Uniwersytet Medyczny w Białymstoku

Paulina Głuszyńska

# Ocena wpływu laparoskopowej rękawowej resekcji żołądka na niealkoholową stłuszczeniową chorobę wątroby

Assessment of the impact of laparoscopic sleeve gastrectomy on non – alcoholic fatty liver disease

Rozprawa doktorska

Promotor: prof. dr hab. n. med. Hady Razak Hady

Pracę wykonano w I Klinice Chirurgii Ogólnej i Endokrynologicznej
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Kierownik jednostki: prof. dr hab. n. med. Jacek Dadan

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*Pragnę złożyć najszczersze podziękowania*

*mojemu promotorowi Profesorowi Hady Razak Hady*
*za zaangażowanie, wsparcie, nieustającą motywację, wiele cennych wskazówek oraz*
*za stworzenie warunków do rozpoczęcia pracy naukowej,*

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*wsparcie.*

**SPIS TREŚCI**

**INDEKS SKRÓTÓW**

ALT (*alanine transaminase*) – aminotransferaza alaniniowa

AST (*aspartate transaminase*) – aminotransferaza asparaginianowa

BMI (*body mass index*) – wskaźnik masy ciała

%EBMIL (*percentage of excess BMI loss*) – procent utraty nadmiaru BMI

%EWL (*percentage of excess weight loss*) – procent utraty całkowitej masy ciała

GGT (*gamma – glutamyl transferase*) – gamma – glutamylotranspeptydaza

HDL (*high – density lipoprotein*) – lipoproteina o wysokiej gęstości

LDH (*lactate dehydrogenase*) – dehydrogenaza mleczanowa

LDL (*low – density lipoprotein*) – lipoproteina o niskiej gęstości

LSG (*laparoscopic sleeve gastrectomy*) – laparoskopowa rękawowa resekcja żołądka

NAFLD (*non – alcoholic fatty liver disease*) – niealkholowa stłuszczeniowa choroba wątroby

NAFLD Fibrosis Score (*Non – alcoholic fatty liver disease Fibrosis Score*) – wskaźnik zwłóknienia wątroby w niealkoholowej stłuszczeniowej chorobie wątroby

NASH *(non – alcoholic steatohepatitis*) – niealkoholowe stłuszczeniowe zapalenie wątroby

TG (*triglycerides*) - triglicerydy

%TWL (*percentage of total weight loss*) – procent utraty całkowitej masy ciała

**WYKAZ TABEL I RYCIN**

## 1. Zestawienie publikacji doktoranta

| Rodzaj publikacji | Liczba | Impact Factor | Punktacja MNiSW |
|---|---|---|---|
| Prace włączone do rozprawy doktorskiej | 2 | 9.928 | 280.0 |
| Prace, które nie zostały włączone do rozprawy doktorskiej | 25 | 24.803 | 1172.0 |
| Streszczenia zjazdowe | 26 | 0 | 0 |
| **Razem** | 53 | 34.731 | 1452.0 |

## 2. Wstęp

Rosnąca powszechność występowania otyłości oraz cukrzycy typu 2 na świecie przyczynia się do nieustannego wzrostu częstości występowania niealkoholowej stłuszczeniowej choroby wątroby (ang. non – alcoholic fatty liver disease – NAFLD). Szacuje się, że NAFLD dotyczy 25 – 30% populacji ogólnej i aż 50 – 90% pacjentów otyłych, co koreluje ze wskaźnikiem otyłości [1,2]. Całkowitą liczbę przypadków dotyczących przewlekłych chorób wątroby szacuje się na ok. 1,5 miliarda na całym świecie, z czego NAFLD stanowi aż 59%. Pozostałe diagnozy obejmują zakażenie wirusem wątroby typu B (29%) i C (9%) oraz alkoholową chorobę wątroby (2%) [3]. Z uwagi na powyższe powikłania oraz odległe następstwa NAFLD stają się coraz większym wyzwaniem dla zdrowia publicznego.

Niealkoholową stłuszczeniową chorobę wątroby definiuje się jako ektopowe, patologiczne gromadzenie się tłuszczu w hepatocytach, przy wykluczeniu innych, wtórnych przyczyn nadmiernej akumulacji tłuszczu w wątrobie takich jak: alkoholizm, wirusowe zapalenie wątroby, polekowe uszkodzenie wątroby czy choroby genetyczne [4]. Spektrum choroby obejmuje kilka stadiów zaczynając od niealkoholowego prostego stłuszczenia wątroby i stłuszczeniowego zapalenia wątroby (ang. non-alcoholic steatohepatitis – NASH) do włóknienia i marskości wątroby ze wszystkim klinicznymi powikłaniami takimi jak: encefalopatia wątrobowa, krwawienie z żylaków przełyku, wodobrzusze, samoistne bakteryjne zapalenie otrzewnej czy niewydolność nerek [5,6].

Zdecydowana większość pacjentów, u których diagnozuje się NAFLD jest bezobjawowa. Objawy, na które mogą uskarżać się pacjenci są niespecyficzne i obejmują: dyskomfort

oraz tępy ból w nadbrzuszu, ogólne osłabienie, wzmożone pragnienie oraz wzdęcia. Najczęstszą nieprawidłowością stwierdzaną w badaniu przedmiotowym jest hepatomegalia [7]. Z odchyleń w badaniach biochemicznych można zauważyć nieznaczne zwiększenie aktywności aminotransferazy asparaginianowej i alaninowej oraz gamma – glutamylotranspeptydazy, choć ich aktywność może być w normie nawet u 80% pacjentów. W zaawansowanych przypadkach obserwuje się hipoalbuminemię, trombocytopenię, hiperbilirubinemię oraz wydłużenie czasu protrombinowego [8].

Złotym standardem w rozpoznawaniu niealkoholowej stłuszczeniowej choroby wątroby pozostaje biopsja wątroby, pomimo tego, że jest badaniem inwazyjnym, niosącym ze sobą ryzyko powikłań oraz ograniczeń związanych z wysokimi kosztami procedury [9]. Badanie ultrasonograficzne jamy brzusznej jest zalecane jako badanie obrazowe „pierwszego rzutu" w przypadku podejrzenia NAFLD [10]. Podstawą rozpoznania stłuszczenia wątroby w badaniu USG jamy brzusznej jest stwierdzenie zwiększenia echogeniczności miąższu wątroby w porównaniu z korą prawej nerki [11]. Z uwagi na swój nieinwazyjny charakter oraz powszechny dostęp badanie to jest szeroko wykorzystywane do diagnostyki NAFLD, pomimo, że jego wykonanie może być problematyczne u pacjentów z otyłością olbrzymią ze względu na znaczne nagromadzenie tkanki podskórnej.

Postępowanie terapeutyczne w przypadku rozpoznania NAFLD opiera się głównie o modyfikację diety oraz stylu życia celem redukcji masy ciała. Dane dostępne w literaturze dowodzą, iż 5 – 10% spadek masy ciała może prowadzić do poprawy wszystkich cech niealkoholowego stłuszczeniowego zapalenia wątroby, włącznie ze stanem zapalanym oraz zwłóknieniem [12].

W ostatnich latach laparoskopowa rękawowa resekcja żołądka (ang. laparoscopic sleeve gastrectomy – LSG) stała się najczęściej wykonywaną procedurą bariatryczną na świecie [13]. LSG jest przykładem operacji restrykcyjnej, w której poprzez zmniejszenie objętości żołądka o 75 – 80% ograniczona zostaje ilość spożywanego pokarmu. Dodatkowy mechanizm wpływający na skuteczność tego zabiegu wiąże się z usunięciem dna żołądka, a co za tym idzie komórek, które odpowiadają za wytwarzanie hormonu o nazwie grelina odpowiedzialnego za uczucie głodu. Zmniejszenie stężenia greliny w krwiobiegu wiąże się z szybszym uczuciem sytości i nieodczuwaniem głodu [14].

Dane dostępne w piśmiennictwie dowodzą, iż laparoskopowa rękawowa resekcja żołądka powoduje znaczną oraz długotrwałą utratę masy ciała u pacjentów z otyłością olbrzymią [15,16]. Dodatkowo LSG prowadzi do poprawy kontroli oraz ustępowania chorób współistniejących z otyłością, w tym: cukrzycy typu 2, nadciśnienia tętniczego, dyslipidemii, obturacyjnego bezdechu sennego oraz do zmniejszenia ryzyka chorób sercowo – naczyniowych [17, 18]. Skutkuje to znaczną poprawą jakości życia pacjentów oraz redukcją ryzyka przedwczesnej śmierci w porównaniu z osobami z otyłością olbrzymią [19, 20].

W literaturze dostępne są prace, które analizują związek pomiędzy spadkiem masy ciała a przebiegiem niealkoholowej stłuszczeniowej choroby wątroby [21]. Coraz częściej ocenia się także wpływ operacji bariatryczno-metabolicznych i pooperacyjnej redukcji masy ciała na ustępowanie NAFLD i NASH [22, 23]. Zadowalające wyniki doprowadziły do umieszczenia NAFLD na liście chorób współistniejących z otyłością, które stanowią wskazanie do kwalifikacji do zabiegu operacyjnego u pacjentów otyłością I stopnia (BMI 30-34.9 kg/m$^2$) [24].

Powodem podjęcia przeze mnie rozważań nad wpływem laparoskopowej rękawowej resekcji żołądka na przebieg niealkoholowej stłuszczeniowej choroby wątroby jest fakt, iż problem ten dotyczy coraz większego odsetka populacji ogólnej i stanowi istotne zagadnienie kliniczne dla specjalistów z różnych dyscyplin. Niezmiernie interesujące z perspektywy klinicznej, a dotychczas niedostatecznie zbadane wydaje się określenie korelacji pomiędzy ustępowaniem niealkoholowej stłuszczeniowej choroby wątroby a pooperacyjną redukcją masy ciała. Badania w prezentowanej pracy doktorskiej jako jedne z pierwszych w Polsce i nielicznych na świecie podnoszą tematykę wpływu laparoskopowej rękawowej resekcji żołądka na przebieg niealkoholowej stłuszczeniowej choroby wątroby u pacjentów z otyłością olbrzymią w obserwacji rocznej.

## 3. Cel pracy

Celem niniejszej pracy doktorskiej była ocena wpływu laparoskopowej rękawowej resekcji żołądka na przebieg niealkoholowej stłuszczeniowej choroby wątroby w obserwacji rocznej u pacjentów poddanych zabiegowi z powodu otyłości olbrzymiej, w tym:

a) Porównanie wyników badania ultrasonograficznego jamy brzusznej z uwzględnieniem stopnia stłuszczenia wątroby przed zabiegiem operacyjnym, jak i 6 oraz 12 miesięcy po leczeniu chirurgicznym;
b) Porównanie wyników wybranych parametrów biochemicznych (w tym aktywności enzymów wątrobowych, profilu lipidowego oraz glikemii na czczo) i ich zmian w obserwacji rocznej;
c) Ocena wyniku bariatrycznego oraz analiza, czy pooperacyjna redukcja masy ciała wpływa na ryzyko rozwoju zaawansowanego włóknienia wątroby na podstawie NAFLD Fibrosis Score.

## 4. Metodyka i materiał

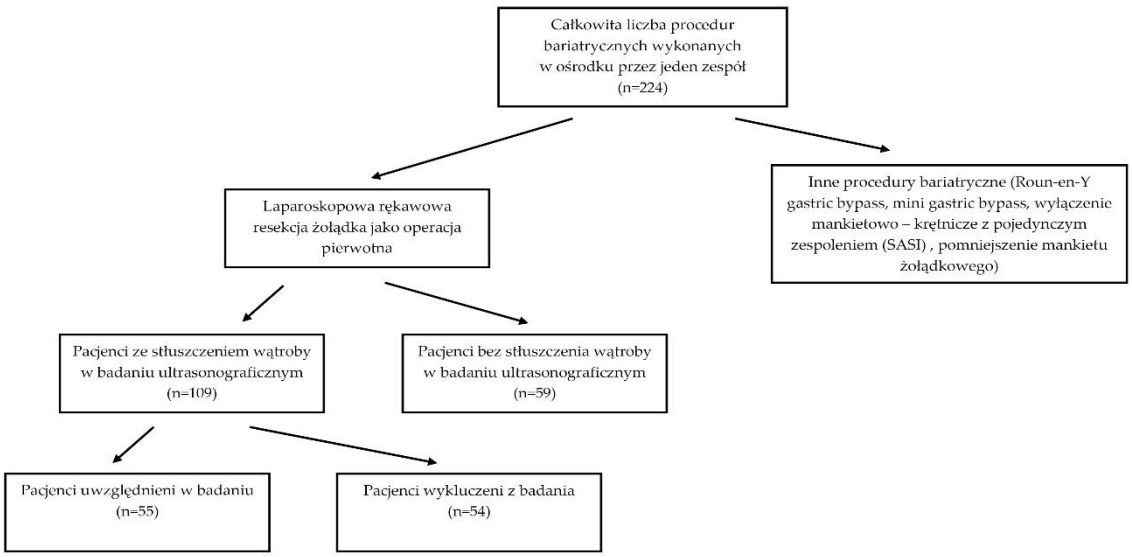
Badania uwzględnione w pracy doktorskiej przeprowadzone zostały w latach 2019 – 2021 w I Klinice Chirurgii Ogólnej i Endokrynologicznej Uniwersyteckiego Szpitala Klinicznego w Białymstoku. Grupę badaną stanowili pacjenci poddani laparoskopowej rękawowej resekcji żołądka z powodu otyłości olbrzymiej ze współistniejącą niealkoholową stłuszczeniową chorobą wątroby rozpoznaną w badaniu ultrasonograficznym jamy brzusznej. Analizy laboratoryjnej zgromadzonego materiału dokonano w Centrum Badań Klinicznych oraz laboratorium przy Poradni I Chirurgii Ogólnej i Endokrynologicznej Uniwersyteckiego Szpitala Klinicznego w Białymstoku. Ocena patomorfologiczna zebranego materiału została przeprowadzona w Zakładzie Patomorfologii Lekarskiej Uniwersytetu Medycznego w Białymstoku.

**Kryteria włączenia:**

- Świadoma zgoda pacjenta na udział w badaniu,
- Wiek 18 – 65 lat,
- Spełnienie kryteriów kwalifikacji do chirurgicznego leczenia otyłości zgodnie z wytycznymi Sekcji Chirurgii Metabolicznej i Bariatrycznej Towarzystwa Chirurgów Polskich [25],
- Rozpoznanie stłuszczenia wątroby w przedoperacyjnej ocenie ultrasonograficznej jamy brzusznej.

