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Rola otyłości w leczeniu przewlekłej choroby nerek metodą transplantacji nerki.

The role of obesity in treatment of chronic kidney disease with kidney transplantation.

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Spis treści

Spis skrótów

PChN, przewlekła choroba nerek;

ESKD, *end stage kidney disease*;

CKD, *chronic kidney disease*;

BMI, *body mass index*, indeks masy ciała;

OAGB, *one-anastomosis gastric bypass*, wyłączenie żołądkowo-jelitowe na pętli omega;

RYGB, *Roux-en-y gastric bypass*, wyłączenie żołądkowo-jelitowe na pętli Roux;

LSG, *laparoscopic sleeve gastrectomy*, resekcja mankietowa żołądka;

PRISMA, *Preferred Recording Items for Systematic Review and Meta-Analyses*;

DGF, *delayed graft function*, opóźniona funkcja graftu;

KT, *kidney transplantation*, przeszczepienie nerki;

KTR, *kidney transplant recipient*, biorca przeszczepu nerkowego;

CIT, *cold ischemia time*, czas zimnego niedokrwienia;

WIT, *warm ischemia time*, czas ciepłego niedokrwienia;

ARE, *acute rejection episode*, epizod ostrego odrzucania;

Słowa kluczowe

Otyłość, przewlekła choroba nerek, przeszczepienie nerki.

Streszczenie

Wstęp

Otyłość jest związana nie tylko z rozwojem przewlekłej choroby nerek (PChN), lecz ma także udowodniony wpływ na przyspieszenie jej postępu[1]. Wraz ze wzrostem częstości występowania otyłości i chorób współistniejących w populacji ogólnej, a także u pacjentów z PChN, otyłość może nie tylko wpływać na kwalifikację do przeszczepienia nerki, ale także na wczesne i odległe wyniki leczenia operacyjnego[2–4]. Właściwe leczenie otyłości u pacjentów z PChN jest istotne dla poprawy wyników jej leczenia metodą transplantacji nerki[5]. Niniejsza praca doktorska składa się z trzech publikacji analizujących wpływ otyłości na przebieg zabiegu przeszczepienia nerki oraz bezpieczeństwo i skuteczność operacyjnego leczenia otyłości u pacjentów z PChN. Chirurgia metaboliczna może odgrywać wiodącą rolę w leczeniu otyłości u pacjentów z PChN, przygotowaniu do przeszczepienia nerki i poprawie wyników leczenia.

Cel badań

Publikacja 1

Pierwszorzędowym celem badania była analiza parametrów śródoperacyjnych oraz krótko- i długoterminowego przebiegu pooperacyjnego w trzech kohortach biorców nerki od dawcy zmarłego stratyfikowanych według indeksu masy ciała (BMI). Dodatkowo wykonano analizę przeżywalności nerki i biorcy w zależności od BMI.

Publikacja 2

Celem badania była analiza przedoperacyjnej i pooperacyjnej utraty masy ciała u pacjentów z otyłością chorobliwą i PChN w porównaniu do pacjentów z otyłością chorobliwą bez PChN operowanych z powodu otyłości chorobliwej.

Publikacja 3

Celem przeglądu systematycznego była analiza aktualnych wytycznych praktyki klinicznej (CPG) dotyczących diagnostyki i leczenia otyłości u biorców nerek. Zidentyfikowano i przeanalizowano osiem aktualnych krajowych i międzynarodowych wytycznych dotyczących praktyki klinicznej z szczególnym uwzględnieniem roli diagnostyki i leczenia otyłości.

Materiał i metody

Publikacja 1

W badaniu przeprowadzono retrospektywną analizę prospektywnie tworzonej bazy danych 433 biorców nerki od dawców zmarłych w latach 2014-2017, leczonych w jednym ośrodku transplantacyjnym. Analizie poddano powiązanie BMI w momencie przeszczepienia nerki, z parametrami śródoperacyjnymi, zdarzeniami niepożądanymi we wczesnym okresie pooperacyjnym oraz całkowitą śmiertelnością i utratą przeszczepu w kohortach stratyfikowanych według BMI: prawidłowe BMI (18.5 – 24.9 kg/m^2), nadwaga (25-29.9 kg/m^2) i otyłość (≥30 kg/m^2).

Publikacja 2

W badaniu porównano utratę masy ciała pacjentów z PChN leczonych chirurgicznie z powodu otyłości chorobliwej w Centrum Doskonałości Chirurgii Bariatrycznej i Metabolicznej w latach 2015-2019 z pacjentami z bazy danych 1199 pacjentów z otyłością chorobliwą bez stwierdzonej PChN. Analizowano dane demograficzne, choroby współistniejące oraz BMI na początku okresu przygotowawczego, bezpośrednio przed zabiegiem oraz podczas rocznego okresu obserwacji.

Publikacja 3

Przegląd CPG opublikowanych do stycznia 2020 r, przeprowadzono zgodnie z wytycznymi *Preferred Recording Items for Systematic Review and Meta-Analyses* (PRISMA)[6]. Analizie poddano CPG dotyczące kwalifikacji do przeszczepienia nerki od dawcy zmarłego i zalecenia diagnostyki i leczenia otyłości chorobliwej w tej grupie chorych.

Wyniki

Publikacja 1

Otyłość była związana z dłuższym całkowitym czasem trwania zabiegu operacyjnego ($p=0.0025$) i dłuższym czasem ciepłego niedokrwienia ($p=0.0003$). U pacjentów z otyłością przebieg pooperacyjny był powikłany większą częstością opóźnionej funkcji graftu (DGF) ($p=0.0002$), większą częstością wczesnych reoperacji ($p=0.001$) i innych wczesnych powikłań chirurgicznych, takich jak: powikłania naczyniowe, występowanie limfocele i rozejście się rany pooperacyjnej. Nie stwierdzono różnic w analizowanych parametrach pomiędzy pacjentami z normalną masą ciała, a pacjentami z nadwagą. Funkcja nerki przeszczepionej w miesięcznej obserwacji ($p=0.0001$) i przeżycie narządu przeszczepionego w okresie obserwacji ($p=0.029$) były gorsze u pacjentów z otyłością. Nie stwierdzono różnic między pacjentami z prawidłową masą ciała, a pacjentami z nadwagą. Roczne, stratyfikowane przeżycie narządu przeszczepionego było lepsze u pacjentów z BMI<30 kg/m^2 (88.6 vs 94.8%; $p=0.05$).

Publikacja 2

Nie stwierdzono różnic w przedoperacyjnej utracie masy ciała (odpowiednio 13.00±11.69 kg i 15.22±15.96 kg, $p=0.619$) między pacjentami z schyłkową PChN i bez niej. W pierwszych 3 miesiącach obserwacji stwierdzono szybszą utratę masy ciała u pacjentów ze schyłkową PChN ($p=0.03$). Podczas rocznego okresu obserwacji utrata masy ciała pacjentów ze schyłkową PChN nie różniła się istotnie w żadnym z punków obserwacji. Wartości BMI na początku i w całym okresie obserwacji nie różniły się istotnie między badanymi grupami.

Publikacja 3

Wszystkie wytyczne podkreślają rolę wczesnego wykrywania otyłości i chorób współistniejących związanych z otyłością u pacjentów ze schyłkową PChN. W dwóch z nich oceniono rolę chirurgii metabolicznej, ale ze względu na brak wystarczających dowodów nie sformułowano zaleceń dotyczących kwalifikacji do leczenia chirurgicznego otyłości chorobliwej w tej grupie chorych.

Wnioski

Wykonane badania dostarczają informacji dotyczących analizy wpływu otyłości na przebieg zabiegu przeszczepienia nerki od dawcy zmarłego, okres okołooperacyjny oraz skuteczność i bezpieczeństwo chirurgicznego leczenia otyłości chorobliwej u pacjentów z PChN celem poprawy wyników jej leczenia metodą przeszczepienia nerki.

W pierwszej publikacji wykazano, że otyłość u biorców nerki wpływa na przebieg śródoperacyjny, a w okresie pooperacyjnym wiąże się z większym ryzykiem powikłań chirurgicznych, gorszą funkcją nerki przeszczepionej i krótszym czasem przeżycia narządu.

Druga publikacja dostarcza dowodów na to, że pacjenci kwalifikowani do przeszczepienia nerki z otyłością chorobliwą odnoszą korzyści z zastosowania procedur chirurgii metabolicznej w okresie przedtransplantacyjnym i mogą być bezpiecznie kwalifikowani do programów leczenia chirurgicznego otyłości chorobliwej. Ponadto chirurgia metaboliczna umożliwia skuteczną utratę masy ciała w okresie przedtransplantacyjnym i powinna być uwzględniana jako metoda leczenia otyłości chorobliwej w celu poprawy wyników leczenia PChN metodą transplantacji nerki.

Trzecia publikacja jest analizą aktualnych wytycznych dotyczących leczenia otyłości u pacjentów z PChN. Obecne wytyczne nie uwzględniają roli chirurgicznego leczenia otyłości w tej grupie chorych. Niezbędna wydaje się ich aktualizacja w oparciu o wyniki najnowszych badań ze szczególnym uwzględnieniem leczenia operacyjnego.

Podsumowując, epidemia otyłości istotnie wpływa na diagnostykę i leczenie pacjentów z PChN[7,8]. Wyższe BMI, nie tylko wiąże się z istotnie z przebiegiem śródoperacyjnym i okresem pooperacyjnym przeszczepienia nerki, ale również jest związane z upośledzeniem funkcji nerki przeszczepionej. Chirurgia metaboliczna jest bezpieczną i skuteczną metodą redukcji masy ciała w okresie przedtransplantacyjnym. Chirurgiczne leczenie otyłości powinno być rozważane u każdego chorego z PChN i otyłością chorobliwą oraz uwzględnione w aktualnych wytycznych jako metoda bezpiecznej i skutecznej utraty masy ciała i poprawy stanu metabolicznego pacjenta.

Abstract

Introduction

Obesity is related to both the development and acceleration of chronic kidney disease[1]. Increased incidence of obesity and comorbidities in patients with end-stage renal disease (ESKD) may affect the eligibility for kidney transplantation, as well as the early and late outcomes of surgical treatment[2–4]. Proper management of obesity is important to improve the results of kidney transplantation[5]. This doctoral thesis consists of three publication which analyze the influence of obesity on the course of kidney transplantation and the safety and efficiency of surgical treatment of morbid obesity in patients with chronic renal failure. Metabolic surgery may play a leading role in management of morbid obesity in ESKD patients and improve the results of kidney transplantation.

Aims

Publication 1

The primary aim of the study was to analyze intraoperative parameters and postoperative short- and long-term course of kidney transplantation (KT) in body mass index (BMI) stratified cohorts of kidney transplant recipients (KTR). Additionally, the analysis of overall mortality and graft loss in BMI stratified cohorts was performed.

Publication 2

Matched pairs analysis was designed to analyze the pre- and postoperative weight loss after bariatric procedures in end-stage kidney disease (ESKD) and non-ESKD morbidly obese patients.

Publication 3

The aim of this review was to summarize current guidelines on the role of obesity treatment in kidney transplant recipients. Eight current national and international clinical practice guidelines were identified in a comprehensive database search with the special consideration of obesity diagnosis and treatment.

Material and methods

Publication 1

A retrospective analysis of a prospectively built database of 433 KTRs between 2014 to 2017 from a single transplant center was performed. The objective of the study was to analyze the association between the BMI at the time of transplantation and intraoperative parameters, adverse events in early postoperative course, overall mortality and graft loss in BMI stratified cohorts: normal (18.5 and 24.9 kg/m^2), overweight (25-29.9 kg/m^2) and obese (≥30 kg/m^2).

Publication 2

Twenty patients with ESKD underwent bariatric surgery in our Centre of Excellence for Bariatric and Metabolic Surgery between 2015-2019.They were compared with matched pairs from a dataset of 1199 morbidly obese patients without ESKD. Data on demographic factors and comorbidities was recorded. BMI was obtained at the start of the preparatory period preceding the bariatric procedure, at the time of procedure, and during the 1-year follow-up.

Publication 3

The review of clinical practice guidelines (CPG) was performed according to *Preferred Recording Items for Systematic Review and Meta-Analyses* (PRISMA) guidelines[6] to search for literature published until January 2020. We included only CPG for the selection of candidates for deceased donor kidney transplantation and extracted the following data: society, year of publication, inclusion of obesity into recommendation, recommendations for obesity treatment, grade of recommendation.

Results

Publication 1

Obesity was related to longer total procedure time (p=0.0025) and longer warm ischemia time (p=0.0003). The postoperative course was inferior in obese patients: higher incidence of DGF (p=0.0002), early reoperation rate (p=0.001) and other early surgical complications: vascular complications rate, incidence of lymphocele and wound dehiscence was recorded. There was no difference between normal weight and overweight KTRs. The one-month kidney function (p=0.0001) and long-term allograft survival (p=0.029) were significantly inferior in obese patients with no difference between normal weight and overweight patients. 1-year death-censored graft survival was better in patients with BMI<30 kg/m^2 (88.6 vs 94.8% p=0.05).

Publication 2

The ESKD and non-ESKD patients did not differ significantly in preoperative weight loss (13.00±11.69 kg and 15.22±15.96 kg respectively, p=0.62). In the first 3 months follow-up period faster weight loss was observed in ESKD patients (p=0.03). During the one-year follow-up the weight loss was similar to the non-ESKD group. Initial and follow-up BMI values did not differ significantly between groups.

Publication 3

All guidelines underline early detection of obesity and obesity-related comorbidities in ESKD patients. Only two guidelines explored the role of metabolic surgery but due to the lack of sufficient evidence no formal recommendation of surgical approach was given.

Conclusions

Presented studies provide a wide analysis of the influence of obesity on the course of kidney transplantation and the efficiency and safety of pretransplant surgical treatment of obesity in patients with chronic kidney disease.

In the first publication we demonstrate that obesity in kidney transplant recipients affect intraoperative and postoperative course of KT procedure and is related to higher risk of complications, inferior kidney function and shorter graft survival.

The second publication provides the evidence that morbidly obese kidney transplantation candidates benefit from bariatric surgery and can be eagerly included in bariatric surgery weight loss programs. Moreover, bariatric surgery allows efficient pre-transplantation weight loss results and should be included as a method of obesity treatment to improve the results of the transplantation.

Third publication is analyzing the current evidence on the treatment of obesity in CKD patients. It seems to be necessary to update the guidelines with results of recent studies on the new methods of assessment and treatment of obesity, with special attention to surgical procedures.

In conclusion, obesity epidemic has major implications on CKD patients treatment[7,8]. Higher BMI not only affects significantly intraoperative and postoperative course of KT procedure, but also is related to inferior function of transplanted kidney. Bariatric surgery provides a safe and effective method of weight loss in pretransplant period. Bariatric surgery should be considered in all CKD patients with obesity and should be included in current transplant guidelines.

Wstęp

Otyłość jest jednym z najpoważniejszych problemów zdrowotnych współczesnego świata. Obecnie częstość występowania otyłości gwałtownie wzrasta, osiągając skalę epidemii. W ciągu ostatnich 30 lat liczba osób otyłych na świecie niemal potroiła się[9]. W populacji polskiej odpowiednio 68% mężczyzn i 53% kobiet ma nadwagę (BMI powyżej 25 kg/m^2), a prawie 25% otyłość (BMI>30 kg/m^2)[10].

Częstość występowania przewlekłej choroby nerek na świecie wynosi 13.4%, a schyłkowa niewydolność nerek wymagająca leczenia nerkozastępczego występuje u 4-7 milionów pacjentów[11]. Wzrost zachorowalności jest spowodowany głównie poprzez powikłania chorób przewlekłych takich jak cukrzyca, nadciśnienie tętnicze, lecz także większą częstością otyłości[3,8,12]. Otyłość jest, nie tylko przyczyną rozwoju przewlekłej choroby nerek, ale może także przyspieszać jej progresję. Ponadto stanowi uznaną barierę do leczenia niewydolności nerek metodą transplantacji nerki[13,14].

