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Ocena znaczenia greliny, obestatyny i leptyny w patogenezie choroby refluksowej przelyku w przebiegu obturacyjnego bezdechu sennego.

Evaluation of the role of ghrelin, obestatin and leptin in the pathogenesis of gastro-oesophageal reflux disease in the course of obstructive sleep apnea.

Rozprawa doktorska w dziedzinie nauk medycznych w oparciu o cykl publikacji naukowych

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Spis treści:

1. Wykaz publikacji stanowiących rozprawę doktorską	5
2. Zestawienie publikacji doktoranta	6
3. Komentarz	7
3.1. Wstęp	7
3.2. Cel rozprawy doktorskiej	11
3.3. Omówienie prac składających się na pracę doktorską	12
3.3.1. Praca pt. „Gastro-esophageal reflux and obstructive sleep apnea – is there a link?” ..	14
3.3.2. Praca pt. „The Impact of Sleep-Disordered Breathing on Ghrelin, Obestatin, and Leptin Profiles in Patients with Obesity or Overweight.”.....	15
3.3.3. Praca pt. „Associations of Obstructive Sleep Apnea, Obestatin, Leptin, and Ghrelin with Gastroesophageal Reflux.”	17
3.3.4. Praca pt. „The importance of obesity and carbohydrate metabolism disorders on the course of gastroesophageal reflux disease – a pilot study.”	19
3.4. Piśmiennictwo	21
4. Streszczenie	30
5. Summary	32
6. Kopie publikacji wchodzących w skład rozprawy doktorskiej	35
7. Oświadczenia współautorów	82
8. Załączniki	92

Wykaz skrótów:

W celu ujednoczenia pracy skróty wykorzystane w komentarzu oparto na mianownictwie angielskim, zgodnie z mianownictwem wykorzystanym w publikacjach wchodzących w skład rozprawy doktorskiej.

AHI- wskaźnik bezdechów i słyceń oddechu (ang. *apnea hypopnea index*)

CPAP- ciągle dodatnie ciśnienie w drogach oddechowych (ang. *Continuous Positive Airway Pressure*)

GERD- choroba refluksowa przełyku (ang. *gastroesophageal reflux disease*)

IQR- rozstęp międzykwartyłowy (ang. *interquartile range*).

OSA- obturacyjny bezdech senny (ang. *obstructive sleep apnea*)

1. Wykaz publikacji stanowiących rozprawę doktorską.

Praca pogładowa:

1. **Pardak P**, Pękala A, Jarmakiewicz S, Rafał Filip R. Gastro-esophageal reflux and obstructive sleep apnea – is there a link?. *Eur J Clin Exp Med.* 2020;18(2):110–115. doi: 10.15584/ejcem.2020.2.5

IF = 0; MNiSW = 20 ptk.

Prace oryginalne:

2. **Pardak P**, Filip R, Woliński J. The Impact of Sleep-Disordered Breathing on Ghrelin, Obestatin, and Leptin Profiles in Patients with Obesity or Overweight. *Journal of Clinical Medicine.* 2022; 11(7):2032. <https://doi.org/10.3390/jcm11072032>

IF = 4.242; MNiSW = 140 ptk.

3. **Pardak P**, Filip R, Woliński J, Krzaczek M. Associations of Obstructive Sleep Apnea, Obestatin, Leptin, and Ghrelin with Gastroesophageal Reflux. *Journal of Clinical Medicine.* 2021; 10(21):5195. <https://doi.org/10.3390/jcm10215195>

IF = 4.242; MNiSW = 140 ptk.

4. **Pardak P**, Rafał F, Krzaczek M. The importance of obesity and carbohydrate metabolism disorders on the course of gastroesophageal reflux disease – a pilot study. *Eur J Transl Clin Med.* 2022;5(1):0-0. DOI: 10.31373/ejtcml/149190

IF = 0; MNiSW = 40 ptk.

2. Zestawienie publikacji doktoranta

Rodzaj publikacji	Liczba	Impact Factor	Punktacja MNiSW
Prace włączone do rozprawy doktorskiej	4	8.484	340
Prace, które nie zostały włączone do rozprawy doktorskiej	6	1.013	94
Razem	10	9.497	434

3. KOMENTARZ

3.1. Wstęp

Współczesny styl życia, któremu towarzyszy pośpiech, stres i zaniedbywanie zachowań prozdrowotnych sprzyja występowaniu otyłości i powoduje wzrost występowania choroby refluksowej przełyku (GERD ang. *Gastroesophageal Reflux Disease*). GERD jest powszechnym problemem zdrowotnym dotykającym 10- 20% populacji [1]. Rozpoznanie wymaga stwierdzenia uciążliwych dolegliwości lub powikłań związanych z cofaniem się treści żołądkowej do przełyku [2]. Diagnostyka obejmuje zebranie wywiadu dotyczącego objawów klinicznych, oceny morfologii przełyku i połączenia żołądkowo- przełykowego w esofagogastroduodenoskopii, wyniku testu z inhibitorem pompy protonowej oraz w części przypadków wykonania 24- godzinnej impedancji przełyku z pH- metrią. Obraz kliniczny GERD jest zróżnicowany i obejmuje objawy kliniczne związane z drażnieniem i uszkodzeniem śluzówki przełyku (typowo zgaga, kwaśne regurgitacje oraz objawy powikłań) oraz objawy związane z działaniem treści żołądkowej na układ oddechowy i szkliwo zębów. W niewielkim odsetku przypadków prowadzi do rozwoju powikłań, do których zaliczamy zwężenia pozapalne oraz przełyk Barrett'a, którego progresja prowadzi do rozwoju dysplazji i gruczolaka przełyku [2,3]. Dostępne publikacje pokazują, że na ryzyko rozwoju przełyku Barrett'a i gruczolaka przełyku poza ciężkością GERD niekorzystnie wpływa otyłość i zaburzenia wodorowęglanowe [4,5].

Obturacyjny bezdech senny (OSA ang. *Obstructive Sleep Apnea*) jest zaburzeniem oddechu w czasie snu występującym w populacji z częstością od 6% do 33% [6]. Głównym czynnikiem ryzyka jest otyłość, której stopień koreluje z ciężkością OSA [7,8]. Choroba polega na występowaniu licznych epizodów zamknięcia lub istotnego zwężenia dróg oddechowych na

poziomie gardła (bezdechów lub spłyceń oddechu) [9]. Konsekwencją są liczne wybudzenia, spadek efektywności snu oraz występowanie objawów klinicznych, do których zaliczamy przede wszystkim przewlekłe zmęczenie i senność także po nocnym odpoczynku, poranne bóle głowy, nykturię, nadmierne pocenie i zaburzenia depresyjne [10]. Z objawów sugerujących OSA, zgłaszanych przez rodzinę chorego zaliczamy występowanie bezdechów w czasie snu oraz chrapanie. Rozpoznanie OSA stawiamy na podstawie polisomnografii, która polega na całonocnej analizie parametrów oddechowych, parametrów układu krążenia oraz elektroencefalogramu i elektrookulogramu [9]. Rozpoznanie i kwalifikacja ciężkości OSA opiera się na wskaźniku ilości bezdechów i spłyceń oddechu na godzinę snu (AHI ang. *Apnea Hypopnea Index*). Chorobę rozpoznaje się gdy $AHI \geq 15$ lub $AHI \geq 5$ przy obecności objawów klinicznych. Łagodny OSA rozpoznajemy gdy AHI wynosi 5-14, umiarkowany 15-29 natomiast ciężki gdy $AHI > 30$ [9,11].

OSA prowadzi do rozwoju licznych schorzeń, zwłaszcza związanych z układem krążenia [12]. OSA ma także istotny wpływ na schorzenia układu pokarmowego, najlepiej udowodnionym związkiem jest jego powiązanie z GERD [13,14]. Ponadto pogarsza przebieg choroby wrzodowej, zespołu jelita drażliwego, dyspepsji czynnościowej czy chorób zapalnych jelit [15-18]. Leczenie opiera się na eliminacji przyczyn OSA (redukcji wagi, chirurgicznej korekty zwężenia dróg oddechowych na poziomie gardła), wprowadzeniu zaleceń dotyczących higieny snu, unikania alkoholu i leków obniżających napięcie mięśniowe. W cięższych postaciach, zwłaszcza powikłanych chorobami układu krążenia, najskuteczniejszą metodą leczenia jest terapia CPAP (CPAP ang. *Continuous Positive Airway Pressure*). Leczenie polega na wytwarzanemu stałego dodatniego ciśnienia przez pompę CPAP podłączoną do specjalnej maski pokrywającej nos lub nos i usta. Zapobiega to zapadaniu się ścian gardła i przeciwdziała wystąpieniu bezdechów [19,20]

Otyłość jest wspólnym czynnikiem ryzyka GERD i OSA. W otyłości główne przyczyny GERD to zaburzenia funkcji dolnego zwieracza przełyku, obecność przepukliny rozworu przełykowego przepony, obniżona motoryka przełyku powodująca wydłużenie klirensu przełykowego oraz podwyższone ciśnienie wewnątrzbrzuszne [19,21-23]. O ile związek otyłości z GERD jest dobrze poznany, to powiązanie OSA z GERD nadal pozostaje przedmiotem badań. W przypadku OSA głównym mechanizmem GERD jest zwiększona ilość relaksacji dolnego zwieracza przełyku [24]. Ponadto za cięższy przebieg GERD odpowiada wydłużony klirens przełykowy, upośledzona motoryka żołądka i zmniejszona ilość buforującej treści żołądkową śliny [21,25-27]. Przyczyna zaburzeń funkcji dolnego zwieracza w OSA nie została wyjaśniona. Brak korelacji między bezdechami, a epizodami refluksu oraz korzystny wpływ leczenia bezdechu na przebieg GERD [26,27] wskazuje na znaczenie mechanizmów związanych z hipoksją, działaniem mediatorów stanu zapalnego lub zaburzeń hormonalnych. Zarówno otyłość jak i OSA wywierają wpływ na stężenia neuropeptydów: greliny, obestatyny i leptyny. Związki te są powiązane z homeostazą energetyczną ustroju oraz regulują prace przewodu pokarmowego. Zaburzenia w zakresie wydzielania i działania zaburzenia mogą współuczestniczyć w rozwoju GERD [28-30].

Grelina i obestatyna są produktami genu GHRL syntetyzowanymi głównie w obrębie przewodu pokarmowego [29,30]. Główne funkcje greliny to inicjacja przyjmowania posiłków, stymulacja motoryki przewodu pokarmowego oraz regulacja procesów zapalnych ustroju. Wydzielanie greliny do krwi ma charakter pulsacyjny, związany z przyjmowaniem posiłków oraz rytmem snu i czuwania. W fizjologicznych warunkach stężenie greliny wzrasta przed przyjęciem posiłku i koreluje z nasileniem uczucia głodu [29-31]. Po posiłku stężenie greliny spada wraz z wzrostem stężenia insuliny. W czasie snu, początkowo stężenie greliny wzrasta i pozostaje na stosunkowo wysokim poziomie. Natomiast w drugiej części nocy stężenie greliny stopniowo spada, aż do porannego wzrostu poprzedzającego spożycie

śniadania [32,33]. W otyłości dochodzi do obniżenia dobowych stężeń greliny, zarówno jej średnich wartości jak i amplitudy wahań związanej z posiłkami [32,34,35]. Wyniki badań oceniających wpływ OSA na stężenie greliny różną się. W jedynym badaniu oceniającym profil dobowy nie stwierdzono odchyleń odchylen greliny w OSA [36]. W większości prac w których wykorzystywano poranne oznaczenia obserwowano wyższe wartości greliny w OSA [37-41]. Tylko w jednej pracy rozpoznanie OSA wiązało się z niższymi stężeniami greliny [42]. W literaturze brak jest prac oceniających profil greliny w GERD. Nieliczne dostępne prace opierają się na porannych oznaczeniach, a uzyskane wyniki są rozbieżne. W części stężenia greliny w GERD były niższe [43,44], a w jednym z badań podanie agonisty greliny wiązało się ze zmniejszeniem ilości epizodów refluksu [45]. W pozostałych nie obserwowano różnic [46,47] lub stwierdzano jedynie tendencję do wyższych wartości greliny w GERD [48].

Leptyna syntetyzowana w adipocytach jest wskaźnikiem statusu energetycznego ustroju, ponieważ jej stężenie koreluje z ilością tkanki tłuszczowej [28,49]. Fizjologicznie działania leptyny mają na celu redukcję ilości tkanki tłuszczowej i spadek wagi poprzez redukcję uczucia głodu i stymulację metabolizmu. W otyłości wskutek przewlekłej hiperleptynemii dochodzi do rozwoju oporności na leptynę objawiającej się utratą działania hamującego apetyt [50]. W większości badań nie obserwowano odchyleń leptyny w OSA [36-41,51,52] lub tendencje do jej wyższych wartości [53,54]. Brak jest doniesień, w których stężenia leptyny byłyby niższe w OSA. W nielicznych pracach obserwowano dodatnią korelację między wartościami leptyny, a nasileniem GERD [46,55]. Opisywane w OSA i w GERD wahania leptyny wydają się wynikać z otyłości i nadmiernej ilości tkanki tłuszczowej, niż z mechanizmów związanych z tymi schorzeniami [37].

Obestatyna jest najsłabiej poznanym z omawianych neuropeptydów, a jej znaczenie w organizmie nadal jest przedmiotem badań. Do jej działań zaliczamy redukcję wchłaniania

jelitowego oraz hamowanie perystaltyki jelit. Jej stężenia są niższe w otyłości, a wahania dobowe niższe niż w przypadku greliny [56-58]. Uważa się, że obestatyna odgrywa rolę w regulacji metabolizmu glukozy i tłuszczu, zmniejsza nasilenie stanu zapalnego oraz wywiera korzystny efekt na funkcje wielu narządów poprzez stymulację proliferacji komórek oraz hamowanie apoptozy [59].

W dwóch dostępnych pracach nie stwierdzono istotnych zmian w stężeniach obestatyny wśród osób z OSA [42,53]. Także leczenie CPAP nie wywarło wpływu na poziom obestatyny [53]. W literaturze nie ma dostępnych badań oceniających stężenia obestatyny w GERD.

3.2. Cel rozprawy doktorskiej

Związek otyłości i omówionych neuropeptydów jest stosunkowo dobrze poznany. Mniej wiadomo o ich odchyleniach w OSA i w GERD. Ponieważ otyłość pozostaje we wzajemnej relacji z powyższymi schorzeniami, celem rozprawy była ocena nocnego profilu greliny, leptyny i obestatyny w grupie otyłych pacjentów i analiza korelacji między OSA i GERD, a stężeniami tych neuropeptydów.

Celem dodatkowym była charakterystyka GERD w otyłości i znalezienie różnic w obrazie klinicznym w zależności od rozpoznania zaburzeń węglowodanowych, w celu wyjaśnienia zwiększonego ryzyka występowania powikłań GERD w tej grupie pacjentów. Cele szczegółowe zostały zaprezentowane w omówieniu prac oryginalnych wchodzących w skład rozprawy doktorskiej.

3.3. Omówienie prac składających się na pracę doktorską

Artykuły wchodzące w skład rozprawy doktorskiej zostały napisane w oparciu o dane zebrane wśród pacjentów hospitalizowanych w celu diagnostyki i leczenia OSA w Klinice Chorób Wewnętrznych Instytutu Medycyny Wsi w Lublinie w okresie od listopada 2014 do grudnia 2015 roku. Wszyscy uczestnicy wyrazili pisemną zgodę na udział w badaniu. Zgodę na przeprowadzenie badania wyraziła Komisja Bioetyczna funkcjonująca przy Instytucie Medycyny Wsi w Lublinie (Decyzja nr 6/2014).

Protokół badania obejmował następujące procedury:

1. Badanie lekarskie z wykonaniem pomiarów antropometrycznych.
2. Zebranie danych ankietowych dotyczących zaburzeń snu oraz dolegliwości związanych z refluksem żołądkowo- przełykowym.
3. Wykonanie całonocnego badania snu (polisomnografii lub poligrafii).
4. Pobranie krwi celem oznaczeń neuropeptydów:
 - pobrania w godzinach 23:00, 1:00, 3:00, 5:00, 7:00.
 - pobrania wykonywano w nocy następującej po badaniu snu.
 - pobieranie krwi odbywało się na sali pacjenta i nie wymagało budzenia.

Uzyskaną surowicę przechowywano w temperaturze – 80 stopni C, do czasu wykonywania oznaczeń. Wszystkie procedury wykonywano zgodnie z zaleceniami producentów testów.

5. Endoskopowe badanie górnego odcinka przewodu pokarmowego i pH- metrię przełyku.

Zebrane dane wykorzystano do przeprowadzenia analiz statystycznych. Wszystkie analizy wykonano przy użyciu pakietu statystycznego Statistica, wersja 13 (TIBCO Software Inc.,2017). W pierwszym etapie sprawdzano normalność rozkładu badanych zmiennych, następnie zmienne z rozkładem normalnym opisywano przy pomocy średniej i odchylenia standardowego. Jeśli rozkład nie był normalny, w opisie zmiennej wykorzystywano medianę, zakres i rozstęp międzykwartyłowy (IQR ang. *interquartile range*). W porównywaniu korelacji między dwoma zmiennymi wykorzystywano test korelacji Spearmanna, natomiast przy porównywaniu zmiennych między grupami wykorzystywano test Mann-Whitney'a (jeśli porównywano dwie grupy) lub test Kruskal-Wallis'a (przy porównaniu więcej niż dwóch grup, test zastosowano przy porównaniu stężeń neuropeptydów między grupami z różnymi stopniami otyłości). Wyniki z wartością prawdopodobieństwa testowego poniżej 0,05 przyjmowano za istotne statystycznie. W celu określania wpływu na zmienną wielu czynników wykorzystywano modele analizy wieloczynnikowej. W przypadku określania wpływu płci, BMI, parametrów i rozpoznania OSA na stężenia greliny wykorzystano regresję liniową. Natomiast przy ocenie wpływu czynników BMI, obwodu talii, rozpoznania zaburzeń węglowodanowych i cukrzycy typu 2 dla rozpoznania GERD wykorzystano regresję logistyczną.

Szczegółowe informacje dotyczące materiałów i metod oraz przeprowadzonych analiz statystycznych zostały zaprezentowane w pracach oryginalnych wchodzących w skład rozprawy doktorskiej.

3.3.1. Praca przeglądowa pt. „Gastro-esophageal reflux and obstructive sleep apnea – is there a link?”

Cel pracy

Przeгляд piśmiennictwa dotyczący mechanizmu refluku- żołądkowo przełykowego w przebiegu OSA z uwzględnieniem znaczenia zaburzeń metabolicznych i hormonalnych. Omówienie potencjalnej roli zaburzeń greliny dla rozwoju GERD.

Szczegółowe informacje dotyczące celu pracy, materiałów i metod, wyników oraz wniosków zostały zaprezentowane w pracy poglądowej wchodzącej w skład rozprawy doktorskiej:

Pardak P, Pękala A, Jarmakiewicz S, Rafał Filip R. *Gastro-esophageal reflux and obstructive sleep apnea – is there a link?*. Eur J Clin Exp Med. 2020;18(2):110–115. doi: 10.15584/ejcem.2020.2.5

Wyniki:

1. Otyłość i OSA pozostają we wzajemnej zależności, oba schorzenia są istotnym czynnikiem ryzyka wystąpienia GERD. W obu przypadkach mechanizm rozwoju GERD jest konsekwencją dysfunkcji dolnego zwieracza przełyku.
2. Otyłość i OSA wpływają na profil greliny. W otyłości związek ten jest stosunkowo dobrze poznany, natomiast w OSA wnioski z dostępnych badań są rozbieżne.

3. Funkcje greliny w przewodzie pokarmowym wskazują na potencjalne znaczenie jej zaburzeń w rozwoju GERD.

4. Wyniki nielicznych badań oceniających stężenia greliny w GERD różnią się.

Wnioski:

Wskazane są dalsze badania oceniające rolę zaburzeń greliny w rozwoju GERD u pacjentów z OSA.

3.3.2. Praca pt. „The Impact of Sleep-Disordered Breathing on Ghrelin, Obestatin, and Leptin Profiles in Patients with Obesity or Overweight.”

Cel pracy

Badanie miało na celu przedstawienie nocnego profilu neuropeptydów (greliny, obestatyny i leptyny) wśród pacjentów z otyłością i OSA. Drugim celem było określenie wpływu otyłości i OSA na stężenia neuropeptydów. W tym celu porównano stężenia neuropeptydów między grupami w zależności od stopnia otyłości oraz w zależności od rozpoznania bezdechu. Następnie przeprowadzono analizę korelacji między parametrami otyłości i OSA, a stężeniami neuropeptydów.

Szczegółowe informacje dotyczące celu pracy, materiałów i metod, wyników oraz wniosków zostały zaprezentowane w pracy oryginalnej wchodzącej w skład rozprawy doktorskiej:

Pardak P, Filip R, Woliński J. The Impact of Sleep-Disordered Breathing on Ghrelin, Obestatin, and Leptin Profiles in Patients with Obesity or Overweight. *Journal of Clinical Medicine*. 2022; 11(7):2032. <https://doi.org/10.3390/jcm11072032>

Wyniki:

1. W badanej grupie OSA występował częściej wśród pacjentów z otyłością, a jego ciężkość korelowała z parametrami otyłości.
2. Stwierdzono istotną ujemną korelację między parametrami i stopniem otyłości, a średnim stężeniem greliny oraz jej oznaczeniami w pierwszej połowie nocy. Nie obserwowano korelacji między parametrami otyłości, a wartościami obestatyny i leptyny.
3. W grupie z OSA stwierdzono istotnie niższe wartości greliny w oznaczeniach o godzinie 5.00 i 7.00. Stężenia leptyny wśród osób z OSA także były niższe, jednak nie była to różnica istotna statystycznie. Nie stwierdzono różnic w stężeniach obestatyny w zależności od rozpoznania OSA.

Wnioski:

OSA występuje częściej wśród osób otyłych, a jego ciężkość koreluje ze stopniem otyłości.

Otyłość i OSA negatywnie korelują ze stężeniami greliny. Związek ten jest wyraźniejszy w przypadku otyłości, a OSA wydaje się nasilać te zaburzenia.

