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# Comprehensive lifestyle modification as complementary therapy to prevent and manage post-transplant diabetes mellitus*

## Kompleksowa modyfikacja stylu życia jako terapia uzupełniająca w zapobieganiu i leczeniu cukrzycy po przeszczepie

**Authors' Contribution:**
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
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**Summary:**

Post-transplant diabetes mellitus (PTDM) is one from the most common metabolic complications after kidney transplantation. PTDM develops in the early period after transplantation. The risk factors of PTDM are carbohydrate imbalances occurring in the patient prior to transplantation, surgery and the inclusion of immunosuppressive treatment. Kidney transplant patients tend to gain weight, which is associated with an increased risk of post-transplant diabetes, cardiovascular diseases and abnormal transplanted kidney function.

Patients after kidney transplantation should be advised to adopt a lifestyle based on a proper diet, exercise, weight control and smoking cessation. The strategy to reduce the risk factors for PTDM development should start before transplantation and continue after kidney transplantation. A targeted, non-pharmacological approach to patients already during the dialysis period may have a significant impact on reducing post-transplantation diabetes.

Lifestyle interventions can effectively reduce the risk of development and inhibit the progression of post-transplantation diabetes. The article describes elements of comprehensive non-pharmacological management based on available knowledge of rehabilitation, dietetics and psychology.

**Keywords:** **post-transplant diabetes mellitus, lifestyle modification, kidney transplant recipients, rehabilitation, utrition intervention, smoking cessation**

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**Abbreviations:** **BMI** – body mass index, **CKD** – chronic kidney disease, **HbA1c** – glycated hemoglobin, **IFG** – impaired fasting glucose, **IGT** – impaired glucose tolerance, **KDIGO** – Kidney Disease: Improving Global Outcomes, **KTx** – kidney transplantation, **OGTT** – oral glucose tolerance test, **PNA** – protein of nitrogen appearance, **PTDM** – post-transplant diabetes mellitus, **SGA** – subjective global assessment, **WHO** – World Health Organization, **WHR** – waist/hip ratio.

## INTRODUCTION

Post-transplantation diabetes mellitus (PTDM), also called new-onset diabetes mellitus after transplantation (NODAT), is one of the most common metabolic complications after kidney transplantation (KTx). PTDM increases morbidity, mortality, and significantly reduces the quality of life of kidney transplant recipients [6, 23]. The incidence of PTDM in kidney transplant recipients ranges from 15% to 30% [8]. PTDM develops in the early post-transplant period, most often in the first year after the kidney transplantation and is related to the use of immunosuppressive treatment, including corticosteroids. The risk of PTDM is also increased by overweight and obesity. Kidney transplant recipients tend to gain weight, which further increases the risk of diabetes, cardiovascular disease and graft function [15, 26, 27].

Risk factors for the development of PTDM are divided into modifiable and non-modifiable (Table 1). The modifiable factors should be considered with regard to the period before and after transplantation [15, 26, 27]. All post-transplant patients, in particular those at high risk of developing PTDM, should be advised to change their lifestyle by increasing physical activity, consuming an appropriate diet, controlling their weight (maintaining weight gain), and quitting smoking [48, 49]. The activities aimed at mitigating the impact of modifiable risk factors for PTDM development should be taken before undergoing transplantation and continued during the post-transplantation period.

A targeted, non-pharmacological approach to patients with chronic kidney disease (CKD) during the dialysis period may have a significant impact on reducing PTDM. Promotion of a healthy lifestyle and education should be part of the essential elements comprising a comprehensive patient care process. Medical personnel should discuss with patients the consequences of inappropriate behavioral habits for their health.

Unfortunately, in practice, the aspects of non-pharmacological therapy are often overlooked or implemented in an inadequate manner. This is due, among other things, to the lack of adequate time that medical personnel could devote to patient education.

## OBJECTIVES

The aim of the review was to present risk factors for the development of post-transplantation diabetes mellitus with a description of methods of its prevention and support of PTDM treatment. The article reviews the collected scientific evidence on the influence of lifestyle-related factors (diet, physical activity, obesity, smoking habits) on the development of PTDM. Lifestyle interventions can effectively reduce the risk of development and inhibit the progression of post-transplantation diabetes. This article presents a summary of lifestyle interventions in pre- and post- transplant patient management.

