ORIGINAL ARTICLE

Single-centre experience with the treatment of high-prevalence metabolic syndrome in kidney transplant patients in Bosnia and Herzegovina

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ABSTRACT

Aim To analyse prevalence of metabolic syndrome (MS) in kidney transplant recipients at the University Clinical Centre Tuzla in Bosnia and Herzegovina (B&H), and determine effects of a modern drug therapy in achieving target metabolic control in kidney transplant patients.

Methods A single-centre prospective study that included 142 kidney transplant patients over one year follow-up period was conducted. Patient data were collected during post-transplant periodical controls every 3 months including data from medical records, clinical examinations and laboratory analyses.

Results Out of 142 kidney transplant patients, MS was verified in 85 (59.86%); after a pharmacologic treatment MS frequency was decreased to 75 (52.81%). After a one-year period during which patients were receiving therapy for MS, a decrease in the number of patients with hyperlipoproteinemia, decrease in average body mass index (BMI), glycemia and haemoglobin A1C (HbA1C) were observed. Hypertension did not improve during this period, which can be explained by transplant risk factors in the form of immunosuppressive drugs and chronic graft dysfunction.

Conclusion A significant reduction in components of the metabolic syndrome after only one year of treatment was recorded, which should be the standard care of kidney transplant patients.

Key words: abdominal obesity, diabetes mellitus, dyslipidaemia, immunosuppressive drugs, renal graft

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INTRODUCTION

Metabolic disorders are highly prevalent in kidney transplant candidates and recipients and can adversely affect post-transplant graft outcomes (1). Metabolic syndrome (MS) is characterized by a combination of cardiovascular risk factors (hypertension, dyslipidaemia, obesity, and alterations in glucose homeostasis), and insulin resistance is suggested to be the common pathogenic background (2). The appearance of MS among renal recipients is one of the greatest post-transplant complications and it is associated with an increased risk of graft failure and high rates of obesity and new onset diabetes (3MS developed after kidney transplantation is a result of several factors which are identical with risk factors in normal population, however, also some factors typical for the transplanted patients, especially the effects of immunosuppressive therapy (4).

Metabolic syndrome is an increasing public health concern globally (5). In Europe, the prevalence of metabolic complications in the transplant population is high and ranges from 44% to 58% (2,6). Metabolic syndrome is defined as clustering of metabolic abnormalities that include central obesity, insulin resistance, hypertriglyceridemia, hypercholesterolemia, hypertension, and reduced high-density lipoprotein (HDL)-cholesterol concentration (7).

Hypertension is one of the clusters of metabolic disorders in MS and one of the most common but modifiable cardiovascular risk factors (8). Hypertension is a more prevalent risk factor for cardiovascular morbidity and mortality among renal transplant recipients and almost 80% of patients had posttransplant hypertension (9). Pathogenesis of post-transplant hypertension is primarily related to immunosuppression (10).

Prevalence of hyperlipidaemia was estimated at 80% in kidney transplant recipients (11). The physiopathology of posttransplant dyslipidaemia is multifactorial, but the main role is played by some immunosuppressive drugs, such as calcineurin inhibitor (CNI), particularly cyclosporine, mTOR inhibitors, and glucocorticoids. (12). According to the 2019 ESC and EAS guidelines for the treatment of dyslipidaemia, statins remain the gold standard for the treatment, even in these patients (13).

Post-transplant diabetes mellitus (PTDM) or new-onset diabetes after-transplantation (NODAT) occurs in 10–30% of kidney transplant recipients (14). The PTDM shows a relationship with risk factors including obesity and tacrolimus-based immunosuppression, which decreases pancreatic insulin secretion (15). The management of diabetes mellitus in transplant patients is more challenging than the general population because of a greater risk of fluctuating kidney function (16).

Obesity is increasingly prevalent in the kidney transplant populations with an increased risk of delayed graft function in obese recipients (17). Kidney transplantation significantly alters the metabolic status (18). In kidney transplant patients, a complex interaction between metabolic syndrome and kidney function has been observed in transplant factors, as metabolic syndrome can worsen kidney function and increase the rejection rate (19,20). Medications used after transplantation could further exacerbate components of the metabolic syndrome (12,19).

