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Original article

The Influence of Body Composition on Graft Function in Patients with Transplanted Kidney

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SUMMARY

Introduction/Aim. Patients who undergo kidney transplantation can encounter significant changes in body composition because of weight gain caused by fat mass accumulation and muscle mass loss, resulting in poor graft outcomes. The study aimed to investigate the impact of different obesity parameters on graft function in kidney transplant recipients.
Methods. A cross-sectional study was conducted on 80 kidney transplant patients aged 25 - 75 years (40% females). All were on triple immunosuppressive therapy. Weight, height, waist, and hip circumferences measurements were taken to calculate body mass index (BMI) and waist-to-hip ratio (WHR). Body fat percentage (BF%) was measured using a 4-site skinfold method calculated through the Jackson-Pollock equation utilizing a Cescorf caliper. The patients were divided into two groups depending on their glomerular filtration rate (GFR).
Results. BMI showed that 16.28% of males and 10% of females were obese. However, according to BF%, as many as 44.68% of males and 72.72% of females were obese. Statistically significant differences in BMI, WHR, and BF% were observed among patients with normal and lower GFR. After adjustment for covariables, lower GFR was related to higher levels of all obesity parameters. The combination of central obesity (WHR>0.85 for women and > 0.9 for men) and higher BF% was associated with lower GFR compared with that in lean subjects (p < 0.001 for both groups).
Conclusion. High BF% and WHR may be important risk factors for reducing GFR in kidney transplant recipients.

Keywords: **kidney transplantation, obesity, body fat percentage, body mass index**

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INTRODUCTION

Kidney transplantation (KT) is the treatment of choice for patients with end-stage renal disease. Compared to dialysis, transplantation is less expensive and positively impacts life expectancy and quality of life. However, KT raises concerns regarding post-transplant new-onset diabetes mellitus and obesity. The prevalence of obesity among kidney transplant recipients has considerably increased over the past few decades, reflecting the trend in the general population. Regardless of pre-transplant nutritional status, approximately 50% of patients gain weight after KT, especially within the first year. The average weight gain during the first year after transplantation is estimated to be 5 – 10 kg (1 - 3). Worse long-term outcomes and the development of certain comorbidities, most notably diabetes and hypertension, are associated with this rapid and significant weight gain (3). Diet, genetics, gender, and age are the most common risk factors for developing obesity (4). In addition, most immunosuppressives used in patients with transplanted kidneys can lead to an increase in body weight (5). Several studies have demonstrated that excessive body weight and high body mass index (BMI) negatively impact both patient and graft survival (6, 7).

BMI is widely used as a screening tool for obesity due to its cost-effectiveness and practicality. However, it has been shown that using body fat percentage as a tool for identifying obese patients is more precise than BMI (8). More than half of the people with normal BMI have a high body fat percentage (8). Also, BMI is not a good indicator of body composition and regional fat distribution, which is, actually a significant risk factor for cardiovascular diseases (9) because body fat, especially visceral abdominal fat, is considered to be a primary mediator in the development of cardiovascular diseases. Visceral fat can secrete considerable amounts of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNFα) and interleukins 1 and 6 (IL-1 and IL-6), which contribute to the development of cardiovascular disease. (10). Visceral fat is also metabolically active and secretes hormones such as leptin and resistin, which are proven to be responsible for the development of type 2 diabetes, cardiovascular diseases, and certain malignancies (11, 12).

As visceral body fat may influence kidney transplant outcomes, a precise characterization of the changes in the body fat as well as the distribution of the body mass has notable clinical significance. There are different methods to measure body composition, including measurement of skinfold thickness, bioelectrical impedance analysis, "DEXA-scans", and imaging tests (MRI and CT) (13, 14). Skinfold measurement is a simple and non-invasive method widely used in clinical practice to estimate body fat (15, 16).

The aim of this study was to investigate the impact of different obesity parameters on graft function in kidney transplant recipients by conducting anthropometric measurements.

PATIENTS AND METHODS

A cross-sectional study was conducted on 80 patients who underwent KT. Immunosuppression consisted of triple maintenance tacrolimus, mycophenolate mofetil, and corticosteroid taper. Patients were divided into two groups according to their glomerular filtration rate (GFR). Group A comprised 29 patients with GFR > 60 mL/min, while Group B comprised 51 patients with GFR < 60 mL/min. eGFR was calculated using the CKD_EPI equation (17).

