the groups.

**Conclusion:** The results of our study revealed that no ultrastructural changes were observed in the structure of IMA, suggesting that this graft would provide a good graft patency.

**Keywords:** Coronary artery bypass grafting, chronic renal failure, internal mammary artery, ultrastructural study, electron microscope.

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### Introduction

Cardiovascular diseases and associated complications are the most important factors in morbidity and mortality in patients who have

developed chronic kidney disease (CKD) and continue their lives with dialysis therapy [1,2]. Cardiovascular diseases account for about one third of the causes of hospitalization in these uremic patients [3]. The rate of mortality due to the cardiovascular diseases is approximately 8 to 20 folds higher in dialysis patients compared to general population [4]. Ischemic heart disease is usually resulted from coronary artery disease, but it occurs with non-atherosclerotic

reasons in 27% of hemodialysis patients. Ischemic heart disease occurring due to non-atherosclerotic reasons is associated with underlying cardiomyopathy, small vessel disease (caused by hypertension, diabetes mellitus or calcium-phosphate accumulation), decreased capillary density and abnormal myocyte bioenergy [5]. Myocardial infarction has been remarkable during autopsy in about 25% of dialysis patients [6]. In an angiographic study on patients with end stage renal disease and who were planned to receive hemodialysis treatment, significant coronary stenosis was found in over than 75% of the patients [7].

Capability to widely and successfully perform topic that these operations could also be performed in patients with accompanying high-risk group diseases of other systems. Today, in patients with chronic kidney disease, coronary artery bypass grafting (CABG) surgery has been gradually increased and successfully performed [8-11].

Structural and functional properties of conduits during the surgical myocardial revascularization is of important issue which affects the success of the surgery [12,13]. It is possible that examination of histologic and morphologic features of coronary bypass grafts used in patients with CKD may provide information about graft patency in CABG. However, in the existing literature, the studies investigating the quality of coronary bypass grafts are very limited for patients with CKD.

The aim of this study was to examine the endothelial functions and vascular damage resulted from CKD in internal mammary artery (IMA) that is a coronary bypass grafts, in patients with CKD who underwent CABG, under transmission electron microscope. Therefore, we investigated whether the use of IMA, a very valuable graft, for CABG in patients with CKD is safe or not.

## **Materials and Methods**

### ***Preoperative features of patients***

A total of 30 patients scheduled for CABG operation were included in this prospective study. Of the patients scheduled for CABG, 10 had CKD and 20 had no CKD. This study was conducted after receiving approval from the institutional ethics committee (Date: 16.03.2009; Decision no.: 2009/03/05) and written informed consents were obtained from all participants. The principles of the Helsinki Declaration were completely complied in the study. Patients were divided into two groups; as CKD and non-CKD (control) groups. Patients undergoing reoperation, non-renal organ failure and with an IMA which was not suitable for use were excluded from the study. The control group was randomly selected among the patients scheduled for CABG who had no organ failure and reoperation.

### ***Operative procedure***

After standard anesthesia protocol, all patients were underwent CABG with standard fashion with sternotomy. The operations were performed as off-pump CABG in 4 and on-pump CABG in 6 patients in the patient group while off-pump operations were performed in 3 and on-pump operations in 17 patients in the control group. In this study, all samples were obtained from the left internal mammary artery (LIMA) grafts. LIMA grafts were harvested as conventional fashion with no touch technique, by using an electrocautery from the subclavian artery to the site where it was branched as superior epigastric artery and musculophrenic artery. Side branches were hemoclipped. Systemic heparinization was applied with unfractionated heparin of 200 IU/kg in patients who underwent off-pump CABG, and 350 IU/kg in those who underwent on-pump CABG with cardiopulmonary bypass.

**Preparation and examination of IMA samples**

For the analysis, approximately 1 cm terminal segment of LIMA graft was removed before LIMA-left anterior descending (LAD) artery anastomosis. The samples were fixed in 2.5% glutaraldehyde solution for 24 hours. The samples were then rinsed with pH 7.4 SBP (Sorenson's Phosphate Buffer) buffer solution, and subjected to post-fixation treatment with 0.1% osmium tetroxide solution. The samples were rinsed again with SBP buffer solution, and dehydrated. Propylene oxide and epoxy resin material were mixed at 1:1 ratio and the samples were kept in this solution for 1 hour. At the end of one hour, same amount of epoxy resin material was added on this mixture and the mix ratio was raised to 1:3. The samples were kept at the rotator for one night, embedded into the epoxy material using plastic capsules and kept at 60°C for 48 hours. Sections of 2 µm was cut and stained with methylene blue and examined under the light microscopy to determine the sites where thin sections would be cut. Thin sections of about 60 nanometers were obtained with the same ultramicrotome. These thin sections were stained with uranyl acetate and lead citrate with double contrast method, and examined under the transmission microscope (Jeol JEM 1200 EX, Japan) and the images were obtained. Each arterial samples were ultrastructurally examined and the changes were recorded. Samples of the CKD and control groups were compared.