The aim of our study was to analyse the prevalence of metabolic syndrome and its components in kidney transplant recipients at the University Clinical Centre Tuzla and investigate the effectiveness of the metabolic syndrome therapy after kidney transplantation in achieving target metabolic control. This is the first study related to metabolic syndrome in kidney transplant recipients in Bosnia and Herzegovina.

PATIENTS AND METHODS

Patients and study design

A single-centre prospective study was conducted among 160 patients after kidney transplantation followed in the Clinic for Internal Diseases of the University Medical Centre Tuzla, Department of Nephrology, Dialysis and Transplantation, who received a kidney transplant by January 2021. The patients were divided into two groups according to the presence or absence of metabolic syndrome. The patients underwent a follow-up for one year after the use of the metabolic syndrome therapy according to the latest guidelines for the treatment of metabolic syndrome in transplant patients (antihypertensives, oral antidiabetics and/or insulin therapy, statins and lifestyle

changes - dietary recommendations and physical activity) (12,16.21,22). Inclusion criteria for the enrolment of the patients in the study were: age ≥18 and stable graft function 3 months after transplantation. Exclusion criteria were: patients with known diabetes before transplantation, patients in the terminal phase of graft function, patients with malignant disease and acute inflammatory disease, and patients who do not cooperate and do not follow the study protocol. After the exclusion of 18 patients, 142 patients were analysed. Patient data were collected during post-transplant periodical controls every 3 months and they included data from medical records, clinical examination and laboratory analyses.

The study was approved by the Ethics Committee of the University Clinical Centre of Tuzla.

Methods

Data collected from medical records included: sex, age, family history, primary disease leading to end-stage renal failure, number of months after transplantation, type of transplantation (living relative, living unrelated and from a deceased donor), presence of metabolic disorders at the start of the study, and 1 year after the application of the metabolic syndrome therapy, type of immunosuppressive and type of antihypertensive, diabetic and hypolipemic therapy. Anthropometric and clinical parameters included: body weight (kg), body height (cm), body mass index (BMI kg/m2), waist circumference (cm), blood pressure (mmHg). Hypertension was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg in 3 repeated measurements, or information on previously diagnosed hypertension and the use of antihypertensive drugs.

The definition of obesity is (22) BMI > 30 kg/m², and overweight with 25<BMI<30 kg/m². Abdominal obesity was defined as waist circumference >102 cm in males, >88 cm in females. Post-transplant metabolic syndrome (PTMS) was defined according to the National Cholesterol Education Program-Adult Treatment Panel III (NCEP ATP III) (23) criteria with a minimum of 3 of any 5 criteria: abdominal obesity, high blood pressure, impaired fasting glucose, high triglyceride levels, and low HDL cholesterol levels. Glomerular filtration of the transplanted kidney was determined by the MDRD formula (The Modification of Diet in Renal Disease), and the value of eGFR (Estimated Glomerular Filtration Rate) was calculated with a calculator, according to the MDRD formula (24). Biochemical variables include glycaemic control parameters (fasting plasma glucose, 2-hours-postprandial plasma glucose, HbA1c), urea, creatinine, complete lipid status, uric acid, proteinuria, microalbumin in urine. A number of patients with the new onset diabetes after transplantation (NODAT) was recorded. Diabetes mellitus is defined as a fasting blood glucose level ≥7 mmol/L and postprandial blood glucose ≥11.1 mmol. All patients received a standard immunosuppressive protocol including a calcineurin inhibitor (CNI) cyclosporine or tacrolimus, mycophenolic acid and steroids (pronisone).

Statistical analysis

From descriptive statistical parameters, absolute and percentage frequencies, and arithmetic means with corresponding standard deviations were calculated. From non-parametric statistical methods, McNemar's test was applied, while from parametric statistical methods Student's t-test of independent samples was applied.

