GDAŃSKI UNIWERSYTET MEDYCZNY

Analiza klinicznych i metabolicznych efektów One Anastomosis Gastric Bypass

Analysis of clinical and metabolic effects of One Anastomosis Gastric Bypass

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Pragnę podziękować

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Za to, że odkrył i obudził we mnie potencjał do rozwoju na specjalistę i naukowca,

Przyjaciołom za pomoc,

Rodzicom za życie,

Ali za wsparcie,

Leo za cel.

Spis treści

Indeks skrótów

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

LSG, *laparoskopic sleeve gastrectomy*, laparoskopowa gastrektomia rękawowa

OAGB, *one-anastomosis gastric bypass*, wyłączenie żołądkowo-jelitowe z jednym zespoleniem;

OAGBc, *one-anastomosis gastric bypass conversion*, wyłączenie żołądkowo-jelitowe z jednym zespoleniem konwersyjne;

RYGB, *Roux-en-Y gastric bypass*, wyłączenie żołądkowo-jelitowe sposobem Roux-en-Y

RYGBc, *Roux-en-Y gastric bypass conversion*, wyłączenie żołądkowo-jelitowe sposobem Roux-en-Y konwersyjne

%EWL, % *excess weight loss*, procent utraty nadmiernej masy ciała

%TWL, % *total weight loss*, procent utraty całkowitej masy ciała

HOMA-IR, *Homeostatic Model Assessment – Insulin Resistance*, Homeostatyczny Model Oceny Insulinooporności

DM*, diabetes mellitus,* cukrzyca

HT, *hypertension,* nadciśnienie tętnicze

DL, d*yslipidemia*, dyslipidemia

OSAS, *obstructive sleep apnea syndrome*, zespół obturacyjnego bezdechu sennego

GERD, gastroesophageal reflux disease, choroba refluksowa przełyku

FA, *fatty acids*, kwasy tłuszczowe

MUFA, monounsaturated fatty acids, jednonienasycone kwasy tłuszczowe

BCFA, *branched chain fatty acids*, kwasy tłuszczowe o rozgałęzionych łańcuchach

OCFA, *odd chain fatty acids*, kwasy tłuszczowe o nieparzystej liczbie atomów węgla

PUFA, *polyunsaturated fatty acids*, wielonienasycone kwasy tłuszczowe

BCAA, *branched chain amino acids,* aminokwasy o rozgałęzionych łańcuchach

Słowa kluczowe

Otyłość, chirurgia bariatryczna, gastric bypass

Streszczenie

Wstęp

W odpowiedzi na stale rosnącą populację pacjentów cierpiących z powodu otyłości oraz chorób jej towarzyszących[1], dochodzi do ciągłego rozwoju chirurgii bariatrycznej. Opracowano wiele metod leczenia chirurgicznego tej grupy pacjentów[2]. Zgodnie ze współczesnym trendem indywidualnego doboru terapii do potrzeb chorego w celu zwiększenia jej skuteczności, potrzebna jest dokładna analiza efektów poszczególnych operacji. Różnią się one wpływem na metabolizm człowieka oraz przebiegiem okresu pooperacyjnego. One anastomosis gastric bypass (OAGB), pomimo że opracowany przez dr R. Rutledge'a już w 1997 roku[3], wciąż w wielu krajach uznawany jest za innowacyjną metodę operacyjną. W licznych badaniach udowodniono jego bardzo dobre efekty terapeutyczne[4], przez wieloczynnikowy wpływ na metabolizm i funkcjonowanie ludzkiego organizmu. Wiele z tych mechanizmów wciąż nie jest wyjaśnionych i wymaga głębszej analizy, zwłaszcza wpływ wyłączonej długiej pętli enzymatycznej na gospodarkę lipidową. Wyniki takich badań mogą pomóc rozwinąć obecne standardy opieki nad pacjentami chorymi na otyłość, a nawet opracować nowe, jeszcze skuteczniejsze, metody terapeutyczne.

Cele

Poniższy przewód doktorski miał na celu zbadanie klinicznych i metabolicznych efektów One Anastomosis Gastric Bypass. Umożliwił to cykl publikacji, w którym zawarta jest praca opisująca długoterminowe wyniki OAGB jako metody konwersyjnej, publikacja opisująca pooperacyjne zmiany w gospodarce lipidów oraz opracowanie poszukujące korelacji pomiędzy pooperacyjnym spadkiem insulinooporności, a zmianami w metabolizmie tłuszczy i aminokwasów.

Publikacja 1

Badanie porównujące wpływu konwersyjnych Roux-en-Y Gastric Bypass (RYGB) i One Anastomosis Gastric Bypass (OAGB) na pacjentów po nieskutecznym leczeniu otyłości metodą laparoskopowej gastrektomii rękawowej (*Laparoscopic*

Sleeve Gastrectomy, LSG). Celem pierwszorzędowym było porównanie pięcioletniej utraty masy ciała po operacji rewizyjnej mierzonej zmianą odsetka utraty nadmiernej masy ciała (*excess weight loss*, %EWL) oraz odsetka utraty całkowitej masy ciała (*total weight loss,* %TWL). Celem drugorzędowym było porównanie odsetka remisji chorób towarzyszących otyłości w obserwacji pięcioletniej. Celem trzeciorzędowym było porównanie bezpieczeństwa obu metod przez określenie ich profilu powikłań.

Publikacja 2

Badanie miało na celu przeanalizować wpływ OAGB na skład kwasów tłuszczowych (*fatty acids*, FA) w surowicy dwa tygodnie po operacji. Było to wtedy pierwsze takie badanie na grupie pacjentów po OAGB mające na celu wykryć hipotetyczne niedobory wyszczególnionych grup kwasów tłuszczowych.

Publikacja 3

Celem badania była ocena wpływu OAGB na osoczowe stężenia specyficznych kwasów tłuszczowych oraz krążących w ustroju rozgałęzionych aminokwasów (*branched chain amino acids,* BCAA) w dłuższej obserwacji pooperacyjnej. Ocenie poddano również ekspresję genów zaangażowanych katabolizm rozgałęzionych kwasów tłuszczowych (*branched chain fatty acids,* BCFA) i BCAA w tkance tłuszczowej pacjentów z otyłością. Miało to na celu zbadanie hipotetycznej korelacji pomiędzy zmianami w stężeniach BCFA i BCAA oraz ich katabolizmie, jako potencjalnych przyczynach zmniejszania się insulinooporności u pacjentów poddanych OAGB.

Materiały i Metody

Publikacja 1

Badanie kliniczno-kontrolne oparte na prospektywnie prowadzonej bazie danych pacjentów poddanych ponownemu leczeniu operacyjnemu po nieudanym zabiegu LSG, obejmujące 33 pacjentów, którzy przeszli konwersję RYGB i 47 pacjentów, którzy przeszli konwersję OAGB.

Publikacja 2

Analiza składu kwasów tłuszczowych w surowicy 38 pacjentów przed i dwa tygodnie po operacji OAGB przy użyciu chromatografii gazowej ze spektrometrią mas. Uzyskane rezultaty porównano z wynikami analizy składu kwasów tłuszczowych w surowicy grupy kontrolnej, którą stanowiło 30 pacjentów bez stwierdzonej otyłości czy chorób jej towarzyszących.

Publikacja 3

Stężenie BCFA i BCAA na czczo oznaczono odpowiednio za pomocą chromatografii gazowej i cieczowej, sprzężonej ze spektrometrią mas, u 50 pacjentów z otyłością przed i 6-9 miesięcy po operacji OAGB oraz u 32 osób z grupy kontrolnej bez stwierdzonej otyłości. Biopsje trzewnej i podskórnej tkanki tłuszczowej zostały pobrane śródoperacyjnie w celu określenia poziomu mRNA dla enzymów zaangażowanych w katabolizm BCAA. Wpływ na insulinooporność został oceniony przez zmianę wartości Homeostatycznego Modelu Oceny Insulinooporności (HOMA-IR) przed i 6-9 miesięcy po operacji.

Wyniki

Publikacja 1

Średni %EWL po 5-letniej obserwacji dla RYGBc vs OAGBc wyniósł odpowiednio 84,04% vs 72,95% (p = 0,218). Całkowitą długoterminową remisję cukrzycy (DM) obserwowano istotnie częściej w grupie OAGBc niż w grupie RYGBc (97,3% vs 33%; p = 0,035). Nie stwierdzono innych istotnych statystycznie różnic w odsetku remisji chorób współistniejących pomiędzy RYGBc a OAGBc: nadciśnienia tętniczego (HT) 30% vs 27,3% (p = 0,261), dyslipidemii (DL) 83,3% vs 59,1% (p = 0,277), zespołu obturacyjnego bezdechu sennego (OSAS) 100% vs 60% (p = 0,639) oraz choroby refluksowej przełyku (GERD) 40% vs 71,4% (p > 0,99). U 7 pacjentów po OAGBc stwierdzono wystąpienie GERD de novo, czego nie zaobserwowano u żadnego pacjenta po RYGBc. Nie stwierdzono istotnych statystycznie różnic w liczbie powikłań pomiędzy grupami OAGBc i RYGB. Wskaźnik Comprehensive Complication

Index wyniósł 17,85 (± IQR 29,6) w grupie OAGBc i 14,92 (± IQR 21,75) w grupie RYGBc (p = 0,375).

Publikacja 2

Zaobserwowaliśmy istotne statystycznie zmniejszenie niezbędnych PUFA ($p < 0,001$ dla kwasu linolenowego i $p < 0,001$ dla kwasu linolowego) i kwasów tłuszczowych o nieparzystej liczbie atomów węgla (OCFA) (p = 0,004) w surowicy otyłych pacjentów 2 tygodnie po OAGB. Związki te wykazują właściwości przeciwzapalne i antyoksydacyjne oraz zmniejszają ryzyko chorób sercowo-naczyniowych[5,6]. Zaliczane są do egzogennych kwasów tłuszczowych i stanowią niezbędny składnik diety, gdyż nie są syntetyzowane przez organizm.

Publikacja 3

Przed operacją OAGB, pacjenci z otyłością mieli niższe stężenie BCFA i większe stężenie BCAA niż osoby z grupy kontrolnej. Po operacji zwiększył się poziom BCFA i zmniejszył poziom BCAA. Insulinooporność (oceniana metodą HOMA-IR) korelowała odwrotnie z BCFA i dodatnio z BCAA. Ekspresja genów zaangażowanych w katabolizm BCAA w tkance tłuszczowej trzewnej (ale nie podskórnej) była niższa u pacjentów z otyłością niż w grupie kontrolnej.

Wnioski

Uzyskane w powyższych publikacjach wyniki, realizując założone cele badawcze, przynoszą nam wiele dodatkowych, interesujących wniosków dotyczących wyników leczenia po OAGB.

Na podstawie uzyskanych wyników z pięcioletniej obserwacji uznano całkowitą długoterminową remisję cukrzycy typu 2 po operacji konwersyjnej za najistotniejszą różnicę, w której OAGB został uznana za lepszą metodę pod względem skuteczności w porównaniu do RYGB. Nie stwierdzono żadnych innych istotnych statystycznie różnic w następstwach po obu zabiegach. Obie metody można uznać za dobre uzupełnienie chirurgicznego leczenia otyłości po niepowodzeniu LSG. Na podstawie uzyskanych wyników można wskazać specyficzny scenariusz kliniczny np. pacjenta z cukrzycą i niepowodzeniem leczenia otyłości metodą restrykcyjną, dla którego możliwe jest indywidualne dopasowanie terapii do jego potrzeb.

Ocena zmiany składu kwasów tłuszczowych w surowicy pacjentów poddanych OAGB skłania do rozbudowania pooperacyjnego schematu leczenia żywieniowego w tej grupie chory, bowiem biorąc pod uwagę korzyści płynące z wielonasyconych kwasów tłuszczowych, wdrożenie diety bogatej we wskazane kwasy tłuszczowe lub stosowanie suplementacji może wpłynąć korzystnie na przebieg leczenia w tej grupie pacjentów.

Dalsza analiza zmian w stężeniach kwasów tłuszczowych w dłuższym okresie obserwacji po OAGB poszerzona o analizę stężeń rozgałęzionych aminokwasów, wskazuje na korzystny wpływ tej operacji na leczenie chorób towarzyszących otyłości. W wyniku zmian jakie zachodzą w organizmie człowieka poddanego OAGB zwiększa się ilość krążących BCFA i zmniejsza ilość krążących BCAA, być może poprzez zmianę katabolizmu BCAA w trzewnej tkance tłuszczowej. Na podstawie tych wyników, można wysunąć hipotezę, że to przesunięcie może być związane z poprawą wrażliwości na insulinę po operacji. Może to stanowić podstawę do przyszłych badań nad nowymi metodami leczenia cukrzycy.

Abstract

Introduction

In response to the constantly growing population of patients suffering from obesity and its associated diseases[1], there is a continuous development of bariatric surgery. Many different surgical treatment options have been designed for this group of patients[2]. In accordance with the modern trend of tailoring therapy to the patient's needs in order to increase its effectiveness, a thorough analysis of the effects of different surgical methods is needed. They differ in their effects on human metabolism and the course of the postoperative period. One anastomosis gastric bypass (OAGB), although developed by Dr. R. Rutledge in 1997[3], is still considered a novel surgical method in many countries. Numerous studies have proven its very good therapeutic effects[4], through its multifactorial effects on the metabolism and functioning of the human body. Many of these mechanisms are still unexplained and require deeper analysis, especially the effect of the long enzymatic jejunal loop on lipid metabolism. The results of such studies can help develop current standards of care for obese patients and even develop new therapeutic methods.

Aims

The following doctoral thesis was designed to investigate the clinical and metabolic effects of One Anastomosis Gastric Bypass. This was accomplished through a series of publications, which includes a study describing the long-term results of OAGB as a conversion method, a publication describing postoperative changes in lipid metabolism, and a study examining the correlation between the postoperative decrease in insulin resistance and changes in lipids and amino acids metabolism.

Publication 1

A study comparing the effects of Roux-en-Y Gastric Bypass (RYGB) and OAGB on patients after unsuccessful Laparoscopic Sleeve Gastrectomy (LSG) treatment of obesity qualified for conversion surgery. The primary objective was to compare five-year weight loss after revision surgery as measured by change in percentage of excess

weight loss (%EWL) and total weight loss (%TWL). The secondary objective was to compare the effectiveness of the two methods in remission of comorbidities associated with obesity at five-year follow-up. The tertiary objective was to compare the safety of the two methods by determining their complication profiles.

Publication 2

The study was designed to investigate the effect of OAGB on serum fatty acid (FA) composition two weeks after surgery. At the time, it was the first such study on a group of patients after OAGB to detect hypothetical deficiencies of the specified FA groups.

Publication 3

The study aimed to evaluate the effects of OAGB on plasma concentrations of specific FA and circulating branched-chain amino acids (BCAAs) during long-term postoperative follow-up. The expression of genes involved in branched-chain fatty acid (BCFA) and BCAA catabolism in the adipose tissue of obese patients was also evaluated to investigate the hypothetical correlation between changes in BCFA and BCAA concentrations and their catabolism as potential causes of decreased insulin resistance in patients undergoing OAGB.

Material and methods

Publication 1

A case-control study based on a prospectively maintained database of patients undergoing surgical reoperation after failed LSG, including 33 patients who underwent RYGB conversion and 47 patients who underwent OAGB conversion.

Publication 2

Analysis of serum FA composition of 38 patients before and two weeks after OAGB surgery using gas chromatography-mass spectrometry. The results were compared with the results of the analysis of serum fatty acid composition of the control group, which consisted of 30 patients without diagnosed obesity or associated diseases.

Publication 3

Fasting BCFA and BCAA concentrations were determined by gas chromatography and liquid chromatography coupled to mass spectrometry, respectively, in 50 obese patients before and 6-9 months after OAGB surgery, and in 32 control subjects without diagnosed obesity. Visceral and subcutaneous adipose tissue biopsies were taken intraoperatively to determine mRNA levels for enzymes involved in BCAA catabolism. The effect on insulin resistance was assessed by the change in Homeostatic Model Assessment for Insulin *Resistance* (HOMA-IR) values before and 6-9 months after surgery.

Results

Publication 1

The mean %EWL after 5-year follow-up for RYGB conversion (RYGBc) vs OAGB conversion (OAGBc) was 84,04% vs 72,95%, respectively (p = 0,2176). Complete long-term remission of diabetes (DM) was observed significantly more often in the OAGBc group than in the RYGBc group (97,3% vs 33%; p = 0,035). There were no other statistically significant differences in remission rates of comorbidities between RYGBc and OAGBc: hypertension (HT) 30% vs 27,3% (p = 0,261), dyslipidemia (DL) 83,3% vs 59,1% (p = 0,277), obstructive sleep apnea syndrome (OSAS) 100% vs 60% (p = 0,639), and gastroesophageal reflux disease (GERD) 40% vs 71,4% (p > 0,99). Seven patients after OAGBc developed GERD de novo, which was not observed in any patient after RYGBc. There were no statistically significant differences in the number of complications between the OAGBc and RYGB groups. The Comprehensive Complication Index was 17.85 (± IQR 29,6) in the OAGBc group and 14,92 (± IQR 21,75) in the RYGBc group (p = 0,375).

Publication 2

We observed statistically significant reductions in essential polyunsaturated fatty acids (PUFA) ($p < 0,001$ for linolenic acid and $p < 0,001$ for linoleic acid) and odd-chain fatty acids (OCFA) ($p = 0,004$) in the serum of obese patients two weeks after OAGB. These compounds, obtained exclusively from the diet and not synthesized in the human body, exhibit anti-inflammatory and antioxidant properties and reduce the risk of cardiovascular disease[5,6].

Publication 3

Before surgery, patients with obesity had lower BCFA levels and higher BCAA levels than controls. OAGB increased BCFA levels and decreased BCAA levels. Insulin resistance (assessed by HOMA-IR) correlated inversely with BCFA and positively with BCAA. The expression of genes involved in BCAA catabolism in visceral (but not subcutaneous) adipose tissue was lower in obese patients than in controls.

Conclusions

The results obtained in the above publications bring us many interesting conclusions regarding the effects of bariatric surgery such as OAGB.

Based on the results obtained from the five-year follow-up, the complete long-term remission of type 2 diabetes after conversion surgery was considered the most significant difference, in which OAGB was found to be a better method in terms of efficacy compared to RYGB. There were no other statistically significant differences in follow-up after these two procedures. Both methods can be considered good options to surgical treatment of obesity after LSG failure. Based on the results, it is possible to identify a specific clinical scenario Based on the results, it is possible to identify a specific clinical scenario, for example, a patient with diabetes and failure of restrictive obesity treatment, for whom it is possible to tailor therapy to his needs on an individual basis.

The evaluation of the change in the composition of serum fatty acids in patients undergoing OAGB suggests that the postoperative nutritional treatment regimen should be enhanced in this group of patients, because, given the benefits of polyunsaturated fatty acids, the implementation of a diet rich in the indicated fatty acids or the use of supplementation may favorably affect the outcome of treatment in this group of patients.

However, further analysis of changes in fatty acid concentrations over a longer period of observation after OAGB extended by analysis of branched-chain amino acid concentrations, indicates that this surgery is beneficial for the remission of comorbidities. As a result of the changes that occur in the body of a patient undergoing OAGB, the amount of circulating BCFA increases, and the amount of circulating BCAA decreases, perhaps by altering the catabolism of BCAAs in visceral adipose tissue. Based on these results, it can be hypothesized that this shift may be related to improved insulin sensitivity after surgery. This could form the base for future research into new treatments for diabetes.

Wstęp

Chirurgia bariatryczna jest najskuteczniejszą metodą leczenia otyłości, ponieważ pozwala na stabilną utratę masy ciała oraz trwałe ustąpienie zaburzeń metabolicznych. Daje jej to kluczową rolę w walce z globalną epidemią otyłości i chorób jej towarzyszących, które obecnie stanowią główną przyczynę zgonów w krajach rozwijających się[1]. Międzynarodowo środowisko chirurgów w odpowiedzi na rosnące zapotrzebowanie opracowało wiele strategii operacyjnych leczenia otyłości. Według panelu ekspertów chirurgii bariatrycznej (*The Bariatric Metabolic Surgery Standardization World Consensus Meeting*, BMSS-WOCOM) opracowano standardy dla ponad 25 różnych metod operacyjnych[2]. Różnorodność ta pozwala na zindywidualizowane i skoncentrowane na pacjencie podejście do potrzeb osób z otyłością. Wszystkie zabiegi bariatryczne są relatywnie innowacyjne, dlatego też wymagają wciąż dogłębnej analizy naukowej w celu poprawy efektów leczenia.

