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ROZPRAWA DOKTORSKA

Czynniki żywieniowe oraz metody wspomagające monitorowanie glikemii jako determinanty statusu redoks u młodzieży z cukrzycą typu 1

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Spis treści

Rozdział 1. Wykaz publikacji będących podstawą rozprawy doktorskiej

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P.1 Publikacja nr 1 – **Grabia M**, Markiewicz-Żukowska R, Socha K. Prevalence of Metabolic Syndrome in Children and Adolescents with Type 1 Diabetes Mellitus and Possibilities of Prevention and Treatment: A Systematic Review. Nutrients 2021, 13, doi:10.3390/nu13061782
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P.2 Publikacja nr 2 – **Grabia M**, Markiewicz-Żukowska R, Socha K, Polkowska A, Zasim A, Boruch K, Bossowski A. Prevalence of Metabolic Syndrome in Relation to Cardiovascular Biomarkers and Dietary Factors among Adolescents with Type 1 Diabetes Mellitus. Nutrients 2022, 14, 2435, doi:10.3390/nu14122435
IF= 6,706; MEiN= 140

P.3 Publikacja nr 3 – **Grabia M**, Socha K, Soroczyńska J, Bossowski A, Markiewicz-Żukowska R. Determinants Related to Oxidative Stress Parameters in Pediatric Patients with Type 1 Diabetes Mellitus. Nutrients 2023, 15, 2084, doi:10.3390/nu15092084
IF= 6,706; MEiN= 140

P.4 Publikacja nr 4 – **Grabia M**, Socha K, Bossowski A, Markiewicz-Żukowska R. Metabolic Syndrome as a Factor of Impairment of Antioxidant Defense System in Youth with T1DM. International Journal of Molecular Sciences 2023, 24, 9428, doi:10.3390/ijms24119428
IF= 6,208; MEiN= 140

Rozdział 2. Wprowadzenie

Cukrzyca typu 1 (ang. type 1 diabetes mellitus, T1DM) należy do chorób autoimmunologicznych i głównie rozpoznawana jest u dzieci i młodzieży. W trakcie jej rozwoju układ immunologiczny niszczy komórki β wysp trzustkowych, których zadaniem jest produkcja insuliny. Skutkuje to wydzielaniem niewystarczającej ilości tego hormonu, co prowadzi do wzrostu stężenia glukozy we krwi. Konsekwencją częstych i długich hiperglikemii jest powstanie uszkodzeń różnych narządów i tkanek w organizmie [1]. Na przestrzeni ostatnich lat obserwuje się wysoki przyrost zachorowań na T1DM. Według raportu International Diabetes Federation (IDF) z 2023 roku, prawie 9 mln osób jest chorych, w tym ponad 1,5 mln to osoby młode do 20 roku życia. W Polsce szacuje się, że dotyczy ona ponad 15 tysięcy dzieci i młodzieży [2].

Do głównych celów leczenia T1DM w grupie pacjentów pediatrycznych należą m.in. utrzymywanie glikemii, gospodarki lipidowej oraz ciśnienia tętniczego w wartościach docelowych. Pozwala to zapobiec wystąpieniu ostrych i przewlekłych powikłań cukrzycowych oraz umożliwia prawidłowy rozwój fizyczny i dojrzewanie organizmu [3]. Złotym standardem leczenia jest funkcjonalna intensywna insulinoterapia metodą ciągłego podskórnego wlewu insuliny (ang. continuous subcutaneous insulin infusion, CSII) przy pomocy osobistej pompy insulinowej lub wielokrotnych wstrzyknięć insuliny (ang. multiple daily injections, MDI) przy użyciu wstrzykiwaczy typu pen. Do monitorowania odpowiedzi organizmu na stosowaną insulinoterapię służą samodzielne pomiary stężenia glukozy nie rzadziej niż 8 razy na dobę. Najpopularniejszą i jednocześnie najtańszą metodą kontroli glikemii jest zastosowanie glukometru, za pomocą którego dokonuje się pomiaru we krwi włośniczkowej. Obecnie na rynku mamy także do dyspozycji nowoczesne systemy tzw. ciągłego monitoringu glikemii (ang. continuous glucose monitoring, CGM) metodą skanowania (ang. intermittently scanned, isCGM lub dawniej ang. flash, FGM) oraz w czasie rzeczywistym (ang. real time, rtCGM). Sensor umieszcza się w tkance podskórnej, a pomiar odbywa się w płynie śródtkankowym. Dużą zaletą tych systemów jest pełny wgląd w dobową glikemię oraz informacja o tempie i kierunku zmian przy pomocy tzw. strzałek trendu. Jednakże przewagą systemów rtCGM są alarmy ostrzegające przed hipo- i hiperglikemią oraz połączenie z pompą insulinową umożliwiające zatrzymanie podawania insuliny. Jest to niezmiernie istotne u najmłodszych pacjentów, ale także osób z nieświadomością hipoglikemii oraz często podejmujących aktywność fizyczną [3-6].

Równie istotną rolę w leczeniu T1DM, oprócz farmakoterapii, odgrywa dietoterapia. Każdy z pacjentów ma indywidualne potrzeby i dlatego dieta uniwersalna w cukrzycy nie istnieje. Diabetycy powinni być zachęcani do przestrzegania podstawowych zasad prawidłowego żywienia, kontrolowania ilości spożywanych węglowodanów w poszczególnych posiłkach oraz ograniczania żywności zawierającej przede wszystkim cukry dodane. W przypadku istniejących nieprawidłowych nawyków żywieniowych istotna jest odpowiednio zaplanowana edukacja żywieniowa, która pozwoli je zmienić i dostosować do stylu życia pacjenta oraz dodatkowo nauczy komponować posiłki odpowiednio zbilansowane o możliwie niskim ładunku glikemicznym. Zastosowanie powyższych zaleceń może wspomóc nie tylko proces leczenia, ale także wpłynąć korzystnie na prawidłowy rozwój młodego organizmu [3,7,8].

Odsetki młodych osób z nadwagą lub otyłością stale rosną i wynika to m.in. z nieprawidłowych nawyków żywieniowych i niskiej aktywności fizycznej [9]. Obraz dziecka w momencie rozpoznania T1DM jest diametralne odmienny od tego, który charakteryzuje pacjenta z cukrzycą typu 2, szczególnie w aspekcie występowania nadwagi i otyłości. Początkowe stadium T1DM obejmuje m.in. spadek masy ciała [3]. Jednakże obserwacje pacjentów przebywających w klinikach oraz diabetyków żyjących w społeczeństwie, stały się inspiracją do naukowego zgłębienia tematu pojawiającej się nadmiernej masy ciała również wśród takich pacjentów. Nasze badanie pilotażowe ujawniło niekorzystne różnice w stanie odżywienia pomiędzy młodymi diabetykami a grupą zdrowych

rówieśników [10]. Nagromadzenie tkanki tłuszczowej ma negatywny wpływ na organizm nie tylko w zdrowej populacji [9]. Wśród osób z T1DM otyłość może przyczyniać się do pogorszenia wyrównania metabolicznego i pojawienia się zespołu metabolicznego (ang. metabolic syndrome, MetS), który wiąże się z rozwojem powikłań kardiometabolicznych. MetS definiuje się jako grupę różnych czynników (fizjologicznych, biochemicznych i metabolicznych), które zwiększają ryzyko powstania powyższych komplikacji [11]. W opiece nad młodym pacjentem z T1DM stosuje się badania przesiewowe pod kątem występowania pojedynczych zaburzeń cukrzycowych, jednakże czasami nie uwzględniają one jednoczesnej analizy składowych MetS. Temat ten jest poruszany szeroko w literaturze opisującej dorosłych diabetyków, niewiele jest jednak badań wśród młodszych pacjentów, szczególnie połączonych z analizą ich stanu odżywienia i sposobu żywienia [12]. Dodatkowo, wartą uwagi jest problematyka diagnostyki tego zespołu. Wytycznych rozpoznania jest wiele i do najczęściej stosowanych zalicza się utworzone przez IDF [11], National Cholesterol Education Program Adult Treatment Panel III (ATP) [13] oraz Światową Organizację Zdrowia (ang. World Health Organisation, WHO) [14]. Pomimo tego, że korzystają one z tych samych kryteriów (wyjątkiem jest WHO, które bierze również pod uwagę dodatkowy parametr – mikroalbuminurię), to mają one różny stopień ważności lub nie uwzględniają wieku, a zatem często różnią się od krajowych standardów rozwoju fizycznego w populacji pediatrycznej. Takie rozbieżności wpływają na odsetek stawianych diagnoz. Na podstawie naszego przeglądu systematycznego, biorącego pod uwagę badania, które zostały wyselekcjonowane i ocenione pod względem wiarygodności, procent ten oscyluje od 3% do prawie 30%, w zależności od zastosowanych wytycznych [12]. Jest to duży przedział, a co niepokojące, stanowi to znaczny odsetek. Mając na uwadze, że jest to realny problem w grupie młodych pacjentów z T1DM i brakuje jednorodnych zaleceń rozpoznawania MetS oraz badań naukowych, które uwzględniałyby analizy porównawcze różnych wytycznych wraz z włączeniem grup kontrolnych, wydaje się być uzasadnione zgłębienie tego tematu. Jest to również niezwykle istotne z punktu widzenia klinicystów, ponieważ zaproponowanie dodatkowych markerów MetS, mogłoby być pomocne we wczesnej diagnostyce i zapobieganiu odległym powikłaniom kardiometabolicznym, co znacząco podniosłoby komfort życia pacjentów w dorosłym życiu. Nadmierna masa ciała w połączeniu ze zwiększonym ryzykiem kardiometabolicznym jest mocno związana z dysfunkcją adipocytów oraz wydzielaniem prozapalnych adipokin. Może to prowadzić m.in. do wyczerpania zasobów systemu obrony antyoksydacyjnej (ang. antioxidant defense, AOD) i w konsekwencji powstania stresu oksydacyjnego (ang. oxidative stress, OS), który jest stanem zaburzonej równowagi pomiędzy powstawaniem reaktywnych form tlenu (ang. reactive oxygen species, ROS) a zdolnością ich neutralizacji przez systemy AOD [15-17]. Cząsteczki, które posiadają co najmniej jeden atom tlenu i niesparowany elektron nazywa się ROS. Charakteryzują się one wysokim stopniem reaktywności ze składnikami komórek i z perspektywy przemian metabolicznych, jest to zjawisko niekorzystne dla organizmu. W momencie przeciążenia systemów AOD dochodzi do ich nagromadzenia i powstania OS. Aby uniknąć szkodliwych skutków, organizm wykształcił systemy chroniące przed ROS – układ enzymatyczny i nieenzymatyczny. Pierwszy z nich składa się z licznych enzymów, których współpraca jest nakierowana na neutralizowanie ROS, tak aby uniemożliwić uszkodzenie istotnych struktur komórkowych. Do najważniejszych należą m.in. dysmutaza ponadtlenkowa (ang. superoxide dismutase SOD), katalaza (ang. catalase, CAT) i peroksydaza glutationowa (ang. glutathione peroxidase, GPx). Drugi ze wspomnianych układów – nieenzymatyczny – składa się z antyoksydantów, które przede wszystkim można dostarczyć z dietą (witamina E, C, β-karoten, cynk, selen). Współpraca obu tych układów stanowi o całkowitym potencjale antyoksydacyjnym organizmu [17,18]. Badania sugerują, że jednym z możliwych mechanizmów będących u podstaw rozwoju i progresji T1DM jest OS. Może on wynikać z wielu przyczyn m.in hiperglikemii i autoagresji. Długotrwała wysoka glikemia sprzyja nadprodukcji ROS, a niedostateczna aktywność AOD sprawia, że komórki β stają się bardziej podatne na negatywne skutki OS [19-21]. Natomiast autoimmunologia leży u podstaw patogenezy T1DM,

a wywoływanie oksydacyjnych modyfikacji białek i lipidów może wzmacniać odpowiedź immunologiczną prowadząc do powstania OS. W konsekwencji może on doprowadzać do upośledzenia wydzielania oraz działania insuliny, prowadząc m.in. do dalszej hiperglikemii lub uszkodzenia komórek śródbłonka naczyniowego oraz niszczenia komórek β, tym samym pogarszając przebieg T1DM i doprowadzając do rozwoju powikłań, takich jak retinopatia, nefropatia lub neuropatia [19,22].