Transplantacja nerki jest uznawana za najlepszą metodę leczenia nerkozastępczego. W Polsce według danych Poltransplantu w 2021 roku wykonano ponad 700 przeszczepień nerki od dawcy zmarłego, a około 1000 pacjentów oczekuje na Krajowej Liście Oczekujących[15]. Otyłość istotnie wpływa na ryzyko okołooperacyjne i wyniki leczenia metodą transplantacji nerki. Leczenie otyłości obejmuje indywidualnie planowane strategie dietetyczne i aktywność fizyczną, które wiążą się z niską skutecznością w tej grupie chorych. Farmakoterapia przy użyciu analogów ludzkiego glukagonopodobnego peptydu-1 (GLP-1) wydaje się obiecującą metodą redukcji masy ciała. Leczenie chirurgiczne otyłości jest przedmiotem dyskusji w aktualnych zaleceniach[16].

Niniejszy przewód doktorski składa się z dwóch publikacji oryginalnych i pracy przeglądowej. Publikacja pt. *„Pretransplant BMI significantly affects perioperative course and graft survival* *after kidney transplantation – retrospective analysis"* jest analizą związku BMI biorcy nerki z przebiegiem okołooperacyjnym przeszczepienia nerki i wyników pooperacyjnych.

Druga publikacja pt. *„Weight Loss After Bariatric Surgery in Morbidly Obese End-Stage Kidney Disease Patients as Preparation for Kidney Transplantation. Matched Pair Analysis in a High-Volume Bariatric and Transplant Center"* stanowi analizę przedoperacyjnej i pooperacyjnej utraty masy ciała u pacjentów ze schyłkową PChN w porównaniu z pacjentami bez schyłkowej PChN operowanych z powodu otyłości chorobliwej.

W trzeciej publikacji pt. *„Obesity in work-up of kidney transplant candidates – review of clinical practice guidelines"* oceniono aktualne zalecenia leczenia otyłości w okresie poprzedzającym przeszczepienie nerki.

Cele badań

Publikacja 1

„Pretransplant BMI significantly affects perioperative course and graft survival after kidney transplantation – retrospective analysis"

Pierwszorzędowym celem badania była ocena wpływu BMI biorcy nerki na przebieg zabiegu przeszczepienia nerki i parametry śródoperacyjne. Drugorzędowym celem była analiza zdarzeń niepożądanych we wczesnym okresie pooperacyjnym, całkowitej śmiertelności i utraty przeszczepu w średnim czasie obserwacji 2.15 lat, w trzech kohortach stratyfikowanych według BMI.

Publikacja 2

„Weight Loss After Bariatric Surgery in Morbidly Obese End-Stage Kidney Disease Patients as Preparation for Kidney Transplantation. Matched Pair Analysis in a High-Volume Bariatric and Transplant Center".

W badaniu porównano przedoperacyjną i pooperacyjną utratę masy ciała u pacjentów otyłych ze schyłkową PChN z grupą kontrolną pacjentów otyłych bez schyłkowej PChN poddawanych zabiegom chirurgii bariatrycznej w dużym centrum bariatrycznym i transplantacyjnym.

Publikacja 3

„Obesity in work-up of kidney transplant candidates – review of clinical practice guidelines"

Celem przeglądu była ocena dostępności, jakości i spójności zaleceń dotyczących diagnostyki i leczenia otyłości przed przeszczepieniem nerki, zawartych w aktualnych krajowych i międzynarodowych wytycznych praktyki klinicznej w procesie kwalifikacji kandydatów do przeszczepienia nerki.

Materiał i metody

Publikacja 1

Do tego retrospektywnego jednoośrodkowego badania klinicznego włączono 433 pacjentów z PChN, biorców nerek od dawcy zmarłego, leczonych w ośrodku transplantacji nerek w Gdańsku w okresie od 1 stycznia 2014 r. do 31 grudnia 2017 r. W celu wykonania analizy statystycznej grupę badaną podzielono według BMI na trzy grupy badawcze: pacjenci z prawidłowym BMI (od 18.5 do 24.9 kg/m^2), z nadwagą (BMI 25-29.9 kg/m^2) i z otyłością (BMI $\geq$30 kg/m^2). Analizowano parametry śródoperacyjne: całkowity czas zabiegu, czas zimnego niedokrwienia (CIT), czas ciepłego niedokrwienia (WIT) oraz czas hospitalizacji. Ponadto dokonano analizy pooperacyjnych zdarzeń niepożądanych, czynności nerki przeszczepionej i przeżycia graftu w okresie obserwacji. Wszystkie analizy przeprowadzono w trzech ww. grupach badawczych stratyfikowanych według BMI.

Publikacja 2

Publikacja jest retrospektywną analizą dynamiki utraty masy ciała pacjentów z otyłością chorobliwą i schyłkową PChN i otyłością chorobliwą bez schyłkowej PChN, leczonych zabiegami chirurgii bariatrycznej. Do badania włączono 20 pacjentów z PChN leczonych z powodu otyłości chorobliwej, w jednym ośrodku, w latach 2015-2019. W celu wykonania analizy porównawczej pacjentów dobrano pod względem wieku, płci i rodzaju operacji w stosunku 1 do 1. Do operacji kwalifikowano pacjentów, których BMI przekraczało 40 kg/m^2 lub BMI mieściło się w zakresie od 35 do 40 kg/m^2, ale obecne były istotne choroby współistniejące zgodnie z wytycznymi IFSO[17]. Pacjenci ze schyłkową PChN byli konsultowani nefrologicznie i poddawani hemodializoterapii bez heparyny dzień przed operacją oraz w 1. Dobie po operacji. Maksymalne BMI obliczono na podstawie maksymalnej masy ciała podczas kwalifikacji w okresie przygotowawczym do leczenia chirurgicznego. Początkowe BMI obliczono na podstawie masy ciała w momencie operacji po obowiązkowym okresie utraty masy ciała w okresie przygotowawczym. Zabiegi bariatryczne zostały wykonane zgodnie z wytycznymi IFSO[17], przez tych samych chirurgów. W okresie obserwacji pomiary kontrolne wykonywano podczas wizyt kontrolnych 1, 3, 6 i 12 miesięcy po zabiegu.

Publikacja 3

Przegląd aktualnych wytycznych leczenia pacjentów ze schyłkową niewydolnością nerek metodą transplantacji nerki pobranej od dawcy zmarłego przeprowadzono zgodnie z rekomendacjami „*Preferred Recording Items for Systematic Review and Meta-Analyses*" (PRISMA). Dwóch niezależnych badaczy przeprowadziło analizę literatury opublikowanej do stycznia 2020 r. W badaniu porównano następujące dane: kraj i datę publikacji, diagnostykę otyłości w zaleceniach, zalecenia dotyczące leczenia otyłości oraz stopień zaleceń.

Wyniki

Publikacja 1

W badanym okresie wykonano 433 zabiegi przeszczepienia nerek u 272 (62.8%) mężczyzn i 161 (37.2%) kobiet. Pacjenci z otyłością (BMI≥30 kg/m^2) stanowili 16.6% badanej grupy (72 pacjentów w tym 42 mężczyzn, 30 kobiet). Średni wiek badanej grupy wynosił 49.3±13.8 lat z różnicą statystyczną pomiędzy grupą pacjentów z otyłością, a grupą z prawidłową masą ciała oraz pacjentami z otyłością i z nadwagą ($p<0.05$). Średni CCI był istotnie wyższy w grupie otyłych ($p=0.029$). Nie było różnic w metodzie dializoterapii przed KT pomiędzy badanymi grupami (hemodializoterapia – $p=0.09$, dializa otrzewnowa – $p=0.16$). Najczęstszą formą leczenia nerkozastępczego we wszystkich grupach była hemodializoterapia stanowiąca 76% przypadków. W analizie przebiegu zabiegu przeszczepienia nerki prawa nerka została przeszczepiona u 220 pacjentów (50.9%), a lewa u 213 pacjentów (49.1%). Obecność pojedynczej tętnicy nerkowej stwierdzono w 345 przypadkach (79.7%).

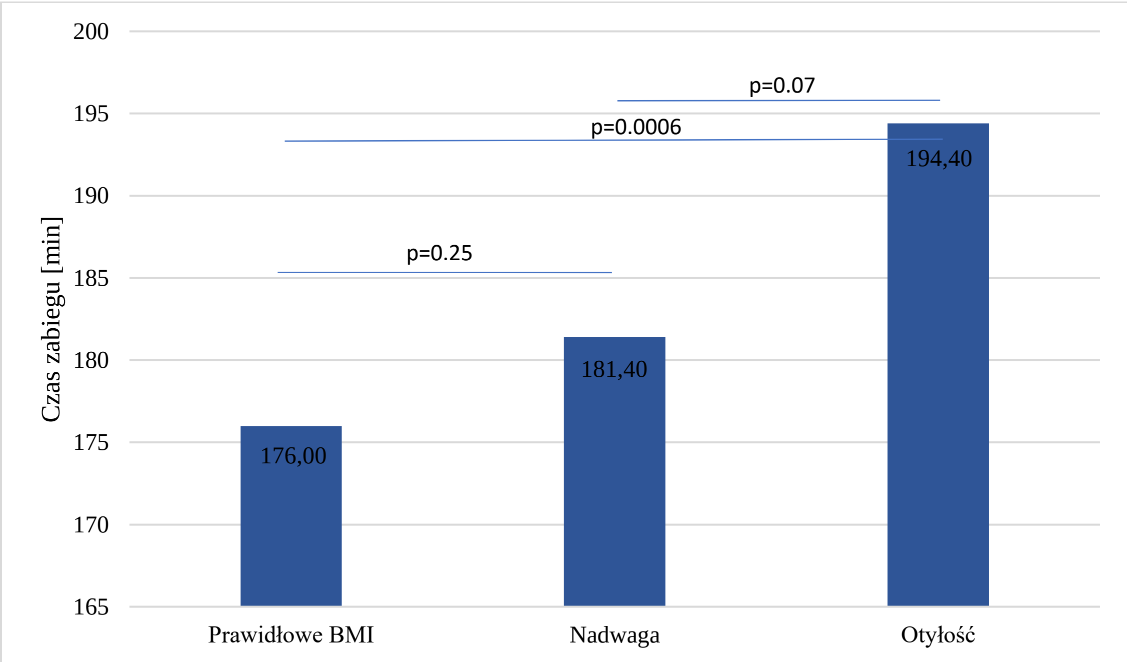
Średni czas zabiegu wynosił 181.98±37.6 min (mediana 180 min.) z istotną różnicą między trzema badanymi kohortami ($p=0.0025$). Najdłuższy średni czas zabiegu zaobserwowano u pacjentów z otyłością (194.4±38.9 min.). Ponadto stwierdzono statystycznie istotną różnicę między pacjentami z otyłością, a pacjentami z prawidłową masą ciała oraz nie zaobserwowano różnicy między pacjentami z prawidłową masą ciała, a pacjentami z nadwagą.

Czas ciepłego niedokrwienia (WIT) był istotnie dłuższy u pacjentów z otyłością. Średni czas ciepłego niedokrwienia wynosił 27.827 ± 9.38 minut (mediana 26 ± 4.5 minuty). Wykazano różnice w WIT między pacjentami z otyłością i nadwagą oraz pacjentami z otyłością i prawidłową masą ciała ($p=0.0003$), natomiast nie stwierdzono różnic pomiędzy pacjentami z prawidłową masą ciała a nadwagą. W analizie płci u mężczyzn z otyłością i nadwagą wykazano istotnie dłuższy całkowity czas zabiegu i WIT (odpowiednio p=0.039 i p=0.007).

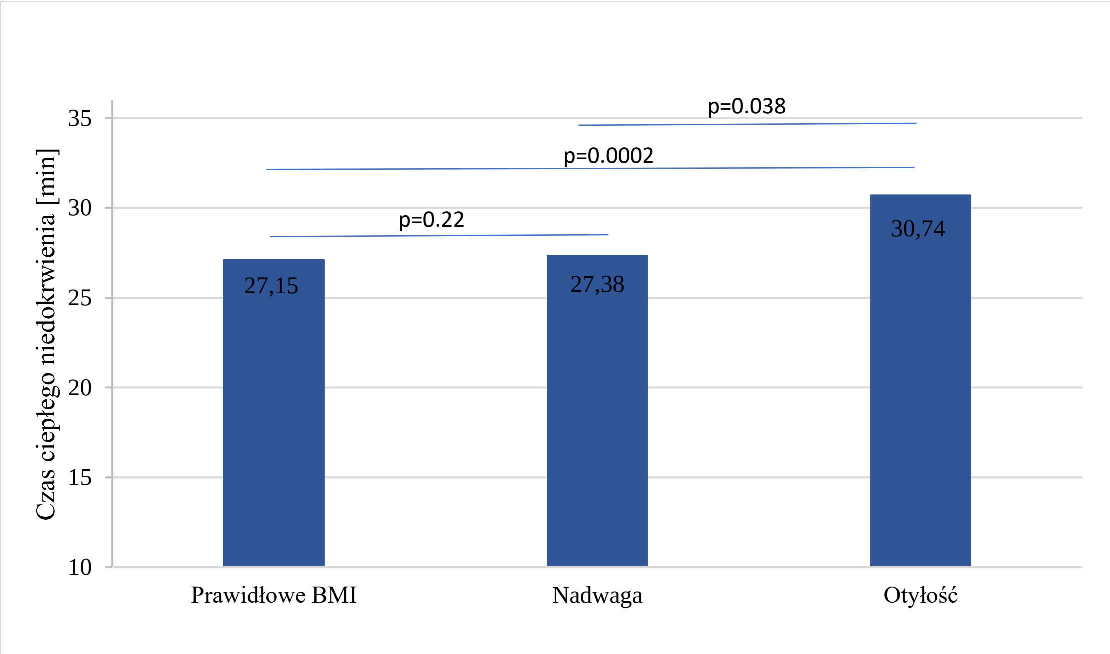
Powyższe różnice między badanymi grupami w zależności od BMI biorcy przedstawiono na Rycinie 1.

Rycina 1.

1. Całkowity czas zabiegu.



2. Czas ciepłego niedokrwienia.



Kolejnym elementem analizy była ocena okresu pooperacyjnego w trzech badanych kohortach. Zaobserwowano 42 przypadki (9.7%) epizodów ostrego odrzucenia (ARE) i 144 przypadki (33.26%) opóźnionej funkcji graftu (DGF). Częstość występowania ARE nie różniła się wśród pacjentów z otyłością, nadwagą i prawidłową masą ciała (odpowiednio 11.4%, 8.5%, 10.04%, p=0.36).

Wykazano istotną różnicę pod względem częstości występowania DGF, który występował istotnie częściej u pacjentów z otyłością niż u pacjentów z nadwagą (p=0.0015) i z prawidłową masą ciała (p=0.0005). Co interesujące nie wykazano różnicy między pacjentami z nadwagą i prawidłową masą ciała (p=0.86).

W badanej grupie wystąpiło 86 przypadków pooperacyjnych zdarzeń niepożądanych wymagających reoperacji w ciągu 30 dni po zabiegu (19.86%). U otyłych biorców nerek częściej występowały wczesne powikłania chirurgiczne, reoperacje, limfocele, powikłania naczyniowe i powikłania gojenia rany. Co interesujące, pomimo większej częstości zdarzeń niepożądanych w grupie pacjentów z otyłością, nie stwierdzono różnicy w całkowitym czasie hospitalizacji między analizowanymi grupami (p=0.15).

Różnice między badanymi grupami w częstości występowania pooperacyjnych zdarzeń niepożądanych przedstawiono w Tabeli 1.

Tabela 1. Pooperacyjne zdarzenia niepożądane w badanej grupie w zależności od BMI biorcy.