**Kryteria wykluczenia:**

- Wywiad w kierunku alkoholizmu
- Współistniejące wirusowe zapalenie wątroby
- Polekowe uszkodzenie wątroby
- Przebyta choroba nowotworowa
- Rewizyjna operacja bariatryczna
- Powikłania w trakcie zabiegu operacyjnego
- Powikłania pooperacyjne w analizowanym okresie




**Rycina 1.** Graficzne przedstawienie wyboru grupy do badania

Dane kliniczne dotyczące pacjentów biorących udział w badaniu obejmowały: wiek w trakcie zabiegu operacyjnego, płeć, przedoperacyjną masę ciała, przedoperacyjny BMI oraz główne choroby współistniejące takie jak: cukrzyca typu 2, nadciśnienie tętnicze,

hipercholesterolemia, choroby sercowo – naczyniowe, depresja, bezdech, żylaki kończyn dolnych, choroba zwyrodnieniowa stawów. Badania laboratoryjne obejmowały następujące parametry: płytki krwi, stężenie albumin, bilirubinę, aminotransferazę asparaginianową (AST) i alaninową (ALT), dehydrogenazę mleczanową (LDH), gamma – glutamylotranspeptydazę (GGTP), cholesterol całkowity, cholesterol HDL i LDL, triglicerydy oraz glikemię na czczo. Na podstawie danych klinicznych oraz laboratoryjnych dokonano oceny włóknienia wątroby na podstawie wskaźnika zwłóknienia wątroby w niealkoholowej stłuszczeniowej chorobie wątroby (NAFLD Fibrosis Score). Do jego wyliczenia zastosowano poniższą formułę:

**NAFLD Fibrosis Score** = -1.675 + 0.037 × wiek (lata) + 0.094 × BMI (kg/m$^2$) + 1.13 × hiperglikemia na czczo/cukrzyca typu 2 (tak = 1, nie = 0) + 0.99 × AST/ALT - 0.013 × płytki krwi (×10$^9$/L) - 0.66 × stężenie albumin (g/dL).

Wartości poniżej -1,455 wskazują na brak zaawansowanego włóknienia wątroby, a powyżej 0,676 na duże ryzyko zaawansowanego włóknienia wątroby. Wartości od -1,455 do 0,676 wskazują na umiarkowane ryzyko w odniesieniu do obecności zaawansowanego zwłóknienia wątroby [26].

Powyższe parametry zostały ocenione zarówno przedoperacyjnie jak i pół roku oraz rok po zabiegu rękawowej resekcji żołądka.

Efekt leczenia bariatrycznego został oceniony 6 i 12 miesięcy po zabiegu przy użyciu następujących wskaźników:

- Procent utraty nadmiernej masy ciała (%EWL – percentage of excess weight loss) = (przedoperacyjna masa ciała – masa ciała w trakcie kontroli)/(przedoperacyjna

masa ciała – idealna masa ciała) x 100, gdzie idealna masa ciała została zdefiniowana jako masa ciała odpowiadająca BMI = 25 kg/m$^2$,

- Procent utraty całkowitej masy ciała (%TWL – percentage of total weight loss) = (przedoperacyjna masa ciała – masa ciała w trakcie kontroli)/przedoperacyjna masa ciała x 100,
- Procent utraty nadmiaru BMI (%EBMIL – percentage of excess BMI loss) = (przedoperacyjne BMI – BMI w trakcie kontroli)/(przedoperacyjne BMI – 25) x 100.

Ocena stopnia stłuszczenia wątroby w badaniu ultrasonograficznym jamy brzusznej została dokonana przedoperacyjnie oraz pół roku i rok po zabiegu operacyjnym. Stopień stłuszczenia wątroby w badaniu ultrasonograficznym jamy brzusznej został oceniony według poniższej klasyfikacji:

- Stopień 0 (brak stłuszczenia) – prawidłowa echogeniczność wątroby,
- Stopień 1 (łagodne stłuszczenie) – nieznaczny i rozlany wzrost echogeniczności wątroby,
- Stopień 2 (umiarkowane stłuszczenie) – umiarkowany wzrost echogeniczności wątroby,
- Stopień 3 (ciężkie stłuszczenie wątroby) – wyraźny wzrost echogeniczności wątroby.

W trakcie zabiegu operacyjnego został pobrany wycinek z wątroby do badania histopatologicznego, w którym oceniono obecność bądź brak stłuszczenia, włóknienia oraz stanu zapalnego wątroby.

## 5. Analiza statystyczna

Analizę statystyczną wyników przeprowadzono za pomocą oprogramowania GraphPad Prism 9.0.0 (GraphPad Software, San Diego, California, USA). Ocenę normalności rozkładu przeprowadzono przy pomocy testu W Shapiro-Wilka, natomiast ocenę homogeniczności wariancji za pomocą testu Leven'a. Do porównania między dwiema grupami zastosowano test kolejności par Wilcoxona. Do porównania między więcej niż dwiema grupami zastosowano test rang Friedmanna oraz sparowany test Dunna do analizy post-hoc. Uzyskane wyniki przedstawiano jako medianę oraz wartość 25 i 75 percentyla.

W poszukiwaniu współzależności pomiędzy badanymi parametrami i dla określenia siły tych współzależności zastosowano nieparametryczną korelację rang R Spearmana. Przy weryfikacji wszystkich hipotez statystycznych za istotny przyjęto poziom istotności $p < 0,05$.

## 6. Zagadnienia etyczne

Wszystkie procedury przeprowadzone w ramach pracy doktorskiej były zgodne z normami etycznymi Kodeksu Etyki Lekarskiej oraz z Deklaracją Helsińską z 1964 roku z jej późniejszymi poprawkami. Badania uzyskały akceptację Komisji Bioetycznej Uniwersytetu Medycznego w Białymstoku (Nr R-I-002/248/2018 oraz R-I-002/386/2018).

## 7. Cykl prac wchodzących w skład rozprawy doktorskiej

Cykl składa się z dwóch prac: jednej oryginalnej i jednej poglądowej, które zostały opublikowane w międzynarodowych czasopismach naukowych umieszczonych na Liście Filadelfijskiej. Łączny współczynnik oddziaływania (IF) cyklu wyniósł 9.928. Łączna punktacja MNiSW to 280.0 punktów.

a) Paulina Głuszyńska, Dorota Lemancewicz, Janusz Bogdan Dzięcioł, Hady Razak Hady.

   *"Non-alcoholic fatty liver disease (NAFLD) and bariatric/metabolic surgery as its treatment option: a review."*

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b) Paulina Głuszyńska, Aleksander Łukaszewicz, Inna Diemieszczyk, Jan Chilmończyk, Joanna Reszeć, Anna Citko, Łukasz Szczerbiński, Adam Krętowski, Hady Hady Razak.

   *"The effect of laparoscopic sleeve gastrectomy on the course of non-alcoholic fatty liver disease in morbidly obese patients during one year of follow up."*

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# Non-Alcoholic Fatty Liver Disease (NAFLD) and Bariatric/Metabolic Surgery as Its Treatment Option: A Review

**Paulina Głuszyńska [1,*], Dorota Lemancewicz [2], Janusz Bogdan Dzięcioł [2] and Hady Razak Hady [1]**

[1] Department of General and Endocrine Surgery, Medical University of Bialystok, 15-089 Białystok, Poland; hadyrazakh@wp.pl
[2] Department of Human Anatomy, Medical University of Bialystok, 15-089 Białystok, Poland; dorota.lemancewicz@umb.edu.pl (D.L.); anatomia@umb.edu.pl (J.B.D.)
* Correspondence: Paulina.gluszynska@gmail.com; Tel.: +48-85-831-8279

**Abstract:** The prevalence of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) has considerably increased over the last years. NAFLD is currently the most common cause of chronic liver disease in the developing world. The diagnosis of NAFLD/NASH is often incidental, as the early-stage of disease is frequently free of symptoms. Most patients recognized with NAFLD have severe obesity and other obesity-related disease such as type 2 diabetes mellitus (T2DM), insulin-resistance, dyslipidemia and hypertension. The only proven method for NAFLD improvement and resolution is weight loss. Bariatric surgery leads to significant and long-term weight loss as well as improvement of coexisting diseases. There is a lot of evidence suggesting that metabolic/bariatric surgery is an effective method of NAFLD treatment that leads to reduction in steatosis, hepatic inflammation and fibrosis. However, there is still a need to perform long-term studies in order to determine the role of bariatric surgery as a treatment option for NAFLD and NASH. This review discusses current evidence about epidemiology, pathogenesis and treatment options for NAFLD including bariatric/metabolic surgery and its effect on improvement and resolution of NAFLD.

**Keywords:** non-alcoholic fatty liver disease; non-alcoholic steatohepatitis; obesity; bariatric surgery; laparoscopic sleeve gastrectomy; Roux-en-Y gastric bypass



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## 1. Introduction

Unhealthy lifestyle and dietary habits have contributed to an alarming increase in obesity and obesity-related diseases worldwide. The epidemic of obesity has led to a significant increase in the prevalence of non-alcoholic fatty liver disease (NAFLD). The prevalence of NAFLD is 25–30% of the general population and 50–90% in patients with obesity [1,2]. A recent report estimates the constant increase in the prevalence of NAFLD by the year 2030 with significant rise in hepatocellular carcinoma (HCC) and liver-related deaths [3]. NAFLD is the initial, uncomplicated medical condition that may lead to end-stage liver disease from non-alcoholic simple steatosis and steatohepatitis (NASH) to fibrosis and liver cirrhosis with its clinical consequences such as: variceal bleeding, ascites, renal failure, encephalopathy and spontaneous bacterial peritonitis [4,5]. Data from the European Liver Transplant Registry (ELTR) and United Network for Organ Sharing (UNOS) show that NAFLD and NASH have been the most rapidly growing indication for liver transplant within the last 20 years. Additionally, NAFLD is presently the most frequent non-viral hepatitis-related indication for liver transplant among adults in the United States [6,7].

NAFLD is frequently recognized as the hepatic manifestation of metabolic syndrome (MS) and remains in close association with components of MS that include increased fasting plasma glucose level and type 2 diabetes mellitus (T2DM), increased waist circumference,

hypertension and dyslipidemia [8,9]. Recent studies have shown that over 80% of patients undergoing bariatric surgery have been diagnosed with NAFLD or NASH [10,11].

Bariatric/metabolic surgery is an effective treatment for morbid obesity that provides sustained and considerable weight loss with the improvement of obesity-related diseases. Reduction in body weight induced by bariatric surgery leads to potential decrease in hepatic inflammation, fat accumulation and fibrosis [12]. In the forthcoming sections of this review, we provide the information about pathogenesis, diagnosis and potential treatment options including conservative, pharmacological and bariatric surgery procedures for NAFLD according to the available literature.

## 2. Epidemiology

A systematic review conducted by Younossi et al. estimated the pooled, overall global prevalence of NAFLD diagnosed by imaging to be 25.24% (95% confidence interval (CI): 22.10–28.65). Their study reported the highest prevalence of NAFLD in South America (30.4%) and the Middle East (31.8%), whereas the lowest rate was reported in Africa (13.5%). The prevalences of NAFLD among patients diagnosed by blood test were 13.00% (95% CI: 4.44–32.47) for Europe, 12.89% (95% CI: 8.32–19.44) for North America, and 9.26% (95% CI: 7.07–12.05) for Asia [13]. According to Cholangitas et al., pooled NAFLD prevalence was 26.9% in the adult European population. Pooled NAFLD prevalence was higher in men than in women (32.8% vs. 19.6%). There were no differences between Mediterranean and non-Mediterranean countries. The pooled prevalence of NAFLD was higher in studies using ultrasonography and fatty liver index (FLI) for NAFLD diagnosis (27.2% and 30.1%, respectively) [14]. Current trends in dietary habits and preponderance of sedentary lifestyle contribute to the constant growth in the incidence of NAFLD worldwide. The National Health and Nutrition Examination Surveys data demonstrated a rise in the prevalence of NAFLD in the US from 5.5% (1988–1994) to 11% (2005–2008) [8], as it is estimated that the epidemic of obesity will continue to fuel the burden of NAFLD.

## 3. Pathogenesis of NAFLD

The pathogenesis of NAFLD is multifactorial; however, its understanding is crucial for the proper therapeutic interventions. A two-hit model of NAFLD development was proposed with the first hit consisting of hepatic steatosis, which then sensitizes the liver to injury mediated by "second hits" including: inflammatory cytokines, adipokines and oxidative stress leading to steatohepatitis and fibrosis [15]. This two-hit model has lost some favor, as it turned out too simplistic to fully describe the evolution of NAFLD, as different factors affecting disease development and progression were unveiled. Nowadays, the two-hit hypothesis was replaced with the "multiple hit" theory, which recognizes the following components in NAFLD pathophysiology: insulin resistance, obesity, gut microbiota, environmental and genetic factors. The key concept of NAFLD pathogenesis is excessive triglycerides hepatic accumulation as a result of imbalance between free fatty acids influx and efflux [16]. Excessive hepatic fat accumulation occurs in patients with obesity and T2DM, who have impaired insulin signaling. Insulin resistance leads to an uncontrolled lipolysis in adipose tissue that results in significant deposition of nonesterified free fatty acids (NFFA) in the liver [17]. Other factors contributing to excessive hepatic fat accumulation are dietary fats and de novo lipogenesis. Among dietary factors, fructose seems to have an important role, as it is both a substrate and an inducer for de novo hepatic lipogenesis [18]. The excessive inflow of triglycerides to the liver leads to inflammation, reactive oxygen species (ROS) formation, hepatocyte impaired function and lipotoxicity. Hepatocellular cells injury activates apoptotic pathways causing cellular death. This results in the progression from noninflammatory isolated steatosis to the development of nonalcoholic steatohepatitis with a risk of further evolution to fibrosis, cirrhosis and at worst to the development of hepatocellular carcinoma [19,20].

Available research shows that gut microbiota is also associated with the development of NAFLD and NASH [21,22]. The imbalance between protective and harmful bacteria,

damage of intestinal barrier and disturbed immune response cause that bacterial products reach the liver through the portal vein and activate pathways responsible for proinflammatory response. Additionally, microbiota dysbiosis increases lipoprotein lipase activity and triglycerides accumulation by either decreasing choline levels or increasing methylamine level, which promotes development of NAFLD [23]. Damage of intestinal epithelial membrane leads to an impaired transport across the mucosa. Rahman et al. proved that compromised intestinal epithelial permeability contributes to development of NAFLD. The above-mentioned study showed that mice with defects or loss of junctional adhesion molecule A (JAM-A) in intestinal epithelial membrane develop more severe steatohepatitis after a diet high in saturated fat, fructose and cholesterol for 8 weeks. They also found out that colon tissue from patients with NAFLD has lower level of JAM-A and higher inflammation status as compared to patients without NAFLD [24]. Significant changes in gut microbiota are reported after bariatric surgery. Possible mechanisms for the intestinal microbiota changes include reduction in body weight, changes in food consumption, changes in ghrelin and leptin secretion and alternations in stomach pH [25,26].

