Chron Precis Med Res 2026; 7(1): 59-65
DOI: 10.5281/zenodo.19242391

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Atherosclerosis in Patients Undergoing Kidney Transplantation: Insulin Resistance and Its Relationship with Serum Fetuin-A

Böbrek Nakli Yapilan Hastalarda Ateroskleroz: İnsülin Direnci ve Serum Fetuin-A ile İlişkisi

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ABSTRACT

Aim: Cardiovascular disease (CVD) is the most important cause of mortality in patients undergoing kidney transplantation. In addition to classical CVD risk factors, insulin resistance and fetuin-A, a vascular calcification inhibitor, may also affect the pathogenesis of atherosclerosis in this group of patients. In our study, we investigated the risk factors for atherosclerosis in patients who underwent kidney transplantation and the relationship between atherosclerosis and insulin resistance and fetuin-A.

Material and Method: The study included 103 kidney transplant patients (69 males, mean age 35.14±9.51 years; mean kidney transplant time 54.99±39.51 months) and 70 healthy controls. Patients over 18 years of age, with a kidney transplant period of at least 6 months, and without diabetes mellitus, acute or chronic infection, acute hepatitis, or malignancy were included in the study. Demographic, clinical and laboratory data of the control group and patient group were recorded. All participants in the study had carotid-intima media thickness (C-IMT) measured by the same radiologist.

Results: Body mass index, systolic and diastolic blood pressures, mean arterial blood pressure values, serum creatinine, cholesterol, triglyceride, high-density lipoprotein, parathyroid hormone, calcium and C-reactive protein (CRP) levels, HOMA insulin resistance values and C-IMT values were higher in the recipients compared to the control group, and creatinine clearance and serum fetuin-A levels were lower. When the patients were examined in three groups according to serum fetuin-A level; In the group with the lowest fetuin-A levels, age (p=0.005), hepatitis B or C disease rate (p=0.005), serum CRP (p=0.001) and C-IMT (p<0.001) were higher, and albumin value (p=0.02) was found to be lower. Multivariant linear regression analysis found age (ß=0.436; p<0.001) and fetuin-A (ß=–0.229; p=0.04) as independent risk factors associated with C-IMT.for what ??

Conclusion: Apart from the classical CVD risk factors, insulin resistance and low serum fetuin-A levels were also found to be associated with the development of early atherosclerosis in kidney transplant patients. Prospective long-term studies showing the course of serum fetuin-A levels in kidney transplant patients are needed.

Keywords: Atherosclerosis, kidney transplantation, fetuin-A, insulin resistance

ÖZ

Amaç: Böbrek nakli yapılan hastalarda kardiyovasküler hastalık (KVH) en önemli mortalite nedenidir. Klasik KVH risk faktörlerinin yanı sıra, insülin direnci ve vasküler kalsifikasyon inhibitörü fetuin-A da bu gurup hastalarda ateroskleroz patogenezini etkileyebilir. Çalışmamızda böbrek nakli yapılan hastalarda ateroskleroz risk faktörlerini ve aterosklerozun insülin direnci ve fetuin-A ile ilişkisini araştırdık.

Gereç ve Yöntem: Çalışmaya 103 böbrek nakli yapılan hasta (69 erkek, ortalama yaş 35,14±9,51 yıl; ortalama böbrek nakli süresi 54,99±39,51 ay), 70 sağlıklı kontrol grubu alındı. 18 yaşından büyük, böbrek nakil süresi en az 6 ay olan, diabetes mellitus, akut veya kronik enfeksiyonu, akut hepatiti, malignitesi olmayan hastalar çalışmaya dahil edildi. Kontrol grubu ve hasta grubunun demografik, klinik ve laboratuar verileri kaydedildi. Çalışmaya katılan kişilerin hepsine aynı radyolog tarafından karotis-intima media kalınlığı (K-İMK) ölçümü yapıldı.