Cynk (Zn) i selen (Se) należą do składników mineralnych wchodzących w skład nieenzymatycznej obrony antyoksydacyjnej [17]. Ponadto, Zn jest również niezbędnym mikroelementem pełniącym ważną rolę w funkcjonowaniu układu odpornościowego, gojeniu się ran, wzroście i metabolizmie organizmu. Jest magazynowany wraz z insuliną w pęcherzykach wydzielniczych komórek β i odpowiada za prawidłową syntezę oraz wydzielanie insuliny i glukagonu [23]. Miedź (Cu), podobnie jak Zn, należy do składników mineralnych odgrywających rolę w wielu procesach fizjologicznych w organizmie człowieka, w tym w metabolizmie glukozy. Ponadto jest kluczowa dla prawidłowej aktywności enzymów antyoksydacyjnych, takich jak np. SOD. Zbyt niska jej zawartość może prowadzić do zaburzeń w wydzielaniu insuliny i tolerancji glukozy. Z drugiej strony, nadmierne jej spożycie może być niekorzystne dla zdrowia i stanowić jeden z czynników powstania OS. Kluczowe powinno być utrzymanie optymalnego stężenia powyższych pierwiastków w organizmie [24,25]. Dodatkowo, należą one do składników wchodzących w skład centrum aktywnego SOD, który jest jednym z najbardziej efektywnych enzymów mających za zadanie neutralizowanie anionów ponadtlenkowych poprzez przemianę do tlenu i mniej reaktywnego ditlenku diwodoru (H_2O_2) [17]. Drugim istotnym elementem systemu AOD jest CAT, która chroni komórki przed szkodliwym działaniem H_2O_2, uczestnicząc w jego konwersji do tlenu i wody [17,26]. Selen jako pierwiastek o silnym potencjale antyoksydacyjnym warunkuje prawidłowe działanie układu AOD. Z badań wynika, że może mieć istotny wpływ na przebieg T1DM poprzez redukcję OS i poprawę insulinowrażliwości. Jednakże ze względu na liczne rozbieżne doniesienia wymaga to dalszych badań. Wchodzi on w skład centrum aktywnego GPx – jednego z najważniejszych selenoenzymów, którego istotną funkcją jest katalizowanie redukcji H_2O_2 przy udziale zredukowanego glutationu do utlenionej formy glutationu i wody [27]. Natomiast chrom (Cr) jest składnikiem mineralnym biorącym udział w metabolizmie węglowodanów, a badania sugerują jego możliwy wpływ na poprawę wrażliwości tkanek na insulinę, co może ułatwiać kontrolę glikemii, a tym samym potencjalnie wspomagać terapię T1DM [28].

Istnieją badania potwierdzające, że narażenie na niektóre toksyczne pierwiastki może zwiększać ryzyko rozwoju lub progresji cukrzycy. Należą do nich arsen (As), kadm (Cd), ołów (Pb) i rtęć (Hg). Mogą one wpływać negatywnie na funkcjonowanie komórek β odpowiedzialnych za produkcję insuliny w trzustce, powodować ich destrukcję oraz zaburzać metabolizm glukozy [29]. Jednym z pierwiastków toksycznych najczęściej występujących w środowisku (gleba, woda, powietrze) jest Cd, który w organizmie człowieka gromadzi się m.in. w trzustce, nerkach i tarczycy i może upośledzać funkcję tych narządów [29,30]. W przypadku Pb wykazano, że nawet niewielkie ilości mogą negatywnie wpływać na pamięć i koncentrację, a także powodować drażliwość, co może być szczególnie niekorzystne w procesie dojrzewania młodego organizmu [29]. Ludvigsson i wsp. odnotowali podwyższone, w porównaniu z grupą kontrolną, stężenia Hg i As we krwi pępowinowej pacjentów, u których w późniejszych latach rozwinęła się T1DM [31]. Ponadto stwierdzono, że wiele pierwiastków toksycznych może wpływać na wzmożoną peroksydację lipidów. Jednym z produktów tego procesu są substancje reagujące z kwasem tiobarbiturowym (ang. thiobarbituric acid reactive substance, TBARS), w tym dialdehyd malonowy (ang. malondialdehyde, MDA). Powstaje on podczas peroksydacji wielonienasyconych kwasów tłuszczowych. Ze względu na często występujący stan hiperglikemii diabetycy są szczególnie podatni na wytwarzanie TBARS [32]. W związku z powyższym kluczowe wydaje się poszukiwanie czynników wpływających na status redoks u młodzieży z T1DM.

Rozdział 3. Cel pracy z uzasadnieniem podjętej tematyki badawczej

Na przestrzeni ostatnich lat zaobserwowano wzrost występowania nadwagi oraz otyłości, szczególnie wśród dzieci i młodzieży. Tendencja ta jest obserwowana również wśród nastolatków z T1DM [9,10]. Sprzyjają temu nieprawidłowe zachowania żywieniowe, które w połączeniu z nadmierną ilością tkanki tłuszczowej mogą istotnie pogarszać insulinowrażliwość i wyrównanie metaboliczne, przyczyniając się do rozwinięcia MetS, a w konsekwencji powstania wielu powikłań kardiometabolicznych [10,11]. W zapobieganiu wyżej opisanym komplikacjom w T1DM, istotną rolę odgrywa zapewnienie normoglikemii. Występowanie hiperglikemii (przede wszystkim poposiłkowej), nawet przez krótki czas, ze względu na zjawisko „pamięci metabolicznej", powoduje powstanie nieodwracalnych zmian, takich jak np. ekspresja genów lub białek, które mają decydujący wpływ na powstanie powikłań naczyniowych [33-35]. Ważnym czynnikiem przyspieszającym ich powstawanie jest OS. Z kolei nagromadzenie ROS, spowodowane wyczerpaniem zasobów AOD, powoduje, że komórki β wysp trzustki stają się bardziej podatne na jego negatywne skutki [19].

Powyższe aspekty podkreślają znaczenie wczesnej diagnostyki MetS oraz współtowarzyszącego OS w pediatrycznej populacji T1DM w celu zapobiegania zwiększaniu się ryzyka współwystępowania chorób kardiometabolicznych. Częstość ich występowania jest szeroko opisywana u dorosłych [36]. Mimo, że na przestrzeni ostatnich lat wzrasta zainteresowanie OS w cukrzycy [32], w literaturze naukowej brakuje badań dotyczących kompleksowego podejścia do tego zagadnienia u młodzieży z T1DM. Istotne jest również podjęcie tematu oceny sposobu żywienia wraz z podkreśleniem roli żywności o potencjale antyoksydacyjnym oraz uwzględnieniem innych możliwych czynników.

Biorąc pod uwagę wymienione kwestie oraz zebrane i omówione w publikacji **P.1** badania, została spercyzowana hipoteza badawcza, która zakłada, że czynniki żywieniowe, w tym sposób żywienia, ale także stan odżywienia oraz nowoczesne metody monitorowania glikemii wpływają na równowagę redoks u młodzieży z T1DM.

Chcąc sprawdzić słuszność powyższej hipotezy sformułowano następujące cele:

1. Analiza stężeń składników mineralnych, pierwiastków toksycznych i markerów statusu redoks u pacjentów pediatrycznych z cukrzycą typu 1, w zależności od rodzaju insulinoterapii, stosowanego systemu monitorowania glikemii, wyrównania metabolicznego i stażu choroby.
2. Ocena spożycia z dietą składników o potencjale antyoksydacyjnym w grupie młodych diabetyków.
3. Ocena występowania zespołu metabolicznego w grupie młodzieży z cukrzycą typu 1 w zależności od zastosowanych wytycznych diagnostycznych.
4. Zbadanie powiązań między występowaniem zespołu metabolicznego a statusem redoks, wskaźnikami kardiometabolicznymi, stanem odżywienia oraz czynnikami żywieniowymi u młodych pacjentów z cukrzycą typu 1, z uwzględnieniem stosowanego rodzaju monitorowania glikemii.
5. Określenie wartości diagnostycznej wykorzystanych markerów statusu redoks oraz wyrównania metabolicznego choroby jako nowych potencjalnych predyktorów zespołu metabolicznego.

Rozdział 4. Realizacja celów naukowych, zwięzłe omówienie materiałów i metod badawczych, wyniki badań i dyskusja

Badania były realizowane w Zakładzie Bromatologii na Wydziale Farmaceutycznym z Oddziałem Medycyny Laboratoryjnej Uniwersytetu Medycznego w Białymstoku we współpracy z Kliniką Pediatrii, Endokrynologii, Diabetologii z Pododdziałem Kardiologii Uniwersyteckiego Dziecięcego Szpitala Klinicznego (UDSK) im. L. Zamenhofa w Białymstoku. Badania zostały sfinansowane w ramach subwencji Uniwersytetu Medycznego w Białymstoku nr SUB/2/DN/20/002/2216, SUB/2/DN/21/003/2216 oraz SUB/2/DN/22/005/2216. Na przeprowadzenie badań otrzymano zgodę (nr R-I-002/587/2019) Komisji Bioetycznej Uniwersytetu Medycznego w Białymstoku (rozdział 12). Od każdego z pacjentów oraz ich rodziców lub prawnych opiekunów uzyskano pisemną zgodę na przystąpienie do badania.

1) Przegląd literatury naukowej dotyczącej tematyki pracy doktorskiej

W celu przygotowania publikacji **P.1 – P.4** dokonano przeglądu artykułów naukowych dostępnych w bazach PubMed, Web of Science, Scopus, Cochrane Library oraz Google Scholar. Wyszukiwanie odbyło sie w oparciu o kryteria zgodne z tematyką publikacji.

2) Materiał badawczy

Badaniem objęto 168 osób w wieku 10-17 lat.