All patients underwent blood analysis (hemoglobin, serum albumin, CRP, total cholesterol, LDL, HDL, and triglycerides), as well as anthropometric measurements (height, body weight, body fat percentage, waist and hip circumference, and waist-to-hip ratio). Body weight was measured by using a digital weight scale before meals. Patients wore light clothes and were barefoot. The results were expressed in kilograms. Height was assessed by a stadiometer. Patients wore light clothes and were barefoot, standing straight and right below the stadiometer with relaxed shoulders and palms facing thighs. Waist circumference (WC) was determined using a measuring tape placed on a horizontal plane, midway between the lowest costal margin and the iliac crest, whereas hip circumference was measured at the level of the widest circumference over the great trochanters. The waist-to-hip ratio (WHR) was calculated by dividing these two values. WC and WHR were used to estimate body fat distribution, particularly as intraabdominal or visceral fat mass indicators. BMI was calculated using a formula BMI= weight/(square of height) (standard unit of measure is kg/m^2). According to the American Association of Clinical Endocrinologists and The American College of Endocrinology, there are four BMI classifications (underweight, normal weight, overweight and obese) (18). The quantity and distribution of body fat were assessed by measuring four skinfold thicknesses. Skinfold thickness was measured by using the Cescorf skinfold body fat caliper, the device that allows the assessment of the thickness of the subcutaneous adipose tissue. All measurements were done on the left side of the body. Measurement sites were identified and marked with a pencil. The skin was pinched with the thumb and index fingers without pinching the underlying muscles. The skinfold was then pinched with an opened caliper, which spontaneously closed after a few seconds. The final value was the mean value of three consecutive measurements. The thickness of the following four skinfolds was measured: triceps, abdominal, suprailiac, and thigh. The triceps skinfold was measured on the posterior surface of the arm, with the caliper placed halfway between the acromion and the olecranon process. The suprailiac skinfold was measured diagonally at the intersection of the anterior axillary line and iliac crest. The abdominal skinfold was measured horizontally, between the navel and anterior superior iliac spine, whereas the thigh skinfold was measured vertically, at the anterior surface of the thigh, between the kneecap and the great trochanter of the thigh bone.

After conducting the measurements, Jackson and Pollock formula was used to calculate %BF (19, 20). In males, %BF = (0.29288 x sum of the skinfolds measured) – (0.0005 x square of the sum of the skinfolds measured) + (0.15845 x age) – 5.76377, whereas in females, %BF = (0.29669 x sum of the skinfolds measured) – (0.00043 x square of the sum of the skinfolds measured) + (0.02963 x age) + 1.4072. If the body fat percentage was higher than 35% in females and 25% in males, patients were considered obese (21).

Descriptive and analytical methods were used for the statistical analysis. Standard deviation (SD) and mean values were used to analyze the results. Student t-test, Pearson's Chi-squared, and Mann-Whitney tests were used to identify significant differences. Factors related to the GFR in the univariable analysis ($p < 0.05$) were used in the multivariable analysis so that the independent influence of these factors on GFR could be estimated. Receiver operating characteristics (ROC) curves were created to compare the sensitivity and specificity of certain parameters of obesity in order to predict values of GFR. ROC curves were used to find the optimal cut-off points.

Data were analyzed by SPSS 21.0 program (Statistical Package for the Social Sciences, Chicago, IL, USA) for Windows.

RESULTS

Basic demographic characteristics of the patients are shown in Table 1. The study included 80 kidney transplant recipients, 47 men and 33 women. All the patients were on triple immunosuppressive therapy, and there was no difference in the medication dosing between the patients with normal and reduced kidney function. As seen in Table 1, dialysis vintage and kidney donor age

Table 1. *Demographic characteristics of the study population*

Variable	GFR < 60 mL/min (n = 51)	GFR > 60 mL/min (n = 29)	p
Gender (Male/Female)	30/21	17/12	NS
Recepient age	46.20 ± 12.56	44.38 ± 9.93	NS
Time since Tx	8.14 ± 4.7	7.63 ± 4.7	NS
Living donors (n)	38	19	0.038
Cadaver (n)	13	10	0.047
Duration of HD before Tx	4.6 ± 2.12	2.4 ± 1.85	< 0.001
Donor age	62.54 ± 15.3	58.15 ± 9.6	0.043
Medication			
Mycophenolic acid (mg)	751 ± 231.2	896.6 ± 450.4	NS
Tacrolimus (mg)	4.25 ± 2.71	2.86 ± 0.82	NS
Prednisolone (mg)	6.2 ± 2.4	6.1 ± 2.44	NS