**Statistical analysis**

Statistical analysis was performed using SPSS version 16.0 software. Numerical parameters were expressed as mean ± standard deviation, minimum and maximum values, while categorical variables were expressed as frequency and percentage. Normality of the variables was tested using Kolmogorov-Smirnov test. Independent Sample t test

(student t test) among the parametric tests was used in comparison of the normally distributed variables, and Mann-Whitney U test among the non-parametric test was used in comparison of the skewed data. Chi-square, Fisher's and Mantel Haenszel tests were used in comparison of the categorical variables. A  $p < 0.05$  value was considered as statistically significant.

**Results**

The mean age was 54.2±9.7 years in CKD group, and 60.9±12.1 in the control group. Nine of patients with CKD were male and 1 was female, while 16 of patients in the control group were male and 4 were female.

**Table 1.** Sociodemographic features and comorbidities of the groups.

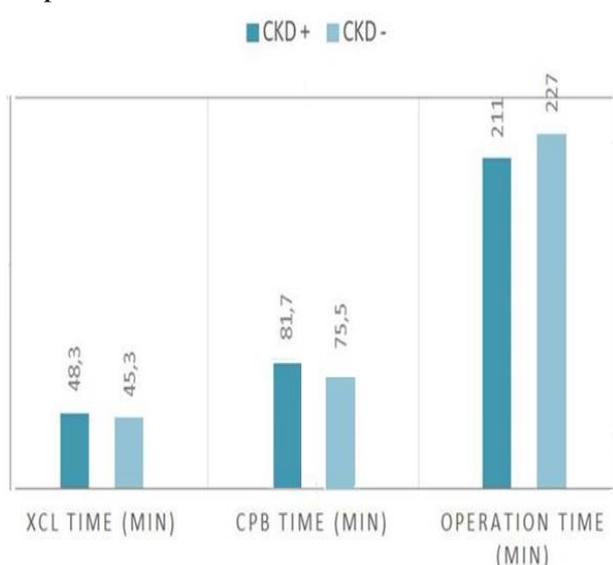
Parameters	CKD +		CKD -		P value
	N	%	N	%	
Patient number	10	33	20	67	
Age (year)	54.2 ± 9,7		60.9 ± 12,1		0.141
Gender (M/F)					0.488
Male	9	90	16	80	
Female	1	10	4	20	
Smoking					0.017
Current	0	0	9	45	
Former	3	30	1	5	
Never	7	70	10	50	
Unstable AP	4	40%	6	30	0.270
Stable AP	4	60%	16	80	0.375
NYHA					0.442
Class 2	6	60	8	40	
Class 3	4	40	12	60	
Hypertension	8	80	10	50	0.235
Diabetes mellitus	4	40	4	20	0.243
Previous CVE	0	0	1	5	0.472
Carotid artery disease	3	30	1	5	0.095
COPD	7	30	3	15	0.330
PVD	1	10	2	10	1.000

CKD: Chronic kidney disease; AP: Angina pectoris; COPD: Chronic obstructive pulmonary disease; CVE: Cerebrovascular event; PVD: Peripheral vascular disease; NYHA: New York Heart Association.

There were no statistically significant differences between the groups in terms of baseline clinical characteristics ( $p>0.05$ ), except for smoking ( $p=0.017$ ). Sociodemographic features and comorbidities of 10 patients with CKD and 20 patients without CKD are presented in Table 1.

When operative data were considered, there were no statistically significant differences between both groups in terms of aortic cross clamp (XCL), cardiopulmonary bypass (CPB) and operation times ( $p>0.05$ ) (Figure 1).