	Grupa badana (n=433)	**Prawidłowe BMI (n=209)**	**Nadwaga (n=153)**	**Otyłość (n=71)**	**wskaźnik p**
Pooperacyjna funkcja nerki przeszczepionej					
Ostre odrzucanie (%)	42 (9.7)	21 (10.04)	13 (8.5)	8 (11.3)	p>0.05
Opóźniona funkcja nerki przeszczepionej (%)	144 (33.2)	61 (29.2)	46 (30.1)	37 (52.1)	otyłość vs prawidłowe BMI p=0.0005 otyłość vs nadwaga p=0.0015 prawidłowe BMI vs nadwaga p=0.86
Ogólne zdarzenia pooperacyjne					
Powikłania kardiologiczne[1] (%)	20 (4.6)	9 (4.3)	8 (5.2)	3 (4.2)	p>0.05
Powikłania infekcyjne[2] (%)	106 (24.5)	44 (21.0)	41 (26.8)	21 (29.6)	p>0.05
Cukrzyca potransplantacyjna (%)	46 (10.6)	19 (9.1)	22 (14.4)	5 (7.0)	p>0.05
Chirurgiczne zdarzenia niepożądane					
Powikłania chirurgiczne <30 dni(%)	111 (25.65)	53 (25.3)	27 (16.3)	31 (43.7)	otyłość vs prawidłowe BMI p=0.0036 otyłość vs nadwaga p=0.00001 prawidłowe BMI vs nadwaga p=0.08
Powikłania chirurgiczne >30 dni (%)	24 (5.5)	10 (4.8)	7 (4.6)	7 (9.8)	p>0.05
Reoperacja (%)	86 (19.9)	37 (17.7)	23 (15.0)	26 (36.6)	otyłość vs prawidłowe BMI p=0.001 otyłość vs nadwaga p=0.0003 prawidłowe BMI vs nadwaga p=0.4997
Limfocele (%)	51 (11.8)	17 (8.1)	15 (9.8)	19 (26.8)	otyłość vs prawidłowe BMI p=0.0001 otyłość vs nadwaga p=0.01 prawidłowe BMI vs nadwaga p=0.58
Powikłania urologiczne (%)	32 (7.4)	18 (8.6)	7 (4.6)	7 (9.8)	p>0.05
Rozejście rany pooperacyjnej *(%)*	21 (4.8)	2 (0.96)	7 (4.6)	12 (16.9)	otyłość vs prawidłowe BMI p=0.0000

Powikłania naczyniowe (%)	76 (17.5)	42 (20.1)	15 (9.8)	19 (26.8)	otyłość vs nadwaga p=0.0021 prawidłowe BMI vs nadwaga p=0.0329 otyłość vs prawidłowe BMI p=0.2398 otyłość vs nadwaga p=0.001 prawidłowe BMI vs nadwaga p=0.0079

Funkcja nerki przeszczepionej w miesięcznym okresie obserwacji była gorsza u pacjentów z otyłością. Średnie wartości kreatyniny w badanej grupie przedstawiono w Tabeli 2.

Tabela 2. Funkcja nerki przeszczepionej w miesięcznym okresie obserwacji w badanej grupie.

	Grupa badana (n=433)	**Prawidłowe BMI (n=209)**	**Nadwaga (n=153)**	**Otyłość (n=71)**	**wskaźnik p**
Średni poziom kreatyniny w osoczu miesiąc po przeszczepieniu nerki (mediana) [mg/dl]	1.575±0.571 (1.52±0.34)	1.474±0.527 (1.360±0.345)	1.596±0.502 (1.545±0.335)	1.838±0.742 (1.750±0.225)	p<0.05 prawidłowe BMI vs nadwaga p=0.014 otyłość vs prawidłowe BMI p=0.027 otyłość vs nadwaga p=0.000

W odległej obserwacji nie stwierdzono różnic w śmiertelności całkowitej między pacjentami bez otyłości i z otyłością. Odnotowano 43 przypadki (9.9%) utraty nerki przeszczepionej. Częstość utraty narządu była wyższa u pacjentów z otyłością (p=0.029), z istotną różnicą między pacjentami z otyłością i z nadwagą (p=0.009). Najczęstszą przyczyną wczesnej utraty narządu była zakrzepica tętnicza lub żylna (55% przypadków wczesnych utrat graftu). W analizie jednoczynnikowej czynnikami istotnie związanymi z ryzykiem utraty przeszczepu były: ARE, DGF i BMI>30kg/m^2. Wśród tych czynników jedynie ARE był istotnym predyktorem utraty narządu przeszczepionego w analizie wieloczynnikowej.

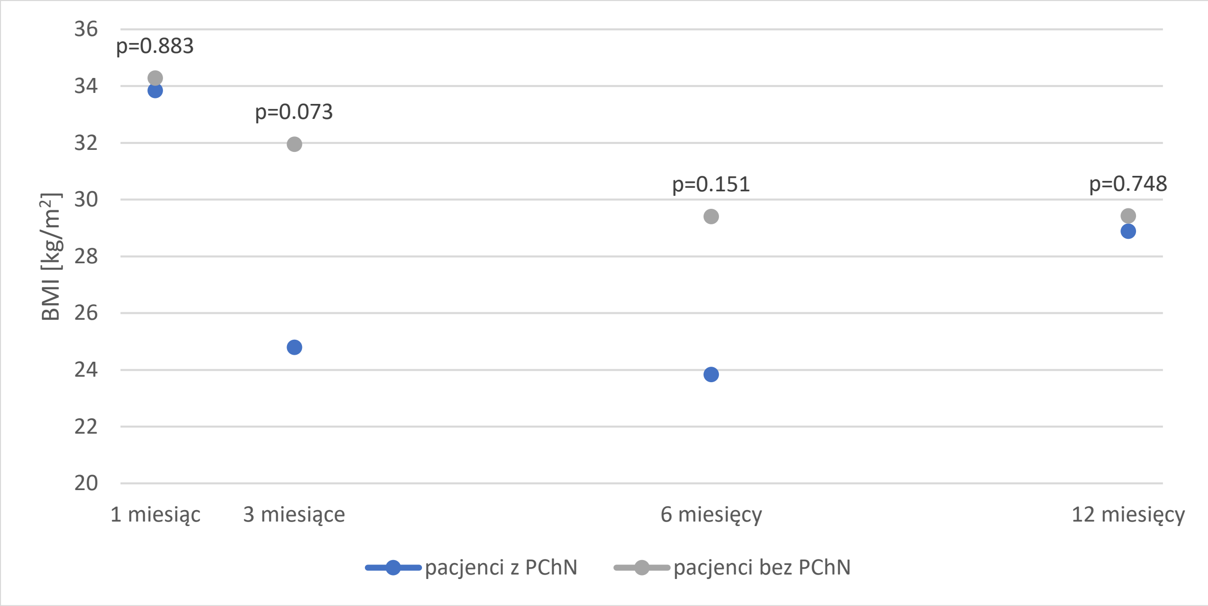
Publikacja 2

U pacjentów ze schyłkową PChN średnia maksymalna masa ciała wynosiła 128 ± 18.5 kg z przedoperacyjnym spadkiem masy ciała do 115 ± 14.5 kg. Średnie maksymalne BMI wynosiło 42.8 kg/m^2, a początkowe BMI 38.5 kg/m^2. U pacjentów z PChN częściej występowało nadciśnienie tętnicze (70% vs 35%, p=0.027). Zabieg bariatryczny OAGB (one-anastomosis gastric bypass) wykonano u 9/20 (45%) pacjentów, RYGB (roux-en-Y gastric bypass) u 9/20 (45%), LSG (laparoskopowa rękawowa resekcja żołądka) u 2/20 pacjentów (10%). W grupie z PChN zanotowano jedno poważne powikłanie w pierwszym dniu po operacji OAGB. Średni czas hospitalizacji (LOS) pacjentów z PChN wynosił 3.8 ± 0.5 dnia (z wyłączeniem jednego przypadku z LOS 26 dni).

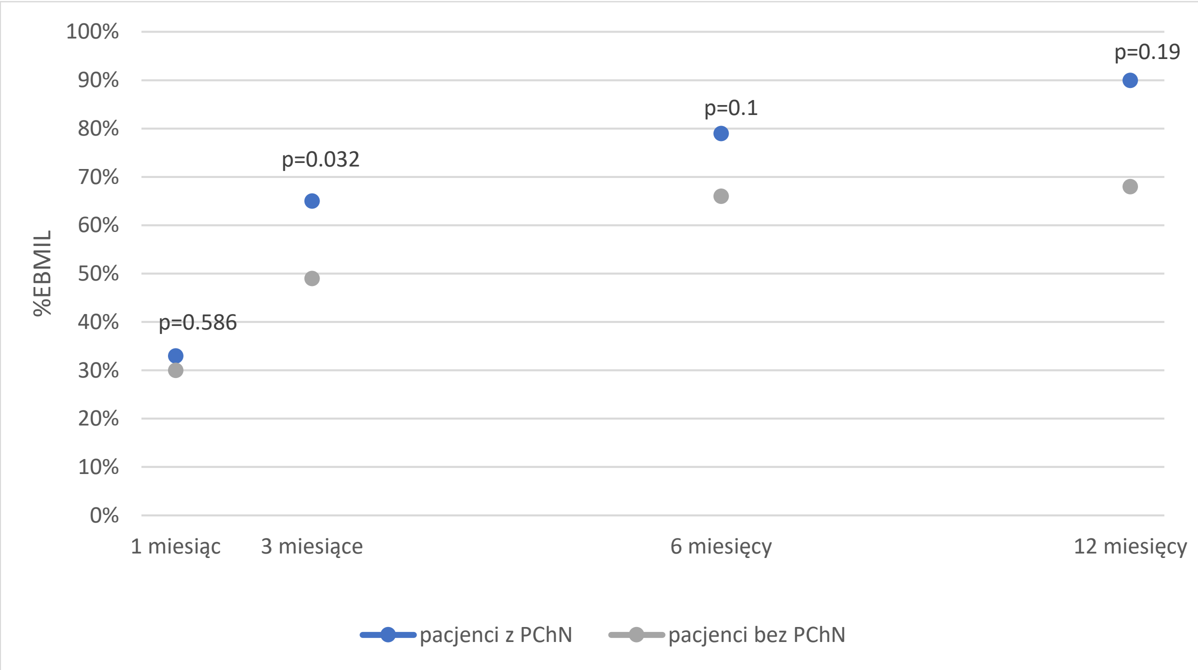
W grupie kontrolnej bez PChN średnia maksymalna masa ciała wynosiła 131.5 ± 20.5 kg z spadkiem do 116.3 ± 14.5 kg przed operacją. W grupie kontrolnej uzyskano 12% redukcję masy ciała w okresie przedoperacyjnym w porównaniu z 10% w grupie badanej (p=0.619). Średnie maksymalne BMI wynosiło 43.6 kg/m^2, a początkowe BMI 38.4 kg/m^2. LOS w grupie kontrolnej wynosił 2.1 ± 0.5 dnia.

W badaniu nie stwierdzono różnic w maksymalnej masie ciała między pacjentami z PChN i bez PChN (odpowiednio 128 ± 18.5 kg vs 131.5 ± 20.5 kg, p=0.583), maksymalnym BMI (odpowiednio 43.2 kg/m^2 vs 43.6 kg/m^2, p=0.66) i utracie BMI w okresie przygotowawczym (odpowiednio 4.36 vs 5.13, p=0.6). W rocznym okresie obserwacji na kolejnych wizytach kontrolnych nie stwierdzono różnić w utracie masy ciała i spadku BMI między badanymi grupami. Utratę BMI i nadmiarowego BMI (EBMIL%) w okresie obserwacji przedstawiono na Rycinach 2 i 3.

Rycina 2. Porównanie BMI pacjentów w trakcie okresu obserwacji między pacjentami z PChN i bez PChN, ($p<0.05$ istotne statystyczne).



Wykres 3. Porównanie procentowej utraty nadmiarowego BMI (EBMIL%) między pacjentami z PChN i bez PChN, ($p<0.05$ istotne statystyczne).



Publikacja 3

Z przeglądu 419 artykułów wyodrębniono 8 wytycznych praktyki klinicznej. Aktualnie obowiązujące wytyczne zalecają rutynową ocenę w kierunku rozpoznania otyłości u każdego pacjenta przed przeszczepieniem nerki. Dwa spośród analizowanych wytycznych zalecają zmniejszenie masy ciała przed zabiegiem jeśli BMI przekracza 30 kg/m^2, a w jednym z badań ustalono górną granicę BMI na 40 kg/m^2. Według wszystkich zaleceń otyłość nie jest przeciwwskazaniem, ale związana z innymi chorobami współistniejącymi biorcy (zaawansowane choroby sercowo-naczyniowe, choroby naczyń obwodowych, choroba wątroby lub płuc, aktywne zapalenie wątroby) powoduje duże ryzyko powikłań okołooperacyjnych i może skracać przeżycie narządu i pacjenta.

W leczeniu otyłości w okresie przedtransplantacyjnym potwierdzono bezpieczeństwo leczenia indywidualnie zaplanowaną dietą z deficytem kalorycznym w wysokości 500–1000 kcal/ dzień wraz ze zwiększoną aktywnością fizyczną oraz terapią behawioralną. Metody te związane są jednak z krótkotrwałą skutecznością. Według wytycznych nie przeprowadzono badań dotyczących bezpieczeństwa stosowania terapii farmakologicznej otyłości (antagonista lipaz – orlistat) w tej grupie chorych, nie formułują one również zaleceń dotyczących zastosowania chirurgii bariatrycznej. Dwa z ośmiu badań zalecają operację bariatryczną przed przeszczepieniem nerki. Istniejące badania są niewystarczające aby sformułować zalecenia dotyczące kwalifikacji, preferowanej procedury i czasu jej wykonania.

Wnioski

Prezentowane prace pozwoliły na analizę wpływu otyłości na przebieg zabiegu przeszczepienia nerki oraz ocenę skuteczności i bezpieczeństwa chirurgicznego leczenia otyłości u pacjentów z przewlekłą chorobą nerek.

Pierwsza publikacja dostarcza wysokiej jakości dowodów na to, że BMI biorcy nerki istotnie wpływa na parametry śródoperacyjne, okres pooperacyjny oraz wyniki zabiegu przeszczepienia nerki. Badanie w szczególności wykazało wydłużony czas ciepłego niedokrwienia i całkowity czas zabiegu u pacjentów z otyłością, gorszą funkcję nerki przeszczepionej, częstsze występowanie DGF i pooperacyjnych zdarzeń niepożądanych. Zabieg operacyjny jest trudniejszy i dłuższy u pacjentów z otyłością, wczesny przebieg pooperacyjny powikłany, a utrata przeszczepu występuje częściej w tej grupie chorych. Co interesujące, nie stwierdzono różnic między pacjentami z normalną masą ciała i pacjentami z nadwagą. Opublikowane dane sugerują odniesienie korzyści z utraty masy ciała przed przeszczepieniem nerki u pacjentów ze schyłkową PChN, mającej na celu osiągnięcie BMI <30 kg/m^2 aby poprawić zarówno wczesne, jak i długoterminowe wyniki leczenia metodą transplantacji nerki

Druga publikacja przedstawia interesujące wnioski, że pacjenci z schyłkową PChN operowani chirurgicznie z powodu otyłości chorobliwej odnoszą takie same korzyści z leczenia jak pacjenci bez PChN. Zabiegi chirurgii bariatrycznej wykonywane w doświadczonym ośrodku pozwalają na skuteczną i bezpieczną utratę masy ciała przed transplantacją.

Ostatnia publikacja, będąca przeglądem systematycznym aktualnych wytycznych leczenia pacjentów z przewlekłą niewydolnością nerek przedstawia konieczność uwzględnienia nowych badań w grupie pacjentów z otyłością i uwzględnienia chirurgicznego leczenia otyłości w aktualizowanych wytycznych.