Bulgular: Alıcılarda kontrol grubuna göre vücut kitle indeksi, sistolik ve diyastolik kan basınçları, ortalama arteriyel kan basıncı değerleri, serum kreatinin, kolesterol, trigliserid, yüksek dansiteli lipoprotein, paratiroid hormon, kalsiyum ve C-reaktif protein (CRP) düzeyleri, HOMA insülin direnci değerleri ve K-İMK değerleri daha yüksek, kreatinin klerensi ile serum fetuin-A düzeyi daha düşüktü. Hastalar serum fetuin-A düzeyine göre üç grupta incelendiğinde; fetuin-A düzeyi en düşük grupta yaş (p=0,005), hepatit B veya C hastalığı oranı (p=0,005), serum CRP (p=0,001) ve K-İMK'nın (p<0,001) daha yüksek, albümin değerinin (p=0,02) daha düşük olduğu tespit edildi. Multivariyent lineer regresyon analizinde yaş (ß=0,436; p<0,001) ve fetuin-A (ß=–0,229; p=0,04) bağımsız risk faktörleri olarak bulundu.

Sonuç: Klasik KVH risk faktörlerinin dışında insülin direnci ve düşük serum fetuin-A düzeyinin de böbrek nakli yapılan hastalarda erken ateroskleroz gelişimiyle ilişkili olduğu bulundu. Böbrek nakli yapılan hastalarda serum fetuin-A düzeyinin seyrini gösteren prospektif uzun süreçli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Ateroskleroz, böbrek nakli, fetuin-A, insülin direnci

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Received/Başvuru Tarihi: 20.01.2026
Accepted/Kabul Tarihi: 01.03.2026

INTRODUCTION

Although kidney transplantation is the gold standard treatment for patients with end-stage renal disease, cardiovascular disease (CVD) is still the main cause of mortality and morbidity in this population. The risk of cardiovascular death in transplant recipients is significantly higher than in the general population, and this level of risk is often similar to the data of dialysis patients (1). The high-risk profile results from both traditional risk factors and metabolic disturbances and insulin resistance which develop because of immunosuppressive drugs used following transplantation (2). Carotid intima-media thickness (C-IMT) is considered one of the most reliable and non-invasive parameters predicting future major cardiovascular events in the detection of subclinical atherosclerosis that develops in this process (3).

In the literature, it is known that Fetuin-A is an essential protein that inhibits vascular calcification and its deficiency accelerates vascular damage (4). However, studies on the course of serum fetuin-A levels in the post-renal transplant period and the complex interaction of this protein with insulin resistance offer conflicting results. While some data link low levels to calcification, some recent studies indicate that high fetal A levels may be linked to metabolic syndrome and insulin resistance (5). The research study does not explain how serum fetuin-A levels affect C-IMT measurements in transplant patients who take immunosuppressive drugs (6). The research provides a complete assessment to determine how biochemical markers affect subclinical atherosclerosis.

MATERIAL AND METHOD

Study Population and Sample

In this cross-sectional study, 103 patients who underwent kidney transplantation who visited the transplantation clinic and 70 healthy volunteers in the control group between March 2007 and October 2007 were included in the study. Patients over the age of 18 who had completed the transplant period for at least six months were included in the recipient group. Patients with a diagnosis of diabetes mellitus, active infection, acute hepatitis, or malignancy were excluded. The control group consisted of individuals who did not have known hypertension, atherosclerotic heart disease, diabetes, kidney disease or signs of infection. Smoking was determined as the exclusion criterion in both groups.

Operating Procedures

Demographic data, clinical characteristics and drug use information of the participants were recorded. Blood pressure measurement was performed with a mercury sphygmomanometer after ten minutes of rest; the average of the two measurements taken two minutes apart was evaluated. Mean arterial pressure was calculated. Systolic pressure above 140 mmHg or diastolic pressure above 90 mmHg or the use of antihypertensive drugs were defined as hypertension. Serum creatinine, calcium, phosphorus, PTH, CRP, albumin, fasting glucose, insulin, lipid profile and fetuin-A levels were measured in blood samples taken after twelve hours of fasting. Creatinine clearance was calculated by MDRD (7) formula and insulin resistance was calculated by HOMA-IR index (8). Fetuin-A determination was performed by ELISA method. Carotid intima-media thickness was measured ultrasonographically using a 2-4 MHz linear probe. Measurements were taken from 1.5-2 cm proximal to the bifurcation on the bilateral main carotid artery, repeated from three different angles, and the average was recorded. All measurements were performed by a single radiologist who was unaware of the clinical information.