**Figure 1.** Distribution of the cross clamp (XCL), cardiopulmonary bypass (CPB) and operation times of patients.



Preoperative and postoperative blood urea and creatinine values were statistically significantly higher in CKD group compared to the control group ( $p<0.001$ ). No statistically significant difference was found between the groups in terms of pre- and postoperative sodium and potassium levels ( $p>0.05$ ). Postoperative blood urea and sodium values were statistically significantly increased compared to the preoperative values in CKD group ( $p<0.05$ ). Postoperative creatinine and potassium values were higher than the preoperative values, although the difference was not statistically

significant ( $p>0.05$ ). There was no significant difference between pre- and postoperative biochemical values in the control group ( $p>0.05$ ). Preoperative and postoperative biochemical values of the groups are given in Table 2.

**Table 2.** Preoperative and postoperative biochemical values of the groups.

Parameters	CKD +	CKD -	P value	
Preoperative	Urea	91.3 ± 32,9	39.75 ± 9,0	<0.001
	Creatinine	4.6 ± 2,3	1.2 ± 0,9	<0.001
	Na	136.9 ± 4,4	139.1 ± 2,8	0.107
	K	4.3 ± 0,7	4.2 ± 0,4	0.424
Postoperative	Urea	112.7 ± 29,7 <sup>a</sup>	43.2 ± 11,4	<0.001
	Creatinine	4.9 ± 2,3	1.2 ± 0,3	<0.001
	Na	141 ± 5,3 <sup>a</sup>	141.0 ± 6,2	0.864
	K	4.6 ± 0,9	4.4 ± 0,3	0.382

There were no significant differences between the groups in terms of IMA flow and early postoperative outcomes including revision due to severe bleeding, atrial fibrillation and the necessity of intraaortic balloon pump ( $p>0.05$ ) (Table 3).

**Table 3.** Comparison of IMA flow, IABP, revision, and postoperative AF status between the groups.

Parameters	CKD +		CKD -		P value
	N	%	N	%	
IMA flow					0.472
	Good	10	100	19	
Poor	0	0	1	5	
IABP requirement	1	10	2	10	1.000
Revision due to bleeding	1	10	1	5	0.605
Postoperative AF	0	0	5	25	0.083

AF: Atrial fibrillation; CKD: Chronic kidney disease; IABP: Intraaortic balloon pump; IMA: Internal mammary artery.

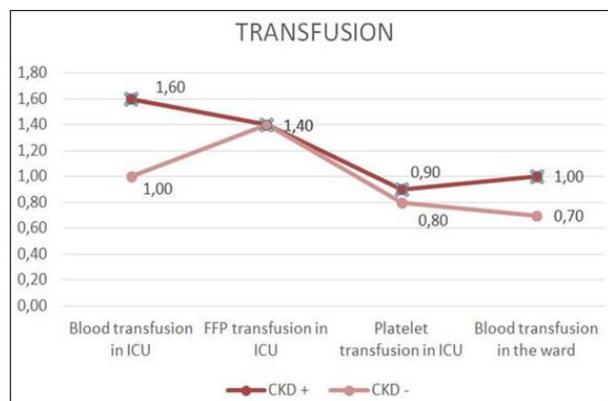
Although higher amounts of blood products were transfused in the intensive care unit and ward in CKD group, the differences between the groups were not statistically significant ( $p>0.05$ ). Comparison of the groups in terms of transfusion amounts is shown in Table 4 and Figure 2.

**Table 4.** Blood product transfusions in the groups.

Parameters	CKD +	CKD -	P value
ES transfusion in ICU	1.6 ± 0.96	1.0 ± 0.92	0.108
FFP transfusion in ICU	1.4 ± 1.89	1.4 ± 1.50	1.000
Platelet transfusion in ICU	0.9 ± 1.52	0.8 ± 1.77	0.821
ES transfusion in ward	1.0 ± 0.47	0.7 ± 0.57	0.163

CKD: Chronic kidney disease; ES: Erythrocyte suspension; FFP: Fresh frozen plasma; ICU: Intensive care unit.