Podsumowując, otyłość u pacjentów z przewlekłą niewydolnością nerek jest związana z większym ryzykiem operacyjnym, a bariatryczne leczenie chirurgiczne pozwala na bezpieczną utratę masy ciała w okresie przedtransplantacyjnym i może wpływać na poprawę wyników leczenia metodą transplantacji nerki.

Cykl prac wchodzących w skład rozprawy doktorskiej i dane bibliometryczne

Cykl składa się z trzech prac opublikowanych w międzynarodowych czasopismach naukowych umieszczonych na Liście Filadelfijskiej.

Łączny Impact Factor (IF) cyklu to 9.093.

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Publikacja 1

Dobrzycka Małgorzata, Bzoma Beata, Bieniaszewski Ksawery, Dębska-Ślizień Alicja, Kobiela Jarosław.

Pretransplant BMI significantly affects perioperative course and graft survival after kidney transplantation – a retrospective analysis.

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Publikacja 2

Dobrzycka Małgorzata, Proczko-Stepaniak Monika, Kaska Łukasz, Wilczyński Maciej, Kobiela Jarosław

Weight Loss After Bariatric Surgery in Morbidly Obese End-Stage Kidney Disease Patients as Preparation for Kidney Transplantation. Matched Pair Analysis in a High-Volume Bariatric and Transplant Center.

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Publikacja 3

Dobrzycka Małgorzata, Spychalski Piotr, Łącka Monika, Proczko-Stepaniak Monika, Dębska-Ślizień Alicja, Kaska Łukasz, Kobiela Jarosław

Obesity in work-up of kidney transplant candidates – review of clinical practice guidelines.

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Bibliometria: Impact Factor: 0, punktacja MNiSW: 40 punktów.

Publikacje

Poniżej umieszczono oryginalne wydruki publikacji stanowiących podstawę przewodu doktorskiego.

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Article

Pretransplant BMI Significantly Affects Perioperative Course and Graft Survival after Kidney Transplantation: A Retrospective Analysis

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Abstract: Background. The number of kidney transplant recipients (KTRs) with overweight and obesity is increasing. It was shown that obesity is related to inferior patient and graft survival. We aimed to analyze intraoperative parameters and postoperative short and long-term course of kidney transplantation (KT) in body mass index (BMI)-stratified cohorts of KTRs. Methods. A retrospective analysis of a prospectively built database of 433 KTRs from 2014 to 2017 from a single transplant center was performed. The objective of the study was to analyze the association between BMI at the time of transplantation with intraoperative parameters, adverse events in early postoperative course, and the overall mortality and graft loss in BMI-stratified cohorts: normal (18.5 and 24.9 kg/m^2), overweight (25–29.9 kg/m^2) and obese ($\geq$30 kg/m^2). Results. Obesity was related to longer total procedure time (p = 0.0025) and longer warm ischemia time (p = 0.0003). The postoperative course in obese patients was complicated by higher incidence of DGF (delayed graft function), early surgical complications (defined as surgical complications <30 days from KT), reoperation rate, vascular complications, incidence of lymphocele and wound dehiscence. There was no difference between the normal weight and overweight KTRs. The one-month kidney function (p = 0.0001) and allograft survival (p = 0.029) were significantly inferior in obese patients with no difference between normal weight and overweight patients. One-year death-censored graft survival was better in patients with BMI < 30 (88.6 vs. 94.8% p = 0.05). BMI was a significant predictor of graft loss in univariate (p = 0.04) but not in multivariate analysis (p = 0.09). Conclusion. Pretransplant obesity significantly affects the intraoperative and postoperative course of kidney transplantation and graft function and survival. The course of transplantation of overweight is comparable to normal BMI KTRs, and presumably pretransplant weight reduction to the BMI < 30 kg/m^2 may improve the short-term postoperative course of transplantation as well as may improve graft survival. Thus, pretransplant weight reduction in obese KTRs may significantly improve the results of kidney transplantation. Metabolic surgery may play a role in improving results of KT.

Keywords: kidney transplantation; obesity; metabolic surgery

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1. Introduction

The number of end-stage kidney disease (ESKD) patients with obesity worldwide is growing [1]. Obesity has not only been shown to be an independent risk factor for developing ESKD but also is related to the development of comorbidities that may impact the results of ESKD treatment [2]. Kidney transplantation (KT) is considered the most cost-effective therapy for ESKD [3]. Due to the obesity epidemic, the number of obese transplant candidates is rapidly increasing [1]. Recent studies have confirmed the relationship between obesity and many important comorbidities in kidney transplant recipients (KTRs) [4,5]. It has been proven that obesity is associated with significantly shorter allograft survival and higher overall mortality [6,7]. The increasing number of obese KTRs is also related to a higher incidence of late complications [1,5]. Interestingly, the association between recipient body mass index (BMI) and the intraoperative and early postoperative course has not been extensively studied.

The primary objective of the current study was to determine the association between BMI at the time of transplantation with intraoperative parameters. We also aimed to analyze the adverse events in early postoperative course, overall mortality and graft loss in BMI-stratified cohorts.

2. Materials and Methods

The study was a retrospective analysis of a prospectively built database of 433 patients with ESKD who received deceased donor KT in one large kidney transplantation center in Gdansk between 1 January 2014 and 31 December 2017. Clinical data were obtained from a prospectively built database of ESKD patients. All patient information was anonymized. All adult patients who underwent KT in that period of time were included. Patients were qualified for KT according to national practice guidelines and listed on a transplantation list [8]. All transplantations were performed by a group of six transplant surgeons. The vascular anastomosis of the renal artery to external iliac artery, and the renal vein to the external iliac vein were performed with continuous vascular suture. They were followed by ureterovesical anastomosis with JJ stenting. All patients received induction therapy with calcineurin inhibitor and mycophenolate mofetil (MMF). Anti-thymocyte globulin was administered when indicated. In the postoperative course, patients were treated with triple immunosuppressive protocols, including calcineurin inhibitor (tacrolimus or cyclosporine based on individual recommendation), mycophenolate mofetil (MMF) and glucocorticoids. Antibiotic prophylaxis was administered in all KTRs. CMV prophylaxis was recommended for all donor positive/recipient negative patients.

The database included both donor and recipient data. Data analysis included patient demographics (gender, age, BMI). Body weight (kg) and body height (m) were measured to calculate the BMI as weight in kg/m^2 height. Obesity was defined by BMI of $\geq$30 kg/m^2. For statistical analysis the study group was stratified by BMI into three study groups: normal BMI (between 18.5 and 24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2) and obese (BMI 30 kg/m^2 and higher) according to WHO guidelines. Total procedure time, cold ischemia time (CIT), warm ischemia time (WIT) and hospitalization time were analyzed. Intraoperative, 30 day postoperative and delayed follow-up data were reviewed. Study follow-up was conducted up to 7 years. The primary cause of ESKD and most common comorbid conditions were noted. The comorbidities were identified at the time of KT (baseline) in patient clinical examination. The Charlson Comorbidity Index (CCI) was used for baseline characteristics as a predictor not only of the patient's clinical situation, but also to demarcate differences among three cohorts of our patients sharing the same medical diagnosis (ESKD). We chose the Charlson Comorbidity index because it was designed to predict mortality and also may be used to predict future outcome or stratify patients into different prognostic groups better than the analysis of single comorbid conditions. Delayed graft function (DGF) was defined as the need for hemodialysis (HD) during the first week after transplantation. An acute rejection episode (ARE) is characterized by an acute post-transplant decline in kidney function as a consequence of an immune response of the host to the graft. Surgical complications included wound infection, hematoma and lymphocele. We separately recorded vascular complications (vascular anastomosis leak and embolism) and urological complications (ureteral injury and anastomosis leak). All analyses were performed in three above mentioned study groups stratified by BMI.

The study was approved by Institutional Ethics Board and was performed in accordance with the ethical standards (NKBBN/340/2016).

Statistical Methods

Descriptive statistics were used to report continuous data as mean and standard deviation. Bivariate comparisons were made using the Student *t* test or the Mann-Whitney U test. Categorical data were expressed as values and percentages. Categorical data were compared with either $\chi 2$ test or Fisher's exact test. Analysis of variance (ANOVA) or, when the assumptions for ANOVA were not fulfilled, the Kruskal-Wallis test was used to investigate the associations between BMI and postoperative adverse events in three groups, with post hoc analysis multiple comparison of mean ranks and Bonferroni correction.

Graft and patient survival curves were generated using the Kaplan-Meier estimator. Analyses of survival were performed in two groups: non-obese (BMI < 30 kg/m^2) and obese (BMI $\geq$ 30 kg/m^2). Statistically significant variables in the univariate analysis were introduced in a multivariate model with multiple logistic regression. Associations are given as odds ratios with a 95% confidence interval. The significance limit was set at 0.05. All statistical analysis was performed using Statistica 13.3 Software (TIBCO Software Inc., Palo Alto, CA, USA).

3. Results

A total of 433 heterotopic cadaveric KTs were performed in 272 (62.8%) men and 161 (37.2%) women during the studied period. All consecutive KTRss were enrolled into study. The mean BMI of the study group was 25.33 ± 4.2 kg/m^2. Patients with obesity (BMI $\geq$ 30 kg/m^2) constituted 16.6% of the study group. The obese cohort consisted of 72 patients (42 males, 30 females), with an age range of 20–74 (mean 53.4 ± 13) years. Mean age of the study group was 49.3 ± 13.8 years, with a statistical difference between obese versus normal weight and obese versus overweight ($p < 0.05$). There were more men in the overweight group ($p = 0.002$). The most common comorbidity was hypertension, observed in 322 (74.3%) of KTRs. Only the incidence of diabetes mellitus was different between the analyzed BMI stratified groups ($p = 0.001$). The mean CCI was significantly higher in the obese group, in relation to both overweight and normal weight subjects ($p = 0.029$) (Table 1).

Table 1. Baseline characteristics of all studied groups of patients, the kidney transplantation procedure, and the comparison between normal (BMI < 25), overweight (BMI 25–30) and obese (BMI $\geq$ 30) kidney recipients.

Variables	All Patients (*n* = 433)	Normal BMI 18.5–24.9 (*n* = 208)	Overweight BMI 25–29.9 (*n* = 153)	Obese BMI $\geq$ 30 (*n* = 72)	*p*-Value
Donor					
Age	48.6 (51)	47.1 (49)	49.8 (51)	50.9 (52)	$p = 0.05$
Body weight (kg)	77.9 (76)	76.7 (75)	78.1 (75)	80.7 (80)	$p = 0.06$
Body height (cm)	173.1 (174)	173.1 (174)	172.9 (173.5)	173.5 (174)	$p = 0.95$
BMI [kg/m^2]	25.9 (24.9)	25.5 (24.7)	26.1 (24.9)	26.7 (26)	$p = 0.08$
Donor/recipient BMI ratio	1 (1)	1.2 (1.2)	0.9 (0.9)	0.8 (0.8)	$p < 0.05$
Donor/recipient body weight ratio	1.1 (1.1)	1.3 (1.2)	0.9 (1)	0.9 (0.8)	$p < 0.05$
Recipient					
Male (%)	272 (62.8)	115 (55.3)	114 (74.5)	42 (58.3)	normal vs. overweight $p = 0.0002$ normal vs. obese $p = 0.65$ overweight vs. obese $p = 0.014$
Female (%)	161 (37.2)	93 (44.7)	39 (25.5)	30 (41.7)	
BMI (kg/m^2)	25.3	21.97	27.22	31.71	$p < 0.05$
Mean age (median; years)	49.3 ± 13.8 (51 ± 11.5)	45.3 ± 14.4 (46 ± 12)	52.7 ± 11.6 (55 ± 9)	53.3 ± 13.1 (57 ± 8.5)	normal vs. overweight $p = 0.00$ normal vs. obese $p = 0.00$ overweight vs. obese $p = 1$

Table 1. *Cont.*

Variables	All Patients (n = 433)	Normal BMI 18.5–24.9 (n = 208)	Overweight BMI 25–29.9 (n = 153)	Obese BMI ≥ 30 (n = 72)	p-Value
Mean Charlson Comorbidity Index (median)	3.4 ± 1.4 (3 ± 1)	3.14 ± 1.2 (3 ± 1)	3.6 ± 1.4 (4 ± 1.5)	3.86 ± 1.7 (3 ± 1.5)	p = 0.029 normal vs. overweight p = 0.01 normal vs. obese p = 0.01 overweight vs. obese p = 1
Comorbidities					
Hypertension	322 (74.3)	147 (70.3)	121 (76.1)	54 (83.1)	p = 0.09
Diabetes Mellitus type 1 and	64 (14.8)	16 (7.7)	31 (19.5)	17 (26.2)	p = 0.0001
Coronary artery disease	65 (15)	30 (13.4)	21 (13.2)	14 (21.5)	p = 0.26
Other heart diseases [1]	44 (10.2)	26 (12.4)	13 (8.2)	5 (7.7)	p = 0.31
Benign prostate hyperplasia	22 (5.1)	7 (3.3)	11 (6.9)	4 (6.2)	p = 0.27
Thyroid disease	32 (7.4)	15 (7.2)	12 (7.5)	5 (7.7)	p = 0.98
Parathyroid disease	47 (10.9)	18 (8.6)	24 (15.1)	5 (7.7)	p = 0.09
Pulmonary disease [2]	30 (6.9)	14 (6.7)	10 (6.3)	6 (9.2)	p = 0.72
Cerebral stroke	17 (3.9)	8 (3.8)	7 (4.4)	2 (3.1)	p = 0.89
Digestive track diseases [3]	72 (16.6)	28 (13.4)	28 (17.6)	16 (24.6)	p = 0.1
Neoplasms history	29 (6.7)	13 (6.2)	11 (6.9)	5 (7.7)	p = 0.91
Hepatitis infection	34 (7.9)	21 (10)	12 (7.5)	1 (1.5)	p = 0.08
Active tobacco abuse	10 (2.3)	4 (1.9)	2 (1.3)	4 (6.2)	p = 0.08
ESKD etiology					n/a
Glomerulonephritis	151 (35.6)	83 (39.9)	49 (32)	19 (26.4)	
Diabetic nephropathy	52 (12.3)	18 (8.7)	22 (14.4)	12 (16.7)	
Hypertensive nephropathy	38 (8.9)	11 (5.3)	20 (13.1)	7 (9.7)	
Interstitial nephropathy	49 (11.6)	28 (13.5)	16 (10.5)	5 (6.9)	
ADPKD	56 (13.2)	19 (9.1)	28 (18.3)	9 (12.5)	
Other [4]	22 (5.2)	10 (4.8)	6 (3.9)	6 (8.3)	
Unknown	56 (13.2)	25 (12)	23 (15)	8 (11.1)	
Dialysis modality before KT (%)	HD 329 (76) PD 70 (16.2) PREE 34 (7.8)	HD 151 (72.6) PD 34 (16.3) PREE 14 (6.7)	HD 120 (78.4) PD 27 (17.6) PREE 16 (10.4)	HD 58 (82.8) PD 9 (11.4) PREE 4 (5.7)	p = 0.09 p = 0.16 p = 0.33
Transplantation					
2nd and 3rd KT (%)	59 (13.6)	38 (18.2)	16 (10.5)	5 (6.9)	p = 0.056 normal vs. overweight p = 0.04 normal vs. obese p = 0.02 overweight vs. obese p = 0.52
Total procedure time, mean (median; min)	181.98 (180)	176 ± 36.2 (180 ± 22.5)	181.4 ± 36.1 (180 ± 17.5)	194.4 ± 38.9 (195 ± 30.0)	p = 0.0025
WIT mean (median; min)	27.83 ± 9.3 (26 ± 4.5)	27.15 ± 10.6 (25 ± 4.5)	27.38 ± 7.0 (27 ± 4.5)	30.74 ± 9.2 (30.0 ± 5.5)	p = 0.0003
CIT mean (median; min)	922.6 ± 636 (894 ± 223)	927.0 ± 370 (903 ± 206)	899.5 ± 343 (863 ± 215)	958.7 ± 389 (935 ± 236)	p = 0.1509
Post-transplant hospitalization					
Serum creatinine mean (median) one month after KT (mg/dL)	1.575 ± 0.571 (1.52 ± 0.34)	1.474 ± 0.527 (1.360 ± 0.345)	1.596 ± 0.502 (1.545 ± 0.335)	1.838 ± 0.742 (1.750 ± 0.225)	p = 0.000 normal vs. overweight p = 0.014 normal vs. obese p = 0.027 overweight vs. obese p = 0.000
AR (%)	42 (9.7)	21 (10.04)	13 (8.5)	8 (11.3)	p = 0.36
DGF (%)	144 (33.2)	61 (29.2)	46 (30.1)	37(52.8)	p = 0.0002
Total hospitalization time (days)	21.57 ± 12.3 (18 ± 5.5)	20.19 ± 11.3 (18 ± 4.5)	21.87 ± 12.6 (19 ± 6.0)	25.04 ± 13.6 (20 ± 8.5)	p = 0.1509

Abbreviations: HD—hemodialysis. PD—peritoneal dialysis. PREE—preemptive transplantation and retransplantation. KT—kidney transplantation. AR—acute rejection. DGF—delayed graft function. WIT—warm ischemia time. CIT—Cold ischemia time. [1] Other heart diseases including: arrhythmias, valvular defects. [2] chronic obstructive pulmonary disease, asthma, sarcoidosis. [3] Peptic ulcer disease, gastroesophageal reflux disease, diverticulosis, inflammatory bowel disease. [4] Other causes of ESKD including: hemolytic uremic syndrome. amyloidosis. ESKD after nephrectomy because of cancer or after chemotherapy).