RESULTS

The study included 142 kidney transplant patients over one year follow-up period at the University Clinical Centre Tuzla (Table 1). The mean age of kidney transplant recipients was 49.2 years; 77 (54%) were males and 65 (46%) females. Most of our study population was on tacrolimus-based immunosuppression, 128 (90.14%), and had received kidney graft from living related donors, 98 (69%) (Table 1).

Table 1. Kidney transplant recipients' characteristics

Variable	Value
Mean age (years)	49.2
	No (%) of patients
Gender (years)	
Male	77 (54.00)
Female	65 (46.00)
Tacrolimus based immunosuppression	128 (90.14)
Cyclosporine based immunosuppression	14 (9.86)
Living related donor kidney Tx	98 (69.00)
Living unrelated donor kidney Tx	27 (19.00)
Deceased donor kidney Tx	17 (12.00)

Tx, transplantation;

Glomerulonephritis being the most prevalent cause of primary kidney disease, 48 (34%); unknown kidney disease, 38 (26%) (Table 2).

Table 2. Causes of primary kidney disease in kidney transplant recipients

Variable	No (%) of patients
Glomerulonephritis	48 (34)
Polycystic kidney disease	20 (14)
Nephroangiosclerosis	12 (9)
Interstitial nephritis	11 (8)
Reflux nephropathy	7 (5)
Systemic connective tissue disease	6(4)
Unknown	38 (26)

More than half of the study population, 85 (59.86%), had the diagnosis of MS at the beginning of the study; after one year of therapy a significant decrease was found, 75 (52.81%) (p=0.02). There was no significant difference in the prevalence of arterial hypertension at the beginning of the study and after one year of therapy, 84 (59%) and 85 (60%), respectively (p=1.00). Also, there was no significant difference in the number of patients with hyperlipoproteinemia, 63 (44%), and after one-year treatment 60 (42%) (p=0.453) (Table 3).

Table 3. Prevalence of arterial hypertension (HTA), hyperlipoproteinemia (HLP) and metabolic syndrome (MS) before and after the therapy of MS

Variable	No (%) of patients		p
	At the baseline	After treatment	
HTA	84 (59)	85 (60.00)	1.00
HLP	63 (44)	60 (42.00)	0.453
MS	85 (59.86)	75 (52.81)	0.02

Following one-year therapy of MS, a significant decrease in mean values comparing to the study beginning was found for BMI (26.34% and 26.04%, respectively**)** (p <0.05), waist circumference (96.9648 and 96.4648, respectively) (p<0.05), blood glucose (5.9943 and 5.7972, respectively) (p <0.05), triglycerides (1.9222 and 1.8519, respectively) (p<0.05) , cholesterol (5.3225 and 5.2304, respectively) (p<0.05) , LDL (3.1742 and 3.1176, respectively) (p <0.05) , and HbA1C (5.7289 and 5.6056, respectively) (p <0.05) (Table 4).

Table 4. Significant changes of clinical and biochemical parameters of kidney transplant recipients with metabolic syndrome (MS) before and after the therapy

Parameters	At the baseline	After treatment	p
Blood pressure (mm Hg)	155/95	140/85	0.000
Waist circumference (cm)	96.9648	96.4648	0.032
BMI (kg/m^2)	26.3415	26.0401	0.000
Blood glucose (mmol/L)	5.9943	5.7972	0.000
Triglycerides (mmol/L)	1.9222	1.8519	0.000
Cholesterol (mmol/L)	5.3225	5.2304	0.005
LDL (mmol/L)	3.1742	3.1176	0.000
HbA1C (%)	5.7289	5.6056	0.000

BMI, body mass index; LDL, low density lipoprotein; HbA1C, haemoglobin A1C

DISCUSSION

The results showed a higher prevalence of PTMS according to the original NCEP-ATP III criteria in kidney transplant recipients (25). Many studies have shown that patients after the kidney transplantation have metabolic syndrome more often (2,6, 26-29,). This increase in PTMS is associated with drug-induced effects on components of the metabolic syndrome, particularly dyslipidaemia, glucose intolerance, and hypertension (19). In our research, metabolic syndrome was verified in 59.86% of patients, and after the treatment in 52.81%, which represents a decrease of 11.76%. MS was more common in male patients (56%) than in female patients (44%). Patients with MS have the highest percentage of relatives transplants, which can be explained by the fact that this type of transplant is the most common at our Centre. Results of other studies related to the high prevalence of MS after kidney transplantation are similar, 61.3% (three years after kidney transplantation) (26), 63% (29), 44% (4).