Abbrevation: Tx-transplantation; CKD-chronic kidney disease; NS-no significant

Table 2. *Baseline laboratory data according to GFR*

Variable	GFR < 60 mL/min (n = 51)	GFR > 60 mL/min (n = 29)	p
Hemoglobin (g/dL)	10.0 ± 1.4	11.3 ± 1.5	0.058
Serum albumin (g/dL)	33.8 ± 5.1	37.8 ± 5.5	< 0.05
CRP (mg/L)	5.8 ± 0.7	3.9 ± 0.5	< 0.05
Total cholesterol (mmol/L)	4.93 ± 0.9	4.16 ± 1.3	NS
LDL (mmol/L)	3.1 ± 0.8	2.4 ± 1.1	< 0.05
HDL (mmol/L)	1.2 ± 0.6	1.1 ± 0.1	NS
Triglycerids (mmol/L)	2.1 ± 1.7	2.0 ± 1.2	NS

Abbrevation: LDL-low density lipids; HDL-high density lipids; CRP-C reactive protein

Table 3.*Values of anthropometric data of the study population*

Variables	GFR < 60 mL/min (n = 51)	GFR > 60 mL/min (n = 29)	p
Body weight (kg)	73.52 (45 - 115)	72.3 (43 - 92)	NS
BMI (kg/m^2)	28.83 (17.22-39.79)	25.62 (16.14 – 34.22)	< 0.05
Waist circumference (cm)			
Women	80.52 ± 12.02	74.52 ± 10.76	< 0.05
Men	96.17 ± 18.23	88.24 ± 19.16	< 0.05
Waist to hip ratio (cm)	-	-	-
Women	0.92 ± 0.1	0.86 ± 0.14	< 0.05
Men	0.88 ± 0.12	0.90 ± 0.11	< 0.05
%BF (%)	-	-	-
Women	30.2 ± 5.8	27.41 ± 8.05	< 0.001
Men	26.2 ± 6.53	24.06 ± 6.47	< 0.05

Abbreviation: BMI-body mass index; %BF-body fat percentage

Table 4. *Obesity parameters according to gender*

Obesity parameters	Men (n = 47)	Women (n = 33)
BMI (kg/m^2)	28.2 ± 4.1	28.8 ± 4.4
BMI > 30 kg/m^2	16.28 %	10%
Waist circumference (cm)	88.8 ± 12.3	78.7 ± 13.0
Waist to hip ratio	0.91 ± 0.07	0.80 ± 0.07
%BF	25.5 ± 8.4	34.0 ± 7.8
%BF > 25%	44.68% (n = 21)	-
%BF > 35%	-	72.72% (n = 33)

Abbreviation: BMI-body mass index; %BF-body fat percentage

were significantly greater in the group with poorer graft function as compared to the normal GFR group (4.6 ± 2.12 vs. 2.4 ± 1.85, $p < 0.001$ for dialysis vintage and 62.54 ± 15.3 vs. 58.15 ± 9.6, $p < 0.05$ for donor age).

In contrast, there are no significant differences regarding time elapsed from transplantation, gender and recipient age. Most patients received a kidney from a living donor (70%).

CRP and LDL were higher in patients with GFR

< 60 mL/min (5.8 ± 0.7 and 3.1 ± 0.8, respectively) compared to those with GFR > 60 mL/min (3.9 ± 0.5 and 2.4 ± 1.1), p < 0.05 for all (Table 2). On the other hand, patients with lower GFR had lower albumin level (33.8 ± 5.1 vs 37.8 ± 5.5, p < 0.05).

Both women and men with GFR < 60 mL/min had higher BMI, waist-to-hip ratio, and %BF compared to those with normal function of the kidney after transplantation (Table 3).

Based on BMI values, 16.28% of men and 10% of women were obese in post-transplantation period in our study group. However, based on the %BF values, as many as 44.68% of men and 72.72% of women were considered obese (Table 4).

The correlations between GFR and different obesity parameters are shown in Table 5, and significant negative relationship was demonstrated between GFR and BMI, waist-to-hip ratio, and %BF (r = -0.390, -0.456 and -0.438, p < 0.001 for all) and a less significant between GFR and waist circumference (r = -0.219, p < 0.05).

Univariable analysis of data is shown in Table 6. BMI, waist circumference, waist-to-hip ratio and %BF were associated with reduced GFR, whereas gender, donor type and length of time on dialysis prior to KT had no effect on GFR.