There was no difference in dialysis modality before KT between groups (Table 1). The most common form of dialysis in all groups was hemodialysis, accounting for 76% of all cases.

The underlying renal diseases in the studied group included chronic glomerulonephritis (35.6%), chronic interstitial nephritis (11.6%), diabetic nephropathy (12.3%), polycystic kidney disease (13.2%), hypertensive nephropathy (8.9%), and "not known" or "other" in about 18.4% of patients. Other causes of ESKD included hemolytic uremic syndrome, amyloidosis, ESKD after chemotherapy and nephrectomies because of cancer. Mean donor age was 48.6 years ($p = 0.05$), and mean BMI was 25.9 kg/m^2 ($p = 0.08$). There was a significant difference in both donor-recipient weight and BMI ratio, with the difference between analyzed cohorts (for BMI ratio $p = 0.00$, normal vs. overweight $p = 0.00$, normal vs. obese $p = 0.00$, overweight vs. obese $p = 0.0001$, for weight ratio $p = 0.00$, normal vs. overweight $p = 0.00$, normal vs. obese $p = 0.00$, overweight vs. obese $p = 0.013$). The right kidney was transplanted in 220 patients (50.9%) and the left kidney in 213 patients (49.1%). Single graft renal artery was present in 345 patients (79.7%). The standard immunosuppressive protocol included calcineurin inhibitor: tacrolimus in 228 patients (52.7%), everolimus in 14 patients (3.2%), cyclosporine in 204 patients (47.1%); MMF in 394 patients (91%) and glucocorticoids in all patients. Induction therapy with anti-thymocyte globulin was administered in 82 patients (18.9%).

The detailed characteristics of all studied groups of patients after kidney transplantation and the comparison between BMI cohorts are presented in Table 1.

Characteristics and comparison of intraoperative variables in the studied groups.

The average total time of procedure of KT was 181.98 ± 37.6 min, with a median of 180 min. We found significant difference in total procedure time between the three cohorts: normal BMI, overweight and obese ($p = 0.0025$). Mean and median values of total procedure time are presented in Table 1. The comparison of duration of the procedure between BMI cohorts is presented in Figure 1. The longest mean time of the procedure was observed in patients with obesity. A statistically significant difference was observed between the obese and normal weight group, no difference was observed between the normal weight group and overweight group.

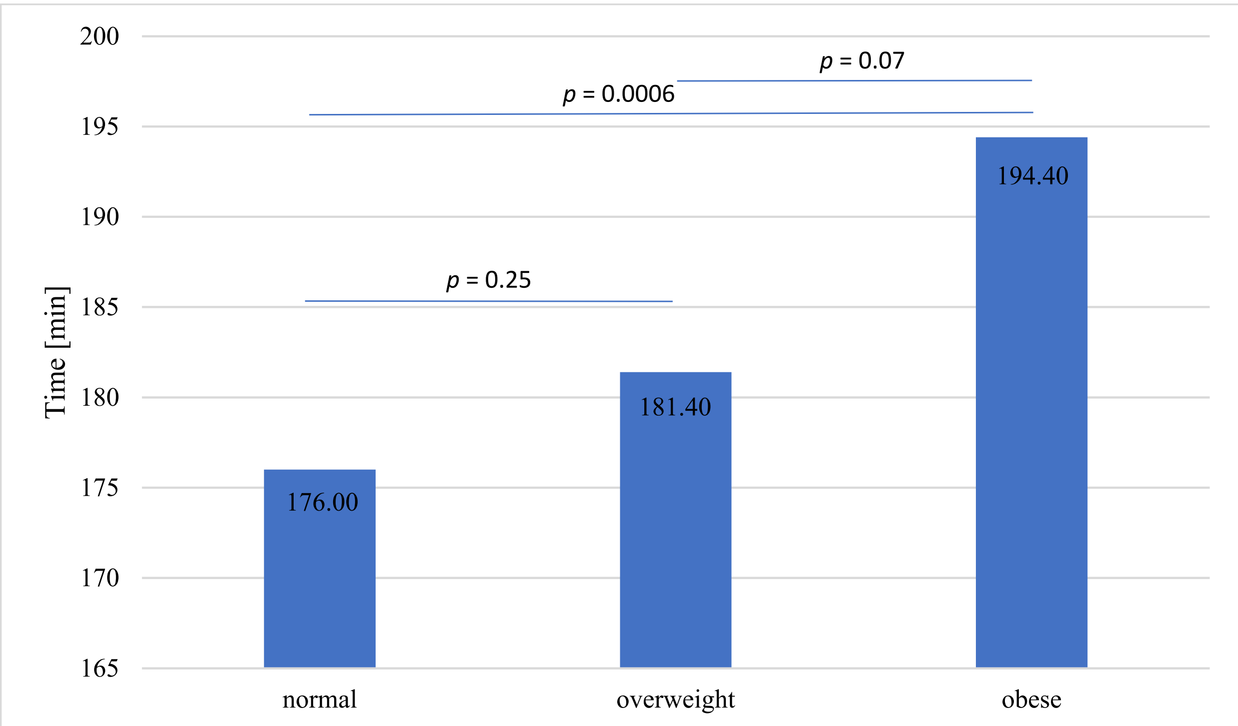

Figure 1. Total procedure time in BMI stratified groups.

Cold ischemia time (CIT) did not differ between the groups, whereas warm ischemia time (WIT) was significantly longer in the patients with obesity (Figure 2). The mean warm ischemia time was 27.827 ± 9.38 min, with a median of 26 ± 4.5 min. There was a difference between obese and overweight KTRs and obese and normal weight KTRs (p = 0.0003), whereas no difference was found between normal weight and overweight KTRs (Table 1 and Figure 2).

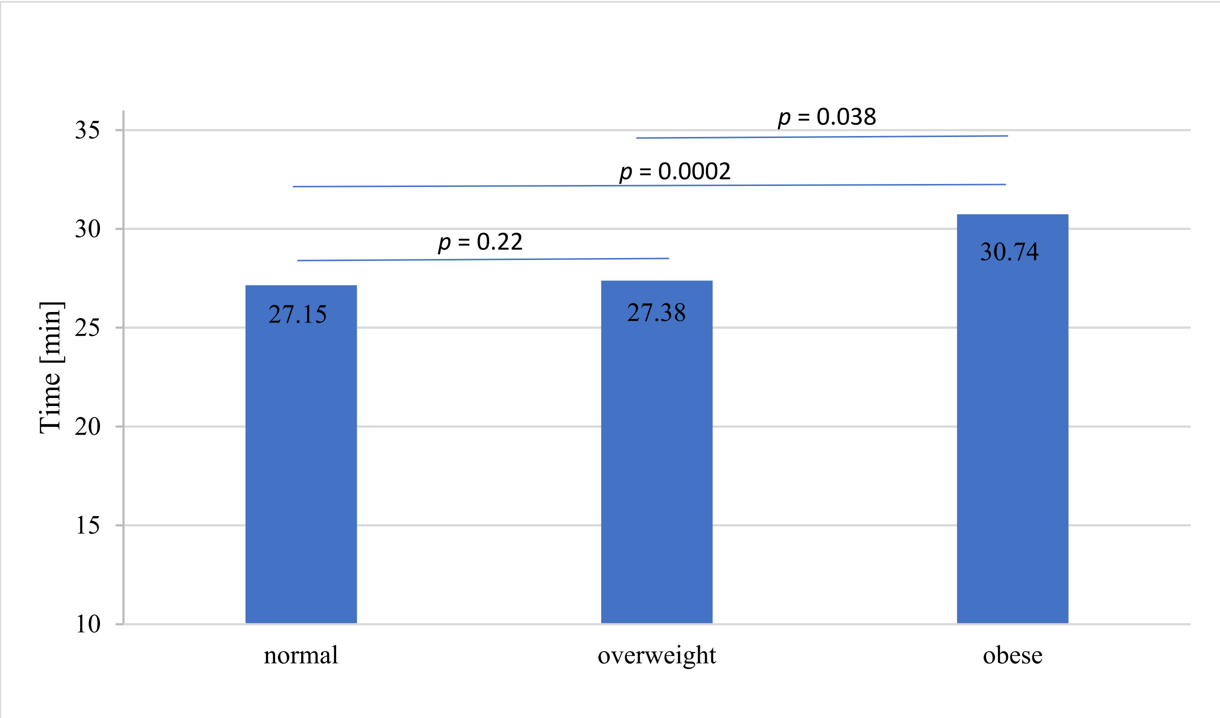

Figure 2. Warm ischemia time in BMI stratified groups.

In a gender subset comparison, obese and overweight male KTRs had significantly longer total procedure time and WIT (p = 0.039 and p = 0.007, respectively). This relationship was not present in female recipients (p = 0.29 and p = 0.42, respectively). No intraoperative deaths were reported. There was no difference in total hospitalization time between the analysed groups (p = 0.15).

The incidence of postoperative adverse events and early kidney function in BMI stratified kidney transplant recipients included forty-two cases (9.7%) of acute rejection episodes (ARE) and 144 cases (33.26%) of delayed graft function (DGF). The incidence of ARE was not different among obese, overweight, and normal weight KTRs (11.4%, 8.5%, 10.04% respectively, p = 0.36).

The groups differed significantly in respect of the DGF incidence. DGF was significantly more frequent in patients with obesity than in overweight (p = 0.0015) and normal weight patients (p = 0.0005). There was no difference between overweight and normal-weight patients (p = 0.86).

In the study group, there were 86 cases of adverse events requiring reoperation within 30 days after transplantation (19.86%).

The short-term surgical complications, reoperation rate, incidence of lymphocele, vascular complications and wound dehiscence were more frequent in obese KTRs. The analysis of postoperative adverse events stratified by type and the comparison between BMI cohorts are reported in Table 2.

Table 2. Postoperative adverse events of kidney transplantation stratified by type and BMI ($p < 0.05$ statistically significant).

Adverse Event	All Patients ($n = 433$)	Normal ($n = 209$)	Overweight ($n = 153$)	Obese ($n = 71$)	p-Value
Postoperative kidney function					
Acute rejection (%)	42 (9.7)	21 (10.04)	13 (8.5)	8 (11.3)	$p > 0.05$
Delayed graft function (%)	144 (33.2)	61 (29.2)	46 (30.1)	37 (52.1)	obese vs. normal $p = 0.0005$ obese vs. overweight $p = 0.0015$ normal vs. overweight $p = 0.86$
General adverse events					
Cardiological complications [1] (%)	20 (4.6)	9 (4.3)	8 (5.2)	3 (4.2)	$p > 0.05$
Infectious complications [2] (%)	106 (24.5)	44 (21.0)	41 (26.8)	21 (29.6)	$p > 0.05$
Posttransplant diabetes (%)	46 (10.6)	19 (9.1)	22 (14.4)	5 (7.0)	$p > 0.05$
Surgical adverse events					
Surgical complications < 30 days (%)	111 (25.65)	53 (25.3)	27 (16.3)	31 (43.7)	obese vs. normal $p = 0.0036$ obese vs. overweight $p = 0.00001$ normal vs. overweight $p = 0.08$
Surgical complications > 30 days (%)	24 (5.5)	10 (4.8)	7 (4.6)	7 (9.8)	$p > 0.05$
Reoperation (%)	86 (19.9)	37 (17.7)	23 (15.0)	26 (36.6)	obese vs. normal $p = 0.001$ obese vs. overweight $p = 0.0003$ normal vs. overweight $p = 0.4997$
Lymphocele (%)	51 (11.8)	17 (8.1)	15 (9.8)	19 (26.8)	obese vs. normal $p = 0.0001$ obese vs. overweight $p = 0.01$ normal vs. overweight $p = 0.58$
Urological complications (%)	32 (7.4)	18 (8.6)	7 (4.6)	7 (9.8)	$p > 0.05$
Wound dehiscence (%)	21 (4.8)	2 (0.96)	7 (4.6)	12 (16.9)	obese vs. normal $p = 0.0000$ obese vs. overweight $p = 0.0021$ normal vs. overweight $p = 0.0329$
Vascular complications (%)	76 (17.5)	42 (20.1)	15 (9.8)	19 (26.8)	obese vs. normal $p = 0.2398$ obese vs. overweight $p = 0.001$ normal vs. overweight $p = 0.0079$

[1] Myocardial infarct. atrial fibrillation. heart failure. [2] Urinary tract infections, pneumonia, CMV infection.

The function of the transplanted kidney one month after KT was inferior in patients with obesity. A comparison of the concentration of serum creatinine one month after KT showed significantly higher levels between all groups ($p < 0.05$), between normal versus overweight ($p = 0.014$), normal versus obese ($p = 0.027$) and overweight versus obese ($p = 0.000$), as shown in Table 1. Superior function of the transplanted kidney was observed in normal weight subjects (Table 1).

3.1. Mortality and Graft Loss after Kidney Transplantation in BMI Stratified Groups of Patients

Mean observation time was 2.15 years (range from 3 to 7 years) after KT. In this observation period, 33 (7.6%) deaths were reported. Based on above results in normal weight and overweight KTRs groups, long term results of kidney transplantation were analyzed in two groups: non-obese (BMI < 30 kg/m^2) and obese (BMI $\geq$ 30 kg/m^2) KTRs. The mortality rate did not differ between obese and non-obese KTRs: (4.3% in obese and 8.3% non-obese respectively, $p = 0.19$). There were 43 (9.9%) graft losses in follow-up. The incidence of graft loss was higher in obese patients: 17.1% versus 8.5 ($p = 0.029$). The most frequent cause of early graft loss during first year of observation was artery or vein thrombosis that accounted for 55% of recorded graft losses. The number of graft losses was higher in obese versus overweight KTRs: 17.1% in obese and 7.9% in overweight ($p = 0.009$).

In survival analysis, patients with obesity did not differ significantly with respect to 1-year patient survival compared to non-obese (normal weight and overweight) (98.5 vs. 97.8%, respectively, $p = 0.56$), and 1-year graft survival (non-censored for death)—87.1% vs. 92.6%, $p = 0.11$. One-year death-censored graft survival was better in non-obese patients (88.6 vs. 94.8% $p = 0.05$).