Immunosuppressive Protocol

All kidney transplant recipients were receiving triple immunosuppressive therapy. 60 patients were using cyclosporine and 43 patients were using tacrolimus as calcineurin inhibitors. The cyclosporine dose was adjusted to maintain blood levels in the range of 100-200 ng/mL. Mycophenolate mofetil and prednisolone were given to all patients (9).

Statistical Analysis

The data were analyzed with SPSS 13.0 software. Continuous variables were presented as mean (SD) and categorical variables as percentages. In the comparison of the recipient and control groups, Student's t test was applied for normally distributed variables and Mann Whitney U test was applied for those that did not. Recipients were divided into three subgroups according to serum fetuin-A levels: high, medium, and low. Group 1(n:34): lowest serum fetuin-A level (fetuin-A < 45.6 ng/ml), group 2 (n:35): A third group with moderate serum fetuin-A levels (fetuin-A 45.6–60.4 ng/ml), group 3 (34): The third group with the highest serum fetuin-A level (fetuin-A > 60.4 ng/ml). Between groups compared with ANOVA or Kruskal-Wallis test. Categorical data were evaluated by chi-square or Fisher exact test. Factors affecting carotid intima-media thickness were examined by univariate and multivariate linear regression analysis. A p value below 0.05 was considered statistically significant.

Ethical Approval

The study was approved by the Başkent University Faculty of Medicine Clinical and Drug Research Local Ethics Committee (KA06/268-DATE14/12/2006). All participants were informed about the research and their written consent was obtained. The research followed all principles which the Declaration of Helsinki establishes.

RESULTS

Demographic and Clinical Characteristics

When the 103 kidney transplant recipients included in the study were compared with 70 healthy volunteers, there was no difference between the groups in terms of gender distribution. The mean age was found to be close to each other in both groups. However, the body mass index was higher in the recipient group compared to the control group. When blood pressure values were examined, both systolic and diastolic pressure were significantly higher in the recipients. Mean arterial pressure was also higher in the recipient group, supporting this situation. More than half of the recipients were receiving antihypertensive therapy. The mean pre-transplant dialysis time was about 20 months, and the mean post-transplant time was around 55 months. The majority of the patients had been transplanted from a living donor (**Table 1**).

Table 1. Demographic and Clinical Characteristics of the Recipient and Control Group

Variable	Receiver (n=103)	Control Group (n=70)	P
Gender (male/female)	69/34	39/31	0.1
Age (years)	35.14±9.51	36.02±9.42	0.6
BMI (kg/m^2)	25.09±5.53	22.96±2.03	0.017*
Systolic blood pressure (mmHg)	130.43±17.03	120.14±12.27	0.001*
Diastolic blood pressure (mmHg)	80.21±11.14	75.85±7.12	0.03*
Mean arterial blood pressure (mmHg)	96.89±12.18	90.28±8.50	0.004*
Presence of hepatitis B (n/%)	7/6.7%	–	–
Presence of hepatitis C (n/%)	13/12.5%	–	–
Dialysis period before transplantation (months)	20.5±12.86	–	–
Transplant time (months)	54.99±39.51	–	–
Donor source (living/cadaver)	81/22	–	–
Drug use			
Cyclosporine (n/%)	60/58.2%	–	–
Tacrolimus (n/%)	43/41.7%	–	–
Antihypertensive drug (n/%)	55/53.3%	–	–
Statin (n/%)	37/35.9%	–	–

Note: Data are presented as mean±standard deviations (SD). Abbreviations: BMI: Body mass index.*P < 0.05 was considered statistically significant.

Laboratory Findings

When biochemical parameters were examined, total cholesterol and triglyceride levels were found to be significantly higher in the recipient group than in the control group. HDL cholesterol was also higher in recipients, but the groups were similar in terms of LDL cholesterol. Serum creatinine was high and creatinine clearance was low in recipients, as expected. CRP, a marker of inflammation, was approximately four times higher in the recipient group than in the control group. The insulin resistance indicator HOMA-IR value increased significantly in buyers. Calcium was slightly elevated and PTH was measured at nearly three times the level of the control group. As a remarkable finding, serum fetuin-A levels were found to be lower in the recipient group than in the control group. Carotid intima-media thickness, which is an indicator of subclinical atherosclerosis, was found to be significantly increased in recipients (**Table 2**).