Grupę diabetyków stanowiło 103 pacjentów z T1DM, którzy znajdowali się pod opieką Kliniki Pediatrii, Endokrynologii, Diabetologii z Pododdziałem Kardiologii UDSK w Białymstoku, w okresie od marca 2020r. do września 2022r. Rozpoznania T1DM dokonywali lekarze ze specjalizacją z diabetologii, zgodnie ze standardami diagnostycznymi opartymi na ocenie obecności przeciwciał [1]. Kryteriami włączenia były: wiek pomiędzy 10 a 17 rokiem życia, potwierdzone występowanie T1DM oraz chęć wzięcia udziału w badaniu. Wykluczono pacjentów, którzy mieli inny typ cukrzycy oraz ciężkie choroby przewlekłe.

Do **grupy kontrolnej** zaliczono 65 zdrowych rówieśników, którzy zgłosili się do Zakładu Bromatologii Uniwersytetu Medycznego w Białymstoku i podczas rekrutacji w wywiadzie nie deklarowali żadnych objawów wskazujących na możliwość występowania cukrzycy lub innych chorób przewlekłych.

3) Przygotowanie materiału biologicznego do oznaczeń

Materiał do badań (krew) pobrano na czczo do dwóch typów probówek Vacutainer zawierających aktywator skrzepu wraz z żelem separującym oraz antykoagulant K2EDTA (Becton Dickinson, Francja). Próbki wirowano przez 10 minut przy użyciu wirówki laboratoryjnej (M-diagnostic, MPW, Polska) ustawionej na 2000 obrotów na minutę. Następnie surowicę zdekantowano do probówek typu Eppendorf i przechowywano w temperaturze –20°C (do oznaczania zawartości pierwiastków) i –80°C (do oznaczania aktywności enzymów antyoksydacyjnych oraz stężenia markerów stresu oksydacyjnego i peroksydacji lipidów).

4) Wykonanie oznaczeń zawartości pierwiastków w materiale biologicznym

W celu przygotowania prób do oznaczenia zawartości Zn, Cu, Se i Cr oraz Cd, Pb, As i Hg materiał poddano odbiałczeniu 1 mol/l kwasem azotowym (V) oraz zastosowano 1% Triton X-100 jako środek powierzchniowo czynny. Materiał odwirowano (10 min.; 6000 obr./min.) przy użyciu wirówki

laboratoryjnej (Centrifuge IKA mini G, IKA, Niemcy), zdekantowano i w nadsączu oznaczono stężenie Zn, Cr, Pb i As. W przypadku Cu i Cd nadsącz rozcieńczono 0,1 mol/l kwasem azotowym (V). Natomiast w celu dokonania pomiaru Se do prób dodatkowo dodano 0,2% Triton X-100. Do wszystkich oznaczeń wykonano krzywe kalibracyjne przy użyciu roztworów podstawowych. Do przeprowadzenia kontroli dokładności zastosowanych metod oznaczeń użyto certyfikowane materiały odniesienia (Seronorm Trace Elements Serum L-1; Seronorm Trace Elements Whole Blood L-2, Sero AS, Norwegia).

Stężenie pierwiastków oznaczono przy użyciu atomowej spektrometrii absorpcyjnej (ASA) z wykorzystaniem spektrofotometru z korekcją tła Zeemana (Z-2000, Hitachi, Japonia). Technikę atomizacji płomieniowej wykorzystano do pomiaru stężenia Zn (surowica), a atomizację elektrotermiczną w kuwecie grafitowej do Cu, Cr, Se (surowica), Cd i Pb (krew pełna). Do oznaczenia As (krew pełna) zastosowano spektometrię mas ze wzbudzeniem w plazmie indukcyjnie sprzężonej (ICP-MS, NexION300D, PerkinElmer, USA) z komorą dyskryminacji energii kinetycznej (KED). Zawartość Hg (krew pełna) oznaczono bezpośrednio w materiale metodą ASA z wykorzystaniem techniki amalgamacji (AMA-254, Leco Corp., Czechy). Powyższe metody zostały opisane i wykorzystane w publikacjach **P.3 – P.4**.

5) Wykonanie oznaczeń aktywności enzymów antyoksydacyjnych oraz stężenia markerów stresu oksydacyjnego i peroksydacji lipidów

Techniką spektrofotometryczną przy pomocy czytnika mikropłytek (Infinite M200 Pro Tecan, Szwajcaria) wykonano pomiar aktywności enzymów antyoksydacyjnych (CAT, SOD, GPx), stężenia całkowitego statusu antyoksydacyjnego (TAS) i oksydacyjnego (TOS) oraz peroksydacji lipidów (MDA). Odczytu dokonano przy użyciu sprzętu udostępnionego przez Zakład Analizy i Bioanalizy Leków Wydziału Farmaceutycznego z Oddziałem Medycyny Laboratoryjnej Uniwersytetu Medycznego w Białymstoku. Katalazę oznaczono przy długości fali 540 nm poprzez pomiar szybkości rozkładu H_2O_2 w reakcji enzymu z metanolem. Ogólną aktywność SOD analizowano przy długości fali 450 nm wykorzystując sól tetrazolową do wykrycia rodników ponadtlenkowych powstałych w reakcji z oksydazą ksantynową i hipoksantyną. Do sprawdzenia aktywności powyższych dwóch enzymów użyto zestawu odczynników z firmy CaymanChem (Cayman Chemical Company, USA). Metoda pomiaru GPx opiera się o reakcję, podczas której katalizuje ona utlenianie glutationu (GSH) przy użyciu wodoronadtlenku kumenu. W obecności reduktazy glutationowej (GR) i NADPH dochodzi do utlenienia glutationu (GSSG), który jest przekształcany w formę zredukowaną. Zmiany zabarwienia były oceniane poprzez pomiar absorbancji przy długości fali 340 nm. Oznaczenie wykonano we krwi pełnej przy użyciu zestawu odczynników Ransel (Randox Laboratories, Wielka Brytania). Stężenie TOS zostało zmierzone bichromatycznie (560/800 nm) w oparciu o utlenianie Fe^{2+} do Fe^{3+}, a wyniki zostały wyrażone jako μmol ewkiwalentu H_2O_2/l. Odczynniki przygotowano zgodnie z metodyką opisaną przez Erel i wsp. [37]. Stężenie TAS określono przy użyciu zestawu odczynników Randox (Randox Laboratories, Wielka Brytania). Obecność przeciwutleniaczy w surowicy powoduje zahamowanie produkcji barwnika, w stopniu proporcjonalnym do ich stężenia, powstałego podczas inkubacji ABTS z peroksydazą i H_2O_2, co umożliwia wykonanie odczytu przy długości fali 600 nm. Wyniki zostały wyrażone jako mmol ewkiwalentu troloksu/l. W celu oznaczenia peroksydacji lipidów wykonano pomiar stężenia MDA metodą TBARS z wykorzystaniem zestawu odczynników z firmy CaymanChem (Cayman Chemical Company, USA). W wyniku reakcji MDA i kwasu tiobariturowego (TBA) w wysokiej temperaturze i kwaśnym środowisku powstaje MDA-TBA, a odczytu dokonuje się przy długości fali 535 nm. Poszczególne metody zostały wykorzystane w publikacjach **P.2 – P.4**.

6) Wykonanie oznaczeń profilu lipidowego i hemoglobiny glikowanej

Stężenia cholesterolu całkowitego (TC), triglicerydów (TG), lipoproteinie o wysokiej gęstości (HDL) oraz niskiej gęstości (LDL), glukozy na czczo oznaczono metodą enzymatyczną przy użyciu analizatora biochemicznego (Alinity c, Abbott Laboratories, USA). Pomiar hemoglobiny glikowanej (HbA1c) wykonano metodą jonowymiennej wysokosprawnej chromatografii cieczowej. Oznaczenia wykonano we współpracy z akredytowanym laboratorium zewnętrznym, poszczególne metody opisano i wykorzystano w publikacjach **P.2 – P.4**.

7) Pomiar ciśnienia tętniczego krwi

Uczestnikom zmierzono ciśnienie tętnicze krwi techniką oscylometryczną przy pomocy medycznego ciśnieniomierza. Metoda została opisana i wykorzystana w publikacji **P.2** oraz **P.4**.

8) Ocena sposobu żywienia

Do oceny zachowań żywieniowych stworzono autorski kwestionariusz składający się z 3 modułów. Pierwszy zawierał pytania mające na celu zebranie ogólnych informacji o pacjencie, drugi obejmował zagadnienia dotyczące insulinoterapii i nowoczesnych metod monitorowania glikemii, zaś trzeci nawiązywał do sposobu żywienia. Dodatkowo, z każdym z uczestników został przeprowadzony 24-godzinny wywiad żywieniowy metodą retrospektywną. Następnie badani otrzymali 2-dniowy dzienniczek żywieniowy, w którym zapisywali spożywane posiłki przez następne dwa dni po teście (grupa kontrolna) lub po opuszczeniu szpitala (grupa T1DM). Młodzież oraz rodzice zostali poinstruowani jak poprawnie wypełnić dokument. W celu oceny spożycia składników odżywczych z dietą zastosowano program “Dieta 6” wykorzystujący polską bazę wartości odżywczych produktów spożywczych i potraw. Uzyskane wartości porównano z polskimi normami żywieniowymi dla zdrowej młodzieży [38], a w przypadku diabetyków zgodnie z wytycznymi Polskiego Towarzystwa Diabetologicznego [3] i International Society for Pediatric and Adolescent Diabetes (ISPAD) [39]. Powyższe metody zostały opisane i wykorzystane w publikacjach **P.2** oraz **P.4**.

9) Ocena stanu odżywienia

Ocena stanu odżywienia opierała się na pomiarach antropometrycznych (wzrost, masa ciała, obwód talii i bioder). Do pomiaru wysokości ciała na stojąco w pozycji frankfurckiej wykorzystano wysokościomierz InLab (InBody, USA) mierzący z dokładnością do 0,1 cm. Obwód talii oraz bioder zmierzono taśmą antropometryczną Gulicka (Baseline 12-1201) z dokładnością do 0,5 cm zgodnie z wytycznymi National Health and Nutrition Examination Survey [40]. W celu zminimalizowania ryzyka rozbieżności pomiary antropometryczne zostały wykonane przez jednego dietetyka. Analizę składu ciała przeprowadzono metodą impedancji bioelektrycznej, przy użyciu profesjonalnego analizatora medycznego Inbody 720 (Inbody, USA). Metoda opiera się na różnicy w przewodnictwie prądu elektrycznego między tkanką tłuszczową i mięśniową [41]. Pomiary zostały wykonane z dokładnością do 0,1 g. Poszczególne metody zostały opisane i wykorzystane w publikacjach **P.2–P.4**.