3.2. Univariate and Multivariate Analysis of Patient Death and Graft Loss

Based on univariate analysis, factors significantly associated with death-censored graft loss were acute rejection episode (ARE), DGF and BMI > 30. Among these factors, only ARE was a significant predictor of graft loss on multivariate analysis (Table 3).

Table 3. Univariate and Multivariate Analysis of predictors of Graft's Loss (Death Censored) in patients after kidney transplantation.

Variable	Univariate Analysis, OR (95% CI)	*p*-Value	Multivariate Analysis, OR (95% CI)	*p*-Value
Age (y)	0.997 (0975–1.02)	0.8	-	-
Gender (F/M)	2.2 (1.073–4.55)	0.69	-	-
Charlson comorbidity index	0.84 (0.664–1.076)	0.16	-	-
HD before KT	1.221 (0.565–2.637)	0.6	-	-
BMI	1.05 (0.973–1.131)	0.21	-	-
BMI > 30	2.209 (1.073–4.55)	0.04	1.9 (0.898–4.035)	0.09
ARE	2.293 (1.215–4.327)	0.005	2.9 (1.295–6.649)	0.01
DGF	2.293 (1.215–4.327)	0.001	1.84 (0.947–3.576)	0.07
WIT	1.019 (0.978–1.061)	0.4	-	-
CIT	1.0 (0.999–1.001)	0.76	-	-
KT number 1	1.051 (0.423–2.613)	0.42	-	-

Abbreviations: ARE—acute rejection episode; BMI—body mass index; CIT—cold ischemia time; DGF—delayed graft function; HD—hemodialysis; KT—kidney transplantation; WIT—warm ischemia time.

Based on univariate analysis, the age and CCI were associated with mortality. CCI was also an independent predictor of death based on multivariate analysis (OR 1.521 (1.107–2.09) ($p = 0.01$). BMI $\geq$ 30 was not a predictor of patient mortality (OR 0.505 (0.15–1.702), $p = 0.27$) (Table 4).

Table 4. Univariate and Multivariate Analysis of predictors of mortality after kidney transplantation.

Variable	Univariate Analysis, OR (95% CI)	*p*-Value	Multivariate Analysis, OR (95% CI)	*p*-Value
Age (y)	1.079 (1.04–1.119)	0.00	1.04 (0.994–1.087)	0.088
Gender (F/M)	1.167 (0.055–2.474)	0.686	-	-
Charlson comorbidity index	1.833 (1.442–2.33)	0.00	1.521 (1.107–2.09)	0.01
HD before KT	1.465 (0.588–3.653)	0.412	-	-
BMI	0.983 (0.902-1.07)	0.691	-	-
BMI > 30	0.505 (0.15-1.702)	0.27	-	-
PD before KT	0.918 (0.342–2.464)	0.863	-	-
KT number 2 or 3	0.863 (0.292–2.549)	0.786	-	-
Serum creatinine concentration mg/dL one month after KT	1.389 (0.741–2.601)	0.305	-	-
Kidney graft loss	0.921 (0.269–3.156)	0.894	-	-

Abbreviations: BMI—body mas index, KT—kidney transplantation, HD—hemodialysis, PD—peritoneal dialysis.

4. Discussion

Our study provides an exceptionally broad insight into the effect of recipient's BMI on both intraoperative and perioperative parameters in a large population of KTRs. This study is unique because, until now, little has been known about intraoperative and perioperative outcomes of KT in different BMI groups [7,9]. Our study demonstrates that the percentage of KTRs with obesity reached 16%, whereas patients with overweight constituted 36.8% of KTRs. These results reflect the trend of increasing incidence of overweight and obese KTRs observed in the literature [10,11].

Longer total procedure time and warm ischemia time are observed in patients with obesity. The results of the present study demonstrate that higher BMI ($\geq$30 kg/m^2) was associated with significantly longer total KT procedure time. Excessive BMI make KT procedure longer, technically more demanding and represent a challenge for the transplant surgeon than in normal BMI patients. What is more, this association was especially observed in males, which may be related to higher incidence of abdominal type of obesity than in females. Interestingly, we did not observe a statistically significant difference in total procedure time between normal BMI and overweight KTRs (Figure 1). Overweight patients seemed to have total procedure time comparable to normal BMI patients. This may indicate the limit of pretransplant weight loss graded by BMI to <30 kg/m^2 which can be found in current guidelines [8,12]. Significantly longer total procedure time was observed only in the obesity group, which may support the concept of pretransplant weight loss discussed in the literature [10]. Pre-transplant qualification to metabolic surgery in treatment of obesity increases access to kidney transplantation [13].

Secondly, we showed that BMI $\geq$ 30 is associated with longer warm ischemia time during the transplantation procedure. Obese KTRs have significantly longer warm ischemia times than normal and overweight patients. It was previously shown that long warm ischemic injury during vascular anastomoses in obese KTRs may contribute to induction of chronic allograft nephropathy, interstitial fibrosis, tubular atrophy and graft loss [14,15]. In the context of these data, prolonged warm ischemia present in obese KTRs is related to higher risk of chronic allograft disfunction.

In our analysis the function of the transplanted kidney was significantly inferior in patients with obesity (creatinine concentrations were 1.76 and 1.53 mg/dL in obese and non-obese respectively, p = 0.0001) after one-month observation. The best kidney function one month after KT was observed in normal weight recipients. The effect of prolonged warm ischemia time may be exacerbated by calcineurin inhibitors used in post-transplant immunosuppression [16]. Due to this fact, adequate immunosuppressive therapy may be necessary in prevention of chronic nephropathy in obese KT recipients.

There was no difference in the incidence of ARE between the BMI cohorts. The immunological risk of the patient was not related to pretransplant BMI. The most important factors related to calculation of immunological risk were the number of human leukocyte antigen mismatches, sensitization based on panel reactive antibodies, recipient age and immunosuppression regiments. In our analysis, we found a higher incidence of postoperative DGF in excessive BMI patients: 52.1% in obese and 30.1% in overweight KTRs. In BMI group analysis, a significant difference was found between the obese and normal (p = 0.0005) and obese and overweight KTRs (p = 0.0015) groups, whereas DGF rate was similar in normal and overweight KTRs (p = 0.86) groups. Large metanalyses confirm that BMI was found to be an independent predictor of a higher rate of DGF [6,17]. Another recent metanalysis (of 209,000 patients) of KTRs with BMI < 30 kg/m^2 revealed lower mortality, incidence of DGF, AR, infectious complication rate and better 1-, 2- and 3-year graft survival [7]. Additionally, DGF was found to be an independent risk factor of 1-year graft loss in metanalysis [18]. This supports the necessity of pretransplant obesity treatment in ESKD patients to lower the risk of DGF and improve graft survival.

Despite no difference in total hospitalization time between BMI cohorts in our study, in the literature obese KTRs produce higher costs of transplantation because of higher direct costs of procedure and higher readmission rates [19].

Adverse events were proved to be more frequent in obese patients. Our study demonstrates that short term surgical complications, vascular complications, impaired wound healing, incidence of lymphocele and reoperation rate were more frequent in obese than in overweight and normal weight recipients (Table 2). Additionally, the rate of surgical complications may be impacted by immunosuppression protocol. In the literature, cyclosporin A is related to higher risk of post-transplant bleeding than tacrolimus, and mTOR inhibitors are related to a higher incidence of lymphocele [20,21]. The bariatric procedure before KT is associated with significant changes of pharmacokinetics of tacrolimus and mycophenolate mofetil (increased maximal concentration and decreased clearance) [13]. Both obesity and weight loss related to metabolic surgery should be considered in planning the immunosuppression protocol in patients with obesity.

Early surgical complications after KT are usually emergent and need a rapid response to prevent the early graft loss [22,23]. They are commonly associated with reoperation and can severely affect overall graft survival [22]. Most of them are related to vascular complications, which in our cohort were observed in 17.5% of KTRs. In our analysis, early surgical complications and specific vascular complications were more common in obese KTRs (Table 2). These may expose patients with obesity to higher risk of early graft loss. In the literature, obesity (p = 0.0007) and the occurrence of intraoperative complications (p = 0.026) were independent risk factors of early graftectomy because of the graft failure [23].

Lymphocele is associated with pain and reduced renal function. Higher incidences in obese than overweight and normal weight may necessitate ultrasound guided aspiration and reoperation to drain the large fluid collection to prevent the deterioration of KT function and infection [24,25].

There is also significant association between obesity and inferior graft survival in KTRs (p = 0.029), but only in univariate analysis. In multivariate analysis, there was no significant difference (Table 3). These results are comparable with those in the literature, which makes our cohort representative. In our analysis BMI was related to inferior allograft function at discharge. These may be the result of higher post-transplant DGF incidence and higher rate of surgical complications that are related to decline in kidney function. We believe that in depth analysis of the quality of donors, as well as detailed analysis of comorbidities of the recipients, would enable improved understanding of the actual effect of BMI on the early and late results of KT.

The higher incidence of postoperative adverse events and inferior renal function in patients with obesity supports the need for pretransplant weight loss to improve the results of transplantation and reduce treatment costs. Our data highlight the course of transplantation of overweight is comparable to normal BMI KT recipients, and we believe that pretransplant weight reduction to the BMI < 30 kg/m^2 might allow a better short-term course of transplantation as well as long-term graft survival. Previous studies support the advantage of weight reduction in this group of patients [26,27]. In our previous study we proved that metabolic surgery was safe and efficient in ESKD patients [28]. Moreover, our long-term observation of graft and patient survival confirmed inferior results of transplantation in obese patients. Greater effort should be made to improve the results of KT in KTRs with obesity to improve the potential benefits of KT in that group of patients and minimize the risk.

There are considerable limitations of our study. The study was single-center, which may limit the generalizability of the results. The nature of the study was a retrospective analysis of a prospectively build database. To minimize selection bias, we included data from all consecutive transplanted patients from our institutional registry. Due to national guidelines, patients with BMI > 35 kg/m^2 should not be qualified for KT at all. Thus, our cohort of obese KTRs may be not representative if used in inter-study comparisons. Third, we used patients' BMI, which may be inappropriate in assessing obesity in ESKD patients. Due to preoperative fluid overload, and type of pretransplant renal replacement therapy, BMI may not be reflective in obesity grading in that group of patients. What is more, the number of individual complication types might have been too low to allow for sufficiently powered analysis. Thus, conclusions related to this matter cannot be drawn from this study.

5. Conclusions

In summary, kidney recipient's BMI affects significantly the intraoperative and postoperative course of the KT procedure. Patients with obesity have longer total procedure time and warm ischemia compared to normal and overweight KTRs. The function of the transplanted kidney is inferior in obese KTRs, they are at higher risk of DGF, and postoperative adverse events commonly associated with reoperation. The procedure of kidney transplantation and early postoperative course is more demanding in KTRs with obesity. Graft loss is more frequent in patients with obesity. These data suggest benefits of pretransplant weight loss in ESKD patients, aimed at achieving a body weight within at least the overweight limit to improve both early and long-term results of KT.

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ORIGINAL CONTRIBUTIONS

Weight Loss After Bariatric Surgery in Morbidly Obese End-Stage Kidney Disease Patients as Preparation for Kidney Transplantation. Matched Pair Analysis in a High-Volume Bariatric and Transplant Center

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Abstract

Background The number of morbidly obese kidney transplant candidates is growing. They have limited access to kidney transplantation and are at a higher risk of postoperative complications. Bariatric surgery is considered as a safe weight loss method in those patients.

Objectives Matched pair analysis was designed to analyze the preparatory and postoperative weight loss after bariatric procedures in end-stage kidney disease (ESKD) and non-ESKD morbidly obese patients.

Methods Twenty patients with ESKD underwent bariatric surgery in our Centre of Excellence for Bariatric and Metabolic Surgery between 2015 and 2019 (nine one-anastomosis gastric bypasses, nine Roux-en-Y gastric bypasses, and two sleeve gastrectomies). They were compared with matched pairs from a dataset of 1199 morbidly obese patients without ESKD. Data on demographic factors and comorbidities was recorded. BMI was obtained at the start of the preparatory period preceding the bariatric procedure, at the time of procedure, and during the 1-year follow-up.

Results The ESKD and non-ESKD patients did not differ significantly in preoperative weight loss (13.00 ± 11.69 kg and 15.22 ± 15.96 kg respectively, $p = 0.619$). During the 1-year follow-up, the weight loss was similar to the non-ESKD group. In the first 3 months, faster weight loss in ESKD was observed. Initial and follow-up BMI values did not differ significantly between groups. We demonstrated that obese patients with ESKD can lose weight as effectively as non-ESKD patients.

Conclusion Morbidly obese ESKD patients have an equal weight loss to patients without ESKD. Bariatric surgery could improve access to kidney transplantation and may potentially improve transplantation outcomes of obese patients with ESKD.

Keywords Bariatric surgery · Kidney transplantation · End-stage kidney disease · Weight loss

Introduction

Obesity is a growing problem worldwide. The prevalence of obesity has doubled since 1980, and now, nearly a third of the world's population is classified as overweight or obese. Obesity is associated with numerous comorbidities including diabetes type 2, peripheral vascular disease, cardiovascular disease, asthma, and osteoarthritis and was shown to be an independent risk factor for developing an end-stage kidney disease (ESKD) [1, 2]. Moreover, the relative risk correlates with a higher body mass index (BMI). The risk of ESKD progression was also increased by obesity [3]. Due to the obesity epidemic, the number of obese transplant candidates has also increased. Nearly 60% of all kidney transplant recipients are overweight or obese with male predominance [4]. It was proven that obesity limits, or at least delays, access to kidney transplantation [5]. Bariatric surgery is considered a safe method to achieve rapid and sustainable weight loss before kidney transplantation [6]. Pretransplant weight loss may

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allow to sustain body weight and prevent common post-transplant weight gain [7]. In the current study, we compare the preoperative and postoperative weight loss in patients with ESKD with matched controls without ESKD treated with bariatric surgery in a high-volume bariatric and transplant center.

Subjects and Methods

We have compared retrospectively the dynamics of weight loss of patients with and without ESKD who underwent bariatric surgery in a large bariatric and transplant center. In our institutional registries, 20 patients with ESKD were treated for morbid obesity between 2015 and 2019. ESKD was defined as the presence of an estimated glomerular filtration rate less than 15 mL/min/1.7 m^2 [8].

For the purpose of this analysis, patients were matched for age, gender, and type of surgery with 20 patients without ESKD from our institutional dataset of 1199 patients. Matching was executed in a 1 to 1 ratio based on data queries. Data analysis included patient's demographics. The ESKD patients (14 males, 6 females) were between 42 and 64 years of age. The non-ESKD group consisted of 14 males and 6 females between 42 and 64 years of age. Body weight (kg) and body height (m) were used to calculate BMI. All patients were qualified to bariatric procedure according to IFSO guidelines after a multidisciplinary consultation [9]. Patients were qualified to surgery if their BMI exceeded 40 kg/m^2 or they had BMI between 35 and 40 kg/m^2 with significant comorbidities. The preoperative diet plan is exercised under the supervision of a dietitian. It is designed to give approximately 100 g of carbohydrate per day, low in fat and moderate in protein. The energy value of the diet is between 800 and 1000 kcal per day. Two weeks before surgery, a liver-shrinking diet (600 kcal per day) was administered. ESKD patients had consulted with a nephrologist and undergone hemodialysis without heparin 1 day before surgery and on postoperative day 1. They do not require distinctions in anesthesia compared with the non-ESKD group. Postoperatively, routine thromboembolism prophylaxis with dalteparin sodium (5000 IU subcutaneous) was conducted except on the days with hemodialysis. The maximal BMI was calculated from maximal body weight at the start of the preparatory period for bariatric treatment. The initial BMI was calculated from the weight at the time of surgery after an obligatory weight loss period with the low-calorie diet. Three bariatric procedures were performed according to our institutional regulations by the same surgeons [10]. The follow-up measurements were performed during routine follow-up in the outpatient department 1, 3, 6, and 12 months after surgery.