Jedną z tych metod jest zaproponowana przez dr R. Rutledge'a operacja *Mini Gastric Bypass* (nazwana później *One anastomosis gastric bypass*, OAGB), jako alternatywa do ominięcia żołądkowo-jelitowego metodą Roux-en-Y (*Roux-en-Y gastric bypass*, RYGB), uznawanego współcześnie za złoty standard leczenia otyłości chorobliwej z współistniejącą cukrzycą[3]. Przez zmniejszenie ilości wykonywanych zespoleń z dwóch do jednego, OAGB miało charakteryzować się krótszym czasem zabiegu oraz bezpieczniejszym profilem powikłań przy porównywalnych wynikach. Obecnie wiemy, że populacja chorych z otyłością i jej potrzeby są bardziej zróżnicowane. Powinno się unikać więc unikać stosowania jednego „złotego standardu", a raczej dopasowywać, dostępną z szerokiego wachlarza zabiegów bariatrycznych, metodę leczenia do indywidualnych potrzeb naszego pacjenta.

W celu osiągnięcia jak najlepszych wyników konieczne jest dogłębne zbadanie efektów proponowanych metod operacyjnych i ich porównanie. Pomimo niesamowitego rozwoju technik chirurgicznych, w dalszym ciągu trzeba być gotowym na rozpoznawanie i leczenie powikłań oraz niepowodzeń terapii. Znając szczegółowo mechanizm w jakim zabiegi wpływają na metabolizm, będzie można szybciej diagnozować i leczyć potencjalne komplikacje oraz opracowywać standardy wdrażane w przypadku niesatysfakcjonujących wyników leczenia.

One Anastomosis gastric Bypass charakteryzuje się długą pętlą enzymatyczną jelita cienkiego wyłączoną z pasażu treści pokarmowej. Fizjologicznie to w niej dochodzi m.in. do mieszania się żółci i soku trzustkowego z treścią pokarmową pozwalając na trawienie i dalsze wchłanianie tłuszczy. Ograniczenie absorpcji lipidów jest więc jedną z kluczowych funkcji tej operacji. Niestety niesie to ze sobą konsekwencji w postaci ograniczenia wchłaniania witamin rozpuszczalnych w tłuszczach, ale i wchłaniania niektórych specyficznych kwasów tłuszczowych o funkcjach kardioprotekcyjnych oraz regulujących stan zapalny w organizmie. Większość z tych tłuszczy nie jest syntetyzowanych w organizmie, więc droga egzogenna jest jedyną możliwą do ich pozyskania. Zakres tych zmian nie został do tej pory dokładnie opisany.

Niniejszy przewód doktorski składa się z trzech prac oryginalnych badających efekty kliniczne i metaboliczne ominięcia żołądkowo-jelitowego z jednym zespoleniem (One anastomosis gastric bypass, OAGB). Główną część rozprawy doktorskiej stanowi praca pt. „Comparison of the Long-term Outcomes of RYGB and OAGB as Conversion Procedures After Failed LSG — a Case–Control Study". Jest ona porównaniem pięcioletnich efektów OAGB i RYGB wykonanych jako operacje konwersyjne zaproponowane pacjentom z niepowodzeniem leczenia otyłości po zabiegu laparoskopowej gastrektomii rękawowej (LSG). Porównaniu poddano nie tylko wyniki utraty masy ciała, ale również wpływ na choroby towarzyszące otyłości oraz profil powikłań. Kolejna praca pt. "Short-Term Effect of One-Anastomosis Gastric Bypass on Essential Fatty Acids in the Serum of Obese Patients" jest próbą określenia profilu zmian w składzie osoczowym kwasów tłuszczowych (FA) we wczesnym okresie pooperacyjnym po OAGB w celu określenia specjalnych wymagań żywieniowych dla pacjentów w okresie rekonwalescencji po zabiegu. Trzecia praca oryginalna pt. „The Effect of One Anastomosis Gastric Bypass on Branched-Chain Fatty Acid and Branched-Chain Amino Acid Metabolism in Subjects with Morbid Obesity" to jeszcze dokładniejsza analiza zmian stężeń specyficznych kwasów tłuszczowych u pacjentów po OAGB w dłuższym okresie obserwacji. Badanie poszerzono o ocenę stężeń rozgałęzionych aminokwasów oraz ekspresji genów białek je katabolizujących.

Korelacja zmian tych parametrów może potencjalnie tłumaczyć mechanizm ustępowania insulinooporności u pacjentów poddanych OAGB.

Cele

Publikacja 1

Comparison of the Long-term Outcomes of RYGB and OAGB as Conversion Procedures After Failed LSG — a Case–Control Study. Porównano efekty OAGB i RYGB jako operacji konwersyjnej u pacjentów z niepowodzeniem leczenia metodą LSG. Celem pracy było wskazanie metody dającej lepsze wyniki utraty masy ciała po 5 latach od operacji konwersyjnej, mierzone jako zmiana %EWL i %TWL. Celem drugorzędowym było wskazanie metody charakteryzującej się skuteczniejszą remisją chorób współistniejących z otyłością po 5 latach obserwacji. Ponadto, celem trzeciorzędowym była ocena bezpieczeństwa obu metod, mierzone jako odsetek występowania powikłań.

Publikacja 2

Short-Term Effect of One-Anastomosis Gastric Bypass on Essential Fatty Acids in the Serum of Obese Patients. Celem pracy było określenie wpływu OAGB na stężenie poszczególnych kwasów tłuszczowych w surowicy pacjentów z otyłością w dwutygodniowym okresie obserwacji pooperacyjnej oraz porównanie ich do stężeń osoczowych kwasów tłuszczowych w populacji kontrolnej bez otyłości.

Publikacja 3

The Effect of One Anastomosis Gastric Bypass on Branched-Chain Fatty Acid and Branched-Chain Amino Acid Metabolism in Subjects with Morbid Obesity. Celem pracy była ocena, jak OAGB wpływa na poziom krążących w organizmie bioaktywnych kwasów tłuszczowych (FA), w tym rozgałęzionych kwasów tłuszczowych (BCFA) i kwasów tłuszczowych o nieparzystej liczbie atomów węgla (OCFA). Celem drugorzędowym była analiza zmiany pooperacyjnej poziomów osoczowych rozgałęzionych aminokwasów (BCAA), a także ocena ekspresji genów zaangażowanych w ich katabolizm w trzewnej i podskórnej tkance tłuszczowej u pacjentów z otyłością chorobliwą. Celem trzeciorzędowym była próba odszukania korelacji powyższych wyników z ustępowaniem insulinooporoności ocenianej zmianą wskaźnika HOMA-IR.

Materiał i metody

Publikacja 1

Retrospektywne badanie kliniczno-kontrolne na podstawie prospektywnie prowadzonej bazy danych pacjentów Kliniki Chirurgii Ogólnej, Endokrynologicznej i Transplantacyjnej Gdańskiego Uniwersytetu Medycznego z lat 2009-2020. Konieczne kryteria włączenia do badania były następujące: niepowodzenie lub nietolerancja leczenia otyłości metodą LSG, przejście konwersji operacyjnej do RYGB lub OAGB, zabieg wykonany w trybie planowym, co najmniej 5 lat regularnej obserwacji w poradni uniwersyteckiego ośrodka leczenia otyłości. Kwalifikację, operacje i kontrolę pooperacyjną prowadził stały zespół chirurgów specjalizujących się w chirurgii bariatrycznej i metabolicznej według standardów International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO)[7]. OAGB wykonywano w konfiguracji 180cm-250cm wyłączonej pętli enzymatycznej jelita cienkiego (w zależności od BMI, wieku i stanu cukrzycy pacjenta, zgodnie z regułą Garcia-Caballero[8], wykonując jedno zespolenie żołądkowo-jelitowe ze zbiornikiem żołądkowym objętości ok. 50ml. RYGB wykonywano w konfiguracji 100-150 cm wyłączonej pętli enzymatycznej jelita cienkiego, 100-150 cm pętli alimentarnej, wykonując zespolenie żołądkowo-jelitowe z 50ml zbiornikiem żołądkowym oraz zespolenie jelitowo-jelitowe bok do boku. Ambulatoryjne wizyty pooperacyjne odbywały się według schematu: 1 miesiąc, 3 miesiące, 6 miesięcy, 1 rok, 2 lata, 3 lata, 4 lata, 5 lat. Podczas każdej wizyty wykonywano panel badań laboratoryjnych oraz pomiary antropometryczne. W celu obiektywnej oceny efektów leczenia otyłości oceniano procent utraty nadmiernej masy ciała (%EWL) liczony od idealnej masy ciała oraz procent utraty całkowitej masy ciała (%TWL) liczony od daty operacji konwersyjnej. Kryteria całkowitej remisji chorób towarzyszących otyłości tj. cukrzycy (DM), nadciśnienia tętniczego (HT), dyslipidemii (DL) oraz zespołowi obturacyjnego bezdechu sennego (OSAS) stwierdzano na podstawie aktualnych wytycznych polskich towarzystw lekarskich. Chorobę refluksową przełyku (GERD) oceniano w badaniu endoskopowym górnego odcinka przewodu pokarmowego przed zabieg operacyjnym, następnie przynajmniej raz w okresie pooperacyjnym nie wcześniej niż 2 lata po zabiegu, oraz dodatkowo w przypadku objawowych pacjentów. Status niedoborów żywieniowych porównano oceniając częstość występowania anemii oraz porównując osoczowe stężenia kluczowych parametrów: albumin, żelaza, witaminy B12, witaminy D. Bezpieczeństwo metod oceniono porównując częstość występowania powikłań oraz kategoryzując je według klasyfikacji Clavien-Dindo i wskaźnika *comprehensive complication index* (CCI)[9].

Statystykę opisową przeprowadzono przy użyciu średnich i odchyleń standardowych (SD) dla danych o rozkładzie normalnym, oraz median i zakresów międzykwartylowych (IQR) dla pozostałych danych. Normalność sprawdzono testem Shapiro-Wilka. Dane kategoryczne porównywano za pomocą testów chi kwadrat lub testu Fishera. Dane ciągłe o rozkładzie normalnym porównywano za pomocą testów t, dla prób o nierównej wariancji stosowano poprawkę Welcha. Dane ciągłe z rozkładem innym niż normalnym porównywano za pomocą testów U Manna-Whitneya. Próg istotności dla wartości p przyjęto na poziomie < 0.05. Wszystkie testy były dwustronne.

Publikacja 2

Badanie przeprowadzono na grupie pacjentów z otyłością chorobliwą poddanych pierwotnemu zabiegowi OAGB w Klinice Chirurgii Ogólnej Endokrynologicznej i Transplantacyjnej. Krew pobierano rano w dniu zabiegu. W okresie przygotowawczym pacjenci byli na diecie niskokalorycznej (posiłki wysokobiałkowe, niskotłuszczowe i niskowęglowodanowe) przez 2-3 miesiące przed operacją. Pacjenci nie przyjmowali przed operacją żadnych leków odchudzających. OAGB wykonywano w konfiguracji 180cm wyłączonej pętli enzymatycznej jelita cienkiego, wykonując jedno zespolenie żołądkowo-jelitowe ze zbiornikiem żołądkowym objętości ok. 50ml. Wszyscy zakwalifikowani do badania pacjenci przeszli wizytę kontrolną 2 tygodnie po operacji. Grupę kontrolną stanowili pacjenci bez zdiagnozowanej otyłości i zaburzeń metabolicznych. W ciągu pierwszych 2 tygodni po operacji pacjenci stosowali dietę bogatobiałkową (przynajmniej 60g białka na dobę) o zmniejszonej zawartości węglowodanów i tłuszczy, w formie płynnej lub półpłynnej. Schematy suplementacji witaminowej specyficzne dla pacjentów bariatrycznych były stosowane od pierwszej doby pooperacyjnej. Suplementacja kwasami omega nie była rutynowo zalecana.

Lipidy były ekstrahowane z surowicy przy użyciu mieszaniny chloroformu i metanolu (2:1, v/v) i suszone pod strumieniem azotu. Próbki były hydrolizowane 0,5 M roztowrem wodortlenku potasu w metanolu w temperaturze 90 ◦C przez 3 godziny i zakwaszane 0,5 ml 6 M roztworu kwasu chlorowodorowego. Następnie dodano 1 mL wody, a kwasy tłuszczowe ekstrahowano przy użyciu 3 × 1 mL n-heksanu. Kwasy tłuszczowe były następnie derywatyzowane do estrów metylowych kwasów tłuszczowych i analizowane przy użyciu chromatografii gazowej z jonizacją elektronów i spektrometrii masowej. Identyfikację kwasów tłuszczowych przeprowadzono z wykorzystaniem standardów referencyjnych (37 FAME MIX, Sigma Aldrich, Saint Louis, MO, USA) oraz biblioteki referencyjnej National Institute of Standards and Technology 2011. Zastosowanym standardem wewnętrznym był kwas 19-metyloarachidowy.

Różnice między zmiennymi mierzonymi przed i po operacji u osób otyłych analizowano za pomocą sparowanych testów t. Różnice między osobami otyłymi a szczupłymi kontrolami analizowano za pomocą dwustronnych testów t.

Publikacja 3

Było to jednoośrodkowe badanie obejmujące pacjentów operowanych metodą OAGB z powodu otyłości chorobliwej w Klinice Chirurgii Ogólnej, Endokrynologicznej i Transplantacyjnej UCK w latach 2016-2018. Zastosowano kryteria kwalifikacji do OAGB określone przez International Federation for the Surgery of Obesity (IFSO)[7]. Grupę kontrolną stanowili pacjenci bez stwierdzonej otyłości poddani planowej cholecystektomii laparoskopowej w Klinice Chirurgii Ogólnej, Endokrynologicznej i Transplantacyjnej UCK oraz w Oddziale Chirurgii Ogólnej Szpitala Pomorskiego Sp. z o.o. w Gdyni. Kryteria włączenia chorych do grupy kontrolnej obejmowały wskazania do leczenia operacyjnego w trybie planowym, bez podejrzenia procesu nowotworowego. Kryteriami wykluczającymi z grupy kontrolnej były: otyłość, cukrzyca, zespół metaboliczny, sterydoterapia, przewlekłe stosowanie niesteroidowych leków przeciwzapalnych oraz aktywny proces zapalny. Próbki krwi pobrano na czczo od wszystkich pacjentów przed, a następnie 6-9 miesięcy po zabiegu. OAGB wykonywano przez wyłączenie z pasażu enzymatycznej pętli jelita cienkiego długość 180-250 cm (w zależności od BMI, wieku i stanu cukrzycy pacjenta, zgodnie z regułą Garcia-Caballero[8]) przez zespolenie żołądkowo-jelitowe z 50ml zbiornikiem żołądkowym. Po wykonaniu próby szczelności, w celu wykluczenia ewentualnych nieszczelności zespolenia, pobierano próbki tkanki trzewnej (VAT). Po zamknięciu rany pobierano również próbki podskórnej tkanki tłuszczowej (SAT). Wszystkie próbki tkanki tłuszczowej były natychmiast zamrażane w ciekłym azocie i przechowywane w temperaturze - 80°C. Próbki tkanki tłuszczowej uzyskano z tych samych miejsc anatomicznych od pacjentów z grupy kontrolnej podczas cholecystektomii. Stężenie kwasów tłuszczowych oznaczano stosując chromatografię gazową ze spektrometrią mas (GC-MS) w lipidach wyekstrahowanych z tkanek i surowicy metodą opisaną przez Folcha i wsp.[10] Stężenie aminokwasów w surowicy oznaczano metodą wysokosprawnej chromatografii cieczowej z tandemową spektrometrią mas (LC-MS) wg Olkowicza i wsp.[11]

Całkowite RNA ekstrahowano z zamrożonych próbek VAT i SAT przy użyciu Qiagen RNeasy Lipid Tissue Mini Kit. Poziom mRNA analizowano za pomocą real-time PCR przy użyciu CFX Connect Real-Time System (Bio-Rad). Względne poziomy mRNA dla kompleksu rozgałęzionej dehydrogenazy α-ketokwasów (BCKDH) i aminotransferazy rozgałęzionej (BCAT) obliczono według Piehlera i wsp.[12] Amplifikację specyficznych transkryptów potwierdzono na podstawie profili krzywych topnienia i elektroforezy produktów amplifikacji w żelu agarozowym.

Istotność statystyczną różnic między wartościami przed i po operacji u osób z otyłością chorobliwą określono za pomocą sparowanych testów t, natomiast różnice między osobami z otyłością chorobliwą a grupą kontrolną oceniono za pomocą testów t dla prób niezależnych. Różnice uznano za istotne statystycznie przy $p < 0.05$. Zależności między interesującymi nas zmiennymi określano za pomocą analizy regresji liniowej oraz wielokrotnej regresji liniowej.

Wyniki

Publikacja 1

Spośród 3140 chorych leczonych chirurgicznie w Klinice Chirurgii Ogólnej, Transplantacyjnej i Endokrynologicznej w latach 2009-2020 początkowo wyodrębniono dwie grupy pacjentów, którzy przeszli zabieg RYGB (n = 93) lub OAGB (n = 760). Spośród nich kryteria włączenia spełniło 33 pacjentów po RYGB i 47 po zabiegu OAGB. W badanej grupie przyczynami konwersji były: niezadowalająca utrata masy ciała u 44 (93,6%) w grupie OAGBc i 20 (60,6%) w grupie RYGBc, ponowne przybranie masy ciała u 2 (4,3%) w grupie OAGBc i 5 (15,2%) w grupie RYGBc oraz objawowy refluks u 1 (2,1%) w grupie OAGBc i 8 (24,2%) w grupie RYGBc.

Utrata masy ciała

Po operacji konwersji nie stwierdzono istotnych statystycznie różnic we wskaźnikach utraty masy ciała (po 5 latach %EWL OAGBc 84,04 ± 18.81/RYGBc 72,95 ± 20,3, p=0,218) oraz zmianie BMI między grupami RYGBc i OAGBc, z wyjątkiem wyższego %TWL po 4 latach obserwacji w grupie OAGBc niż w grupie RYGBc (odpowiednio 25,17 ± 11,87% vs 13,4 ± 9,38% p = 0,018). Różnica nie została stwierdzona po piątym roku obserwacji.

Wpływ na choroby współistniejące

Po 5-letnim okresie obserwacji remisję DM osiągnięto istotnie częściej u chorych po OAGBc (11/12; 91,7%) niż u chorych z RYGBc (2/6; 33%) (p = 0,035).
Remisję GERD osiągnięto u 5 (71,4%) pacjentów z grupy OAGBc i 4 (40%) z grupy RYGBc (p > 0.99) z całkowitym ustąpieniem objawów refluksu i cech zapalenia przełyku w endoskopii. W grupie RYGBc nie stwierdzono nowych przypadków GERD po operacji natomiast po konwersji do OAGBc rozpoznano 7 nowych przypadków objawowego GERD bez cech zapalenia przełyku w endoskopii. Zmiany w częstości ustępowania pozostałych chorób współistniejących nie różniły się istotnie statystycznie po operacji. Odsetki kompletnych remisji wynosiły kolejno: HT OAGBc 27,3% (n

6)/RYGBc 30% (n 3); OSAS OAGBc 60% (n 3)/RYGBc 100% (n 1); DL OAGBc 59,1% (n 13)/RYGBc 83,3% (n 5);

Wpływ na stan odżywienia

W okresie 5 lat obserwacji niedokrwistość rozwinęła się u 22 (46,8%) chorych po OAGBc i 14 (42,4%) po RYGBc (p = 0.698). We wszystkich przypadkach była to niedokrwistość mikrocytarna leczona dodatkową doustną suplementacją żelaza, z wyjątkiem dwóch pacjentów wymagających suplementacji dożylnej (po jednym z każdej grupy). Nie stwierdzono istotnych statystycznie różnic w stężeniu hemoglobiny pomiędzy pacjentami po OAGBc i RYGBc. Nie stwierdzono istotnych statystycznie różnic między grupami w stężeniach żelaza, witaminy B12, witaminy D oraz albuminy w surowicy w kolejnych latach.