Table 2. Comparison of Laboratory Values of Recipient and Control Group and C-IMT

Parameters	Receiver (n=103)	Control Group (n=70)	P
Total cholesterol (mg/dl)	202.69±49.25	163.42±33.75	<0.001*
LDL (mg/dl)	111.21±37.22	104.80±28.19	0.3
HDL (mg/dl)	61.69±13.96	55.47±15.01	0.02*
Trigliseride (mg/dl)	155.36±74.87	102.05±40.57	<0.001*
Serum creatinine (mg/dl)	1.54±0.58	0.85±0.16	<0.001*
Creatinine clerence (ml/dk)	71.49±23.89	102.99±15.65	<0.001*
Albumin (mg/dL)	4.64±0.43	4.68±0.44	0.5
CRP (mg/L)	6.02±9.82	1.62±1.87	0.004*
HOMA-IR	2.90±1.63	1.22±0.77	<0.001*
Calcium (mg/dl)	9.75±0.62	9.56±0.44	0.012*
Phosphorus (mg/dl)	3.40±0.65	3.61±0.50	0.058
Ca × P	33.11±6.12	34.45±5.87	0.2
PTH (pg/ml)	127.45±115.34	45.00±13.83	<0.001*
Fetuin-A(ng/ml)	53.28±18.62	63.40±9.09	0.001*
C-IMT (mm)	0.45±0.17	0.35±0.08	0.001*

Note: Data are presented as mean±standard deviations (SD). Abbreviations: LDL: Low-density lipoprotein; HDL: High-density lipoprotein; CRP: C-reactive protein; HOMA-IR: Homeostasis model assessment–insulin resistance; Ca×P: Calcium-phosphorus product; PTH: Parathyroid hormone; C-IMT: Carotid intima-media thickness.*P < 0.05 was considered statistically significant.

Subgroup Analysis According to Fetuin-A Levels

Kidney transplant recipients were evaluated according to their serum fetuin-A levels by dividing them into three equal groups. The group with the lowest fetuin-A level was older than the other groups in terms of mean age. Hepatitis B or C positivity was significantly higher in the lowest fetuin-A group; and in the highest fetuin-A group, there was no hepatitis positivity at all. Renal function and mineral metabolism parameters were similarly distributed between the groups. There was no significant difference in terms of lipid profile. On the other hand, serum albumin level tended to rise as fetuin-A increased. CRP levels were about three times higher in the lowest fetuin-A group than in the other two groups. Most importantly, carotid intima-media thickness was measured as the thickest in the group with the lowest fetuin-A level and the thinnest in the group with the highest fetuin-A level (**Table 3**) (**Figure 1**).

Table 3. Comparison of Clinical and Laboratory Values of Recipients Based on Serum Fetuin-A Levels

Parameters	Group 1 (n=34)	Group 2 (n=35)	Group 3 (n=34)	P
Gender (male/female)	23/10	27/8	19/16	0.17
Age (years)	38.8±9.8	35.3±9.1	31.3±8.3	0.005*
BMI (kg/m^2)	25.8±5.0	24.7±5.0	24.5±6.5	0.59
Dialysis period before transplantation (months)	29.8±37.8	19.1±23.5	20.7±22.4	0.25
Transplant time (months)	51.4±38.1	59.6±42.6	51.3±36.3	0.59
Presence of hepatitis B or C (n/%)	11/%32.3	7/%20	0	0.005*
Serum creatinine (mg/dl)	1.5±0.5	1.6±0.7	1.4±0.4	0.51
Creatinine clerence (ml/dk)	70.0±22.1	72.6±25.9	71.7±23.9	0.7
Calcium (mg/dl)	9.74±0.70	9.74±0.60	9.78±0.57	0.9
Phosphorus (mg/dl)	3.41±0.69	3.49±0.62	3.40±0.65	0.4
Ca × P	33.1±6.2	33.9±6.0	32.2±6.2	0.5
PTH (pg/ml)	130.8±128.7	129.2±144.6	121.9±66.9	0.9
Total cholesterol (mg/dl)	196.3±42.4	214.4±63.6	194.8±34.4	0.18
LDL (mg/dl)	102.4±31.6	123.3±44.9	105.7±29.3	0.05
HDL (mg/dl)	61.3±12.5	60.7±15.7	62.2±13.9	0.92
Trigliseride (mg/dl)	156.8±75.3	151.5±72.3	158.6±79.6	0.92
Albumin (mg/dL)	4.4±0.4	4.5±0.4	4.7±0.3	0.02*
CRP (mg/L)	11.1±13.8	3.5±5.3	3.6±6.6	0.001*
HOMA-IR	3.29±1.41	2.65±1.71	2.81±1.81	0.25
C-IMT (mm)	0.55±0.22	0.43±0.14	0.38±0.10	<0.001*