Genes also have a role in the development of NAFLD. It has been discovered that genetic polymorphism can influence the NAFLD development and progression by variability in oxidative stress, inflammation and FFAs accumulation. The main genetic determinant of interindividual differences in hepatic fat content is nonsynonymous variant of patatin-like phospholipase 3 (*PNPLA3*) gene (rs738409 C/G, I148M), also known as adiponutrion [27]. The PNPLA3 variant has impaired hydrolysis activity and is less available for degradation, which leads to retention in of TG and polyunsaturated fatty acids priming accumulation of hepatic fat [28]. Another relevant genetic variant related to progressive NAFLD is the transmembrane 6 superfamily member 2 (*TM6SF2*), which is responsible for lipid retention and impairment of very low-density lipoprotein (VLDL) release by liver [29]. Loss of function in rs1260326 variant in the *GCKR* gene is also associated with increased TG concentration, steatosis and liver damage [30]. The understanding of possible nutrigenomic approaches may lead to improvement of NAFLD management and introduction of proper therapeutic strategy Figure 1.

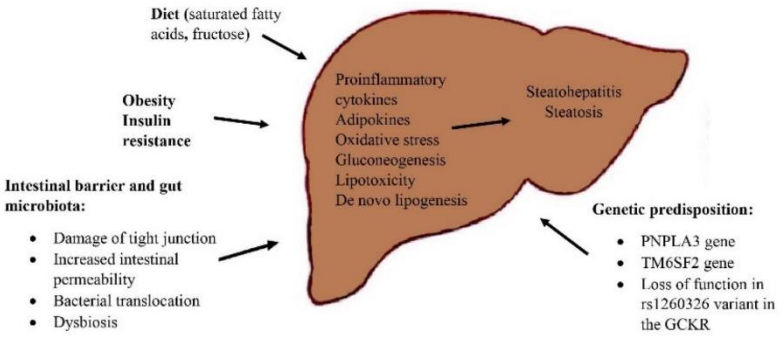


**Figure 1.** Pathogenesis of NAFLD.

## 4. Diagnosis of NAFLD

NAFLD is defined as an excessive accumulation of triglycerides in hepatocytes either by imaging or histology, simultaneously with exclusion of any significant alcohol consumption and other liver diseases [31]. Mildly elevated serum aminotransferases are the primary abnormality in NASH, although they may remain at normal level in up to 80% of patients. The alanine transaminase (ALT) level is generally higher than that of aspartate aminotransferase (AST). Other common findings in blood examination include high serum triglyceride and low HDL cholesterol level. With the development of the disease hypoalbuminemia, hyperbilirubinemia and thrombocytopenia may occur due to

progression of liver injury [32]. Ultrasound is a non-invasive and widely available tool for the diagnosis of NAFLD. Characteristic sonographic findings for NAFLD include heterogeneity of liver; thick subcutaneous depth (>2 cm); quick attenuation of image 4–5 cm of depth, making deeper structures difficult to decipher, and; dispersion of echogenicity [33]. However, the use of ultrasound is very limited in patients with overweight and obesity due to excessive subcutaneous fat accumulation. The assessment of liver fibrosis without histological examination can be made by a combination of serological and imaging tests. There are several scoring systems used to estimate liver fibrosis without performing liver biopsy. NAFLD fibrosis score (NFS) is calculated based on following measurements: age, BMI, glucose blood concentration, platelet count, albumin serum level and AST/ALT ratio. Another one is the BARD score, which is composed of 3 variables: ALT/AST ratio, BMI and the presence of diabetes. BARD score of 0 or 1 are of high (96%) negative predictive value (NPV) for advanced fibrosis [34]. The AASSLD guidelines suggest the use of NFS or APRI score as non-invasive tools for clinical diagnosis. It is worth mentioning that NFS was developed as a scoring system for usage in patients with NAFLD [35]. The available ways to estimate liver fibrosis together with measured parameters are listed in Table 1 [36].

**Table 1.** Noninvasive assessment of liver fibrosis based on biochemical parameters.

| Name of Scoring System | Used Measures |
| --- | --- |
| NAFLD fibrosis score (NFS) | Age, blood glucose level, BMI, platelet count, albumin, AST/ALT ratio |
| APRI score | aspartate aminotransferase to platelet ratio index |
| BAAT score | BMI, age, ALT, triglyceride level |
| BARD score | BMI, AST/ALT ratio, presence/absence of diabetes |
| Enhanced liver fibrosis (ELF) index | Plasma level of hyaluronic acid (HA), tissue inhibitor of metalloproteinase (TIMP-1), procollagen III amino terminal peptide (PIIINP) |
| Hepascore | Bilirubin, gamma-glutamyl transpeptidase (γ-GTP), α2-macroglobulin, hyaluronic acid levels |
| FIBROSpect | hyaluronic acid, TIMP-1 and α2-macroglobulin |
| Fibrometer | prothrombin index, platelet count, AST, urea, α2-macroglobulin, hyaluronic acid |
| NashTest | age, sex, height, weight, serum triglycerides, cholesterol, α2-macroglobulin, apolipoprotein A1, haptoglobin, γ-GTP, ALT, AST, total bilirubin |

Magnetic resonance imaging (MRI) is a non-invasive method widely accepted by patients and doctors, and may be used as an alternative to liver biopsy in assessment of hepatic fat content [37]. Several studies have shown that magnetic resonance elastography (MRE) is a diagnostic tool for prediction of hepatic fibrosis stage in NAFLD with sensitivity of 63–87%, and specificity of 81–95% [38]. Another tool is magnetic resonance imaging-proton density fat fraction (MRI-PDFF), which has high accuracy in detecting hepatic steatosis and quantifying the degree of steatosis in NAFLD [39]. However, the gold standard for NAFLD diagnosis remains the percutaneous liver biopsy. Although liver biopsy is expensive, has increased risk of adverse events and requires professional interpretation, it should be performed in patients who benefit the most from making the right diagnosis.

According to the American Association of Liver Disease (AASLD), liver biopsy should be considered in patients with NAFLD who are at higher risk of steatohepatitis and advanced fibrosis, including those with diabetes and/or metabolic syndrome. Referral for liver biopsy should be also considered in patients who have findings of concern for cirrhosis, such as hypoalbuminemia, thrombocytopenia, AST > ALT and in patients undergoing cholecystectomy or bariatric surgery, when intraoperative biopsy is a low risk procedure [40]. The main histological characteristics of NAFLD is the accumulation of fat in the form of triglycerides within hepatocytes. The presence of >5% steatotic hepatocytes

in a liver tissue is the criteria for the histological definition of NAFLD. In NAFLD, steatosis is usually macrovesicular, which means that lipid vacuole fills nearly the whole hepatocyte, and the nucleus is pushed to the side. A simple four-point scoring system that takes into account only macro- and/or mediovesicualar steatosis and estimates the percentage of hepatocytes covered with steatosis is used for steatosis grading. Normal liver (grade 0) contains fat in <5% of hepatocytes; in grade 1, 2, 3 steatotic hepatocytes are present in <33%, 33–66% and >66% of hepatocytes, respectively, [41]. In the case of NASH histological diagnosis criteria include steatosis with hepatocellular (usually in the form of ballooning) and lobular inflammation [42]. There are three scoring systems that are currently used in grading the histological features of NAFLD/NASH, which are the Brunt system, the NAFLD Activity Score (NAS) and the Steatosis-Activity-Fibrosis (SAF) System [42–45]. Scoring in individual systems together with scored histological features are presented in Tables 2–5.

**Table 2.** Brunt system to grade NASH activity.

| Grade | Steatosis<br>1: ≤33%<br>2: 33–66%<br>3: ≥66% | Ballooning<br>(Zonal Location and Severity Recorded) | Inflammation | |
|---|---|---|---|---|
| | | | L-Lobular (0–3)<br>0: Absent<br>1: <2 foci/20× field<br>2: 2–4 foci/20× field<br>3: >4 foci/20× field | P-Portal (0–3)<br>0: Absent<br>1: Mild<br>2: Moderate<br>3: Severe |
| **Grade 1 (mild)** | 1–2 | Minimal, zone 3 | L = 1–2 | P = 0–1 |
| **Grade 2 (moderate)** | 2–3 | Present, zone 3 | L = 2 | P = 1–2 |
| **Grade 3 (severe)** | 2–3 | Marked, predominantly zone 3 | L = 3 | P = 1–2 |

**Table 3.** Brunt system for staging NASH fibrosis.

| Stage | Zone 3, Sinusoidal | Portal Based | Bridging | Cirrhosis |
|---|---|---|---|---|
| **1** | Focal or extensive | 0 | 0 | 0 |
| **2** | Focal or extensive | Focal or extensive | 0 | 0 |
| **3** | Bridging septa | Bridging septa | + | 0 |
| **4** | ± | ± | Extensive | + |

**Table 4.** The NAFLD Activity Score.

| Steatosis Grade (S) | Lobular Inflammation (L) | Hepatocyte Ballooning (B) |
|---|---|---|
| 0: <5% | 0: none | 0: none |
| 1: 5–33% | 1: <2 foci/20× field | 1: mild, few ballooned cells |
| 2: 34–66% | 2: 2–4 foci/20× field | 2: moderate-marked, many ballooned cells |
| 3: >66% | 3: >4 foci/20× field | |
| **Fibrosis** (evaluated with Masson trichrome stain) | | |
| | 0 | None |
| | 1a | Mild zone 3 sinusoidal fibrosis (trichrome stain to be identified) |
| | 1b | Moderate zone 3 sinusoidal fibrosis (could be detected on H&E examination) |
| | 1c | Portal fibrosis only |
| | 2 | Zone 3 sinusoidal fibrosis and periportal fibrosis |
| | 3 | Bridging fibrosis |
| | 4 | Cirrhosis |

**Table 5.** Steatosis-Activity-Fibrosis (SAF) scoring system of NAFLD.

| Steatosis Grade (S): 0–3 (Based on Percentage of Hepatocytes with Large and/or Medium Size Intracytoplasmic Lipid) | Lobular Inflammation: 0–2 | Hepatocyte Ballooning: 0–2 | Activity Grade (A): 0–4 (Sum of Score for Ballooning and Lobular Inflammation) | Fibrosis Stage (F) |
|---|---|---|---|---|
| S0: <5% | 0: none | 0: none | A1 (A = 1): mild activity | F0: no significant fibrosis |
| S1: 5–33% | 1: ≤2 foci/20× field | 1: cluster of rounded hepatocytes with pale/reticulated cytoplasm | A2 (A = 2): moderate activity | F1: 1a mild zone 3 sinusoidal fibrosis 1b moderate zone 3 sinusoidal fibrosis 1c portal fibrosis only |
| S2: 34–66% | 2: >2 foci/20× field | 2: same as 1 with enlarged hepatocytes (more than twice of normal size) | A3 and A4 (A > 2): severe activity | F2: zone 3 sinusoidal fibrosis with periportal fibrosis |
| S3: >66% | | | | F3: bridging fibrosis F4: cirrhosis |

## 5. Treatment Options of NAFLD

A considerable amount of research points out strong evidence between NASH and lifestyle modifications such as: weight loss, dietary changes and physical exercises. It has been proven that weight reduction by 5 to 10% in individuals with obesity can result with improvement in all features of NASH, including inflammation and fibrosis [46]. Dietary changes should include decrease in calorie intake, as well as changes in composition of a diet that includes reduction of carbohydrate intake (particularly simple carbohydrates, e.g., sweets, fruit juices, honey, fruits, flavored yoghurts), reduction of dietary fats with emphasis on saturated and trans fatty acids, increase in protein intake, ensuring supply of antioxidants, probiotics and prebiotics. Abstinence from alcohol is also recommended as a lifestyle intervention in NAFLD treatment [47]. However, it is very important to notice that implementing lifestyle modifications in patients with obesity can be problematic and usually does not bring the intended results. A study conducted by Dudekula et al. that aimed to find weight loss predictors in patients with obesity and NAFLD showed that 66% of research participants experienced weight reduction of less than 5% during the observation period. Weight loss between 5 to 10% was observed in 12.9% patients and reduction in body weight >10% was seen only in 6.9% of study participants [48]. Additionally, most individuals with obesity are more likely to regain weight in a short period of time [49]. The general idea of NAFLD treatment focuses on co-existing diseases such as obesity, dyslipidemia, insulin resistance and diabetes mellitus.

According to the European Association for the Study of the Liver (EASL) guidelines, pharmacological therapy should be implemented in patients with progressive NASH (bridging fibrosis and cirrhosis); early stage NASH with high risk for disease progression (increased ALT, presence of metabolic syndrome and diabetes mellitus, age >50 years) and active NASH with high necroinflammatory activities [50]. Pharmacological therapy options for NAFLD include: antidiabetic drugs, drugs modifying lipid profile, anti-obesity drugs, vitamin supplementation and novel therapeutic treatment that includes interference with inflammatory, fibrotic and apoptotic pathways. Among antidiabetics drugs pioglitazone, glucagon-like-peptide (GLP-1) analogues and liraglutide were found to be effective in NAFLD/NASH treatment. Pioglitazone was shown to significantly improve steatosis and inflammation, together with systemic and adipose- tissue resistance in one-year observation in patients with T2DM [51]. Research conducted by Bril et al. confirmed reduction of liver fibrosis and increase in adipose tissues insulin sensitivity. However, the effect was

significantly greater in patients with type 2 diabetes than in patients with prediabetes [52]. Liraglutide is a long-acting GLP-1 agonist that improves key metabolic risk factors: weight, body mass index and glucose level. Besides its metabolic improvement, liraglutide was found to significantly improve liver steatosis in NAFLD patients by downregulating the expression of inflammatory mediators in the TNF-α signaling pathway [53,54]. Additionally, liraglutide affects the renin-angiotensin system (RAS), which is overactivated during NAFLD. Liraglutide was found to down regulate the ACE/Ang II/AT1R axis and antagonizes hepatocellular steatosis [55].