3.3.3. Praca pt. „Associations of Obstructive Sleep Apnea, Obestatin, Leptin, and Ghrelin with Gastroesophageal Reflux.”

Cel pracy

Celem pracy było zbadanie związku między OSA i GERD. Drugim celem była ocena stężeń greliny, obestatyny i leptyny w zależności od rozpoznania OSA i GERD. Trzecim celem badania była odpowiedź na pytanie czy wpływ OSA na profil greliny, obestatyny i leptyny może mieć znaczenie w rozwoju GERD.

Szczegółowe informacje dotyczące celu pracy, materiałów i metod, wyników oraz wniosków zostały zaprezentowane w pracy oryginalnej wchodzącej w skład rozprawy doktorskiej:

Pardak P, Filip R, Woliński J, Krzaczek M. Associations of Obstructive Sleep Apnea, Obestatin, Leptin, and Ghrelin with Gastroesophageal Reflux. *Journal of Clinical Medicine*. 2021; 10(21):5195. <https://doi.org/10.3390/jcm10215195>

Wyniki:

1. W badanej grupie GERD występował częściej wśród osób z OSA.
2. Zarówno w GERD jak i w OSA stwierdzono odchylenia w zakresie badanych greliny i leptyny. Wyniki te były istotne statystycznie jedynie dla części oznaczeń.
3. W grupie z OSA obserwowano niższe wartości greliny, nie obserwowano odchyleń w stężeniach leptyny i obestatyiny.
4. Nie obserwowano istotnych różnic w stężeniach neuropeptydów w zależności od rozpoznania GERD.
5. Stwierdzono tendencję do wyższych wartości greliny i leptyny wraz z wzrostem nasilenia parametrów GERD (objawów klinicznych, zmian zapalnych w przełyku oraz wyniku pH-metrii przełyku).

Wnioski:

OSA wiąże się z częstszym występowaniem refluksu żołądkowo- przełykowego. OSA koreluje z niższymi stężeniami greliny, natomiast w GERD stwierdzono tendencję do jej wyższych wartości. Dlatego też można przyjąć, że związek OSA z GERD nie jest związany z zaburzeniami greliny.

Ponadto mając na względzie opisaną w poprzednim artykule („*The Impact of Sleep-Disordered Breathing on Ghrelin, Obestatin, and Leptin Profiles in Patients with Obesity or Overweight*”) ujemną korelację otyłości ze stężeniami greliny należy wnioskować, że związek otyłości z GERD także nie jest wynikiem zaburzeń greliny.

3.3.4. Praca pt. „The importance of obesity and carbohydrate metabolism disorders on the course of gastroesophageal reflux disease – a pilot study.”

Cel pracy

Celem pracy była charakterystyka GERD w grupie pacjentów z nadmierną wagą oraz poszukiwanie różnic w obrazie klinicznym GERD w zależności od występowania zaburzeń węglowodanowych. Uzyskane wyniki miały na celu wyjaśnienie zwiększonego ryzyka powikłań GERD obserwowanego w otyłości oraz w przebiegu zaburzeń węglowodanowych.

Szczegółowe informacje dotyczące celu pracy, materiałów i metod, wyników oraz wniosków zostały zaprezentowane w pracy oryginalnej wchodzącej w skład rozprawy doktorskiej:

Pardak P, Rafał F, Krzaczek M. The importance of obesity and carbohydrate metabolism disorders on the course of gastroesophageal reflux disease – a pilot study. *Eur J Transl Clin Med.* 2022;5(1):0-0.

DOI: 10.31373/ejtc/149190

Wyniki:

1. W badanej grupie wśród osób z nadmierną wagą i z zaburzeniami węglowodanowymi GERD występował częściej niż w populacji ogólnej.

2. Nie obserwowano korelacji między parametrami otyłości, a ciężkością GERD. Nie stwierdzono różnic w nasileniu parametrów GERD w zależności od rozpoznania zaburzeń węglowodanowych.

Wnioski:

Opisywany w licznych publikacjach nietypowy lub łagodny przebieg GERD wśród pacjentów z otyłością i z zaburzeniami węglowodanowymi może opóźniać diagnostykę, przez co zwiększać ryzyko powikłań, w szczególności przełyku Barrett'a.

Pacjenci z cukrzycą typu 2, wśród których częściej występuje przełyk Barrett'a i gruczolakorak przełyku mogą zyskać dzięki wczesnej, przesiewowej ocenie przełyku w gastroscopii.

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4. Streszczenie

Wstęp: Choroba refluksowa przełyku (GERD) jest powszechnym problemem zdrowotnym o wieloczynnikowej patogenezie. Do chorób często współistniejących z GERD zaliczyć można między innymi obturacyjny bezdech senny (OSA) i otyłość. Za objawy GERD w tych schorzeniach odpowiadają zaburzenia pracy dolnego zwieracza przełyku. Przyczyna tych zaburzeń jest nieznana. W otyłości i w OSA dochodzi do odchyień w stężeniach neuropeptydów: greliny, leptyny i obestatyny. Wymienione neuropeptydy wpływają na motorykę przewodu pokarmowego, z tego powodu zaburzenia ich stężeń mogą oddziaływać na obraz kliniczny GERD.

Cel: Głównym celem badania była analiza wpływu OSA na profil greliny, obestatyny i leptyny oraz ocena znaczenia tego wpływu dla rozwoju GERD. Celem dodatkowym było zbadanie różnic obrazu klinicznego GERD w zależności od występowania zaburzeń metabolizmu węglowodanów.

Material i metody: Analizie poddano dane zebrane od 58 pacjentów Kliniki Chorób Wewnętrznych Instytutu Medycyny Wsi w Lublinie. Dane obejmowały pomiary antropometryczne, dane ankietowe dotyczące objawów OSA i dolegliwości związanych z GERD, wyniki polisomnografii, wyniki gastrokopii i pH-metrii przełyku oraz oznaczenia stężeń greliny, leptyny i obestatyny w surowicy.

Wyniki: Na podstawie analizy zebranych danych opisano wzajemne powiązania otyłości, OSA i GERD. Stwierdzono częstsze występowanie GERD wśród osób z OSA oraz z otyłością. W zakresie badanych neuropeptydów stwierdzono, że otyłość wiązała się z niższymi stężeniami greliny, korelacja ta była istotna statystycznie dla wartości średniej greliny i oznaczeń pobranych w pierwszej połowie nocy. Podobnie w OSA stwierdzono tendencję do niższych stężeń greliny, w tym przypadku korelacja ta była istotna statystycznie

tylko dla oznaczeń w drugiej połowie nocy. W przeprowadzonym badaniu nie obserwowano korelacji między parametrami otyłości, a wartościami obestatyny i leptyny. Nie stwierdzono korelacji obestatyny i OSA, natomiast stężenia leptyny w OSA były niższe, jednak wykazana różnica nie była istotna statystycznie. Przeprowadzone analizy nie wykazały istotnych korelacji między stężeniami greliny, obestatyny i leptyny a rozpoznaniem i wykładnikami GERD. Stwierdzono jedynie tendencję do wyższych stężeń greliny i leptyny w GERD. Obserwacja ta jest istotna w kontekście celu badania, ponieważ przemawia przeciw znaczeniu greliny rozwoju GERD w OSA i w otyłości. Ponadto na podstawie wykonanych analiz nie stwierdzono różnic w zakresie objawów klinicznych GERD, nasilenia zmian zapalnych w przełyku oraz parametrów ocenianych w pH- metrii przełyku mogących tłumaczyć zwiększone ryzyko powikłań GERD wśród pacjentów z zaburzeniami węglowodanowymi i z otyłością.

Wnioski:

- 1/ Obturacyjny bezdech senny występuje częściej wśród osób otyłych, a stopień otyłości koreluje z pogorszeniem parametrów snu ocenianych w polisomnografii.
- 2/ Otyłość i OSA negatywnie korelują ze stężeniami greliny. Związek ten jest wyraźniejszy w przypadku otyłości, a OSA wydaje się nasilać te zaburzenia.
- 3/ W grupie pacjentów z nadmierną wagą OSA wiąże się z częstszym występowaniem refluksu żołądkowo- przełykowego.
- 4/ Otyłość i OSA koreluje z niższymi stężeniami greliny, natomiast w GERD obserwowano tendencję do jej wyższych wartości. Dlatego też można przyjąć, że związek otyłości i OSA z GERD nie jest związany z zaburzeniami greliny.

Słowa kluczowe: choroba refluksowa przełyku, obturacyjny bezdech senny, otyłość, grelina, obestatyna, leptyna.

5. Summary

Background: Gastroesophageal reflux disease (GERD) is a common health problem with multiple factors involved in its pathogenesis. Risk factors for GERD include obstructive sleep apnea (OSA) and obesity. Dysfunction of the lower esophageal sphincter leads to development of GERD in these diseases. However, the mechanism by which this dysfunction develops is unknown. In obesity and OSA, deviations in the concentrations of the neuropeptides ghrelin, leptin, and obestatin are observed. These neuropeptides affect gastrointestinal tract motility, and therefore, disturbances in their concentrations may affect the clinical course of GERD.

Aim: The aim of our study was to evaluate the influence of OSA on the ghrelin, obestatin, and leptin profile and to investigate the importance of this influence on the development of GERD. An additional aim was to investigate the differences in the clinical course of GERD depending on the presence of carbohydrate metabolism disorders.

Methods: Statistical analysis was performed on the data collected from 58 patients hospitalized in the Department of Internal Medicine at the Institute of Rural Medicine in Lublin. The data included anthropometric measurements, survey data on OSA symptoms and GERD-related complaints, polysomnography results, esophagogastroduodenoscopy and esophageal pH-measurement results, and the nocturnal profile of ghrelin, leptin, and obestatin levels.

Results: Based on the analysis of the collected data, relationships between obesity, OSA and GERD were observed. Gastroesophageal reflux disease was found to be more common among people with OSA and obesity. Statistical analyses of the studied neuropeptides showed that obesity was associated with lower ghrelin concentrations. This correlation was statistically significant for the mean value of ghrelin and for measurements taken in the first half of the

night. Similarly, in OSA, there was a trend towards lower ghrelin concentrations, but in this case, the correlation was statistically significant only for measurements from the second half of the night. In our study, no correlation was observed between the obesity parameters and the values of obestatin and leptin. Moreover, values of obestatin and OSA showed no correlation. In turn, leptin concentrations in OSA were lower, but the difference was not statistically significant. Our analyzes did not show any significant correlation between the concentrations of ghrelin, obestatin, and leptin and the diagnosis and severity of GERD. However, unlike in OSA and obesity, there was a trend towards greater ghrelin and leptin levels in GERD. This observation is important for the conclusions of the study because it argues against the importance of ghrelin disturbances in the development of GERD in OSA and obesity. Moreover, no differences in the clinical course of GERD were found which could explain the increased risk of complications among patients with carbohydrate metabolism disorders and obesity.

Conclusions:

1 / Obstructive sleep apnea is more common among obese people and its severity correlates with the degree of obesity.

2/ Obesity and OSA negatively correlate with ghrelin levels. Deviation in ghrelin levels is, to a greater extent, due to obesity, while OSA appears to exacerbate these deviations.

3/ Obstructive sleep apnea is associated with a more frequent occurrence of gastroesophageal reflux disease.

4/ Obesity and OSA correlate with lower ghrelin concentrations, while GERD was associated with greater values of ghrelin. Taken together, our data show that the association of obesity and OSA with GERD is not due to disturbances in ghrelin levels.

Key words: gastroesophageal reflux disease, obstructive sleep apnea, obesity, ghrelin, obestatin, leptin.

6. Kopie publikacji wchodzące w skład rozprawy doktorskiej.



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REVIEW PAPER

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Gastro-esophageal reflux and obstructive sleep apnea – is there a link?

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ABSTRACT

Introduction. The epidemic of obesity has led to an increase in the occurrence of obstructive sleep apnea and gastro-esophageal reflux disease. The mechanism of development of gastro-esophageal reflux disease is multifactorial, and studies conducted in the last decade have shed new light on the causes of its development in patients with sleep apnea and obesity.

Aim. The aim of the study was to discuss the mechanism of development of gastro-esophageal reflux disease is multifactorial, and studies conducted in the last decade have shed new light on the causes of its development in patients with sleep apnea and obesity and the dysfunction of the lower esophageal sphincter.

Material and methods. An analysis of literature regarding gastro-esophageal reflux and obstructive sleep apnea.

Results. In obstructive sleep apnea and obesity, high levels of cytokines and insulin resistance are observed, resulting in disorders in the levels of ghrelin – a hormone responsible for normal gastrointestinal motility.

Conclusion. The effect of deviations in the ghrelin profile on the development of gastro-esophageal reflux disease remains a matter for further research.

Keywords. gastro-esophageal reflux, ghrelin, obesity, obstructive sleep apnea

Introduction

For several decades, an epidemic of obesity has been one of the major health problems in many countries. This results, among other things, in an increase in the occurrence of gastro-esophageal reflux disease (GERD) and obstructive sleep apnea (OSA).¹⁻³ GERD affects from 8-33% of the population and is defined as a disorder in which the stomach contents flow back up into the esophagus, causing complaints and/or leading to the development of complications.⁴ Due to an increasing fre-

quency of the occurrence of GERD-related esophageal adenocarcinoma, an effective prevention of GERD is an increasingly important health problem.⁵ GERD most frequently occurs in males and persons with an excessive body weight, whereas inadequate diet, an intensive physical effort, some medicines, and the presence of the esophageal hiatal hernia favour its development.⁶ Complaints associated with gastro-esophageal reflux (GER) include a burning sensation in the chest, regurgitation, epigastric pain, empty burping, and discomfort during swallowing.

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In addition, the stomach contents which flow backwards causing extra-esophageal symptoms, such as hoarseness and chronic cough. GER leads to the development of esophagitis and changes of the type of metaplasia, dysplasia and ultimately esophageal cancer.⁴ In order to prevent GER, it is recommended to reduce body weight, discontinue smoking, modify diet, and resign from eating before bedtime. In therapy, prokinetic drugs are used, and drugs that suppress gastric acid secretion, while in the case of the therapy being ineffective, or the presence of complications, surgical treatment is considered.⁷

OSA is the most frequent breathing disorder during sleep, and concerns up to 7-20% of adults.³ In OSA, there occurs a closure or significant narrowing of the airways while sleeping, resulting in an intensified breathing and waking-up effort. Multiple episodes of apnea cause drops in blood oxygen saturation levels and an increase in sympathetic tone, whereas episodes of waking-up result in sleep fragmentation and decrease in the effectiveness of sleep.⁸ It was confirmed that an increase in heart rate and arterial blood pressure, an effect of oxidative stress, and elevation of parameters of the inflammatory state, lead to the development of complications within the cardiovascular system.⁹ Clinical symptoms of OSA may be divided into those related with the occurrence of episodes of breathing cessation, pauses in breathing during sleep, snoring and waking-up with the sensation of gasping and, resulting from the lack of effectiveness of sleep, excessive sleepiness in the daytime, chronic fatigue, deterioration of cognitive functions, low mood and morning headaches. The main risk factors of OSA include excessive body weight, male gender, age over 40, large neck circumference and anatomical facial malformations.¹⁰ The diagnosis is made based on the result of polysomnography (PSG), and the degree of severity depends on the value of apnea and hypopnea events (AHI). The strategy of sleep apnea therapy depends on the degree of its severity and concomitant diseases. Apart from the normalization of weight and improvement of sleep hygiene, the use of CPAP therapy is considered as the basic method of treatment which, by maintaining positive airway pressure, prevents collapse of the walls of the throat and maintains patency of the upper airway. In selected cases, preventive treatment brings about good outcomes, consisting mainly in the plasty of the soft palate.⁸

Gastro-esophageal reflux in the course of OSA and in obesity

In OSA, especially in its severe forms, GERD is a serious health problem.^{11,12} It remains a matter of debate to what extent GERD is related with OSA, and to what degree it results from common with obesity risk factors.¹³⁻¹⁵ The relationship between the two disorders is indicated by a study in which a beneficial effect of the CPAP

therapy was confirmed on the course of both nocturnal and daytime GERD by improvement of the function of the lower esophageal sphincter (LES).^{16,17} In the past, the occurrence of GER in OSA was explained by drops of pressure in the chest during futile respiratory efforts accompanying apnea. Due to the development of diagnostic techniques and possibilities to perform simultaneously esophageal pH-metry and impedance during PSG, the mechanism of GER has been described among patients with OSA. In their study, Penzel et al. observed the symptoms of GERD in all patients with OSA; however, during simultaneous performance of PSG and esophageal pH-metry, no time relationship was found between the occurrence of the episodes of apnea and esophageal pH drops.¹⁸ Kuribayashi et al. also observed a more frequent occurrence of GER in the group of patients with OSA. Due to simultaneous performance of PSG with manometry and pH-metry, it was indicated that in the pathogenesis of nocturnal GER in OSA, the transient lower esophageal sphincter relaxation (TLESR) plays the major role, and not the accompanying changes in the pressure gradient between the esophagus and the stomach. The researchers found that TLESR occurred more frequently in patients with OSA, and their number correlated with the number of reflux episodes.¹⁹ In their subsequent study, Kuribayashi et al. observed that during the period of apnea episodes, the reflux of the gastric contents into the esophagus was prevented by compensatory tone increase on the level of gastro-esophageal junction and upper esophageal sphincter.²⁰ In turn, Xiao et al., in the group of patients with OSA, apart from the observation of a more frequent occurrence of acidic GER, observed an impaired cleaning of the esophagus from refluxed gastric contents.²¹

Obesity, especially of the visceral type, is an important risk factor for GERD. It has been confirmed that an excessive amount of visceral fat (VF) better correlated with the occurrence of GERD than the BMI value or body weight.^{14,22-24} The mechanism of GER in obesity is complex and results mainly from a decreased tone and increased number of LES relaxations. An elevated intra-abdominal pressure, a high pressure gradient between the stomach and esophagus, and bad eating habits, were considered as less important factors.^{25,26} The role of inflammatory parameters remains unclear, the value of which in obesity is elevated and correlates with the intensity of inflammatory changes in the esophagus. In their study, Nam et al. evaluated the relationships between the occurrence of GERD, and values of inflammatory cytokines and adipokines associated with VF. A significant relationship was observed between the amount of VF, leptin level, and occurrence of inflammatory changes in the esophagus. A similar relationship was found for the level of inflammatory cytokines IL-6 and IL-1; however, the consideration of the amount of

VF and leptin level resulted in cytokines no longer being significant as independent factors related with GERD.²⁷ Tseng et al., in their study, confirmed morning levels of peptide YY (PYY), ghrelin, leptin and adiponectin between patients with GERD and a control group. In the group of patients with GERD, the morning PYY levels were lower, while the levels of ghrelin slightly higher; however, the observed differences were statistically insignificant.²⁸

Obesity is the most important factor for the development of GERD, whereas OSA increases its severity and frequency of occurrence.¹⁵ In both disorders, GERD is the result of LES dysfunction; however, the cause of this dysfunction remains unknown.^{19,25} The disorder common for OSA and obesity is an increase in the level of proinflammatory cytokines.^{29,30} The concentrations of leptin, motilin, obestatin, adiponectin and resistin are related with the amount of adipose tissue in the body; nevertheless, no significant effect of OSA on their values has been observed.^{31–33} Both OSA and obesity exert an effect on the levels of ghrelin.³⁴ Ghrelin stimulates intestinal motility and accelerates gastric emptying; therefore, its deficiency may result in a prolonged retention of the gastric contents favouring the development of GER.

Ghrelin is a hormone produced mainly within the gastrointestinal tract which, together with obestatin, is produced from preproghrelin- a precursor encoded by the GHRL gene. After disconnection from the precursor, ghrelin- by means of ghrelin O- acetyltransferase- is subject to modification to an acylated form, considered as biologically active. Apart from the acylated form of ghrelin, a des-acylated form of ghrelin is distinguished, the role of which in the body is unknown.^{35–37} In addition, the results of determinations of the forms of ghrelin using mass spectrophotometry suggest that all the ghrelin in the body is acylated, while the des-acylated form is an artefact formed in the course of the preparation of samples.³⁸ Ghrelin participates in the regulation of body energy, and through central effects causes an increased appetite, initiates the intake of meals, exerts an effect on the sensation of taste and the reward center.^{39–41} It also participates in the regulation of the metabolism of carbohydrates (by exerting an effect on the levels of insulin and increase in insulin sensitivity), regulation of the sleep-wake rhythm.^{42–44} It is credited with a beneficial effect on the cardiovascular system and anti-inflammatory effect.^{45,46} The peripheral effects of ghrelin include the stimulation of motility of the gastrointestinal system, acceleration of emptying of the stomach and increase in the secretion of hydrochloric acid.⁴⁷ The concentrations of ghrelin show daily variability, its secretion into the blood is of a pulse character and is related with the consumption of meals and the sleep-wake rhythm. The highest levels of ghrelin in blood occur approximately 30 minutes before meals, and their values

are proportional to the intensity of the feeling of hunger. After the meal, together with an increase in insulin level, the concentration of ghrelin decreases. At night, the level of ghrelin initially increases and remains on a relatively high level, whereas during the second part of the night it gradually decreases, to increase again before the consumption of breakfast.^{39,42,43}

Ghrelin profile in the course of sleep disorders and eating disorders

With obesity, decreased ghrelin values in a daily rhythm are observed, also its amplitude and mean levels are lower, except for morning levels which, according to the majority of reports, are higher in individuals with a normal body weight.³⁹ One of the potential causes is hyperinsulinemia accompanying obesity. This is suggested by the results of a study in which a mealtime increase in the level of insulin, similar to administration of exogenous insulin, resulted in a decrease in the ghrelin level.⁴⁴ In turn, while losing weight, the reduction of calories in the diet is associated with an increase in the ghrelin levels, up to very high values observed in the course of anorexia nervosa.^{39,48} The subsequent disorder potentially decreasing ghrelin values is an increase in the levels of inflammatory parameters observed in obesity. Ghrelin is considered as a factor inhibiting inflammatory state, in addition, decreased ghrelin levels accompany an elevation of inflammatory parameters in the course of rheumatoid arthritis and in the case of Takayasu's arteritis.^{49,50} The lack of effective sleep is the subsequent factor related with disorders in the ghrelin level. The result of studies assessing the effect of sleep deprivation and OSA on the level of ghrelin vary; in the majority of observations an elevated fasting level of ghrelin is noteworthy, as well as its lower values during the first hours of sleep.^{33,43,45,51} In their study, Spiegel et al. evaluated the effect of short-term sleep deprivation on diurnal levels of ghrelin and leptin in a group of healthy individuals. During the period when the study participants experienced sleep deprivation, higher diurnal ghrelin levels and lower leptin levels were observed, and these changes were accompanied by a greater feeling of hunger and an increased appetite.⁵² In turn, Dzaja et al., in their study of persons subjected to sleep deprivation, did not observe any increase in ghrelin levels during the first hours of the night, while no differences in ghrelin values were observed during the day.⁴² Motivala et al. in a conducted study found that nocturnal ghrelin values were lower in a group of patients with chronic insomnia, compared to the control group.⁵³ In their study, Takahashi et al. evaluated morning levels of acylated and des-acylated ghrelin in patients with OSA, and the effect of treatment using the CPAP therapy. In the group of patients with OSA, ghrelin values were higher, while a repeated assessment after one-month CPAP therapy showed a de-

crease in the level of acylated form of ghrelin, compared to the values observed in the control group.⁵⁴ Nevertheless, in a study by Weiyang et al., in a group of patients with OSA, morning ghrelin levels were lower than those observed in the control group.³⁴ In turn, Papaioannou et al. examined patients with OSA and did not observe any deviations in the determinations of fasting ghrelin, and those performed at 22.30.⁵⁵ Similarly, in the study by Sanchez-de-la-Torre et al. conducted among patients with OSA, no differences were found in the daily ghrelin profile, compared to the control group.³² Fluctuation in ghrelin levels, similar to obesity, may be secondary with respect to elevated levels of inflammatory parameters and insulin resistance, accompanying sleep deprivation and OSA.^{30,51} Higher fasting ghrelin levels are associated with a stronger feeling of hunger; therefore, they may be responsible for the tendency towards consumption of a higher amount of calories observed among persons with sleep disorders.⁵² Unfortunately, in patients with OSA, this mechanism, by increasing the calorific value of diet, may lead to an increase in body weight and further intensification of breathing problems during sleep.