Group Definitions: Group 1: The third group with the lowest serum fetuin-A level (fetuin-A < 45.6 ng/ml). Group 2: A third group with moderate serum fetuin-A levels (fetuin-A 45.6–60.4 ng/ml). Group 3: The third group with the highest serum fetuin-A level (fetuin-A > 60.4 ng/ml). Note: Data are presented as mean±standard deviations (SD). Abbreviations: BMI: Body mass index; Ca×P: Calcium-phosphorus product; PTH: Parathyroid hormone; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; CRP: C-reactive protein; HOMA-IR: Homeostasis model assessment–insulin resistance; C-IMT: Carotid intima-media thickness.*P < 0.05 was considered statistically significant.

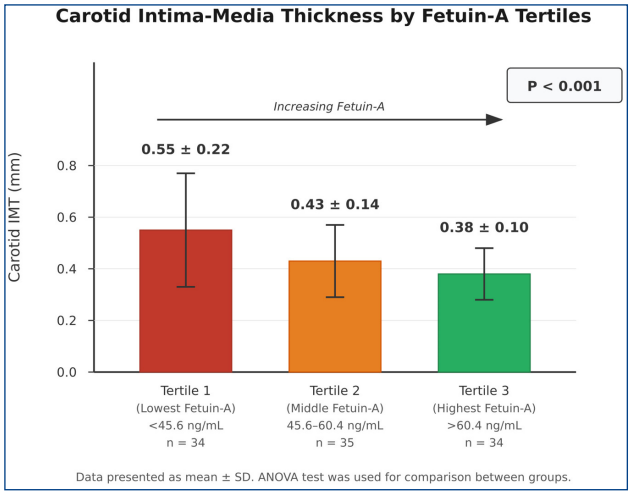

Figure1: Carotid IMT by Fetuin-A Tertiles in Kidney Transplant Recipients. IMT: intima-media thickness

Risk Factor Analysis for C-IMT

In the univariate analysis performed to determine the factors affecting carotid intima-media thickness, age, male gender, kidney transplantation time, CRP, HOMA-IR and fetuin-A stood out as parameters that showed significant correlation. There was a negative relationship between Fetuin-A and C-IMT; that is, as fetuin-A decreased, the thickness of intima-media increased. In the multivariate analysis, in which all these variables were evaluated together, only age and fetuin-A remained independent predictors. Older age showed a positive relationship with C-IMT increase, while low fetuin-A level showed a negative independent relationship. Other traditional risk factors lost their significance in this model (**Table 4**) (**Figure 2**).

Table 4. Evaluation of Risk Factors Affecting C-IMT by Univariant and Multivariance Linear Regression Analysis

Parameters	Univariyent Analiz ß	P	Multivariyent Analysis ß	P
Male gender	0.243	0.013*	0.144	0.181
Age	0.483	0.001*	0.436	<0.001*
Duration of dialysis (months)	0.066	0.51	0.111	0.30
Kidney transplant time (months)	0.203	0.04*	0.073	0.50
BMI (kg/m^2)	0.134	0.188	0.035	0.79
Hypertension	–0.008	0.90	–0.045	0.66
Cholesterol (mg/dl)	0.011	0.90	0.634	0.52
LDL (mg/dl)	0.021	0.84	–0.034	0.89
CRP (mg/L)	0.214	0.03*	0.038	0.723
HOMA-IR	0.258	0.009*	0.128	0.208
Ca × P	0.044	0.66	0.085	0.385
PTH (pg/ml)	0.019	0.86	–0.106	0.340
Fetuin-A(ng/ml)	–0.388	<0.001*	–0.229	0.04*
Creatinine clerence (ml/dk)	–0.151	0.13	–0.188	0.154

