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Nutritional Predictors of Cardiovascular Risk in Patients after Kidney Transplantation-Pilot Study

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Abstract: Asymmetric dimethylarginine (ADMA) is a marker of endothelial damage. Research confirms the association of ADMA with an increased cardiovascular risk (CVR) among kidney transplant recipients (KTRs). Additionally, increased circulating levels of fibroblast growth factor 23 (FGF-23) are associated with pathological cardiac remodeling and vascular alterations. The aim of the study is the analysis of the relationship between ADMA, FGF-23, nutritional, biochemical parameters in healthy subjects and KTRs. 46 KTRs and 23 healthy volunteers at mean age of 50.8 ± 15.4 and 62.5 ± 10.7 years were enrolled. The anthropometric and biochemical parameters such as ADMA, FGF-23, albumin, prealbumin were assessed. Fat tissue mass among KTRs was 30.28 ± 9.73%, lean body mass 64.5 ± 14.8%. Overweight and obesity was presented by 65.2% of recipients. Albumin level was 38.54 ± 3.80 g/L, prealbumin 27.83 ± 7.30 mg/dL and were significantly lower than in the control ($p < 0.05$). Patients with ADMA > 0.66 µmol/L had a lower concentration of prealbumin, albumin and increased concentration of oxidized low density lipoprotein (oxLDL), high sensitive C-reactive protein (hsCRP) and FGF-23. FGF-23 was significantly higher in patients with higher hsCRP ($p < 0.05$). KTRs with elevated ADMA had a longer transplantation vintage, lower eGFR and higher albuminuria. Diabetes mellitus (DM) was associated with higher levels of ADMA and FGF-23. Even in stable KTRs a relationship between inflammatory state, nutritional status, graft function and endothelial dysfunction biomarkers was observed.

Keywords: kidney transplantation; cardiovascular risk; nutritional status; ADMA; FGF-23

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1. Introduction

The epidemics of overweight, obesity, diabetes mellitus (DM) and hypertension increase the risk of developing chronic kidney disease (CKD). According to Hill et al.'s meta-analysis from 2016, the worldwide CKD prevalence of stage 3–5 was 10.6% [1]. Unfortunately, many patients go undiagnosed and find out about the disease shortly before end-stage kidney disease (ESKD) when the renal replacement therapy (RRT) is required. RRT includes dialysis and kidney transplantation (KT), which is more effective. Kidney transplant recipients (KTRs) have a better quality of life and their prognosis is better compared to dialysis patients; however, compared to healthy people, KTRs have a three- to five-fold higher cardiovascular risk (CVR) [2–5]. It has been estimated that a 20-year-old healthy European will live for another 62 years, but KTRs only 44 years. The main cause of death in KTRs is cardiovascular disease (CVD), which results from the presence of traditional and non-traditional risk factors [6–8]. Traditional risk factors, that also apply

to the general population, include, e.g., lipid disorders, obesity, DM, hypertension, hyperhomocysteinaemia and smoking. Non-traditional risk factors include, e.g., inflammation, oxidative stress, uremic toxins, disturbances of calcium-phosphorus levels, disorders of nutritional status, lipoprotein (a) and asymmetric dimethylarginine (ADMA). Similar risk factors exist in dialysis patients, but their severity is much greater. The risk of CVD in a dialysis patient who has undergone a successful transplant is significantly reduced, but not as low as in healthy subjects. CVR among KTRs is also influenced by the use of immunosuppressants, glucocorticosteroids and CKD progression [9–11].

Endothelial dysfunction (ED) is a major cause of CVD development. One of the mechanisms of ED is a defect in nitric oxide (NO) production [12]. ADMA is an endogenous inhibitor of endothelial nitric oxide synthase, a marker of endothelial damage and progression of atherosclerosis. Research confirms the association of ADMA with an increased risk of cardiac complications and an increased risk of death and graft loss among KTRs [13–15]. Additionally, CKD-mediated increased circulating levels of fibroblast growth factor 23 (FGF-23) are associated with pathological cardiac remodeling and vascular alterations. In addition, FGF-23 is independently associated with all-cause mortality. KT reduces FGF-23 levels, but the values are not as low as in healthy subjects. ADMA and FGF-23 levels can be associated with nutritional status [16,17], while obesity negatively affects graft survival and CVR [18,19].