10) Analiza statystyczna

Dane opracowano zgodnie z zasadami wnioskowania statystycznego wykorzystując oprogramowania Statistica (wersja 13, TIBCO Software Inc., Palo Alto, Kalifornia, USA). W celu prawidłowego przedstawienia danych i dobrania odpowiednich testów statystycznych określono normalność rozkładu zmiennych przy pomocy testów Shapiro-Wilka, Kołmogorowa-Smirnowa

i Lillieforsa. Ze względu na brak normalności rozkładu wszystkie dane zostały przedstawione w formie mediany (Me) oraz zakresu kwartylowego (Q_1-Q_3). Dla zmiennych ilościowych przeprowadzono test U Mann-Whitney'a oraz ANOVA Kruskala-Wallisa z analizą post-hoc. Do wykazania korelacji między badanymi parametrami wykorzystano współczynnik korelacji rang Spearmana. Do oceny zależności pomiędzy zmiennymi jakościowymi zastosowano test niezależności chi-kwadrat, w przypadku niskich liczebności oczekiwanych stosowano test V-kwadrat lub poprawkę Yatesa. Wielowymiarowa analiza korespondencji (ang. multiple correspondence analysis, MCA) jest jedną z eksploracyjnych technik statystycznych, która została wykorzystana do wykrycia wspólnych cech. Liczbę wymiarów wiarygodnie reprezentujących dane określono przy pomocy wykresu osypiska. Następnie dane przeanalizowano i przedstawiono w postaci macierzy Burta. Do oceny przydatności diagnostycznej parametrów wykorzystano analizę krzywej ROC (ang. receiver operating characteristic). Ogólną wartość diagnostyczną wyrażono poprzez pole pod krzywą ROC (ang. area under curve, AUC) z 95% przedziałem ufności (ang. confidence interval, CI) i wartością p. Obliczono punkt odcięcia, czułość i swoistość, indeks Youdena oraz dodatnie i ujemne współczynniki prawdopodobieństwa. Wartości $p<0,05$ uznawano za istotne statystycznie.

11) Wyniki badań i dyskusja

W skład rozprawy doktorskiej jako pierwsza została włączona publikacja (**P.1**), która w formie przeglądu systematycznego przedstawia problematykę diagnostyki MetS oraz częstości jego występowania u dzieci i młodzieży z T1DM. Dodatkowo zawiera omówienie możliwości jego zapobiegania i leczenia. Oszacowanie częstości występowania MetS było utrudnione ze względu na stosowanie różnych kryteriów w badaniach. Ogólny odsetek osób z MetS w badanych populacjach oscylował od 3,2% do 29,9%. Największy procent rozpoznań dokonano w oparciu o wytyczne ATP, dużo mniejszy według IDF. Problem samej otyłości dotyczył średnio prawie 10% badanych, a nadwagi 20%. Na podstawie przeprowadzonych analiz została wskazana potrzeba opracowania jednorodnych wytycznych diagnostycznych, które uwzględniałyby punkty odcięcia opierające się na krajowych siatkach centylowych biorących pod uwagę płeć i wiek, jak zaproponowane np. przez Weissa i wsp. [42]. Jednym z przykładów takich rozbieżności jest kryterium nadciśnienia tętniczego, które opiera się na określonych wartościach liczbowych. Odniesienie wyniku do siatek centylowych pokazuje, że wartość ta może być prawidłowa dla niektórych chłopców np. wysokich i/lub należących do starszej grupy wiekowej [43]. Do podobnych wniosków doszli również Ahrens i wsp. [44]. Każdy z parametrów wchodzący w skład MetS osobno wiąże się ze zwiększonym ryzykiem rozwoju powikłań, w tym także cukrzycowych, a jednoczesne występowanie kilku może znacznie je przyspieszyć lub nasilić [45]. Wobec tego istotne jest nie tylko skupianie się na osiągnięciu optymalnych wartości każdego z osobna, ale przede wszystkim na kompleksowej analizie wszystkich parametrów równocześnie. Wyniki przeglądu (**P.1**) podkreśliły potrzebę dalszych badań w kierunku oceny częstości występowania nadmiernej masy ciała oraz komponentów, jak i samego MetS, w grupie młodych diabetyków. Kolejnym ważnym aspektem wskazanym w przeprowadzonym przeglądzie systematycznym (**P.1**) jest konieczność porównania różnych wytycznych oraz opracowanie dodatkowych lub ujednolicenie aktualnych parametrów.

Ostatnie lata badań pokazały, że coraz więcej nastolatków ma nadwagę. Problem ten zaczyna dotyczyć również pacjentów pediatrycznych z T1DM [9,10]. Na podstawie wniosków wyciągniętych z pracy **P.1** stwierdzono, że sytuacja nie tylko dotyczy nadmiernej masy ciała, ale także może obejmować występowanie MetS, który jako zespół czynników znacząco zwiększa ryzyko występowania powikłań kardiometabolicznych [46]. Stanowiło to podstawę do zgłębienia w kolejnej publikacji (**P.2**) tematyki zależności pomiędzy występowaniem MetS a biomarkerami sercowo-naczyniowymi, stanem odżywienia oraz czynnikami żywieniowymi. Każdy z uczestników został oceniony pod kątem

występowania MetS zgodnie z wytycznymi IDF, ATP, WHO oraz opracowanymi w oparciu o zaproponowane przez Weiss i wsp. Odsetek osób z MetS wahał się od 8% (według IDF) do 25% (według ATP), a w przypadku zmodyfikowanych wytycznych wynosił 18%. W literaturze naukowej zaobserwowano podobne wyniki, najniższe według IDF – 3,2% [47], 8,6% [48] i 9,5% [49], a najwyższe według ATP – 14% [50] i 30% [51]. Jest to przede wszystkim związane z różnym stopniem ważności parametru oceniającego otyłość brzuszną. Wytyczne ATP pozwalają wybrać trzy z pięciu kryteriów, podczas gdy w IDF najpierw powinien zostać spełniony warunek występowania otyłości brzusznej, aby stwierdzić spełnienie kolejnych składowych. W celu dalszych analiz porównawczych wydzielono grupę MetS+, do której zakwalifikowano pacjentów, którzy spełniali kryteria diagnostyczne według co najmniej jednego z powyższych wytycznych. Szczegółowa analiza wykazała istnienie opisanego w poprzedniej pracy (**P.1**) potencjalnego problemu dotyczącego warunku wystąpienia nadciśnienia tętniczego. Potwierdza to fakt, że u znacznie większej ilości osób stwierdzono podwyższone parametry SBP i DBP posługując się percentylami niż w przypadku zastosowania liczbowych punktów odcięcia (**P.2**).

Grupę MetS+ w większości stanowili diabetycy z HbA1c >7% i szacunkowym wskaźnikiem dystrybucji glukozy (ang. estimated glucose disposal rate, eGDR) <8 mg/kg/min, TAS <1,3 mmol/l, średnim (51-99 cm^2) lub wysokim (>100 cm^2) obszarem tkanki tłuszczowej wisceralnej oraz stosujący tylko kontrolę glikemii przy pomocy glukometru, bez wsparcia systemów CGM. Zauważono również, że osoby stosujące którykolwiek z CGM miały istotnie statystycznie niższe stężenia HbA1c (6,7% vs. 8,1%, $p<0,001$) oraz osiągały lepsze parametry profilu lipidowego, takie jak: HDL (61 mg/dl vs. 50 mg/dl, $p<0,05$) oraz TG (58 mg/dl vs. 80 mg/dl, $p<0,05$) niż pacjenci nie wspomagający się CGM. Ponadto w grupie MetS+ odnotowano istotnie statystycznie niższe wartości TAS (1,249 mmol/l) niż w grupie MetS− (1,394 mmol/l) i kontrolnej (1,579 mmol/l), co prawdopodobnie jest konsekwencją długotrwałych i często występujących hiperglikemii przy medianie HbA1c wynoszącej 8,9%. Takie zjawisko sprzyja nadprodukcji ROS, obniżaniu się aktywności enzymów antyoksydacyjnych i nasileniu insulinooporności (IO) [52]. Jednym z parametrów mogącym świadczyć o intensyfikacji IO jest eGDR, który był znacząco niższy w grupie MetS+ (8 mg/kg/min) niż MetS− (10,8 mg/kg/min). Podobne wyniki otrzymali również inni autorzy [53,54]. Zarówno HbA1c, jak i eGDR, przy odpowiedniej wartości diagnostycznej, mogłyby stanowić potencjalne dodatkowe kryterium rozpoznania MetS (**P.2**).

Ponadto, u pacjentów z MetS wykazano istotne statystycznie różnice w spożyciu niektórych składników pokarmowych z dietą, w porównaniu do zdrowych rówieśników. Stwierdzono wysokie spożycie nasyconych kwasów tłuszczowych (17,6 g/dobę vs. 16,0 g/dobę, $p<0,01$) oraz niskie jedno- i wielonienasyconych kwasów tłuszczowych, w tym kwasu oleinowego (12,3 g/dobę vs. 21,4 g/dobę, $p<0,001$), ω-3 (0,831 g/dobę vs. 1,3 g/dobę, $p<0,001$) i ω-6 (4,9 g/dobę vs. 7,6 g/dobę, $p<0,001$). Diabetycy z MetS częściej wybierali chleb pszenny (90% osób, od kilku razy w tygodniu do kilku razy dziennie) niż chleb razowy (45%). Co najmniej raz w tygodniu ponad 35% osób spożywało produkty typu fast-food, 80% jadło smażone potrawy, natomiast 90% wybierało czerwone mięso, a tylko 60% białe. Codziennie warzywa spożywała tylko połowa badanych, podczas gdy po owoce sięgało 65% (**P.2**).

Wstępne wyniki analizujące całkowity status antyoksydacyjny w publikacji **P.2** wskazały potrzebę rozszerzenia oznaczeń w kierunku markerów zaburzeń układu redoks, dlatego obie grupy (badana i kontrolna) zostały powiększone o nowozdiagnozowanych pacjentów. Publikacja **P.3** opisuje zaobserwowane istotności w całej grupie T1DM, a **P.4** zawiera wyniki dotyczące grupy diabetyków podzielonych na spełniających (MetS+) i niespełniających (MetS–) kryteriów rozpoznania MetS.

U diabetyków, w porównaniu do grupy zdrowej, wykazano istotnie statystycznie wyższy stosunek Cu/Zn (1,057 vs. 0,981, $p<0,05$), ale także niższe wartości Zn (0,891 mg/l vs. 0,979 mg/l, $p<0,001$) (**P.3**). Inni autorzy również zaobserwowali zbliżone stężenia Zn, ale wyższe Cu w grupie młodych

diabetyków [55,56]. Pomimo, że znajdowały się one w zakresie referencyjnym, jest to ważna obserwacja, w tej grupie chorych, ze względu na wcześniej wspomniane istotne funkcje pełnione przez te mikroelementy. Podwyższony stosunek Cu/Zn może wskazywać na powstawanie ROS, sprzyjające wystąpieniu OS w organizmie [23,25,57].

Jednak, aby otrzymać kompleksowy obraz, dokonano oznaczeń parametrów związanych z enzymatycznym układem AOD. W porównaniu do grupy zdrowych rówieśników, diabetycy wykazywali wyższe stężenia TOS (7,568 μmol/l vs. 4,847 μmol/l, p<0,001) i OSI (0,575 vs. 0,284, p<0,001), ale także niższe TAS (1,304 mmol/l vs. 1,580 mmol/l, p<0,001), SOD (1,470 U/ml vs. 2,114 U/ml, p<0,001) oraz CAT (43,2 n/mol/min vs. 58,3 n/mol/min, p<0,01) (**P.3**).