Note: The ß values indicate standardized regression coefficients. Abbreviations: BMI: Body mass index; LDL: Low-density lipoprotein; Ca×P: Calcium-phosphorus product; PTH: Parathyroid hormone; HOMA-IR: Homeostasis model assessment–insulin resistance; CRP: C-reactive protein; C-IMT: Carotid intima-media thickness.*P < 0.05 was considered statistically significant.

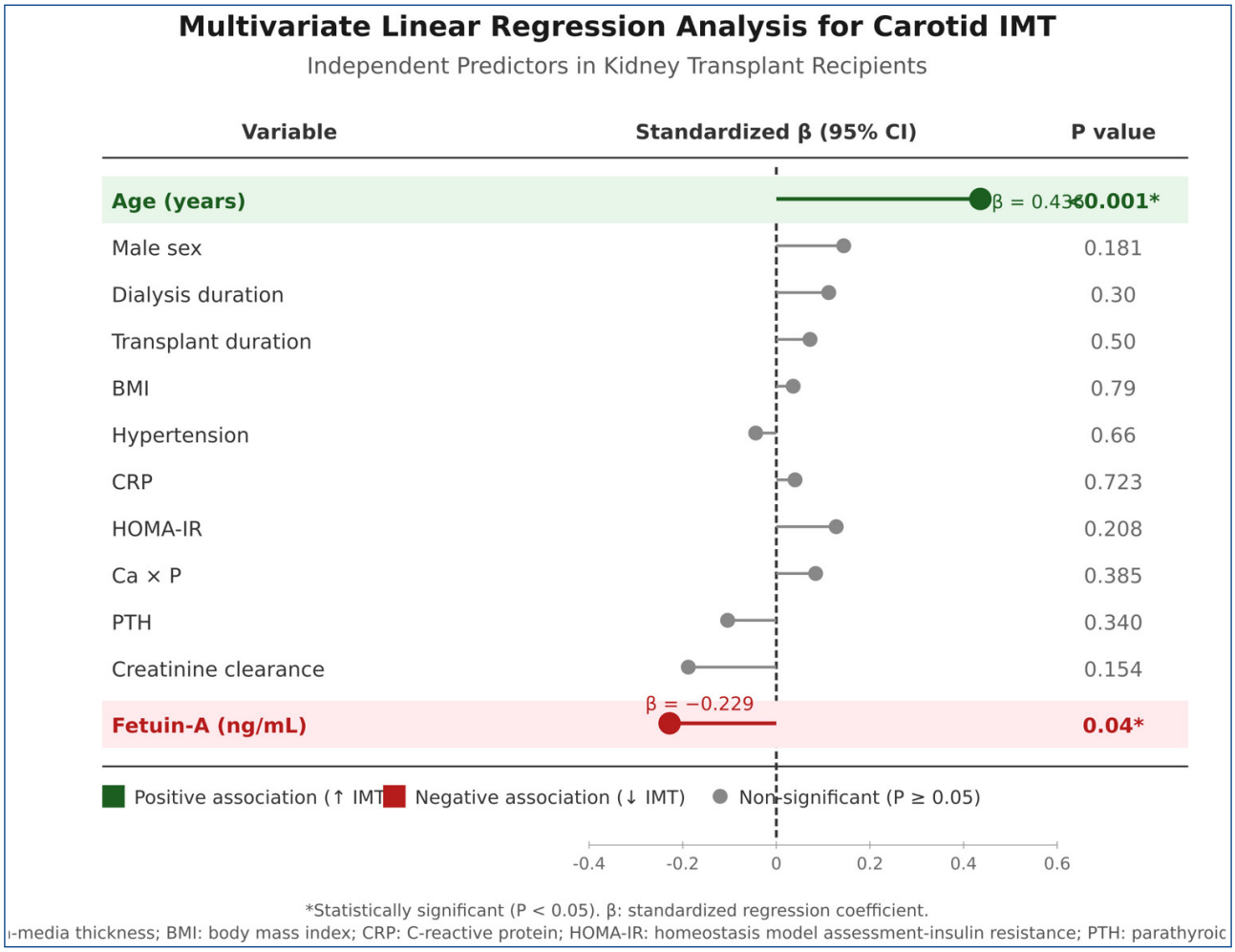

Figure 2. Independent Predictors of Carotid IMT: Multivariate Regression Analysis. IMT: intima-media thickness; BMI: body mass index; CRP: C-reactive protein; HOMA-IR: homeostasis model assessment-insulin resistance; PTH: parathyroid hormone; Ca × P: calcium-phosphorus product. *P < 0.05.

DISCUSSION

In our study, we compared classical CVD risk factors and non-classical CVD risk factors such as insulin resistance and fetuin-A with the control group by measuring C-IMT, which is an early sign of atherosclerosis, in patients who underwent kidney transplantation, and investigated the relationship between these risk factors and C-IMT. We found that C-IMT, was higher in recipients than in the control group with similar demographics. In the multivariant analysis, age remained important as a risk factor affecting C-IMT. Serum CRP levels were found to be higher in recipients than in the control group, and we found that C-IMT increased as serum CRP levels increased in the patient group. The HOMA value indicating insulin resistance was found to be higher in the recipients than in the control group, and we observed a positive correlation between C-IMT and HOMA. We found that serum fetuin-A levels were lower in patients who underwent kidney transplants. While fetuin-A was found to be negatively correlated with C-IMT, we found that multivariate analysis identified an independent risk factor associated with C-IMT.The research data revealed that C-IMT measurements in kidney transplant recipients were higher than those of the control group by 0.10 mm (0.45 mm vs. 0.35 mm, P=0.001). Junarta et al. study showed that C-IMT values rose by 0.35 mm throughout the observation period for patients who received transplants and had stable conditions (10). The research shows that atherosclerotic disease progresses in