Occurrence of GERD and ghrelin

The mechanism of the development of GERD is multifactorial. Observations carried out by Nataha et al. conducted on rats indicate the role of ghrelin in the occurrence of gastrointestinal motility disorders accompanying GERD.⁵⁶ Ghrelin stimulates intestinal peristalsis and accelerates the emptying of the stomach; therefore, its low values, through prolonged gastric emptying may play a role in the development of GERD.⁵⁷ This hypothesis has been supported by Agrawal et al., who after administration to three groups of patients subsequently ghrelin, capromorelin/ghrelin receptor agonist, and placebo, observed in the first two groups a significant reduction in the number of reflux episodes.⁵⁸ Similarly, in a study by Rubenstein et al, lower fasting ghrelin levels correlated with the occurrence of GERD.⁵⁹ In turn, in the previously mentioned study by Tseng et al. conducted in patients with GERD, morning ghrelin levels were higher than in the control group; however, this difference was statistically insignificant.²⁸ In a study by Eren et al. no relationship was found between fasting ghrelin values and the intensity of GERD.⁶⁰ The available studies do not consider the pulsating character of ghrelin secretion; therefore, an assessment in a daily profile would allow full determination of its importance for the development of GERD.

Conclusion

GERD is an important health problem among patients with OSA and obesity. In both disorders, LES dysfunction plays the major role in the pathogenesis of GERD. Ghrelin is responsible for gastric emptying; therefore,

its low values may favour the development of GER. A decrease in nocturnal ghrelin levels observed in sleep deprivation and OSA, and in the case of obesity in the whole daily profile, may be responsible for a different course of GERD. For this reason, further studies and evaluation the role of ghrelin in the pathogenesis of GERD are recommended, especially in the context of LES function and esophageal motility.

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Article

The Impact of Sleep-Disordered Breathing on Ghrelin, Obestatin, and Leptin Profiles in Patients with Obesity or Overweight

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Abstract: Background: The impact of concomitant obesity and sleep disorders on neuropeptides related to energy balance is poorly understood. The aim of this study was to assess the nocturnal profile of total ghrelin, obestatin, and leptin in patients with elevated BMI and to investigate the impact of breathing-related sleep disorders on these hormone levels. Methods: The study involved 58 patients with suspicion of obstructive sleep apnea (OSA). Patients underwent anthropometric and sleep examination and measurements of night ghrelin, leptin, and obestatin levels. Results: In patients with OSA ($n = 46$), recognized on the basis of sleep examination outcomes, the correlation of anthropometric measurements with parameters of sleep disorders and ghrelin levels was observed, contrary to the control group ($n = 12$). In the OSA group, levels of ghrelin were significantly lower than in the control group at 5:00 and 7:00. Levels of leptin in the OSA group were also lower than those in the control groups (not statistically significant). Profiles of obestatin in both groups were similar. Conclusions: Our results confirm the relationship between obesity and sleep-disordered breathing. Both these disorders affect ghrelin levels—parameters of obesity negatively correlate with hormone concentration, and OSA seems to lower ghrelin values in the second half of the night.

Keywords: obesity; sleep-disordered breathing; ghrelin; leptin; obestatin; sleep apnea



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1. Introduction

Obesity, defined as the excessive or abnormal accumulation of fat tissue in the body, is diagnosed based on a body mass index (BMI) value of at least 30 kg/m². This disease affects approximately 13% of the world's adult population, and over the past 40 years, the number of obese people has tripled. Obesity adversely affects all aspects of human health and increases the risk of developing many diseases, including type 2 diabetes, cardiovascular disease, metabolic syndrome, and various cancers [1,2].

The primary cause of obesity is an energy imbalance between calories consumed and calories expended resulting from increased consumption of high-energy foods and low physical activity. However, genetic/familial factors or hormonal disorders also play an important role in the development of obesity [2,3].

Population-based studies indicated that the risk of obesity is also significantly increased by sleep deprivation. Lifestyle changes made sleep deficiency commonplace in recent decades. Increasing working hours, stress, work-related rush, widespread access to social media, and depressive disorders, particularly exacerbated in the era of the COVID-19 epidemic, adversely affect the quantity and the quality of sleep [4]. Sleep deprivation can

promote obesity in two ways: on the one hand, it leads to hedonic eating and more frequent high-calorie meal choices, and on the other, it causes sleepiness during the day, which impedes physical activity [5–7].

In turn, excessive weight is a major risk factor for obstructive sleep apnea (OSA) because fatty tissue accumulated in the neck region narrows the airway reducing the airflow and also contributes to hypotonia of the pharyngeal muscles and repeated closure of the upper airway at the level of the throat during sleep, leading to apnea and multiple awakenings.

Although sleep duration is normal, a decrease in sleep efficiency occurs, and as a result, patients experience daytime symptoms such as drowsiness, fatigue, impaired concentration, and metabolic disturbances. Further consequences include stimulation of the sympathetic nervous system, increased inflammatory parameters, an increased risk of developing insulin resistance, hyperinsulinemia, and glycemic disturbances with a tendency toward hyperglycemia and abnormal glucose tolerance [8,9]. The prevalence of OSA ranges widely from 6% to as much as 49%, depending on the studied population and diagnostic criteria; however, it is thought that these data are under-reported [10].

Obesity has been recognized as one of the main risk factors for OSA. According to epidemiological studies, up to 60% of OSA cases are the result of obesity. In the adult population, the prevalence of OSA is estimated to be above 50% in obese subjects. Numerous studies correlated weight gain and loss with increasing and decreasing the severity of OSA, respectively. Therefore, the primary treatment for OSA in obese patients is weight reduction. The effectiveness is confirmed by studies in which a reduction in the severity of OSA and an improvement in the quality of night sleep were observed in response to weight loss caused by surgery or diet [11–13].

Obesity and sleep disorders are thus linked by a bidirectional causal relationship, and identifying effective methods to interrupt this mechanism is important for patients' prognosis and their quality of life. Numerous mechanisms are involved in the regulation of energy balance, one of which is the action of the neuropeptides that regulate energy homeostasis: ghrelin, leptin, and obestatin.

Ghrelin is synthesized mainly by the cells of stomach gastric mucosa, but it is also found in the hypothalamus, pituitary, and intestines. This hormone has orexigenic action, i.e., it stimulates food intake, so under physiological conditions, its concentration in blood increases during starvation and decreases after eating [14,15]. Paradoxically, in patients with obesity, fasting ghrelin concentrations are lower than in subjects with normal weight. However, after eating, reductions in ghrelin concentrations occur to a small extent in obese individuals, leading to the persistence of relatively high postprandial values and excessive food intake [16,17].

On the contrary, the conclusions from the studies of the influence of OSA on ghrelin levels differ. In the only study evaluating the effect of ghrelin profile, no differences were found depending on the diagnosis of OSA [18]. Most of the studies mainly involved morning measurements, and their results were dominated by observations showing higher values or no effect of OSA on ghrelin levels [19–23]. The levels of ghrelin in the course of OSA were only lower in one study [24].

Leptin is secreted by adipocytes, and its concentration in blood correlates with the amount of adipose tissue, which is an indicator of body energy status. Under physiological conditions, leptin reduces hunger and enhances metabolism; hence, its concentration decreases during starvation and increases during eating [15,25]. In obesity, the leptin level is elevated due to increased adipocytes and also due to leptin resistance, which is characterized by a lack of appetite suppression despite high leptin concentrations [26].

In the majority of reports, diagnosis of OSA correlated with higher leptin concentrations; less frequently, no deviations in leptin levels were found. We did not find any reports where OSA correlated with lower leptin levels. A review of the literature by Mashaqi et al. indicated greater importance of obesity and adipose tissue on leptin levels than

OSA [19]. However, few studies show a decrease in leptin levels in response to CPAP therapy [19,27,28]

Obestatin is the least understood of the mentioned neuropeptides, and its importance in metabolism is still under investigation. What is known is that obestatin decreases nutrient absorption and intestinal peristalsis. Its concentration is lower in individuals with obesity than in those with normal weight, and its diurnal fluctuations are much smaller than those of ghrelin [29,30]. Obestatin is thought to play a role in the regulation of glucose and fat metabolism and the reduction in inflammation and to have a beneficial effect on the preservation of organ function by stimulation of proliferation and inhibition of apoptosis of cells [31].

The available studies showed no significant deviations of obestatin in OSA. In a study by Liu et al., in OSA, obestatin values were lower, but this difference did not reach the level of statistical significance [24]. While in the study by Zirlik et al., obestatin levels between OSA patients and the control group were similar; moreover, CPAP therapy did not affect the level of obestatin [27].

The relationship between the values of the mentioned neuropeptides related to energy balance and obesity is relatively well understood. Obesity, in turn, remains in a reciprocal relationship with sleep disorders.

Therefore, the aim of this observational study was to assess the nocturnal profile of total ghrelin, obestatin, and leptin in patients with elevated BMI and investigate the impact of breathing-related sleep disorders on the levels of appetite-regulating hormones.

2. Materials and Methods

2.1. Study Group

The study was conducted on patients with excessive weight ($\text{BMI} \geq 25 \text{ kg/m}^2$) hospitalized in the Department of Internal Medicine of the Institute of Rural Medicine in Lublin due to clinical suspicion of sleep-disordered breathing. The suspicion was based on the presence of symptoms such as pauses in breathing during sleep, snoring, or excessive daytime sleepiness. Patients with decompensation of chronic cardiovascular or respiratory diseases and those taking medications with potential effects on sleep parameters were excluded from the study, as were patients with factors that might affect ghrelin, leptin, or obestatin levels, such as significant gastrointestinal pathology (active inflammatory bowel disease, celiac disease) or a history of abdominal surgery (e.g., gastrectomy, intestinal resection).

A total of 58 subjects were eligible to participate in the study, and all of them gave informed consent. The study was approved by the Bioethics Committee of the Institute of Rural Medicine (Decision No. 6/2014).

The population described in this article served as a study group in our other research, the results of which were published in the article "Associations of Obstructive Sleep Apnea, Obestatin, Leptin, and Ghrelin with Gastroesophageal Reflux" [32].

2.2. Anthropometric Data

All participants underwent a physical examination. The BMI was calculated as the body weight in kilograms divided by the height in meters squared (kg/m^2). Overweight was diagnosed if BMI was in the range of 25–29.9 kg/m^2 , and obesity was recognized with $\text{BMI} \geq 30 \text{ kg/m}^2$ (30–34.9 kg/m^2 —class I, 35–39.9 kg/m^2 —class II, and $> 40 \text{ kg/m}^2$ —class III). The waist circumference (WC), i.e., the smallest circumference between the rib cage and the iliac crest, was measured in the standing position.

2.3. Sleep Examination

An all-night sleep examination was performed according to the current guidelines of the American Academy of Sleep Medicine (AASM) [33]. Sleep assessment was carried out in all patients based on polygraphic testing (type III according to AASM) using an Embletta MPR PG (formerly Embla, currently Natus; Pleasanton, CA, USA). Additionally, in 12 patients (10 from the OSA group and 2 from the control group), polysomnography

was performed (type II according to AASM) with EmblaS4500 devices (formerly Embla, currently Natus; Pleasanton, CA, USA) and RemLogic diagnostic software (formerly Embla, currently Natus; Pleasanton, CA, USA). Categorization of respiratory incidents and assessment of sleep apnea severity was performed according to standard criteria by an experienced physician. The following parameters of sleep disorders assessed by polysomnography were selected for statistical analyses: apnea/hypopnea index (AHI), indicating the number of apneas/hypopneas occurring per hour of sleep; percentage snoring time during sleep; and the value of the mean and lowest saturation during sleep (SpO₂ mean; SpO₂ lowest). According to current guidelines, OSA was diagnosed when AHI \geq 15 or AHI \geq 5 in the presence of clinical symptoms. The disorder was classified as “mild”, “moderate”, or “severe” when the number of episodes per hour was 5–14, 15–29, or $>$ 30, respectively [34].

2.4. Laboratory Measurements

On the day after the sleep examination, blood was drawn from a catheter inserted into a peripheral vein at the following times: 23:00, 01:00, 03:00, 05:00, and 07:00. Drawing blood samples did not require waking the patient. The first blood sample was taken at least three hours after the end of supper, and the last blood sample was drawn at least 60 min before breakfast. Patients were instructed to refrain from meals on the night of blood sampling. For one patient, only one sample at 23:00 could be obtained because the patient did not consent to further samples being taken. Blood was collected into tubes containing EDTA and then centrifuged at 3000 rpm for 20 min at 4 °C. The obtained blood serum was stored in Eppendorf tubes at -80 °C until assays were performed. Hormonal assays were performed using radioimmunoassays (RIA): total ghrelin—Ghrelin (Human) RIA Kit (EMD Millipore’s Corp. Inc. Billerica, MA, USA); leptin—Leptin (Human) RIA Kit (EMD Millipore’s Corp. Inc. Billerica, MA, USA); obestatin—Obestatin (Human, Monkey) RIA Kit (Phoenix Pharmaceuticals, Inc. Burlingame, CA, USA). For technical reasons, obestatin and leptin determinations were not performed in all patients ($n = 39$ – 42).

2.5. Statistical Analysis

Statistical analyses were performed using the software package Statistica (data analysis software system), version 13 (TIBCO Software Inc., 2017; Palo Alto, CA, USA).

Descriptive statistics were computed for the analyzed parameters as appropriate: mean with standard deviation (SD) for parameters with normal distribution or median and range for parameters without normal distribution.

Spearman rank correlation analysis was used to analyze the relationship between hormone determinations and parameters of obesity and sleep. A comparison of neuropeptide levels in subgroups with and without OSA was performed with the Mann–Whitney test, and the Kruskal–Wallis test was used in the comparison of neuropeptides levels according to the degree of obesity (based on BMI values). Results for which the p -value was below 0.05 were considered statistically significant.

Additionally, a multivariate model for the whole study group was constructed with mean ghrelin concentration as the dependent variable and BMI, AHI, gender, OSA diagnosis, and lowest and mean saturation as independent variables. Linear regression was used, and due to asymmetric distribution, ghrelin values were logarithmized before analysis. All algorithms led to the same univariate model with BMI as the independent variable.

3. Results

3.1. Characteristics of the Study Population

The study was conducted on 58 subjects (48 males and 10 females) aged between 34 and 75 years (mean = 54.5; SD = 11.2). Based on BMI values, it was noted that most patients (44 subjects, 75.9%) were obese, with class I, II, and III of obesity recognized in 17, 12, and 15 subjects, respectively. In other patients (14 subjects, 24.1%), overweight was diagnosed. The characteristics of the study group are presented in Table 1.

Table 1. Basic characteristics of the study group and subgroups, and comparison of polygraphic parameters between the OSA and control groups.

Items	Whole study Population (n = 58)		OSA Group (n = 46)		Control Group (n = 12)	
	mean ± SD	min–max	mean ± SD	min–max	mean ± SD	min–max
Gender [M/F]	48/10		41/5		7/5	
Age (years)	55 ± 11.2	34–75	55 ± 10.6	34–75	57 ± 8.7	46–72
Weight (kg)	105 ± 20.8	77–161	108 ± 21.1	78–161	93 ± 15.0	77–117
BMI (kg/m ²)	35 ± 6.4	25–50	36 ± 6.5	27–50	33 ± 5.5	25–43
WC (cm)	116 ± 12.8	96–147	117 ± 13.4	96–147	111 ± 9.0	99–122
AHI	38 ± 28.1	0.7–119.9	46 ± 25.8	13.2–119.9	6 ± 4.2	0.7–12.4
Snoring time (%)	14 ± 15.9	0–71	15 ± 16.3	0–71	8 ± 13.1	0–47
SpO ₂ mean (%)	91 ± 4.7	66–97	91 ± 5.2	66–97	93 ± 1.7	91–96
SpO ₂ lowest (%) ***	76 ± 11.9	49–91	74 ± 12.1	49–91	85 ± 4.9	72–90
Sleep time (min.)	449 ± 80	223–557	447 ± 84	223–557	456 ± 65	328–528
Sleep test time (min.)	484 ± 60	266–580	484 ± 63	266–580	485 ± 47	418–543

*** *p* < 0.001; AHI—apnea/hypopnea index; BMI—body mass index; F—female; M—male; OSA—obstructive sleep apnea; SpO₂ mean—value of mean saturation during sleep; SpO₂ lowest—value of lowest saturation during sleep; WC—waist circumference; SD—standard deviation.

The study group had comorbidities mainly related to the circulatory system and metabolic disorders. The most common were: arterial hypertension (47 patients, 81%); gastroesophageal reflux disease (40 patients, 69%); dyslipidemia (34 patients, 59%), carbohydrate metabolism disorders in 23 patients (40%) of which 14 patients (24%) had type 2 diabetes and 9 patients (16%) had pre-diabetes; coronary heart disease (16 patients, 28%); hyperuricemia (10 patients, 17%); and heart failure (4 patients; 7%). The participants in the study mainly used medications due cardiovascular diseases. These were drugs included in the following groups: beta blockers (37 patients); diuretics (32 patients), angiotensin-converting enzyme inhibitors (28 patients), and angiotensin receptor blockers (8 patients); calcium channel blockers (18 patients); doxazosin (6 patients); clonidine (3 patients); antiplatelet agent (acetylsalicylic acid and/or clopidogrel in 17 patients); anti-coagulant (warfarin or rivaroxaban in 7 patients); statin (22 patients); fibrate (9 patients).

3.2. Obstructive Sleep Apnea Assessment

Based on AHI values, OSA was diagnosed in 46 patients (79.3%)—severe in 31, moderate in 12, and mild in three patients. These patients were included in the OSA group. The remaining 12 patients served as the control group.

The anthropometric parameters did not differ significantly between subgroups except for weight. However, when only men were analyzed, the BMI and weight values were significantly higher in the OSA group than in the control group.

Among the evaluated polygraphic parameters, only SpO₂ lowest significantly differed between the OSA and control subgroups. The characteristics of the subgroups are presented in Table 1.

3.3. Neuropeptide Profile Evaluation

In the whole study group of patients with elevated BMI, similar patterns of nocturnal blood levels were observed for ghrelin and leptin, with median, minimum values at 01:00. The night profile for obestatin had almost the opposite pattern. The results of the neuropeptide determinations are presented in Figures 1–3.

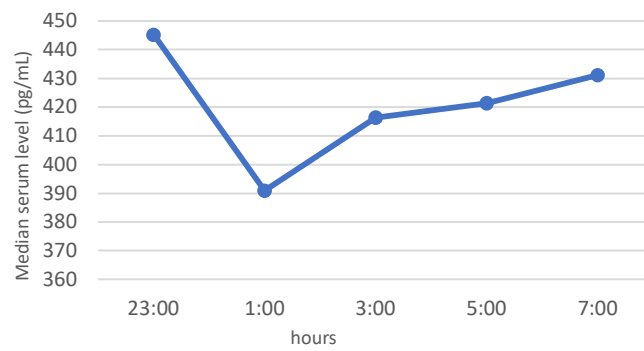


Figure 1. Night profile of ghrelin in the study group.

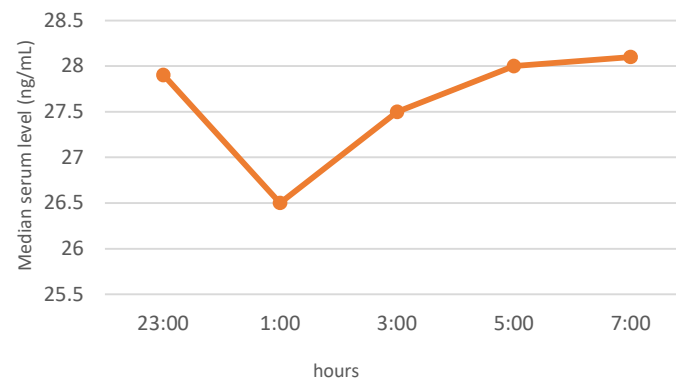


Figure 2. Night profile of leptin in the study group.