Powikłania

Nie stwierdzono istotnych statystycznie różnic w liczbie powikłań pomiędzy grupami OAGBc i RYGBc. Wskaźnik Comprehensive Complication Index (CCI®) wynosił średnio 17,85 (± IQR 29,6) w grupie OAGBc i 14,92 (± IQR 21,75) w grupie RYGBc przy p = 0,375. Krwawienie z górnego odcinka przewodu pokarmowego wystąpiło u dwóch chorych z każdej grupy. Owrzodzenie brzeżne zespolenia żołądkowo-jelitowego stwierdzono u 3 chorych po OAGBc i 4 po RYGBc. Perforacja miejsca zespolenia wystąpiła u 3 (6,3%) pacjentów z grupy OAGBc, ale u żadnego z grupy RYGBc (odpowiednio po 3, 3 i 5 lat po OAGBc). Pierwszym przypadkiem była pacjentka z zapaleniem błony śluzowej żołądka w wywiadzie, u której położnik odstawił inhibitory pompy protonowej w czasie ciąży, perforacja wystąpiła kilka miesięcy po porodzie, a pacjentka nie poddała się zalecanej kontroli endoskopowej. Drugi przypadek to pacjentka, u której doszło do perforacji zespolenia w trakcie leczenia przeciwwirusowego WZW C. Trzeci przypadek to perforacja miejsca zespolenia o niejasnej etiologii jatrogennej lub wrzodowej w pierwszej dobie po cholecystektomii. Nie stwierdzono wczesnych nieszczelności zespolenia (< 30 dni po konwersji). Zwężenie zespolenia żołądkowo-jelitowego stwierdzono u dwóch chorych z każdej grupy. U jednego chorego z grupy OAGBc stwierdzono perforacje jelita cienkiego z powodu jatrogennego urazu po zabiegu abdominoplastyki. Krwawienie do jamy otrzewnej stwierdzono u jednego pacjenta po RYGBc i u żadnego z grupy OAGBc. Zakażenie rany operacyjnej stwierdzono u dwóch chorych z każdej grupy. Ponownej hospitalizacji z powodu bólu brzucha wymagały dwie pacjentki po OAGBc i jedna po RYGBc. Objawowy zespół niedożywienia stwierdzono u 4 chorych OAGBc i 3 chorych RYGBc. Tylko pacjent z perforacją jelita cienkiego wymagał reoperacji. Perforacje miejsca zespolenia żołądkowo-jelitowego były skutecznie leczone endoskopowo za pomocą protezy samorozprężalnej.

Publikacja 2

Do badania włączono 38 chorych (32 kobiety i 6 mężczyzn), u których wykonano OAGB jako leczenie chirurgiczne otyłości. Trzynastu pacjentów miało cukrzycę typu 2. Grupę kontrolną stanowiło 30 osób (15 mężczyzn i 15 kobiet) bez otyłości i zaburzeń metabolicznych. Zaobserwowano istotne zmniejszenie BMI (37,1 ± 2,73 vs 33,8 ± 2,33 kg/m^2 p < 0,001) i stężenia glukozy w surowicy na czczo (132 ± 35,8 vs 111 ± 20,7 mg% p = 0,001) u pacjentów po OAGB. Stężenia albuminy i białka całkowitego wzrosły, co było najprawdopodobniej wynikiem zalecanej po operacji diety wysokobiałkowej.

Pacjenci z otyłością wykazywali poważnie zaburzony skład FA w surowicy w porównaniu z osobami z grupy kontrolnej. Dotyczyło to zmniejszenia zawartości BCFA (0,29 ± 0,08/otyłość vs 0,42 ± 0,10/kontrola p < 0,001) i zwiększenia zawartości jednonienasyconych kwasów tłuszczowych (MUFA) (33,31 ± 3,59/otyłość vs 0,16 ± 3,53/kontrola p <0,001). U pacjentów z otyłością stwierdzono również zmniejszenie zawartości niektórych szczególnych wielonienasyconych kwasów tłuszczowych (PUFA) z grupy omega-3 (statystyczne różnice wykazano dla m.in. kwasów 18:3 n-3 (ALA), 20:5 n-3 (EPA), 20:4 n-3 (ETA) i pozostałych kwasów omega 3, z wyjątkiem 22:6 n-3 (DHA) p = 0,053) oraz omega-6 (statystyczne różnice wykazano dla kwasów 18:2 n-6 (LA) i 20:2 n-6 (kwas eikosadienowy), istotnych statystycznie różnic nie wykazano dla kwasu 20:4 n-6 (ARA) p = 0,118 oraz pozostałych kwasów omega 6 p = 0.944) w porównaniu do grupy kontrolnej.

Stężenie kwasów tłuszczowych OCFA w surowicy u pacjentów po OAGB było istotnie obniżone w porównaniu do grupy kontrolnej (0,55 ± 0,11/OAGB vs 0,64 ± 0,10/kontrola p < 0,001). Po operacji znaczne spadki obserwowano również w przypadku PUFA omega-3 (statystycznie istotne różnice wykazano dla wszystkich kwasów tej podgrupy z wyjątkiem 22:6 n-3 (DHA) p = 0,445) i omega-6 (statystyczne różnice wykazano poszczególnie dla wszystkich badanych kwasów z podgrupy, ale nie dla wartości totalnej PUFA omega 6 (p=0,241)). Są to niezbędne kwasy tłuszczowe, które nie mogą być syntetyzowane w organizmie człowieka i muszą być pozyskiwane z diety. Poziomy BCFA nie zmieniły się istotnie po OAGB, ale pozostały znacząco niższe w porównaniu do poziomów grupy kontrolnej (0,28 ± 0,11/OAGB vs 0,42 ± 0.10/kontrola p < 0,001). Zaobserwowano wzrost kwasu arachidonowego dwa tygodnie po OAGB (6,20 ± 2,00/otyłość vs 7,85 ± 2,12/OAGB p < 0,001). Ta zmiana jest związana z toczącym się stanem zapalnym. Odnotowaliśmy również zmiany w niektórych nasyconych kwasach tłuszczowych i MUFA, ale wartości ich liczone całościowo nie zmieniły się znacząco.

Publikacja 3

Badanie obejmowało grupę 50 pacjentów (średni wiek 48,6 ± 10,5 roku; 42 kobiety, 8 mężczyzn) operowanych z powodu otyłości chorobliwej metodą OAGB. Wśród pacjentów było 25 osób z cukrzycą typu 2. Grupę kontrolną stanowiły 32 osoby bez otyłości (średnia wieku 52 ± 12 lat; 21 kobiet, 9 mężczyzn) poddane planowej cholecystektomii laparoskopowej.

W porównaniu z grupą kontrolną pacjenci z otyłością mieli istotnie niższe stężenie BCFA przed operacją (iso- 0.190 ± 0,05/ otyłość vs 0,244 ± 0,058/kontrola p<0,001), jednak po 6-8 miesiącach po OAGB doszło do znacznego wzrostu zarówno izo-, jak i anteizo- BCFA (iso-0,190 ± 0,05/otyłość vs 0,234 ± 0,06/OAGB p < 0,001; ante- 0,094 ± 0,03/otyłość vs 0,135 ± 0,05/OAGB p < 0,001), tak że całkowite stężenie BCFA po operacji nie różniło się już istotnie od stężenia w grupie kontrolnej. Wywołany przez OAGB wzrost stężenia BCFA był podobny u pacjentów z cukrzycą i bez niej. Analiza porównawcza profili FA u pacjentów z otyłością przed i po OAGB oraz w grupie kontrolnej wykazała wiele istotnych różnic. Zarówno przed, jak i po operacji pacjenci z otyłością mieli niższe stężenie OCFA niż osoby z grupy kontrolnej (0,649 ± 0,111/kontrola vs 0,572 ± 0,09/otyłość p = 0,02; 0.649 ± 0,111/kontrola vs 0,581 ± 0,01/OAGB p = 0,012). Ponadto przedoperacyjne stężenie PUFA omega-3 (2,99 ± 1,27/kontrola vs 2,44 ± 0,69/otyłość p = 0,032) oraz pooperacyjne stężenie zarówno

PUFA omega-3 (2,99 ± 1,27/kontrola vs 2,27 ± 0,54/OAGB p = 0,005), jak i omega-6 (34,1 ± 3,70/kontrola vs 29,5 ± 4,13/OAGB p < 0,001) było istotnie niższe u osób z otyłością niż w grupie kontrolnej. Z drugiej strony, zarówno przed jak i po OAGB, pacjenci z otyłością mieli wyższe poziomy MUFA niż osoby z grupy kontrolnej (29,6 ± 3,60/kontrola vs 33,6 ± 2,64/otyłość p < 0,001; 29,6 ± 3,60/kontrola vs 34,3 ± 3,06/OAGB p < 0,001).

Wpływ OAGB na skład BCAA w surowicy krwi

Całkowite krążące BCAA (leucyna (57,6 ± 19,2 vs 77,1 ± 20,0 p < 0,001) i izoleucyna (32,0 ± 12,7 vs 45,9 ± 14,5 p < 0,001), ale nie walina (p = 0,42)) były znacząco większe u osób z otyłością przed operacją niż w grupie kontrolnej. Zabieg OAGB znacząco obniżył stężenie wszystkich BCAA (leucyna 77,1 ± 20,0 vs 47,4 ± 18,3 p < 0,001; izoleucyna 45,9 ± 14,5 vs 28,4 ± 10,5 p < 0,001; walina 123 ± 25,9 vs 97,7 ± 24,5 p < 0,001), tak że wartości pooperacyjne były istotnie niższe u pacjentów po operacji bariatrycznej niż w grupie kontrolnej (z wyjątkiem izoleucyny, dla której nie wykryto różnicy istotnej statystycznie p = 0,19).

Korelacja pomiędzy BCAA i BCAA a HOMA-IR, trójglicerydami i BMI

Na poziomie wyjściowym stwierdziliśmy, że BCAA korelowały bezpośrednio z HOMA-IR (r = 0,30, p = 0,007) i stężeniem trójglicerydów (r = 0,33, p = 0,003), podczas gdy BCFA korelowały odwrotnie z tymi dwoma parametrami (HOMA: r = - 0,28, p = 0,012; trójglicerydy: r = - 0,37, p = 0,001). Ponadto BMI korelowało negatywnie z BCFA (r = - 0,60, p < 0,001) i pozytywnie z BCAA (r = 0,27, p = 0,015). Analiza wielokrotnej regresji liniowej wykazała, że zawartość BCFA w surowicy była najsilniej przewidywana przez BMI (p < 0,001), a BCAA przez triglicerydy (p = 0,007).

Ekspresja genów zaangażowanych w katabolizm BCAA w tkance tłuszczowej

Nie stwierdziliśmy żadnych istotnych statystycznie różnic pomiędzy osobami z otyłością, a grupą kontrolną w ekspresji genów dehydrogenzay alfa ketokwasów rozgałęzionych (BCKDH) (izoformy A i B) i aminotransferazy rozgałęzionych aminokwasów (BCAT) (izoformy 1 i 2) w podskórnej tkance tłuszczowej (BCKDHA 1,0 ± 0,38 vs 1,07 ± 0,38, p = 0,59; BCKDHB 1,0 ± 0, 26 vs 1,03 ± 0,39, p = 0,78; BCAT1

1,0 ± 0,54 vs 1,18 ± 0,66, p = 0,22; BCAT2 1,0 ± 0,35 vs 0,86 ± 0,22, p = 0,11; odpowiednio u osób kontrolnych i pacjentów z otyłością). Natomiast poziom mRNA dla izoformy B BCKDH i obu izoform BCAT w trzewnej tkance tłuszczowej był istotnie niższy u osób z otyłością niż w grupie kontrolnej. Odpowiednio, niższej ekspresji genów enzymów katabolizujących BCAA (biorących udział w syntezie BCFA) towarzyszyły niższe poziomy BCFA w trzewnej tkance tłuszczowej u osób z otyłością niż u osób z grupy kontrolnej. W podskórnej tkance tłuszczowej poziomy BCFA nie różniły się między pacjentami z otyłością, a grupą kontrolną (odpowiednio0,47 ± 0,11 vs 0,44 ± 0,15, p = 0,34).

Wnioski

Przedstawione publikacje pozwoliły na szczegółową analizę wielu aspektów nowoczesnej metody leczenia otyłości chorobliwej jaką jest OAGB. Oceniono długoterminowe wyniki obserwacji klinicznej, natomiast wpływ na metabolizm człowieka (w szczególności na gospodarkę lipidów) został poddany innowacyjnej analizie naukowej.

Pierwsza publikacja na podstawie analizy pięcioletniej obserwacji wykazała, że OAGBc jest równie skuteczną procedurą jak RYGBc, gdy zastosowano ją po niepowodzeniu leczenia otyłości metodą LSG. Obie procedury wykazują podobny profil bezpieczeństwa i efekt utraty masy ciała. OAGBc może również przynieść potencjalne dodatkowe korzyści pacjentom z cukrzycą, natomiast jego wpływ na chorobę refluksową wymaga głębszego opracowania w kolejnych badaniach. Wyniki uzyskane w tym szczególnym scenariuszu klinicznym mogą pomóc stworzyć algorytm doboru metody leczenia do konkretnych potrzeb pacjenta.

Wyniki drugiej publikacji wykazały zmniejszenie stężenia OCFA i niezbędnych PUFA w surowicy pacjentów 2 tygodnie po wykonaniu OAGB. Poziomy BCFA o potencjalnym działaniu przeciwnowotworowym również pozostawały niskie w krótkim okresie pooperacyjnym. Biorąc pod uwagę korzyści przynoszone przez wymienione kwasy tłuszczowe, wdrożenie bogatej w nie diety lub stosowanie odpowiedniej suplementacji powinno być zalecane u pacjentów bezpośrednio po zabiegu OAGB.

Zwiększone spożycie tłuszczy może wiązać się w tej grupie pacjentów z wystąpieniem biegunki tłuszczowej, dlatego projektowane w przyszłości preparaty powinny ograniczać się do wąsko-wyselekcjonowanej grupy lipidów. Wyniki te powinny też stanowić podstawę do dalszych badań i opracowania suplementacji dla pacjentek poddanych OAGB planujących ciążę jak również opracowanie schematów leczenia żywieniowego dla nieletnich pacjentów poddanych leczeniu bariatrycznemu w wieku rozwojowym.

W ostatniej publikacji wykazaliśmy, że w dłuższej obserwacji OAGB spowodował znaczący wzrost stężenia BCFA i znaczący spadek stężenia BCAA w surowicy u pacjentów z chorobliwą otyłością. Co więcej wyniki naszych analiz sugerują, że zmiana ta może być wynikiem wpływu OAGB na relację między katabolizmem BCAA a syntezą BCFA w trzewnej tkance tłuszczowej. Prawdopodobnie zmiany w poziomie BCFA i BCAA po OAGB mogą być związane z pewnymi korzyściami metabolicznymi, takimi jak spadek insulinooporności, a w efekcie tego ustępowanie cukrzycy w dłuższym okresie obserwacji.

Podsumowując OAGB jest skutecznym sposobem leczenia otyłości chorobliwej. Jego wyniki potencjalnie można poprawić dodatkową suplementacją szczególnych kwasów tłuszczowych w okresie pooperacyjnym. Metoda ta wykazując dodatkowe korzyści dla pacjentów obarczonych insulinoopornością, przy głębszym zrozumieniu jej wpływu na metabolizm, może dać początek innowacyjnym metodom leczenia cukrzycy.

Cykl prac wchodzących w skład rozprawy doktorskiej i dane bibliometryczne

Cykl składa się z trzech prac oryginalnych opublikowanych w międzynarodowych czasopismach naukowych umieszczonych na Liście Filadelfijskiej. Łączny Impact Factor (IF) cyklu to 13,452. Łączna punktacja MNiSW to 340 punktów.

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   "Short-Term Effect of One-Anastomosis Gastric Bypass on Essential Fatty Acids in the Serum of Obese Patients"

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ORIGINAL ARTICLE

Comparison of the Long-term Outcomes of RYGB and OAGB as Conversion Procedures After Failed LSG — a Case–Control Study

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Abstract

Objective To compare the effect of RYGB and OAGB on patients after failed treatment of obesity by laparoscopic sleeve gastrectomy (LSG).

Study Design A case–control study based on a prospectively maintained database of reoperated patients after failed LSG, which included 33 patients who underwent RYGB conversion and 47 patients who underwent OAGB conversion.

Result The mean %EBWL after a 5-year follow-up for RYGBc vs OAGBc was 84.04% vs 72.95% ($p=0.2176$), respectively. Complete long-term diabetes remission was observed significantly more frequently in the OAGBc than in the RYGBc group (97.3% vs 33%; $p=0.035$). There were no other statistically significant differences in the remission rate of comorbidities between RYGBc and OAGBc: hypertension 30% vs 27.3% ($p=0.261$), dyslipidemia 83.3% vs 59.1% ($p=0.277$), OSAS 100% vs 60% ($p=0.639$), and GERD 40% vs 71.4% ($p>0.99$), respectively. 7 patients were newly diagnosed with GERD after OAGBc and none after RYGBc. There were no statistically significant differences in the number of complications between the OAGBc and RYGB groups. The Comprehensive Complication Index was 17.85 (±IQR 29.6) in the OAGBc group and 14.92 (±IQR 21.75) in the RYGBc group ($p=0.375$).

Conclusion The authors recognized complete long-term type 2 diabetes remission after conversion surgery as the most relevant difference, where the OAGB variety was found superior for its better efficacy. Any other statistically significant differences in the consequences after both conversion procedures used after the failure of LSG have not been stated. Both methods therefore can be considered to complete the initial treatment, considering the preferences and individual burdens of the patients.

Keywords Bariatric surgery · Sleeve gastrectomy · Gastric bypass

Introduction

The constant demand for bariatric surgery drives its continuous development and has resulted in a wide range of surgical methods available. This variety allows for a personalized, patient-centered approach to the needs of persons with morbid obesity. Still, the most popular procedure is laparoscopic sleeve gastrectomy (LSG), which has had increasing acclaim in recent years.[1] All bariatric procedures are relatively novel; thus, their complications are still not well known and understood. Moreover, the treatment of such complications is not standardized. Patients after LSG may need secondary surgical treatment due to staple line leaks, unsuccessful weight loss, weight regain, or reflux. In this regard, there is a worldwide tendency to offer this group of patient conversion surgery in the form of a gastric bypass. There are several ways to perform this procedure, but Roux-en-Y gastric bypass (RYGB) and one anastomosis gastric bypass (OAGB) should be distinguished. The former, a widely accepted procedure, has the status of a gold standard of treatment for patients with obesity and concurrent diabetes mellitus. OAGB, on the other hand, as a more recent version of the gastric by-pass, was designed to be simpler and safer, but still is not accepted in all bariatric centers due to possible biliary reflux. Both of these procedures are comparable as a primary procedure.[2–4] However, there still is a

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lack of research comparing these two as conversion methods after LSG. Thus, this study aimed to compare the therapeutic effectiveness and safety of RYGB and OAGB performed as conversion surgery after failed LSG.

Materials and Methods

Study Subjects

This was a retrospective review of data from a prospectively maintained patient database at the Department of General, Endocrine and Transplant Surgery of the Medical University of Gdansk, Poland, from the years 2009–2020. The following inclusion criteria had to be met: failure or intolerance of LSG treatment for obesity, treated with either RYGB or OAGB, an elective procedure regimen, at least 5 years of regular follow-up at the outpatient clinic of the university obesity center. The qualification, operations, and postoperative observation were conducted by a fixed team of surgeons specializing in bariatric and metabolic surgery. All patients with identified failure of LSG were qualified for a conversion operation. The choice of OAGB versus RYGB procedure as the conversion operation was the joint decision of the patient and the operating surgeon based on the patient's preference. The primary exclusion criteria from the OAGB group were confirmed Barrett's esophagus or severe esophagitis (Los Angeles classification C or D).[5]These patients were offered RYGB according to International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) recommendations[6] and are included in the RYGB conversion group.

Medical Procedures

As part of the preoperative preparation, all patients underwent standard blood testing, an upper gastrointestinal endoscopy, an echocardiogram, and an abdominal ultrasound. Two weeks before surgery, a low-calorie and low-carbohydrate diet was recommended.

RYGB Technique[7,8]Fig. 1

Our clinical standard includes a transection of the gastric sleeve at the level of the crow's foot, a biliary-pancreatic limb (BPL) with a length of 100–150 cm, and an alimentary limb (AL) with a length of 100–150 cm. Anastomoses are performed side to side using laparoscopic linear staplers. A 3-cm gastrointestinal anastomosis is located on the anterior wall of the gastric pouch. Gastrointestinal loops are placed anterior to the transverse colon. As a standard, a leak test with methylene blue is per-formed and a closed vacuum drainage is left. The total length of the intestine is not measured, and the mesenteric defects are closed.