Weight loss was reported according to the American Society for Metabolic and Bariatric Surgery (ASMBS) guidelines [11]. The change in BMI (ΔBMI) was calculated according to the formula = (initial BMI) − (postoperative BMI on each follow-up point). The % of reduction of BMI was calculated according to the formula = follow-up BMI/initial BMI × 100% on each follow-up point. The percentage of excess BMI loss (%EBMIL) was calculated using the formula = [ΔBMI/(Initial BMI − 25)] × 100% [11]. In the preparatory period, we used maximal BMI to calculate %EBMIL.

Statistical Analysis

Statistical analyses were performed using the Statistica 13.3 Software (TIBCO Software Inc.). Data was presented as mean ± standard deviation. The Chi^2 and t-tests were used for comparisons. Statistical significance was considered for $p < 0.05$. The graphs were drawn in the Microsoft Excel software.

Results

Baseline demographic characteristics of the patients are presented in Table 1.

ESKD Group

The ESKD patients' mean maximal weight was 128 ± 18.5 kg and was reduced to 115 ± 14.5 kg preoperatively. In the preparatory period, a 10% reduction of body weight was achieved. Mean maximal BMI was 42.8 kg/m^2; the initial BMI was 38.5 kg/m^2. In the baseline characteristics of ESKD, a higher incidence of hypertension was noted (70% vs 35%, $p = 0.027$). OAGB (one-anastomosis gastric bypass) was performed in 9/20 patients (45%), RYGB (Roux-en-Y gastric bypass) in 9/20 patients (45%), LSG (laparoscopic sleeve gastrectomy) in 2/20 patients (10%). In the ESKD group, one serious complication on the first postoperative day after OAGB was noted. The patient required revision surgery for a leak at the gastrojejunal anastomosis, which was identified and sutured. In ESKD patients, the length of hospital stay was 3.8 ± 0.5 day (excluded one case with LOS of 26 days).

Matched Non-ESKD Group

The non-ESKD patients' mean maximal weight was 131.5 ± 20.5 kg and was reduced to 116.3 ± 14.5 kg preoperatively. In the control group, a 12% reduction of weight was achieved, compared with 10% in the study group ($p = 0.619$). Mean maximal BMI was 43.6 kg/m^2; the initial BMI was 38.4 kg/m^2. There were no surgical complications in that group. The LOS was 2.1 ± 0.5 day.

Table 1 Baseline demographic characteristics of the patients

	ESKD group ($n = 20$)	Non-ESKD group ($n = 20$)	p*
Gender (male/female)	70/30%	70/30%	n/a
Dialysis type			
Hemodialysis	16 (80%)	0	n/a
Peritoneal dialysis	2 (10%)	0	n/a
Preemptive	2 (10%)	0	n/a
ESKD etiology			
Diabetes mellitus	4	0	n/a
Hypertension	3	0	n/a
Glomerulonephritis	4	0	n/a
ADPKD	3	0	n/a
Unknown	6	0	n/a
Comorbidities			
Hypertension	14 (70%)	7 (35%)	0.027
Diabetes mellitus type 2	12 (60%)	10 (50%)	0.525
Hyperlipidemia	5 (25%)	2 (10%)	0.212
Coronary disease	6 (30%)	0	
Obstructive sleep apnea	2 (10%)	1 (5%)	0.548
Gastrointestinal reflux disease	3 (15%)	3 (15%)	1
Chronic obstructive pulmonary disease	4 (20%)	1 (5%)	0.340
Cardiac rhythm abnormalities	4 (20%)	0	
Previous surgeries	12 (60%)	10 (50%)	0.751

*Chi^2 test was used for all comparisons

Comparisons

The maximal weight did not differ significantly between ESKD and non-ESKD groups (128 ± 18.5 kg vs 131.5 ± 20.5 kg respectively, $p = 0.583$). The maximal BMI did not differ significantly (43.2 kg/m^2 vs 43.6 kg/m^2 respectively, $p = 0.66$). The change in BMI in the preparatory period was similar between the groups (4.36 vs 5.13 respectively, $p = 0.6$). The characteristics of follow-up measurements were presented in Table 2.

Bariatric surgery resulted in weight loss compared on four follow-up points. The comparison of %EBMIL in ESKD and non-ESKD patients is illustrated in Fig. 1.

Discussion

In this study, we have demonstrated that ESKD patients can achieve substantial weight loss comparable with non-ESKD patients during surgical treatment of morbid obesity as preparation to kidney transplantation. This was to our knowledge never demonstrated in a matched pair analysis. The aim of this study was to evaluate weight loss in the preparatory period, and after bariatric surgery, in morbidly obese patients with ESKD before kidney transplantation, compared with non-ESKD morbidly obese patients.

In the literature, the most frequent cause for non-inclusion into the transplant waiting list is attributed to obesity (up to 30%) [12]. Based on the analysis of 19,524 dialysis patients, patients with BMI ≥40 kg/m^2 were half as likely to undergo kidney transplantation than those with a BMI between 21 and 31 kg/m^2 [5]. Several obesity treatments were proposed. Those including behavioral modification (physical activity, dietary modification) result only in a mean of 5 to 15% weight loss, and that result was maintained only in 5.3 to 10.5% of participants during a 1-year observation [13]. Similarly, psychosocial interventions such as group-based diet, group physical activity are related to a 3.5-kg weight loss in 6 months (95% CI, − 4.2 to − 2.8) and 3.4 kg in 12 months (95% CI, − 4.2 to − 2.9) [14]. Among all weight loss intervention, surgical treatment was considered the most effective. Our results present significant reduction of BMI, similar to matched pairs without ESKD in the 1-year follow-up (Table 2). In other studies, patients undergoing RYGB lost 29.9% (95% CI, 29.3–30.5%) more of their baseline weight at the 1 year follow-up than the non-surgical matches [15]. For LSG, 1-year weight loss was 23.4% (95% CI, 21.8–24.7%) [15]. As compared with behavioral modifications, reduction of BMI at 1 year was − 11.3 kg/m^2 for OAGB, − 10.1 kg/m^2 for sleeve gastrectomy (SG), and − 9.0 kg/m^2 for RYGB [16]. The achieved weight loss was maintained for a long time (28.6% (95% CI, 19.5–37.6%) of their initial weight at 10 years) [15].

Table 2 Weight loss in ESKD and non-ESKD patients

	ESKD group	Non-ESKD group	*p*
Maximum BMI (mean/median)	43.2/43.5	43.6/41.5	0.663
Initial BMI (mean/median)	38.7/37.9	38.4/37.9	0.973
ΔBMI	4.36	5.13	0.608
Percentage BMI loss	10%	11%	0.640
%EBMIL	22%	25%	0.650
Follow-up visit 1 month after surgery ($n = 20/20$)			
BMI	33.8/33.5	34.3/34.2	0.883
ΔBMI	4.4	4.1	0.763
Percentage BMI loss	11%	10%	0.651
%EBMIL	33%	30%	0.586
Follow-up visit 3 months after surgery ($n = 18/20$)			
BMI	24.8	32/32	0.073
ΔBMI	8.4	6.5	0.077
Percentage BMI loss	22%	17%	0.038
%EBMIL	65%	49%	0.032
Follow-up visit 6 months after surgery ($n = 18/18$)			
BMI	22.8	29.4/29.4	0.151
ΔBMI	10.3	8.6	0.228
Percentage BMI loss	27%	22%	0.126
%EBMIL	79%	66%	0.100
Follow-up visit 12 months after surgery ($n = 14/17$)			
BMI	28.9	29.4/29.4	0.748
ΔBMI	12.3	9.4	0.275
Percentage BMI loss	25%	24%	0.716
%EBMIL	90%	68%	0.190

n = number of patients in ESKD and non-ESKD group respectively

Those studies have shown that bariatric surgery not only can allow a 1-year substantial weight loss but also is the most effective way of achieving sustained weight reduction in obese patients [16]. The type of surgical procedure of choice in ESKD patients is still discussed. Our patients were qualified to a specific type of weight loss surgery according to the IFSO guidelines for the general population, which may in turn be inappropriate for ESKD patients [9]. Over the years, SG has

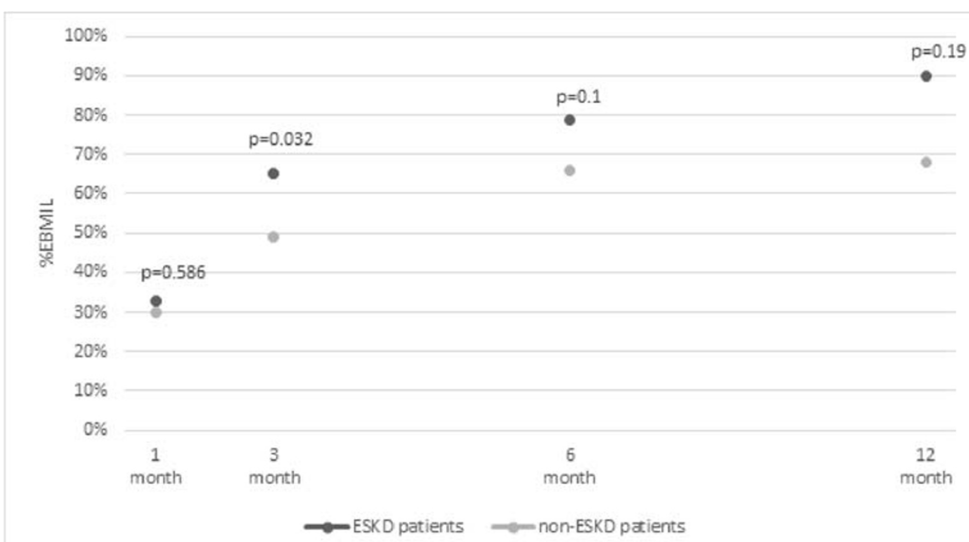

Fig. 1 The comparison of the percentage of excess BMI loss after bariatric surgery between ESKD and non-ESKD patients ($p < 0.05$ statistically significant)

replaced RYGB in that group of patients because of its relatively safe profile [17, 18]. Our national practice guidelines are not following those recent results [19, 20]. In morbidly obese patients with the indications for intestinal bypass methods, OAGB and RYGB were successfully implemented with the caution of hyperoxaluria presence during the rapid weight loss period and the risk of nephrolithiasis [21]. ESKD obese patients often fail to non-surgical intervention and are considered refractory to behavioral therapy. Bariatric surgery offers them not only a decrease in BMI but also an improvement of the altered kidney function and deceleration of the progression of renal diseases in patients with ESKD of various etiologies. Our matched pair analysis resulted in comparable weight loss in the preparatory period before bariatric surgery. Pretransplant renal replacement therapy of ESKD can influence the ability of patients to adhere to preoperative period weight loss instructions (i.e., steroids, osteoporosis) [22]. Despite those burdens, the results of the preparatory period did not differ significantly between the compared groups. They achieved − 4.36% and − 5.13% BMI loss in the preparatory period respectively, $p = 0.608$. The ESKD patients lost 21.78% of excess BMI and non-ESKD lost 24.53% EBMI. Moreover, our ESKD patients strictly meet the mandatory weight loss criteria (the median preoperative total weight change was − 10.2% and − 11.6% in the ESKD and non-ESKD groups respectively; $p = 0.619$) [23]. The preparatory weight reduction was not impaired by comorbidities (in our material, no statistical difference between groups except from hypertension). In the literature, a satisfactory preoperative weight loss correlates positively with postoperative weight loss as well as weight loss after 1 year [24, 25]. Moreover, successful preoperative weight loss is associated with a significant decrease in perioperative complications in a systematic review on 4611 patients (2 studies on 1234 patients) [25].

In our study, ESKD patients have comparable postoperative weight loss to non-ESKD obese patients (Fig. 1). The groups did not differ significantly in postoperative weight loss measured during the 1-year follow-up (1-year BMI was 28.9 kg/m^2 vs 29.4 kg/m^2, $p = 0.748$ and %EBMIL 90.5% vs 67.5%, $p = 0.190$ in ESKD and non-ESKD patients respectively). This fact indicates the possibility of safe and effective weight loss similar to non-ESKD. Although in the literature ESKD patients experienced a higher risk of postoperative complications compared with those without kidney disease, the absolute complication rates were low and bariatric treatment is considered safe in that group of patients [26]. Interestingly, in our study, the weight loss and decrease in BMI are significantly higher in the first month following bariatric surgery. This can be related to changes in plasma adipocytokines following surgery and a positive correlation with lowering insulin resistance in ESKD patients [27]. Moreover, ESKD patients in that period lost more excessive weight and the relative cardiovascular risk is starting to decline faster than non-ESKD patients. It was proven that weight loss is related to remission of diabetes (remission rate up to 61%), low-density lipoproteins (73%), and blood pressure (63%) [28, 29]. Not only weight loss but also resolution of ESKD-related comorbidities (diabetes mellitus, hypertension, hyperlipidemia, coronary heart disease, sleep apnea) is associated with metabolic and clinical benefits and lowers the risk of kidney transplantation.

According to the European Renal Best Practice Guideline recommendations, patients with a BMI > 30 kg/m^2 should reduce weight before transplantation [19]. Literature data on the association of obesity and post-transplant graft function is conflicting. It was proven that obesity was associated with a higher risk of delayed graft function, graft loss, and lower patient and graft survival, but interestingly, obese individuals without comorbidities can experience similar survival to non-obese recipients [30–32]. However, often due to obesity-associated comorbidities, their access to the transplant list and transplantation is inferior to non-obese [5, 33]. Bariatric surgery is considered as a safe method of obesity treatment in that specific group of patients and feasible as a bridge therapy to kidney transplantation [6, 34–36]. Additionally, weight loss after bariatric surgery may improve kidney function to an acceptable level and delay the qualification to dialysis therapy in patients undergoing bariatric surgery before ESKD development. It was proven that weight loss resulted in an improvement of proteinuria and albuminuria and normalization of the glomerular filtration rate [22]. For dialyzed ESKD patients, bariatric surgery can slow the progression and allows them to stay on the transplant waiting list. Eight of our patients were already successfully transplanted within a few months up to 3 years after bariatric surgery. The optimal interval between the bariatric procedure and kidney transplantation has not been established yet. Long-term follow-up after bariatric surgery can be important in setting the optimal time of transplantation in obese ESKD patients. Furthermore, pretransplant weight loss as a result of bariatric surgery can improve the prehabilitation process before kidney transplantation, and as a result improve the functional and physiological capacity for a fast recovery sooner after kidney transplantation. Larger, long-term studies are needed to analyze the durability of this improvement and the effects on renal transplantation outcomes.

Our study has the following limitations. First, the results need to be interpreted acknowledging that the effects of surgery may vary, based on the characteristics of the individual patient, i.e., age, sex, and pre-surgery BMI comorbidities. Second, the group size was small, and the analysis was performed retrospectively. Although we matched patients for type of bariatric procedure performed, there are many factors related to specific procedure qualifications which may impact upon the results. Third, follow-up was limited to 1 year, thus long-term results of bariatric surgery in that group of patients were not analyzed. Lastly, three different bariatric procedures are included in analysis, which blurs the difference of outcome related to procedure type [37]. Research aimed to indicate the most effective type of bariatric surgery in ESKD patients is needed.

Conclusion

Successful kidney transplantation requires elimination of possible pretransplant risks. Obesity is related to a higher risk of intra- and postoperative complications. Morbidly obese kidney transplantation candidates benefit from bariatric surgery and can be eagerly included in bariatric surgery weight loss programs. Bariatric surgery allows efficient pre-transplantation weight loss results, and the procedures in ESKD patients seem as safe as previously published.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval Statement For this type of study, formal consent is not required.

Informed Consent Statement Informed consent does not apply.