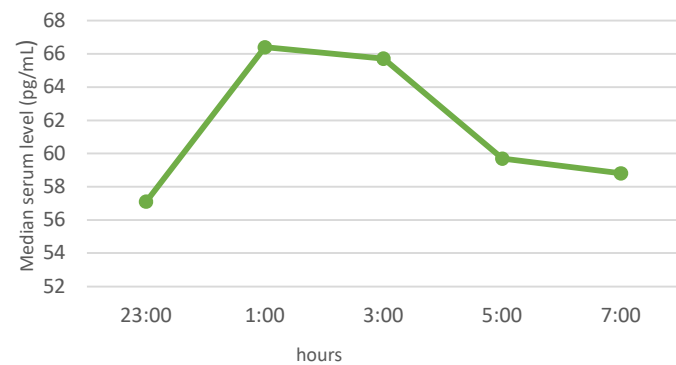


Figure 3. Night profile of obestatin in the study group.

3.4. Association of Anthropometric Measurements with Sleep Disorder Parameters

The group of patients with OSA comprised 36 (78%) patients with obesity and 10 (22%) patients with overweight. Evaluating the occurrence of OSA in the context of BMI values, it was noted that the highest proportion of OSA was noted in patients with BMI > 40 kg/m² (Table 2).

A statistically significant correlation was observed between anthropometric measurements (BMI and WC) and sleep disorder parameters (except for AHI) in the whole study population, and in the OSA group, no significant correlations were noted in the control group (Table 3).

Table 2. Occurrence of obstructive sleep apnea in patients with obesity or overweight.

	Overweight <i>n</i> = 14 (<i>n</i> ,%)	Obesity			Total <i>n</i> = 44 (<i>n</i> ,%)
		Class I <i>n</i> = 17 (<i>n</i> ,%)	Class II <i>n</i> = 12 (<i>n</i> ,%)	Class III <i>n</i> = 15 (<i>n</i> ,%)	
OSA group <i>n</i> = 46	10 (71%)	13 (76%)	9 (75%)	14 (93%)	36 (82%)
Control group <i>n</i> = 12	4 (29%)	4 (24%)	3 (25%)	1 (7%)	8 (18%)

OSA—obstructive sleep apnea.

Table 3. Correlation between parameters of sleep disorders and anthropometric measurements in patients with and without obstructive sleep apnea.

	OSA Group		Control Group	
	BMI	WC	BMI	WC
AHI	0.21	0.19	−0.56	−0.04
Snoring time (%)	0.31 **	0.30 **	−0.13	0.30
SpO ₂ mean (%)	−0.52 **	−0.53 **	−0.57	0.07
SpO ₂ lowest (%)	−0.41 **	−0.39 **	−0.04	0.24

** *p* < 0.05; BMI—body mass index; OSA—obstructive sleep apnea; SpO₂ mean—value of mean saturation during sleep; SpO₂ lowest—value of lowest saturation during sleep; WC—waist circumference.

3.5. Association of Gender and Anthropometric Measurements with Neuropeptide Levels

Among the evaluated neuropeptides, only ghrelin levels correlated with obesity parameters. In the OSA group, significant negative correlation was found between BMI and average median ghrelin level ($-0.32, p = 0.03$) and ghrelin levels at 23:00 ($-0.41, p = 0.005$) and at 01:00 ($-0.40, p = 0.007$), and also between WC and ghrelin levels at 23:00 ($-0.36, p = 0.01$) and at 01:00 ($-0.37, p = 0.01$). No significant correlation between these parameters was observed in the control group.

In subgroups of patients classified according to BMI, average median values of ghrelin and the majority of night ghrelin levels were highest in patients with overweight and lowest in patients with class II and III obesity (Figure 4). Statistically significant differences were noted between ghrelin values at 23:00 ($p = 0.002$), at 01:00 ($p = 0.02$), and at 03:00 ($p = 0.04$) and between average median values of ghrelin ($p = 0.01$).

No correlation between leptin or obestatin levels and anthropometric measurements was observed in the OSA group or in the control group.

The levels of neuropeptides were compared between males and females. Males had significantly lower levels of ghrelin than females (Me = 411; Range: 212–1928 vs. Me = 499; range: 407–861). However, after including gender in the regression analysis, it turned out to be an insignificant variable. The observed difference probably results from a significantly lower value of BMI and weight in the group of women participating in the study. No significant differences in the levels of obestatin or leptin depending on gender were found.

3.6. Association of Sleep Disorder Parameters with Neuropeptide Levels

The results of neuropeptide determinations were compared between the group with OSA and the control group in the context of the average median value (Table 4) and median values within the night profile. In the OSA group, the levels of ghrelin were lower than in the control group. However, the differences were statistically significant only for values at 05:00 and 07:00 (Figure 5). Levels of leptin in the OSA group were also lower than those in the control group (not statistically significant), but the profiles had a similar pattern (Figure 6). Profiles of obestatin in the OSA and in the control group were similar in pattern and in values (Figure 7).

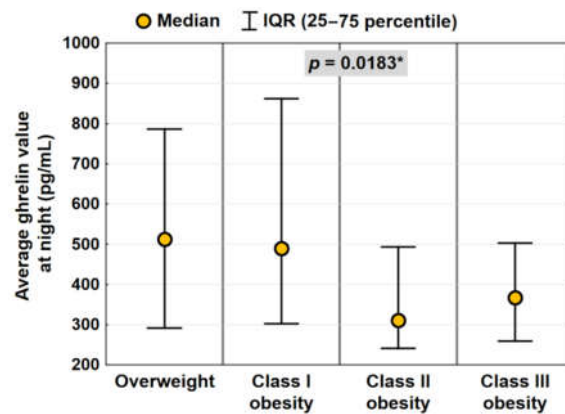


Figure 4. Night levels of ghrelin in subgroups classified according to BMI values (statistically significant correlation is marked using *). IQR—interquartile range.

Table 4. Average median values (and ranges) of appetite-regulating hormones in patients with and without obstructive sleep apnea. OSA—obstructive sleep apnea.

	OSA Group	Control Group
Ghrelin (pg/mL) $p = 0.05$	426.6 (211.5–1928.0)	496.2 (324.2–1147.1)
Leptin (ng/mL) $p = 0.19$	25.9 (16.5–44.8)	31.9 (21.5–37.1)
Obestatin (pg/mL) $p = 0.7$	61.9 (55.5–98.2)	61.6 (53.9–71.4)

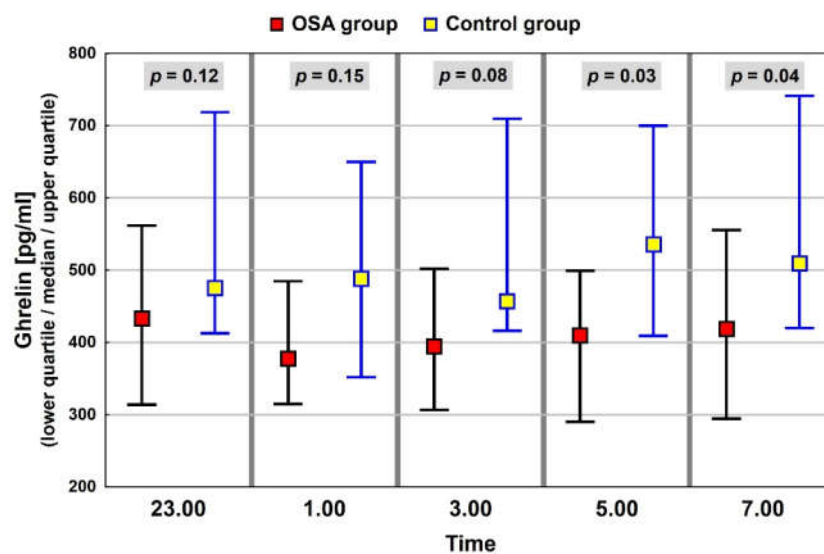


Figure 5. Night ghrelin values in groups of patients with and without OSA. The interquartile range (IQR) of neuropeptide concentrations is marked with black and blue lines.

In the next step, the correlation between neuropeptide levels and sleep parameters (AHI, snoring time, SpO₂ mean, SpO₂ lowest) was assessed. However, no significant correlation was found except for a weak correlation, near statistical significance, between the lowest saturation value during sleep and ghrelin levels at 23:00 and 01:00.

3.7. Multivariate Analysis of the Association between BMI, Sleep Disorder Parameters, and Ghrelin Levels

Multivariate analyses confirmed an association between ghrelin concentrations and BMI, and a lack of association between ghrelin levels and OSA diagnosis, gender, sleep time, and sleep disturbance parameters. The value of the coefficient of determination indicated that almost one-tenth of the variation in ghrelin concentration resulted from BMI

changes. The negative value of the regression coefficient demonstrates that the higher the BMI, the lower the ghrelin concentration (Table 5).

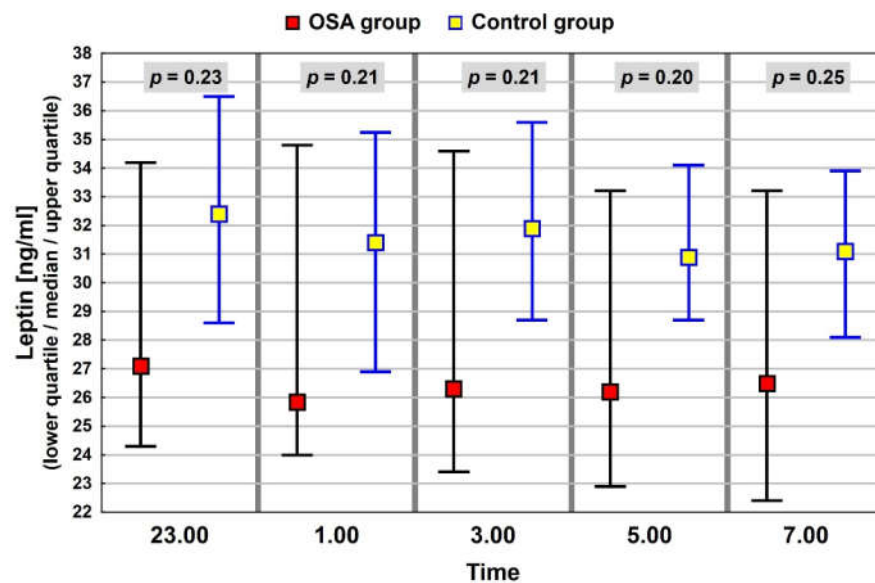


Figure 6. Night leptin values in groups of patients with and without OSA. The interquartile range (IQR) of neuropeptide concentrations is marked with black and blue lines.

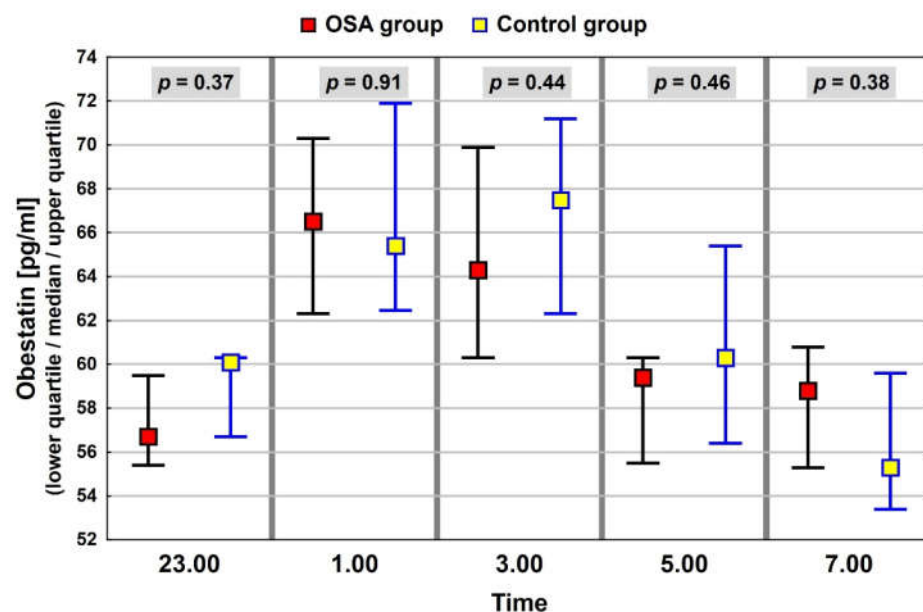


Figure 7. Night obestatin values in groups of patients with and without OSA. The interquartile range (IQR) of neuropeptide concentrations is marked with black and blue lines.

Table 5. Results of regression analysis.

Independent Variable	Logarithm of the Mean Ghrelin Concentration $R^2 = 9.7\%$, $F = 6.0$, $p = 0.0175^*$		
	B (95% CI)	p	β
BMI	-0.020 (-0.037, -0.004)	0.0175 *	-0.31

R^2 —coefficient of determination, BMI—body mass index, F—test statistic and p-value for significance of whole model, B—regression coefficient with 95% CI, p-value for significance of each regression coefficient, β —standardized regression coefficient (statistically significant correlation is marked using *).

4. Discussion

The relationship between obesity and sleep disorders was proven in many studies [10]; however, many issues still require explanation. One of them is the influence of OSA combined with obesity on levels of ghrelin, leptin, and obestatin, i.e., neuropeptides strongly related to body energy homeostasis. In order to assess this impact, we performed a study on a group of patients with elevated BMI (≥ 25 kg/m²) and OSA and compared results with a control group similar in terms of BMI but without OSA.

First, our outcomes confirmed the relationship between obesity and sleep-related breathing disorders because the majority (82%) of studied patients with obesity had OSA diagnosed. Moreover, OSA was diagnosed most frequently in patients with class III obesity, which is consistent with the assumption that more than half of the persons with obesity (especially III class) are affected by OSA [35,36]. In the studied patients with OSA, values of BMI and WC were higher and significantly correlated with saturation during sleep (negative correlation) and snoring time (positive correlation), in contrast to the control group with lower mean values of anthropometric parameters that did not correlate with sleeping disorder parameters.

Numerous studies addressed this topic, showing that habitual sleep duration below 7.7 h leads to an increase in BMI values and that the parameters of obesity, to a limited extent, allow the identification of patients at high risk of OSA and even predict the severity of breathing disorders during sleep [37,38].

The mechanism underlying the association between sleep and body weight is multifactorial; however, homeostatic control seems to play a key role. It involves increased hunger during sleep deprivation through changes in levels of leptin that suppresses appetite and ghrelin, a peptide that stimulates appetite [39–41]. Hence, alterations in these neuropeptide levels promote obesity, while obesity modifies the concentration of neuropeptides.

In people with normal weight, the levels of plasma ghrelin during the day show a pre-prandial increase and postprandial decrease, and at night the concentration increases, reaching the maximum at about 01:00–02:00, followed by a decline until morning awakening with a minimum value at 09:00 [14,42,43]. In turn, in subjects with obesity, ghrelin levels are lower than in normal-weight people, which may be explained by chronic excessive food intake that inhibits ghrelin secretion, or it may be associated with hyperinsulinemia, which is commonly found in obesity. It was proven that patterns of ghrelin and insulin secretion are reciprocal, especially after meals [14,44,45]. Interestingly, this lower level of ghrelin in patients with obesity does not lead to weight reduction. It may be influenced by the fact that in obesity, ghrelin, although decreased, displays blunted meal effects, i.e., the amplitude of pre- and post-prandial levels of ghrelin are low [45]. In obesity, the pattern of ghrelin secretion is also altered—the nocturnal increase is blunted or may not occur [45]. Alteration of the ghrelin night profile was also noted in our study conducted on patients with obesity or overweight. We did not observe a night increase in ghrelin, and we even noted a nadir in the ghrelin level at 01:00. The negative correlation between ghrelin and anthropometric parameters observed in our study confirmed the impact of obesity on ghrelin levels, which is in accordance with other studies [46,47].

Levels of neuropeptides may be affected not only by obesity but also by sleep disorders; however, available data concerning this issue are not consistent. This is probably due to variability in population characteristics and study design. Therefore, the results of a systematic review and meta-analysis are valuable, suggesting that reduction in sleep duration is associated only with ghrelin change, even though sleep deprivation is thought to impact both appetite-regulating hormones. Nevertheless, both qualitative and quantitative sleep disorders were generally associated with increased ghrelin levels [48]. Such results were observed in subjects with normal weight [37,49] but also—less frequently—in populations with elevated BMI [50]. Other studies indicated similar levels of ghrelin among patients with obesity, either with or without OSA [51,52]. In turn, in our research, ghrelin levels in patients with OSA were lower than values in the control group, but the differences reached statistical significance only for values at 05:00 and 07:00. However, the mean BMI values in

our studied groups were higher (about 36 kg/m² and 33 kg/m² in the OSA and control groups, respectively) than in the mentioned papers (30 kg/m² and 28 kg/m²), and this might have had an impact on the results.

As was mentioned, ghrelin levels correlated inversely with BMI, and the high BMI values in our study group were followed by low ghrelin concentrations. Hence, it may be assumed that the impact of obesity on the ghrelin level dominates over the impact of OSA (probably via insulin levels). This assumption is supported by the results of studies performed by Sánchez-de-la-Torre et al., who suggested that sleep apnea is not a determinant factor in ghrelin levels and that the hormone concentration is associated mainly with obesity. This study was conducted primarily on overweight and obese subjects with BMI close to those in our study (mean BMI 34 kg/m² and 32 kg/m²). They also observed that ghrelin levels in patients with OSA and obesity were lower than in obese controls and also significantly lower than in non-obese patients with OSA [18]. This may be explained by the fact that obesity contributes more to insulin resistance and chronic inflammation than OSA, so it decreases ghrelin levels more. Moreover, no correlation between ghrelin level and sleep disorder parameters was found in our study or in the cited study [18]. However, we noticed that in the OSA group, early morning values of ghrelin were lower than in the control group, and this prompted us to suppose that OSA may enhance the mechanism of ghrelin reduction related to obesity, and therefore it may contribute to overeating. This is because low levels of ghrelin, as well as blunted postprandial decline in ghrelin levels, lead to weaker stimulation of the reward or satiety centers in the brain, which is associated with binge-eating disorder [53,54]. Hence, the question arises of whether OSA treatment improves ghrelin levels and eating habits. The literature reports on the subject are inconclusive [19], but our results may provide a rationale for greater emphasis on the diagnosis and treatment of sleep disorders or the use of new drug classes (e.g., ghrelin antagonists/analogues) in the treatment of obesity.

Although the level of leptin is known to correlate with body weight, and to depend mainly on the amount of adipose tissue [25], in our study, no correlation between obesity parameters and leptin concentrations was found. It might be because we assessed BMI and WC, not body fat. In people with obesity, leptin values are generally higher (mainly due to increased adipocytes and leptin resistance), and the profile shows a peak at 02:00 [45]. We observed neither night elevation of leptin nor differences between leptin levels in groups of patients with and without OSA.

The available studies indicate that OSA either increases or has no effect on the values of leptin. In the previously quoted article by Mashaqi et al., the authors indicate greater importance of obesity and the amount of adipose tissue than the influence of OSA on leptin levels [19]. Similar conclusions were obtained in a comprehensive study by Arnardotir et al., which also found no deviations in the level of leptin in OSA [55]. In several other studies, higher values of leptin in OSA were observed [27,28]. This is explained by the theoretical consideration that hypoxia-related to OSA causes an increase in leptin, which in turn is supposed to enhance the respiratory response preventing hypercapnia and increasing neural compensatory mechanisms, minimizing upper airway collapse [56,57]. Our results do not support this theory, as no correlation between sleep parameters and leptin levels was found.

Obestatin is the least understood hormone of those analyzed in the study, and research is still being conducted to determine its significance in the body. Previous studies indicated lower obestatin levels in obese subjects than in lean controls [58]. In our study, no association between obestatin and anthropometric parameters was noted, but the study group was rather homogeneous in terms of BMI, and this fact may have influenced the lack of correlation. We also did not observe any association between obestatin levels and OSA, which is in accordance with the observations of other authors [27].

In summary, it can be said that our results confirm the relationship between obesity and sleep-disordered breathing. Both these disorders have an impact on ghrelin levels—parameters of obesity negatively correlate with hormone concentration, and OSA seems to

lower ghrelin values in the second half of the night. Therefore, OSA potentially exacerbates ghrelin disturbances associated with obesity and worsens eating disorders. No correlation was observed between leptin and obestatin levels and obesity parameters or OSA. However, further studies in this area are indicated.

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Article

Associations of Obstructive Sleep Apnea, Obestatin, Leptin, and Ghrelin with Gastroesophageal Reflux

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Abstract: Gastroesophageal reflux disease (GERD) is commonly observed in patients with obstructive sleep apnea (OSA). Hormonal disorders observed in OSA may be relevant in the development of GERD. The aim of the study was to assess the correlations between ghrelin, obestatin, leptin, and the intensity of GERD in patients with OSA. The study included 58 patients hospitalized due to clinical suspicion of sleep disorders during sleep. All patients underwent a sleep study, and blood samples were collected overnight for hormonal tests. Survey data concerning symptoms of GERD, gastroscopy, and esophageal pH monitoring results were included in the study. In patients with OSA, GERD was twice as common when compared to the group without OSA. Among subjects with severe sleep apnea (AHI > 30; $n = 31$; 53%), we observed lower ghrelin levels, especially in the second half of the night and in the morning ($p_{5.00} = 0.0207$; $p_{7.00} = 0.0344$); the presence of OSA had no effect on obestatin and leptin levels. No significant differences in hormonal levels were observed between the groups depending on the diagnosis of GERD. However, correlations of ghrelin levels with the severity of esophagitis, leptin and ghrelin levels with the severity of GERD symptoms, and leptin levels with lower esophageal pH were found. GERD is more frequent among patients with OSA. In both GERD and OSA, deviations were observed in the levels of ghrelin and leptin. However, our analysis demonstrates that the relationship between OSA and GERD does not result from these disorders.