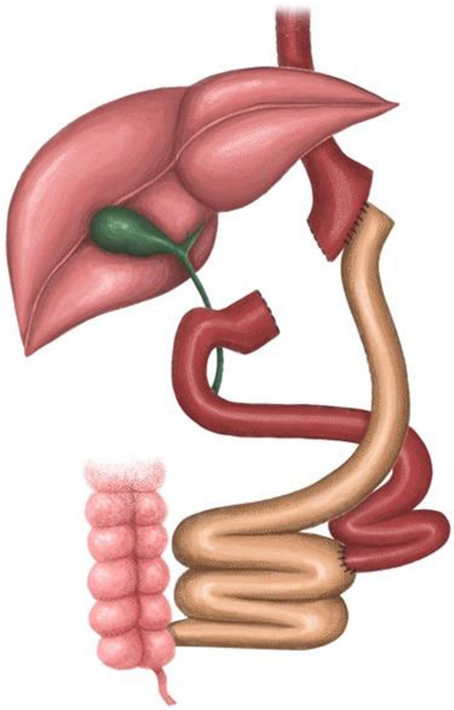

Fig. 1 Roux-en-Y gastric bypass conversion

OAGB Technique[7,8] Fig. 2

OAGB is performed according to our standard by a low transection of the gastric sleeve at the level of the crow's foot. The length of the BPL is calculated for a length of 180–250 cm. The 3-cm side-to-side anastomosis is performed with a laparoscopic linear stapler. An anti-reflux mechanism is applied in the form of a derotation suture between the distal loop and the stomach. A leak test with methylene blue is performed, and a vacuum drainage is left.

Follow-Up

Patients were discharged on the first postoperative day with the recommendation to use a liquid diet for 1 week. The diet was extended subsequently to solid foods enriched with protein-rich powder supplements. Thromboprophylaxis in

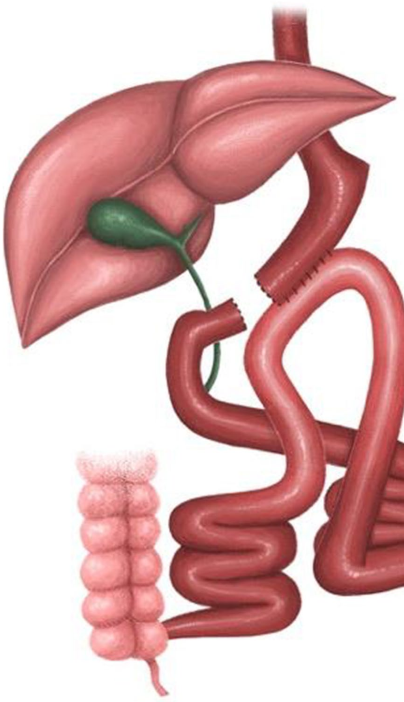

Fig. 2 One anastomosis gastric bypass conversion

the form of low-molecular-weight heparins was applied for 21 days. Peptic ulcer prophylaxis in the form of 40 mg of pantoprazole per day was recommended for 6 months. Additionally, oral supplementation with a multivitamin tablet and cholecalciferol 4000 IU daily was recommended long-term. The following visits took place in the subsequent postoperative interspace according to the scheme: 1 month, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years. During each visit, a panel of laboratory tests and anthropometric measurements were performed.

Study Definitions and Outcomes

Indications for Conversion — Definition of LSG Failure

The indication for elective surgical conversion to RYGBc or OAGBc was failure of LSG treatment defined as unsatisfactory weight loss (defined when the BMI (body mass index) was over 35 kg/m^2 and EWL (excessive weight loss) was less than 50%), referring to the Reinhold criteria[9] or resistant to the medical treatment for symptomatic gastro-esophageal reflux disease after endoscopic evaluation.

Weight Loss

The assessment was carried out regarding the change of body weight and BMI on subsequent visits. To objectively assess the effects of the obesity treatment, the percentage of excess weight loss (%EWL) calculated from the weight before the first bariatric operation and the percentage of total body weight loss (TWL) calculated from the date of the conversion operation were also evaluated.

Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (DM2) was defined according to the Polish guidelines on the management of patients with diabetes.[10] two independent results of fasting glycemia > 126 mg/dl or glycemia at 120 min OGTT (Oral Glucose Tolerance Test) > 200 mg/dl or HbA1c (Glycated hemoglobin) > 6.5%. Complete DM2 remission was defined as the euglycemic results of laboratory tests (fasting glucose level < 100 mg/dL with HbA1c level < 6.0%) at the discontinuation of insulin therapy and oral antidiabetic drugs. Patients who achieved only partial remission (reached only partial improvement on the fasting glucose level, HbA1c level, reduced doses of insulin and/or oral antidiabetic drugs) were not considered as treatment success in the evaluation of the outcome.

Hypertension

Hypertension (HT) was defined as an arterial pressure higher than 140/90 mmHg. The remission of HT was considered to achieve an arterial pressure of < 120/80 mmHg with the simultaneous withdrawal of antihypertensive medicaments.

Obstructive Sleep Apnea Syndrome

OSAS was recognized when the AHI (Apnea–Hypopnea Index) > 14 or AHI > 4 with typical symptoms. The follow-up was not controlled by a polysomnographic examination. Remission was considered to be the resolution of the clinical symptoms typical for OSAS.

Dyslipidemia

Dyslipidemia (DL) remission was diagnosed by levels of total cholesterol < 200 mg/dl and HDL > 40 mg/dl in men and > 50 mg/dl in women.

Nutritional Parameters and Anemia

Nutritional parameters were estimated at each visit to the surgical outpatient clinic. Anemia was diagnosed according to the WHO (World Health Organization) definition, with hemoglobin < 12 g/dl in women and < 13 g/dl in men. Moderate anemia was defined as hemoglobin values of 8–11 g/dl. Severe anemia was defined as hemoglobin at < 8 g/dl. Nutritional status was assessed by determining the levels of albumin (norm 30–50 g/l), iron (norm 50–170 µg/dl), vitamin B12 (norm 180–914 ng/l), and 25-hydroxy vitamin D (norm 10–50 ng/ml).

Gastro-esophageal Reflux Disease

Gastro-esophageal reflux was diagnosed based on symptoms in the form of regurgitation and a feeling of heartburn despite adequate medical treatment. All patients were evaluated preoperatively with esophagogastroduodenoscopy to confirm endoscopic features of reflux such as esophagitis assessed in Los Angeles classification.[5] Thereafter, during the postoperative follow-up period, patients were required to undergo follow-up endoscopy after 2 years or sooner in case of symptoms of gastroesophageal reflux. As a standard, neither multichannel intraluminal impedance nor pH-metry were not performed. Remission was defined as the complete resolution of clinical symptoms and independence from oral anti-reflux medications.

Outcomes and Outcome Measures

The primary outcome was the results of weight loss over a 5-year period after the conversion surgery, measured as a change of %EWL and %TWL. The secondary outcome was the effectiveness of methods in the treatment of comorbidities, measured as the ratio of comorbidities after 5 years. The tertiary outcome was the safety of both methods, measured as the rate of complications. The goal was to indicate a method that would give better weight loss results 5 years after the conversion operation. The secondary goal was to indicate the method characterized by a more effective remission of comorbidities. The tertiary goal was to indicate the method characterized by a safer profile of complications.

Statistical Methods

Descriptive statistics were performed using means and standard deviations (SDs) for normally distributed data, and medians and interquartile ranges (IQRs) for the remaining data. Normality was tested with the Shapiro–Wilk test. Categorical data were compared with the use of contingency tables and chi-squared tests, and if there were less than 5 observations, Fisher's exact test was used. Continuous data with normal distributions were compared with *t*-tests, and for samples with unequal variance, Welch's correction was used. Continuous data with non-normal distribution were compared with Mann–Whitney *U* tests. The *P*-value was considered significant at < 0.05. All tests were two-sided. All analyses were performed, and graphs were plotted with the use of GraphPad Prism 8.4.3 (GraphPad Software, LLC., CA, USA) statistical software.

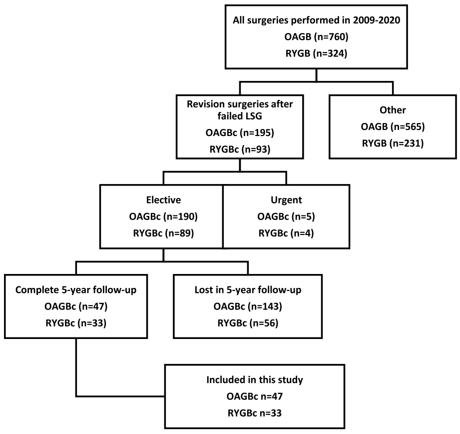

Fig. 3 Group enrolment. LSG laparoscopic sleeve gastrectomy, OAGB one anastomosis gastric bypass, RYGB Roux-en-Y gastric bypass, OAGBc OAGB conversion, RYGBc RYGB conversion

Results

Study Sample

Out of 3140 patients treated surgically in the Department of General, Transplant and Endocrine Surgery between 2009 and 2020, two groups of patients were initially distinguished who underwent RYGB ($n = 93$) or OAGB ($n = 760$) surgery. Out of these, 33 patients after RYGB and 47 after the OAGB procedure met the inclusion criteria. The enrolment process is shown in Fig. 3. Comparative demographic data are presented in Table 1. In the study group, the reasons for conversion were unsatisfactory weight loss in 44 (93.6%) OAGBc and 20 (60.6%) RYGBc patients, weight regain in 2 (4.3%) OAGBc and 5 (15.2%) RYGBc patients, and symptomatic reflux in 1 (2.1%) OAGBc and 8 (24.2%) RYGBc patients. In the preoperative endoscopic evaluation of patients qualified for conversion due to reflux, a patient in the OAGBc group presented with heartburn and regurgitations without features

Table 1 Demographic characteristics before conversion. OAGBc – one anastomosis gastric bypass conversion. RYGBc – Roux-en-Y gastric bypass conversion. BMI – body mass index. WBC – white blood count. DM2 – diabetes mellitus type 2. HT – hypertension. OSAS – obstructive sleep apnea syndrome. DL – dyslipidemia. GERD – gastroesophageal reflux disease

	RYGBc (*n*=33)	OAGBc (*n*=47)	*p* value
Age (mean ± SD)	41.24 ± 8.906	45.02 ± 10.71	0.100
Sex (F/M)	27 / 6	34 / 13	
Weight ± SD (kg)	105.52 ± 18.1	115.17 ± 20.81	0.036
BMI ± SD (kg/m^2)	38.70 ± 6.84	40.44 ± 5.8	0.228
Albumin ± IQR (mg/dl)	38 ± 3	39.79 ± 3	0.146
Creatinine ± IQR (mg/dl)	0.75 ± 0.1	0.8 ± 0.15	0.033
Hemoglobin ± SD (g/dl)	13.5 ± 1.22	14.37 ± 1.3	0.012
WBC ± SD (10′3/ul)	7.331 ± 1.77	7.52 ± 1.53	0.658
DM2 *n* (%)	6 (18%)	12 (25.5%)	0.438
HT *n* (%)	10 (30%)	22 (47%)	0.138
OSAS *n* (%)	1 (3%)	5 (11%)	0.203
DL *n* (%)	6 (18%)	22 (47%)	0.008
GERD n (%)	10 (30%)	7 (15%)	0.097
Conversion reason			
Unsatisfactory weight loss	20 (60.6%)	44 (93.6%)	
Weight regain	5 (15.2%)	2 (4.3%)	
Symptomatic reflux	8 (24.2%)	1 (2.1%)	

Table 2 Weight loss. OAGBc – one anastomosis gastric bypass conversion. RYGBc – Roux-en-Y gastric bypass conversion. EWL% – percentage of excess weight loss. TWL% – percentage of total body weight loss

	OAGBc	RYGBc	*p* value
EWL% after 1 y ± SD (%)	85.1 ± 18.68	79.47 ± 21.15	0.302
EWL% after 2 y ± SD (%)	82.57 ± 21.48	79.6 ± 22.99	0.666
EWL% after 3 y ± SD (%)	78.64 ± 24.85	73.51 ± 23.33	0.578
EWL% after 4 y ± SD (%)	82.86 ± 19.32	70.43 ± 17.19	0.121
EWL% after 5 y ± SD (%)	84.04 ± 18.81	72.95 ± 20.3	0.218
TWL% after 1 y ± SD (%)	26.78 ± 10.09	21.48 ± 11.27	0.073
TWL% after 2 y ± SD (%)	25.66 ± 11.2	19.76 ± 14.34	0.128
TWL% after 3 y ± SD (%)	24.46 ± 13.83	13.85 ± 13.85	0.050
TWL% after 4 y ± SD (%)	25.17 ± 11.87	13.4 ± 9.38	0.018
TWL% after 5 y ± SD (%)	21.81 ± 12.48	18.39 ± 11.85	0.546

of esophagitis. Otherwise, in the RYGBc group, there were six cases of grade C esophagitis and one grade D esophagitis. No patient in the study group had Barrett's esophagus. Patients with reflux burden but qualified for conversion for other reasons had no evidence of esophagitis on preoperative gastroscopy.

Weight Loss

After conversion surgery, no statistically significant differences in weight loss and BMI were found between the RYGBc (RYGB conversion) and OAGBc (OAGB conversion) groups except for a higher %TWL after 4 years of follow-up in the OAGBc group than in the RYGBc group (25.17 ± 11.87% vs 13.4 ± 9.38% $p = 0.018$, respectively). Full results of %EWL and %TWL are shown in Table 2. Changes in weight loss and BMI are shown in Fig. 4.

Impact on Comorbidities

After a 5-year follow-up period, DM2 remission was reached significantly more often in OAGBc (11/12; 91.7%) than in RYGBc (2/6; 33%) patients ($p = 0.035$). GERD remission was reached in 5 (71.4%) OAGBc and 4 (40%) RYGBc patients ($p > 0.99$) with complete resolution of reflux symptoms and features of esophagitis in endoscopy. In the RYGBc group, of the 10 patients with GERD before conversion, 4 patients achieved complete remission — these were patients qualified for conversion due to GERD. The remaining 6 patients achieved a reduction in their symptoms and a reduction in esophagitis to LA grade A. There were no new cases of GERD after conversion in this group. In the OAGBc group of 7 patients with GERD before conversion, 5 achieved complete remission — including the one patient who was eligible for conversion because of GERD. In the other two patients, symptoms of GERD persisted with no endoscopic features of esophagitis before or after conversion. However, there were 7 new cases of symptomatic GERD without features of esophagitis in endoscopy in this group after conversion. Changes in the prevalence of the remaining comorbidities did not differ significantly after the conversion operation and are presented in detail in Table 3.

Impact on Nutritional Status

During the 5-year follow-up period, 22 (46.8%) OAGBc patients and 14 (42.4%) RYGBc patients ($p = 0.698$) developed anemia. In all cases, it was microcytic anemia treated with additional oral iron supplementation, except for two patients requiring intravenous supplementation (one from each group). The details are presented in Table 4. No statistically significant differences in hemoglobin concentrations between patients after OAGBc and RYGBc were found. No statistically significant differences between the groups were detected in the concentrations of iron, vitamin B12, vitamin D, and serum albumin in subsequent years. The results are presented in Table 5.

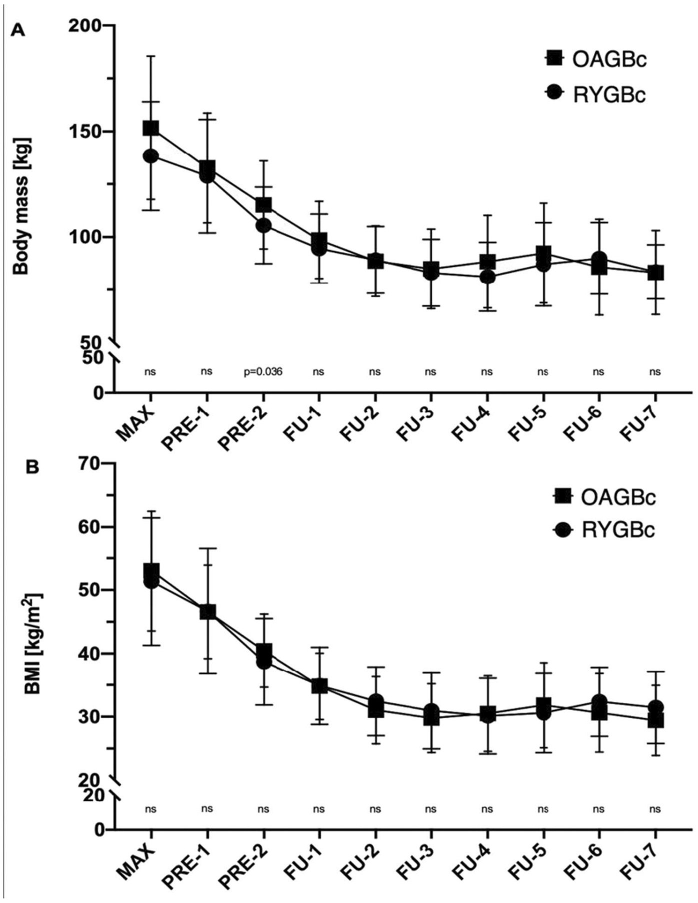

Fig. 4 Weight (panel **A**) and BMI (panel **B**) changes: means with SDs. Significant *p*-values are shown. Non-significant *p*-values are shown as "ns." SDs for RYGBc have long dashes. SDs for OAGBc have short dashes. Note that the *Y*-axis has been divided to better visualize details. OAGBc one anastomosis gastric bypass conversion, RYGBc Roux-en-Y gastric bypass conversion, MAX maximum weight/BMI, PRE-1,2 weight/BMI before conversion. Consecutive follow-up: FU1 — 3 months, FU-2 — 6 months, FU-3 — 1 year, FU-4 — 2 years, FU-5 — 3 years, FU-6 — 4 years, FU-7 — 5 years

Complications

There were no statistically significant differences in the number of complications between the OAGBc and RYGBc groups. The Comprehensive Complication Index (CCI®)[11] was 17.85 (± IQR 29.6) on average in the OAGBc group and 14.92 (± IQR 21.75) in the RYGBc group at $p = 0.375$. Symptomatic GERD occurred in 6 patients after OAGBc and 3 patients after RYGBc. Upper gastrointestinal bleeding occurred in two patients of each group. Marginal ulceration of the gastrointestinal anastomosis was diagnosed in 3 OAGBc and 4 RYGBc patients. Perforation of the anastomotic site occurred in 3 (6.3%) patients of the OAGBc but none from the RYGBc group (respectively after 3, 3, and 5 years post OAGBc). The first case was a patient with a history of gastritis in whom the obstetrician discontinued proton pump inhibitors during pregnancy, the perforation occurred a few months after delivery, and the patient did not undergo the recommended endoscopic follow-up after delivery. The second case was a patient who developed anastomotic perforation during antiviral treatment for hepatitis C. The third case involved a perforation of the anastomotic site on the first day after cholecystectomy of unclear iatrogenic or ulcerative etiology. No early anastomotic leaks (< 30 day post OAGBc/RYGBc) were identified. Stenosis of the gastrointestinal anastomosis was found in two patients from each group. One patient from the OAGBc and none from the RYGBc group experienced a perforation of the small

Table 3 Comorbidities. LSG – laparoscopic sleeve gastrectomy. OAGB – one anastomosis gastric bypass. RYGB – Roux-en-Y gastric bypass. BMI – body mass index. WBC – white blood count. DM2 – diabetes mellitus type 2. HT – hyper-tension. OSAS – obstructive sleep apnea syndrome. DL – dyslipidemia. GERD – gastroesophageal reflux disease

Comorbidities	RYGB (*n* = 33)	OAGB (*n* = 47)	*p* value
DM2 before LSG *n* (%)	10 (30%)	16 (34%)	0.811
DM2 before conversion	6 (18%)	12 (25.5%)	0.588
DM2 after conversion	4 (12%)	1 (2%)	0.026
DM2 remissions *n* (%)	2 (33%)	11 (91.7%)	0.035
HT before LSG	13 (39%)	25 (53%)	0.261
HT before conversion	10 (10%)	22 (47%)	0.168
HT after conversion	7 (21%)	16 (34%)	0.3157
HT remissions *n* (%)	3 (30%)	6 (27.3%)	0.729
OSAS before LSG	3 (9%)	5 (11%)	> 0.999
OSAS before conversion	1 (3%)	5 (11%)	0.392
OSAS after conversion	0	2 (4%)	0.509
OSAS remissions *n* (%)	1 (100%)	3 (60%)	0.639
DL before LSG	6 (18%)	23 (49%)	0.005
DL before conversion	6 (18%)	22 (47%)	0.010
DL after conversion	1 (3%)	9 (19%)	0.041
DL remissions *n* (%)	5 (83.3%)	13 (59.1%)	0.277
GERD before LSG	5 (15%)	8 (17%)	> 0.999
GERD before conversion	10 (30%)	7 (15%)	0.16
GERD after conversion	6 (18%)	9 (19%)*	> 0.999
GERD remissions *n* (%)	4 (40%)	5 (71.4%)	> 0.999

*7 newly diagnosed cases of reflux not seen before conversion

intestine due to iatrogenic injury during abdominoplasty. Hemoperitoneum was found in one patient after RYGBc and in none of the OAGBc patients. An infection of the surgical wound was found in two patients of each group. Rehospitalization due to abdominal pain was necessary for two OAGBc patients and one RYGBc patient. Symptomatic malnutrition syndrome was found in 4 OAGBc patients and 3 RYGBc patients. Only the patient with a perforation of the small intestine required reoperation. Perforations of the gastrointestinal anastomosis site were effectively treated endoscopically with a gastric stent. An analysis of the frequency and severity of complications is presented in Tables 6 and 7.