Multivariable analysis has shown that higher values of waist-to-hip ratio and %BF in both men and women led to a significant decrease in GFR (p < 0.001 in both cases) (Table 7 and Table 8).

Table 5. *Correlation between GFR and obesity parameters*

Variables	Correlation coefficient (r)	p
Body weight	-0.154	0.068
BMI	-0.390	< 0.001
Waist circumference	-0.219	< 0.05
Waist to hip ratio	-0.456	< 0.001
%BF	-0.438	< 0.001

Abbreviation: BMI-body mass index; %BM-body fat percentage

Table 6. *Associations between anthropometric data and GFR in kidney transplant patients*

	Univariate analysis		
Variables	**OR**	**95% CI**	**p**
Gender	0.789	0.633 ± 2.44	0.46
Donor type (living donor or cadaver)	0.901	0.850 ± 1.08	0.07
Length of dialysis before Tx	0.755	0.691 ± 2.91	0.061
Body weight	1.390	0.864 ± 2.235	0.175
BMI	1.046	1.019 ± 1.074	0.031
Waist circumference	2.222	1.172 ± 4.212	0.014
Waist to hip ratio	1.109	1.038 ± 1.185	0.002
%BF	1.251	1.086 ± 1.441	0.002
Gender	0.789	0.633 ± 2.44	0.46

Abbreviation: Tx-transplantation; OR-odds ratio; 95% CI-confidence interval

Table 7. *Multivariate data analysis of different obesity indices associated with the risk of poor graft function in male patients*

Variables	p	OR	95% CI	
			lower	upper
Body weight	0.566	0.549	0.355	0.688
BMI	0.345	0.682	0.455	0.842
Waist circumference	< 0.05	0.549	1.036	1.201
Waist to hip ratio	< 0.001	1.115	1.082	1.233
%BF	< 0.001	1.344	1.148	1.533

Abbreviation: Tx-transplantation; OR-odds ratio; 95% CI-confidence interval

Table 8. *Multivariate data analysis on different obesity indices associated with the risk of poor graft function in female patients*

Variables	p	OR	95% CI	
			lower	upper
Body weight	0.603	0.706	0.645	0.861
BMI	0.642	0.562	0.489	0.756
Waist circumeference	0.08	0.864	0.703	0.963
Waist to hip ratio	< 0.001	1.204	1.141	1.483
%BF	< 0.001	1.302	1.269	1.655

Abbreviation: BMI-body mass index; %BF-body fat percentage; OR-odds ratio); 95% CI- confidence interval

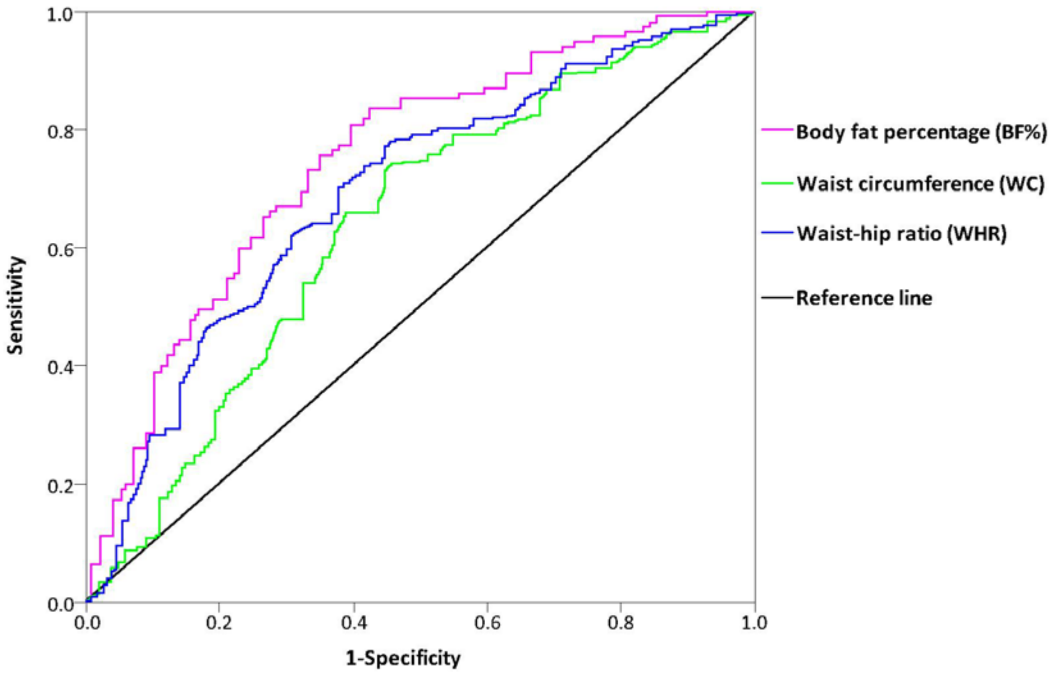

Figure 1. *ROC curve for predicting how different obesity indices influence kidney function after transplantation*