Keywords: gastroesophageal reflux; sleep apnea; ghrelin; obestatin; leptin



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1. Introduction

Gastroesophageal reflux disease (GERD) is commonly observed in patients with obstructive sleep apnea (OSA) [1–5]. This disease is defined as a condition in which the stomach contents flow back into the esophagus, causing clinical symptoms and leading to the development of complications. Gastroesophageal reflux disease is diagnosed based on the clinical presentation and supporting examinations such as esophageal impedance–pH monitoring and gastroscopy [6]. Obstructive sleep apnea is characterized by the presence of multiple obstructions on the level of the upper airways and leads to apnea, waking up, and loss of effective sleep [7]. The main complaints reported by patients included chronic fatigue, drowsiness and fatigue after a night's rest, morning headaches, nocturia, excessive sweating, concentration and memory disorders, decreased libido, and depressed mood [8–12]. Snoring, which often occurs in OSA, is an insensitive indicator of the disease; however, when observed with apnea, it is highly indicative of OSA [13]. Due to the heterogeneous course of the disease and the low sensitivity of symptoms in the prediction of OSA, not every patient is referred for sleep diagnostics [14]. Therefore, tools

were developed to identify patients at high risk for OSA. Some questionnaires in use include the Epworth Sleepiness Scale (ESS), Berlin Questionnaire (BQ), and Stop-Bang and Bang Questionnaires [7,9,10,15]. Assessment of upper respiratory tract morphology is also performed using the Modified Mallampati Score (MMP) and Upper Airway Volume measurement in cone-beam computed tomography (CBCT) [16]. Moreover, devices that monitor respiratory parameters, most often blood saturation or airflow through the respiratory tract, are also used in screening [7,17]. As a result, the qualification for more advanced but difficult to access and more expensive diagnostic methods is more effective. Diagnosis of OSA is based on results of a polysomnography (PSG). In patients without serious comorbidities and with symptoms indicating an increased risk of OSA, a home sleep apnea test (HSAT) performed with a portable monitor (PM) can be used to diagnose OSA [7,15,17]. Polysomnography includes the use of electroencephalogram (EEG), electrooculogram (EOG), and electrocardiogram (ECG). Additionally, airflow, oxygen saturation, respiratory effort, chin electromyogram, and heart rate are monitored. Monitoring of body position and lower limb movements is also recommended. In the home sleep apnea test, PM monitors at least airflow, respiratory performance, and blood oxygenation. In cases of diagnostic difficulties during the HSAT, PSG is recommended [7]. Obstructive sleep apnea is accompanied by numerous diseases, the most important of which are those involving the circulatory system [18]. In OSA, arterial hypertension and arrhythmias are more common, and the risk of coronary artery disease, sudden cardiac death, and stroke is increased [19–21]. Combined with excessive sleepiness and decreased concentration, this leads to a greater occurrence of traffic accidents [8]. Sleep apnea leads to the development of insulin resistance and type 2 diabetes and can be a cause of depression [8,18,22]. Moreover, sleep disorders have a strong impact on gastrointestinal diseases [23]. There is a strong relationship between OSA and GERD. It is estimated that up to 40–60% of people with OSA also suffer from GERD, which is often resistant to treatment and presents intense nocturnal symptoms, further reducing the quality of sleep [3,24,25]. Sleep disorders worsen the course of peptic ulcer disease (PUD), irritable bowel syndrome (IBS), functional dyspepsia (FD), and inflammatory bowel disease (IBD) [23,26–28]. In addition, many gastrointestinal diseases influence the sleep–wake cycle and sleep quality, especially in people with liver disease accompanied by hepatic encephalopathy, exacerbation of Crohn’s disease, or in the course of digestive tract functional disorders (IBS, FD) [26,27,29–32].

Motility disorders of the lower esophageal sphincter play a crucial role in the development of GERD in OSA patients [33,34]. The lack of association of apnea with reflux episodes and the beneficial effect of CPAP (Continuous Positive Airway Pressure) therapy indicate that hypoxia, inflammation, or other hormonal disorders might have a role in the development of GERD [34–36]. This can potentially result from disturbances in ghrelin, obestatin, and leptin concentrations, which are observed in OSA. This acts to worsen esophageal motility, LES dysfunction, or decrease the rate of gastric emptying, which may increase the likelihood of developing GERD.

Ghrelin and obestatin are products of the GHRL gene, synthesized mainly within the gastrointestinal tract. Functions of ghrelin include the stimulation of appetite and improvement of gastrointestinal motility. Furthermore, ghrelin can reduce inflammatory processes in the body. The level of ghrelin has considerable daily variability, and its secretion into the blood is of a pulsatile character, associated with the consumption of meals and the sleep–wake rhythm [37–41]. The physiological role of obestatin has not yet been fully elucidated due to, among other things, difficulties with the identification of the receptor on which it acts. It is presumed that obestatin affects glucose and lipid metabolism, decreases the inflammatory state, and exerts a beneficial effect on the survival of many cell types through the regulation of proliferative processes and inhibition of apoptosis [42]. Leptin is a hormone that is synthesized in adipose tissue. Through the inhibition of appetite, increased metabolism, and reduction in the amount of fatty tissue, leptin acts to regulate body weight. Chronically high leptin levels in obesity result in decreased sensitivity and loss of appetite inhibition [43]. Results from studies regarding

the levels of ghrelin, leptin, and obestatin in OSA differ. In the majority of studies, elevated ghrelin and leptin levels were observed; however, the conclusions were formulated based on morning measurements [44–47]. In two available reports assessing the daily profile in OSA patients, greater leptin levels were observed, while significant deviations with respect to ghrelin and obestatin were not seen [46,48]. In the few available studies evaluating ghrelin and leptin levels in GERD, divergent results have also been noted. In some of these studies, lower ghrelin levels were observed in GERD, along with a decrease in the number of reflux episodes after administration of ghrelin. However, in other studies, either no significant deviations were found, or there was a clear tendency towards greater ghrelin levels in GERD. [49–54]. In the case of leptin, the majority of studies have demonstrated its greater levels in GERD [51,55]; however, there are no known studies evaluating the levels of obestatin in GERD.

Conclusions from these observations differ. Therefore, in our study, our aim was to determine whether the influence of OSA on the concentrations of obestatin, ghrelin, and leptin is important in the development of GERD. As a result, we hope to shed some light on the pathomechanisms linking OSA to GERD and to identify potential novel therapies for GERD.

2. Materials and Methods

The aim of the study was to assess the correlations between ghrelin, obestatin, and leptin and the intensity of GERD in patients with OSA.

2.1. Study Group

The study included patients hospitalized due to clinical suspicion of sleep breathing disorders. The majority of patients presented with snoring and pauses in breathing during sleep, excessive daytime sleepiness and chronic fatigue, drug-resistant hypertension, and cardiac arrhythmias. The exclusion criteria were: taking medications that disturbed sleep (sedatives and hypnotics) and GERD assessment (proton pump inhibitors, histamine receptor blockers, alkali); central sleep apnea; previous significant gastrointestinal surgery (gastrectomy, bowel resection); hypothyroidism, exacerbation of heart failure or COPD; or a history of stroke. The study was approved by the Ethics Committee at the Institute of Rural Health (Decision No. 6/2014). All patients signed an informed consent form prior to participating in the study. The study group consisted of 46 patients with OSA, while the control group consisted of 12 subjects in whom OSA was excluded. Sleep apnea was diagnosed when the AHI (apnea/hypopnea index) was at least 15 or at least 5 if clinical symptoms of OSA were present [7]. Survey data were collected concerning the clinical symptoms of GERD, sleepiness was assessed according to the Epworth Sleepiness Scale (ESS) [5,7], and blood was collected during the night. If indicated, patients were referred to the hospital gastroenterology outpatient department. Results obtained in the course of further diagnostics (gastroscopy and 24 h pH-metry) were included in the analysis. The diagnosis of GERD was made using the Lyon consensus definitions [6].

2.2. Sleep Examination

The overnight sleep study was performed according to current guidelines [7]. Sleep assessment was carried out based on the polygraph test (Type III acc. to AASM) using Embletta MPR PG (formerly Embla; currently Natus; Pleasanton CA, USA). Twelve patients underwent polysomnography (Type II acc. to AASM) using EmblaS4500 devices (formerly Embla; currently Natus; Pleasanton CA, USA) and RemLogic diagnostic software (formerly Embla; currently Natus; Pleasanton CA, USA). Classification of respiratory events and assessment of sleep apnea severity were performed by a sleep physician using the standard criteria defined by the guidelines of the American Academy of Sleep Medicine [7].

2.3. Questionnaire for Assessment of GERD Complaints

The intensity of complaints related to GERD was assessed based on a modified version of the questionnaire, which was used in a previous study (available online at Supplementary data) [56]. This modified questionnaire contained items concerning an overall assessment of the intensity of GERD-related complaints (within the range 0–10 points) and questions pertaining to typical symptoms of GERD, with a distinction between those occurring during the day (within the range 0–40 points) and those occurring at night (within the scope 0–12 points). Regarding daytime complaints, the questions concerned their intensity and the frequency of a burning sensation in the chest (after meals, while lying down, or bending over); occurrence of burping or the feeling of stomach contents backing up into the esophagus accompanied by a sour or bitter taste in the mouth; and the sensation of difficulty swallowing (dysphagia). With respect to nighttime symptoms, patients were asked about the occurrence of GERD-related problems while falling asleep or waking up and the frequency of a sour or bitter taste in the mouth after a night's sleep. The frequency of symptoms was classified according to a point scale: 0—when the symptoms did not occur; 1—when the symptoms occurred once or twice during the last month; 2—when the symptoms occurred no more than once a week; 3—several times a week; 4—several times a day. The intensity of complaints was assessed as follows: 1 point when complaints were mild; 2 points when they were clearly experienced; 3 points when complaints were troublesome; 4 points when complaints were difficult to tolerate. All questionnaires were collected from the patients by the primary investigator (P.P).

2.4. Gastroscopy and 24 h pH-Metry

To be included into our analysis, gastroscopy and pH-metry must have been performed prior to introduction of OSA treatment. All gastroscopic examinations were performed by an experienced endoscopist (systems: Fujifilm, Japan; Pentax, Japan) (R.F). For the purpose of statistical analyses, the intensity of inflammatory changes in the esophagus was ascribed a numerical value as follows: 0 for a normal result and from 1 to 4 for the subsequent inflammatory grades of the esophagus evaluated according to the Los Angeles classification [6]. pH-metry was performed using the ComforTEC Plus- PHNS single-channel probe (Sandhill Scientific, Highlands Ranch, CO, USA) placed 5 cm above the lower esophageal sphincter and REF: Z07-2000-A, SN: H109007C recorder (Sandhill Scientific, USA). After the performance of automatic analysis, the record was assessed by an experienced physician (M.K).

2.5. Determination of Total Ghrelin, Leptin, and Obestatin Levels

Blood was collected through a catheter inserted into the peripheral vein on the day following the sleep study at the following times: 23:00, 01:00, 03:00, 05:00, and 07:00. Blood sampling was performed at the patient's bedside and did not require waking up the patient. Patients completed supper at least 3 h prior to collecting the first sample, and the last blood sample was collected more than 60 min before breakfast. In one patient, blood was collected only at 23:00 because the patient did not consent to collection of subsequent samples. Blood was collected using EDTA tubes, then centrifuged for 20 min at 3000 revolutions/min and a temperature of 4 °C (centrifuge MPW 260 R with angular rotor, MPW MED. INSTRUMENTS, Poland). Blood serum was transferred into Eppendorf tubes, frozen, and stored at a temperature of −80 °C until the measurements were performed (P.P). Hormonal measurements were carried out using commercially available radioimmunoassays (RIA): total ghrelin—Ghrelin (Human) RIA Kit (EMD Millipore's Corp. Inc., St. Louis, MI, USA); leptin—Leptin (Human) RIA Kit (EMD Millipore's Corp. Inc., St. Louis, MI, USA); obestatin—RIA Obestatin (Human, Monkey) RIA Kit (Phoenix Pharmaceuticals, Inc., Burlingame, CA, USA) (J.W).

2.6. Statistical Analysis

Statistical analyses were performed using the software package Statistica (data analysis software system), version 13 (TIBCO Software Inc. 2017; Palo Alto, CA, USA). The normality of the distribution of laboratory measurements was tested using the Shapiro-Wilk test. Because most of the features did not have a normal distribution, positional statistics (median, interquartile range—IQR) were mainly used to describe the results. Normality of the distribution was not observed, and this required the use of nonparametric statistical tests. Correlations between variables were calculated by means of Spearman's rank correlation coefficient, while in order to assess differences between the two independent groups of patients, the Mann-Whitney U test was applied.

3. Results

3.1. Characteristics of the Study Group

The study included 58 patients (48 males and 10 females) aged 34–75 (mean = 54.5; Me = 56; s = 11.1). The patients were divided into two groups: one with the diagnosis of OSA (N = 46, including 5 females) and a control group (N = 12, including 5 females). A majority of the patients had an excessive body weight: 44 were obese (75.9%), while 14 were overweight (24.1%). The mean BMI was 34.8 kg/m², while BMI values remained within the range of 25.1–49.7 kg/m². Table 1 presents the basic characteristics of the study population.

Table 1. Basic characteristics of the study population, severity of GERD symptoms, and polysomnographic parameters' distribution and comparison of variables between the test and control groups.

	OSA Group (n = 46) Mean ± Std. Dev.	Control Group (n = 12) Mean ± Std. Dev.	Both (n = 58) Mean ± Std. Dev.
Sex (M:F)	41:5	7:5	48:10
Age (year)	54.8 ± 10.6	56.5 ± 8.7	55.2 ± 10.2
Height (m)	173.9 ± 7.4	168.8 ± 13.2	172.8 ± 9.0
Weight (kg)	108.1 ± 21.1	92.5 ± 15.0	104.8 ± 20.8
BMI (kg/m ²)	35.7 ± 6.5	32.7 ± 5.5	35.1 ± 6.4
Waist circumference	116.7 ± 13.4	111.0 ± 9.0	115.5 ± 12.8
GERD symptoms day (p = 0.3895)	11.4 ± 9.3	14.4 ± 9.2	12.1 ± 9.2
GERD symptoms night (p = 0.8637)	2.8 ± 3.0	2.7 ± 2.4	2.8 ± 2.9
GERD symptoms overall (p = 0.4416)	14.3 ± 11.7	17.1 ± 11.4	14.9 ± 11.6
ESS (p = 0.9209)	10.7 ± 5.2	11.3 ± 4.5	10.8 ± 5.0
AHI (p = x)	45.9 ± 25.8	6.3 ± 4.2	37.7 ± 28.1
Snoring time (p = 0.0744)	15.0 ± 16.3	7.8 ± 13.1	13.5 ± 15.9
SpO ₂ mean (p = 0.1693)	90.6 ± 5.2	93.0 ± 1.7	91.1 ± 4.7
SpO ₂ lowest (p < 0.001)	73.9 ± 12.1	85.4 ± 4.9	76.3 ± 11.9

3.2. GERD and ESS Questionnaires, Outcomes of the Sleep Study and Hormonal Measurements

No differences in the intensity of reflux symptoms were observed between the study and control groups. Additionally, no difference was noted in the level of sleepiness when evaluated according to the ESS score. In the group with OSA, a significantly lower value of minimum saturation during sleep was observed (73.9% vs. 85.1%; p < 0.001) along with a longer duration of snoring (Table 1). Table 2 presents the distribution of ghrelin, obestatin, and leptin levels. For technical reasons, the measurements of leptin and obestatin were performed in a smaller group of patients.

Table 2. Distribution of ghrelin, leptin and, obestatin in the study group.

Laboratory Parameters	n	Mean	Median	IQR	Min	Max
Ghrelin at 23 (pg/mL)	58	509.1	445.2	244.9	240.2	2050.9
Ghrelin at 1 (pg/mL)	57	466.1	390.9	202.9	205.7	1762.4
Ghrelin at 3 (pg/mL)	57	476.0	416.3	193.6	191.5	2133.1
Ghrelin at 5 (pg/mL)	57	464.4	421.4	214.5	197.4	1798.4
Ghrelin at 7 (pg/mL)	57	490.8	431.1	247.9	188.0	1895.4
Ghrelin (mean) (pg/mL)	58	478.1	428.8	231.1	211.5	1928.0
Leptin at 23 (ng/mL)	40	30.2	27.9	12.2	17.9	48.7
Leptin at 1 (ng/mL)	41	29.1	26.5	10.7	16.5	43.2
Leptin at 3 (ng/mL)	41	29.5	27.5	10.8	15.9	47.7
Leptin at 5 (ng/mL)	40	28.9	28.0	9.6	16.0	44.2
Leptin at 7 (ng/mL)	41	28.7	28.1	10.7	16.2	44.1
Leptin (mean) (ng/mL)	42	29.2	27	10.3	17	45
Obestatin at 23 (pg/mL)	40	58.6	57.1	4.8	51.3	72.3
Obestatin at 1 (pg/mL)	41	67.9	66.4	8.0	55.4	89.4
Obestatin at 3 (pg/mL)	41	66.2	65.7	9.6	53.5	90.3
Obestatin at 5 (pg/mL)	39	59.8	59.7	5.6	50.9	70.2
Obestatin at 7 (pg/mL)	40	58.7	58.8	5.3	50.9	70.4
Obestatin (mean) (pg/mL)	42	64.1	61.9	5.5	53.9	98.2

3.3. Gastroscopy and pH-Metry

Gastroscopy was performed in 27 patients. Inflammatory changes in the esophagus were observed in the majority of cases and were graded according to the Los Angeles classification. Grade A changes were seen in 22 patients, Grade B changes were seen in 7 patients, Grade C changes were seen in 1 patient, while no Grade D lesions were observed. Furthermore, in two patients, no inflammatory lesions were found [6]. PH-metry was performed in 23 patients; Table 3 presents the distribution of the variables.

Table 3. Distribution of esophageal pH monitoring results.

Parameters from pH-Metry	n	Mean	Me	IQR	Min	Max
De Meester index	23	27.8	15.1	30.2	1.7	136.4
De Meester index (post-meal)	23	9.8	7.5	10.5	1.5	37
GER episodes—recumbent	22	34.5	10	37.0	0	250
GER episodes—24 h	22	136.1	107	159.0	7	570
Mean pH (night)	23	6.4	6.5	0.9	4.3	8.1
Mean pH—24 h	23	6.2	6.2	0.8	5.0	7.2
Esophageal clearance time	22	37.0	35.5	24.0	8	91
Esophageal clearance time—recumbent	22	31.7	22.5	35.0	0	138
Longest GER episode	23	13.7	4.9		0.3	59.3

Correlations were investigated between the severity of esophageal inflammation, the symptoms of GERD, and results of pH-metry. Correlations near the level of statistical significance were found between the severity of esophageal inflammation, the symptoms of GERD, the DeMeester index, esophageal acid clearance time, and duration of the longest reflux episode (Table 4) [6].

Table 4. Correlations of esophagitis severity with GERD symptoms and esophageal pH monitoring parameters (statistically significant correlations, where $p < 0.05$, are marked using *).

GERD Symptoms and Parameters from pH-metry	The Severity of Inflammatory Changes in the Esophagus–Gastroscopy Assessment
GERD symptoms—day	0.42 ($p = 0.0172$ *)
GERD symptoms—night	0.07 ($p = 0.7034$)
GERD symptoms—overall	0.33 ($p = 0.0692$)
De Meester index	0.38 ($p = 0.0721$)
De Meester index (post-meal)	0.40 ($p = 0.0580$)
GER episodes—recumbent	0.11 ($p = 0.6258$)
GER episodes 24 h	0.28 ($p = 0.1994$)
Mean pH—night	−0.01 ($p = 0.9559$)
Mean pH—24 h	−0.33 ($p = 0.1234$)
Esophageal clearance time	0.37 ($p = 0.0858$)
Esophageal clearance time—recumbent	0.42 ($p = 0.0528$)
Longest GER episode	0.38 ($p = 0.0700$)

3.4. OSA and Gastroesophageal Reflux Disease

In the OSA group, the diagnosis of GERD was confirmed in 35 (76.1%) patients, whereas in the control group, GERD was confirmed in 5 (38.5%) patients. Correlations were investigated between sleep parameters and the severity of reflux symptoms as assessed via questionnaires. The only significant correlation was observed in the study group and concerned the AHI values and symptoms of GERD during the day ($r_s = 0.31$; $p = 0.0332$); however, the correlation between AHI and symptoms of reflux during the night was near the level of statistical significance ($r_s = 0.25$; $p = 0.0908$). The correlation between the results of pH-metry and parameters of the sleep study was also examined. Correlations were found between the mean esophageal acid clearance time (after a reflux episode) and the mean ($r_s = -0.55$; $p = 0.0084$) and minimum ($r_s = -0.41$; $p = 0.059$) saturation at sleep, as well as between the duration of snoring and DeMeester score after meals ($r_s = 0.39$; $p = 0.0657$). No relationships were observed between sleep parameters and the severity of esophageal inflammatory lesions as assessed via gastroscopy.

3.5. OSA and Levels of Ghrelin, Leptin, and Obestatin

Hormonal levels were compared (ghrelin, leptin, and obestatin) between patients with AHI > 30 (31 patients, 53%) and patients with AHI ≤ 30. The lowest ghrelin levels were noted in the group with severe sleep apnea, which were statistically significant for measurements performed at 05:00 and 07:00; however, no statistically significant differences were observed in the levels of obestatin and leptin (Figure 1; Table 5).

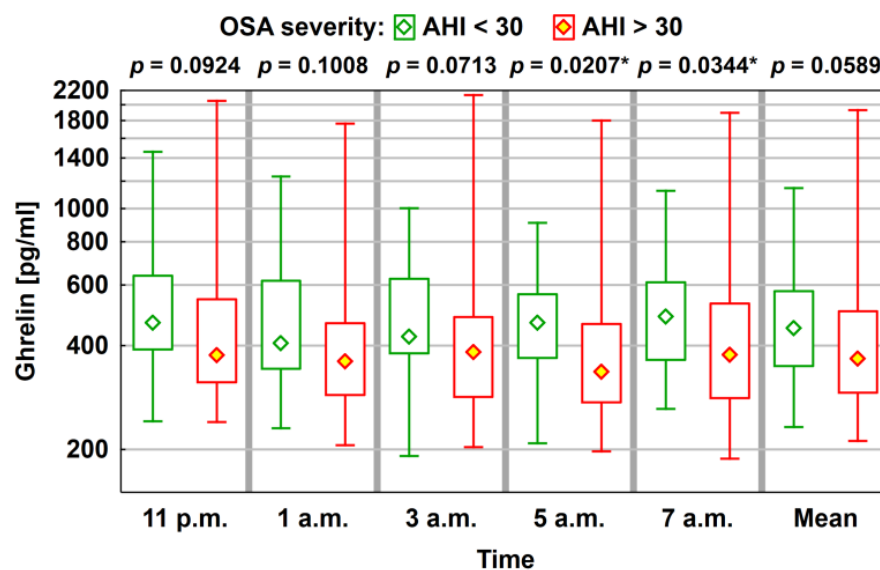


Figure 1. Average level (median) of ghrelin concentration (median) with a typical range of variability (lower and upper quartile) and the total range of variation (statistically significant correlations, where $p < 0.05$, are marked using *).