In the case of metformin, which is commonly used in prediabetes and diabetes treatment, no strong evidence for histological response was found in NAFLD patients [56]. Despite the fact that metformin has no specific influence on liver histology, it is recommended in NAFLD/NASH patients with T2DM due to its pleiotropic effect including reduction in body mass, and decrease in ALT activity and improvement of cardiovascular system [57]. Furthermore, a recent animal study conducted by Brandt et al. suggests that metformin has a protective effect on the development of NAFLD, which results from a protection against intestinal barrier impairment, e.g., loss of tight junction proteins. Metformin also alters intestinal microbiota composition in the proximal small intestine, which has a beneficial effect on steatosis development [58].

Vitamin supplementation has been also found to have its role in NAFLD treatment. Vitamins with antioxidant properties, such as Vitamin C and E decrease the oxidative stress that is seen in patients with NAFLD and NASH. Additionally, Vitamin E has anti-inflammatory and anti-apoptotic properties that can retard the fibrosis process and prevent from cirrhosis by modulating inflammatory response and cellular proliferation [59]. It should be mentioned that supplementation of Vitamin E is recommended for patients with NASH and stage 2 fibrosis proven in biopsy and without a family history of prostate cancer, as it was proven that high daily dose of Vitamin E ($\geq$400 IU per day) is associated with progression of prostate cancer [60].

Data about usage of weight-loss medication in NAFLD are very scarce in the available literature. To date, only Orlistat was found to contribute to improvement in hepatic fat content, as well as the activity of ALT and AST during at least 24 weeks of therapy [61]. It is thought that Orlistat may have a potential beneficial effect on NAFLD as it stimulates weight loss, however it is not clear whether it has an independent effect on liver function. Other weight-loss medications such as naltrexone, bupropion and topiramate have no evidence of usefulness in NAFLD treatment [62].

The use of statins in NAFLD treatment is still controversial. Undoubtedly, statins decrease the level of total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglycerides, and hence limit the cardiovascular risk [63]. In the study conducted by Hyogo et al., patients were treated with 10 mg atorvastatin daily. Researchers observed significant reduction in AST, ALT and GGT concentrations as well as decrease in NAFLD Activity Score (NAS), which includes steatosis, hepatocyte ballooning and lobular inflammation [64]. The use of statins among patients with NAFLD should be implemented with co-existing dyslipidemia, as its protective effect on the cardiovascular system outweighs other adverse events and low efficacy on hepatic histopathology [47].

Among novel therapeutic perspectives, farnesoid X receptor (FXR) agonist has been investigated. Obeticholic acid (OCA or 6α-ethyl chenodeoxycholic acid, initially known as INT-747) is an FXR agonist registered for the treatment of primary biliary cholangitis due to its anticholestatic and hepatoprotective properties [65]. Data from recently performed clinical trials prove that OCA is effective in patients with biopsy-proven NASH or NAFLD [66,67]. The primary endpoint of FLINT study was histological improvement in NAFLD activity score of at least 2 points, which was achieved in 45% of patients receiving 25 mg OCA daily [66]. A study conducted by Mudaliar et al. showed that the administration of 25 or 50 mg OCA daily increases insulin sensitivity and reduces markers of hepatic inflammation and fibrosis in patient with NAFLD and T2DM [67]. Another farnesoid X receptor agonist, cilofexor (GS-9674) is under investigation as monotherapy

or in combination with an acetyl-CoA carboxylase inhibitor, firsocostat (GS-0976). The combination of these two drugs showed improvement in liver steatosis and stiffness and serum markers of hepatic fibrosis [68]. Peroxisome proliferator-activated receptor (PPAR)-γ agonists such as rosiglitazone and pioglitazone have been under investigation for potential effects in NAFLD/NASH patients. The use of pioglitazone in patients with biopsy-proven NASH improves liver function and decreases liver fat content. Cusi et al. conducted a placebo-controlled RCT of 101 adults with NASH and T2DM. They documented that 58% of patients assigned to pioglitazone group (45 mg once daily) achieved the primary outcome (reduction in NAFLD activity score of at least 2 points without worsening of fibrosis) and 51% had resolution of NASH. Pioglitazone treatment was also associated with improvement in individual histological scores, including the fibrosis score, reducing hepatic triglyceride content from 19% to 7%, and improving adipose tissue, hepatic, and muscle insulin sensitivity [69]. A Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) trial showed that rosiglitazone improved steatosis and normalized transaminase levels in 47% of patients. However, no effect on other histologic lesions was documented [70].

Some experimental studies have focused on the specific inhibition of the fibrosis process in liver with the use of an inhibitory antibody to lysyl oxidase-2 (LOXL-2). LOXL-2 up-regulation was noticed in patients with NAFLD and T2DM and LOXL-2 hepatic and circulating levels correlate with histological fibrosis progression [71]. LOXL-2 inhibition paves the way for macrophage-mediated collagen degradation in liver fibrosis. However, in two phase 2b trails of patients with bonding fibrosis due to nonalcoholic steatohepatitis, simtuzumab (monoclonal LOXL-2 antibody) was found to be ineffective in decreasing hepatic collagen content [72]. Additionally, compounds interfering with apoptotic pathways have been investigated as a treatment option for NAFLD/NASH. An example is selonsertib, which is an inhibitor of the apoptosis signal-regulating kinase 1 (ASK1), and plays a significant role in hepatocyte inflammation, injury and fibrosis. In a phase 2 trial, selonsertib appeared to improve liver fibrosis in a substantial proportion of patients with NASH and stage 2 or 3 fibrosis, suggesting its potential use in NAFLD pharmacological therapy [73]. However, results from randomized phase III STELLAR trials did not show evidence that selonsertib reduces fibrosis in patients with NASH and advanced liver scarring [74].

## 6. Bariatric Surgery and NAFLD

Bariatric surgery aims not only to achieve considerable, long-term weight loss but also to improve the course of obesity-related diseases such as T2DM, hypertension, dyslipidemia, obstructive sleep apnea. It also reduces the risk of cardiovascular diseases such as myocardial infarction and ischemic stroke and decreases overall mortality [75–77]. A meta-analysis conducted by Sutanto et al. showed significant reduction in the incidence of major adverse cardiovascular events in bariatric surgery group as compared to the no-surgery group (OR = 0.49; 95% CI 0.40–0.60; $p < 0.00001$; I2 = 93%) [78]. Among recently available surgical methods, Roux-en-Y gastric bypass (RYGB) and laparoscopic sleeve gastrectomy (LSG) are the most commonly performed worldwide. A study conducted by Mummadi et al. summarized 15 studies with 766 paired liver biopsies. Their investigation showed the pooled proportion of patients with improvement or resolution in steatosis was 91.6% (95% confidence interval (CI), 82.4–97.6%), in steatohepatitis was 81.3% (95% CI, 61.9–94.9%), in fibrosis was 65.5% (95% CI, 38.2–88.1%), and for complete resolution of NASH was 69.5% (95% CI, 42.4–90.8%) after bariatric surgery [79]. The Swedish Obese Subjects (SOS) study showed reduction in both ALT and AST values after bariatric surgery in both short and long-term observation (2 and 10-year follow-up) [80].

NAFLD is closely associated with obesity, T2DM and other features of metabolic syndrome. All mechanisms involved in improving obesity and T2DM that appear after bariatric surgery seem to have a crucial role in amelioration or resolution of NAFLD. Weight reduction due to bariatric surgery causes inflammatory changes in patients with obesity. Klein et al. showed that gastric bypass procedure decreases the hepatic expression

of factors involved in the progression of liver inflammation (macrophage chemoattractant protein 1 (MCP-1), and interleukin (IL-8)) and fibrogenesis (transforming growth factor-β1 (TGF-β1), tissue inhibitor of metalloproteinase 1 (TIMP-1), α-smooth muscle actin (α-SMA), and collagen-α1(I)) [81]. Cazzo et al. showed a significant decrease in mean NAFLD fibrosis score after RYGB and resolution rate of 55% of severe fibrosis in 12-month observation [82]. Moreover, RYGB contributes to significant reduction in NAFLD activity score, steatosis, inflammation and liver ballooning during 1-year observation [83,84].

LSG is also considered to improve the course of NAFLD. Nobili et al. showed reduced activation of local cellular compartments (hepatic progenitor cells, hepatic stellated cells, macrophages) induced by LSG, which led to the improvement in NAFLD Activity Score and liver fibrosis [85]. A study conducted by Cabré et al. proved that the histology and liver function of patients with morbid obesity significantly improved after LSG due to mechanisms involved in the reduction of oxidative stress and inflammation. They observed significant reduction in the hepatic immunochemical expression of oxidation, inflammation and fibrosis markers such as: PON-1, 4-hydroxy-2-nonenal, CD68, chemokine ligand 2 (CCL2), C-C chemokine receptor type 2 (CCR2), TNF-α, and galectin-3 between baseline liver tissue and 12 months after LSG [86]. Weight loss induced by LSG leads to the improvement in liver histology in terms of steatosis, liver fibrosis, lobular inflammation and hepatocyte ballooning. In a study conducted by Salman et al., among 81 patients undergoing LSG, 9 (11.1%) showed no steatosis at the end of 18-month follow-up, 25 (30.9%) showed no hepatocyte ballooning, 37 (45.7%) showed no lobular inflammation, and 33 (40.7%) showed complete absence of fibrosis. The above-mentioned study also showed significant improvement in postoperative liver function tests (AST, ALT, GGTP). An 18-month observation also revealed an increase in adiponectin levels and a reduction in serum levels of leptin and resistin, when compared to presurgical values. The above-mentioned data prove that both LSG and RYGB are significant surgical methods for NAFLD/NASH treatment [87].

As presented above, bariatric surgery provides proven NAFLD amelioration; however, the remaining question is whether RYGB or LSG is more effective. A systematic review and meta-analysis performed by Baldwin et al. compared RYGB and LSG using 4 separate criteria: AST and ALT concentration, NAFLD activity score and NAFLD fibrosis score. Patients undergoing both procedures showed significant reduction in AST and ALT values. Head-to-head comparison of AST mean differences trended toward LSG, but it was statistically non-significant. This study failed to show superiority between RYGB and LSG in ameliorating NAFLD [88]. Cherla et al. also proved the normalization of the liver function test by the end of the first postoperative year; however, they did not find significant differences between the SG and RYGB groups [89]. A meta-analysis performed by Silva et al. showed that RYGB patients achieve significant reduction of steatohepatitis and fibrosis, while patients undergoing LSG presented significant reduction only of steatohepatitis. According to their study, the NAFLD Activity Score significantly improved after both procedures and no differences were found between LSG and RYGB regarding histopathological changes [90]. A study conducted by Pedersen et al. showed that NAS reduced significantly in both RYGB and LSG patients 12-months after the surgery. However, RYGB patients had significantly more reduced ($p = 0.007$) liver steatosis (−0.91 (95% CI −1.47–−1.2) than SG patients (−0.33 (95% CI −0.54–−0.13) and greater improvement in the plasma lipid profile [83]. Luo at el. investigated liver volume and fat density in MRI in patients undergoing bariatric surgery. Their study showed that RYGB patients achieved higher weight loss and higher BMI loss when compared to the LSG group. However, the percentage decrease in liver volume and MRI-PDFF did not differ significantly between groups [91].

Despite the significant role of bariatric surgery in the treatment of NAFLD, there are some patients that will develop new or worsened features of NAFLD after bariatric procedure. The meta-analysis performed by Lee et al. showed that 12% of patients experienced development or worsening of NAFLD (95% CI, 5–20%) [92]. A 5-year prospective study

performed by Mathurin et al. showed that 19.8% of patients experienced fibrosis progression 5 years after bariatric surgery for unknown reason [93]. Aggravation of NAFLD after bariatric procedure should be kept in mind when qualifying patients for bariatric surgery.

## 7. Conclusions

The current evidence suggests that bariatric/metabolic surgery for patients with morbid obesity leads to improvement or resolution of NAFLD/NASH in terms of steatosis, hepatic inflammation and fibrosis. Although the results of available cohort research are satisfying, they have not been proved in clinical randomized trails. Further, long-term studies are still needed to confirm the recommendation of bariatric surgery as a treatment option for NAFLD.

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# The Effect of Laparoscopic Sleeve Gastrectomy on the Course of Non-Alcoholic Fatty Liver Disease in Morbidly Obese Patients during One Year of Follow Up

**Paulina Głuszyńska [1,*], Aleksander Łukaszewicz [1], Inna Diemieszczyk [2], Jan Chilmończyk [1], Joanna Reszeć [3], Anna Citko [4], Łukasz Szczerbiński [4,5], Adam Krętowski [4,5] and Hady Razak Hady [1]**

[1] Department of General and Endocrine Surgery, Medical University of Bialystok, 15-276 Bialystok, Poland; alexander.luk6@gmail.com (A.Ł.); janchilmonczyk@gmail.com (J.C.); hadyrazakh@wp.pl (H.R.H.)
[2] Department of Surgery, Independent Public Health Care Center in Lapy, 18-100 Lapy, Poland; demeschik.inna@gmail.com
[3] Department of Medical Pathomorphology, Medical University of Bialystok, 15-269 Bialystok, Poland; joasia@umb.edu.pl
[4] Clinical Research Centre, Medical University of Bialystok, 15-276 Bialystok, Poland; anna.citko@umb.edu.pl (A.C.); lukasz.szczerbinski@umb.edu.pl (Ł.S.); adam.kretowski@umb.edu.pl (A.K.)
[5] Department of Endocrinology, Diabetology and Internal Diseases, Medical University of Bialystok, 15-276 Bialystok, Poland
* Correspondence: paulina.gluszynska@gmail.com; Tel.: +48-85-831-8279

**Abstract:** Background: Morbid obesity co-exists with non-alcoholic fatty liver disease in up to 90% of cases. Laparoscopic sleeve gastrectomy leads to a reduction in body mass and thus may improve the course of non-alcoholic fatty liver disease. The aim of this study was to evaluate the effect of laparoscopic sleeve gastrectomy on the resolution of non-alcoholic fatty liver disease. Methods: The study included 55 patients with non-alcoholic fatty liver disease who underwent laparoscopic sleeve gastrectomy at a tertiary institution. The analysis consisted of preoperative liver biopsy, abdominal ultrasound, weight loss parameters, Non-Alcoholic Fatty Liver Fibrosis Score and selected laboratory parameters. Results: Before the surgery, 6 patients were diagnosed with grade 1 liver steatosis, 33 patients with grade 2 and 16 patients with grade 3. One year after the surgery, only 21 patients had features of liver steatosis at ultrasound. All weight loss parameters showed statistically significant changes during the observation; the median percentage of total weight loss was 31.0% (IQR: 27.5; 34.5) with $p = 0.0003$, the median percentage of excess weight loss was 61.8% (IQR: 52.4; 72.3) with $p = 0.0013$ and the median percentage of excess body mass index loss was 71.0% (IQR: 61.3; 86.9) with $p = 0.0036$ 12 months after laparoscopic sleeve gastrectomy. The median Non-Alcoholic Fatty Liver Fibrosis Score at baseline was 0.2 (IQR: −0.8; 1.0) and decreased to −1.6 (IQR: −2.4; −0.4) ($p < 0.0001$). Moderate negative correlations between Non-Alcoholic Fatty Liver Fibrosis Score and percentage of total weight loss ($r = -0.434$, $p < 0.0001$), percentage of excess weight loss ($r = -0.456$, $p < 0.0001$) and percentage of excess body mass index loss ($r = -0.512$, $p < 0.0001$) were found. Conclusions: The study supports the thesis that laparoscopic sleeve gastrectomy is an effective method for treatment of non-alcoholic fatty liver disease in patients with morbid obesity.