Table 9. *The areas under the ROC curve (AUC), sensitivity, and specificity by the optimized cut-off points for obesity indices in predicting poor graft function in kidney transplanted patients*

Variables	AUC (95% CI)	Sensitivity	Specificity	cut-off
BMI	0.688 (0.621 - 0.802)	0.69	0.7331	30.12
Waist circumference	0.702 (0.675 – 0.811)	0.736	0.793	85.6
Waist to hip ratio	0.750 (0.666 – 0.836)	0.754	0.781	1.02
%BF	0.789 (0.691 – 0.868)	0.793	0.791	32.05

Abbreviation: BMI-body mass index; %BF-body fat percentage; AUC (95% CI)-confidence interval

Finally, a ROC curve was created, and cut-off values of different obesity parameters were calculated to predict how they affect GFR in patients who underwent KT (Figure 1). Table 9 provided the cut-off, sensitivity, specificity, and AUC of anthropometric indices for a total sample of patients. As shown in Table 9, the AUCs of all anthropometric indices were greater than 0.5, implying that they were clinically significant predictors of poorer graft function. However, body fat percentage with the cut-off value of 32.05% had the highest sensitivity (0.793) and specificity (0.791) in the prediction of poor graft performance [AUC 0.789 (0.691 – 0.868)]

DISCUSSION

The current demand for kidney transplants exceeds the supply, leading to increased research on factors that could improve long-term graft outcomes and survival. This study was conducted to determine whether excess body fat can affect graft function.

A well-known consequence of kidney transplantation is weight gain. It typically occurs in the first few months following transplantation and is mainly caused by increased fat mass. These changes are induced by kidney transplantation factors (corticosteroid therapy) and patient behavior (physical activity). Weight gain following KT increases the risk of both short- and long-term graft and patient survival (5, 8, 18) and the risk of hypertension, cardiovascular disease, diabetes, and dyslipidemia development (22, 23).

WHO defines obesity as BMI ≥ 30 kg/m^2 and/or an excess of adiposity: when body fat exceeds 35% in males and 25% in females (24). Despite BMI being the most utilized anthropometric measure of obesity it has some limitations, including the inability to differentiate sarcopenia from adiposity and visceral fat accumulation since it does not provide information on muscle mass or fluid status.

Our study demonstrated that the whole-body composition is significantly modified by kidney transplantation and that patients with graft dysfunction had higher body weight, BMI, and %BF levels than patients with normal graft function. The findings of this study are consistent with the results of Lafranca et al. who performed a meta-analysis on graft survival at three different time points after kidney transplantation and found that lower BMI groups consistently had better outcomes (25).

Nevertheless, it was shown that BMI and %BF do not accurately predict obesity in transplant recipients, with %BF defining more recipients as obese than BMI (26). The results of our study also showed that, although having normal BMIs, the patients were considered obese due to their high body fat percentage and low muscle mass. We found that more than 50% of patients were obese when categorized by %BF, which was substantially higher than those categorized as obese utilizing BMI. This pattern was observed independently of gender. Surprisingly, this discordance was particularly prominent in our female patients. BMI may have low sensitivity and/or specificity for specific groups of patients because it fails to differentiate body mass components and to assess regional fat distributions.

Recently, waist circumference and waist-to-hip ratio have been used to predict obesity-related health risks, as they are more strongly correlated with abdominal fat than BMI (27). Waist to hip ratio enables individuals to determine their risk for specific health-related conditions such as diabetes, heart disease and other chronic diseases. Individuals with a larger mid-section than hips are at greater risk for these conditions because of the fat accumulation in the mid-section. We demonstrated that patients with poorer graft function had a greater waist-to-hip ratio compared to patients with normal graft function. Our study is the first to link graft function to WHR; however, the study of Kovesdy et al. examined the relationship of WHR to mortality in kidney transplant patients. They concluded that patients with increased visceral adiposity as measured by waist circumference, were at a higher risk (28).