Zarówno cukrzyca, jak i otyłość zwiększają ryzyko rozwoju MetS, który może stanowić dodatkowy czynnik prowadzący do zmian w organizmie, skutkujący zaburzeniem równowagi redoks promującym wystąpienie OS [58]. Podobne zależności stwierdzono w grupie diabetyków, którzy spełniali kryteria rozpoznania MetS (**P.4**). Wykazano u nich istotnie statystycznie niższe stężenia TAS (1,186 mmol/l vs. 1,330 mmol/l, p<0,05) oraz wyższe OSI (0,666 vs. 0,533, p<0,01) w porównaniu z pacjentami MetS−. Dokonując analizy porównawczej pomiędzy badanymi MetS+ a zdrowymi rówieśnikami zaobserwowano również niższe wartości TAS (1,186 mmol/l vs. 1,605 mmol/l, p<0,001), ale także SOD (1,165 U/ml vs. 2,101 U/ml, p<0,001), CAT (49,1 n/mol/min vs. 57,7 n/mol/min, p<0,01) i Zn (0,875 mg/l vs. 0,976 mg/l, p<0.01) oraz wyższe TOS (8,176 μmol/l vs. 4,937 μmol/l, p<0.001), OSI (0,666 vs. 0,284, p<0,001) i Cu/Zn (1,113 vs. 0,978, p<0,05) (**P.4**). Powyższe parametry wskazują na zaburzenie równowagi redoks, co w przyszłości może przyspieszyć rozwój powikłań w cukrzycy [21]. Zarówno dla parametrów zawartych w **P.3** jak i w **P.4** nie wykazano istotnych statystycznie różnic pomiędzy chłopcami i dziewczętami oraz rodzajami insulinoterapii. Natomiast w przypadku dodatkowego włączenia któregokolwiek z systemów CGM obserwowano korzystne zmiany parametrów. U pacjentów, którzy zamiast tylko glukometru korzystali ze wsparcia CGM, odnotowywano wyższe wartości TAS (1,336 mmol/l vs. 1,236 mmol/l, p<0,01) i niższe wartości OSI (0,533 vs. 0,706, p<0,01). Ponadto, diabetycy ze słabo wyrównaną (HbA1c w zakresie 7 % do 9,9 %) lub niewyrównaną (powyżej 10 %) metabolicznie chorobą wykazywali znaczące zaburzenia w AOD (TAS, Cu, OSI) w porównaniu do osób z HbA1c poniżej 7% (**P.3**).

Zaobserwowano również, że do grupy MetS+ należeli głównie diabetycy z ponad dwuletnim stażem choroby, a także z gorszą kontrolą metaboliczną choroby (HbA1c ≥8 %, eGDR ≤8 mg/kg/min), co mogło być powiązane ze stosowaniem tylko glukometru jako jedynego sposobu monitorowania glikemii (**P.4**). Wnioski te potwierdzają również inne badania, które wykazują wpływ zastosowania CGM na osiąganie lepszych wartości HbA1c [6,59]. W pracy **P.4** stwierdzono istotne statystycznie korelacje między parametrem HbA1c a eGDR (R=−0,8, p<0,001) i TAS (R=−0,5, p<0,05), ale także innymi parametrami kardiometabolicznymi, jak np. TG (R=0,6, p<0,01) oraz SBP (R=0,5, p<0,05). Obserwowany w **P.4** spadek wartości TAS wraz ze wzrostem stężenia HbA1c, może niekorzystnie wpływać na organizm przyczyniając się do intensyfikacji degradacji komórek β wysp Langerhansa [60]. Zaklasyfikowanie pacjentów do trzech grup ze względu na stężenie (niskie, średnie i wysokie) markerów statusu redoks, pozwoliło dodatkowo potwierdzić powyższe obserwacje – wzrostowi HbA1c towarzyszyło pogorszenie parametrów świadczących o pogłębieniu się OS w grupie T1DM. Dodatkowo, u diabetyków stwierdzono znacząco niższe spożycie z dietą witaminy A oraz β-karotenu w porównaniu do grupy zdrowych rówieśników. Jednak warto zauważyć, że ponad 80% diabetyków z wysokim TAS pokrywało średnie zapotrzebowanie na witaminę A, natomiast ponad 60% na witaminę C (**P.3**).

Analizując stężenia pierwiastków we krwi, zaobserwowano dużo niższe stężenia Cr w grupie T1DM niż w zdrowej (0,648 μg/l vs. 1,530 μg/l, p<0,001) (**P.3**), co również wykazali Lin i wsp. [61]. Ponadto, stwierdzono istotnie statystycznie niższe stężenia Cd (0,629 μg/l vs. 0,784 μg/l, p<0,01)

i wyższe Hg (0,680 μg/l vs. 0,391 μg/l, p<0,01) wśród pacjentów nowozdiagnozowanych niż z T1DM trwającą powyżej 2 lat (**P.3**).

El Amrousy i wsp. wykazali, że pacjenci z T1DM ze względu na częste hiperglikemie, są bardziej podatni na podwyższoną produkcję ROS oraz produktów ubocznych peroksydacji lipidów [62]. Podobne wyniki zaobserwowano w **P.3**. Stężenie MDA było wyższe u diabetyków niż u zdrowych rówieśników (3,912 μmol/l vs. 2,520 μmol/l, p<0,01). Ponadto, osoby ze stażem choroby ponad 2 lata w porównaniu do osób niedawno zdiagnozowanych wykazywały również wyższe stężenie MDA (4,171 μmol/l vs. 3,341 μmol/l, p<0,05) (**P.3**).

Na podstawie przeprowadzonej analizy ROC stwierdzono, że parametry takie jak OSI (AUC: 0,87; p<0,001), TOS (AUC: 0,83; p<0,001) i TAS (AUC: 0,77; p<0,001) mogą być dobrymi predyktorami występowania stresu oksydacyjnego u młodych diabetyków (**P.3**). Co więcej, zaobserwowano również istotną wartość diagnostyczną dla eGDR (AUC: 0,85; p<0.001), HbA1c (AUC: 0,71; p<0,001), TAS (AUC: 0,67; p<0,01), TOS (AUC: 0,63; p<0,05) i OSI (AUC 0,71; p<0,001), które można byłoby zaproponować jako nowe potencjalne składowe MetS (**P.4**). Koken i wsp. w swojej publikacji również zwrócili uwagę, że eGDR mógłby być nowym istotnym parametrem MetS u osób z T1DM [63].

Omówione badania zostały wykonane zgodnie z Indywidualnym Planem Badawczym, realizowanym w ramach kształcenia w Szkole Doktorskiej UMB, z zastosowaniem szerokiego spektrum technik badawczych oraz nowoczesnej aparatury. Pozwoliły one ocenić skalę występowania błędów dietetycznych oraz ryzyko rozwoju MetS u młodzieży z T1DM. Należy zauważyć, że uzupełniły one luki w piśmiennictwie naukowym, które były omawiane w publikacji **P.1**. Większość dostępnych prac dotyczących pacjentów pediatrycznych z T1DM to badania nieuwzględniające grupy kontrolnej, dlatego włączenie zdrowych rówieśników, istotnie podniosło wartość merytoryczną i znaczenie przeprowadzonych analiz. Otrzymane wyniki zostały rozpowszechnione zarówno na arenie krajowej, jaki i międzynarodowej poprzez wystąpienia konferencyjne oraz publikacje prac z pełnym dostępem. Ponadto, spotkały się one z szerokim zainteresowaniem gremium naukowego, co przełożyło się na liczne wyróżnienia wystąpień konferencyjnych oraz wielokrotne cytowanie prac.

Ważnym aspektem praktycznym przeprowadzonych badań było indywidualne przekazanie osobom badanym wyciągniętych wniosków i spersonalizowanych zaleceń w celu zwiększenia efektywności ich terapii.

Rozdział 5. Wnioski

Na podstawie przeglądu systematycznego dostępnych danych literaturowych (**P.1**) i wyników otrzymanych z badań (**P.2-P.4**) możliwe było sformułowanie następujących wniosków:

1. We krwi młodych diabetyków wykazano niższe stężenia markerów statusu redoks prowadzące do występowania stresu oksydacyjnego w organizmie, a także niższe spożycie składników o potencjale antyoksydacyjnym w porównaniu do grupy zdrowych rówieśników.
2. Stwierdzono zależności między parametrami wyrównania metabolicznego i spożyciem składników o potencjale antyoksydacyjnym a wskaźnikiami statusu redoks.
3. Czynnikami wpływającymi korzystnie na markery statusu redoks były: wyrównanie metaboliczne choroby oraz dodatkowe stosowanie systemu ciągłego monitorowania glikemii.
4. Wykazano rozbieżności w częstości rozpoznawania zespołu metabolicznego w grupie pacjentów pediatrycznych z cukrzycą typu 1 ze względu na stosowanie różnych wytycznych o odmiennych punktach odcięcia.
5. Badani z rozpoznaniem zespołu metabolicznego charakteryzowali się nieprawidłowym sposobem żywienia (dieta uboga w jedno- i wielonienasycone kwasy tłuszczowe oraz bogata w nasycone kwasy tłuszczowe), nadmierną zawartością tkanki tłuszczowej, szczególnie wisceralnej oraz pogorszonymi parametrami kardiometabolicznymi.
6. Na podstawie stwierdzonej największej wartości diagnostycznej parametry eGDR oraz HbA1c wytypowano jako nowe potencjalne predyktory zespołu metabolicznego u młodzieży z cukrzycą typu 1.

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Rozdział 7. Streszczenie w języku polskim

Odpowiednie zarządzanie glikemią jest kluczowym elementem leczenia cukrzycy typu 1 (T1DM), a także zapobiega wczesnym powikłaniom cukrzycowym. Niewłaściwie kontrolowana glikemia może sprzyjać rozwojowi lub nasileniu występowania stresu oksydacyjnego (OS). Ponadto, badania wskazują, że wśród młodych diabetyków może rozwijać się otyłość, a nawet zespół metaboliczny (MetS), w przypadku nieprawidłowych zachowań żywieniowych, nieodpowiednio wyrównanej choroby i pojawienia się zaburzeń parametrów kardiometabolicznych. Rozpoznanie MetS znacząco wpływa na przebieg T1DM, powodując pogorszenie wrażliwości tkanek na insulinę oraz wyrównania metabolicznego. Predysponuje to do gromadzenia się reaktywnych form tlenu (ROS), których nadmierna ilość sprzyja pojawieniu się OS.

Biorąc pod uwagę powyższe aspekty została sformułowana hipoteza badawcza zakładająca, że czynniki żywieniowe, w tym sposób żywienia, ale także stan odżywienia oraz nowoczesne techniki monitorowania glikemii wpływają na równowagę redoks u młodzieży z T1DM.