CVD is the main cause of death in KTRs. Therefore, it is necessary to know the risk factors, which may allow for the introduction of modern treatment therapies in the future. The primary outcome of our study is finding risk factors for increased ADMA and FGF-23 concentration in the stable KTRs.

The aim of its study is the analysis of the relationship between ADMA, FGF-23, nutritional, biochemical parameters in KTRs and healthy subjects. The purpose of the research is also to compare KTRs with different levels of ADMA and with DM.

2. Materials and Methods

2.1. Study Participants

The study group consisted of clinically stable KTRs (26 men; mean age 50.8 $\pm$ 15.4 years). The transplantation vintage was 69.0 (median 51.0) months. None of the patients experienced any surgical or infectious complications related to the KT. There was also no allograft rejection. All patients were under care in the Outpatient Transplantation Unit at the Department of Nephrology, Transplantology and Internal Disease, Medical University of Gdansk, Poland and were treated with triple immunosuppressive therapy (glucocorticosteroids, calcineurin inhibitor, mycophenolate mofetil). The control group consisted of 23 healthy volunteers (8 men; mean age 62.5 $\pm$ 10.7 years). Other clinical data were based on the medical records. This study was approved by Independent Bioethics Committee for Scientific Research at Medical University of Gdańsk (NKBBN/291-367/2020, NKBBN/291-437/2018). The clinical and research activities were consistent with the Principles of the Declaration of Istanbul, as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

2.2. Biochemistry

Plasma samples were taken after an overnight fast and stored at -80 °C until analyzed. High sensitive C-reactive protein (hsCRP) was measured in serum by the enzyme-linked immunoassay (ELISA) method. ADMA, FGF-23 and oxidized low-density lipoprotein (oxLDL) were measured in plasma also by the ELISA method. Albumin (serum albumin), creatinine, blood urea nitrogen (BUN), sodium, potassium, magnesium, total cholesterol and blood morphology were measured by routine laboratory methods.

2.3. Anthropometric Measurements and Nutritional Status

Body mass and height were assessed. Body Mass Index (BMI) was calculated according to the current body mass/height^2 (kg/m^2) and classified as: <18.5–underweight, 18.5–24.99–normal weight, 25–29, 99–overweight and $\geq$30–obesity. For the evaluation of

body composition parameters such as lean tissue mass (LTM) and fat tissue mass (FAT), multi-frequency bioimpedance analysis (BIA) with Body Composition Monitor (BCM, Fresenius SA, Bad Homburg, Germany) was carried out. Nutritional status was assessed with the 7-points Subjective Global Assessment (SGA) and classified patients as well-nourished when they received 6–7 points, moderately/slightly malnourished when they had 4–5 points and malnourished when they had 1–3 points [20].

2.4. Statistical Analysis

Statistical analysis was performed using Statistica 13.3 version for Windows. All data are presented as mean ± SD or median. Comparisons of the groups were examined by Student's *t*-test (for parametric data) and U Mann-Whitney Rank Sum Test (for non-parametric data). Spearman's correlation was used for nonparametric measure of statistical dependence between two variables. Independent associations among variables were assessed with stepwise multiple regression analysis; it consisted of a constructing a model that includes all potential explanatory variables and then in the gradual elimination of variables so as to maintain the model with the highest value of the coefficient of determination while maintaining the significance of the parameters. For all performed analyses, $p < 0.05$ was considered statistically significant.

3. Results

The biochemical and anthropometric characteristics of the study and control group are presented in Table 1.

Table 1. The comparison between KTRs and control group.