A number of factors contribute to the higher risk of graft dysfunction in obese KT recipients. Obesity can have an impact on kidney hemodynamics, resulting in increased renal plasma flow, glomerular filtration rate, and filtration fraction (29). Obesity is also linked to the development of hyperfiltration and proteinuria, which leads to glomerulosclerosis and a decrease in the glomerular filtration rate. Obese patients produce higher levels of proinflammatory cytokines in adipose tissue, which can contribute to renal deterioration through glomerular injury. Another possibility is that obesity-related pharmacokinetic abnormalities predispose to immunologically mediated graft damage due to insufficient immunosuppression (30).

The study found a correlation between poor graft outcome and BMI, body fat percentage, waist circumference, and waist-to-hip ratio in both univariate and multivariate analyses. Additionally, in the multivariate analysis with continuous BF% and WHR values, it was found that both of them were significantly associated with poor graft function, independently of the co-variables. Finally, we analyzed the ROC curve and evaluated sensitivity and specificity for our patients. It was shown that BF% > 32.05 and waist-to-hip ratio > 1.02 best characterize individuals' risk of poor graft function.

Apart from body composition, our study demonstrated that patients with longer dialysis time had worse graft function outcomes than patients with shorter dialysis time, which is in accordance with the study of Aufhauser et al. (31). Additionally, donor age was also a contributing factor for poorer graft function. Most authors report poorer long-term kidney survival outcomes from older donors, although the issue remains controversial (32).

CONCLUSION

The findings of this study emphasize that an increased % BF, especially visceral adipose tissue, has a negative impact on graft function. Increased values of all measured anthropometric parameters related to obesity directly correlated with reduced glomerular filtration rate, consequently increasing risks of developing cardiovascular diseases and graft failure. After kidney transplantation, all patients are advised to be on a balanced diet, to exercise regularly, to have their lipid panel monitored, and take lipid-lowering drugs, if necessary.

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Uticaj telesnog sastava na funkciju grafta kod bolesnika sa transplantiranim bubregom

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SAŽETAK

Uvod/Cilj. Transplantacija bubrega često dovodi do promene telesnog sastava bolesnika, prvenstveno do porasta telesne težine, porasta masne mase tela i gubitka mišićne mase, što može negativno uticati na funkciju grafta. Cilj rada bio je da se ispita uticaj koji različiti parametri gojaznosti imaju na bubrežnu funkciju kod bolesnika sa transplantiranim bubregom.
Metode. Sprovedena studija preseka obuhvatila je 80 bolesnika, starih od 25 do 75 godina (od toga, 40% njih činile su žene), sa transplantiranim bubregom i na trojnoj imunosupresivnoj terapiji. Određivane su sledeće antropometrijske mere: telesna masa, visina, obim struka i kuk. Takođe, izračunati su indeks telesne mase (ITM) i odnos struk–kuk. Procenat telesnih masti (PTM) određen je metodom merenja četiri kožna nabora pomoću Cescorfovog kalipera, uz korišćenje Jackson–Pollockove jednačine. Žene čiji je PTM bio viši od 35% i muškarci sa PTM-om višim od 25% smatrani su gojaznim. Bolesnici su podeljeni u dve grupe na osnovu jačine glomerulske filtracije (JGF).
Rezultati. ITM je pokazao da je 16,28% muškaraca i 10% žena sa transplantiranim bubregom bilo gojazno. Istovremeno, prema vrednosti PTM-a, čak 44,68% muškaraca i 72,72% žena bilo je gojazno. Nađene su statistički značajne razlike u ITM-u, odnosu struk–kuk i PTM-u kod bolesnika sa normalnim i smanjenim JGF-om. Uzimajući u obzir brojne kovarijable, multivarijantna analiza je pokazala da je smanjen JGF direktno povezan sa povećanim vrednostima svih parametara gojaznosti. Bolesnici sa centralnim tipom gojaznosti (odnos struk–kuk > 0,85 za žene i > 0,9 za muškarce) i povećanim PTM-om imali su značajno niži JGF u poređenju sa funkcijom grafta kod normalno uhranjenih bolesnika (p < 0,001 za obe grupe).
Zaključak. Visok PTM i visoke vrednosti odnosa struk–kuk predstavljaju važne faktore rizika za smanjenje funkcije transplantiranog bubrega.

Ključne reči: transplantacija bubrega, gojaznost, procenat telesnih masti, indeks telesne mase