Do badania włączono 103 pacjentów w wieku 10-17 lat ze zdiagnozowaną T1DM. Grupę porównawczą stanowiło 65 zdrowych rówieśników. Przed przystąpieniem do analiz, zebraną od badanych osób krew poddano procesom przygotowawczym. Do oznaczenia stężenia pierwiastków wykorzystano metodę atomowej spektrometrii absorpcyjnej (ASA) przy użyciu spektrofotometru z korekcją tła Zeemana z atomizacją płomieniową (Zn) lub elektrotermiczną w kuwecie grafitowej (Cu, Cr, Se oraz Cd i Pb). W celu oznaczenia zawartości As zastosowano spektometrię mas ze wzbudzeniem w plazmie indukcyjnie sprzężonej (ICP-MS) z komorą dyskryminacji energii kinetycznej (KED). Natomiast stężenie Hg oznaczono bezpośrednio w materiale metodą ASA z wykorzystaniem techniki amalgamacji. W celu oceny statusu redoks wykonano pomiar aktywności enzymów antyoksydacyjnych (CAT, SOD, GPx) i stężenia markerów stresu oksydacyjnego (TAS, TOS, OSI) oraz peroksydacji lipidów (MDA) za pomocą techniki spektrofotometrycznej przy użyciu czytnika mikropłytek. Stężenia parametrów wchodzących w skład profilu lipidowego (TC, HDL, LDL, TG) oraz glukozy na czczo oznaczono metodą enzymatyczną przy użyciu analizatora biochemicznego. Pomiar wartości hemoglobiny glikowanej (HbA1c) wykonano metodą jonowymiennej wysokosprawnej chromatografii cieczowej. Do przeprowadzenia kontroli dokładności zastosowanych metod oznaczeń użyto certyfikowane materiały odniesienia. Pomiar ciśnienia tętniczego krwi dokonano przy pomocy medycznego ciśnieniomierza wykorzystującego technikę oscylometryczną. Ponadto, z osobami badanymi została przeprowadzona ankieta oraz wywiad żywieniowy, na podstawie którego oceniono spożycie składników odżywczych z dietą. Zebrano parametry antropometryczne oraz wykonano analizę składu ciała metodą impdenacji bioelektrycznej. Uzyskano pisemną zgodę rodziców oraz Komisji Bioetycznej UMB. Wyniki opracowano statystycznie w programie Statistica.

Stwierdzono zależności między parametrami wyrównania metabolicznego i spożyciem składników o potencjale antyoksydacyjnym a wskaźnikiami statusu redoks wśród młodych diabetyków. Do czynników, które poprawiały stężenia markerów statusu redoks należą: wyrównanie metaboliczne choroby oraz dodatkowe stosowanie systemu ciągłego monitorowania glikemii. Badani z rozpoznaniem zespołu metabolicznego charakteryzowali się wieloma nieprawidłowymi nawykami żywieniowymi, nadmierną zawartością tkanki tłuszczowej, szczególnie wisceralnej oraz pogorszonymi parametrami kardiometabolicznymi. Dodatkowo, wykazano najwyższą wartość diagnostyczną dla parametrów eGDR oraz HbA1c, które wytypowano jako nowe potencjalne predyktory zespołu metabolicznego u młodzieży z cukrzycą typu 1.

Streszczenie w języku angielskim

Appropriate glycemic management is an essential component of the treatment of type 1 diabetes mellitus (T1DM), and prevents early diabetes-related complications. Improperly controlled glycemia can promote the development or exacerbation of oxidative stress (OS). Moreover, studies point out that obesity and even metabolic syndrome (MetS) may begin to appear among young diabetics, in the case of abnormal dietary behavior, inadequately controlled diabetes, and abnormal cardiometabolic parameters. Diagnosis of MetS significantly affects the progression of T1DM, causing deterioration of tissue insulin sensitivity and metabolic management. It predisposes to the accumulation of reactive oxygen species (ROS), excessive amounts of which contribute to the appearance of OS.

Taking these aspects into consideration, a research hypothesis was formulated, assuming that nutritional factors, including the dietary pattern, as well as the nutritional status and modern glycemic monitoring technologies, influence the redox balance of adolescents with T1DM.

The study group included 103 patients aged 10-17 years with known T1DM. The comparison group consisted of 65 healthy peers. The collected blood from the patients underwent preparatory processes prior to analysis. Atomic absorption spectrometry (ASA) was used to determine concentrations of elements using a Zeeman background-corrected spectrophotometer and flame atomization (Zn) or electrothermal atomization in a graphite cuvette (Cu, Cr, Se and Cd and Pb). To detect As content inductively coupled plasma mass spectrometry (ICP-MS) with a kinetic energy discrimination (KED) chamber was used. The Hg concentration was determined directly in the material by ASA using the amalgamation technique. To assess the redox status, the activity of antioxidant enzymes (CAT, SOD, GPx), the concentration of oxidative stress markers (TAS, TOS, OSI) and lipid peroxidation (MDA) were measured by spectrophotometric technique using a microplate reader. The concentrations of parameters included in the lipid profile (TC, HDL, LDL, TG) and fasting glucose were assayed by enzymatic method using a biochemical analyzer. Glycated hemoglobin (HbA1c) was determined by ion-exchange high-performance liquid chromatography. Certified reference materials were used to check the accuracy of the determination methods performed. The blood pressure was measured with a medical blood pressure device based on the oscillometric method. In addition, a questionnaire and dietary interview were conducted with the participants, upon which dietary nutrient intake was assessed. Anthropometric parameters were collected and body composition analysis was carried out via bioelectrical impedation. Written consent was obtained from the parents and the UMB Bioethics Committee. The results were statistically analyzed using Statistica software.

The relationships between parameters of metabolic compensation and intake of components with antioxidant properties, and markers of redox status among young diabetics have been found. Factors that improve markers of redox status were: metabolic compensation of diabetes and additional usage of a continuous glycemic monitoring system. Respondents with a diagnosis of metabolic syndrome were characterized by a wide range of unhealthy eating habits, excessive body fat (especially visceral), and impaired cardiometabolic parameters. Furthermore, the highest diagnostic value was shown for eGDR and HbA1c parameters, which were singled out as new potential predictors of metabolic syndrome among adolescents with type 1 diabetes.

Rozdział 8. Prevalence of Metabolic Syndrome in Children and Adolescents with Type 1 Diabetes Mellitus and Possibilities of Prevention and Treatment: A Systematic Review

nutrients

MDPI

Review

Prevalence of Metabolic Syndrome in Children and Adolescents with Type 1 Diabetes Mellitus and Possibilities of Prevention and Treatment: A Systematic Review

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Abstract: Overweight and obesity are an increasingly common problem, not only among the healthy population, but also in adolescents with type 1 diabetes (T1DM). Excess body weight is related to many cardiometabolic complications as well as a high risk of metabolic syndrome (MetS). The purpose of this systematic review is to provide a concise and critical overview of the prevalence of MetS in children and adolescents with T1DM and, ultimately, to discuss prevention and treatment options. The study was conducted in accordance with PRISMA guidelines. This review shows that, apart from the growing percentage of overweight and obese children and adolescents with T1DM (on average 20.1% and 9.5%, respectively), the problem of the increasing incidence of MetS (range from 3.2 to 29.9%, depending on the criteria used) is one of the most important phenomena of our time. One of the methods of prevention and treatment is a combined approach: changing eating habits and lifestyle, but there are also reports about the beneficial effects of the gut microflora.

Keywords: type 1 diabetes mellitus; pediatric diabetes; metabolic syndrome; obesity; children; adolescents; nutrition; physical activity; lifestyle; microbiome

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1. Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease where islet β cells are degraded by the body's immune system. These cells are responsible for the secretion of insulin; their death means that less and less of this hormone is released [1]. For many years, the incidence of T1DM has been increasing by about 130,000 new cases each year. Currently, according to a report by the International Diabetes Federation (IDF), T1DM affects over 1.1 million children and adolescents under the age of 20 worldwide [2]. Unfortunately, the rates of overweight and obesity are steadily rising, not only among the healthy population, but also in adolescents with T1DM [3]. Excessive body weight is associated with a heightened risk of cardiometabolic complications [4]. Metabolic syndrome (MetS) is defined as a set of multiple factors (physiological, biochemical and metabolic ones) which directly increase the risk of atherosclerotic cardiovascular diseases (CVD). These are a complication that should be prevented in people with diabetes mellitus (DM) [5]. In 2007, a group of experts from around the world gathered to develop a consensus on the definition of MetS [6]. The IDF recommended that the criteria for patients above 16 years old should be similar to those applied to the adult population, but for children and adolescents between 10 and 16 years of age, they should be adjusted for percentile grids. MetS cannot be diagnosed under 10 years of age unless there are disturbances in these parameters in the family history. In 2009, the American Heart Association published its statement in which it recommended additional identification of cardiometabolic risk but did not specify the exact definition of MetS for the pediatric population [7].

The above-mentioned aspects emphasize the importance of early diagnosis of children in order to prevent the increased risk of comorbid cardiometabolic diseases. An inter-

national consensus on the criteria should be reached so that preventive examination can be performed before the syndrome becomes manifest. The incidence of MetS is widely reported in adults, including DM patients [8]. However, over the past decade, attention has been drawn to the fact that certain components of MetS have begun to appear in children with T1DM.

The purpose of this systematic review is to provide a concise and critical overview of the prevalence of MetS in children and adolescents with T1DM and discuss the possibilities of prevention and treatment.

2. Materials and Methods

2.1. Search Strategy and Selection Criteria

Our systematic review follows the PRISMA guidelines [9]. A search was conducted on PubMed, Scopus, Web of Science and Cochrane Library in May 2020 and updated for studies published up to October 2020. The MeSH terms are shown in Table S1. Analogous terms were used to search other databases. The following were exclusion criteria from this review: adult age (above 21 years of age), non-T1DM, non-English language, animal/cell studies and case-reports. The investigation involved describing the occurrence of MetS using guidelines (Table 1) proposed by, e.g., IDF [6], Adult Treatment Panel III (ATP) [10], Weiss et al. [11], World Health Organization (WHO) [12] in pediatric patients (up to 21 years of age) diagnosed with T1DM (e.g., presence of anti-GAD (Glutamic Acid Decarboxylase) or anti-insulin antibodies). Two reviewers assessed the studies based on the selection criteria and all divergences were resolved by consensus. The search strategy using the PRISMA scheme is shown in Figure 1.

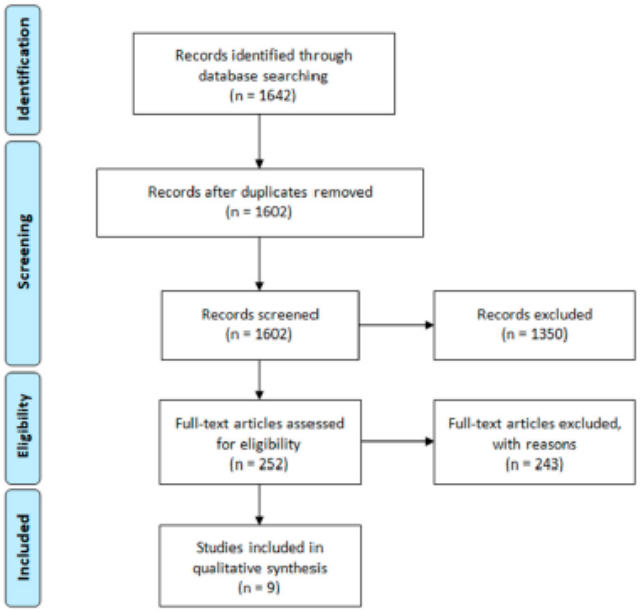

Figure 1. Flow diagram for systematic review.

Table 1. Definitions of metabolic syndrome (MetS) in children.