## ASSESSMENT OF RISK FACTORS FOR DEVELOPMENT OF PTDM

The assessment of risk factors for the development of PTDM should include an analysis of traditional indicators such as age (over 40–45 years), hypertension, positive family history of diabetes, obesity, elevated body mass index (BMI), and racial or ethnic factors (black people, Hispanics) [34, 38]. In addition to the aforementioned, the use of immunosuppressive drugs such as corticosteroids, calcineurin inhibitors (tacrolimus, cyclosporine), mTOR pathway inhibitors (sirolimus, everolimus) should also be regarded as a risk factor. The evaluation of fasting blood glucose should be performed periodically in each patient before and after KTx. The oral glucose tolerance test (OGTT-75g) has the highest sensitivity for diagnosing PTDM [8, 18]. Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are strong predictors of PTDM [18, 44]. The highest prevalence of PTDM among patients without previous diabetes was described by Bergrem et al., who reported PTDM developed in as many as 70% of post-transplant recipients [7]. In our observation of 80 kidney transplant recipients, PTDM developed in 14% of respondents within a year after kidney transplantation (KTx). We noticed a significant frequency of glucose disorders status change after KTx [18].

Blood glucose tests should also be performed after transplantation, especially in the very first weeks after surgery. It is advisable to measure fasting blood glucose every time the patient visits the clinic, at least once a month [16, 39]. The determination of glycated hemoglobin HbA1c is not recommended for the diagnosis of PTDM in the first three months after transplantation. Then, it can be used in special cases for diagnostic purposes and, of course, to monitor the effectiveness of diabetes treatment [8, 23, 35].

Early detection and initiation of diabetes treatment has a positive effect on patient survival and transplantation [39, 44]. A number of authors suggest that lifestyle modification and adequate education of patients waiting for a transplant and kidney transplant recipients significantly reduce the risk of PTDM development [39, 44].


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**Table 1.** Risk factors for the development of post-transplant diabetes mellitus PTDM [15, 26, 27]

| Modifiable risk factors PTDM | Non-modifiable risk factors PTDM |
|---|---|
| Overweight (BMI > 25 kg/m$^2$) or Obesity (BMI > 30 kg/m$^2$) | Positive family history of type 2 diabetes |
| Hepatitis C (HCV) | Age at day of transplantation (> 40 years) |
| Cytomegalovirus infection (CMV) | Ethnic origin (African-Americans, Hispanics) |
| Hypertension | Polycyclic kidney disease – ADPKD |
| Immunosuppression | HLA A26 or B27 |
| Low physical activity | Male gender |
| Smoking | Peritoneal dialysis |
| Pre-diabetes conditions (impaired fasting glucose IFG and/or impaired) | |
| Hypertriglyceridemia | |

## OBESITY/OVERWEIGHT

The success of KTx may be cancelled out by the occurrence of metabolic disorders. Obesity in adults is defined as a medical condition in which BMI excesses 30 kg/m$^2$. Nevertheless, BMI does not determine the type of fat distribution in the body; therefore, a waist circumference measurement is proposed to estimate the amount of fat in the visceral region. Taking into consideration the above, it is recommended to include the waist circumference measurements in the definition of adult obesity. Values excessing 102 cm in men and 88 cm in women indicate visceral (abdominal) obesity [24]. Studies confirm that patients with large waist circumferences are at greater risk of cardiovascular disease, type 2 diabetes and hypertension [10, 24]. Studies to date have shown that obese patients waiting for the kidney transplant are at risk of delayed transplantation, require longer hospitalization, have a higher incidence of postoperative complications, reduced survival and PTDM development [2, 24]. Kidney transplant recipients are likely to put on weight in the first months after KTx [10, 48]. BMI increase during 12 months after transplantation ranges from 2.0–3.8 kg/m2 [2]. The following factors influence weight gain after KTx: easing up dietary restrictions, increased appetite, well-being associated with no uremic condition, use of corticosteroid and lack of physical activity [2]. It is also believed that the risk of putting on weight as a result of the kidney transplant is greater in women [2].