**Keywords:** bariatric/metabolic surgery; laparoscopic sleeve gastrectomy; non-alcoholic fatty liver disease; morbid obesity

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## 1. Introduction

The pandemic of obesity has become a serious issue of public health worldwide as the size of the obese population has almost tripled over the last four decades and continues to rise [1]. This HAS resulted in a significant increase in the prevalence of non-alcoholic fatty liver disease (NAFLD). NAFLD is currently the most common chronic liver disease, with an estimated global prevalence at 25–30%, rising up to 90% in morbidly obese patients [2].

According to US guidelines, NAFLD is recognized when there is ≥ 5% steatotic hepatocytes in imaging or histology with no alcohol-, drug- or viral-induced steatosis [3]. The spectrum of NAFLD ranges from benign hepatocellular steatosis to non-alcoholic steatohepatitis (NASH), fibrosis and eventually cirrhosis and may lead to the development of hepatocellular carcinoma (HCC). It is believed that one third of patients at an early stage of NASH will progress to fibrosis within 5 to 10 years after the diagnosis. Considering indications for liver transplant, NAFLD/NASH is currently the most rapidly growing cause of HCC among patients on the waiting list in the United States, increasing from 2.1% in 2002 to 16.2% in 2016 ($p < 0.0001$) [4]. According to the US National Liver Transplantation Registry from 2018, 34.6% of liver transplant recipients had a BMI >3 0 kg/m$^2$, and almost 14% had a BMI > 35 kg/m$^2$ [5]. The main management option for obesity-related NAFLD is weight reduction by 7–10% with lifestyle modifications including dietary changes and physical activity. However, this goal may be difficult to achieve in obese patients and even more problematic to maintain. Studies have shown that more than 90% of obese patients cannot achieve this target during one year of observation [6,7]. Bariatric surgery is an option for obese individuals who fail to achieve suitable weight loss with lifestyle changes and pharmacological methods. Bariatric surgery can help obese individuals achieve recommended weight reduction and thus improve the course of NAFLD. The additional benefits of bariatric surgery include resolution or amelioration of hypertension, hyperlipidemia and type 2 diabetes and reduction of cardiovascular risk and mortality [8,9]. One of the most commonly performed bariatric procedures worldwide is laparoscopic sleeve gastrectomy (LSG). The IFSO Global Registry 2018 Report provided data from 51 different countries; data were reported on 87,467 sleeve gastrectomy operations (46.0%), 72,645 Roux-en-Y gastric bypass operations (38.2%), 14,516 one-anastomosis gastric bypass procedures (7.6%) and 9534 gastric banding operations (5.0%) [10]. LSG reduces stomach volume and also causes a decrease in ghrelin level, which is also called "a hormone of appetite" [11,12]. The following study aims to show changes in the course of NAFLD in morbidly obese patients undergoing laparoscopic sleeve gastrectomy in one year of observation and support the thesis that the above-mentioned bariatric procedure is an effective method for treating the liver manifestation of metabolic syndrome.

## 2. Materials and Methods

This is a retrospective study of patients who underwent laparoscopic sleeve gastrectomy and were diagnosed with liver steatosis in abdominal ultrasound prior to the surgery. The procedures were performed in the University Hospital at a tertiary institution between 2019 and 2021. Patients were qualified for surgical treatment of morbid obesity according to the Polish Guidelines on Metabolic and Bariatric Surgery [13]. The inclusion criteria for the surgical procedure comprised inability to achieve sustained weight loss with conservative management and BMI ≥ 40.0 kg/m$^2$ or 35–40 kg/m$^2$ with the presence of at least one obesity-related co-morbidity such as type 2 diabetes mellitus or insulin resistance, hypertension, dyslipidemia, obstructive sleep apnea, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, osteoarthritis, coronary artery disease and infertility in women resulting from polycystic ovary syndrome. Patients with obesity-related endocrine diseases, clinically significant or unstable mental health concerns and addiction to alcohol or psychostimulants and women planning on pregnancy within two years after a potential surgery were excluded from the surgical procedure. Study inclusion criteria: patients who underwent LSG as a primary obesity surgery, patients with diagnosed NAFLD based on abdominal ultrasound and no additional procedures during laparoscopic sleeve gastrectomy. The approximate time between diagnosis of NAFLD and bariatric procedure was 6 months. Exclusion criteria were viral hepatitis, autoimmune hepatitis, hemochromatosis, alcoholic liver cirrhosis and complications during the surgery or observation period. Patients were also excluded from the study when there was a lack of necessary data. Figure 1 presents the explanation of the ultimate definition of the study group.

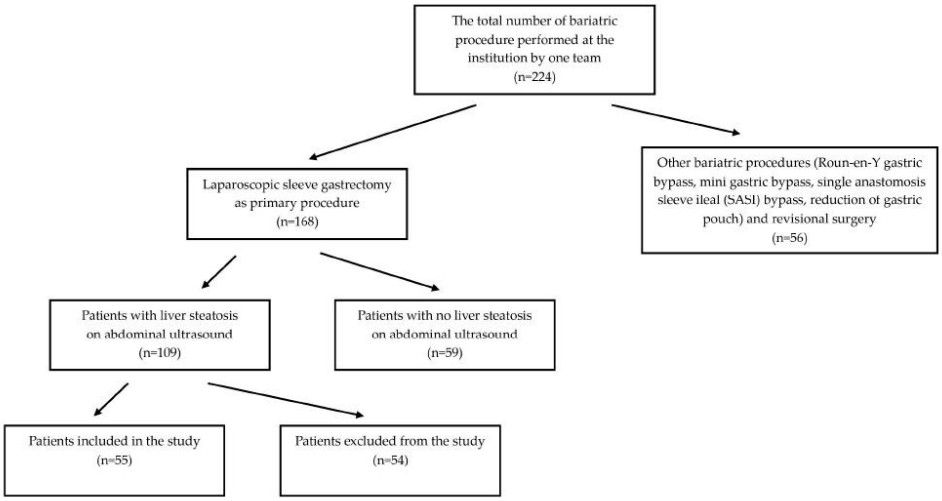


**Figure 1.** Graphical guidelines for study group selection.

Demographic and clinical data were gathered before the surgery, as well as 6 and 12 months after the bariatric procedure. Postoperative weight loss was expressed in terms of percent total weight loss (%TWL), percent excess weight loss (%EWL) and percent excess BMI loss (%EBMIL). The following equations were used:

- Percent total weight loss: %TWL = (initial weight-current weight)/(initial weight) × 100;
- Percent excess BMI loss: %EBMIL = (initial BMI-postoperative BMI)/(initial BMI-25) × 100;
- Percent excess weight loss: %EWL = (initial weight-postoperative weight)/(initial weight-ideal weight) × 100, where ideal weight is defined by the weight corresponding to a BMI of 25 $kg/m^2$.

Biochemical analysis included aspartate aminotransferase (AST), alanine aminotransferase, (ALT), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), bilirubin, serum albumin, fasting glucose level, platelet count, total cholesterol, triglyceride, HDL cholesterol and LDL cholesterol levels.

Advanced hepatic fibrosis was assessed by the Non-Alcoholic Fatty Liver Disease Fibrosis Score (NAFLD Fibrosis Score). The calculation was performed according to the following formula:

NAFLD Fibrosis Score = −1.675 + 0.037 × age (years) + 0.094 × BMI ($kg/m^2$) + 1.13 × hyperglycemia/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelets (× $10^9$/L − 0.66 × albumin, g/dL). Values below −1.455 were considered as the absence of liver fibrosis and those above 0.676 as the presence of advanced hepatic fibrosis. Values between −1.455 and 0.676 were considered as indeterminate hepatic fibrosis [14].

Abdominal ultrasound was performed before the surgical procedure and 6 and 12 months after the surgery. Liver steatosis in abdominal ultrasound was graded as follow:

- Score 0 (absent)—normal echotexture of the liver;
- Score 1 (mild)—a slight and diffuse increase in liver echogenicity with normal visualization of the diaphragm and of the portal vein wall;
- Score 2 (moderate)—a moderate increase in liver echogenicity with slightly impaired appearance of the portal vein wall and the diaphragm;

- Score 3 (severe)—marked increase in liver echogenicity with poor or no visualization of portal vein wall, diaphragm and posterior part of the right liver lobe.

The hepatic biopsy was performed during the laparoscopic sleeve gastrectomy. Histopathological examination included the assessment of the presence or absence of steatosis, fibrosis and lobular inflammation.

### 2.1. Surgical Technique

The greater curvature of the stomach was dissected starting by 6 cm to the pylorus up to the His angle. The reduction in stomach volume was performed using a 36-Fr bougie and 60 mm linear staplers. At the end, the leak test was performed with the use of methylthioninium chloride solution and air. The gastric specimen was sent to pathology examination. Patients were discharged home a day after the surgery if no complications occurred.

### 2.2. Data Analysis

Data were analyzed using GraphPad Prism 9.0.0 software (GraphPad Software, San Diego, CA, USA). Normality of distribution was checked by the W Shapiro–Wilk test. The Wilcoxon matched-pairs signed-rank test was used for comparison between the two groups. The ANOVA Friedmann test was applied to comparisons between more than two groups and the paired Dunn's test for post hoc analysis. Continuous values are presented as medians with interquartile ranges. The correlation between examined parameters and the strength of that relationship was measured with the nonparametric Spearman rank-order correlation coefficient. The significance level was set at $p < 0.05$.

## 3. Results

The study group included 55 patients, 32 men (58%) and 23 women (42%). The median age of patients at the time of surgery was 43.5 years (22–54 years). The median preoperative BMI was 45.6 (IQR: 42.5; 50.2) kg/m$^2$. Of the patients, 62% ($n$ = 34) had hypertension, 27% insulin resistance or type 2 diabetes ($n$ = 15) and 41% hypercholesterolemia ($n$ = 23). Preoperatively, 6 patients were diagnosed with grade 1 liver steatosis, 33 patients with grade 2 and 16 patients with grade 3. One year after the surgery, only 21 patients had features of liver steatosis in abdominal ultrasound—grade 1 was observed in 19 patients and grade 2 in 2 patients. The assessment of liver steatosis and its changes in abdominal ultrasound during one year of observation is presented in Table 1 and Figure 2. The analysis of preoperative liver specimens revealed hepatic steatosis in all patients, inflammatory features in 32 patients (58.2%) and liver fibrosis in 12 patients (21.8%).

**Table 1.** The assessment of liver steatosis in abdominal ultrasound during one year of observation.

| Liver Steatosis Status \ Follow Up | | 0 | 6 Months | 12 Months |
|---|---|---|---|---|
| Steatosis | Grade 0 | N/A | 20 (37%) | 34 (62%) |
| | Grade 1 | 6 (11%) | 20 (37%) | 19 (35%) |
| | Grade 2 | 33 (60%) | 13 (24%) | 2 (4%) |
| | Grade 3 | 16 (29%) | 2 (4%) | 0 |
| Partial remission | | N/A | 27 (49%) | 16 (29%) |
| Total remission | | N/A | 20 (37%) | 34 (62%) |

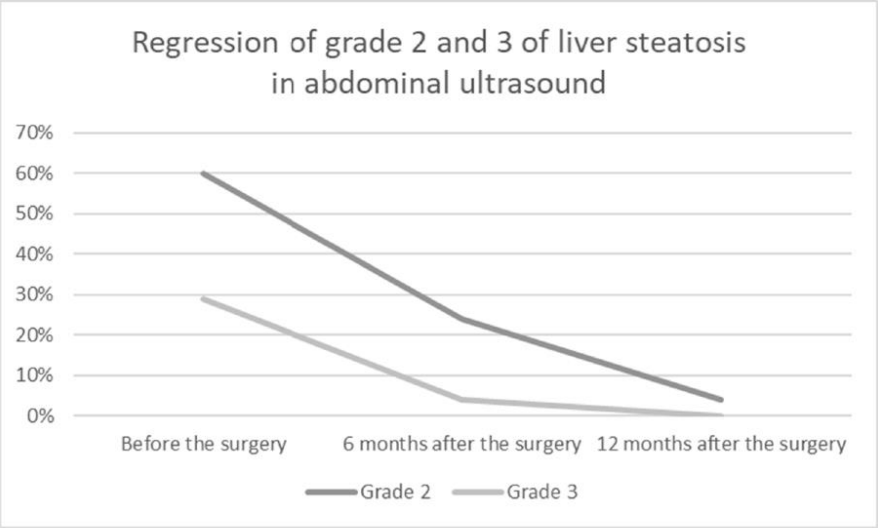


**Figure 2.** Graphical presentation of liver steatosis regression in abdominal ultrasound.

All parameters representing postoperative weight loss showed a statistically significant increase in one year of observation. The median %EBMIL rose from 61.8% (IQR: 53.6; 74.4) 6 months after the surgery to 71.0% (IQR: 61.3; 86.9) 12 months after the bariatric procedure ($p$ = 0.0036). The median %EWL increased to 61.8% (IQR: 52.4; 72.3) with $p$ = 0.0013 and median %TWL to 32.5% (IQR: 28.2; 36.9) with $p$ = 0.0003 one year after the bariatric procedure. The results of bariatric effect in the study group are presented in Table 2 and Figure 3.

The amelioration in liver enzymes profile was observed in one year of follow up, including AST (25.5 (IQR: 19.0; 37.0) vs. 20.0 (IQR: 17.0; 26.0)), ALT (41.10 (IQR: 21.0; 53.9) vs. 19.0 (IQR: 16.0; 24.0)), GGT (28.5 (IQR: 21.6; 56.5) vs. 18.0 (IQR: 13.7; 35.0)) and LDH (235.0 (IQR: 186.0; 271.0) vs. 176.0 (IQR: 152.0; 184.0)). Table 3 presents changes in selected laboratory parameters and NAFLD Fibrosis Score during the observation.