Table 5. Comparison of ghrelin, obestatin, and leptin levels depending on the severity of OSA (statistically significant correlations, where $p < 0.05$, are marked using *).

Laboratory Parameters	OSA Severity						p
	AHI ≤ 30			AHI > 30			
	Mean	Median	IQR	Mean	Median	IQR	
Ghrelin at 23 (pg/mL)	544.6	469.2	249.2	484.5	374.6	232.2	0.0924
Ghrelin at 1 (pg/mL)	509.2	431.7	273.7	432.7	359.5	176.9	0.1008
Ghrelin at 3 (pg/mL)	501.2	434.8	245.3	457.6	382.3	200.0	0.0713
Ghrelin at 5 (pg/mL)	496.6	482.5	195.0	440.2	336.1	188.1	0.0207 *
Ghrelin at 7 (pg/mL)	531.8	494.4	218.4	462.6	376.5	247.4	0.0344 *
Ghrelin (mean) (pg/mL)	508.7	463.8	232.1	455.5	366.7	211.2	0.0589
Leptin at 23 (ng/mL)	29.6	28.3	9.7	30.4	27.6	14.4	0.9445
Leptin at 1 (ng/mL)	29.2	26.5	9.1	28.8	26.1	11.3	0.7455
Leptin at 3 (ng/mL)	29.6	28.7	9.9	29.1	26.9	11.2	0.7049
Leptin at 5 (ng/mL)	28.7	28.1	8.9	28.9	27.1	9.3	0.8129
Leptin at 7 (ng/mL)	28.4	28.6	10.4	28.6	27.3	11.1	0.9464
Leptin (mean) (ng/mL)	29.1	28	10.3	29.0	27	11.3	0.8864
Obestatin at 23 (pg/mL)	58.4	58.9	4.7	58.3	56.7	4.4	0.5489
Obestatin at 1 (pg/mL)	68.5	67.6	6.0	67.1	66.4	9.1	0.5334
Obestatin at 3 (pg/mL)	66.4	66.6	9.8	65.9	64.3	9.6	0.8711
Obestatin at 5 (pg/mL)	59.8	59.6	5.7	59.7	59.6	5.2	0.8966
Obestatin at 7 (pg/mL)	58.0	57.6	5.5	59.0	59.1	6.2	0.6061
Obestatin (mean) (pg/mL)	62.0	61.6	5.4	65.5	62.1	5.9	0.3829

Analysis of the relationships between sleep parameters and the results of hormonal measurements indicated a correlation between the mean saturation during sleep and the level of obestatin at 03:00 ($r_s = -0.29$; $p = 0.0631$). In addition, together with an increase in the minimal saturation value during sleep, a tendency was observed towards greater levels of total ghrelin at 23:00 and 01:00 ($r_{s\ 23.00} = 0.25$; $p_{23.00} = 0.0561$; $r_{s\ 1.00} = 0.26$; $p_{1.00} = 0.0509$).

3.6. GERD and Levels of Ghrelin, Obestatin, and Leptin

No significant difference in the average level of ghrelin, obestatin, and leptin was observed between the group with GERD (N = 40) and the group without GERD (N = 18). However, a tendency towards greater values of ghrelin was found, together with greater severity of inflammatory changes in the esophagus. When divided into two groups, depending on the grade of esophageal lesions, significantly greater ghrelin values were noted in the group with more severe esophageal inflammatory changes (Figure 2; Table 6).

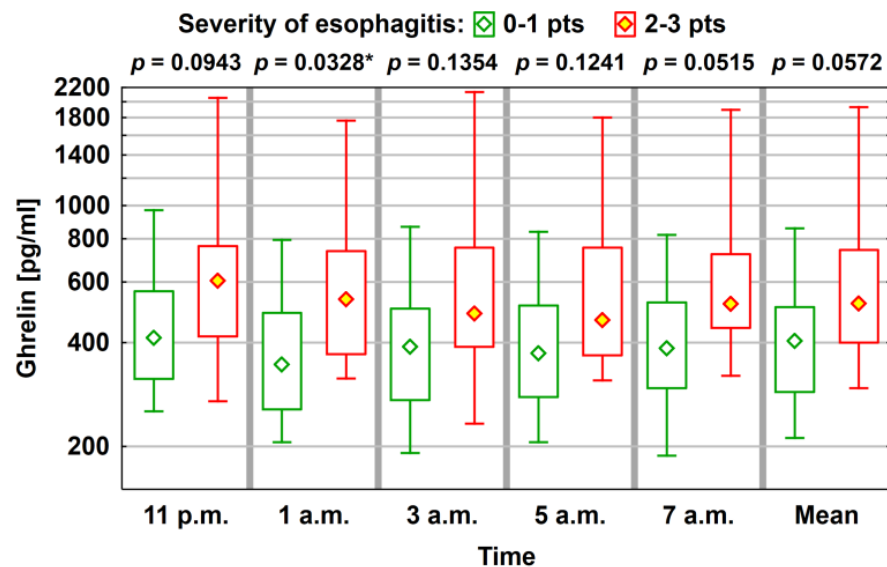


Figure 2. Average level (median) of ghrelin concentration with a typical range of variability (lower and upper quartile) and the total range of variation (statistically significant correlations, where $p < 0.05$, are marked using *).

Analysis of relationships between the intensity of GERD clinical symptoms (based on questionnaires) and hormonal levels in the whole group did not show any significant differences, whereas, in the group of patients with GERD, significant correlations were found between the intensity of reflux symptoms and the levels of leptin and ghrelin (Table 7).

We analyzed the relationships between hormonal levels and parameters from pH-metry. Statistically significant correlations were observed between leptin levels and parameters from pH-metry. Furthermore, we noted a significant correlation between mean esophageal pH (at nighttime and during the whole day) and the mean esophageal acid clearance time in a recumbent position (Table 8).

Table 6. Comparison of ghrelin, obestatin, and leptin levels depending on the severity of esophagitis (statistically significant correlations, where $p < 0.05$, are marked using *).

Laboratory Parameters	The Severity of Inflammatory Changes in the Esophagus–Gastroscopy Assessment						<i>p</i>
	0–1 pts (N = 24)			2–3 pts (N = 8)			
	Mean	Median	IQR	Mean	Median	IQR	
Ghrelin at 23 (pg/mL)	452.7	412.1	250.4	735.9	604.0	345.5	0.0943
Ghrelin at 1 (pg/mL)	391.2	345.0	231.1	670.1	534.6	366.2	0.0328 *
Ghrelin at 3 (pg/mL)	413.3	388.6	229.0	702.9	485.3	364.9	0.1354
Ghrelin at 5 (pg/mL)	404.1	372.4	234.4	660.5	464.5	387.4	0.1241
Ghrelin at 7 (pg/mL)	423.3	384.4	227.1	697.3	518.0	281.7	0.0515
Ghrelin (mean) (pg/mL)	416.9	404.1	220.1	693.3	518.5	342.0	0.0572
Leptin at 23 (ng/mL)	32.1	30.0	18.0	30.0	28.3	7.3	0.9635
Leptin at 1 (ng/mL)	29.6	26.3	10.8	28.7	26.9	6.0	0.9023
Leptin at 3 (ng/mL)	29.8	24.9	13.0	29.2	28.1	5.6	0.7120
Leptin at 5 (ng/mL)	29.8	28.7	12.8	28.8	28.1	4.3	0.9635
Leptin at 7 (ng/mL)	30.2	31.1	9.6	29.2	29.3	4.4	0.6977
Leptin (mean) (ng/mL)	30.1	26.5	13.4	29.3	28	5.5	0.7743
Obestatin at 23 (pg/mL)	59.0	56.6	7.0	59.6	60.2	5.6	0.6167
Obestatin at 1 (pg/mL)	71.0	69.5	9.0	68.6	68.9	3.2	0.6521
Obestatin at 3 (pg/mL)	67.6	66.6	8.7	65.7	66.4	7.3	0.8375
Obestatin at 5 (pg/mL)	60.9	59.6	9.6	60.0	60.0	0.4	0.7505
Obestatin at 7 (pg/mL)	59.8	59.3	8.4	58.6	59.8	3.1	0.8916
Obestatin (mean) (pg/mL)	65.7	62.5	9.2	62.5	62.9	2.0	0.8375

Table 7. Correlations between ghrelin, leptin, and obestatin levels and the severity of GERD symptoms—group diagnosed with GERD (statistically significant correlations, where $p < 0.05$, are marked using *).

Laboratory Parameters	Severity of GERD Symptoms		
	DAY	NIGHT	OVERALL
Ghrelin at 23 (pg/mL)	0.31 ($p = 0.0537$)	0.10 ($p = 0.5263$)	0.27 ($p = 0.0902$)
Ghrelin at 1 (pg/mL)	0.29 ($p = 0.0742$)	0.05 ($p = 0.7569$)	0.23 ($p = 0.1453$)
Ghrelin at 3 (pg/mL)	0.24 ($p = 0.1334$)	0.14 ($p = 0.3824$)	0.23 ($p = 0.1592$)
Ghrelin at 5 (pg/mL)	0.29 ($p = 0.0655$)	0.14 ($p = 0.3938$)	0.26 ($p = 0.0985$)
Ghrelin at 7 (pg/mL)	0.28 ($p = 0.0838$)	0.02 ($p = 0.9086$)	0.21 ($p = 0.1858$)
Ghrelin (mean) (pg/mL)	0.30 ($p = 0.0634$)	0.09 ($p = 0.5712$)	0.25 ($p = 0.1156$)
Leptin at 23 (ng/mL)	0.35 ($p = 0.0758$)	0.30 ($p = 0.1336$)	0.39 ($p = 0.0467$ *)
Leptin at 1 (ng/mL)	0.37 ($p = 0.0517$)	0.30 ($p = 0.1275$)	0.39 ($p = 0.0384$ *)
Leptin at 3 (ng/mL)	0.36 ($p = 0.0589$)	0.29 ($p = 0.1305$)	0.39 ($p = 0.0390$ *)
Leptin at 5 (ng/mL)	0.39 ($p = 0.0423$ *)	0.26 ($p = 0.1878$)	0.40 ($p = 0.0390$ *)
Leptin at 7 (ng/mL)	0.25 ($p = 0.2039$)	0.23 ($p = 0.2377$)	0.27 ($p = 0.1656$)
Leptin (mean) (ng/mL)	0.36 ($p = 0.0519$)	0.27 ($p = 0.1553$)	0.38 ($p = 0.0412$ *)
Obestatin at 23 (pg/mL)	−0.01 ($p = 0.9521$)	−0.11 ($p = 0.5955$)	−0.03 ($p = 0.8924$)
Obestatin at 1 (pg/mL)	−0.08 ($p = 0.6852$)	0.19 ($p = 0.3307$)	0.00 ($p = 0.9922$)
Obestatin at 3 (pg/mL)	0.00 ($p = 0.9850$)	0.01 ($p = 0.9422$)	−0.02 ($p = 0.9254$)
Obestatin at 5 (pg/mL)	0.00 ($p = 0.9894$)	−0.08 ($p = 0.7048$)	−0.04 ($p = 0.8372$)
Obestatin at 7 (pg/mL)	0.01 ($p = 0.9569$)	0.09 ($p = 0.6627$)	0.01 ($p = 0.9721$)
Obestatin (mean) (pg/mL)	0.11 ($p = 0.5829$)	0.08 ($p = 0.6870$)	0.13 ($p = 0.5152$)

Table 8. Correlations between ghrelin, leptin, and obestatin concentrations and selected parameters of esophageal pH monitoring (statistically significant correlations, where $p < 0.05$, are marked using *).

Laboratory Parameters	De Meester Index	De Meester Index (Post Meal)	GERD Episodes—Recumbent	GERD Episodes—24 h	Mean pH (Night)	Mean pH—24 h	Esophageal Clearance	Esophageal Clearance—Recumbent	Longest Episode of GERD
Ghrelin at 23 (pg/mL)	0.31	0.30	0.25	0.36	0.02	−0.31	0.07	0.37	0.17
Ghrelin at 1 (pg/mL)	0.32	0.42 *	0.14	0.33	0.04	−0.27	0.16	0.37	0.21
Ghrelin at 3 (pg/mL)	0.30	0.37	0.27	0.33	−0.04	−0.26	0.23	0.39	0.23
Ghrelin at 5 (pg/mL)	0.34	0.38	0.29	0.32	−0.13	−0.29	0.24	0.41	0.22
Ghrelin at 7 (pg/mL)	0.25	0.24	0.26	0.25	−0.18	−0.37	0.19	0.34	0.14
Ghrelin (mean) (pg/mL)	0.31	0.35	0.24	0.32	−0.07	−0.30	0.19	0.41	0.20
Leptin at 23 (ng/mL)	0.31	0.07	0.33	0.33	−0.67 *	−0.59 *	0.01	0.62 *	0.14
Leptin at 1 (ng/mL)	0.17	0.05	0.14	0.17	−0.41	−0.41	−0.26	0.41	−0.01
Leptin at 3 (ng/mL)	0.34	0.11	0.34	0.32	−0.56 *	−0.60 *	−0.13	0.52 *	0.12
Leptin at 5 (ng/mL)	0.25	0.08	0.24	0.29	−0.45	−0.55 *	−0.13	0.49	0.04
Leptin at 7 (ng/mL)	0.30	0.16	0.25	0.25	−0.62 *	−0.60 *	−0.11	0.53 *	0.10
Leptin (mean) (ng/mL)	0.30	0.12	0.27	0.28	−0.55 *	−0.59 *	−0.09	0.53 *	0.09

Table 8. Cont.

Laboratory Parameters	De Meester Index	De Meester Index (Post Meal)	GERD Episodes—Recumbent	GERD Episodes—24 h	Mean pH (Night)	Mean pH—24 h	Esophageal Clearance	Esophageal Clearance—Recumbent	Longest Episode of GERD
Obestatin at 23 (pg/mL)	0.18	0.36	0.26	0.09	−0.20	−0.16	−0.04	0.24	0.18
Obestatin at 1 (pg/mL)	−0.06	−0.05	0.32	−0.09	0.09	0.09	−0.32	−0.07	−0.21
Obestatin at 3 (pg/mL)	−0.06	0.26	−0.14	−0.11	0.24	0.15	0.19	0.09	0.07
Obestatin at 5 (pg/mL)	0.28	0.41	0.22	0.35	0.20	0.01	0.43	0.07	0.26
Obestatin at 7 (pg/mL)	0.09	0.16	0.03	−0.08	0.17	0.00	−0.05	0.01	−0.14
Obestatin (mean) (pg/mL)	−0.04	−0.06	0.17	−0.04	0.21	0.23	−0.25	−0.06	−0.27

4. Discussion

Our study presents the incidence and characteristics of reflux disease in patients with sleep apnea. In addition, we examined the profile of ghrelin, leptin, and obestatin in GERD and OSA. Correlations were also investigated between the levels of ghrelin, leptin, and obestatin and the parameters of GERD and OSA. Similar to other studies, we observed that GERD was more frequently diagnosed in the group with OSA compared to the control group [3–5,57]. Correlations were noted between OSA severity, the intensity of GERD clinical symptoms, and the minimum saturation values with prolonged esophageal clearance. This may indicate the importance of low saturation in the course of GERD and could explain the beneficial effect of CPAP therapy in patients without OSA who have been diagnosed with GERD [34–36]. A prolonged esophageal clearance and a more severe course of GERD in OSA were also observed in a study by Xiao et al. [58]. Similarly, an improvement in parameters of pH-metry was observed in several studies after the introduction of CPAP therapy [7,35,36]. In contrast, a study by Sabaté et al. did not observe a significant relationship between AHI and parameters of pH-metry, despite the more frequent occurrence of GERD in OSA [3].

In the presented study, parameters of pH-metry and clinical symptoms of GERD correlated with the severity of inflammatory lesions in the esophagus, whereas no correlation was found between OSA parameters and the severity of esophagitis. A study by Lee et al. reported more severe esophageal inflammatory lesions in OSA, which is in line with a study by Demeter et al. showing that the AHI value correlated with their severity [1,2].

After analyzing the ghrelin results, the group with severe obstructive apnea clearly differs from the others. In this group, lower levels of ghrelin were noteworthy, especially in the second part of the night and in the morning. In the available literature, conclusions regarding the level of ghrelin in patients with sleep apnea mainly involve morning measurements. A single study by Sanchez-de-la-Torre et al. evaluated the 24 h profile and observed no significant discrepancies in the ghrelin level in OSA [48]. A previous study by Liu et al. investigated the correlation between OSA and morning ghrelin levels. In line with our study, they noted lower ghrelin levels, especially in severe OSA [59]. In the majority of reports, the severity of OSA positively correlated with the level of ghrelin, and in studies by Garcia et al. and Chihara et al., effective CPAP therapy led to a decrease in ghrelin levels [44,45,60,61]. However, other studies showed no deviations in ghrelin levels in OSA, with CPAP therapy having no effect on its values [47,62].

In our presented study, no deviations in the level of leptin in OSA were observed, which is in line with the majority of previous reports [44,45,48,60–62]. In a comprehensive study by Arnardotir et al., no deviations in morning leptin levels in OSA were found [63]. We have not found any reports where leptin levels are lower, whereas in several studies, including one which evaluated its daily profile, a greater level of leptin was observed in OSA [46,47]. It appears that elevated levels of leptin result from obesity, which frequently accompanies OSA, rather than the mechanisms related to sleep disorders. In our study, no deviations in the level of obestatin were found in the OSA group. Similarly, Zirlik et al. did not observe any significant deviations in the daily obestatin profile in OSA patients [46]. On the other hand, a study by Liu et al. showed that morning obestatin levels in the OSA group were lower; however, this observed difference did not reach the level of statistical significance [59].

In our study, no significant deviations were observed in the average levels of ghrelin, obestatin, and leptin in the group with a diagnosis of GERD. However, after analysis of GERD parameters (clinical symptoms, gastroscopic findings, and pH-metry), tendencies were observed towards greater levels of leptin and ghrelin, together with an increase in the severity of GERD. Similarly, greater levels of leptin in the group of patients with reflux esophagitis were observed by Nam et al., while Tomas et al. found correlations between leptin levels and the severity of GERD clinical symptoms [51,55]. Leptin does not exert an effect on the mechanisms associated with GERD, and therefore, it may be presumed that

the observed correlation results from the fact that obese patients comprised a significant number in the examined group. The relationship between ghrelin and GERD is indicated by its action within the gastrointestinal tract and from observations in an animal model, as well as a study by Agrawal et al., where, after administration of ghrelin and capromorelin (a ghrelin agonist), a reduction in the number of reflux episodes was seen when compared to placebo [49,64]. To the best of our knowledge, there have been no reports regarding ghrelin levels in GERD. Moreover, in studies analyzing its morning levels, divergent results are encountered. In a study by Nishizawa et al. concerning functional dyspepsia, a tendency is clearly noted towards greater ghrelin values in the group with GERD [50]. In contrast, a study by Tseng et al. found no differences in ghrelin levels between the group with GERD and the control group [52]. Similarly, in a study by Thomas et al., no relationship was found between ghrelin levels and the severity of GERD symptoms; however, ghrelin levels correlated with an increased risk for the development of Barrett's esophagus [51]. Additionally, Rubenstein et al. found a relationship between ghrelin values and an elevated risk for the development of Barrett's esophagus; however, there was a negative correlation between ghrelin levels and GERD [53]. In another study, Shindo et al. also reported lower levels of ghrelin in GERD [54]. Discrepancies between the above-mentioned reports may indicate a complex relationship between ghrelin and GERD. Theoretically, high ghrelin levels may lead to GERD by increasing the secretion of gastric juice and decreasing its pH or may also result from esophageal wall lesions as a result of the inflammatory process, as in the case of IBD or celiac disease [40,65,66]. On the other hand, ghrelin stimulates stomach motility; thus, decreased levels of ghrelin prolong the duration of gastric emptying, which may be conducive to GERD. No deviations in obestatin levels were observed, and our study is the first to present its profile among patients with GERD.

Strengths and Limitations of the Study

Our study has several limitations. Firstly, our study involved patients with a suspicion of OSA. Next, the control group was small and was not adjusted for BMI or distribution of adipose tissue. Additionally, the evaluation of OSA was performed on a different night than the collection of blood specimens. Finally, a gastroscopy was performed on some patients, while other patients did not undergo endoscopic examination. However, a strength of our study is that we assessed numerous objective parameters of GERD and OSA in a relatively large group of patients. Another advantage of this study is the performance of hormonal measurements in a nocturnal profile (when apnea and decreases in saturation occur) and the fact that each procedure was performed by the same investigator, which allows for greater repeatability and minimization of errors associated with subjective assessment. Although we did not compare our results with patients of normal BMI, we would like to emphasize the relatively large number of patients in our study group, as well as our measurement of hormonal profiles, as opposed to individual measurements of hormones.

5. Conclusions

The results of our study confirm the frequent occurrence of GERD among patients with OSA. In both GERD and OSA, deviations were observed in the levels of total ghrelin and leptin; however, analysis of the results did not indicate that the relationship between OSA and GERD results from these hormonal deviations.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/jcm10215195/s1>, Supplementary data: Questionnaire for Assessment of GERD Complaints.

Author Contributions: P.P.: study concept and design, acquisition of data (collection and preparation of blood samples, collection of questionnaires), analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, and technical or material support. R.F.: study concept and design, acquisition of data (gastroscopic examinations), analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, technical or material support, and study supervision. J.W. and M.K.: study design, acquisition of data (J.W.—laboratory determinations of hormones,

M.K.—pH-metry tests), analysis and interpretation of data, and critical revision of the manuscript for important intellectual content and technical or material support. All authors have read and agreed to the published version of the manuscript.