According to the observation of 62 kidney transplant recipients carried out for the purpose of this research, BMI increase was observed both in women and men. Nevertheless, taking into consideration the results of a two-year observation, women have shown a twofold increase in BMI compared to men (1.90 ±2.20 kg/m$^2$ versus 0.89±1.85 kg/m2, P<0.001) [17].

Introduction of therapeutic intervention based on physical exercise, diet modification and weight control are aimed at minimizing, inhibiting and preventing obesity among renal transplant recipients [38].

## PHYSICAL ACTIVITY

Often, patients who have CKD receive dialysis; kidney transplant recipients also often have reduced physical performance, cardiopulmonary and respiratory capacity, weakened muscle strength [9].

Physical activity, together with a proper diet, are regarded as the factors which have the strongest influence on maintaining proper body weight, improving glucose tolerance, as well as mitigating risk and severity of PTDM among kidney transplant recipients [49].

It should be emphasized that there are no detailed guidelines specifying comprehensive management, including kinesiotherapy, dedicated to nephrological patients. This may potentially result in not taking the required activities by both patients and medical personnel, which may increase the rate of transplant failures.

## PHYSICAL ACTIVITY DURING THE PRE-TRANSPLANTATION PERIOD

Physical activity gradually decreases in CKD. Symptoms resulting from the advancement of CKD (metabolic acidosis, malnutrition syndrome, infections, osteodystrophy, cachexia) further deteriorate the physical condition of the patient, leading to a decrease in strength, muscle mass and cardiopulmonary capacity, as well as skeletal system disorders. Ultimately, it leads to significant, progressive functional limitations, which additionally reduce the life quality of patients awaiting transplants [13, 41, 49].

The KDIGO guidelines (Kidney Disease: Improving Global Outcomes) for CKD patients recommend moderate intensity aerobic exercises five times a week, which involve large muscle groups-upper and lower limb muscles and the trunk. These include activities such as walking, cycling, swimming, during which there is no aerobic debt. Optimally, the training session should last thirty minutes [25]. Training should consist of three parts: warm-up, basic exercises and calm down.

Type and exercise intensity should be individually adjusted according to the patient's condition and preferences. The aerobic training should be also gradually extended to include strengthening exercises (with tensioning belts, balls, weights). Resistance training combined with aerobic exercises strengthen muscles, helps to build muscle mass, improve physical performance, coordination and mobility, as well as reduce the risk of osteoporosis to which patients are exposed by immunosuppressive and chronic insulin therapy (if applied). The rehabilitation program of patients receiving dialysis can be carried out during dialysis, between them, in the patient's home and in rehabilitation outpatient clinics [14].

Kinesiotherapy during hemodialysis should involve exercise engaging lower limbs and trunk muscles. Training should include alternating anti-thrombotic, respiratory and aerobic exercise interspersed with resistance exercises. In the main part of the training session, it is advisable to use bicycle cyclometers mounted at the patient's bedside. The optimum time for physical exercise is the beginning of hemodialysis. During the first hour of the procedure, most patients tolerate physical effort well. Physical and mental state becomes worse when ultrafiltration exceeds 2.5 l of fluid [14]. The main limitation of doing exercise during hemodialysis is a vascular fistula on the patient's forearm. Physical activity increases the risk of dislocation of the needle in the vascular anastomosis and interferes with hemodialysis by activating the artificial kidney alarm. Therefore, the upper limb with a vascular fistula should be engaged for exercise outside HD surgery [35]. In a meta-analysis conducted by Huang M. et al., twenty randomized case-control studies (677 participants) were analyzed to assess the effect of training on the physical performance of hemodialysis patients. Based on this analysis, the authors emphasized the positive impact of physical training (physical training lasting at least eight weeks, up to twelve months, conducted three times a week) on increasing physical performance and improving the quality of life of hemodialysis patients. At the same time, the authors reported the great need to develop detailed guidelines determining which of the exercises performed during dialysis therapy should dominate [19].

Training recommendations should accompany hemodialysis patients throughout their treatment. Assessment of their physical performance should be performed at six-month intervals, based on specific tests and questionnaires. The use of muscle strength and fitness assessment tests helps to plan, monitor and evaluate the course and effects of treatment [6, 33].