Discussion

Our study did not reveal statistically significant differences in weight loss between the RYGBc and OAGBc operations. Both evaluated procedures are also characterized by a similar course of postoperative BMI change, in which a rapid decline in the first year after surgery and a slight increase and stabilization in the third year of observation has been noticed. These results show that both bypass methods of conversion allow the criteria of the effectiveness of bariatric treatment to be achieved with a similar stability profile; however, it was not possible to indicate the more effective one. This result may correspond to the results of the primary operations obtained in the YOMEGA study[2] in which %EWL of 87.9% in RYGB patients and 85.8% in OAGB patients after a 2-year follow-up period and found no significant statistical difference between these procedures. A similar lack of differences was published by Lee et al. in 2005[12] after a 2-year follow-up period. Regarding the remission of diseases accompanying obesity, the potential advantage of OAGBc over RYGBc was demonstrated in the treatment of diabetes. A potential explanation could be that the high concentration of bile in a distinctly long BPL promotes the enhancement of the portal recirculation of bile acids, which eventually influences metabolism improvement.[13] Similar results were obtained in a weighty YOMEGA[2] study and a meta-analysis published by Magouliotis et al.[14] suggesting that patients with DM2 may benefit more from OAGB review surgery.

GERD is often the reason for qualification for conversion after LSG. It has been evidenced to increase the incidence of esophagitis and Barrett's esophagus.[15] The beneficial

Table 4 Anemia and hemoglobin levels. OAGBc – one anastomosis gastric bypass conversion. RYGBc – Roux-en-Y gastric bypass conversion. Hb – hemoglobin serum level

Anemia	OAGBc *n* = 47	RYGBc *n* = 33	*p* value
Mild anemia	9	8	0.592
Moderate anemia	12	6	0.588
Severe anemia	1	0	> 0.999
Anemia general	22 (46.8%)	14 (42.4%)	0.352
Hb level before LSG ± SD (g/dl)	14.54 ± 1.31	14.19 ± 0.68	0.471
Hb level before conversion ± SD (g/dl)	14.37 ± 1.3	13.5 ± 1.22	0.012
Hb level after 1 y ± IQR (g/dl)	13.04 ± 1.55	12.69 ± 2.27	0.079
Hb level after 2 y ± SD (g/dl)	12.61 ± 2	12.79 ± 1.82	0.744
Hb level after 3 y ± IQR (g/dl)	12.78 ± 1.68	11.95 ± 1.95	0.116
Hb level after 4 y ± SD (g/dl)	12.73 ± 1.79	11.98 ± 1.88	0.251
Hb level after 5 y ± SD (g/dl)	12.36 ± 1.84	11.82 ± 2.1	0.548

Table 5 Nutritional status parameters. OAGBc – one anastomosis gastric bypass conversion. RYGBc – Roux-en-Y gastric bypass conversion

	OAGBc	RYGBc	*p* value
Iron before conversion ± SD (μg/dl)	100.9 ± 34.45	130.2 ± 87.61	0.204
Iron after 1 y ± IQR (μg/dl)	96.14 ± 51.05	106.8 ± 38	0.341
Iron after 2 y ± SD (μg/dl)	75.85 ± 34.29	61.58 ± 32.12	0.215
Iron after 3 y ± IQR (μg/dl)	78.68 ± 57.3	59.3 ± 33.75	0.140
Iron after 4 y ± SD (μg/dl)	81.16 ± 40.6	91.27 ± 54.35	0.539
Iron after 5 y ± SD (μg/dl)	67.05 ± 41.23	67.83 ± 40.43	0.968
Vit. B12 before conversion ± IQR (ng/ml)	490.9 ± 286.2	324.5 ± 132.5	0.109
Vit. B12 1 y ± IQR (ng/ml)	444 ± 238	448.4 ± 430.5	0.953
Vit. B12 2 y ± IQR (ng/ml)	653 ± 307.5	568.3 ± 719.2	0.662
Vit. B12 3 y ± IQR (ng/ml)	2809 ± 274.2	561.3 ± 376	0.614
Vit. B12 4 y ± IQR (ng/ml)	454 ± 180.5	398.2 ± 332.2	0.809
Vit. B12 5 y ± SD (ng/ml)	379.1 ± 155.9	370.5 ± 130	0.905
Vit. D before conversion ± SD (ng/ml)	20.23 ± 9.58	24.68 ± 8.80	0.389
Vit. D 1 y ± IQR (ng/ml)	22.01 ± 14.8	20.44 ± 21.98	0.344
Vit. D 2 y ± SD (ng/ml)	19.84 ± 10.29	27.91 ± 20.32	0.088
Vit. D 3 y ± IQR (ng/ml)	23.49 ± 15	25.16 ± 31	0.964
Vit. D 4 y ± IQR (ng/ml)	22.82 ± 16.7	21.25 ± 15.9	0.525
Vit. D 5 y ± IQR (ng/ml)	39.11 ± 49.95	28.4 ± 22.55	0.545
Albumin before conversion ± IQR (g/l)	39.79 ± 3	38 ± 3	0.146
Albumin 1 y ± IQR (g/l)	37.65 ± 4	37.25 ± 5.5	0.522
Albumin 2 y ± IQR (g/l)	37.88 ± 4	38.15 ± 6	0.496
Albumin 3 y ± IQR (g/l)	37.15 ± 3.38	36.33 ± 6.8	0.702
Albumin 4 y ± IQR (g/l)	36 ± 3.75	36.44 ± 7	0.668
Albumin 5 y ± SD (g/l)	37.21 ± 3.58	40.33 ± 1.97	0.055

Table 6 Complications. OAGBc – one anastomosis gastric bypass conversion. RYGBc –Roux-en-Y gastric bypass conversion. GERD – gastroesophageal reflux disease. GI – gastro-intestinal

	OAGBc	RYGBc	*p*	Clavien-Dindo
GERD	6	3	0.729	2
Anemia	22	14	0.352	2
GI bleeding	1	1	> 0999	3a
Hematoperitoneum	0	1	0.413	2
Malnutrition	4	3	> 0.999	2
Anastomosis ulceration	3	4	0.439	2
Anastomosis stenosis	1	1	> 0.999	3a
Abdominal pain	2	1	> 0.999	1
Anastomosis perforation	3	0	0.264	3b
Bowel perforation	1	0	> 0.999	4b
Wound infection	1	1	> 0.999	3b

Table 7 Clavien-Dindo scoring

Clavien-Dindo	OAGBc	RYGBc	*p*
I	2	1	0.043
II	35	25	0.13
IIIa	2	1	0.043
IIIb	6	1	0.128
IVa	0	0	0.000
IVb	1	0	0.21
V	0	0	0.000

effect found in our study on the resolution of esophagitis in patients after RYGBc is confirmed by similar Felsenreich et al. findings.[16] The limitation of our study is the lack of analysis of the effect of OAGBc on esophagitis. It resulted from following the IFSO recommendations[6] from the period in which the patients were qualified for conversion. RYGBc was recommended method in patients with esophagitis following LSG. However, the analysis of the effect of conversion to gastric bypass on the treatment of reflux is very difficult. This is mainly because both acid and biliary reflux have similar symptoms, and tests that distinguish between them, e.g., multichannel intraluminal impedance (MII), have only recently started to appear in the standards of care for bariatric patients. First study analyzing this indicates an increased incidence of biliary reflux after OAGB assessed in MII.[17] Thus, it may be the cause of newly diagnosed GERD in patients in the OAGBc group. However, its role in the persistence of reflux in RYGBc patients should also be considered. A more detailed analysis of the prevalence of biliary reflux and its impact on patients after gastric bypass surgery needs to be further investigated in future studies. The concern regarding the oncological consequences of biliary reflux[18,19] , still is widely debated on international forums.[20]

With regard to the risk of developing anemia and malnutrition complications following our proposed conversion options, no statistically significant differences have been found. Studies suggesting more frequent deficiency complications after OAGB surgery, such as by Genser et al.[21] , are based on the analysis of patients with an average BPL length of 320 cm. On the basis of these results, a simple correlation between the length of the BPL and the risk of deficiency complications can be suspected. How-ever, in the YOMEGA[2] study, when comparing 200 cm BPL–OAGB to RYGB with 150 cm AL and 50 cm BPL, a statistically significant difference in the incidence of malnutrition complications was reported, exposing OAGB as the more hazardous procedure. This may indicate that the mechanism of occurrence of such distant complications is still insufficiently studied and requires a deeper analysis; however, the standardization of the procedures should first be established. The guidelines for reporting the technical details described in publications on bariatric operations also should be unified. The education and compliance of patients in the postoperative long-term period are commonly approved as being the fundamental independent factor influencing the effect of primary and conversion surgeries.[22, 23, 24] Although the authors' institution provides postoperative psychological and dietetic care, the remote measurement of compliance with diet and supplementation seems to be extremely difficult. However, continuous monitoring of the nutritional status of post-bariatric patients is the obvious duty of the multidisciplinary team.

The percentage of complications found in the study group appears to be high. They are coherent with the fact stated in a large multicenter analysis that conversion surgery is burdened with a higher rate of complications and perioperative mortality than primary surgery.[25] However, as in our material, most of them can be successfully treated with endoscopy. It is noteworthy that most late surgical complications arise from ulceration of the anastomotic region. The risk of ulcer formation seems to accompany patients after gastric bypass surgery for the rest of their lives. Therefore, it is important to pay attention to endoscopic follow-up and prompt treatment of diagnosed peptic ulcer disease.

The limitations of the present study include the retrospective and observational character of the collected data. The database, however, was constructed and has been maintained prospectively and contains the parameters needed for the study. A relatively small study sample is the result of a combination of the long follow-up and unsatisfactory compliance to the follow-up scheme. The latter may be a trait typical for this group of patients.[26] The observed loss to follow-up after 5 years was 74.5% for OAGBc and 60.7% for RYGBc. In accordance, Higa et al. reported a follow-up rate after RYGB of 33% at 2 years and 7% at 10 years.[27] During the procedures, the total intestinal length was not measured, which is the standard of care at our Institution and is confirmed in the IFSO recommendations.[7] Bias may also have occurred at the time of qualification. The data in Table 1 shows that the group of patients eligible for conversion due to the GERD was qualified for RYGBc. It was probably due to the willingness to follow the IFSO recommendations of the time and concern about overlapping consequences of bile reflux with acid reflux. That caused GERD with severe esophagitis to be an exclusion criterium from the OAGBc group. Nevertheless, OAGBc also presents an anti-reflux effect against acid reflux, specifically when improved with one of the anti-reflux mechanisms.[28] An independent comparison of the treatment of this complication of LSG would require a randomized controlled, blinded trial that could reliably answer the question regarding the superiority of either method. Furthermore, the low number of diabetes cases may bias the achieved outcome. The remission of diabetes depends on multiple factors that are not assessed in this study, such as age, sex, duration of the disease, drug treatment with oral hypoglycemic agents or insulin, and pancreatic reserve. Similarly, due to the lack of initial data regarding nonalcoholic fatty liver disease and liver function parameters, we were not able to evaluate these outcomes. Furthermore, the standard of care in the years of the observation period did not include an assessment of compliance with following the recommended vitamin supplementation regimen, and indicators of the change in the quality of life after surgery. The lack of significant differences in weight loss and BMI change between analyzed groups may also be due to the aforementioned retrospective nature and limited study sample, and therefore, these results should be interpreted with care. Some of the presented analyses may have been underpowered to detect significant changes. However, due to the specific clinical scenario that was analyzed and a relatively long follow-up, we believe that this study adds to the state of knowledge despite the limitations listed above.

Conclusion

Based on the results obtained in our study, OAGBc is an equally effective procedure as RYGBc for patients after the failure of LSG treatment. Both procedures demonstrate a similar safety profile and weight loss effect. OAGBc can also bring potential additional benefits to diabetic patients. Unfortunately, the consequences of reflux complications, which are more likely to affect patients during the follow-up period after OAGB, require further study.

Author Contribution Conceptualization, Ł.K. and M.W.; methodology, P.S.; validation, M.W., P.S. and M.S.; formal analysis, P.S.; investigation, M.W.; resources (performed the surgical procedures and were responsible for the qualification process and conducting the follow-up) Ł.K., M.P.-S., J.B. and M.S.; data curation, P.S.; writing—original draft preparation, M.W.; writing—review and editing, Ł.K., M.P.-S., J.B., M.D., O.R., M.S. and P.S.; visualization, P.S.; supervision, Ł.K.; project administration, M.W. All authors have read and agreed to the published version of the manuscript.

Declarations

Institutional Review Board Statement The study was conducted in accordance with the Declaration of Helsinki and approved by the Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk (nr NKBBN/368/2017).

Conflict of Interest The authors declare no competing interests.

References

1. Ozsoy, Z.; Demir, E. Which Bariatric Procedure Is the Most Popular in the World? A Bibliometric Comparison. Obes. Surg. 2018, 28, 2339–2352, doi:https://doi.org/10.1007/s11695-018-3163-6.
2. Robert, M.; Espalieu, P.; Pelascini, E.; Caiazzo, R.; Sterkers, A.; Khamphommala, L.; Poghosyan, T.; Chevallier, J.M.; Malherbe, V.; Chouillard, E.; et al. Efficacy and safety of one anastomosis gastric bypass versus Roux-en-Y gastric bypass for obesity (YOMEGA): a multicentre, randomised, open-label, non-inferiority trial. Lancet 2019, 393, 1299–1309, doi:https://doi.org/10.1016/S0140-6736(19)30475-1.
3. Navarrete, S.; Leyba, J.L.; Ll, S.N.; Borjas, G.; Tapia, J.L.; Alcázar, R. Results of The Comparative Study of 200 Cases: One Anastomosis Gastric Bypass vs Roux-en-Y Gastric Bypass. Obes. Surg. 2018, 28, 2597–2602, doi:https://doi.org/10.1007/s11695-018-3224-x
4. Level, L.; Rojas, A.; Piñango, S.; Avariano, Y. One anastomosis gastric bypass vs. Roux-en-Y gastric bypass: a 5-year follow-up prospective randomized trial. Langenbeck's Arch. Surg. 2021, 406, 171–179, doi:https://doi.org/10.1007/s00423-020-01949-1.
5. Lundell, L.R.; Dent, J.; Bennett, J.R.; Blum, A.L.; Armstrong, D.; Galmiche, J.P.; Johnson, F.; Hongo, M.; Richter, J.E.; Spechler, S.J.; et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999, 45, 172–180, doi:https://doi.org/10.1136/GUT.45.2.172.
6. Braghetto, I., Csendes, A. Patients Having Bariatric Surgery: Surgical Options in Morbidly Obese Patients with Barrett's Esophagus. Obes. Surg. 2016, 26, 1622–1626. https://doi.org/10.1007/s11695-016-2198-9
7. Bhandari, M.; Fobi, M.A.L.; Buchwald, J.N.; Bariatric Metabolic Surgery Standardization (BMSS) Working Group:. Standardization of Bariatric Metabolic Procedures: World Consensus Meeting Statement. Obes. Surg. 2019, 29, 309–345, doi:https://doi.org/10.1007/S11695-019-04032-X.
8. Almalki, O.M.; Lee, W.J.; Chen, J.C.; Ser, K.H.; Lee, Y.C.; Chen, S.C. Revisional Gastric Bypass for Failed Restrictive Procedures: Comparison of Single-Anastomosis (Mini-) and Roux-en-Y Gastric Bypass. Obes. Surg. 2018, 28, 970–975, doi:https://doi.org/10.1007/S11695-017-2991-0/TABLES/5.
9. Reinhold, R.B. Critical analysis of long term weight loss following gastric bypass. Surg. Gynecol. Obstet. 1982, 155, 385–394.
10. Araszkiewicz, A.; Bandurska-Stankiewicz, E.; Budzyński, A.; Cypryk, K.; Czech, A.; Czupryniak, L.; Drzewoski, J.; Dzida, G.; Dziedzic, T.; Franek, E.; et al. 2020 Guidelines on the management of diabetic patients. A position of Diabetes Poland. Clinical Diabetology Vol 9, No 1. Gdańsk: Via Medica, 2020. DOI:https://doi.org/10.5603/DK.2020.0001
11. Slankamenac, K.; Graf, R.; Barkun, J.; Puhan, M.A.; Clavien, P.A. The comprehensive complication index: A novel continuous scale to measure surgical morbidity. Ann. Surg. 2013, 258, 1–7, doi:https://doi.org/10.1097/SLA.0b013e318296c732.
12. Lee, W.J.; Yu, P.J.; Wang, W.; Chen, T.C.; Wei, P.L.; Huang, M. Te Laparoscopic Roux-en-Y versus mini-gastric bypass for the treatment of morbid obesity: A prospective randomized controlled clinical trial. Ann. Surg. 2005, 242, 20–28, doi:https://doi.org/10.1097/01.sla.0000167762.46568.98.
13. Risstad, H.; Kristinsson, J.A.; Fagerland, M.W.; le Roux, C.W.; Birkeland, K.I.; Gulseth, H.L.; Thorsby, P.M.; Vincent, R.P.; Engström, M.; Olbers, T.; et al. Bile acid profiles over 5 years after gastric bypass and duodenal switch: results from a randomized clinical trial. Surg. Obes. Relat. Dis. 2017, 13, 1544–1553, doi:https://doi.org/10.1016/j.soard.2017.05.024.
14. Magouliotis, D.E.; Tasiopoulou, V.S.; Tzovaras, G. One anastomosis gastric bypass versus Roux-en-Y gastric bypass for morbid obesity: a meta-analysis. Clin. Obes. 2018, 8, 159–169, doi:https://doi.org/10.1111/cob.12246.
15. Felsenreich, D.M., Ladinig, L.M., Beckerhinn, P. et al. Update: 10 Years of Sleeve Gastrectomy—the First 103 Patients. Obes. Surg. 2018, 28, 3586–3594. https://doi.org/10.1007/s11695-018-3399-1
16. Felsenreich, D.M., Steinlechner, K., Langer, F.B. et al. Outcome of Sleeve Gastrectomy Converted to Roux-en-Y Gastric Bypass and One-Anastomosis Gastric Bypass. Obes. Surg. 2022, 32, 643–651. https://doi.org/10.1007/s11695-021-05866-0
17. Tolone S, Cristiano S, Savarino E, Lucido FS, Fico DI, Docimo L. Effects of omega-loop bypass on esophagogastric junction function. Surg Obes Relat Dis. 2016;12(1):62-69. doi:https://doi.org/10.1016/j.soard.2015.03.011
18. Bruzzi, M.; Duboc, H.; Gronnier, C.; Rainteau, D.; Couvelard, A.; Le Gall, M.; Bado, A.; Chevallier, J.M. Long-Term Evaluation of Biliary Reflux After Experimental One-Anastomosis Gastric Bypass in Rats. Obes. Surg. 2017, 27, 1119–1122, doi:https://doi.org/10.1007/s11695-017-2577-x.
19. Nishijima, K.; Miwa, K.; Miyashita, T.; Kinami, S.; Ninomiya, I.; Fushida, S.; Fujimura, T.; Hattori, T. Impact of the biliary diversion procedure on carcinogenesis in Barrett's esophagus surgically induced by duodenoesophageal reflux in rats. Ann. Surg. 2004, 240, 57–67, doi:https://doi.org/10.1097/01.sla.0000130850.31178.8c.
20. Mahawar, K.K.; Borg, C.M.; Kular, K.S.; Courtney, M.J.; Sillah, K.; Carr, W.R.J.; Jennings, N.; Madhok, B.; Singhal, R.; Small, P.K. Understanding Objections to One Anastomosis (Mini) Gastric Bypass: A Survey of 417 Surgeons Not Performing this