**Table 2.** Results of bariatric effects in study group.

| Variables | 0 | 6 Months | 12 Months | *p*-Value |
|---|---|---|---|---|
| BMI (kg/m$^2$) | 45.6 (42.5–50.2) | 33.5 (29.4–35.8) | 31.0 (27.5–34.5) | **<0.0001** |
| %TWL | N/A | 29.2 (25.2–32.4) | 32.5 (28.2–36.9) | **0.0003** |
| %EWL | N/A | 53.5 (46.3–62.4) | 61.8 (52.4–72.3) | **0.0013** |
| %EBMIL | N/A | 61.8 (53.6–74.4) | 71.0 (61.3–86.9) | **0.0036** |

Values are expressed as median (IQR). BMI, body mass index; %EBMIL, percentage of excess BMI loss; %EWL, percentage of excess weight loss; %TWL, percentage of total weight loss; N/A, not applicable.

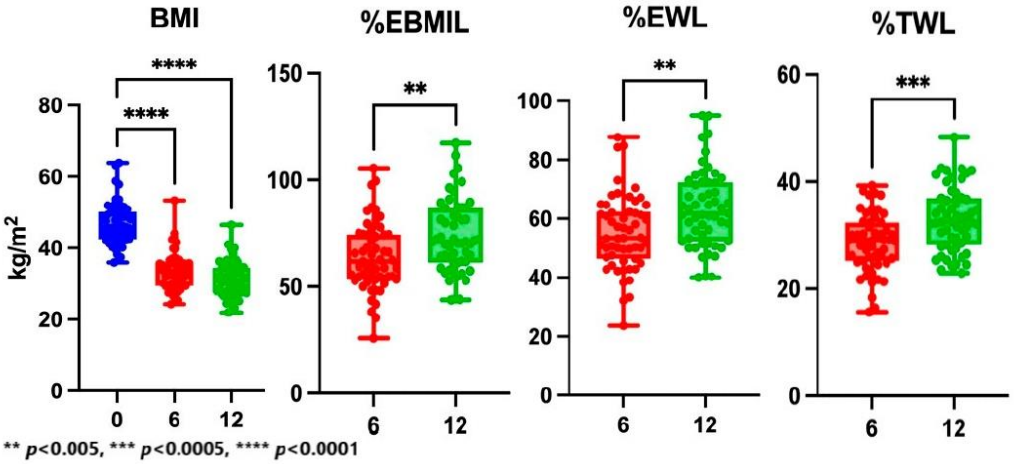


**Figure 3.** Changes in weight loss parameters during the observation. BMI, body mass index; %EBMIL, percentage of excess BMI loss; %EWL, percentage of excess weight loss; %TWL, percentage of total weight loss. Blue color refers to the preoperative examination, red—6 months after the surgery and green—12 months after the surgery.

**Table 3.** Results of selected laboratory parameters during one year of follow up.

| Variables | 0 | 6 Months | 12 Months | *p*-Value |
|---|---|---|---|---|
| ALB (g/dL) | 3.8 (3.7–3.9) | 4.0 (3.9–4.2) | 4.0 (3.9–4.1) | **<0.0001** |
| PLT ($\times 10^9$/L) | 234.0 (20.5–274.0) | 218.0 (190.0–276.0) | 233.0 (200.0–268.0) | 0.5600 |
| FPG (mg/dL) | 110.0 (94.0–130.0) | 94.0 (89.0–99.0) | 89.0 (83.0–96.0) | **<0.0001** |
| Bilirubin (mg/dL) | 0.6 (0.4–0.7) | 0.8(0.5–0.9) | 0.9 (0.6–1.1) | **0.0002** |
| GGT (IU/L) | 28.5 (21.6–56.5) | 18.0 (12.5–27.0) | 18.0 (13.7–35.0) | **0.0003** |
| LDH (IU/L) | 235.0 (186.0–271.0) | 179.0 (154.0–203.0) | 176.0 (152.0–184.0) | **<0.0001** |
| ALT (IU/L) | 41.1 (21.0–53.9) | 21.0 (14.7–26.0) | 19.0 (16.0–24.0) | **<0.0001** |
| AST (IU/L) | 25.5 (19.0–37.0) | 18.1 (14.0–24.0) | 20.0 (17.0–26.0) | **0.0002** |
| Total cholesterol (mg/dL) | 178.0 (148.0–193.0) | 178.0 (144.0–201.0) | 180.0 (153.0–180.0) | 0.8285 |
| LDL (mg/dL) | 114.4 (96.3–129.0) | 106.4 (82.0–133.0) | 113.5 (76.0–132.6) | 0.6769 |
| HDL (mg/dL) | 45.8 (37.1–50.4) | 47.5 (39.8–57.6) | 54.0 (46.8–65.0) | **<0.0001** |
| TG (mg/dL) | 156.1 (112.0–215.0) | 109.0 (76.0–139.0) | 86.0 (61.0–134.0) | **<0.0001** |
| NAFLD Fibrosis Score | 0.2 (−0.8–1.0) | −1.1 (−2.3–−0.2) | −1.6 (−2.4–−0.4) | **<0.0001** |

Values are expressed as median (IQR). ALB, serum albumin; PLT, platelet count; FPG, fasting plasma glucose; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase (LDH); ALT, alanine transaminase; AST, aspartate transaminase; LDL, low-density lipoprotein; TG, triglyceride; HDL, high-density lipoprotein.

The median NAFLD Fibrosis Score at baseline was 0.2 (IQR: −0.8; 1.0) and decreased to −1.6 (IQR: −2.4; −0.4) one year after the surgery ($p < 0.0001$). There was a negative moderate correlation between NAFLD Fibrosis Score and mean %TWL (r = −0.434, $p < 0.0001$), %EWL (r = −0.456, $p < 0.0001$) and %EBMIL (r = −0.512, $p < 0.0001$). The assessment of the risk of advanced liver fibrosis and its changes during the observation is presented in Figure 4.

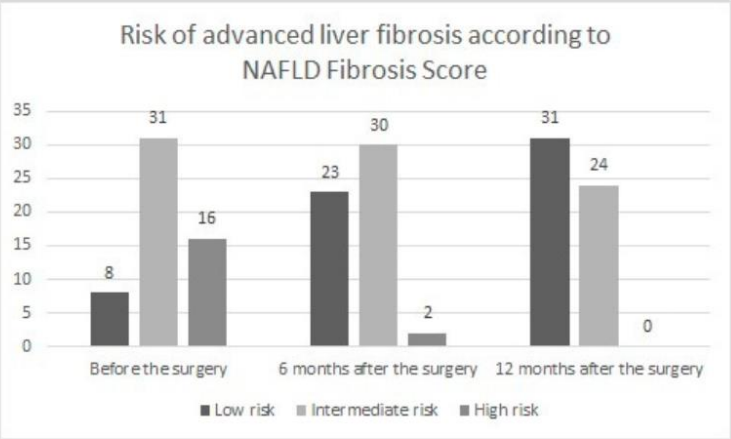


**Figure 4.** Risk of advanced hepatic fibrosis based on NAFLD Fibrosis Score.

## 4. Discussion

This study investigated the impact of one of the bariatric procedures, laparoscopic sleeve gastrectomy, on the course of non-alcoholic fatty liver disease during one year of observation.

Despite a number of promising treatment options for NAFLD, including antidiabetic and anti-obesity drugs, drugs modifying the lipid profile, vitamin E supplementation and novel therapeutic treatments inclusive of medication that interfere with inflammatory, fibrotic and apoptotic pathways, healthy lifestyle modification combined with a decrease in body mass remains at the core of management of NAFLD and NASH [15]. Dietary recommendations for individuals with obesity and non-alcoholic fatty liver disease include: reduction in energy intake, reduction in fructose consumption and a well-balanced diet comprising 40–50% energy from carbohydrates, ≤30% fat (saturated fatty acids >7% and <10% total energy) and about 20% protein [16]. However, very often, the above recommendations are difficult to fulfill, and obese patients fail to achieve the expected weight loss. Several studies have shown that laparoscopic sleeve gastrectomy causes significant weight loss over both short- and long-term observation periods [17–19]. Kraljević et al. analyzed 307 patients who underwent LSG as a primary bariatric procedure. The mean %EBMIL was 62.8 ± 23.1% after 5 years, 53.6 ± 24.6% after 10 years and 51.2 ± 20.3% after 13 years [20]. Our study also proved that laparoscopic sleeve gastrectomy contributes to considerable body mass reduction in patients with morbid obesity, reaching a median %EBMIL of 71.0% (IQR: 61.3; 86.9) after 12 months. Algooneh et al. analyzed the impact of %EWL on the resolution of NAFLD. A significant resolution of NAFLD was seen in patients achieving a mean %EWL > 50% (OR 10.1; $p < 0.001$). However, resolution of NAFLD was observed even in patients with a mean %EWL of 30% (OR 7.0, $p = 0.024$) [21]. In this study, the median percentage of excess weight loss reached 61.8% (IQR: 52.4; 72.3) one year after laparoscopic sleeve gastrectomy.

In a study conducted by Mattar et al., it was observed that weight loss induced by bariatric surgery (Roux-en-Y gastric bypass (RYGB) or LSG) causes significant improvement or resolution of NAFLD and NASH in liver histology, including steatosis, inflammation and fibrosis [22]. Fakhry et al. conducted a wide metanalysis that included 21 studies with a total number of 2374 patients who had undergone bariatric surgery (vertical-banded gastroplasty (VGB), laparoscopic adjustable gastric banding (LAGB), RYGB or LSG). They provided strong evidence that bariatric surgery not only improves biochemical and histological features of NAFLD but also terminates the progression of the disease and resolves it in up

to 30% of patients [23]. In our study, the total resolution rate for liver steatosis in abdominal ultrasound was 62% (34 patients) one year after laparoscopic sleeve gastrectomy.

Bower et al. conducted a systematic review and proved that bariatric surgery is associated with improvement of the histological features of NAFLD, including steatosis (50.2 and 95%CI of 35.5–65.0), fibrosis (11.9 and 95% CI of 7.4–16.3%) and lobular inflammation (50.7 and 95% CI, 26.6–74.8%) [24]. Another metanalysis that included 32 cohort studies comprising 3093 biopsy specimens showed that bariatric surgery is an effective method for the treatment of NAFLD, resulting in biopsy-confirmed resolution of steatosis in 66% patients (95% CI, 56–75%), inflammation in 50% (95% CI, 35–64%), ballooning degeneration in 76% (95% CI, 64–86%) and fibrosis in 40% (95% CI, 29–51%). However, this metanalysis showed new features or worsening of NAFLD in 12% (95% CI, 5–20%) of patients [25]. Moretto et al. analyzed 78 morbidly obese patients who had undergone gastric bypass and had undergone liver biopsy during the surgery and after weight loss. They found that the prevalence of liver fibrosis was 44.9% (CI 95% 33.6–56.6%) at the first biopsy and 30.8% (CI 95% 20.8–42.2%) after weight loss ($p = 0.027$) [26]. However, it is also known that rapid weight loss may increase the risk of hepatic fibrosis. Weight loss of more than 1.6 kg per week results in a rapid reduction in hepatic fat and a subsequent increase in visceral free fatty acids and proinflammatory cytokines, which may worsen the course of the histological features of NAFLD [27]. An interesting observation was made by Mathurin et al. Their research showed that the improvement of steatosis and ballooning occurred mainly during the first year after bariatric surgery and persisted up to 5 years postoperatively. However, they noticed that liver fibrosis worsened at 5 years even though more than 95% of patients had a Fibrosis Score $\leq$ F1 [28]. The research conducted by Mottin et al. showed that 16 out of 90 patients (17.8%) who underwent bariatric surgery had the same degree of liver steatosis at the second biopsy as during the operation [29].

A study conducted by Ruiz-Tover et al. showed that liver steatosis measured by abdominal ultrasound improves after sleeve gastrectomy. A complete resolution in liver steatosis was observed in 90% of patients included in their study [30]. Complete resolution measured by ultrasonography in our study was seen in 62% of all patients. Another study conducted by Elyasinia et al. proved that both laparoscopic sleeve gastrectomy and gastric bypass significantly enhance hepatic status in ultrasonography. Preoperatively, 81.8% of patients were diagnosed with grade I or II liver steatosis. One year after the surgery, 72.7% of patients presented no NASH signs in ultrasonography [31]. According to our study, 19 patients (34.5%) had grade 1 liver steatosis in abdominal ultrasonography after one year of observation.

The previously mentioned research conducted by Bower et al. also confirmed an amelioration in liver enzymes profile, including ALT (11.36 u/L, 95%CI 8.36–14.39), AST (3.91 u/L, 95%CI 2.23–5.59), ALP (10.55 u/L, 95%CI 4.40–16.70) and gamma-GT (18.39 u/L, 95%CI 12.62–24.16) [19]. A study conducted by Kirkpatrick et al. revealed a reduction in liver enzymes including ALT (66.21 vs. 28.58) and AST (46.28 vs. 24.69) during 12 months of observation [32]. Groth et al. also observed an amelioration in the liver enzymes profile in patients undergoing laparoscopic sleeve gastrectomy during 6 months of follow up (AST 22.0 (19.0–28.0) vs. 16.0 (13.0–22.0), $p < 0.001$, and ALT 27.5 (20.5–41.0) vs. 19.0 (15.0–27.0), $p < 0.001$) with no statistical differences regarding gender ($p = 0.840$) [33]. Similar results were observed in our study. We noted a statistically significant reduction in AST, ALT, GGT and LDH serum activity. A reduction of transaminase levels decreases the risk of progression to fibrosis and the end stage of liver disease. Additionally, Lee et al. proved that patients with elevated serum aminotransferase levels are at a higher risk not only of liver disease but also of all-cause mortality [34].