Among the most popular methods of assessing physical fitness and muscle strength of nephrological patients, the following procedures stand out [33]:

- Exercise tests with oxygen uptake measurement (gold standard): electrocardiographic treadmill/cycloergometer exercise test, ergospirometric exercise test;
- Physical performance tests: 6-minute walk test, The Fullerton Functional Test;
- Muscle strength tests: the Lovett test, manual measurement of muscle strength using a dynamometry.

Additionally, popular methods for subjective evaluation of the functional state of the body are mentioned below:

Katz scale, Lawton scale and quality of life assessment of patients using SF-36 Physical Function Scale [33].

## PHYSICAL ACTIVITY AFTER KIDNEY TRANSPLANTATION

According to current World Health Organization (WHO) recommendations on physical activity for the general population, moderate intensity aerobic exercises should last at least 150 minutes per week, or 75 minutes per week if performed intensively [46]. Unfortunately, there are still no specific guidelines on physical activity in kidney transplant patients. It is important to note that physical activity in kidney transplant recipients increases after transplantation, compared to dialysis patients, but is still lower in relation to the general population [48]. Tzetzanov et al. conducted an interesting study among obese kidney transplant recipients. Patients with BMI exceeding 30 kg/m$^2$ participated in a twelve-month, comprehensive rehabilitation programme that included physical exercises, behavioral interventions, and nutritional education. It was shown that such a regeneration plan, conducted in the group of obese patients after KTx, can significantly improve kidney function and quality of life, as well as producing a positive effect on the recipients' workload [43].

Organizations that popularize sports and physical activity of people after transplantation should be mentioned. Since 2005, the Polish Transplantation Sports Association has been operating on behalf of the European Transplant and Dialysis Sport Federation.

## DIET

The state of nutrition before transplantation affects the results of treatment after the procedure. A targeted dietary approach in the management of a patient waiting for the kidney transplant can maintain good nutritional status, improve kidney function and survival, weaken the development of carbohydrate metabolism disorders, as well as reduce cardiovascular mortality [3, 12, 28]. Unfortunately, no specific guidelines have been developed to provide strict dietary recommendations for patients after KTx.

Kidney transplant recipients with BMI lower than 18 kg/m$^2$ (caloric/protein malnutrition) and BMI exceeding 30 kg/m$^2$ (obesity) are more exposed to mortality risk factors compared to people who fall within the optimal BMI range. Obesity at the time of transplantation is associated with a higher risk of delayed transplant activity and complications associated with the treatment of a postoperative wound. On the other hand, undernourishment during

**Table 2.** Nutritional recommendations for patients with Chronic Kidney Disease (CKD) [30, 31]

| | CHRONIC KIDNEY DISEASE | |
|---|---|---|
| | Hemodialysis [HD] | Peritoneal dialysis [PD] |
| Protein | 1.2 g/kg<br>[stage 5 CKD] | 1.2–1.3 g/kg<br>[stage 5 CKD] |
| Energy | 30–35 kcal/kg/day | 30–35 kcal/kg/day |
| Fat | 30% kcal | 30% kcal |
| Fluids | Loss with urine<br>+ 500–1000 ml | Loss with urine<br>+ 1000 ml |
| Electrolytes and minerals | < 2.4 g sodium/day<br>< 2.4 g potassium/day<br>800–1000 mg phosphorus/day<br>< 2000 mg calcium/day | 2 g sodium/day<br>3–4 g potassium/day<br>800–1000 mg phosphorus/day<br>< 2000 mg calcium/day |
| Vitamins | | 3 µg vitamin B12<br>1–5 mg/day folic acid<br>1.5–2mg/day vitamin B1 |

transplantation is associated with the risk of rejecting the transplant and poorer patient survival [3, 28]. The nutritional recommendations for nephrological patients vary before and after renal transplantation.

Establishing specific dietary recommendations to prevent, inhibit, and control the development of malnutrition prior to transplantation or obesity after renal transplantation is critical with regard to the treatment of nephrological patients.