Procedure. Obes. Surg. 2017, 27, 2222–2228, doi:https://doi.org/10.1007/s11695-017-2663-0.
21. Genser, L.; Soprani, A.; Tabbara, M.; Siksik, J.M.; Cady, J.; Carandina, S. Laparoscopic reversal of mini-gastric bypass to original anatomy for severe postoperative malnutrition. Langenbeck's Arch. Surg. 2017, 402, 1263–1270, doi:https://doi.org/10.1007/s00423-017-1615-4
22. Ristanto, A.; Caltabiano, M.L. Psychological Support and Wellbeing in Post-Bariatric Surgery Patients. Obes. Surg. 2019, 29, 739–743, doi:https://doi.org/10.1007/s11695-018-3599-8.
23. Livhits, M.; Mercado, C.; Yermilov, I.; Parikh, J.A.; Dutson, E.; Mehran, A.; Ko, C.Y.; Shekelle, P.G.; Gibbons, M.M. Is social support associated with greater weight loss after bariatric surgery?: A systematic review. Obes. Rev. 2011, 12, 142–148.
24. Odom, J.; Zalesin, K.C.; Washington, T.L.; Miller, W.W.; Hakmeh, B.; Zaremba, D.L.; Altattan, M.; Balasubramaniam, M.; Gibbs, D.S.; Krause, K.R.; et al. Behavioral predictors of weight regain after bariatric surgery. Obes. Surg. 2010, 20, 349–356, doi:https://doi.org/10.1007/s11695-009-9895-6.
25. Gero D, Vannijvel M, Okkema S, et al.. Defining Global Benchmarks in Elective Secondary Bariatric Surgery Comprising Conversional, Revisional, and Reversal Procedures. Annals of Surgery. 2021; 274 (5): 821-828. doi: https://doi.org/10.1097/SLA.0000000000005117.
26. Sockalingam, S.; Cassin, S.; Hawa, R.; Khan, A.; Wnuk, S.; Jackson, T.; Okrainec, A. Predictors of Post-bariatric Surgery Ap-pointment Attendance: the Role of Relationship Style. Obes. Surg. 2013, 23, 2026–2032, doi:https://doi.org/10.1007/S11695-013-1009-9.
27. Higa, K.; Ho, T.; Tercero, F.; Yunus, T.; Boone, K.B. Laparoscopic Roux-en-Y gastric bypass: 10-year follow-up. Surg. Obes. Relat. Dis. 2011, 7, 516–525, doi:https://doi.org/10.1016/J.SOARD.2010.10.019.
28. Slagter, N., Hopman, J., Altenburg, A.G. et al. Applying an Anti-reflux Suture in the One Anastomosis Gastric Bypass to Prevent Biliary Reflux: a Long-Term Observational Study. Obes. Surg. 2021, 31, 2144–2152, doi:https://doi.org/10.1007/s11695-021-05238-8

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Communication

Short-Term Effect of One-Anastomosis Gastric Bypass on Essential Fatty Acids in the Serum of Obese Patients

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Abstract: One-anastomosis gastric bypass is a promising type of bariatric surgery, but it may lead to a deficiency in important nutrients, such as fatty acids. The short-term effects of one-anastomosis gastric bypass on serum fatty acids have not been studied thus far. Therefore, the aim of this study was to determine the effect of one-anastomosis gastric bypass on serum fatty acid composition two weeks after surgery. This study included 38 patients who underwent one-anastomosis gastric bypass as surgical treatment for morbid obesity. Serum fatty acid composition was analyzed before and two weeks after surgery using gas chromatography–mass spectrometry. We observed a decrease in essential polyunsaturated fatty acids ($p < 0.001$ for linolenic acid and $p < 0.001$ for linoleic acid) and odd-chain fatty acids ($p = 0.004$) in the serum of obese patients shortly after a one-anastomosis gastric bypass. Considering the benefits of the aforementioned fatty acids for human health, the implementation of a fatty-acid-rich diet or the use of supplementation may be recommended for patients immediately after one-anastomosis gastric bypass.

Keywords: essential fatty acids; odd-chain fatty acids; obesity; one-anastomosis gastric bypass

1. Introduction

Bariatric surgery (BS) is currently the most effective method for obesity treatment [1]. However, some studies demonstrated negative BS effects, such as limited nutrient uptake, hypoglycemia, and osteoporosis [1]. Others focused on the advantages of BS, including diabetes remission and a reduction in the risk of coronary disease and cancer [2]. Some emphasized that the effect of BS on obese patients depends on the surgical technique used [3]. The status of BS as a weight-reduction treatment is evolving to reflect its potential use as a treatment for metabolic disorders. It is worth focusing on patient comfort and health in the postsurgical period, when the body is weak and requires nutritional support. Fatty acids (FAs) are important molecules that act as substrates for cellular-energy production, cell-membrane formation, and cell signaling [4]. Some FAs, despite existing in small quantities, play an important role in the human body. Examples of such FAs are omega-3 polyunsaturated FAs (n-3 PUFAs), which have anti-inflammatory properties, branched-chain saturated FAs (BCFAs), which were shown to display antitumor effects, and odd-chain saturated FAs (OCFAs), which were shown to exert antibiotic, anti-inflammatory, and antioxidant effects [4,5]. Reductions in the levels of some FAs in the serum of obese patients were observed after BS due to decreased postoperative dietary intake [6]. Interestingly, reports to date described the short- and long-term effects of laparoscopic sleeve gastrectomy (LSG), biliopancreatic diversion with a duodenal switch (BPDDS) [6], and Roux-en-Y gastric bypass (RYGB) on serum FA composition [7,8]. However, the short-term period after one-anastomosis gastric bypass (OAGB) has not been investigated. OAGB is a promising type of BS that improves metabolic parameters [9]. Therefore, the aim of this study was to determine the effect of OAGB on the levels of particular FAs in the serum of obese patients two weeks after BS. We also compared serum FA composition in obese patients before and after surgery with lean control subjects.

2. Materials and Methods

2.1. Study Subjects

This study included 38 patients (32 females and 6 males) who underwent OAGB as a surgical treatment for morbid obesity. Thirteen patients had type 2 diabetes mellitus. Blood was collected in the morning on the day of the surgery. Obese patients were on a low-calorie diet (high-protein, low-fat, and low-carbohydrate meals) for 2–3 months prior to surgery. Patients did not take any weight-loss medications before surgery. In every case, a 180 cm segment of the small intestine was removed, and a standardized 50 mL stomach pouch was created. All of the enrolled study patients underwent a follow-up visit 2 weeks after surgery. The control group consisted of 30 lean individuals (15 males and 15 females) without metabolic disorders. Fasting blood samples from all study subjects were collected in the morning to assay serum FA composition. During the first 2 weeks after surgery, as the stomachs began to heal, it was recommended that patients consume low-sugar, low-fat, and high-protein liquids and mashed foods, i.e., cream soup consisting of poultry, eggs, and fish. Patients were required to restrict their caloric intake, often to less than 500 kcal per day. Patients were advised to consume natural (unsweetened) milk products such as yogurt, buttermilk, kefir, and vegan milk (i.e., sesame and soya). Pure protein powder was added to these products. It was instructed that food should be frequently consumed and in small portions, i.e., every 3 h. Water, noncarbonated flavored water, ice cubes, tea without sugar, juices diluted with water, sugarfree jelly, protein-containing drinks, and protein-containing fruit drinks (e.g., smoothies) were also recommended. The most important recommendation was that protein intake should be greater than 60 g/day. Vitamin regimens specific for bariatric patients were used from the first postoperative day. Omega acid supplementation was not routinely recommended. The study was performed in agreement with the principles of the Declaration of Helsinki of the World Medical Association. The study protocol was approved by the Local Bioethics Committee at the Medical University of Gdansk (decision no. NKBBN/493/2016), and written informed consent was obtained from all participants.

Characteristics of lean subjects and obese patients before and 2 weeks after OAGB are presented in Table 1.

2.2. Serum Fatty Acid Composition Analysis by Gas Chromatography–Mass Spectrometry

Lipids were extracted from serum aliquots using a chloroform–methanol mixture (2:1, *v/v*) and dried under a nitrogen stream. Samples were hydrolyzed with 0.5 M KOH in methanol at 90 °C for 3 h and acidified with 0.5 mL of 6 M HCl. Following this, 1 mL of water was added, and FAs were extracted using 3 × 1 mL n-hexane. FAs were then derivatized into FA methyl esters and analyzed using gas chromatography–electron ionization–mass spectrometry as previously described [9]. FA identification was carried out using reference standards (37 FAME MIX, Sigma Aldrich, Saint Louis, MO, USA) and the National Institute of Standards and Technology 2011 reference library. The used internal standard was 19-methylarachidic acid.

Table 1. Characteristics of lean controls and obese patients before and 2 weeks after one-anastomosis gastric bypass (OAGB).

	Lean Controls (LC)	Pre-OAGB	Two Weeks Post-OAGB	*p* (Pre-OAGB vs. LC)	*p* (PreOAGB vs. Two Weeks Post-OAGB)	*p* (Two Weeks Post-OAGB vs. LC)
Age (years)	49.97 ± 10.92	48.09 ± 9.57	-	0.461	-	-
BMI (kg/m^2)	24.9 ± 2.68	37.1 ± 2.73	33.8 ± 2.33	<0.001	<0.001	<0.001
Total cholesterol (mg/dL)	218 ± 44.0	206 ± 34.4	212 ± 37.5	0.251	0.487	0.566
Triglycerides (mg/dL)	100 ± 53.4	114 ± 38.5	120 ± 32.7	0.231	0.406	0.086
Glucose (mg/dL)	94.6 ± 24.6	132 ± 35.8	111 ± 20.7	<0.001	0.001	0.004
Albumin (g/L)	45.7 ± 2.99	42.8 ± 3.60	49.9 ± 4.45	<0.001	<0.001	<0.001
Total protein (g/L)	72.6 ± 5.55	69.6 ± 6.11	78.4 ± 7.48	0.043	<0.001	<0.001

2.3. Statistics

Differences between variables measured before and after surgery in obese subjects were analyzed using paired *t*-tests. Differences between obese subjects and lean controls were analyzed using 2-tailed *t*-tests. Data are presented as mean ± standard deviation (SD). Calculations were performed using Microsoft Excel (Microsoft, Redmond, WA, USA).

3. Results

We observed significant decreases in body mass index and fasting serum glucose concentration after OAGB. Concentrations of albumin and total protein increased (Table 1). The increase in total protein was most likely a result of the high-protein diet recommended after surgery. The implementation of a high-protein diet following surgery, prior to the significant reduction in body and muscle mass, may have resulted in the observed increase in serum protein concentrations.

Obese subjects demonstrated severely disturbed serum FA composition compared to the control subjects. This included a decrease in BCFAs and an increase in monounsaturated FAs (MUFAs) (Table 2). Obese patients also showed a decrease in some polyunsaturated FAs (PUFAs), including linolenic acid (18:3 n-3), eicosatetraenoic acid (EPA; 20:5 n-3), and eicosatetraenoic acid (20:4 n-3) (Table 2); these FAs are omega-3 PUFAs. In turn, obese patients showed a decrease in linoleic acid (18:2 n-6) and eicosadienoic acid (20:2 n-6), which are omega-6 PUFAs (Table 2).

Serum OCFA levels were significantly decreased compared to the controls in the two weeks following OAGB (Table 2). Significant decreases were also observed in 18:3 n-3 and 18:2 n-6. These are essential FAs that cannot be synthesized in the human body and must be obtained from the diet. We also noted greater decreases in EPA, 20:4 n-3, and 20:2 n-6 two weeks after OAGB (Table 2). BCFA levels did not significantly change in the period after OAGB, but they remained significantly lower compared to controls. By contrast, we observed increases in arachidonic acid (20:4 n-6) two weeks after OAGB. This change is associated with inflammation. We also noted changes in some saturated FAs and MUFAs, but total saturated FAs and MUFAs did not significantly change (Table 2).

Table 2. Serum fatty acid composition (%) in lean controls and obese subjects before and two weeks after bariatric surgery.

	Lean Control (LC)	Pre-OAGB	2 Weeks Post-OAGB	*p* (Pre-OAGB vs. LC)	*p* (Pre vs. Post-OAGB)	*p* (Post-OAGB vs. LC)
	Mean % of Total Fatty Acid (FA) ± SD					
16:0	23.21 ± 1.77	24.55 ± 1.75	26.06 ± 1.46	0.001	<0.001	<0.001
18:0	7.30 ± 0.72	6.19 ± 0.60	5.52 ± 0.80	<0.001	<0.001	<0.001
Other ECFA	1.82 ± 0.36	1.59 ± 0.39	1.26 ± 0.32	0.011	<0.001	<0.001
ECFA	**32.33 ± 1.87**	**32.33 ± 1.89**	**32.84 ± 1.73**	**0.995**	**0.136**	**0.223**
15:0	0.23 ± 0.05	0.26 ± 0.06	0.24 ± 0.06	0.073	0.334	0.417
17:0	0.24 ± 0.04	0.24 ± 0.04	0.22 ± 0.04	0.226	<0.001	<0.001
Other OCFA	0.15 ± 0.04	0.10 ± 0.03	0.08 ± 0.03	<0.001	<0.001	<0.001
OCFA	**0.64 ± 0.10**	**0.60 ± 0.10**	**0.55 ± 0.11**	**0.146**	**0.004**	**<0.001**
Anteiso-BCFA	0.20 ± 0.05	0.13 ± 0.04	0.13 ± 0.06	<0.001	0.967	<0.001
Iso-BCFA	0.20 ± 0.06	0.014 ± 0.04	0.13 ± 0.05	<0.001	0.231	<0.001
Total BCFA	**0.42 ± 0.10**	**0.29 ± 0.08**	**0.28 ± 0.11**	**<0.001**	**0.673**	**<0.001**
Total SFA	**33.39 ± 1.84**	**33.22 ± 1.93**	**33.66 ± 1.77**	**0.710**	**0.211**	**0.505**
16:1	3.02 ± 0.97	3.50 ± 1.00	3.43 ± 1.14	0.035	0.623	0.092
18:1	26.61 ± 3.09	29.23 ± 3.14	29.94 ± 2.47	<0.001	0.184	<0.001
Other MUFA	0.54 ± 0.13	0.53 ±0.11	0.61 ± 0.11	0.968	<0.001	<0.001
MUFA	**30.16 ± 3.53**	**33.31 ± 3.59**	**34.03 ± 2.93**	**<0.001**	**0.257**	**<0.001**
18:3 n-3	0.34 ± 0.11	0.24 ± 0.11	0.15 ± 0.10	<0.001	<0.001	<0.001
20:5 n-3 (EPA)	1.09 ± 0.72	0.76 ± 0.45	0.54 ± 0.18	0.018	0.001	<0.001
20:4 n-3	0.10 ± 0.03	0.06 ± 0.02	0.04 ± 0.02	<0.001	<0.001	<0.001
22:6 n-3 (DHA)	1.14 ± 0.44	1.36 ± 0.54	1.42 ± 0.39	0.053	0.445	0.004
Other n-3 PUFA	0.29 ± 0.05	0.34 ± 0.09	0.39 ± 0.09	0.003	<0.001	<0.001
n-3 PUFA	**2.97 ± 1.14**	**2.76 ± 0.95**	**2.54 ± 0.54**	**0.384**	**0.095**	**0.041**
18:2 n-6	26.24 ± 3.85	23.00 ± 3.21	20.63 ± 2.79	<0.001	<0.001	<0.001
20:4 n-6 (ARA)	5.61 ± 1.15	6.20 ± 2.00	7.85 ± 2.12	0.118	<0.001	<0.001
20:2 n-6	0.16 ± 0.03	0.11 ± 0.03	0.09 ± 0.03	<0.001	0.019	<0.001
Other n-6 PUFA	1.32 ± 0.25	1.31 ± 0.34	1.10 ± 0.26	0.944	<0.001	<0.001
n-6 PUFA	**33.32 ± 3.96**	**30.62 ± 1.93**	**29.68 ± 3.19**	**0.006**	**0.241**	**<0.001**

ECFA, even-chain saturated fatty acid; OCFA, odd-chain saturated fatty acid; BCFA, branched-chain saturated fatty acid; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; PUFA, polyunsaturated fatty acid; ARA, arachidonic acid; DGLA, dihomo-γ-linolenic acid; AdA, docosatetraenoic acid. Boldface—major groups of fatty acid.

4. Discussion

Our study revealed that OAGB leads to a short-term decrease in some FAs (two weeks). These decreases were seen in diet-derived FAs—OCFAs and essential PUFAs. This suggests that a deficiency in these FAs is most likely the effect of decreased dietary intake after BS. Lin et al. [6] arrived at the same conclusion in their study of short-term BPDDS and LSG effects. The aforementioned types of FAs play an important functional role in the human body, and their depletion can be unfavorable for patients shortly after surgery. OCFAs mainly originate from the milk and meat of ruminants. They display anti-inflammatory and antioxidant properties and reduce cardiovascular-disease risk [10]. Given these properties, OCFA deficiency in patients after BS should be avoided. This is the first study to show the short-term effects of BS on serum OCFAs in obese subjects. Our recent study of the long-term effects of BS did not show significant differences in serum OCFA levels before and six to nine months after BS [9]. This suggests that their levels eventually normalized after BS.

PUFAs n-3 and n-6 play many important functional roles in the human body, including cardioprotection and the regulation of inflammation [4]. Our previous study demonstrated that obese subjects showed decreased serum levels of n-3 and n-6 PUFAs [5]. PUFAs 18:2 n-6 and 18:3 n-3 cannot be synthesized in humans, but they can be converted into other PUFAs by elongases and desaturases [4]. Hence, deficiencies in these two FAs can have particularly severe consequences. Lin et al. also observed a reduction in the serum levels of 18:3 n-3, 18:2 n-6, and EPAs in obese patients as early as three days after BPDDS and LSG. Forbes et al. [8] observed a decrease in the aforementioned PUFAs one month after RYGB, but Walle et al. [7] observed slight increases in n-3 and n-6 PUFAs one year after RYGB. Our previous results showed modest reductions in n-3 and n-6 PUFAs six to nine months after OAGB. These results suggest that PUFA deficiency may be resolved a long time after BS.

Despite the finding that BCFA levels did not change in the two weeks following OAGB, they remained lower than those in lean subjects. Previous studies also suggested the beneficial effects of this type of FA. These include antitumor effects and inverse correlations with inflammation, dyslipidemia, and insulin resistance in obese subjects [5]. Thus, BCFA deficiency is another unfavorable condition that persists in patients after OAGB. Serum BCFA levels return to those seen in lean subjects six to nine months after OAGB [9]. The short-term effects of BS on BCFA levels have also not been studied thus far.

The limitations of our study include the lack of other time points of serum FA composition analysis after BS, and the relatively small cohort used. However, despite this sample size, the statistical significance of the results was quite robust and therefore convincing.

5. Conclusions

Our results showed short-term reduction in the serum concentrations of OCFAs and essential PUFAs after OAGB. BCFA levels also remained low after OAGB. Considering the benefits of the aforementioned FAs in human health, the implementation of a diet rich in these FAs or the use of supplementation is recommended for obese patients immediately after a bariatric procedure.