Parameters	KTRs *n* = 46	Control Group *n* = 23
Gender (M/F)	26/20	8/15
Age (years)	50.8 ± 15.4	62.5 ± 10.7
Type of transplantation (Deceased donor)	*n* = 46	-
Triple drug immunosuppression **	*n* = 46	-
Tacrolimus	*n* = 16	-
Cyclosporine	*n* = 20	-
Dialysis vintage before TX (months)	31.0 ± 27.1	-
Warm ischemic time (minutes)	30.0 ± 8.5	-
Cold ischemic time (minutes)	950.0 ± 398.4	-
BMI (kg/m^2)	26.25 ± 3.51	24.39 ± 4.25
Fat tissue mass (%)	30.28 ± 9.73	26.41 ± 6.7 *
Lean Body Mass (%)	64.5 ± 14.8	66.3 ± 9.8
Prealbumin (mg/dL)	27.83 ± 7.3	33.52 ± 9.23 *
Albumin (g/L)	38.54 ± 3.8	43.56 ± 2.43 *
ADMA (µmol/L)	0.75 ± 0.36	0.32 ± 0.17 *
FGF-23 (pg/mL)	115.71 ± 66.18	64.11 ± 18.58 *
oxLDL (mg/mL)	617.22 ± 535.36	206.48 ± 61.13
Creatinine (mg/dL)	1.44 ± 0.42	0.83 ± 0.21
median	1.37	0.7
eGFR CKD-EPI (mL/min/1.73 m^2)	42.32 ± 10.97	78.0 ± 5.0 *
median	41.0	80.0
Total cholesterol (mg/dL)	196.03 ± 35.2	186.3 ± 23.11
HDL (mg/dL)	50.0 ± 14.41	52.1 ± 15.1
LDL (mg/dL)	125.55 ± 32.2	130.15 ± 47.41
TG (mg/dL)	135.9 ± 62.5	100.78 ± 52.2
hsCRP (mg/L)	4.2 ± 3.96	1.8 ± 1.5 *

* $p < 0.05$, ** glucocorticosteroids, calcineurin inhibitor, mycophenolate mofetil BMI—body mass index; ADMA—asymmetric dimethylarginine; FGF-23—fibroblast growth factor 23; oxLDL—oxidized low density lipoprotein; eGFR—estimated glomerular filtration rate; HDL—high density lipoprotein; LDL—low density lipoprotein; TG—triglyceride; hsCRP—high sensitive C-reactive protein.

3.1. Anthropometry and Nutritional Status

In KTRs, group mean BMI was 26.25 ± 3.51, fat tissue mass 30.28 ± 9.73% and 22.51 ± 8.72 kg, LBM 64.5 ± 14.8%. Excessive body weight (BMI > 25) was presented by 65.2% of KTRs; 23.2% of KTRs presented obesity (Figure 1). In comparison to the control group, KTRs presented significantly higher contents of body fat.

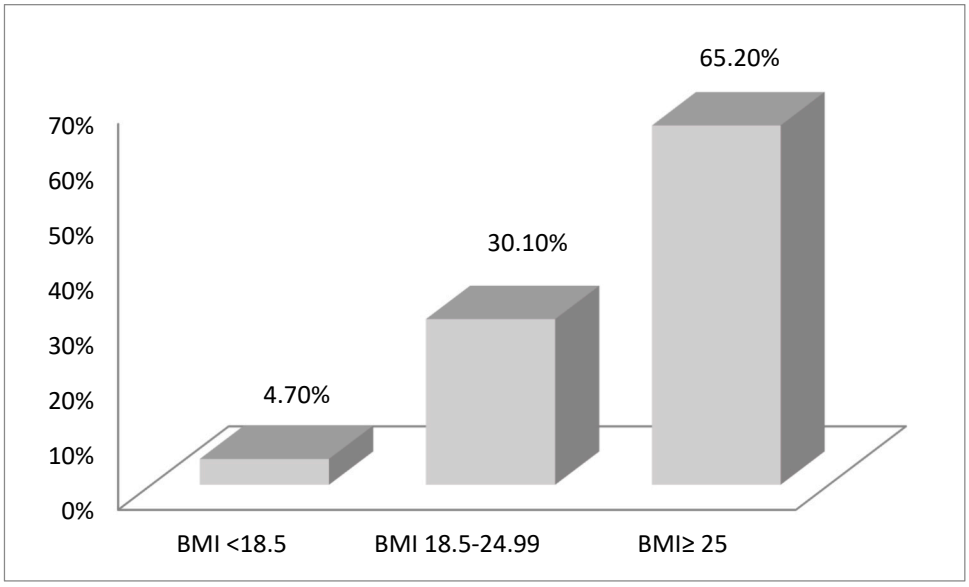

Figure 1. The percentage of BMI categories in KTRs.