	IDF			ATP	WHO	Weiss et al.
Age group (years)	<10	10–16	>16	-	-	-
Criteria	Abdominal obesity + two or more of the four criteria			Any three of the five criteria	GI * + two or more of the other components	Any three of the five criteria
Abdominal obesity	≥90th percentile WC		WC: ≥94 cm for Europid men, ≥80 cm for Europid women, with ethnicity specific values for other groups	≥90th WC percentile	WHR >0.9 in males, >0.85 in females or/and BMI>30 kg/m^2	BMI z-score ≥2
Triglycerides	**		≥1.7 mmol/L (≥150 mg/dL)			≥95th percentile
HDL-cholesterol	**	<1.03 mmol/L (<40 mg/dL)	<1.03 mmol/L (<40 mg/dL) in men <1.29 mmol/L (<50 mg/dL) in women or treatment for lipid abnormalities		<0.91 mmol/L (<35 mg/dL) in men <1.01 mmol/L (<39 mg/dL) in women	≤5th percentile
Blood pressure	**	Systolic ≥ 130 / diastolic ≥ 85 mmHg or treatment hypertension		≥90th percentile (age-, sex- and race-specific)	Systolic ≥140 Diastolic ≥90 mmHg	≥95th percentile
Fasting glucose levels	**		≥5.6 mmol/L (100 mg/dL) or known diabetes mellitus		≥6.1 mmol/L (110 mg/dL), which has been changes to ≥ 5.6 mmol/L (100 mg/dL) *	GI (ADA criteria)
Microalbuminuria			-		Urinary albumin excretion rate ≥20 µg/min or albumin/creatinine ratio ≥30 mg/g	-

Abbreviations: American Diabetes Association (ADA), body mass index (BMI), glucose intolerance (GI), high-density lipoprotein (HDL), International Diabetes Federation (IDF), National Cholesterol Education Program Adult Treatment Panel III (ATP), World Health Organization (WHO), waist circumference (WC), waist-hip ratio (WHR); * Or impaired glucose regulation or diabetes mellitus and/or insulin resistance; ** MetS cannot be diagnosed unless there are disturbances in these parameters in the family history.

2.2. Data Extraction and Assessment of Study Quality

Baseline characteristics (study design, author, year), study cohorts (number of participants, age, country, definition of MetS, components of MetS) and outcomes were extracted into an MS Excel worksheet. Included studies were assessed using the "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies" [13]. The questionnaire consists of 14 questions regarding group representativeness, study group recruitment, appropriately selected diagnostic criteria, complications and possible outcome bias. Each question could be answered with "yes" (the item scored 1 point), "no" or "other" (c/d, cannot determine; n/a, not applicable; n/r, not reported). After counting the scores, every study was placed into a quality category (good, fair or poor). Only studies of good or fair quality (for cross-sectional (C-S) studies—from 6 and 4 points, respectively) were included in the review. All divergences of assessment were resolved by consensus.

3. Results

3.1. Identification of Studies

The search yielded 1642 citations (Figure 1). All of them were screened and 40 duplicate articles were removed. Using the selection criteria, 1602 papers were reviewed by title and abstract and 1350 were excluded. A further 252 studies were identified for full-text assessment and 243 papers were excluded. Nine articles qualified for the quality evaluation. All of them were positively assessed and included in this systematic review [14–22]. The most common reasons for rejection were diabetes mellitus other than type 1, adult population or a mixed population of adults and children without the possibility of isolating data for the pediatric patients, and lack of both percentage and numerical data presenting the incidence of MetS in the cohorts.

3.2. Study Characteristics

The characteristics of the included studies are summarized in Table 2. All the papers are C-S studies. As regards T1DM diagnosis, five articles are consistent with the American Diabetes Association (ADA) criteria [1] and participants had a marked presence of anti-GAD or anti-insulin antibodies [14,16–18,21]. However, in the remaining four research projects, patients also came from hospital clinics [15,19,20,22]. There was no conflict of interest in any of the studies. Most of them ($n = 7$) used the IDF definition [14,16,17,19,20,22]; one used criteria consistent with the ATP [18] and Weiss et al. [21], and another used the IDF, ATP and WHO guidelines [15]. Six studies were conducted in Europe [14–16,20–22], two in Asia [17,18] and one in Africa [19].

Table 2. Data extraction format for studies included to compute the prevalence of MetS in children with T1DM.

Author	Country	Sample Size Total (F/M)	Age (Year)	Duration of T1DM (Years)	HbA1c (%)	Over-Weight	Obesity	Diagnosis of MetS		Components of MetS			
								Total	F/M	Ab. Obesity	Low HDL	High TG	High BP
		n	Min–Max	$\bar{x} \pm$ SD Me (IQR)	$\bar{x} \pm$ SD Me (IQR)	*n* (%)		*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Castro-Correia [14]	Portugal	42 (42/-)	14–18	9.2±3.6	8.6±1	18 (42.9%)		n/d	n/d	17 (40.5%)	7 (16.7%)	4 (9.5%)	7 (16.7%)
Köken [15]	Turkey	200 (96/104)	8–18	4.6 ± 3.3	8.4 ± 1.6	19 (9.5%)	17 (8.5%)	17 (8.5%) WHO 21 (10.5%) IDF 27 (13.5%) ATP	11 (11.5%) /10 (9.6%)	n/d	n/d	n/d	24 (12.0%)
Łuczyński [16]	Poland	500 (245/255)	4–18	4.4 (2.1–7.0)	n/a	78 (15.6%)	73 (14.6%)	16 (3.2%) IDF	n/d	67 (13.4%)	32 (6.4%)	31 (6.2%)	24 (4.8%)
Saki [17]	Iran	87 (48/39)	4–21	8.0 ± 3.9	8 ± 3	n/d	n/d	21 (24.1%) IDF	11 (23.2%) /10 (24.8%)	6 (6.0%)	32 (36.8%)	32 (36.8%)	13 (14.9%)
Saki [18]	Iran	87 (48/39)	4–21	8.0 ± 3.9	8 ± 3	n/d	n/d	26 (29.9%) ATP	14 (29.2%) /12 (30.7%)	1 (1.1%)	33 (41.7%)	48 (55.2%)	13 (14.9%)
Soliman [19]	Egypt	160 (83/77)	<18	5.7 ± 3	9 ± 2.2	n/d	n/d	21 (13.1%) IDF	15 (18.1%) /6 (7.8%)	n/d	n/d	n/d	n/d
Szadkowska [20]	Poland	163 (72/91)	10–18	6.2 ± 4.2	8 ± 1.5	n/d	n/d	14 (8.6%) IDF	8 (11.1%) /6 (6.6%)	32 (19.6%)	4 (2.5%)	14 (8.6%)	33 (20.3%)
Van Vliet [21]	The Nether-lands	283 (145/138)	3–18	5.3 (2.9–8.6)	8.3 (7.5–9.8)	83 (29.3%)	26 (9.2%)	81 (28.6%) WEISS	n/d	26 (9.2%)	60 (21.2%)	49 (17.3%)	37 (13.1%)
Valerio [22]	Italy	412 (193/219)	16–19	8.4 ± 3.9	8.9 ± 1.7	101 (24.5%)	16 (3.9%)	39 (9.5%) IDF	31 (16.1%) /8 (3.7%)	83 (20.1%)	66 (16.0%)	23 (5.6%)	73 (17.7%)

Abbreviations: abdominal (Ab), National Cholesterol Education Program Adult Treatment Panel III (ATP), blood pressure (BP), females (F), high-density lipoprotein (HDL), International Diabetes Federation (IDF), interquartile range (IQR), males (M), median (Me), no data (n/d), number of participants (*n*), metabolic syndrome (MetS), standard deviation (SD), type 1 diabetes mellitus (T1DM), triglycerides (TG), World Health Organization (WHO), mean ($\bar{x}$).

3.3. Methodological Quality

The assessment of methodological quality of the included studies is shown in Supplementary Materials Table S2. In accordance with the interpretative recommendations, the research assessment scale was modified for the evaluation of C-S studies. As recommended by the National Institutes of Health [13], for questions no. 6 and 7, all papers were rated "no" and for question no. 8—"n/a". In the first two cases, this was due to the fact that in C-S studies, exposure and its outcomes are measured over the same time interval. The rationale for the third case is that only two exposures were possible in the study ("yes" or "no"), but this should not negatively affect the final quality assessment. Each of the two researchers separately rated each of the papers according to a modified scale, and in case of discrepancies, the grades were awarded after mutual consensus. Of the nine articles, 5 were of good and 4 of fair quality.

3.4. Prevalence of Metabolic Syndrome

The number of people in all the studies included in the review is 1847, the gender distribution is equal—923 boys and 924 girls. As two publications by the same author described the same cohort, only one group was included in the above estimate in order to avoid artificially increasing the size of the sample [17,18]. The study which was the only one involving a population of girls ($n = 42$), conducted by Castro-Correia et al. [14], was the smallest. Among the studies conducted in both sexes, the ones by Saki et al. [17,18] had the smallest cohort ($n = 87$). It was tested by two different criteria of MetS in two publications. The largest sample size ($n = 500$) was found in the study by Łuczyński et al. [16], and the narrowest age groups in the papers by Valerio et al. (16–19 years) [22] and Castro-Correia et al. (14–18 years old) [14]. It was very difficult to estimate the incidence of MetS in studied cohorts due to the high number of different criteria that had been used. The overall percentage of MetS in the studied populations ranged from 3.2% to 29.9%, depending on the criteria selected by the authors. MetS was observed in 90 girls (76 according to the IDF criterion, 14 according to the ATP) and in 52 boys (40 and 12, respectively). Fasting glucose levels were measured in only one cohort [17,18]. The problem of obesity was experienced on average by 9.5% (range: 3.9–14.6%) of the subjects, and 20.1% (range: 9.5–29.3%) were overweight. The average HbA1c value was 8.5% (range: 8.0–9.4%). Abdominal obesity was found in 232 people (14.7% of the entire study population that took the criterion into account), low high-density lipoprotein (HDL) levels in 234 (14.9%), high triglycerides and blood pressure in 201 (12.8%) and 224 (12.6%), respectively.

4. Discussion

4.1. Problem of Overweight, Obesity and Metabolic Syndrome in Healthy and Diabetes Population

The main problem among people with MetS is overweight and obesity. In our review, both of these conditions occurred on average in 20.1% (range: 9.5–29.3%) and 9.5% (range: 3.9–14.6%) of the studied populations, respectively. This may be due to many factors: research of the International SWEET Registry, collecting data from nearly 60 diabetes centers, highlights that there is a significant correlation with age, duration of DM and metabolic control (HbA1c) [23]. Moreover, the problem is also more common among healthy children because—according to WHO data from 2016—over 340 mln children between 5 and 19 years of age have been diagnosed as overweight or obese [24]. It was found that the highest BMI Z-scores occurred in adolescents with T1DM between 15 and 20 years of age [25]. According to the SWEET Registry, every 5 years this indicator increases on average by 0.5 [23]. One explanation of this phenomenon may be excessive consumption of high-energy food (in the form of, e.g., liquid glucose, sweet beverages or candy) for fear of hypoglycemia. Moreover, insulin is an anabolic hormone and, if secreted in excess, can stimulate the appetite, which in the long term may result in weight gain. Thus, the longer

the duration of DM, poor metabolic control (high HbA1c) and high insulin resistance, the greater the predisposition to overweight or obesity [25,26].