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The importance of obesity and carbohydrate metabolism disorders on the course of gastroesophageal reflux disease – a pilot study

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Abstract

Introduction: Carbohydrate metabolism disorders, obesity and a severe course of gastroesophageal reflux correlate with more frequent development of esophageal complications. The aim of this study was to assess the influence of obesity and carbohydrate disorders on the characteristics of gastroesophageal reflux disease (GERD).

Methods: The study included 58 patients with excess weight. Anthropometric parameters (including the body mass index, BMI), data regarding GERD (severity of symptoms, gastroscopy and esophageal pH monitoring results) were included in the study. Correlations between obesity and GERD parameters were analyzed. Subjects were divided into a diabetic and a control group and the severity of GERD was compared. **Results:** GERD was diagnosed in 40 patients and occurred more frequently in the obese group (73%) than in the overweight group (57%). Increased GERD severity was associated with increased BMI only for postprandial parameters. GERD was diagnosed in most of the group with carbohydrate disorders (78% vs 63% in the non-diabetic group). No differences in the severity of GERD were observed between groups depending on carbohydrate disorders. **Conclusions:** In our study, GERD was common in obesity and in diabetic disorders. Increased severity of postprandial reflux was associated with an increased BMI. Diabetic disorders were not associated with more severe GERD.

Keywords: gastroesophageal reflux disease · obesity · diabetes mellitus

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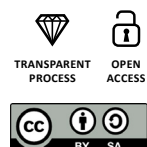
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Introduction

Factors linked to modern lifestyle, e.g. physical inactivity, overnutrition and poor sleep quality have led to the widespread incidence of obesity, type 2 diabetes (T2DM) and gastroesophageal reflux disease (GERD) [1-5]. In many countries obesity is an important public health problem and its prevalence results in an increase in the incidence of GERD and type 2 diabetes [6-8]. Gastroesophageal reflux disease is a common health problem which still requires research. Depending on the region, the prevalence of GERD is estimated at 10-20% of the population [2, 5]. Overweight, especially abdominal obesity, correlates with the severity of GERD. The main causes of GERD are impaired function of the lower esophageal sphincter, hiatal hernia, impaired esophageal motility and increased intra-abdominal pressure [9-18]. Gastroesophageal reflux disease leads to the development of Barrett's esophagus (BE) or metaplasia, which is a precancerous condition leading to the development of dysplasia and subsequently of esophageal adenocarcinoma (EAC) [4, 19-20]. Numerous studies have noted that not only the severity of GERD, but the presence of abdominal obesity and T2DM, increase the risk of developing BE and EAC [21-25].

In abdominal obesity, the development of BE and EAC plays a major role in the increased amount of adipokines and inflammatory cytokines produced by visceral adipose tissue, which leads to a chronic inflammatory process, and thus, promotes cancerous transformation [26-28]. Patients with T2DM are often obese, making them more prone to GERD. In T2DM, as in high-grade obesity, the clinical course of GERD is more often atypical. The differences between patients with T2DM result from additional factors contributing to GERD, including esophageal peristalsis disorders, gastroparesis, hyperglycemia, neuropathy and usage of diabetic medications (e.g. GLP-1 receptor agonists and metformin) [29]. The atypical, often mild or asymptomatic course of GERD in T2DM may delay the decision to perform diagnostics, leading to delayed diagnosis of complications, particularly BE and EAC. Therefore, it is important to study the natural course of GERD in obese and T2DM patients in order to reduce the risk of complications through early diagnosis and treatment.

Aim

The aim of our study was to characterize GERD in overweight patients and to assess the correlation between obesity parameters and the severity of GERD. The second aim of this study was to assess the differences in the clinical characteristics of GERD, depending on the diagnosis of carbohydrate disorders, which could explain the increased risk of complications in this group.

Materials and Methods

Study population

Our analysis covers data collected from 58 patients who were diagnosed for sleep breathing disorders at the Department of Internal Diseases of the Institute of Rural Medicine in Lublin. The exclusion criteria were: chronic use of drugs which may interfere with the assessment of GERD parameters (proton pump inhibitors, H2 blockers, alkali, nitrates) or previous significant gastrointestinal surgery (gastrectomy, bowel resection). This patient group also served as study participants in our previous work [30]. We collected anthropometric measurements and the responses from GERD-complaint questionnaires. If GERD was suspected, patients were referred for additional tests (gastroscopy and esophageal pH-measurement). The results from these additional tests were included in the study.

Criteria for the diagnosis of GERD

The diagnosis of GERD was established according to the definitions of the Lyon consensus [4]. Therefore, the diagnosis was based on the combined assessment of clinical symptoms, endoscopic evaluation of the esophageal mucosa, esophageal pH monitoring and response to therapeutic intervention. Clinical diagnosis was made when the patient had persistent symptoms characteristic of GERD which include heartburn and acid regurgitation. Persistence of symptoms was recognized when symptoms of mild intensity occurred at least 2 days a week or when they were more severe and caused deterioration in general well-being and occurred at least 1 day a week. Moreover, the diagnosis of GERD confirmed the presence of inflammatory changes in the esophagus (LA grade C) and the result of pH-measurement with esophageal acid exposure time > 6%, DeMeester Score > 14.72 or > 80 reflux episodes per 24 hours. Additionally, the diagnosis of GERD was confirmed by the reduction of symptoms after starting treatment with a proton pump inhibitor [4].

Anthropometric data

All participants underwent a physical examination. The body mass index (BMI) was calculated as the body weight in kilograms divided by the height in meters squared (kg / m^2). The waist circumference (the circumference at midpoint between the lower border of the rib cage and the iliac crest) was measured in the standing position. Overweight was diagnosed if BMI was in the range of 25-29.9 kg / m^2 ; class I obesity when BMI was 30-34.9 kg / m^2 , class II obesity when BMI was 35-39.9 kg / m^2 ; and class III obesity when BMI was at $\geq 40 \text{ kg} / \text{m}^2$ [8].

Survey data regarding the severity of GERD complaints

The severity of GERD clinical symptoms was assessed using a questionnaire about the overall intensity of complaints (within a score range of 0-10) and the intensity and frequency of symptoms considered typical for GERD (within a score range of 0-52). GERD symptoms included the feeling of heartburn and presence of regurgitation typical for GERD situations, acid reflux and dysphagia. In addition, the presence of GERD symptoms was assessed at night, during sleep and after an overnight sleeping period. Patients were instructed to describe the symptoms occurring in the month prior to completing the questionnaire. Survey data from all patients were collected by the primary investigator. The full version of the questionnaire is available in the Supplementary Materials [in Polish]: TU BĘDZIE LINK DO PDF.

Gastroscopy and esophageal pH monitoring

All procedures were undertaken by experienced physicians before the introduction of GERD treatment. All gastroscopic examinations were done using the Fujifilm (Japan or Pentax) (Japan). Whereas the esophageal pH monitoring was done using the ComforTEC Plus PHNS single-channel probe and a recorder made by Sandhill Scientific (USA, REF: Z07-2000-A, SN: H109007C). The degree of esophagitis was determined according to the Los Angeles classification, and numerical values with a range of 1 to 4 were given for subsequent grades (grade A-D); 0 was designated as no inflammatory lesions [4, 10].

Diagnosis of pre-diabetes and type 2 diabetes

In order to assess the importance of carbohydrate disorders on the course of GERD, the subjects were divided into a group with carbohydrate disorders (23 patients) and a control group (35 patients). The group with carbohydrate disorders included patients diagnosed with T2DM, impaired glycemic tolerance (IGT) or impaired fasting glycemia (IFG). In all participants with T2DM, diabetes was well-controlled. Diagnoses of carbohydrate disorders were established before inclusion in the study and were based on the Polish Diabetes Association guidelines [31].

Data Analyses and Statistical Methods

All statistical analyses were carried out with the Statistica software package (version 13, TIBCO Software Inc., USA). After confirming that all variables meet the criteria of a normal distribution, Spearman's rank correlation coefficient was used for the analysis. Correlations between variables were calculated using Spearman's rank correlation coefficient,

while comparisons between two independent groups were performed using the Mann–Whitney U test. *P* values < 0.05 were considered statistically significant. Because the distribution of GERD measurements was characterized by a large asymmetry, the median should be taken as the key measurement (possibly including the range of variability in the form of IQR) while assessing its severity depending on the presence of diabetic disorders.

Results

Baseline data

The study population consisted of 58 patients (48 males and 10 females) aged 34-75 years (mean = 54.5 years; Me = 56 years; s = 11.2 years). In the study group, obesity was diagnosed in 44 subjects (75.9%). Of these, class I obesity was seen in 17 subjects, class II obesity was seen in 12 subjects, and class III obesity was seen in 15 subjects. Fourteen (24.1%) patients were overweight. The average patient weight was 104 kg (range 77-161 kg), while average waist circumference was 115.5 cm (range 96-147 cm). The mean BMI was 34.8 kg / m² (range 25.1-49.7 kg / m²). Carbohydrate disorders were reported by 23 subjects (~ 40%), of which 14 subjects (24.1%) had T2DM and 9 subjects (15.5%) had pre-diabetes. Table 1 presents the basic characteristics of the study population.

In our study, GERD was diagnosed in 40 patients (~ 69%). In the obese group, GERD was diagnosed in 32 subjects (73%), while the in overweight group, GERD was diagnosed in 8 subjects (57%). Gastroscopy was performed in 32 patients. In 2 cases, no esophageal inflammatory changes were observed. Most of the gastroscopic examinations revealed esophageal inflammatory changes with grade A, B and C of esophagitis recognized in 22, 7, and 1 subject, respectively. Grade D lesions or peptic stricture were not observed in any of the patients. Moreover, neither BE nor EAC were diagnosed. In 23 patients, pH-metry was performed. Table 1 presents the distribution of the variables.

Apart from obesity, carbohydrate disorders and GERD, the majority participants had comorbidities mainly related to the circulatory system. The most common were: arterial hypertension (47 patients, 81%); dyslipidemia (34 patients, 59%), coronary artery disease (16 patients, 28%); hyperuricemia (10 patients, 17%); chronic obstructive pulmonary disease (5 patients, 9%) and heart failure (4 patients; 7%).

Gastroesophageal reflux in obesity and in diabetic disorders

We investigated the relationship between obesity parameter values (body weight, abdominal circumference, and BMI) and GERD severity parameters. Since all considered

Table 1. Basic characteristics of the study population, severity of GERD symptoms and distribution of esophageal pH monitoring results

Features	Mean	Median	Std. dev.	Min	Max
Age (yr)	54.5	56	11.2	34	75
BMI (kg/m ²)	34.8	34.6	6.7	25.1	49.7
Waist circumference (cm)	115.5	115.0	12.8	96.0	147.0
GERD symptoms day	11.9	12	9.2	0	28
GERD symptoms night	2.8	3	2.9	0	12
GERD symptoms overall	14.7	15	11.5	0	40
De Meester index (N = 23)	27.8	15.1	33.2	1.7	136.4
De Meester index - post meal (N = 23)	9.8	7.5	9.0	1.5	37
Reflux episodes - recumbent (N = 22)	34.5	10	57.7	0	250
Reflux episodes - 24/h (N = 22)	136.1	107	127.9	7	570
Mean pH night (N = 23)	6.4	6.5	0.8	4.3	8.1
Mean pH - 24/h (N = 23)	6.2	6.2	0.5	5.0	7.2
Esophageal clearance time (N = 22)	37.0	35.5	21.2	8	91
Esophageal clearance time - recumbent (N = 22)	31.7	22.5	33.1	0	138
Longest reflux episode (N = 23)	13.7	4.9	17.9	0.3	59.3

features were consistent with a normal distribution, Spearman's rank correlation coefficient was used for the analysis. Table 2 presents correlation coefficient values between individual features along with the assessment of their statistical significance. In the studied group, no statistically significant relationships were found between the obesity parameters and the assessed reflux parameters.

A tendency toward greater values with increasing obesity parameters was seen only for the "feeling of heartburn after meals" parameter.

The relationships between GERD parameters from gastroscopy, pH measurement and obesity parameters were calculated. Only the correlation between the number of postprandial reflux episodes and BMI was near statistical significance (test probability values $p = 0.0084$), however its strength was rather small $rS = 0.36$. In addition, there was a trend toward greater values for the postprandial De Meester index and for the duration of gastric acid exposure with increasing BMI (Table 3).

Table 2. Distribution of correlations between obesity parameters and the severity of GERD complaints

GERD symptoms	Obesity parameters (N = 58)		
	Weight	Waist circumference	BMI
GERD symptoms day	0.05 ($p = 0.7338$)	0.07 ($p = 0.6178$)	0.03 ($p = 0.7973$)
GERD symptoms night	0.07 ($p = 0.5866$)	0.06 ($p = 0.6513$)	0.04 ($p = 0.7892$)
GERD symptoms day and night	0.05 ($p = 0.7039$)	0.07 ($p = 0.5779$)	0.04 ($p = 0.7681$)
Overall intensity of GERD-related complaints	-0.01 ($p = 0.9461$)	0.07 ($p = 0.5988$)	0.10 ($p = 0.4678$)
Burning sensation in the chest (Post Meal)	0.16 ($p = 0.2302$)	0.16 ($p = 0.2440$)	0.19 ($p = 0.1605$)

Table 3. Correlations between GERD parameters from gastroscopy, pH measurement and obesity parameters

GERD severity parameters	Obesity parameters (N = 58)		
	Weight	Waist circumference	BMI
Severity of inflammatory changes in the esophagus (gastroscopy assessment)	-0.08 ($p = 0.6753$)	-0.04 ($p = 0.8218$)	-0.09 ($p = 0.6203$)
De Meester Index (Post Meal)	0.02 ($p = 0.9340$)	0.10 ($p = 0.6415$)	0.24 ($p = 0.2636$)
De Meester Index	-0.10 ($p = 0.6608$)	0,00 ($p = 0.9964$)	0.11 ($p = 0.6198$)
Reflux Episodes (Post Meal)	0.16 ($p = 0.4610$)	0.22 ($p = 0.3198$)	0.36 ($p = 0.0884$)
Reflux Episodes (24 h)	-0.04 ($p = 0.8554$)	-0.06 ($p = 0.7859$)	0.06 ($p = 0.8029$)
Exposure to gastric acid following a meal	0.03 ($p = 0.9055$)	0.12 ($p = 0.5803$)	0.22 ($p = 0.3044$)
Exposure to gastric acid (24 h)	-0.05 ($p = 0.8085$)	-0.05 ($p = 0.8305$)	0.03 ($p = 0.8888$)
Mean pH (Post Meal)	0.12 ($p = 0.5836$)	0.00 ($p = 0.9839$)	-0.11 ($p = 0.6025$)
Mean pH (24 h)	0.15 ($p = 0.4928$)	-0.06 ($p = 0.7962$)	-0.13 ($p = 0.5468$)
Esophageal Clearance (Post Meal)	-0.13 ($p = 0.5452$)	0.04 ($p = 0.8540$)	0.08 ($p = 0.7216$)
Esophageal Clearance (24 h)	-0.05 ($p = 0.8308$)	0.07 ($p = 0.7636$)	0.02 ($p = 0.9284$)

Next, we analyzed the differences between the parameters of GERD severity depending on the diagnosis of carbohydrate disorders. Among the participants with carbohydrate disorders, GERD was diagnosed in 18 patients (78%), of which 12 (86%) had T2DM, and 6 (67%) had pre-diabetes.

Whereas in the group without carbohydrate disorders (n=35) GERD was diagnosed in 22 participants (63%). No differences in the severity of GERD were observed between the groups with and without carbohydrate disorders. In our study, the GERD parameters in both groups were very similar (Table 4).

Table 4. Comparison of GERD severity parameters depending on the presence of diabetic disorders (p – test probability values were calculated using the Mann-Whitney test)

GERD severity parameters	Diabetic disorders								P
	Yes				No				
	N	Mean	Me	IQR	N	Mean	Me	IQR	
GERD symptoms day and night	23	16.5	18	21.0	35	13.8	14	22.0	0.4206
Severity of inflammatory changes in the esophagus (gastroscopy Assessment)	12	1.1	1	0.0	20	1.3	1	1.0	0.2551
Reflux Episodes (24 h)	10	111.8	66.5	165.0	12	156.4	146.5	151.5	0.4562
Reflux Episodes (Post Meal)	10	45.9	28	49.0	13	69.2	34	119.0	0.7381
Exposure to gastric acid following a meal (%)	10	5.6	2.5	8.5	12	8.1	4.5	9.5	0.8718
Mean pH (24 h)	10	6.1	5.9	0.6	13	6.3	6.4	0.6	0.2316
Mean pH (day)	10	6.1	6.0	0.8	13	6.1	6.3	1.1	0.7844
Mean pH (night)	10	6.1	6.1	0.8	13	6,6	6.7	0.3	0.0666
De Meester Index	10	24.7	10.6	27.9	13	30.2	18.1	29.0	1.0000
De Meester Index (Post Meal)	10	7.8	6.4	9.8	13	11.3	8.4	8.8	0.7844
Esophageal Clearance – 24 h (sec)	10	40.7	38	20.0	12	33.8	33	24.5	0.3136
Overall intensity of GERD-related complaints	23	3.8	2.0	8.0	35	2.5	2.0	5.0	0.3271
GERD symptoms day	23	13.7	15	17.0	35	11.0	10	20.0	0.3041
GERD symptoms night	23	2.8	3	4.0	35	2.8	2	5.0	0.9497
Burning sensation in the chest (Post Meal)	23	2.9	3.0	5.0	35	2.5	3.0	4.0	0.4973

The analysis of the probability of GERD depending on the selected variables (BMI, waist circumference, diagnosis of carbohydrate disorders and diagnosis of diabetes) was performed using the logistic regression model. Based on the analyzes performed, no statistical evidence was found that any of the proposed factors had a significant influence on the diagnosis of GERD (Table 5). Moreover, an attempt was made to search for a model containing statistically significant variables. The best model that included only the diagnosis of diabetes was still not statistically significant: OR (95% CI) = 3,429; $p = 0.14$.

Discussion

All participants in our study were overweight and in this group the occurrence of GERD was much more frequent than in the general population. Obesity is an important risk factor for GERD and numerous studies demonstrated its more frequent occurrence in people with excess weight [11-17]. In our study, no statistically significant correlation was found between individual obesity measures and GERD parameters. However, there was a trend towards greater severity of postprandial GERD clinical symptoms and worsening of postprandial GERD pH parameters with increasing BMI. Most of the published data demonstrate a more severe course of GERD in people with excess weight.

Obesity, especially the visceral type, causes GERD due to changes in the anatomy and physiology of the gastroesophageal junction (GEJ) [11, 18]. Additionally, it is believed that the pro-inflammatory effects of cytokines synthesized in visceral adipose tissue plays an important role [12, 26]. Akyuz

et al. showed a significant correlation between BMI and the severity of GERD in pH measurements. They also found that the severity of esophageal inflammatory changes seen in gastroscopy did not differ significantly in the obese group, however the authors did not assess the severity of GERD in the context of its association with abdominal obesity [11]. In our study, we also did not observe any relationship between obesity and the severity of esophageal inflammatory changes in gastroscopy. The correlation between BMI and GERD severity in pH measurements was also present, but did not reach the level of statistical significance.

We did not observe a correlation between abdominal circumference and the severity of GERD. However, most studies indicate that it does have greater a role than BMI in terms of GERD severity. A study by Wu et al. investigated the correlations of obesity parameters with GERD symptoms and esophageal inflammatory activity via the measurement of glucose metabolism in 18F-Fluorodeoxyglucose positron emission tomography (PET-CT). There was a significant correlation between GERD symptoms and esophageal inflammatory activity in PET-CT with all obesity parameters (BMI, abdominal circumference, and the amount of subcutaneous and visceral adipose tissue) [13]. Nam et al. described the correlations between the amount of visceral fat, concentrations of inflammatory cytokines synthesized within it, and the intensity of esophageal inflammatory changes [12]. Similar results were obtained in large-scale studies in Japan and South Korea. An increased incidence of reflux esophagitis has been observed in obesity and in the metabolic syndrome. Hyperglycemia, high BMI, and in particular, greater abdominal circumference and increased visceral fat, correlated with an increased risk for GERD [14-15].

Gastroesophageal reflux disease is linked to a higher risk of BE [4, 20]. Population-based studies have indicated that the risk of BE and EAC is also significantly increased in obesity, especially in the abdominal type. This risk is increased regardless of the presence of GERD symptoms [21, 23-25]. In a study by Nelsen et al., the risk of developing BE and dysplasia correlated with the amount of visceral adipose tissue and adipose tissue in the GEJ fat area; however, it was independent of the BMI value and the presence of GERD symptoms [24]. Similar conclusions were obtained by El-Seraq et al. [19]. Moreover, in an investigation by Corley et al., abdominal circumference and abdominal obesity (but not BMI) correlated with a greater risk for BE [25].

Table 5. Logistic regression model of the probability of GERD diagnosis depending on selected variables

Independent variables	GERD diagnosis	
	OR (95% CI)	<i>p</i>
BMI	1.060 (0.867-1.295)	0.5704
WC	0.975 (0.880-1.079)	0.6207
Diagnosis of carbohydrate disorders	1.158 (0.244-5.496)	0.8532
Diagnosis of diabetes	3.195 (0.392-26.073)	0.2781

OR – odds ratio; CI – confidence interval; GERD – gastroesophageal reflux disease; BMI – body mass index (kg/m²); waist circumference (cm)

Gastroesophageal reflux disease is common in T2DM and is more likely to be atypical or present with mild symptoms [29]. In addition, these patients are at an increased risk for developing metaplasia [22]. In our study, no differences in the severity of GERD were found between subjects with T2DM or pre-diabetes and the group without these disorders. Notably, the two groups were very similar in terms of GERD characteristics. Lorentzen et al. compared the features of GERD in patients with a high degree of obesity, depending on the diagnosis of T2DM. As in our study, GERD was more common in the obese group than in the general population. However, a large proportion of the respondents had asymptomatic GERD, regardless of whether or not they suffered from T2DM. In this study, clinical symptoms were reported by approximately 29% of the respondents, but esophagitis in gastroscopy was seen in 58% of patients in the T2DM group and in 47% of patients in the non-T2DM group. Among subjects with inflammatory changes in the esophagus, 68–80% did not report symptoms of GERD. In the T2DM group (only T2DM patients underwent pH-metry), 55% of subjects had pathologic acid reflux, whereas 67% of subjects were asymptomatic [16]. In our study, the severity of GERD clinical symptoms was similar in both groups, which may be due to the lower number of severely obese patients when compared to the cited study.