Hypertension is one of the most common cardiovascular comorbidities after kidney transplantation. It occurs often in patients with other metabolic disorders such as diabetes, hyperlipidaemia, and obesity (8). The pathogenesis of post-transplantation hypertension is complex, and is a result of the interaction between immunological and non-immunological factors (10). Recommended target blood pressure is <130/80 mmHg (30). In our study, 59% patients had hypertension, and 60% a year after the treatment for MS. The reason for the increase were probably transplant risk factors in the form of immunosuppressive drugs and chronic graft dysfunction (14,19,20). Higher frequency of arterial hypertension was recorded in our patients who received cyclosporine as a part of triple immunosuppressive therapy. Other studies showed a high prevalence of hypertension, 62.2% (31), 92.5% (all patients were diagnosed in the first year after transplantation and only 17% of patients had target arterial pressure values) (32), 95.3% (33), 82.67% (9). Mono- or dual-drug therapy was received by 38.6% of patients, while 38 % received three to four drugs (33). The results of our research are similar, 58% of patients needed combined antihypertensive therapy (calcium channel blockers, ACE inhibitors, beta blockers) to achieve the target arterial pressure.

Reportedly, the NODAT prevalence is high, 33.89% (34), 10–30% (14). In a study by Choudhury et al., (35) prevalence of NODAT is 17.2%, probably because almost all kidney transplant recipients received steroids and tacrolimus as a part of the immunosuppressive regimen. There are similar results in our research: NODAT was present in 17% of patients; after the implementation of therapy for NODAT (oral antidiabetic drugs or insulin), a decrease in the average values of glycemia and HbA1C was observed. Kidney transplant patients developing NODAT have a 67% increased risk of all-cause mortality and a 35% increased risk of graft failure (14). Overweight and obesity were found in 42.1% and 10.5% of patients (36). There was a decrease in the average BMI by 1.14% in our research after the MS therapy; the prevalence reduction in BMI was slightly higher in females compared to males. A significant reduction in waist circumference was also recorded after the therapy in our study. Transplant patients had a high prevalence of increased waist circumference (26).

Obesity did not have an impact on patient's survival, but it affected graft function and graft loss (37).

In the population of transplant patients, dyslipidaemia occurs in 27-71% of recipients (11).

After transplantation, in addition to elevated triglycerides and lowered HDL cholesterol, LDL cholesterol and total cholesterol are often elevated. In the study AlShelleh et al. (38), 36.2% of transplant patients had low HDL values. In our study, 44% of patients had hyperlipoproteinemia, and after statin therapy it slightly decreased to 42%; a significant decrease in the average values of cholesterol, triglycerides and LDL was also observed, while the increase in HDL was insignificant. A recent meta-analysis by Huang (39) reported similar results. There are no strict guidelines for the management of dyslipidaemia in patients after kidney transplantation, but those that suggest an individualized approach regarding the risk of CVB seem most appropriate (40).

In conclusion, this is the first study of metabolic syndrome after kidney transplantation in Bosnia and Herzegovina. Metabolic disorders are highly prevalent in kidney transplant recipients, which is confirmed by our study and may adversely affect the outcome of the graft after transplantation. A significant reduction in components of metabolic syndrome after only one year of treatment was recorded, which should be the standard care of kidney transplant patients. Early recognition, timely diagnosis and effective treatment of PTMS contribute to the improvement of graft function and quality of life after transplantation.

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TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

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