## DIET IN CHRONIC KIDNEY DISEASE

Dietary recommendations for patients with CKD are dependent on the stage of disease [3, 31]. With the progression of CKD, increased metabolic changes occur, resulting in increased catabolic processes. Dialysis further exacerbates catabolism due to raised protein loss; albumin losses during hemodialysis may range from 9–13 g aminoacids/HD. In patients on peritoneal dialysis, the protein loss is 5–15 g protein/day [12, 29, 31]. Dialysis may exacerbate fluid and electrolyte disturbances and increase patients' need for calories and protein. In Rocco et al.'s study, the nutritional status of 1,000 chronically hemodialyzed patients was evaluated. It showed that as many as 29% of dialyzed patients had albumin concentration below 3.5 g/dl, 76% of them had meals below 28 kcal/kg/day, and 61% of patients consumed less than 1 g/kg/day of protein [36]. The results of the study confirm a high risk of malnutrition development in dialyzed patients.

According to the Clinical Practice Guidelines for Nutrition in CKD provided by National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI), the nutritional status should be assessed based on the following parameters: subjective global assessment (SGA), nutritional history, anthropometric studies (BMI, waist/hip ratio - WHR) and biochemical studies (visceral protein concentrations, total cholesterol, protein catabolism factor, C-reactive protein, total lymphocyte count, myoglobin, phosphocreatine kinase, fibronectin, retinol binding protein and nPNA coefficient).

Nutrition assessment should be performed by everyone: every three months in patients with CKD stages 2 through 5 (BMI and PNA price), every month in hemodialysis patients, and every three to four months in peritoneal dialysis patients. Subjective evaluation of nutritional status, SGA with other anthropometric measurements, should be performed at an interval of six months, or more often [30].

Early evaluation of the nutritional status of recipients and active measures to correct malnutrition (electrolyte and micronutrient deficiencies) maintain adequate muscle mass and caloricity, promote weight normalization in at least overweight patients, based on BMI, as well as are integral to nutritional therapy [21, 28, 29].

Dialysis patients are advised to reduce their intake of foods and fluids rich in phosphorus potassium and sodium [3] (Table 2).

Dialysis combined with dietary restrictions causes significant shortages in nephrological patients, which requires supplementation. The most common deficiencies include a lack of vitamins: B6, C, D and folic acid [28, 30].

The diet recommended for patients with end-stage renal failure should inhibit excessive urea production, hypertension, hyperphosphatemia, and hyperkalemia. A controlled diet helps to maintain a healthy dietetic habit in patients waiting for the kidney transplant [30, 42].

## DIET AFTER KIDNEY TRANSPLANTATION

PTDM usually develops within six–twelve months after the kidney transplant. The occurrence of metabolic

**Table 3.** Nutritional recommendations for kidney transplantation patients [30, 31]

| | POST-KIDNEY TRANSPLANTATION | |
|---|---|---|
| | ACUTE PHASE | CHRONIC PHASE |
| Protein | 1.2–2.0 g/kg | 0.6–0.8 g/kg |
| Energy | 30–35 kcal/kg | 25–30 kcal/kg |
| Fat | 30–50% low-fat products | < 30% kcal<br>< 300 mg cholesterol<br>7–10% kcal from saturated fat |
| Carbohydrates | 50–70% kcal | 45–50% kcal |
| Electrolytes and minerals | without salt<br>monitor: potassium, phosphorus, magnesium<br>1000–1500 mg calcium/day | |
| | vitamin D supplementation | |

disorders in the early post-transplantation period highlights the importance of early monitoring and dietary guidelines for renal transplant recipients. Dietary recommendations are dependent on many factors: post-transplantation time, renal function of the transplanted kidney, pattern of immunosuppressive therapy used, as well as postoperative course of treatment (e.g. poor wound healing, recurrent infections) [21]. In addition to the main diabetic effect of immunosuppressive therapy, an increase in lean body mass after transplantation (a particular role of visceral obesity) also constitutes an important risk factor for PTDM development [21, 45].

The dietary recommendations for kidney transplant recipients are divided into two periods [31]:

- early phase after transplantation (acute phase, lasting four–six weeks after kidney transplantation)
- late phase after transplantation (chronic phase, after the first six weeks after kidney transplantation) [31].