**Figure 2.** Comparison of the chronic kidney disease (CKD) + and CKD - groups in terms of transfusion.

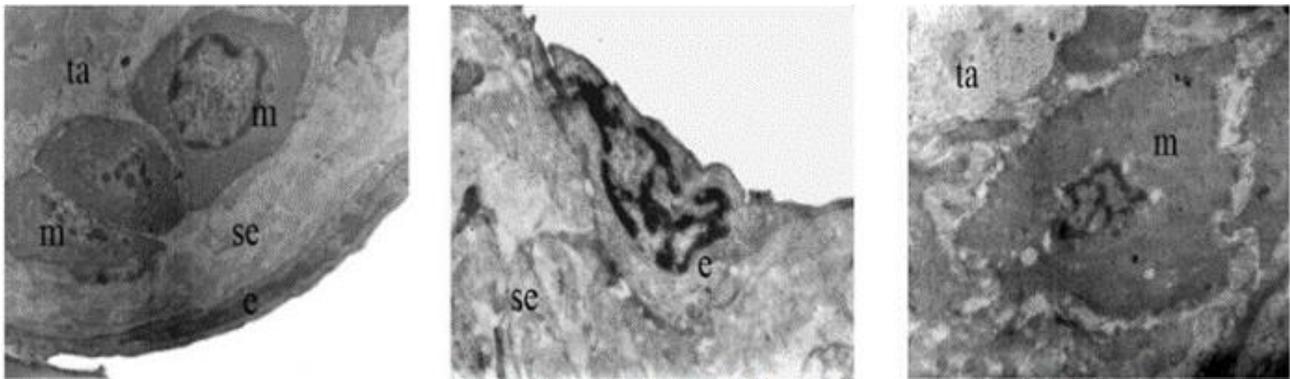


In the electron microscopic evaluation of the tunica intima layer, it was found that endothelial cells lining inner surface of the vessel were ultrastructurally normal. No any ultrastructural pathologic finding was observed in cell membranes, nuclei, intracytoplasmic organelles and basal membranes of the endothelial cells. Whereas subendothelial layer in the tunica intima was observed to consist of a loose connective tissue. Free collagen fibers and connective tissue cells in this layer were

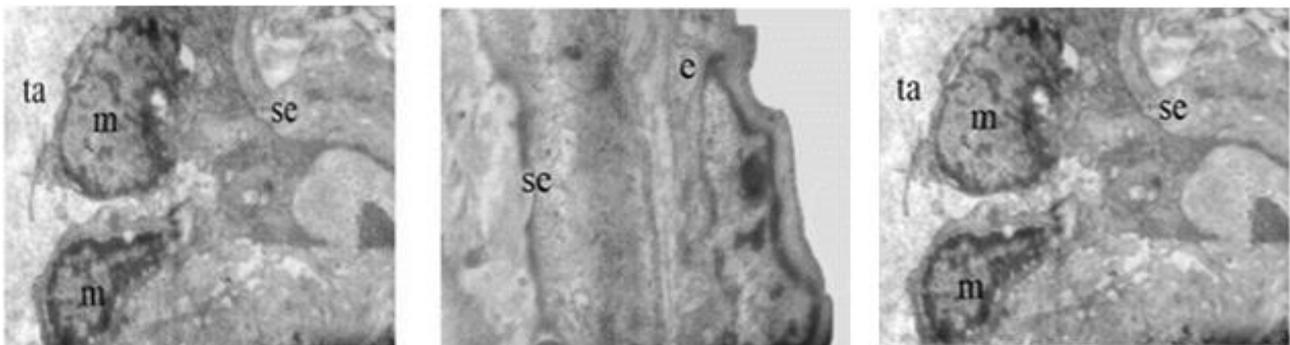
ultrastructurally normal. In the examination of smooth muscle cells found in the tunica media layer, no ultrastructurally pathologic finding was found in the cell membranes, nuclei, intracytoplasmic organelles and basal membranes of these cells. Finally, in the electron microscopic examination tunica adventitia of the vessels, abundant collagen fibers and connective tissue cells were in a normal structure. As a consequence, entire IMA samples collected from the patients with CKD were ultrastructurally normal, and there was no significant ultrastructural difference between these samples and the samples collected from the control group. Although the patients had chronic kidney failure, ultrastructurally they had a completely normal vessel structure (Figure 3, 4).

## Discussion

The remarkable finding of our study was that no any ultrastructural changes in IMA grafts was detected in patients with CKD who underwent CABG, and there were no any ultrastructural differences compared to the control group. Unchanged structure of IMA suggests that long term patency of this graft will be satisfactory. Cardiac surgery which has shown a rapid development with invention of the cardiopulmonary bypass machine in the second half of the 20th century, is still continuing to develop and has been successfully performed in many centers. The aim of CABG operation is to provide sufficient blood flow to ischemic heart site, to improve quality of life of the patient, and to prolong lifetime [14-16]. Patency rate of the autogenous grafts used for this operation determines patients' quality of life and the success of CABG operations. Therefore, the target is to choose the grafts with a good patency rates [17]. Structural and functional properties of CABG conduits used in the



**Figure 3.** Examples of electron microscopy images in the study group. ta: tunica adventitia; m: tunica media; e: endotelium; se: subendotelium.