Nascimento et al. analyzed changes in NAFLD Fibrosis Score before and after bariatric surgery. The NAFLD Fibrosis Score changed from −0.6845 before the surgery to −1.6898 12 months after the procedure ($p < 0.0002$), indicating an absence of advanced liver fibrosis in any patient 12 months after the surgery [35]. An intermediate degree of fibrosis was identified in 12 patients (46.2%) one year after the bariatric procedure. The research

conducted by Yang et al. also revealed statistically significant changes in the NAFLD score (−1.636 vs. −2.123, $p < 0.001$) over a two-year observation period [36]. Sandvik et al. observed a significant overall shift towards lower risk categories of advanced hepatic fibrosis based on NAFLD Fibrosis Score in 11.6 years of observation (NAFLD Fibrosis Score −1.32 (IQR −2.33; −0.39) vs. −1.71 (IQR −2.49; −0.95, $p < 0.001$) 11.6 years after surgery). In the above-mentioned study, a weak negative correlation between the decrease in NAFLD Fibrosis Score and weight loss parameters (%EWL (r = −0.251, $p < 0.0001$) and %TWL (r = −0.280, $p < 0.0001$)) was observed [37]. In our study, a statistically significant decrease in NAFLD Fibrosis Score was also seen. Additionally, we found a moderate negative correlation between NAFLD Fibrosis Score and weight loss parameters, including the percentage of total and excess weight loss and the percentage of excess BMI loss. Salman et al. analyzed patients with NASH-related liver cirrhosis of Child class A scheduled for laparoscopic sleeve gastrectomy due to morbid obesity. In their observation, the fibrosis score regressed to F2 in 19 patients (26.8%) and F3 in 29 (40.8%) during 30 months of follow up. Additionally, patients with improved Fibrosis Score had significantly higher weight loss ($p$ <0.001). Thirty months after surgical treatment, 53.8% of cases with borderline NASH and 36.8% of those with probable NASH showed complete resolution. This study proved that bariatric surgery may be an option in patients with NASH-related hepatic fibrosis and morbid obesity [38]. In a study conducted by Murakami et al., the NAFLD activity score was reduced in 10 of the 11 patients (90.9%), and there was a significant difference between before and 1 year after laparoscopic sleeve gastrectomy ($p < 0.05$). Non-alcoholic steatohepatitis was no longer demonstrated in 81.8% patients in liver biopsy 1 year after the surgery; however, the fibrosis stage did not significantly ameliorate 1 year after laparoscopic sleeve gastrectomy [39].

The main limitation of our study is the fact that postoperative liver steatosis was evaluated with ultrasonography and not by hepatic biopsy to examine histological features of NAFLD. Some researchers may question ultrasonography as an imaging tool to predict the presence and severity of liver steatosis based on the fact that it is a performer-dependent and subjective imaging method. Generalizability of our results could be also impaired by the low number of participants, and therefore it is important to remember that some patients undergoing laparoscopic sleeve gastrectomy will not experience the amelioration of liver steatosis during observation. The surgical procedure may not always improve the grade of hepatic steatosis, or, in rare cases, it may even worsen the condition of the liver. Additionally, longer observation could be performed in order to achieve strong evidence that LSG improves the course of NAFLD.

## 5. Conclusions

In conclusion, our study confirms the thesis that laparoscopic sleeve gastrectomy is an effective method for the treatment of NAFLD in morbidly obese patients. Weight loss induced by LSG resolved NAFLD in more than 50% of patients according to ultrasound features of steatosis in one year of observation. Laparoscopic sleeve gastrectomy led to significant decrease in liver enzymes concentration and a reduction in NAFLD Fibrosis Score. Considering the increasing global prevalence of NAFLD, laparoscopic sleeve gastrectomy may be a crucial method of treatment in patients with morbid obesity and hepatic steatosis.

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## 8. Omówienie cyklu publikacji

Pierwszą pracę w cyklu stanowi praca poglądowa "*Non-alcoholic fatty liver disease (NAFLD) and bariatric/metabolic surgery as its treatment option: a review*", w której omówiono epidemiologię, patogenezę, diagnostykę oraz opcje leczenia niealkoholowej stłuszczeniowej choroby wątroby, poświęcając oddzielny paragraf wpływowi chirurgii bariatryczno – metabolicznej, w tym laparoskopowej rękawowej resekcji żołądka na przebieg wyżej wymienionego schorzenia.

Niealkoholowa stłuszczeniowa choroba wątroby jest obecnie najczęściej spotykaną chorobą wątroby w praktyce klinicznej. Zachorowalność na NAFLD nieustannie rośnie, przez co stanowi ona istotny problem kliniczny oraz zdrowotny na całym świecie. Pomimo aktualnej wiedzy na temat epidemiologii, patogenezy oraz przebiegu NAFLD, leczenie nadal pozostaje wyzwaniem w praktyce klinicznej, gdyż do tej pory nie zatwierdzono żadnych swoistych terapii farmakologicznych. Leczenie opiera się głównie na modyfikacji stylu życiu z uwzględnieniem diety o obniżonej energetyce, ograniczeniu spożycia węglowodanów prostych oraz zwiększeniu aktywności fizycznej. Celem powyższych działań jest redukcja masy ciała o 5 – 10% w przypadków pacjentów z nadwagą i otyłością. W ostatnich latach szeroko badano wpływ dostępnych leków, które mogłyby być użyte w terapii oraz modyfikacji przebiegu NAFLD. Należą do nich leki przeciwcukrzycowe [metformina, pioglitazon, analogi glukagonopodobnego peptydu 1 (ang. glucagon-like peptide 1 – GLP-1), inhibitory kotransportera sodowo – glukozowego 2 (ang. sodium – glucose co – transporter 2 – SGLT2)], leki obniżające stężenie lipidów oraz witamina E. Prowadzone są również badania nad nowymi lekami, które mogłyby być wykorzystane w terapii NASH oraz

NAFLD. Są to między innymi: agoniści receptora X farnesoidu (ang. farnesoid X receptor – FXR), kwas obetycholowy, przeciwciała przeciwko oksydazie lizylowej typu 2 (ang. inhibitory antibody to lysyl oxidase 2 – LOXL-2) czy inhibitory kinazy regulującej sygnał apoptozy (ang. apoptosis signal-regulating kinase 1 – ASK1). Niestety wszystkie wymienione leki pozostają w trakcie badań klinicznych i nie zostały zatwierdzone w leczeniu NASH. Jedyną skuteczną metodą leczenia NAFLD jest redukcja masy ciała, która w przypadku pacjentów z otyłością olbrzymią jest często trudna do osiągnięcia w wyniku modyfikacji diety oraz leczenia farmakologicznego. Laparoskopowa rękawowa resekcja żołądka jest metodą chirurgicznego leczenia otyłości olbrzymiej, która nie tylko zapewnia znaczą redukcję masy ciała, ale także pozwala na długotrwałe utrzymanie efektu. Dostępne dane w literaturze sugerują, że LSG poprawia przebieg NAFLD prowadząc do całkowitego ustąpienia bądź zmniejszenia stłuszczenia wątroby, co jest widoczne w badaniach laboratoryjnych oraz obrazowych, w tym w badaniu ultrasonograficznym jamy brzusznej.

Drugą pracę w cyklu stanowi artykuł *"The effect of laparoscopic sleeve gastrectomy on the course of non-alcoholic fatty liver disease in morbidly obese patients during one year of follow up"*. Celem powyższej pracy była ocena przebiegu NAFLD po operacji rękawowej resekcji żołądka u pacjentów z otyłością olbrzymią w obserwacji rocznej. Dodatkowo podjęto próbę odpowiedzi na pytanie, czy pooperacyjna redukcja masy ciała ma wpływ na zmniejszenie ryzyka zwłóknienia wątroby na podstawie NAFLD Fibrosis Score.

Badanie zostało przeprowadzone w latach 2019 – 2021 i obejmowało chorych poddanych LSG z współistniejącą NAFLD zdiagnozowaną na podstawie badania USG

jamy brzusznej. Przedoperacyjnie zebrano dane kliniczne oraz pobrano materiał do badań laboratoryjnych. Śródoperacyjnie wykonano pobranie wycinka wątroby do oceny histopatologicznej. Wizyty kontrolne odbyły się 6 i 12 miesięcy po zabiegu operacyjnym, w trakcie których dokonano oceny redukcji masy ciała, wykonano kontrolne badania biochemiczne oraz ultrasonograficzną ocenę wątroby.

W badaniu uczestniczyło 55 pacjentów, z czego kobiety stanowiły 42% (n = 23). Średni wiek pacjentów biorących udział w badaniu wyniósł 43,5 roku. Mediana przedoperacyjnego BMI wyniosła 45.6 (42.5 – 50.2) kg/m$^2$. Spośród chorób współistniejących z otyłością najczęściej zdiagnozowanymi były: nadciśnienie tętnicze (62%), hipercholesterolemia (41%) oraz insulinooporność i cukrzyca typu 2 (27%). W bioptacie wątroby pobranym w trakcie zabiegu operacyjnego do badania histopatologicznego stłuszczenie wątroby zostało potwierdzone u wszystkich pacjentów, cechy zapalenia zostały stwierdzone u 58% badanych (n = 32), a włóknienie wątroby uwidoczniono w 22% przypadków (n = 12).

Przedoperacyjne badania ultrasonograficzne jamy brzusznej ujawniło cechy stłuszczenia I stopnia u 6 pacjentów (11%), II stopnia – 33 pacjentów (60%), III stopnia – 16 badanych (29%). Rok po zabiegu operacyjnym jedynie u 21 pacjentów (38%) obserwowano cechy stłuszczenia wątroby w USG – w stopniu I u 19 pacjentów (35%), II – 2 uczestników badania (4%).

Analiza parametrów pooperacyjnej utraty masy ciała wykazała spadek BMI z 45.6 kg/m$^2$ (42.5 – 50.2) do 31.0 kg/m$^2$ (27.5 – 34.5) rok po zabiegu, $p < 0{,}0001$. Mediana %TWL wzrosła z 29.2% (25.2 – 32.4) 6 miesięcy po zabiegu do 32.5% (28.2 – 36.9) rok po operacji, $p = 0{,}0003$. Obserwowano również istotny statystycznie wzrost

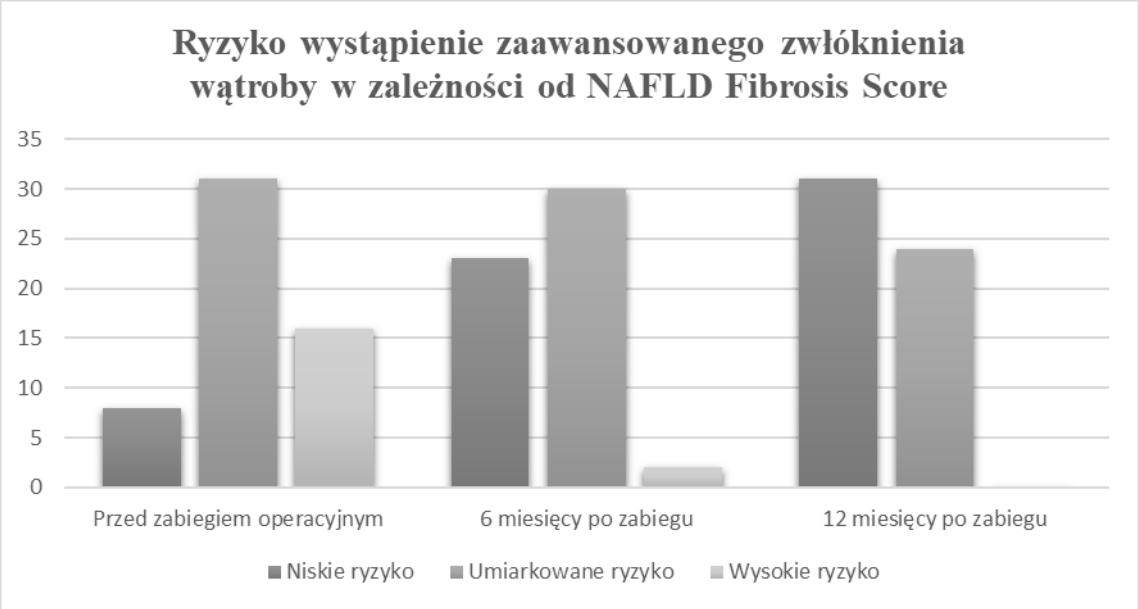
wartości %EWL (53.5% (46.3 – 62.4) vs. 61.8% (52.4 – 72.3), $p$ = 0,0013) oraz %EBMIL (61.8% (53.6 – 74.4) vs. 71.0% (61.3 – 86.9), $p$ = 0,0036).

W tabeli 1 przedstawiono wartości wybranych parametrów laboratoryjnych w trzech punktach czasowych (przed zabiegiem operacyjnym oraz 6 i 12 miesięcy po operacji).

| **Parametry** | **Przed operacją** | **6 miesięcy po zabiegu** | **12 miesięcy po zabiegu** | **Wartość *p*** |
|---|---|---|---|---|
| Albuminy (g/dL) | 3.8 (3.7-3.9) | 4.0 (3.9-4.2) | 4.0 (3.9-4.1) | **<0.0001** |
| Płytki krwi (x*$10^9$/L) | 234.0 (20.5-274.0) | 218.0 (190.0-276.0) | 233.0 (200.0-268.0) | 0.5600 |
| Glukoza na czczo (mg/dl) | 110.0 (94.0-130.0) | 94.0 (89.0-99.0) | 89.0 (83.0-96.0) | **<0.0001** |
| Bilirubina (mg/dl) | 0.6 (0.4-0.7) | 0.8(0.5-0.9) | 0.9 (0.6-1.1) | **0.0002** |
| GGTP (IU/L) | 28.5 (21.6-56.5) | 18.0 (12.5-27.0) | 18.0 (13.7-35.0) | **0.0003** |
| LDH (IU/L) | 235.0 (186.0-271.0) | 179.0 (154.0-203.0) | 176.0 (152.0-184.0) | **<0.0001** |
| ALT (IU/L) | 41.1 (21.0-53.9) | 21.0 (14.7-26.0) | 19.0 (16.0-24.0) | **<0.0001** |
| AST (IU/L) | 25.5 (19.0-37.0) | 18.1 (14.0-24.0) | 20.0 (17.0-26.0) | **0.0002** |
| Cholesterol całkowity (mg/dl) | 178.0 (148.0-193.0) | 178.0 (144.0-201.0) | 180.0 (153.0-180.0) | 0.8285 |
| LDL (mg/dl) | 114.4 (96.3-129.0) | 106.4 (82.0-133.0) | 113.5 (76.0-132.6) | 0.6769 |
| HDL (mg/dl) | 45.8 (37.1-50.4) | 47.5 (39.8-57.6) | 54.0 (46.8-65.0) | **<0.0001** |
| TG (mg/dl) | 156.1 (112.0-215.0) | 109.0 (76.0-139.0) | 86.0 (61.0-134.0) | **<0.0001** |

**Tabela 1.** Wyniki wybranych parametrów biochemicznych w trakcie rocznej obserwacji

Przedoperacyjna mediana NAFLD Fibrosis Score wyniosła 0.18 (-0.8 – 1.0) i zmniejszyła się do -1.59 (-2.4 – -0.4) rok po laparoskopowej rękawowej resekcji żołądka. Rycina 2 przedstawia zmiany ryzyka rozwoju zaawansowanego zwłóknienia wątroby na podstawie NAFLD Fibrosis Score w obserwacji rocznej. Analiza statystyczna wykazała umiarkowaną ujemną korelację pomiędzy NAFLD Fibrosis Score, a %TWL (r = -0, 434, $p < 0{,}0001$), %EWL (r = -0.456, $p < 0{,}0001$) oraz %EBMIL (r = -0.512, $p < 0{,}0001$).