patients who received their transplant. Although both groups had a similar distribution in terms of age, age stood out as the strongest independent risk factor for C-IMT in the multivariate analysis (ß=0.436, P<0.001). Bloemendal et al. reported that vascular resistance index showed a positive relationship with the age of the recipient (11). This determining role of age is also consistent in the transplant population with the general population. Transplant duration was found to be associated with C-IMT in univariate analysis (P=0.04). This may reflect cumulative immunosuppressive exposure. Sotomayor et al. also emphasised that chronic low-grade inflammation continues to trigger vascular calcification

after transplantation (12). In the study of Junarta et al., it was shown that vascular structure and function markers worsened in long-term follow-up (10).

In our study, although classical CVD risk factors were significantly higher in recipients, none of them were found to be independent predictors of C-IMT. Of the patients, 35.9% were using statins and 53.3% were using antihypertensives. These treatments may have masked the effect of LDL and blood pressure on C-IMT. CRP levels were approximately four times in the recipients for the control group (6.02 vs. 1.62 mg/L). Univariate showed a significant correlation with C-IMT in analysis (ß=0.214, P=0.03). Demirci and Sevinç also reported that CRP values were significantly higher in the high C-IMT group in CKD patients (13). The loss of significance of CRP in multivariate analysis may indicate that inflammation has an indirect effect on other markers such as fetuin-A. CRP levels were approximately four times higher in recipients than in the control group. Menez et al. showed that high iPTH levels (>65 pg/ml) were significantly associated with vascular risk, especially in individuals with reduced renal function (14). Morena-Carrere et al. also emphasized that hyperparathyroidism strengthens the effect on coronary artery calcification and that the coexistence of inflammation and mineral disorders increases cardiovascular risk (15). Our finding also supports that persistent hyperparathyroidism after transplantation maintains residual vascular risk.