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REVIEW ARTICLE

Obesity in work-up of kidney transplant candidates – review of clinical practice guidelines

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Abstract

Background: Incidence of morbid obesity is rising worldwide. Current clinical practice guidelines for the pre-transplant evaluation of end-stage kidney disease (ESKD) patients lack clear recommendations on morbid obesity. **Material and methods:** The aim of this review was to summarize the current guidelines on the role and treatment of obesity in kidney transplant recipients. Eight current national and international clinical practice guidelines were identified in a comprehensive literature search. **Results:** All guidelines underline early detection of obesity and obesity-related comorbidities in ESKD patients. Only two guidelines explored the role of weight-loss surgery, however due to the lack of sufficient evidence no formal recommendation of surgical procedure was given. **Conclusions:** Diagnosis and treatment of obesity remains underappreciated in the current guidelines, most of which do not include pharmacological and surgical interventions. High-quality evidence is warranted to assess the role of weight-loss including surgery in ESKD patients and to update the recommendations in future guidelines.

Keywords: obesity · end-stage kidney disease · bariatric surgery

Citation

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Introduction

The number of obese and morbidly obese end-stage kidney disease (ESKD) patients is rising. Due to the obesity epidemic, nearly 60% of all kidney transplant recipients are overweight or obese, with male predominance [1]. Kidney transplantation (KT) is the most effective method of ESKD treatment but it is still a debatable whether obese patients are suitable candidates for KT [2-6]. Clinical practice guidelines (CPGs) review current research and formulate recommendations based on available evidence and expert opinion. Clear guidance regarding obesity assessment and treatment options would be an essential part for the selection process of candidates for KT. The aim of this review is to assess the availability, quality, and consistency of recommendations for obesity evaluation and treatment before KT included in current national and international CPGs for kidney transplant candidates.

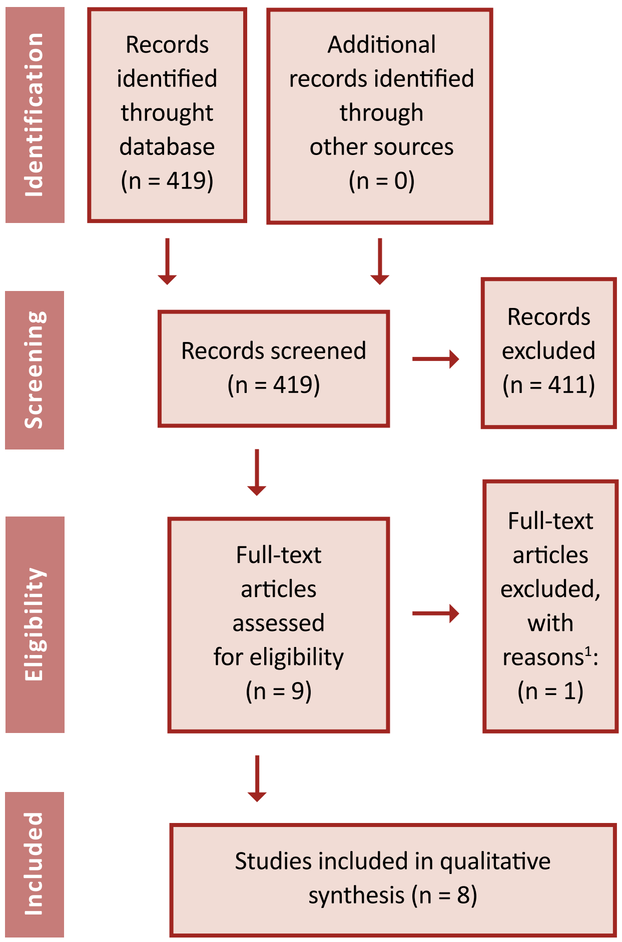

Figure 1. PRISMA flowchart.[1] Clinical Practice Guideline excluded due to lack of recommendation for inclusion to kidney transplantation [7].

Material and methods

A systematic review was performed according to Preferred Recording Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [7]. The search strategy included literature published until January 2020, using the following search query: ("kidney transplantation" OR ("kidney" AND "transplantation" OR "kidney transplantation" OR ("kidney" AND "transplant") OR "kidney transplant") AND ("Assessment") AND ("guideline" OR "guidelines"). Two researches independently searched and assessed the guidelines. We included only CPGs for the selection of candidates for deceased donor kidney transplantation. CPG for living donor kidney transplantation were excluded after screening due to identification of recommendation for obesity only in kidney donors [8-9]. The study protocol was presented in PRISMA flowchart (Figure 1). The following data were extracted: society, year of publication, inclusion of obesity into recommendation, recommendations for obesity treatment and grade of evidence.

Results

The literature search revealed 419 articles. A total of 411 were excluded during screening of titles and abstracts. The remaining 8 CPGs were searched for obesity evaluation recommendations. Key facts about the included studies are summarized in Table 1.

Recommendations for obesity evaluation before kidney transplantation

Three CPGs recommended that obesity should be routinely assessed at each pre-transplant consultation [10-12]. The included measurements should be as follows: patients height, weight, calculation of BMI. Additionally, waist circumference should be assessed when weight and physical appearance suggest obesity, but calculated BMI is < 35 kg/m^2 [10]. The definition of obesity in adults includes waist circumference ≥ 102 cm in men and ≥ 88 cm in women [11]. Two guidelines recommended weight reduction before transplantation if BMI exceeds 30 kg/m^2 [12-13]. One study set the upper limit of BMI to 40 kg/m^2 [14]. Another CGP states that in patients with BMI > 36 kg/m^2 the transplantation is associated with an unacceptably high risk of death and needs careful consideration [12]. All CPGs state that obesity of the kidney recipient byitself is not a contraindication for KT, however if co-existing with other comorbidities (e.g. advanced cardiovascular diseases, peripheral vascular

Table 1. Obesity in current clinical practice guidelines

Guidelines	Region	Obesity in candidates for transplantation	Recommendation in obesity
AST (2001)	USA	Obesity without comorbidities* is not a contraindication for KT (Level of evidence not provided).	Weight reduction (role of limited exercise in dialyzed patients) (Level of evidence not provided).
Canadian Society of Transplantation (2005)	Canada	Obesity without comorbidities is not a contraindication for KT (Grade C). In patients with BMI > 36 kg/m² KT is contraindicated.	• Weight reduction to BMI < 30 kg/m² • Surgical intervention for obesity may be considered in extreme cases (Grade B)
Bunnapradist & Danovich (2007)	USA	In patients with BMI > 40 kg/m² KT contraindicated.	Weight reduction (the benefit is unclear, method not specified) (Level of evidence not provided).
Lisbon Conference Report (2007)	Europe	In morbidly obese KT is contraindicated (BMI not applicable) (Level of evidence not provided).	No recommendation
KDIGO (2009)	Interna-tional	In patients with BMI > 30 kg/m² KT is contraindicated.	• Early diagnosis of obesity (Level of evidence not provided). • Obese individuals should be offered a weight-reduction programme (Level of evidence not provided). • Diet and other behavior modifications are safe in KT recipients (Level of evidence not provided. • Bariatric surgery may be performed safely in selected KT recipients (Level of evidence not provided).
KHA-CARI (2013)	Australia	No recommendation	• Obesity should be assessed at each visit (Grade C). • Diet and behavioral modification are likely to be safe. Diet that is individually planned with a moderate energy restriction of about 30% of energy expenditure, with monthly follow up with a dietician (Level of evidence not provided). • There is insufficient evidence to make recommendations or suggestions with respect to bariatric surgery (Level of evidence not provided).
European Renal Best Practice Guideline (2015)	Europe	BMI > 30 kg/m² is a contraindication for KT (Level of evidence not provided).	Obese patients should reduce weight before KT (Level of evidence not provided).

* advanced cardiovascular, peripheral vascular, liver or pulmonary disease, HIV, active hepatitis, active pulmonary or systemic tuberculosis

diseases, liver or pulmonary disease, active hepatitis) it increases the risk of perioperative complications and may impair graft and patient survival [12, 15].

Recommendations for diet and behavioral therapy

These therapies were considered safe in ESKD population but they were related only to a short-term weight reduction [10]. Only one study clearly stated that overweight kidney transplant recipients should have an individually-planned diet with a moderate energy restriction of about 30% of energy expenditure, with dietician follow-up [11]. It recommended also to create a caloric deficit of 500-1000 kcal/day along with increased physical activity [11].

Recommendations for pharmacological obesity therapies

The analyzed CPGs briefly discussed the role and the risk of novel pharmacological weight reduction therapies [10-11]. There were no trials examining the safety of those interventions in this specific population. Two medications (orlistat and sibutramine) were mentioned in recommendations [10-11]. Orlistat is related to decreased absorption of fat-soluble vitamins and may also interfere with the absorption of immunosuppressive medications and may be associated with higher risk in ESKD patients [10]. Sibutramine may increase blood pressure and heart rate and is not advised in patients with cardiovascular risk [10].

Recommendations for bariatric surgery

Little was mentioned about bariatric surgery in the current CPGs. Two of eight CPGs recommend weight-loss surgery before kidney transplantation [10-11]. However, the quality of existing evidence was insufficient to form recommendations about qualification, procedure type or procedure timing (i.e. before or after the KT).

Discussion

The prevalence of obesity among patients with ESKD continues to increase. Obesity was shown to be an independent risk factor not only of the ESKD development but also to accelerate the progression of that disease [5]. Kidney transplantation is considered as gold standard in ESKD treatment. Obesity is now limiting the access to KT by delaying the enrollment to transplant list and prolonging the waiting time compared to the nonobese candidates [16-17]. Additionally, obesity is associated with inferior short-term results of transplantation [3, 5].

Current CPGs are consistent regarding a strong need of early obesity assessment before enrollment to transplant waiting list. Most guidelines use BMI to assess obesity for waiting listing purposes [10, 13, 18]. BMI < 30kg/m^2 prior transplantation is recommended but in some studies BMI below 35kg/m^2 is considered a selection criterion [19-20]. The limitations of BMI as a metric of body fat must be appreciated. Anthropometric measures (waist circumference and waist-to-hip ratio (WHR)) are considered as an alternative to BMI in body composition assessment. These measures were shown to have a direct association with increased cardiovascular mortality in dialyzed ESKD patients as well as post-transplant mortality more precisely than BMI [21-22]. The existing guidelines are based on available original studies at the time of their publication. All current clinical practice guidelines were published before 2015. The role of diet and pharmacological treatment was poorly discussed but the level of evidence is sufficient to consider them safe for kidney transplant candidates [10-11]. The surgical treatment of obesity was not included in most CPGs due to limited evidence on safety and outcomes of bariatric procedures at the time of their publication. Only two CPGs mentioned possible implementation of bariatric surgery in that indication [11-12]. Since then several large studies were published giving new insights into the management of obese ESKD patients [23-25]. The results of these studies are presented below. It is likely that these data will be included in new editions of CPGs.

Based on the current knowledge, the use of pharmacological interventions for the treatment of obesity is limited in ESKD patients. First, orlistat use in patients with chronic disease is contraindicated because of its association with acute kidney injury and chronic kidney disease due to increased absorption of oxalate and the risk of nephrocalcinosis, inflammation and kidney fibrosis as a result [26-28]. Moreover, post-transplant drug interaction, particularly with cyclosporin, results in reducing their bioavailability and limits its use [29]. Secondly, sibutramine was withdrawn from the obesity treatment due to unacceptable increased cardiovascular risk [30]. A newer drug lorcaserin, is associated with potential kidney benefit, but limited to the lower risk of new-onset of albuminuria. Its use in ESKD patients is contraindicated due to worsening of chronic kidney disease stage [31-32]. Bupropion, likewise, should not be used in ESKD patients [32-33].

The role of physical activity was discussed in only one guideline [11]. Research has shown that pre-

-transplant aerobic exercise, long-term progressive resistance exercise, resistance training, and home-based exercise are tolerable in patients with ESKD [34-35]. Interestingly, the aerobic exercise is not related to weight reduction but has an positive impact on dialyzed patients' quality of life [36]. After transplantation, aerobic exercise, resistance training and individualized progressive exercise programs are effective in weight-loss programs [34].

Feasibility and safety of bariatric surgery is currently investigated and discussed. A recent study has shown an increasing number of patients with ESKD undergoing bariatric surgery as a bridge to KT [23]. Nevertheless, no consensus was reached regarding the management options for obese KT candidates. It was previously believed that bariatric surgery use in ESKD patients may be limited because of higher mortality risk. However the safety and significance of weight loss surgery in ESKD patients increased over the years [25, 37-39]. Two bariatric procedures were preferred [23, 40]. LSG (laparoscopic sleeve gastrectomy) and LRYGB (laparoscopic roux-en-y gastric bypass) appear to cause effective weight-loss before KT and improve surgical access during transplantation [41-42]. Uncertainties exist regarding optimal timing of bariatric surgery [38]. It has not been proven yet if the bariatric procedure should be performed before or after engraftment. Both approaches are related to low risk of graft failure and low mortality in long-term analysis when compared to the mortality rate of obese patients without ESKD [43]. Complication rates of LSG were similar between patients with and without ESKD [23, 44]. It should be noticed that LSG performed before transplantation is associated with significant changes of pharmacokinetics of tacrolimus and mycophenolate mofetil (increased maximal concentration and decreased clearance) in that group of patients [45]. Whereas malabsorptive procedures are related to hyperoxaluria and increased risk of nephrolithiasis [46].

Interestingly, an obesity paradox was described in dialyzed patients [47-48]. It is associated with better survival of obese patients who were transplanted than all patients who stay on transplant waiting list. Howver these results may be confounded by worse outcome of malnourished ESKD patients [47, 49-50]. Moreover, obesity reduces the likelihood of being enrolled to the waiting list, but not the transplantation once enrolled, especially among women [17].

Recent large metanalyses support higher risk of KT of obese patients and better survival in lower BMI patients [51-53]. It was proven that kidney recipients have an inferior survival when their BMI is > 40 kg/m^2 [19, 54]. Recent metanalysis (of 209,000 patients) revealed lower mortality, delayed graft function (DGF), acute rejection, infectious complication rate and better 1-, 2- and 3-year survival in kidney recipients with BMI < 30 kg/m^2 [52]. In another metanalysis (17 studies, 138081 patients) obesity was demonstrated not to be related with higher mortality risk but was associated with higher risk of graft loss and DGF [53]. A metanalysis of 9296 patients confirmed higher risk of DGF but not acute rejection and death risk [55]. The results of those analyses support the necessity of obesity treatment in ESKD patients. Several studies investigated the benefits and risk of bariatric surgery in that group of patients [24, 56-58]. Laparoscopic SG has replaced Roux-en-Y gastric bypass (RYGB) as the most common bariatric surgical procedure in patients with ESKD [23]. SG in ESKD patients is not related to higher risk of leaks, reoperations, or mortality in 1 year follow-up [59]. Our center morbidly obese ESKD patients have similar weight loss results after bariatric procedure than non-ESKD [42, 44]. Nine of twenty of them underwent kidney transplantation without any perioperative complications and with good kidney function in follow-up. Patients who underwent KT after SG have good 1-year and long term transplantation results in small group analysis [58]. Morbidly obese patients after LSG experienced lower rates of DGF and readmission related to graft insufficiency in 1 year follow-up [58]. The mortality rate of obese individuals with ESKD after SG is lower (1.8/100 patient-years compared to 7.3 in the control group) [60]. Moreover, in stage 3 CKD significant improvement of kidney function was observed [60]. The emerging evidence from those studies supports the low risk and safety of bariatric surgery in ESKD patient.

Conclusion

In conclusion, the obesity epidemic has major implications on kidney transplant candidates' evaluation. In existing CPGs there is a consensus regarding the need of obesity assessment in transplant candidates. However, most of the evaluated CPGs are inconclusive concerning the role of pharmacological and surgical interventions for the treatment of obesity. New large-scale studies seem to be the missing link that suggests clear recommendations for obese patients' management. It seems necessary to update the guidelines with results of recent studies on the new measures in the assessment of obesity and its treatment, with special attention to surgical treatment.

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