**Rycina 2.** Zmiany ryzyka wystąpienia zaawansowanego zwłóknienia wątroby na podstawie wartości NAFLD Fibrosis Score

## 9. Podsumowanie wyników

Podsumowując, powyższe prace prezentują wpływ laparoskopowej rękawowej resekcji żołądka na przebieg niealkoholowej stłuszczeniowej choroby wątroby. Jako jedne z pierwszych w Polsce podnoszą ten temat i dotyczą licznej grupy osób uczestniczących w badaniu. Ponadto badanie uwzględniało ocenę stłuszczenia wątroby w badaniu ultrasonograficznym oraz dodatkowo w badaniu histopatologicznym bioptatu wątroby, co jest obecnie złotym standardem w rozpoznawaniu NAFLD. Przeprowadzone badania pozwoliły potwierdzić, że laparoskopowa rękawowa resekcja żołądka prowadzi do znacznej redukcji masy ciała w obserwacji rocznej i pozwala osiągnąć korzystny efekt zabiegu bariatrycznego u osób badanych. W badaniu potwierdzono korzystny wpływ zabiegu operacyjnego na aktywność enzymów wątrobowych w trakcie 12 – miesięcznej obserwacji. Dodatkowo analiza wyników badań ultrasonograficznych wykazała, że w wyniku przebytej laparoskopowej rękawowej resekcji żołądka dochodzi do zmniejszenia stopnia stłuszczenia wątroby bądź jego całkowitego ustąpienia w obserwacji rocznej.

## 10. Wnioski

Przeprowadzone badania pozwoliły wyciągnąć następujące wnioski:

- Laparoskopowa rękawowa resekcja powoduje znaczną redukcję masy ciała w obserwacji rocznej u pacjentów z otyłością olbrzymią oraz współistniejącą niealkoholową stłuszczeniową chorobą wątroby.
- Laparoskopowa rękawowa resekcja żołądka prowadzi do całkowitego ustąpienia bądź zmniejszenia stopnia stłuszczenia wątroby w badaniu ultrasonograficznym w trakcie rocznej obserwacji.
- Laparoskopowa rękawowa resekcja żołądka powoduje istotny spadek aktywności enzymów wątrobowych w obserwacji rocznej.
- Pooperacyjna redukcja masy ciała prowadzi do zmniejszenia ryzyka zwłóknienia wątroby na podstawie NAFLD Fibrosis Score.

## 11. Streszczenie


### Wstęp

Laparoskopowa rękawowa resekcja żołądka jest obecnie najczęściej wykonanym zabiegiem bariatryczno – metabolicznym na świecie. Operacja rękawowej resekcji żołądka prowadzi do ograniczenia ilości spożywanego pokarmu, a co za tym idzie powoduje znaczną utratę masy ciała. Dodatkowo w wyniku pooperacyjnej redukcji masy ciała dochodzi do poprawy kontroli bądź całkowitego ustąpienie chorób współistniejących takich jak: dyslipidemia, nadciśnienie tętnicze czy cukrzyca typu 2. Inną chorobą współistniejącą z otyłością jest niealkoholowa stłuszczeniowa choroba wątroby, która staje się coraz bardziej powszechna i może dotyczyć aż 90% pacjentów z otyłością olbrzymią.

### Cel pracy

Celem powyższej pracy była ocena wpływu laparoskopowej rękawowej resekcji żołądka na przebieg niealkoholowej stłuszczeniowej choroby wątroby w obserwacji rocznej.

### Materiał i metody

Badaniem objęto 55 pacjentów (32 mężczyzn oraz 23 kobiety), którzy w latach 2019 – 2021 przeszli zabieg rękawowej resekcji żołądka z powodu otyłości olbrzymiej ze współistniejącą niealkoholową stłuszczeniową chorobą wątroby rozpoznaną w badaniu ultrasonograficznym. Analiza obejmowała ocenę wybranych parametrów biochemicznych (w tym aktywności enzymów wątrobowych, profilu lipidowego i węglowodanowego), ocenę pooperacyjnej utraty masy ciała i efektu bariatrycznego

na podstawie procentu utraty całkowitej masy ciała (%TWL), nadmiernej masy ciała (%EWL) i nadmiaru BMI (%EBMIL) oraz ocenę stłuszczenia wątroby w badaniu ultrasonograficznym. Pomiarów dokonano przedoperacyjnie oraz pół roku i rok po zabiegu operacyjnym. Śródoperacyjnie pobrano również wycinek wątroby celem oceny stłuszczenia, zapalenia oraz włóknienia w badaniu histopatologicznym.

**Podsumowanie wyników**

Analiza efektu bariatrycznego wykazała istotny statystycznie spadek BMI z 45.6 kg/m$^2$ (42.5 – 50.2) do 31.0 kg/m$^2$ (27.5 – 34.5) rok po zabiegu, $p < 0{,}0001$ oraz wzrost mediany %TWL z 29.2% (25.2 – 32.4) 6 miesięcy po zabiegu do 32.5% (28.2 – 36.9) rok po operacji, $p = 0{,}0003$. Obserwowano również wzrost wartości %EWL (53.5% (46.3 – 62.4) vs. 61.8% (52.4 – 72.3), $p = 0{,}0013$) oraz %EBMIL (61.8% (53.6 – 74.4) vs. 71.0% (61.3 – 86.9), $p = 0{,}0036$) odpowiednio 6 i 12 miesięcy po zabiegu operacyjnym, co wskazuje na korzystny efekt bariatryczny. Przedoperacyjne badania ultrasonograficzne jamy brzusznej ujawniły cechy stłuszczenia wątroby I stopnia u 6 pacjentów (11%), II stopnia u 33 pacjentów (60%), a III stopnia u 16 badanych (29%). Rok po zabiegu operacyjnym tylko 38% pacjentów prezentowało cechy stłuszczenia wątroby w USG – w stopniu I – 19 pacjentów (35%), w stopniu II – 2 uczestników badania (4%). Analiza wskaźnika zwłóknienia wątroby w niealkoholowej stłuszczeniowej chorobie wątroby (NAFLD Fibrosis Score) ujawniła zmniejszanie ryzyka rozwoju zaawansowanego włóknienia wątroby w obserwacji rocznej, co korelowało z pooperacyjną redukcją masy ciała.

## 12. Streszczenie w języku angielskim


### Introduction

Laparoscopic sleeve gastrectomy is currently the most frequently performed bariatric and metabolic procedure in the world. The surgery leads to a reduction in the amount of food intake, and thus causes a significant reduction in body mass. In addition, as a result of postoperative weight reduction, the control of comorbidities such as dyslipidemia, hypertension or type 2 diabetes is improved or completely eliminated. Another disease coexisting with obesity is non-alcoholic fatty liver disease, which is becoming more and more common and may affect up to 90 % of morbidly obese patients.

### Aim of the study

The aim of this study was to assess the effect of laparoscopic sleeve gastrectomy on the course of non-alcoholic fatty liver disease in one-year follow-up.

Material and methods

The study included 55 patients (32 men and 23 women), who undergone laparoscopic sleeve gastrectomy due to morbid obesity and were diagnosed with non – alcoholic fatty liber disease on abdominal ultrasound. The analysis included the assessment of selected biochemical parameters (including the activity of liver enzymes, lipid and carbohydrate profile), assessment of postoperative weight loss and bariatric effect based on percentage of total weight loss (%TWL), excess weight loss (%EWL) and excess BMI loss (%EBMIL), and assessment of hepatic steatosis by ultrasound. All measurements were collected preoperatively, as well as half a year and a year after the surgery. A liver

biopsy was also performed intraoperatively to assess steatosis, inflammation and fibrosis in histopathological examination.

**Results summary**

The analysis of the bariatric effect showed a statistically significant decrease in BMI from 45.6 kg/m$^2$ (42.5 - 50.2) to 31.0 kg/m$^2$ (27.5 - 34.5) one year after surgery, $p < 0.0001$ and an increase in the median %TWL from 29.2% (25.2 - 32.4) 6 months after surgery to 32.5% (28.2 - 36.9) one year after surgery, $p = 0.0003$. There was also an increase in %EWL (53.5% (46.3 - 62.4) vs. 61.8% (52.4 - 72.3), $p = 0.0013$) and %EBMIL (61.8% (53.6 - 74.4) vs. 71.0% (61.3 - 86.9) , $p = 0.0036$), respectively 6 and 12 months after surgery, which indicates a beneficial bariatric effect. Preoperative abdominal ultrasonography revealed features of first degree liver steatosis in 6 patients (11%), grade II in 33 patients (60%), and grade III in 16 patients (29%). One year after the surgery, only 38% of patients presented the features of liver steatosis in abdominal ultrasound - grade I - 19 patients (35%), gradee II - 2 participants of the study (4%). The analysis of the NAFLD Fibrosis Score showed a reduction in the risk of developing advanced liver fibrosis in the one-year follow-up, which was correlated with postoperative weight loss.

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## 14. Oświadczenia współautorów

Białystok, 28.04.2023

**Lek. Paulina Głuszyńska**
I Klinika Chirurgii Ogólnej i Endokrynologicznej
Uniwersytecki Szpital Kliniczny w Białymstoku
Uniwersytet Medyczny w Białymstoku

**OŚWIADCZENIE**

Oświadczam, iż mój udział w przygotowaniu publikacji:

*„Non-Alcoholic Fatty Liver Disease (NAFLD) and Bariatric/Metabolic Surgery as Its Treatment Option: A Review"* autorów Paulina Głuszyńska, Dorota Lemancewicz, Janusz Bogdan Dzięcioł, Hady Hady Razak opublikowanej w Journal of Clinical Medicine, wchodzącej w skład rozprawy doktorskiej *„Ocena wpływu laparoskopowej rękawowej resekcji żołądka na niealkoholową stłuszczeniową chorobę wątroby"* wynoszący 85% polegał na:

- opracowaniu pomysłu pracy poglądowej,
- przeglądzie piśmiennictwa,
- przygotowaniu manuskryptu,
- edycji manuskryptu zgodnie ze wskazówkami.

Paulina Głuszyńska

Białystok, 28.04.2023

**Dr hab. n. med. Dorota Lemancewicz**
Zakład Anatomii Prawidłowej Człowieka
Uniwersytet Medyczny w Białymstoku

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- ocenie merytorycznej pracy,
- krytycznej recenzji manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie przez lek. Paulinę Głuszyńską publikacji w postępowaniu o nadanie stopnia doktora w dziedzinie nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne.

Dorota Lemancewicz

Białystok, 28.04.2023

**Prof. dr hab. n. med. Janusz Bogdan Dzięcioł**
Zakład Anatomii Prawidłowej Człowieka
Uniwersytet Medyczny w Białymstoku

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Białystok, 28.04.2023

**Prof. dr hab. n. med. Hady Razak Hady**
I Klinika Chirurgii Ogólnej i Endokrynologicznej
Uniwersytecki Szpital Kliniczny w Białymstoku
Uniwersytet Medyczny w Białymstoku

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prof. dr hab. n. med.
Hady Razak Hady
specjalista chirurgii ogólnej
2001344

Białystok, 18.06.2023

**Lek. Paulina Głuszyńska**
I Klinika Chirurgii Ogólnej i Endokrynologicznej
Uniwersytecki Szpital Kliniczny w Białymstoku
Uniwersytet Medyczny w Białymstoku

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- stworzeniu bazy danych,
- kwalifikacji pacjentów do badania,
- analizie zebranego materiału,
- analizie statystycznej,
- opracowaniu wyników oraz ich interpretacji,
- przygotowaniu manuskryptu.

Paulina Głuszyńska

Białystok, 18.06.2023

**Lek. Aleksander Łukaszewicz**
I Klinika Chirurgii Ogólnej i Endokrynologicznej
Uniwersytecki Szpital Kliniczny w Białymstoku
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- stworzeniu bazy danych,
- analizie statystycznej,
- opracowaniu i interpretacji wyników,
- przygotowaniu manuskryptu.

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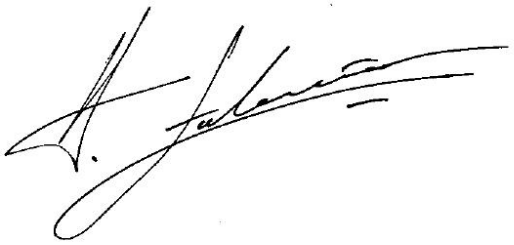

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**Dr n. med. Inna Diemieszczyk**
Oddział Chirurgiczny
Samodzielny Publiczny Zakład Opieki Zdrowotnej
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**OŚWIADCZENIE**

Oświadczam, iż mój udział w przygotowaniu publikacji:

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- kwalifikacji pacjentów do badania,
- opracowaniu wyników oraz ich interpretacji,
- przygotowaniu manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie przez lek. Paulinę Głuszyńską publikacji w postępowaniu o nadanie stopnia doktora w dziedzinie nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne.

Inna Diemieszczyk

Białystok, 18.06.2023

**Lek. Jan Chilmończyk**
I Klinika Chirurgii Ogólnej i Endokrynologicznej
Uniwersytecki Szpital Kliniczny w Białymstoku
Uniwersytet Medyczny w Białymstoku

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- stworzeniu bazy danych,
- analizie statystycznej,
- przygotowaniu manuskryptu.

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Jan Chilmończyk

Białystok, 18.06.2023

**Dr hab. n. med. Joanna Reszeć**
Zakład Patomorfologii Lekarskiej
Uniwersytet Medyczny w Białymstoku

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Białystok, 18.06.2023

**Mgr Anna Citko**
Centrum Badań Klinicznych
Uniwersytet Medyczny w Białymstoku

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Anna Citko

Białystok, 18.06.2023

**Dr n. med. Łukasz Szczerbiński**
Klinika Endokrynologii, Diabetologii i Chorób Wewnętrznych
Uniwersytecki Szpital Kliniczny
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- opracowaniu koncepcji badań,
- nadzorze nad prowadzonymi badaniami,
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Łukasz Szczerbiński

Białystok, 18.06.2023

**Prof. dr hab. n. med Adam Krętowski**
Klinika Endokrynologii, Diabetologii i Chorób Wewnętrznych
Uniwersytecki Szpital Kliniczny
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**Prof. dr hab. n. med. Hady Razak Hady**
I Klinika Chirurgii Ogólnej i Endokrynologicznej
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Hady Razak Hady