In our study, HOMA-IR was 2.4 times that of the control group in recipients (2.90 vs. 1.22). The univariate analysis showed that C-IMT maintained a statistically significant positive relationship with the data (ß=0.258, P=0.009). Manual et al. study discovered that CIMT showed a strong connection with oxidative stress and inflammation markers which exist in stable kidney transplant patients and these factors relate to insulin resistance (16). Rysz et al. study by (17) found that 43% of transplant recipients developed glucose metabolism problems when they were between six months post-transplantation. 58.2% of our patients were using cyclosporine and 41.7% were using tacrolimus. Rysz et al. stated that tacrolimus is more diabetogenic than cyclosporine and that replacing it with alternative agents may reduce the risk of post-transplant diabetes (17). All our patients were taking prednisolone. Steroids are known to reduce insulin sensitivity by increasing gluconeogenesis. Rysz et al. stated that lowering corticosteroid doses leads to better blood sugar management (17). It is noteworthy that HOMA-IR loses its significance in multivariate analysis. Sokooti et al. argued that indirect indices such as HOMA-IR should not be evaluated alone, but together with additional factors such as age and BMI (18). In our data, age and fetuin-A stood out as stronger predictors. The analysis of HOMA-IR values between fetuin-A tertiles showed no significant differences (P=0.25) which indicates that transplant patients develop insulin resistance through distinct pathways than the average population.

The main finding of our study was that fetuin-A was significantly lower in recipients than in the control group (53.28 vs. 63.40 ng/ml, P=0.001). The multivariate analysis showed that fetuin-A emerged as the most important independent variable which caused negative effects on C-IMT results while age became the only factor that reached statistical significance (ß=–0.229, P=0.04). El-Shehaby et al. study found that hemodialysis patients had lower fetuin-A levels than control participants and researchers discovered that patients with low fetuin-A levels developed thicker carotid intima-media (19). A meta-analysis by Welliam et al. study demonstrated that CKD patients who had low fetuin-A levels developed cardiovascular events (20). In tertil analysis, C-IMT was the highest (0.55 mm), CRP was the highest (11.1 mg/L), and albumin was lowest (4.4 mg/dl) in the low fetuin-A group. This picture suggests the association of malnutrition-inflammation-atherosclerosis. El-Shehaby et al. reported that fetuin-A levels which were lower than normal values were strongly associated with inflammation markers hs-CRP and TNF-α (19). Chekol Abebe et al. explained that fetuin-A is a negative acute phase protein and its level decreases during inflammation (21). A remarkable finding was that the prevalence of hepatitis B/C was 32.3% in the low fetuin-A group, while there was no hepatitis in the high fetuin-A group. Chekol Abebe et al. stated that fetuin-A is synthesized mainly in hepatocytes; this biologically supports that liver damage can affect fetuin-A levels (21). El-Shehaby et al. also argued that low serum fetuin-A levels are an important factor in the progression of vascular calcification and may be an indicator for mortality (19).

Due to the cross-sectional nature of our study, fluctuating blood pressure values and lipid parameters, and heterogeneous duration and doses of antihypertensive drug and statin use, we may not have been able to see the correlation between hyperlipidemia and hypertension and C-IMT. Since imaging modalities that directly assess vascular calcification were not used in this study, vascular calcification could not be fully evaluated. Perhaps if we could investigate coronary artery calcification with spiral tomography, we would be able to better evaluate this relationship. Since the pre-transplant serum fetuin-A level of the patients was not measured in our study, it was not possible to evaluate how the fetuin-A level progressed after transplantation. Although our patients did not have acute viral hepatitis, liver functions could not be determined precisely because liver biopsies were not evaluated during the study.

CONCLUSION

Since CVD is the most important cause of mortality in patients who underwent kidney transplantation, as in the whole population, we tried to identify and prevent CVD risk factors in these patients. In our study, it was shown that insulin resistance and low serum fetuin-A levels were associated with the development of early atherosclerosis in patients who underwent kidney transplantation. It was determined that low serum fetuin-A levels were especially affected by inflammation and hepatitis in kidney transplant patients, and creatinine clearance, serum calcium, phosphorus and PTH levels did not affect serum fetuin-A levels. There was no relationship between serum fetuin-A level and insulin resistance. Since both high and low levels of fetuin-A have been found to be atherosclerosis risk factors in different populations, Prospective long-term studies investigating longitudinal changes in serum fetuin-A levels in kidney transplant recipients are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Başkent University Faculty of Medicine Clinical and Drug Research Local Ethics Committee (KA07/24-DATE:15/03/2007).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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