Based on 7-point SGA, 39% of KTRs were moderately/slightly malnourished (Figure 2). 36.2% of moderately/slightly malnourished KTRs (with SGA ≤ 5) were overweight or obese.

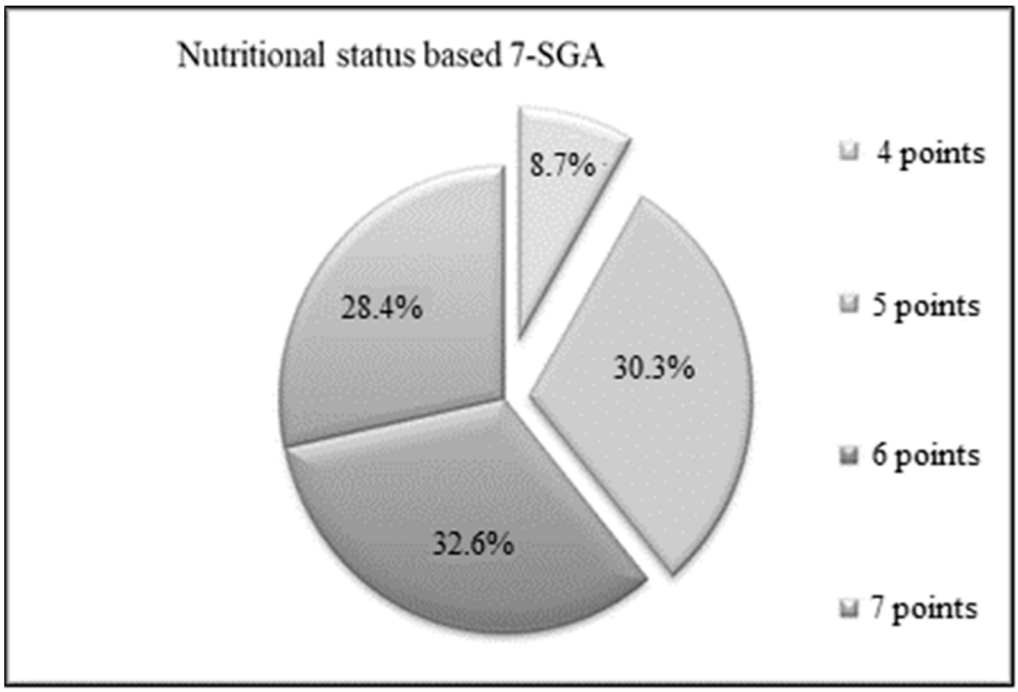

Figure 2. The nutritional status according 7-point SGA in KTRs.

Albumin level was 38.54 ± 3.80 g/L and prealbumin 27.83 ± 7.30 mg/dL and were significantly lower than in the control group ($p < 0.05$).

3.2. Markers of Endothelial Dysfunction and Inflammatory State

As presented in Table 1, the concentrations of ADMA, FGF-23 and hsCRP were significantly higher in KTRs in comparison to the control group. Patients with ADMA > 0.66 µmol/L had a lower concentration of prealbumin, albumin and increased concentration of oxLDL, hsCRP and FGF-23 (Table 2). However, KTRs with an elevated ADMA level had a longer transplantation vintage, lower eGFR and higher albuminuria.

Table 2. The comparison between KTRs with ADMA ≤ 0.66 and > 0.66 µmol/L.