**Figure 4.** Examples of electron microscopy images in the control group. ta: tunica adventitia; m: tunica media; e: endotelium; se: subendotelium.

myocardial revascularization of patients undergoing coronary bypass are important factors affecting outcome of the operation [12,13,18]. Patient's age, clinical status, vessel to be bypassed, utility of the graft, comorbidities and surgeon's experience are determinants of the graft choice. In the present study, IMA was used as a graft in all patients, and IMA-LAD anastomosis was applied as a standard procedure.

Internal elastic lamina plays a critical role in the arterial wall structure. Presence of fenestrations in the internal elastic lamina stimulates early and progressive intimal hyperplasia. It can be expressed that a damage to the internal elastic lamina is less prone to the proliferation of smooth muscle cells in the media, and thus to

intimal hyperplasia than the muscular arteries. In addition, numerous elastic lamellae and internal elastic lamina forms a barrier against the incision of smooth muscle cells [19]. It is known that there is an association between the absence of elastic lamellae in the media and number of fenestrations in the internal elastic lamina, and potential result of this was development of more intimal hyperplasia. Consequently, the presence of elastic lamellae in the media shows a protective effect against the occurrence of fenestrations in the internal elastic lamina and intimal hyperplasia [20].

It is thought that histologic structure in the arterial grafts used in CABG may be affected by atherosclerosis, influencing rate of patency. Choosing the segments to be anastomosed

according to the histological structure and lumen diameter will positively affect rates of patency [13,17,18]. Main part of the IMA, which is the middle part consisting of 60% of the total length is less reactive than the distal and proximal sections [21].

An important factor determining long-term patency of IMA graft is the feature of the graft itself. Biological integrity of the graft and compliance to its new position is closely associated with the rates of long term patency and development of cardiac events. IMA graft has become an indispensable graft because of its superior long-term results up to 20 years [22]. It has been proven that the rate of patency is much higher in IMA compared to saphenous vein grafts, and while atherosclerotic lesions are developed in venous grafts, IMA graft is more resistant [23].

Another issue studied in coronary artery bypass is vasomotor features of IMA grafts in diabetic patients. Considering that vasoactive responses of coronary artery bypass grafts of diabetic patients who underwent myocardial revascularization would affect postoperative outcomes; Wendler et al. investigated vasomotor features of IMA grafts, and reported that biologic integrity of these grafts was preserved even in the presence of impaired glucose metabolism [24]. Similarly, in our study biologic and morphologic integrity was protected even in patients with advanced chronic kidney failure. However, there are several studies in the literature reporting endothelial dysfunction, which resulted in decrease or loss of the antithrombotic and vasodilator functions of IMA in diabetic patients [25,26]. On the other hand, in the present study conducted on IMA grafts of patients with CKD, no ultrastructural pathology was found in the structure of IMA wall and organelles. Therefore, we concluded that

functions will not be impaired in an endothelium with protected cell structure. In a study by Pompilio et al. [25], the authors examined endothelium dependent functions of IMA in normotensive diabetic men who had normal cholesterol values, and found that nitric oxide and Prostaglandin 12 homeostasis was disrupted in this group of patients compared with the patients without known cardiovascular risk factors. They also examined surface features with a scanning microscope and reported that endothelium was intact and no atherosclerotic sign was observed.

Although mortality rates are higher in CKD patients compared to normal population, satisfactory results can be achieved if these patients are operated with correct indications when diagnosed with coronary artery disease. Today CABG operations can be performed with very low morbidity and mortality rates [8-11]. Positive results were obtained from all studies conducted on patency rates on IMA and examination of its histomorphological features. The main limitations of our study were relatively small number of participants and its single-centered design.

### **Conclusions**

IMA grafts of patients with CKD were ultrastructurally examined in our study, and no pathology was observed. In addition, no pathology was found also in the samples collected from the control group, and there was no significant difference between these two groups. Our results reflected that the use of IMA graft in CKD patients undergoing coronary bypass is the most appropriate option among the other revascularization option. In addition, we think that IMA is superior over the other autogenous and artifact grafts used in coronary bypass operations in terms of graft patency. However, further studies with a larger

series of patients about coronary revascularization options and results in CKD patients and the strategy to be followed are warranted.

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**Ethical statement:** *This study was conducted after receiving approval from the institutional ethics committee (Date: 16.03.2009; Decision no.: 2009/03/05) and written informed consents were obtained from all participants.*

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