There are currently no guidelines on how often the nutritional status of patients after kidney transplantation should be assessed.

The objective of early nutritional intervention is regeneration, which includes the provision of appropriate nutrients to mitigate postoperative catabolism (Table 3). The recommended nutrient requirements are the following: for energy: 30–35 kcal/kg/day and for protein: 1.2–2.0 g protein/kg/day [12, 21, 28, 31].

The aim of the late phase after KTx is to prevent the development of obesity, diabetes mellitus, hypertension, osteoporosis and dyslipidemia. There are no specific dietary restrictions during the late phase, except for the ban on grapefruit and pomelo fruit (irrespective of the form of serving) due to the fact they interact with calcineurin inhibitors. Immunosuppressive drugs reduce the absorption of calcium, magnesium, and vitamin D [30]. Kidney transplant recipients should follow general rules of hygiene and food safety, due to the threat of food-borne infections [12]. Patients should eat healthy, lightly digestible, low-fat foods, avoid salt, and try to reduce the intake of simple sugars. The recommended daily calorie intake is 25–35 kcal/kg/day and 0.6–0.8 g protein/kg/day [31] (Table 3). The study by Sharif et al. evaluated the benefits of education on intensive, active lifestyle modification among 115 kidney transplant recipients. The group of renal transplant recipients was divided into two groups as follows: the first group consisted of patients with insulin resistance or diagnosed PTDM (n = 36) who received intensive, active lifestyle modification advice, and the second group was comprised of patients with normal glucose tolerance after kidney transplantation (n = 79) who were provided only with lifestyle modification information leaflets. After six months, the glycemic condition was assessed in both groups. In the first group, the number of patients with PTDM decreased (n = 7 vs n = 3), while in the second group, glucose metabolism disorders were observed in a greater number of patients (n = 12). Researchers have proven that active counselling on lifestyle changes is beneficial for kidney transplant recipients when compared to "passive" advisory, and therefore it should be actively promoted among medical personnel [40].

The dietary recommendations should be individualized, depending on post-transplant period and the nutritional status of the patient. Monitoring risk factors for development of PTDM after a renal transplantation should be regarded as a clinical priority. Dietary caloric control in the early post-transplant period may help patients to maintain normal body weight.

## SMOKING

Smoking is a modifiable factor that significantly increases the risk of cardiovascular disease [5, 11]. Smokers receiving a kidney transplant are at a higher risk of arterial hypertension, PTDM, dyslipidemia, atherosclerosis (which also develops in renal arteries, leading to ischemic nephropathy), cancer and cardiovascular problems compared to non-smokers [5, 11]. It is stated that smoking

after a transplant significantly accelerates the loss of transplanted kidney function, compared to non-smokers [4, 47]. The prevalence of cigarettes in transplant recipients, both in European and American societies, ranges from 25% to 50% [1, 4, 20, 32]. Smoking is associated with an increased risk of death, so any attempt to encourage an addict to stop smoking is justified [1, 4, 22]. Anti-smoking education should be provided for patients with CKD already at the moment when he/she comes to the nephrology clinic. The therapy methods for the treatment of nicotinism include patient self-monitoring, pharmacotherapy, counselling, behavioral methods, group therapy and acupuncture [37]. The KDIGO guidelines for transplanted patients suggest that direct anti-smoking education is effective when it does not take longer than three minutes. Advice may include asking about smoking, giving brief, factual and clear recommendations, assessing the ability of a smoker to quit, as well as organizing/proposing help and support in the fight against smoking [15]. For prevention purposes, education should also be provided to families and patients who do not smoke, as they may be passive smokers at any time.

## CONCLUSIONS

There is a strong need to develop detailed guidelines for monitoring post-transplant patients in order to detect the risk factors for the development of PTDM, as that would provide opportunities for rapid intervention. Targeted preventive management can effectively reduce risk or inhibit the progression of PTDM. The development of guidelines for modifying the lifestyles of kidney transplant recipients based on comprehensive rehabilitation, dietetics and psychology can be of key importance for the decision-making process as regards the therapy and can serve to improve patient care in the field of transplantology.

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