Parameters	ADMA ≤ 0.66 µmol/L *n* = 29	ADMA > 0.66 µmol/L *n* = 17
Transplantation vintage (months)	68.2 ± 64.7	70.7 ± 55.0
Creatinine (mg/dL)/	1.37 ± 0.40	1.56 ± 0.46 */
median	1.3	1.5
eGFR CKD-EPI (ml/min/1.73 m^2)/	44.0 ± 9.5/	39.3 ± 13.2
median	55.5	48.0
oxLDL (mg/mL)	674.12 ± 569.66	332.75 ± 112.41
hsCRP (mg/L)	3.7 ± 3.66	6.75 ± 5.0
ADMA (µmol/L)	0.51 ± 0.08	1.1 ± 0.32 *
FGF–23 (pg/mL)	128.49 ± 74.07	105.86 ± 50.55

* $p < 0.05$ eGFR—estimated glomerular filtration rate; oxLDL—oxidized low-density lipoprotein, hsCRP—high sensitive C-reactive protein; ADMA—asymmetric dimethylarginine; FGF-23—fibroblast growth factor 23.

Malnourished KTRs were significantly older and had a higher prevalence of DM (Table 3). Additionally, DM was associated with higher levels of ADMA and FGF-23 in comparison to KTRs without DM (Figure 3).

Table 3. The comparison between well-nourished and malnourished KTRs.

Parameters	Well-Nourished *n* = 28	Malnourished *n* = 19	Malnourished with BMI > 25 *n* = 6
Age (years)	44.7 ± 13.4	60.2 ± 13.5 *	59.1 ± 14.7 *
DM (n,%)	4, 14.2	10, 52.6 *	6, 100 *
eGFR CKD EPI (ml/min /1.73 m^2)/median	60.4 ± 17.3/ 56.3	48.0 ± 21.7/ 42.6	47.8 ± 18.4/ 44.0
BMI	26.9 ± 4.7	26.1 ± 3.4	29.8 ± 3.9
S-albumin (g/L)	38.1 ± 3.8	37.1 ± 3.8	37.5 ± 3.6
Time after TX (months)	64.4 ± 59.4	76.3 ± 63.5	71.6 ± 58.1
ADMA (µM/L)	0.81 ± 0.35	0.70 ± 0.36	0.70 ± 0.30
FGF-23 (pg/mL)	106.6 ± 52.1	244.4 ± 516.9	139.4 ± 87.3
hs-CRP (mg/L)	4.6 ± 4.0	3.8 ± 4.1	4.6 ± 4.9

* $p = 0.00$ well-nourished vs malnourished DM diabetes mellitus, eGFR—estimated glomerular filtration rate; hsCRP—high sensitive C-reactive protein; ADMA—asymmetric dimethylarginine; FGF-23—fibroblast growth factor 23.

FGF-23 was significantly associated with hsCRP (correlation coefficient R Sperman = 0.4; $p < 0.05$) and were negatively correlated with eGFR (CKD EPI) (R Sperman = 0.5, $p < 0.05$; Figure 4).

3.3. Multivariate Regression Analysis

The multivariate regression model shows (Table 4) that the adjusted R^2 of the model was 0.10; $p < 0.02$), the association between DM and high levels of ADMA and hsCRP, but not FGF-23 (dependent variable DM; independent variables hsCRP, ADMA, FGF-23).