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References

1. Jammah, A.A. Endocrine and metabolic complications after bariatric surgery. *Saudi J. Gastroenterol.* **2015**, *21*, 269–277. [CrossRef] [PubMed]
2. Lee, W.-J.; Ser, K.-H.; Lee, Y.-C.; Tsou, J.-J.; Chen, S.-C.; Chen, J.-C. Laparoscopic Roux-en-Y vs. Mini-gastric Bypass for the Treatment of Morbid Obesity: A 10-Year Experience. *Obes. Surg.* **2012**, *22*, 1827–1834. [CrossRef] [PubMed]
3. Ramos-Molina, B.; Castellano-Castillo, D.; Alcaide-Torres, J.; Pastor, O.; de Luna Díaz, R.; Salas-Salvado, J.; López-Moreno, J.; Fernández-García, J.C.; Macías-González, M.; Cardona, F.; et al. Differential effects of restrictive and malabsorptive bariatric surgery procedures on the serum lipidome in obese subjects. *J. Clin. Lipidol.* **2018**, *12*, 1502–1512. [CrossRef] [PubMed]
4. Mika, A.; Sledzinski, T. Alterations of specific lipid groups in serum of obese humans: A review. *Obes. Rev.* **2017**, *18*, 247–272. [CrossRef] [PubMed]
5. Mika, A.; Stepnowski, P.; Kaska, L.; Proczko, M.; Wisniewski, P.; Sledzinski, M. Obesity A Comprehensive Study of Serum Odd- and Branched-Chain Fatty Acids in Patients with Excess Weight. *Obesity* **2016**, *24*, 1669–1676. [CrossRef] [PubMed]
6. Lin, C.; Vage, V.; Mjos, S.A.; Kvalheim, O.M. Changes in Serum Fatty Acid Levels during the First Year after Bariatric Surgery. *Obes. Surg.* **2016**, *26*, 1735–1742. [CrossRef] [PubMed]
7. Walle, P.; Takkunen, M.; Männisto, V.; Vaittinen, M.; Kakela, P.; Agren, J.; Schwab, U.; Lindström, J.; Tuomilehto, J.; Uusitupa, M.; et al. Alterations in fatty acid metabolism in response to obesity surgery combined with dietary counseling. *Nutr. Diabetes* **2017**, *7*, e285. [CrossRef] [PubMed]
8. Forbes, R.; Gasevic, D.; Watson, E.M.; Ziegler, T.R.; Lin, E.; Burgess, J.R.; Gletsu-Miller, N. Essential Fatty Acid Plasma Profiles Following Gastric Bypass and Adjusted Gastric Banding Bariatric Surgeries. *Obes. Surg.* **2016**, *26*, 1237–1246. [CrossRef] [PubMed]
9. Pakiet, A.; Wilczynski, M.; Rostkowska, O.; Korczynska, J.; Jablonska, P.; Kaska, L.; Proczko-Stepaniak, M.; Sobczak, E.; Stepnowski, P.; Magkos, F.; et al. The effect of omega loop gastric bypass on branched-chain fatty acid and branched-chain amino acid metabolism in subjects with morbid obesity. *Obes. Surg.* **2019**. [CrossRef]
10. Rezanka, T.; Sigler, K. Odd-numbered very-long-chain fatty acids from the microbial, animal and plant kingdoms. *Prog. Lipid Res.* **2009**, *48*, 206–238. [CrossRef] [PubMed]

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ORIGINAL CONTRIBUTIONS

The Effect of One Anastomosis Gastric Bypass on Branched-Chain Fatty Acid and Branched-Chain Amino Acid Metabolism in Subjects with Morbid Obesity

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Abstract

Background Subjects with morbid obesity have low levels of serum branched-chain fatty acids (BCFAs), which correlate inversely with insulin resistance, hypertriglyceridemia, and inflammation. Recent evidence suggests BCFAs are produced during branched-chain amino acid (BCAA) catabolism in human adipose tissue. Elevated concentrations of BCAAs are associated with insulin resistance.

Objectives In this single-center study, we evaluated the effect of one anastomosis gastric bypass (OAGB) on circulating BCFA and BCAA. Moreover, we determined the expression of genes involved in BCAA catabolism in adipose tissue of patients with obesity and lean controls.

Methods Fasting levels of BCFAs and BCAAs were determined by gas and liquid chromatography, respectively, coupled with mass spectrometry, in 50 patients with morbid obesity before and 6–9 months after surgery, and in 32 lean controls. Visceral and subcutaneous adipose tissue (VAT and SAT, respectively) biopsies were collected at baseline to determine mRNA levels for enzymes involved in BCAA catabolism.

Results Before surgery, patients with obesity had lower BCFAs and greater BCAAs than control subjects. OAGB increased BCFA and decreased BCAA levels. Insulin resistance (assessed by HOMA) correlated inversely with BCFAs and positively with BCAAs. Expression of genes involved in BCAA catabolism in VAT (but not SAT) was lower in patients with obesity than in lean controls.

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Conclusions OAGB-induced weight loss increases circulating BCFAs and decreases circulating BCAAs in patients with morbid obesity, perhaps by altering BCAA catabolism in VAT. We speculate that this shift may be related to the improvement in insulin sensitivity after surgery.

Keywords Branched-chain amino acids · Branched-chain fatty acids · Bariatric surgery · Morbid obesity · Insulin resistance

Introduction

Bariatric surgery is a treatment option for morbid obesity and is more effective than diet and pharmacotherapy [1, 2]. Bariatric surgery brings about significant alterations in lipid metabolism, but the exact nature of these changes depends on the surgical procedure [3]. One anastomosis gastric bypass (OAGB) is a promising type of bariatric surgery that improves metabolic parameters (reduction in serum concentrations of triglycerides, total and LDL cholesterol, and C-reactive protein; and increase in HDL cholesterol concentration) [4], causes remission of type 2 diabetes mellitus, and is associated with relatively low morbidity [5, 6]. However, some studies found higher incidence of diarrhea, steatorrhea, and nutritional adverse events after OAGB than after RYGB [7]. Reduced food intake after surgery may result in deficiencies of some important nutrients [8], such as bioactive lipids which, although present in small amounts in the diet, are vital for many physiological functions. On the other hand, bariatric surgery may lead to an increase in serum concentrations of some other lipid classes, e.g., bile acids [3, 4, 9].

Branched-chain fatty acids (BCFAs) and odd-chain fatty acids (OCFAs), both present in small amounts in human blood, possess antibiotic, anticancer, and immunosuppressive properties [10–12]. Similar to unsaturated fatty acids, BCFAs can increase cell membrane fluidity, but are less prone to oxidation than the former [13]. OCFAs have antioxidant properties, acting as hydroxyl radical scavengers, and increased dietary intake of OCFA was shown to be associated with a decrease in serum cholesterol. Accordingly, consumption of BCFAs and OCFAs may reduce the risk of cardiovascular disease [10, 14] and metabolic disorders [15]. These fatty acids originate from ruminant fat and milk [16], but recent evidence suggests that both BCFAs and OCFAs can also be synthesized in mammalian adipocytes from branched-chain amino acids (BCAAs) [17–19]. Wallace et al. [19] demonstrated that BCFAs were synthesized de novo in adipose tissue from BCAAs catabolized in mitochondria, and then exported by carnitine acetyltransferase to the cytosol, where they were elongated by fatty acid synthase. In a previous study, we identified several BCFAs and OCFAs in human serum, and demonstrated that patients with morbid obesity without any dietary or surgical treatment had significantly lower levels of *iso*-BCFAs than lean controls, but similar OCFA levels [16]. We also found inverse correlations between circulating *iso*-BCFAs and C-reactive protein (CRP, an inflammatory marker), hypertriglyceridemia, and insulin concentration in patients with morbid obesity [16]. In contrast to BCFAs and OCFAs, elevated concentrations of BCAAs are associated with obesity and its metabolic complications, such as insulin resistance [17], and many authors have reported alterations in BCAA metabolism in insulin-resistant and obese states [17, 20, 21].

Accordingly, the aim of this study was to evaluate if OAGB-induced weight loss affects circulating levels of bioactive fatty acids, including BCFAs and OCFAs. We also determined BCAAs as well as the expression of genes involved in BCAA catabolism in visceral and subcutaneous adipose tissues.

Materials and Methods

Patients

This single-center study included a group of 50 patients (mean age 48.6 ± 10.5 years; 42 females, 8 males) operated for morbid obesity at the Department of General, Endocrine and Transplant Surgery (Medical University of Gdańsk, Poland) between 2016 and 2018. There were 25 patients with type 2 diabetes (T2DM) and 25 without. The inclusion criteria for OAGB laid out by the International Federation for the Surgery of Obesity (IFSO), International Federation for the Surgery of Obesity–European Chapter (IFSO-EC), and European Association for the Study of Obesity (EASO) were applied [22].

The exclusion criteria for OAGB were as follows: (i) absence of a period of identifiable medical management; (ii) inability to participate in prolonged medical follow-up; (iii) non-stabilized psychotic disorders, severe depression, personality, and eating disorders unless specifically advised by a psychiatrist experienced in obesity; (iv) alcohol abuse or drug dependencies; (v) diseases threatening life in the short term; (vi) inability to self-care and lack of long-term family or social support. Blood samples were obtained from all patients before, and then 6–9 months after surgery.

The control group consisted of 32 lean individuals (mean age 52 ± 12 years; 21 females, 9 males) subjected to laparoscopic cholecystectomy at the Department of General, Endocrine and Transplant Surgery, Medical University of Gdansk, and the Department of General Surgery, Pomeranian Hospital Sp. z o.o., in Gdynia. Criteria for including patients in the control group included indications for surgical treatment in planned mode for non-cancerous reasons. Exclusion criteria were (i) obesity, (ii) diabetes, (iii) metabolic syndrome, (iv) steroid therapy, (v) chronic use of non-steroidal anti-inflammatory drugs, and (vi) acute inflammation. Blood samples from lean patients who would undergo cholecystectomy were obtained before surgery. The blood samples were collected in the morning both from patients and lean controls.

The study was performed in agreement with the principles of the Declaration of Helsinki of the World Medical Association. The study protocol was approved by the Local Bioethics Committee at the Medical University of Gdansk (decision no. NKBBN/493/2016) and written informed consent was obtained from all participants.

Surgical Technique and Adipose Tissue Biopsies

The one anastomosis gastric bypass (OAGB) procedure was performed laparoscopically in all patients with obesity. The length of the intestinal limb excluded from mixed food and biliopancreatic content in OAGB was estimated intraoperatively to be 180–250 cm, depending on patient's BMI, age, and diabetes status, following the rule by Garcia-Caballero et al. [23]. The length of the left common limb was estimated to be 350–400 cm. The measurement of intestinal length was based on the not-strained organ manipulation and the 10-cm marker fixed to the grasping instrument that was used for calibration. Those procedures were performed laparoscopically. After a leakage test was conducted, in order to exclude potential leaks from the anastomosis, visceral adipose tissue (VAT) samples were collected. Upon closing of the wound, samples of subcutaneous adipose tissue (SAT) were also collected. All adipose tissue samples were immediately frozen in liquid nitrogen and stored at − 80 °C. Adipose tissue samples were obtained from the same anatomical locations from the group of lean controls during cholecystectomy. Adipose tissue in both groups has been collected intraoperatively, at the end of the procedure, always from the greater omentum and from the subcutaneous tissue at closing the central trocar.

Anthropometric and Metabolic Data

Anthropometric and laboratory parameters were determined at baseline (before surgery) in patients with morbid obesity and in lean subjects, and again 6–9 months after surgery only in subjects with morbid obesity. All blood samples were collected after an overnight fast. Serum was obtained by centrifugation and stored at − 80 °C. Routine laboratory parameters were determined at the Central Clinical Laboratory, Medical University of Gdansk. Anthropometric and metabolic data of patients with morbid obesity and lean controls are presented in Table 1.

Chromatographic and Mass Spectrometry Analysis

Fatty acid levels were assayed as described previously [16] by using gas chromatography–mass spectrometry (GC-MS) in total lipids extracted from tissues and serum using the method described by Folch et al. [24]. Serum amino acid concentrations were assayed by high-performance liquid chromatography–tandem mass spectrometry (LC-MS) according to Olkowicz et al. [25]. The details of these analytical techniques are provided in Supplementary File 1.

Real-time PCR Analysis of mRNA Levels in Adipose Tissue

Total RNA was extracted from frozen VAT and SAT samples with Qiagen RNeasy Lipid Tissue Mini Kit. The yield and quality were determined for each sample by automated gel electrophoresis (Experion, Bio-Rad). cDNA was synthesized from 0.5 μg of the total RNA using RevertAid™ First Strand cDNA Synthesis Kit (Thermo Fisher Scientific). Each RNA sample was treated with RNase-free DNase I before the cDNA synthesis. mRNA levels were analyzed with real-time PCR using CFX Connect Real-Time System (Bio-Rad). A combination of β-actin and cyclophilin genes was used as reference standards. Relative levels of mRNA for the branched-chain α-ketoacid dehydrogenase (BCKDH) complex and branched-chain aminotransferase (BCAT) were calculated according to Piehler et al. [26]. The following primer sequences were used: F: GATGACAAGCCCCAGTTCCCA, R′: TGGGGTTG ATGATCTGGCCTT for BCKDHA; F′: GCGGCAGG TGGCTCATTTTACT, R: CAGTAGGATCTTTGGCCAAT GAGTTAT for BCKDHB; F: GGTCCCATATTCAA CATCTGCTAGTCT, R: TCCCATCTTGCAGTCCCCAGT for BCAT1, and F: TTACGCGCCGCACGGATCAT, R: GGTCGGTAAATGTCTTCCCAAAC for BCAT2. Amplification of specific transcripts was confirmed based on melting curve profiles and agarose gel electrophoresis of the amplification products.

Statistical Analysis

The statistical significance of differences between values before and after surgery in subjects with morbid obesity was determined with paired *t* tests, whereas differences between subjects with morbid obesity and lean controls were evaluated by independent *t* tests. The differences were considered statistically significant at $p < 0.05$. The relationship between variables of interest was determined with linear regression analysis and multiple linear regression analysis. All statistical analyses were carried out with SigmaPlot version 11.0 (Systat Software Inc., San Jose, CA).

Table 1 Metabolic characteristics of patients with morbid obesity before and after surgery compared with lean controls. Values are mean ± SD. *LC* lean controls, *OAGB* one anastomosis gastric bypass, *BMI* body mass index, *TG* triglycerides, *HDL* high-density lipoprotein cholesterol, *LDL* low-density lipoprotein cholesterol, *TC* total cholesterol, *CRP* C-reactive protein, *HOMA* homeostatic model assessment of insulin resistance

	Lean controls (LC)	Pre-OAGB	6–9 m post-OAGB	*p* (pre-OAGB vs LC)	*p* (pre- vs post-OAGB)	*p* (post-OAGB vs LC)
BMI (kg/m^2)	24.3 ± 2.95	38.5 ± 4.25	29.6 ± 3.73	< 0.001	< 0.001	< 0.001
Age (years)	52 ± 12	48.6 ± 10.5	–	0.456	–	–
HbA1C (%)	–	5.76 ± 0.89	5.22 ± 0.46	–	0.002	–
TG (mg/dl)	104 ± 43.5	113 ± 37.3	87.8 ± 26.7	0.775	0.006	0.149
HDL (mg/dl)	57.4 ± 22.1	50.7 ± 9.52	51.6 ± 11.67	0.066	0.590	0.109
LDL (mg/dl)	97.6 ± 37.4	114 ± 33.8	88.3 ± 25.3	0.093	0.027	0.066
TC (mg/dl)	171 ± 48.3	201 ± 39.8	181 ± 49.1	0.002	0.015	0.189
CRP (mg/l)	1.60 ± 1.20	1.65 ± 0.53	1.02 ± 0.55	0.904	0.010	0.170
Albumin (g/l)	40.3 ± 2.94	37.4 ± 7.60	37.2 ± 2.47	0.018	0.832	< 0.001
Creatinine (mg/dl)	0.85 ± 0.19	0.79 ± 0.22	0.71 ± 0.17	0.287	< 0.001	0.002
Glucose (mg/dl)	96.8 ± 2.32	110 ± 31.6	91.5 ± 10.9	0.057	< 0.001	0.208
Insulin (μU/ml)	9.58 ± 4.79	14.9 ± 7.69	7.70 ± 6.27	0.002	< 0.001	0.204
HOMA-IR	2.48 ± 2.14	4.34 ± 2.96	2.01 ± 1.89	0.008	< 0.001	0.384

Results

The Effect of OAGB on Serum FA Composition

Compared with lean controls, patients with morbid obesity had significantly lower levels of total BCFAs before surgery; however, OAGB-induced weight loss (~ 23% of initial body weight) led to significant increases in both *iso*- and *anteiso*-BCFAs (Table 2, Supplementary Table 1), so that total BCFA levels after surgery were no longer significantly different between groups (Fig. 1A). The OAGB-induced increase in circulating BCFA was similar in patients with morbid obesity with and without T2DM (Supplementary Fig. 1A, B).

Comparative analysis of FA profiles in patients with morbid obesity pre- and post-OAGB and in lean controls demonstrated many significant differences (Table 2). Both before and after surgery, patients with morbid obesity had lower OCFA levels than control subjects (Table 2). Moreover, preoperative serum levels of n-3 polyunsaturated FAs (PUFAs) and post-operative levels of both n-3 and n-6 PUFAs were significantly lower in subjects with morbid obesity than in lean subjects. On the other hand, both before and after OAGB, patients with morbid obesity had higher levels of monounsaturated FAs (MUFAs) than lean controls (Table 2).

The Effect of OAGB on Serum BCAA Composition

Since BCFAs can be synthetized from BCAA precursors in adipose tissue [17, 19], we measured pre- and post-OAGB concentrations of valine, leucine, and isoleucine in patients with morbid obesity and in lean controls. Total circulating BCAAs (leucine and isoleucine, but not valine) were

Table 2 Serum fatty acids (% of total fatty acid concentration) in patients with morbid obesity before and after surgery compared with lean controls. Values are mean ± SD. *LC* lean controls, *OAGB* one anastomosis gastric bypass, *BCFAs* branched-chain saturated FAs, *ECFAs* even-chain saturated FAs, *MUFAs* monounsaturated FAs, *OCFAs* odd-chain saturated FAs, *PUFAs* polyunsaturated FAs, *SFAs* saturated FAs

Fatty acid	Lean controls	Pre-OAGB	Post-OAGB	*p* (pre-OAGB vs LC)	*p* (pre- vs post-OAGB)	*p* (post-OAGB vs LC)
Total OCFAs	0.649 ± 0.111	0.572 ± 0.09	0.581 ± 0.01	0.002	0.542	0.012
Iso-BCFAs	0.244 ± 0.058	0.190 ± 0.05	0.234 ± 0.06	< 0.001	< 0.001	0.437
Anteiso-BCFAs	0.167 ± 0.046	0.094 ± 0.03	0.135 ± 0.05	< 0.001	< 0.001	0.005
Other BCFAs	0.011 ± 0.007	0.010 ± 0.004	0.012 ± 0.01	0.493	0.055	0.555
Total ECFAs	32.1 ± 1.87	32.5 ± 1.78	32.8 ± 2.40	0.276	0.390	0.131
Total SFAs	35.3 ± 1.84	33.6 ± 1.82	33.9 ± 2.60	0.540	0.261	0.200
Total MUFAs	29.6 ± 3.60	33.6 ± 2.64	34.3 ± 3.06	< 0.001	0.175	< 0.001
Total n-6 PUFAs	34.1 ± 3.70	30.4 ± 3.65	29.5 ± 4.13	< 0.001	0.115	< 0.001
Total n-3 PUFAs	2.99 ± 1.27	2.44 ± 0.69	2.27 ± 0.54	0.032	0.036	0.005

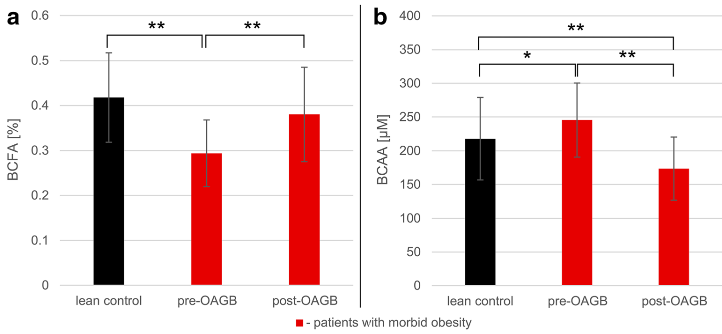


Fig. 1 Serum BCFA (A) and BCAA (B) levels in patients with morbid obesity before and after surgery compared with lean controls

significantly greater in subjects with morbid obesity before surgery than in lean controls (Table 3 and Fig. 1B). OAGB significantly decreased the concentrations of all BCAAs, so that postoperative values were all significantly lower in subjects after bariatric surgery than in lean controls (Table 3 and Fig. 1B).