As reported by Ortiz et al., the asymptomatic course of GERD in obese patients may be related to the decreased esophageal sensitivity to acid content observed in this group. The authors indicated that the absence of typical GERD symptoms in these patients may delay the diagnosis of GERD complications, especially BE [32]. Promberger et al. also observed the frequent occurrence of atypical GERD symptoms in T2DM [33]. Furthermore, Lluch et al. found that GERD was common in diabetic patients, but it was more often asymptomatic [34]. The above conclusions are of clinical significance in the context of a report by Leggett et al, which found an increased risk of BE in patients with metabolic syndrome, regardless of GERD symptoms [23]. The role of carbohydrate disorders in the pathogenesis of GERD is unclear. Gokturk et al. observed a more severe course of GERD in subjects with T2DM, but the presence of reflux episodes was associated with obesity rather than hyperglycemia [17]. In the study by Wang et al., the occurrence of GERD symptoms in diabetes was observed more frequently, and their severity clearly increased in the group of patients with diabetic neuropathy [35].

In our study group, we did not observe an atypical course of GERD in T2DM, but in all cases, these were patients with

pre-diabetes or well-controlled diabetes without complications. Although the patients with carbohydrate disorders more often suffer from GERD and its complications, the clinical course does not correlate with the risk of complications. Because of this, they may benefit from early gastroscopic evaluation.

The limitations of our study include the small number of participants and the lack of assessment of other obesity parameters, such as the waist-hip ratio. Moreover, not all patients underwent endoscopic examinations or pH-metry. Another limitation was the inclusion of only hospitalized patients with suspected sleep apnea who were mostly obese, which makes it difficult to transfer the obtained conclusions to the general population. Despite these limitations, the collected results allowed us to demonstrate a greater incidence of GERD in obesity and to show that the presence of carbohydrate disorders was not associated with a more severe clinical course of GERD (in the context of clinical symptoms, changes in gastroscopy, and pH measurement).

Conclusions

In our study group, we observed that GERD is more common in obesity and in T2DM; however, the diagnosis of diabetic disorders was not associated with more severe GERD. Our results and a review of the current literature indicate that due to a mild or atypical course, GERD may be underdiagnosed in the group of severely obese and T2DM patients. Finally, although patients with carbohydrate disorders more often suffer from GERD and its complications, the clinical course does not correlate with the risk of complications, and because of this, these patients may benefit from early gastroscopic evaluation.

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7. Oświadczenia współautorów.

Rzeszów, dn. 30.06.2020

OŚWIADCZENIE

Jako współautor pracy pt.

Pardak P, Pękala A, Jarmakiewicz S, Rafał Filip R.

Gastro-esophageal reflux and obstructive sleep apnea – is there a

link?. Eur J Clin Exp Med. 2020;18(2):110–115.

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Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Piotra Pardaka jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część w/w pracy wykazuje indywidualny wkład lek. Piotra Pardaka przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników tej pracy.

KIEROWNIK
Kliniki Gastroenterologii
z Ośrodkiem Kompleksowej Diagnostyki
Niewoistych Chorób Żołądka i Jelit



prof. dr hab. n. med. Rafał Filip
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OŚWIADCZENIE

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(podpis współautora)

Sub G4

20.12.2021

OŚWIADCZENIE

Jako współautor pracy pt.

Associations of Obstructive Sleep Apnea, Obestatin, Leptin, and Ghrelin with Gastroesophageal Reflux.

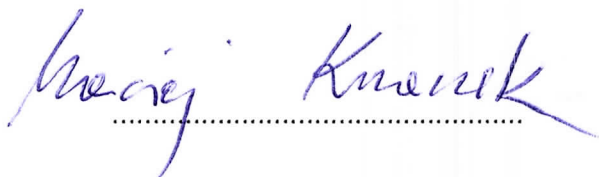
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(podpis współautora)

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Jako współautor pracy pt.

Associations of Obstructive Sleep Apnea, Obestatin, Leptin, and Ghrelin with Gastroesophageal Reflux.

Journal of Clinical Medicine. 2021; 10(21):5195.

<https://doi.org/10.3390/jcm10215195>

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: projekt badania, pozyskiwanie danych (badania gastroskopowe), analiza i interpretacja danych, napisanie tekstu artykułu oraz nadzór naukowy.

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Piotra Pardaka jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część w/w pracy wykazuje indywidualny wkład lek. Piotra Pardaka przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników tej pracy.

KIEROWNIK
Kliniki Gastroenterologii
z Ośrodkiem Kompleksowej Leczenia
Nieswoistych Chorób Jamy Żołądka
.....
prof. dr hab. n. med. Rafał Filip
(podpis współautora)

Dr hab. Jarosław Woliński, profesor instytutu

Warszawa, dn. 06.04.2022

Instytut Fizjologii i Żywienia Zwierząt im. Jana Kielanowskiego

Polskiej Akademii Nauk

05-110 Jabłonna, Instytucka 3

OŚWIADCZENIE

Jako współautor pracy pt.:

“The Impact of Sleep-Disordered Breathing on Ghrelin, Obestatin, and Leptin Profiles in Patients with Obesity or Overweight”

Journal of Clinical Medicine. 2022; 11(7):2032.

<https://doi.org/10.3390/jcm11072032>

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KIEROWNIK
Kliniki Gastroenterologii
z Ośrodkiem Kompleksowego Leczenia
Nieswoistych Chorób Zapalnych Jelit

.....
prof. dr hab. n. med. Rafał Filip
(podpis współautora)

OŚWIADCZENIE

Jako współautor pracy

The importance of obesity and carbohydrate metabolism disorders on the course of gastroesophageal reflux disease – a pilot study.

European Journal of Translational and Clinical Medicine 2022 v. 5 no. 1.

DOI: 10.31373/ejtc/149190

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(podpis współautora)

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KIEROWNIK
Kliniki Gastroenterologii
z Ośrodkiem Kompleksowej Diagnostyki
Nieswoistych Chorób Żołądka i Jelit

prof. dr hab. n. med. Filip Rajat
(podpis współautora)

8. Załączniki.

Załącznik 1. Decyzja Komisji Bioetycznej

Komisja Bioetyczna
Instytutu Medycyny Wsi
ul. Jaczewskiego 2
20-090 Lublin

DECYZJA KOMISJI BIOETYCZNEJ

numer 6/2014

Dnia 15.10.2014 r. Komisja Bioetyczna przy Instytucie Medycyny Wsi w Lublinie, ul. Jaczewskiego 2 zapoznała się z projektem badania pt.

„Znaczenie zaburzeń poziomu greliny u pacjentów z obturacyjnym bezdechem sennym dla występowania objawów refluksu żołądkowo-przelykowego”

przedstawionym przez lek. med. Piotra Pardaka – Klinika Chorób Wewnętrznych i Nadciśnienia Tętniczego z Oddziałem Chorób Zawodowych Instytutu Medycyny Wsi w Lublinie.

Po zapoznaniu się z całością dokumentacji, zgodnie z zasadami GCP (Guidelines for Good Clinical Practice), Komisja Bioetyczna wyraziła zgodę na rozpoczęcie badania klinicznego zgodnie z przedstawionym protokołem.

Niniejsze zezwolenie ważne jest do ukończenia badania.

Do decyzji dołącza się wykaz osób biorących udział w głosowaniu.

Komisja zastrzega sobie prawo do uzyskiwania informacji o efektach niepożądanych oraz do uzyskania raportu końcowego.

Powyższa decyzja może ulec zmianie w przypadku zaistnienia nowych okoliczności.

Od niniejszej decyzji przysługuje odwołanie w ciągu 14 dni do Odwoławczej Komisji Bioetycznej przy Ministrze Zdrowia.

Przewodniczący Komisji Bioetycznej
Instytutu Medycyny Wsi w Lublinie

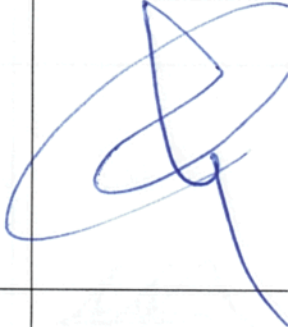


Prof. dr hab. med. Janusz Schabowski





data: 2014-10-15

Podpis Przewodniczącego Komisji

Skład Komisji Bioetycznej Instytutu Medycyny Wsi w Lublinie
podejmującej w dniu **15.10.2014 r.**

Decyzję nr 6/2014

Lp.	Imię i nazwisko	Zawód	Miejsce pracy	Podpis
1.	Prof. dr hab. med. Janusz Schabowski - przewodniczący	Internista Gastrolog	Przychodnia Specjalistyczna i Chorób Zawodowych Wsi Instytutu Medycyny Wsi, Zakład Endoskopowych Badań Klinicznych Instytutu Medycyny Wsi ul. Jaczewskiego 2 20-090 Lublin	
2.	Dr farm. Mariola Drozd vice-przewodnicząca	Farmaceuta	Katedra i Zakład Farmacji Stosowanej Uniwersytetu Medycznego ul. Chodźki 1 20-093 Lublin	
3.	Dr n. o zdr. Krzysztof Brzeziński	Anestezjolog	Przychodnia Specjalistyczna i Chorób Zawodowych Wsi Instytutu Medycyny Wsi ul. Jaczewskiego 2 20-090 Lublin	
4.	Lek. med. Roman Chwedorowicz	Neurolog	Przychodnia Specjalistyczna i Chorób Zawodowych Wsi Instytutu Medycyny Wsi ul. Jaczewskiego 2 20-090 Lublin	
5.	Dr n. hum. Beata Dobrowolska	Pielęgniarka Etyk	Katedra Rozwoju Pielęgniarstwa, Wydział Pielęgniarstwa i Nauk o Zdrowiu Uniwersytet Medyczny w Lublinie Al. Raclawickie 1 20-059 Lublin	
6.	Dr hab. med. Rafał Filip	Internista Gastrolog	Zakład Endoskopowych Badań Klinicznych Instytutu Medycyny Wsi, Przychodnia Specjalistyczna i Chorób Zawodowych Wsi Instytutu Medycyny Wsi ul. Jaczewskiego 2 20-090 Lublin	
7.	Ks. dr Krzysztof Kwiatkowski	Duchowny	Instytut Teologii Moralnej KUL, Metropolitarne Seminarium Duchowne ul. Prymasa Wyszyńskiego 6 Lublin	

8.	Dr hab. med. Lech Panasiuk	Internista Lekarz Rodzinny	Zakład Medycyny Rodzinnej Instytutu Medycyny Wsi, Klinika Chorób Wewnętrznych i Nadciśnienia Tętniczego z Oddziałem Chorób Zawodowych Instytutu Medycyny Wsi ul. Jaczewskiego 2 20-090 Lublin	
9.	Dr med. Piotr Paprzycki	Internista Pulmonolog	Zakład Badań Czynnościowych Instytutu Medycyny Wsi, Klinika Chorób Wewnętrznych i Nadciśnienia Tętniczego z Oddziałem Chorób Zawodowych Instytutu Medycyny Wsi ul. Jaczewskiego 2 20-090 Lublin	
10.	Dr med. Tomasz Saran	Internista Rehabilitant	Oddział Rehabilitacji Instytutu Medycyny Wsi, Ośrodek Rehabilitacji Instytutu Medycyny Wsi ul. Jaczewskiego 2 20-090 Lublin	
11.	Mgr praw Daria Schabowska	Radca prawny	Kancelaria Radcy Prawnego Daria Schabowska ul. Krajewskiego 13 20-738 Lublin	
12.	Prof. dr hab. med. Jerzy Zagórski	Lekarz	Zakład Zdrowia Publicznego oraz Krajowe Obserwatorium Chorób Układu Mięśniowo-Szkieletowego Instytutu Medycyny Wsi ul. Jaczewskiego 2 20-090 Lublin	
13.	Dr hab. n. hum. Lech Zdybel	Filozof	Zakład Antropologii Kulturowej Wydziału Filozofii i Socjologii UMCS ul. Pl. Curie-Skłodowskiej 4 Lublin	

Załącznik 2. Ankieta dotycząca objawów klinicznych GERD.

KWESTIONARIUSZ OBJAWÓW REFLUKSOWYCH

DATA NAZWISKO i IMIĘ

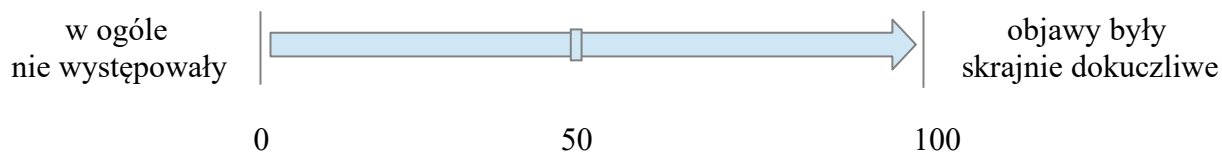
Telefon kontaktowy:

Zgaga- uczucie pieczenia lub palenia za mostkiem które promieniuje do szyi i gardła, któremu towarzyszy cofanie się kwaśnej treści do jamy ustnej.

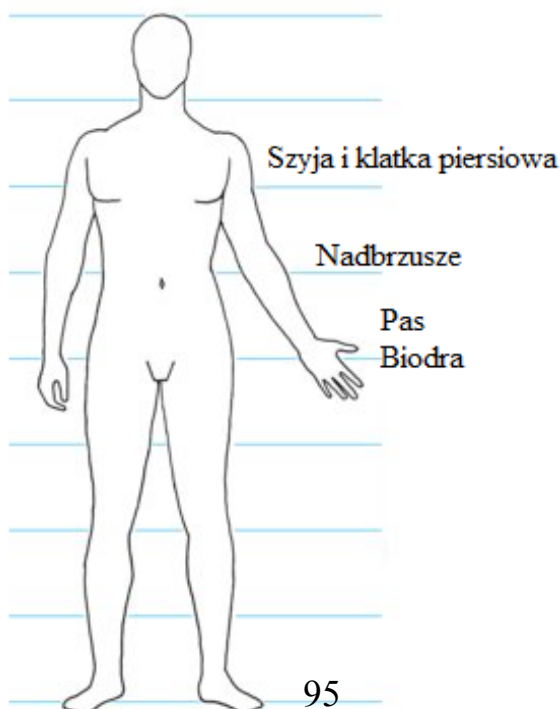
Poniższa skala w postaci strzałki ujmuje dokuczliwość objawów zgagi od 0- brak objawów; do 100- skrajna dokuczliwość (objawy są bardzo częste i niezwykle silne).

Proszę ocenić **dokuczliwość zgagi u Pana(-i) w okresie ostatniego miesiąca**, zakreślając na linii kreskę w wybranym miejscu między 0 a 100.

W ostatnim miesiącu objawy zgagi



Na poniższym rysunku proszę zaznaczyć obszar, w którym zazwyczaj odczuwa Pan(i) pieczenie lub palenie.



OBJAWY W OKRESIE OSTATNIEGO MIESIĄCA

Proszę zakreślić kółkiem wybraną odpowiedź 

1/ Czy uczucie pieczenia/palenia w klatce piersiowej pojawiało się **po posiłkach**?

JAK CZĘSTO?

0

nie występowało

1

sporadycznie
1-2 razy w ciągu miesiąca

2

rzadko
raz w tygodniu lub rzadziej

3

często
kilka razy w tygodniu

4

bardzo często
prawie po każdym posiłku

Z JAKIM NASILENIEM?

1

łagodne
nie zwracające uwagi

2

umiarkowane
zwracało uwagę

3

silne
przeszkadzające

4

bardzo silne
trudne do zniesienia

2/ Czy uczucie pieczenia/palenia pojawiało się **w pozycji leżącej**?

JAK CZĘSTO?

0

nie występowało

1

sporadycznie
1-2 razy w ciągu miesiąca

2

rzadko
raz w tygodniu lub rzadziej

3

często
kilka razy w tygodniu

4

bardzo często
prawie zawsze

Z JAKIM NASILENIEM?

1

łagodne
nie zwracające uwagi

2

umiarkowane
zwracało uwagę

3

silne
przeszkadzające

4

bardzo silne
trudne do zniesienia

3/ Czy uczucie pieczenia/palenia pojawiało się **przy schylaniu**?

JAK CZĘSTO?

0

nie występowało

1

sporadycznie
1-2 razy w ciągu miesiąca

2

rzadko
raz w tygodniu lub rzadziej

3

często
kilka razy w tygodniu

4

bardzo często
prawie przy każdej próbie schylania się

Z JAKIM NASILENIEM?

1

łagodne
nie zwracające uwagi

2

umiarkowane
zwracało uwagę

3

silne
przeszkadzające

4

bardzo silne
trudne do zniesienia

4/ Czy występowały **odbijania** lub uczucie **cofania się pokarmu z żołądka** z pozostawianiem kwaśnego lub gorzkiego smaku w jamie ustnej?

JAK CZĘSTO?	0	1	2	3	4
	nie występowało	sporadycznie 1-2 razy w ciągu miesiąca	rzadko raz w tygodniu lub rzadziej	często kilka razy w tygodniu	bardzo często codziennie lub prawie codziennie
Z JAKIM NASILENIEM?		1	2	3	4
		łagodne nie zwracające uwagi	umiarkowane zwracało uwagę	silne przeszkadzające	bardzo silne trudne do zniesienia

5/ Czy miał (-a) Pan (-i) uczucie **zatrzymywania się połykanego pokarmu** w gardle lub w przełyku?

JAK CZĘSTO?	0	1	2	3	4
	nie występowało	sporadycznie 1-2 razy w ciągu miesiąca	rzadko raz w tygodniu lub rzadziej	często kilka razy w tygodniu	bardzo często przy większości prób połykania
Z JAKIM NASILENIEM?		1	2	3	4
		łagodne nie zwracające uwagi	umiarkowane zwracało uwagę	silne przeszkadzające	bardzo silne trudne do zniesienia

6/ Czy uczucie pieczenia/palenia w klatce piersiowej **utrudniało zaśnięcie lub wybudzało** Pana/Panią w nocy **ze snu**?

JAK CZĘSTO?	0	1	2	3	4
	nie występowało	sporadycznie 1-2 razy w ciągu miesiąca	rzadko raz w tygodniu lub rzadziej	często kilka razy w tygodniu	bardzo często co noc lub prawie co noc

7/ Czy zdarzało się, że miał Pan (-i) uczucie kwaśnego lub gorzkiego smaku w ustach **po nocnym wypoczynku**?

JAK CZĘSTO?

0	1	2	3	4
nie występowało	sporadycznie 1-2 razy w ciągu miesiąca	rzadko raz w tygodniu lub rzadziej	często kilka razy w tygodniu	bardzo często codziennie lub prawie codziennie

8/ Czy zdarzało się, że **odbijania** lub uczucie **cofania się pokarmu z żołądka do z** pozostawianiem kwaśnego lub gorzkiego smaku w jamie ustnej **utrudniało zaśnięcie lub wybudzało** Pana/Panią w nocy **ze snu**?

JAK CZĘSTO?

0	1	2	3	4
nie występowało	sporadycznie 1-2 razy w ciągu miesiąca	rzadko raz w tygodniu lub rzadziej	często kilka razy w tygodniu	bardzo często co noc lub prawie co noc

9/ Jak często w okresie ostatniego miesiąca pojawiały się u Pana/Pani:

0	1	2	3	4
wcale	sporadycznie 1-2 razy w ciągu miesiąca	rzadko raz w tygodniu lub rzadziej	często kilka razy w tygodniu	bardzo często codziennie lub prawie codziennie

Bóle w klatce piersiowej

Uczucie ropierania w klatce
piersiowej w trakcie jedzenia

Ból za mostkiem przy połykaniu

Uczucie pełności w nadbrzuszu

Nudności

Wymioty

Uczucie dławienia w gardle

Krztuszenie się w trakcie jedzenia

Suchość w ustach

Chrypka

Przewlekły kaszel

Uczucie duszności

OBJAWY KLINICZNE GERD:

Suma punktów: dienne (ptk.1-5):

nocne (ptk.6-8):
inne (ptk.9):

BADANIE PODMIOTOWE

Wzrost: _____

Miejsce wkłucia:

Waga: _____

23⁰⁰:

Obwód szyi: _____

1⁰⁰:

Obwód pasa: _____

3⁰⁰:

5⁰⁰:

7⁰⁰:

Przyjmowane leki: _____

PPI/H₂-B (w dawce) _____

Azotany (w dawce) _____

Leki nasilające bezdech: _____

Istotne dla OSA lub GERD i greliny, przebyte operacje (twarzoczaszki, operacje na przewodzie pokarmowym np. resekcja żołądka): _____

Infekcja HP (jest / brak / nie badano): _____

Proszę o zaznaczenie na poniższej tabeli prawdopodobieństwa zaśnięcia we wskazanych sytuacjach w ciągu ostatnich 6 tygodni.

0 – zerowe prawdopodobieństwo zaśnięcia	1 – małe prawdopodobieństwo zaśnięcia
2 – średnie prawdopodobieństwo zaśnięcia	3 – duże prawdopodobieństwo zaśnięcia

Sytuacja	Proszę zaznaczyć właściwą odpowiedź			
Siedzenie i czytanie	0	1	2	3
Oglądanie telewizji	0	1	2	3
Bierne siedzenie w miejscach publicznych (np. w teatrze, na zebraniu)	0	1	2	3
Jako pasażer w samochodzie, jadąc przez godzinę bez odpoczynku	0	1	2	3
Leżenie i odpoczywanie po południu, jeśli okoliczności na to pozwalają	0	1	2	3
W czasie rozmowy, siedząc	0	1	2	3
Spokojne siedzenie po obiedzie bez alkoholu	0	1	2	3
W samochodzie, podczas kilkuminutowego postoju w korku lub na czerwonym świetle	0	1	2	3