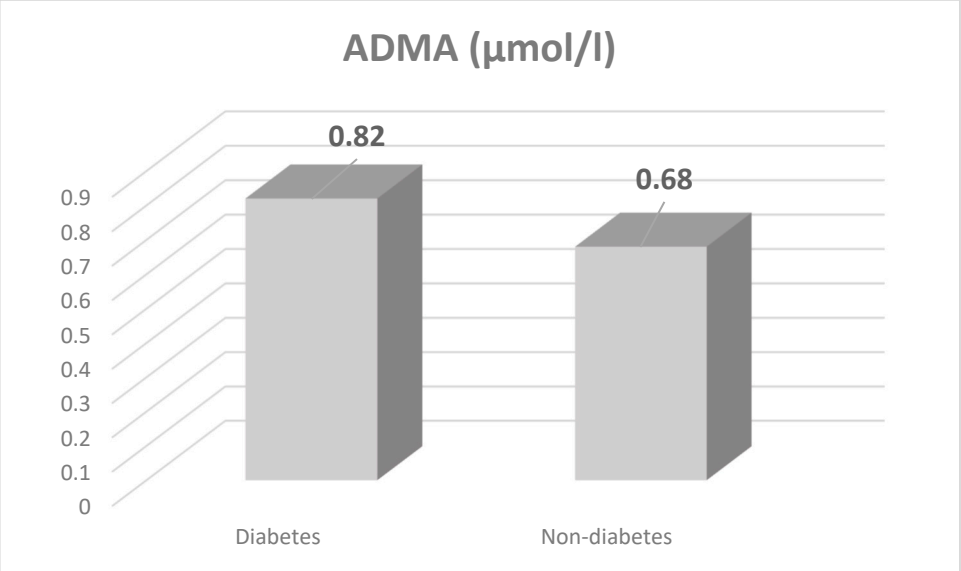

Figure 3. ADMA concentration in KTRs with and without diabetes mellitus ($p < 0.05$).

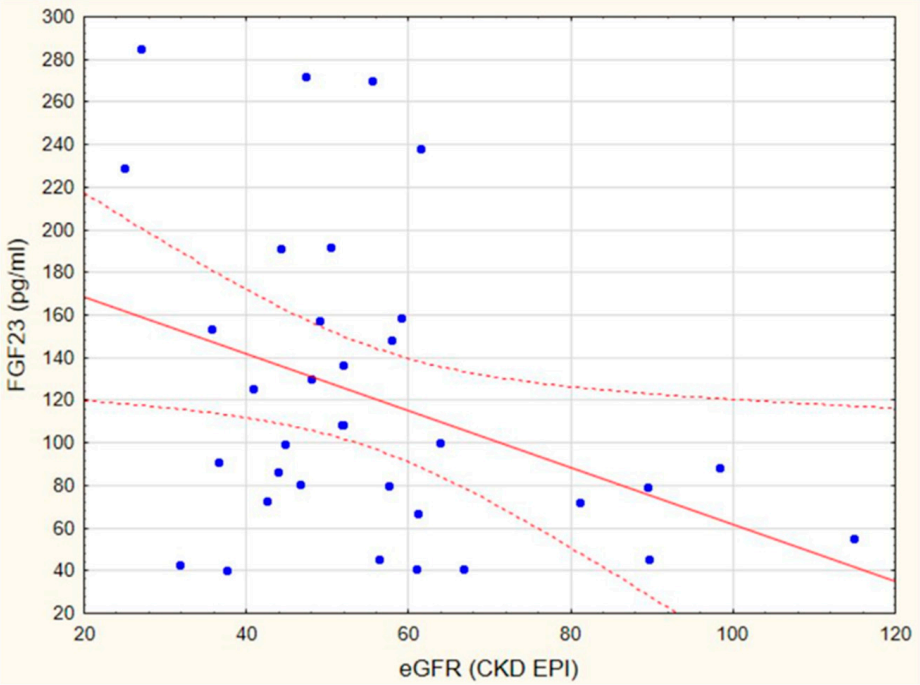

Figure 4. The correlation between FGF-23 and eGFR (CKD EPI) in KTRs group (R Sperman = 0.5; $p < 0.05$).

Table 4. The prevalence of elevated ADMA and hs-CRP depending on DM diagnosis.

Regression Model	B	Standard Error	Beta	*p*-Value
Constant	1.34	0.39		0.000
ADMA	0.79	0.39	−0.2	0.04 *
FGF-23	0.06	0.10	0.06	0.53
hsCRP	0.01	0.00	0.26	0.01 *

* $p < 0.05$ ADMA—asymmetric dimethylarginine; FGF-23—fibroblast growth factor 23; hsCRP—high sensitive C-reactive protein.

4. Discussion

Although KT is the best method of RRT, KTRs have a higher CVR compared to healthy people. The presence of traditional risk factors does not explain the high mortality rate. For this reason, more and more attention is paid to non-traditional factors, such as nutritional status, calcium-phosphate metabolism, oxidative stress and chronic inflammation [3,9,11].