Associations Between BCFAs and BCAAs with HOMA, Triglycerides, and BMI

At baseline, we found that BCAAs correlated directly with the homeostasis model assessment (HOMA) index of insulin resistance ($r = 0.30$, $p = 0.007$) and triglyceride concentration ($r = 0.33$, $p = 0.003$), whereas BCFAs correlated inversely with these two parameters (HOMA: $r = -0.28$, $p = 0.012$; triglycerides: $r = -0.37$, $p = 0.001$). Furthermore, BMI correlated negatively with BCFA ($r = -0.60$, $p < 0.001$) and positively with BCAA ($r = 0.27$, $p = 0.015$). Multiple linear regression analysis revealed that serum BCFA content was predicted most strongly by BMI ($p < 0.001$), whereas BCAA by triglycerides ($p = 0.007$).

Expression of Genes Involved in BCAA Catabolism in Adipose Tissue

We analyzed mRNA levels for the enzymes involved in BCAA catabolism in SAT and VAT. We did not find any statistically significant differences between subjects with morbid obesity and lean controls in the gene expression of BCKDH (isoforms A and B) and BCAT (isoforms 1 and 2) in SAT (BCKDHA 1.0 ± 0.38 vs 1.07 ± 0.38, $p = 0.59$; BCKDHB 1.0 ± 0.26 vs 1.03 ± 0.39, $p = 0.78$; BCAT1 1.0 ± 0.54 vs 1.18 ± 0.66, $p = 0.22$; BCAT2 1.0 ± 0.35 vs 0.86 ± 0.22, $p = 0.11$; in control subjects and patients with obesity, respectively). However, the mRNA levels for BCKDH isoform B and both BCAT isoforms in VAT were significantly lower in subjects with morbid obesity than in lean controls (Fig. 2A). Accordingly, the lower gene expression of enzymes catabolizing BCAAs (which are involved in the synthesis of BCFAs) was accompanied by lower BCFA levels in VAT in subjects with morbid obesity than in lean subjects (Fig. 2B). In SAT, the levels of BCFA did not differ between control subjects and patients with obesity (0.44 ± 0.15 vs 0.47 ± 0.11, $p = 0.34$, respectively).

Discussion

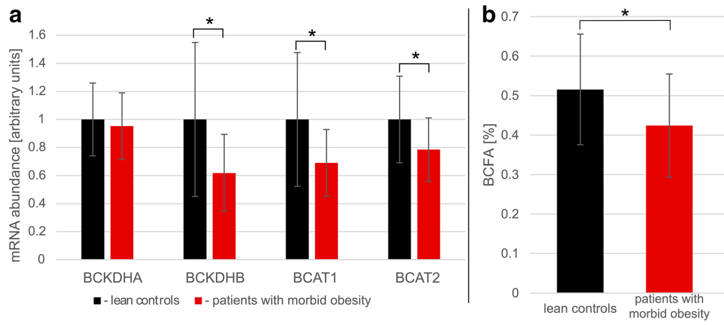
Association Between Serum Levels of BCFA and BCAA in Obese Subjects

In mammalian tissues, BCFAs rarely constitute more than 1–2% of the total FA pool, and the results from previous studies imply that they are primarily synthesized by intestinal bacteria, or consumed with dairy products or ruminant meat [27, 28]. However, recent evidence suggests that BCFAs may also

Table 3 Serum branched-chain amino acids (µmol/l) in patients with morbid obesity before and after surgery compared with lean controls. Values are mean ± SD. *LC* lean controls, *OAGB* one anastomosis gastric bypass

	Lean controls	Pre-OAGB	Post-OAGB	*p* (pre-OAGB vs LC)	*p* (pre- vs post-OAGB)	*p* (post-OAGB vs LC)
Valine	128 ± 35.8	123 ± 25.9	97.7 ± 24.5	0.42	< 0.001	< 0.001
Leucine	57.6 ± 19.2	77.1 ± 20.0	47.4 ± 18.3	< 0.001	< 0.001	0.02
Isoleucine	32.0 ± 12.7	45.9 ± 14.5	28.4 ± 10.5	< 0.001	< 0.001	0.19

Fig. 2 mRNA levels for BCKDHA, BCKDHB, BCAT1, and BCAT2 in VAT of patients with morbid obesity compared with lean controls (A). BCFA levels in VAT of patients with morbid obesity compared with lean controls (B)



be synthesized in mammalian adipose tissue from BCAA-derived precursors [17]. Despite their very low circulating levels, BCFAs have been associated with several beneficial metabolic outcomes in human subjects [16]. Recently, we demonstrated that morbid obesity is associated with decreased serum *iso*-BCFA levels. Our present study confirms this finding and further demonstrates that bariatric surgery–induced weight loss increases serum BCFAs. This may constitute another beneficial metabolic effect of OAGB in patients with morbid obesity. The results of our previous study suggest that BCFA levels in these patients are likely independent of their dietary habits [16]. Thus, the lower levels of BCFAs in people with morbid obesity and the increase in circulating BCFA after surgery may be associated with alterations in the metabolism of BCAAs, namely valine, leucine, and isoleucine, which can serve as precursors of BCFAs [17, 19]. In line with this hypothesis, the first step in the formation of BCFA primers is the conversion of BCAAs to α-keto acids by mitochondrial and cytosolic isoforms of BCAT, followed by production of primer-CoA esters in a reaction catalyzed by the BCKDH complex [29]. While the reaction catalyzed by mitochondrial BCKDH is the rate-limiting step in the synthesis of BCFAs from BCAAs [18], in some tissues (e.g., liver), its products can also be transformed into intermediates of the Krebs cycle. During the last step, the primer-CoA esters derived from BCAAs are elongated into BCFAs [30].

Amino acids comprise a group of metabolites that undergoes significant alterations after bariatric surgery. Many previous studies demonstrated that another type of bypass procedure, Roux-en-Y gastric bypass (RYGB), led to significant decreases in serum BCAA levels [9, 31–33]. Importantly, the effect of RYGB on serum BCAA concentration persisted regardless of the time elapsed since surgery [34]. According to Wijayatunga et al. [9], the RYGB-induced decrease in BCAA may be a consequence of enhanced BCAA catabolism or reduced protein intake after surgery [35]. Our present study confirms these observations after another type of intestinal bypass (OAGB). To the best of our knowledge, ours is the first study to demonstrate the effect of OAGB on serum BCAAs. Previous studies showed that high concentrations of leucine, isoleucine, and valine are associated with diabetes mellitus, insulin resistance, and coronary artery disease [28]. For example, Newgard et al. [20] reported that persons with morbid obesity had higher BCAA levels than lean controls, which contributed to the development of insulin resistance and diabetes. In view of these findings, the post-OAGB decrease in BCAA concentration could be considered another beneficial effect of bariatric surgery for obesity, even though the precise mechanism responsible remains unknown, and cannot be elucidated by our study. Considering that obesity and bariatric surgery had diametrically opposite effects on serum BCAAs and BCFAs (Fig. 1A and B), it is not unreasonable to hypothesize that the lower levels of BCFAs in subjects with morbid obesity may be associated with slower transformation of BCAAs into BCFAs. In line with this hypothesis, the OAGB-induced changes in serum levels of these metabolites may be explained by an improvement of BCAA to BCFA transformation. However, according to Yao et al. [36], the increase in BCAA levels in obesity likely results from an inability to adequately suppress proteolysis rather than from a decrease in the catabolism of BCAA. Thus, the mechanisms for the decrease in BCAA levels after surgery-induced weight loss remain elusive and should be assessed in future studies.

Relationship Between BCAA Catabolism and BCFA Synthesis in Adipose Tissue of Obese Patients

As BCFAs can be produced during BCAA catabolism in adipose tissue [17, 19], we analyzed the expression of genes encoding BCKDH and BCAT, i.e., the enzymes responsible for conversion of BCAAs to BCFAs, in VAT and SAT of patients with morbid obesity and lean controls. We detected no significant differences between groups in SAT, but patients with morbid obesity had significantly lower mRNA levels than lean subjects for BCKDHB, BCAT1, and BCAT2 in

VAT. Accordingly, this was associated with lower BCFA level in VAT in subjects with morbid obesity than in lean subjects, which may represent the functional endpoint of the downregulation of the aforementioned genes. Our findings are consistent with the results published by Boulet et al. [21] who observed that BCAT2, BCKDHA, and BCKDHB mRNA and protein levels in VAT, but not SAT, of patients with morbid obesity were significantly lower than in lean controls. Also, Serralde-Zúñiga et al. [37] reported that gene expressions of BCKDH E1α and BCAT2 in omental adipose tissue (a VAT depot) of persons with morbid obesity with insulin resistance were significantly lower than in overweight persons without insulin resistance. Collectively, these observations suggest that a decrease in serum BCFAs and a concomitant increase in serum BCAAs in patients with morbid obesity might be a consequence of attenuated conversion of BCAAs into BCFAs in VAT. Unfortunately, we were not able to obtain adipose tissue samples from patients after surgery to verify if the increase in serum BCFAs and the decrease in serum OCFAs were associated with a post-OAGB upregulation of enzymes involved in BCAA catabolism in VAT. However, She et al. [35] reported a significant upregulation of BCAT and a non-significant upregulation of BCKDH in VAT (and SAT) of patients with morbid obesity after gastric bypass. Furthermore, Su et al. [17] reported increased SAT BCFA levels and higher expression of fatty acid synthase gene in patients with morbid obesity 1 year after RYGB. Based on those findings, synthesis of BCFAs in adipose tissue likely depends on both BCAA catabolism and FAS-catalyzed lipogenesis [17].

Study Limitations

Our study has several limitations. First, we were not able to obtain adipose tissue samples from patients after surgery to assess its effect on the gene expression of enzymes involved in BCAA catabolism. Second, we assessed metabolic function on the basis of static measurements of cardiovascular risk markers in the fasting state and did not employ methodologies to assess dynamic changes in metabolism (e.g., glucose tolerance tests or glucose/insulin clamps). Third, our cohort was relatively small, but even with this sample size, the statistical significance of the results was quite robust and therefore convincing. The major strength of our study is that, for the first time, we simultaneously determined the effect of bariatric surgery on circulating levels of BCAA and BCFA.

Conclusion

In this study, we showed that OAGB-induced weight loss resulted in significant increases in serum BCFAs and significant decreases in serum BCAAs in patients with morbid obesity. Moreover, our findings suggest that serum levels of BCFAs and BCAAs may be influenced by the relationship between BCAA catabolism and BCFA synthesis in VAT of subjects with morbid obesity. We speculate that the post-OAGB changes in BCFA and BCAA levels may be associated with some metabolic benefits, such as improved glucose homeostasis, but the underlying mechanisms remain to be elucidated.

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Compliance with Ethical Standards

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

Ethical Approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all participants included in the study before any study-related procedures take place.

References

1. Athyros VG, Tziomalos K, Karagiannis A, et al. Cardiovascular benefits of bariatric surgery in morbidly obese patients. Obes Rev. 2011;12:515–24.
2. Wylezoł M, Pasnik K, Dabrowiecki S, et al. Polish recommendations for bariatric surgery. Wideochir Inne Tech Maloinwazyjne. 2009;4(Suppl 1):S5–8.
3. Ramos-Molina B, Castellano-Castillo D, Alcaide-Torres J, et al. Differential effects of restrictive and malabsorptive bariatric surgery procedures on the serum lipidome in obese subjects. J Clin Lipidol. 2018;12:1502–12.
4. Mika A, Kaska L, Proczko-Stepaniak M, et al. Evidence that the length of bile loop determines serum bile acid concentration and glycemic control after bariatric surgery. Obes Surg. 2018;28:3405–14.
5. Lee W-J, Yu P-J, Wang W, et al. Laparoscopic Roux-en-Y versus mini-gastric bypass for the treatment of morbid obesity. Ann Surg. 2005;242:20–8.
6. Rutledge R. The mini-gastric bypass: experience with the first 1,274 cases. Obes Surg. 2001;11:276–80.
7. Robert M, Espalieu P, Pelascini E, et al. Efficacy and safety of one anastomosis gastric bypass versus Roux-en-Y gastric bypass for obesity (YOMEGA): a multicentre, randomised, open-label, non-inferiority trial. Lancet. 2019;393:1299–309.

8. Courcoulas AP, Yanovski SZ, Bonds D, et al. Long-term outcomes of bariatric surgery: a National Institutes of Health symposium. JAMA Surg. 2014;149:1323–9.
9. Wijayatunga NN, Sams VG, Dawson JA, et al. Roux-en-Y gastric bypass surgery alters serum metabolites and fatty acids in patients with morbid obesity. Diabetes Metab Res Rev. 2018;8:e3045.
10. Rezanka T, Sigler K. Odd-numbered very-long-chain fatty acids from the microbial, animal and plant kingdoms. Prog Lipid Res. 2009;48:206–38.
11. Wongtangtintharn S, Oku H, Iwasaki H, et al. Incorporation of branched-chain fatty acid into cellular lipids and caspase-independent apoptosis in human breast cancer cell line, SKBR-3. Lipids Health Dis. 2005;4:29.
12. Vlaeminck B, Fievez V, Cabrita ARJ, et al. Factors affecting odd- and branched-chain fatty acids in milk: a review. Anim Feed Sci Technol. 2006;131:389–417.
13. Yan Y, Wang Z, Wang X, et al. Branched chain fatty acids positional distribution in human milk fat and common human food fats and uptake in human intestinal cells. J Funct Foods. 2017;29:172–7.
14. Warensjo E, Jansson J-H, Berglund L, et al. Estimated intake of milk fat is negatively associated with cardiovascular risk factors and does not increase the risk of a first acute myocardial infarction. A prospective case-control study. Br J Nutr. 2004;91:635–42.
15. Ran-Ressler RR, Bae S, Lawrence P, et al. Branched-chain fatty acid content of foods and estimated intake in the USA. Br J Nutr. 2014;112:565–72.
16. Mika A, Stepnowski P, Kaska L, et al. A comprehensive study of serum odd- and branched-chain fatty acids in patients with excess weight. Obesity. 2016;24:1669–76.
17. Su X, Magkos F, Zhou D, et al. Adipose tissue monomethyl branched-chain fatty acids and insulin sensitivity: effects of obesity and weight loss. Obesity. 2015;23:329–34.
18. Crown SB, Marze N, Antoniewicz MR. Catabolism of branched chain amino acids contributes significantly to synthesis of odd-chain and even-chain fatty acids in 3T3-L1 adipocytes. Tochtrop GP, editor. PLoS One. 2015;10:e0145850.
19. Wallace M, Green CR, Roberts LS, et al. Enzyme promiscuity drives branched-chain fatty acid synthesis in adipose tissues. Nat Chem Biol. 2018;14:1021–31.
20. Newgard CB, An J, Bain JR, et al. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. Cell Metab. 2009;9: 311–26.
21. Boulet MM, Chevrier G, Grenier-Larouche T, et al. Alterations of plasma metabolite profiles related to adipose tissue distribution and cardiometabolic risk. Am J Physiol Endocrinol Metab. 2015;309: E736–46.
22. Fried M, Yumuk V, Oppert J-M, et al. Interdisciplinary European guidelines on metabolic and bariatric surgery. Obes Facts. 2013;6: 449–68.
23. García-Caballero M, Carbajo M. One anastomosis gastric bypass: a simple, safe and efficient surgical procedure for treating morbid obesity. Nutr Hosp. 2004;19:372–5.
24. Folch J, Lees M, Sloane Stanley GH. A simple method for the isolation and purification of total lipides from animal tissues. J Biol Chem. 1957;226:497–509.
25. Olkowicz M, Debski J, Jablonska P, et al. Application of a new procedure for liquid chromatography/mass spectrometry profiling of plasma amino acid-related metabolites and untargeted shotgun proteomics to identify mechanisms and biomarkers of calcific aortic stenosis. J Chromatogr A. 2017;1517:66–78.
26. Piehler AP, Grimholt RM, Ovstebo R, et al. Gene expression results in lipopolysaccharide-stimulated monocytes depend significantly on the choice of reference genes. BMC Immunol. 2010;11:21.
27. Adamska A, Rutkowska J. Odd- and branched-chain fatty acids in milk fat – characteristic and health properties. Postepy Hig Med Dosw. 2014;68:957–66.
28. Newgard CB. Interplay between lipids and branched-chain amino acids in development of insulin resistance. Cell Metab. 2012;15: 606–14.
29. She P, Olson KC, Kadota Y, et al. Leucine and protein metabolism in obese Zucker rats. PLoS One. 2013;8:e59443.
30. Christie WW, Han X. Lipid analysis : isolation, separation, identification and lipidomic analysis. Oily Press, an imprint of PJ Barnes & Associates; 2010.
31. Samczuk P, Ciborowski M, Kretowski A. Application of metabolomics to study effects of bariatric surgery. J Diabetes Res. 2018;2018:1–13.
32. Laferrere B, Reilly D, Arias S, et al. Differential metabolic impact of gastric bypass surgery versus dietary intervention in obese diabetic subjects despite identical weight loss. Sci Transl Med. 2011;3: 80re2.
33. Arora T, Velagapudi V, Pournaras DJ, et al. Roux-en-Y gastric bypass surgery induces early plasma metabolomic and lipidomic alterations in humans associated with diabetes remission. PLoS One. 2015;10:e0126401.
34. Lopes TIB, Geloneze B, Pareja JC, et al. Blood metabolome changes before and after bariatric surgery: a ^{1}H NMR-based clinical investigation. Omics. 2015;19:318–27.
35. She P, Van Horn C, Reid T, et al. Obesity-related elevations in plasma leucine are associated with alterations in enzymes involved in branched-chain amino acid metabolism. Am J Physiol Metab. 2007;293:E1552–63.
36. Yao J, Kovalik JP, Lai OF, et al. Comprehensive assessment of the effects of sleeve gastrectomy on glucose, lipid, and amino acid metabolism in Asian individuals with morbid obesity. Obes Surg. 2018;29:149–58.
37. Serralde-Zuniga AE, Guevara-Cruz M, Tovar AR, et al. Omental adipose tissue gene expression, gene variants, branched-chain amino acids, and their relationship with metabolic syndrome and insulin resistance in humans. Genes Nutr. 2014;9:1–10.

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Piśmiennictwo

1. A, A. *et al.* Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med* **377**, 13–27 (2017).
2. Bhandari, M. *et al.* Standardization of Bariatric Metabolic Procedures: World Consensus Meeting Statement. *Obesity Surgery 2019 29:4* **29**, 309–345 (2019).
3. Rutledge, R. The mini-gastric bypass: experience with the first 1,274 cases. *Obes Surg* **11**, 276–280 (2001).
4. Georgiadou, D. *et al.* Efficacy and safety of laparoscopic mini gastric bypass. A systematic review. *Surg Obes Relat Dis* **10**, 984–991 (2014).
5. Řezanka, T. & Sigler, K. Odd-numbered very-long-chain fatty acids from the microbial, animal and plant kingdoms. *Prog Lipid Res* **48**, 206–238 (2009).
6. Sacks, F. M. *et al.* Dietary Fats and Cardiovascular Disease: A Presidential Advisory From the American Heart Association. *Circulation* **136**, e1–e23 (2017).
7. di Lorenzo, N. *et al.* Clinical practice guidelines of the European Association for Endoscopic Surgery (EAES) on bariatric surgery: update 2020 endorsed by IFSO-EC, EASO and ESPCOP. *Surgical Endoscopy 2020 34:6* **34**, 2332–2358 (2020).
8. One anastomosis gastric bypass: a simple, safe and efficient surgical procedure for treating morbid obesity - PubMed. https://pubmed.ncbi.nlm.nih.gov/15672654/.
9. Slankamenac, K., Graf, R., Barkun, J., Puhan, M. A. & Clavien, P. A. The comprehensive complication index: A novel continuous scale to measure surgical morbidity. *Ann Surg* **258**, 1–7 (2013).
10. A simple method for the isolation and purification of total lipides from animal tissues - PubMed. https://pubmed.ncbi.nlm.nih.gov/13428781/.
11. Application of a new procedure for liquid chromatography/mass spectrometry profiling of plasma amino acid-related metabolites and untargeted shotgun proteomics to identify mechanisms and biomarkers of calcific aortic stenosis - PubMed. https://pubmed.ncbi.nlm.nih.gov/28851525/.
12. Piehler, A. P., Grimholt, R. M., Øvstebø, R. & Berg, J. P. Gene expression results in lipopolysaccharide-stimulated monocytes depend significantly on the choice of reference genes. *BMC Immunol* **11**, (2010).