In this study, we assessed the relationship between ADMA, FGF-23, nutritional, and biochemical parameters among KTRs and in the control group. The nutritional status was evaluated by BMI, body composition and 7-point SGA. According to the results of our previous studies conducted in larger populations, many KTRs were overweight and obese [21,22]. Excessive body weight usually occurs in approximately 40% of KTRs [23], but in this study, almost two-thirds of the patients were overweight or obese. Moreover, KTRs presented significantly higher contents of body fat in comparison to healthy volunteers (30.28 ± 9.73 vs. $26.41 \pm 6.7\%$). Obesity increases the risk of the deterioration of the graft function, e.g., by glomerular hyperfiltration, lipotoxicity, altered secretion from adipose tissue and also obesity increases CVR [24]. Despite excessive body weight, based on 7-point SGA, 36.2% of patients were moderately/slightly malnourished. Biochemical parameters of nutritional status such as albumin and prealbumin were significantly lower in the KTRs compared to the control group. Sezer et al. reported that, based on SGA, 23.4% of KTRs were moderately/slightly malnourished and 10.6% were malnourished [25].

ADMA is the product of proteolysis of proteins containing methylated arginine, which disrupts endothelial function by reducing the phosphorylation of arterial endothelial nitric oxide synthase (eNOS). It is a marker of endothelial damage, progression of atherosclerosis and its elevated levels are connected to CVR [13,15,26]. In this study, KTRs had a significantly higher concentration of ADMA and lower eGFR than healthy volunteers, which has also been observed in other studies [27]. Renal function impairment leads to an increase in plasma ADMA concentration due to disturbances in its urinary excretion [28]. KTRs were divided into two groups depending on ADMA concentration (ADMA ≤ 0.66 and > 0.66 µmol/L). This division was made on the basis of the study by Frenay et al. in which the risk of death was estimated at 686 KTRs. During 3 years of follow-up, 12% of patients died and 7% lost their graft function, defined as a new need for dialysis therapy or retransplantation. The highest risk of death was in the group of patients with ADMA > 0.66 µmol/L [29]. In this study, ADMA > 0.66 µmol/L, among transplant recipients, was associated with a lower eGFR, albumin, prealbumin levels and increased of oxLDL, hsCRP and FGF-23 concentration. DM was associated with higher ADMA levels. In our other study, ADMA was associated with the nutritional status of peritoneal dialysis patients [30]. There are no studies on the relationship between ADMA and nutritional status in patients after KT.

FGF-23 is a protein hormone secreted by osteocyte in response to $1.25(OH)_2D_3$, parathyroid hormone (PTH) and elevated phosphate concentration. Inflammation probably also increases bone-released hormones. FGF-23 reduces renal phosphate reabsorption. The progression of CKD leads to an increase in the concentration of FGF-23 and in consequence to CVD development by vascular calcification. KT reduces FGF-23 levels, but the values are not as low as in healthy subjects, which we also observed in this study [17,31,32]. The control group had a significantly lower level of FGF-23 and hsCRP compared to KTRs (64.11 ± 18.58 vs. 115.71 ± 66.18). Asicioglu et al. also observed a similar dependence [33]. In our study, we observed the correlation between FGF-23 and eGFR. FGF-23 was significantly higher in patients with a higher hsCRP. FGF-23 is associated with all-cause and cardiovascular mortality among KTRs; therefore, it is classified as a non-traditional risk factor [16].

The limitation of our study is a small group of patients and control subjects, but despite its limitations, the results of the present study are valuable because they indicate a problem of occurrence non-traditional risk factors of CVD, also in patients after KT, such as inflammation and nutritional status.

5. Conclusions

Even in stable KTRs, a relationship between inflammatory state, nutritional status, graft function and endothelial dysfunction biomarkers was observed. Further studies in KTRs (e.g., multicenter) are needed to confirm our preliminary results.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Independent Bioethics Committee for Scientific Research at Medical University of Gdańsk (NKBBN/291-367/2020, NKBBN/291-437/2018).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data are not publicly available due to patient privacy concerns.

Conflicts of Interest: The authors declare no conflict of interest.

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