The percentage of MetS in the presented set of studies ranges from 3.2% to 29.9%, depending on the criteria used, but in overweight and obese children and adolescents without DM, it ranges from 2.8% to 29.3% and from 10% to 66%, respectively [27]. Despite the considerable discrepancy in our results, it should be noted that this is still a quite large percentage. Some studies have a fairly wide age range of the cohort, which can be an advantage because it means an extensive range of patients in whom MetS can be diagnosed. However, on the other hand, this can also distort the results as, according to the IDF criteria, MetS should not be diagnosed in children under 10 years of age. This highlights the first problem related to evaluating the diagnosis in children. Another problem encountered by the researchers is the fasting glucose level criterion. Some authors have concluded that since T1DM is characterized by fluctuations in glycemia resulting from the pathophysiology of the disease, the criterion should be considered as met and one group of researchers tested each person for fasting glucose levels.

The prevalence of MetS in the adult population with T1DM is 8–45%, depending on age and definition [8]. The incidence rate is higher in the elderly and when using the WHO criteria. This is probably because of the inclusion of microalbuminuria as a component of MetS [8,28]. Despite strictly defined criteria in the adult population, in children, there are no homogeneous and objective criteria for the diagnosis of MetS. The development of standards should be based on the outcomes related to appropriate norms for sex, age and ethnicity, such as those proposed by Weiss et al. [11]. Taking into consideration the Polish national percentile grids [29] as an example, it was proposed to diagnose central obesity above the 95th percentile. This value does not coincide with the IDF cut-off point (90th percentile). The suggested cut-off points for hypertension are based on a specific numerical value ($\geq$130/85 mmHg), and this value may be normal for tall boys [30]. A similar issue was discussed by Ahrens et al. [31], who emphasized that high BP cut-off values could contribute to the low percentage of children classified as having MetS. Ferranti et al. [32] compared the values of lipid parameters to their grids and observed that the level of HDL (40 mg/dL) was 10–25th percentile for boys, and the 10–15th percentile for girls, which is lower than the 40th percentile for adults. A similar phenomenon occurs in the case of the cut-off points for triglycerides (110 mg/dL), which are higher than in the adult population (85–95th vs. 75–85th percentile). Each MetS parameter is related to a number of health complications. Some writers have suggested that MetS is associated with an increased risk of diabetes complications (nephropathy, neuropathy and retinopathy) [28,33–35]. Obesity is associated with an increased need for insulin and worse metabolic control, which increases the chances of developing atherosclerotic complications and possible hospitalization due to CVD [4,36]. In addition, as an individual factor, it exacerbates the risk of orthopedic complications, cholecystitis and the appearance of psychosocial symptoms in children [37]. Adolescents with T1DM are predisposed to cardiometabolic complications [38], often regardless of body weight but, worryingly, their development of obesity can sometimes result in the development of "double diabetes" with type 2 diabetes mellitus (T2DM). Pozzilli et al. described several such case studies [39]. Some studies indicate an association of low HDL cholesterol with deteriorated metabolic control, which increases the likelihood of micro and macrovascular complications [40]. People with higher levels of this cholesterol fraction are less likely to develop neuropathy [41]. The occurrence of hypertension is associated with diabetic nephropathy, weight gain and insulin resistance [42].

Each of these factors individually significantly increases the risk of health complications, and their simultaneous occurrence may additionally accelerate and intensify them. Therefore, it is important not to focus only on analyzing individual parameters, but to identify all MetS components simultaneously.

Cluster tracking studies have found that some cardiovascular risk factors may persist into later life [43]. Due to the growing statistics of obesity and comorbidities in children,

screening of metabolic risk groups is of great importance for the primary prevention of atherosclerosis [44].

Recent years of above research have shown that obesity-related complications have become a very common phenomenon in the pediatric population, which underlines the urgent need to create a new definition of MetS to assist in the early diagnosis and prevention of cardiometabolic disorders. It would be important to develop additional and better MetS markers to enrich diagnostics, thus helping clinicians recognize the warning signs in time.

4.2. Strategies for the Prevention and Treatment of Metabolic Syndrome

4.2.1. Diet

The main goal of preventing obesity among children is to promote a healthy lifestyle through a balanced diet (increased consumption of fruit and vegetables, avoiding sweetened drinks, refined carbohydrates and processed foods), appropriate health habits (screen and sleep time) and physical activity [45]. Kamath et al. conducted a meta-analysis which showed a small but statistically significant positive effect of lifestyle interventions on the reduction of unhealthy habits (−0.15; CI = −0.22 to −0.08) and sedentary behavior (−0.29; CI = −0.35 to −0.22) [46]. Excessive consumption of calories that come from fat and low intake of fiber, fruit and vegetables has been associated with the risk of CVD in people with T1DM [47,48]. A proper diet reduces facilitates weight control [49] and is correlated with better glycemic control [50] and prevention of cardiometabolic diseases in adolescents with T1DM [47].

Research highlights that healthy eating patterns, such as the Mediterranean diet (MD) and the Dietary Approaches to Stop Hypertension (DASH) diet have a positive effect on improving the parameters of people with MetS. A large pro-health role is attributed to increased consumption of fish, whole grains, vegetables, legumes and dairy products, but also of such nutrients as: antioxidants, calcium and B vitamins. Many studies emphasize the importance of curbing the consumption of red meat, simple carbohydrates and products with a high glycemic index and glycemic load [51].

It has been shown that a very helpful way to reduce the occurrence of MetS in children was to implement the MD, which is characterized by high consumption of olive oil, vegetables and grains, and reduced consumption of red meat and sweets. There was an 11% decrease in the incidence of MetS (16% up to 5%) in people on the MD compared to control group [52]. Other studies have found a 2.5-fold increased risk of MetS from consuming highly processed foods and more than a 5-fold increased risk from consuming sugar-sweetened beverages (SSB) [53,54]. Unfortunately, no studies have been conducted to assess the effect of excluding SSB on MetS, but one study has revealed that their elimination may improve body weight [55]. Therefore, MetS patients should strive to reduce the amount of SSB, saturated fats and highly processed foods in their diets and consume more oils and vegetables.

Asghari et al. conducted a study on 425 healthy children (6–18 years old) with MetS and found that following the DASH diet resulted in a 64% lower risk of MetS and, along with higher scores on this diet, correlated with lower BP, fasting glucose level and abdominal obesity [56]. A study by Peairs et al. investigated the DASH diet and its modified version (30% of calories from fat, 50% from carbohydrates, 20% from protein) adapted to the young with T1DM and compliant with the ADA guidelines. It was shown that the modified version resulted in reducing the levels of glucose, and thus better glycemic control and a reduction in the number of hyperglycemic incidents. In addition, the quality of the diet was improved by higher consumption of fruit, vegetables, fiber and protein, compared to normal intake [57].

Antioxidants reduce oxidative stress and may prevent later complications. Bahadoran et al. proved that a diet rich in antioxidant nutrients (vitamin C, E, β-carotene) improves glucose metabolism and plays a significant role in the prevention of CVD [58]. It was observed that higher calcium intake was significantly associated with lower MetS occurrence, improved BP and increased insulin sensitivity [59,60]. Bian et al. conducted a study

demonstrating that consumption of foods rich in B vitamins negatively correlated with the risk of MetS [61].

4.2.2. Lifestyle and Physical Activity

Research suggests that the quality and duration of sleep may have a positive effect on the management of childhood obesity by reducing food consumption, which contributes to body weight loss [62]. In addition, inadequate duration of sleep is associated with a decrease in insulin sensitivity in patients with T1DM [63].

WHO recommends that moderate physical activity among children and adolescents should last at least 60 min a day [64]. In people with DM, it is particularly important because it improves insulin sensitivity [65]. Therefore, it is crucial to include exercise in a child's routine, e.g.: through family walks, using a pedometer to record the number of steps taken, so that the child can check his achievements on an ongoing basis and share them with friends, which can increase motivation for a more active lifestyle. Parents should encourage their children to attend school sport clubs [66]. A systematic review by Quirk et al. shows an association of physical activity with a statistically significant decrease in some MetS components, such as level of triglycerides and total cholesterol. There were no significant differences in the concentrations of HDL and LDL cholesterol [67]. Salem et al. conducted a study among adolescents with T1DM and observed significantly decreased HbA1c values, insulin requirements, BMI and waist circumference in exercise groups (1 and 3 times a week) [68].

4.2.3. Combined Approach

The most effective intervention to reduce or treat MetS is a combined approach, involving control energy and diet quality along with increasing energy requirements through physical activity. To achieve this, dietary counseling is necessary to help the parents of young patients. The above approach is likely to result in a noticeable decrease in MetS over time, as was the case in the study by Caranti et al., which reports a reduction from the initial 27% of children with MetS to 8.3% after one year of using the combined intervention [69,70].

There are few research papers on the long-term benefits of lifestyle interventions. One of the key approaches is to strike an energy balance between consumption of calories and energy expenditure with an appropriate insulin therapy aimed at avoiding hypoglycemic episodes. This is possible to achieve with the support of a multidisciplinary team with a dietitian involved. Due to insufficient evidence, the Adult Diabetes Prevention Program can serve as an example [71]. It has been confirmed that intensive lifestyle change is associated with a reduction in the severity of MetS and diabetic complications. It should be applied to pediatric diabetic populations in which such an intervention could improve metabolic management and achieve long-term pro-health effects. However, at the beginning of 2021, a protocol in the Cochrane database was developed that presents a reliable source of knowledge on nutritional interventions linked to physical activity in the form of a systematic review and meta-analysis [72].

4.2.4. Gut Microflora

Current research describes the crucial role of the gut microflora in the pathogenesis of both major types of DM [73]. Increased numbers of *Bacteroides* and *Streptococci* and decreased levels of *Clostridium IV* and *XIVa* clusters may contribute to T1DM progression, possibly causing inflammation. Knip and Siljander highlight that the role of the microflora may be important in preventing the onset and aggravation of the T1DM process if the type of healthy gut microflora could be established at birth [74]. Even though chronic low-grade inflammation is not a defining criterion for MetS, it is a proven factor in the etiopathogenesis of obesity, but also insulin resistance, and thus is closely related to the metabolic disturbances in MetS. The role of intestinal permeability in chronic low-grade inflammation confirms the importance of the microbiome, especially in the case of

metabolic disorders [75]. Thaiss et al. conducted a study that demonstrated a relationship between glycemia, inflammation and intestinal permeability in both animal and human models. By inducing intestinal hyperglycemia, the authors discovered that HbA1c was a marker positively connected with an increase in serum receptor pathogen recognition (PRR) ligands [76]. This may imply that the MetS criterion should also include the relationship between impaired metabolic control, inflammation and the gut microbiome, which can be modified through eating habits and lifestyle [75]. Most studies report differences in the composition of the gut microbiota between lean and obese subjects (increase in *Firmicutes* and decrease in *Bacteroidetes*) [77,78]. Several studies have confirmed that there is a difference between the microbiota in people with T1DM and healthy ones [79,80]. The microflora of DM patients has a pro-inflammatory phenotype. So far, the causes have not been identified, but research results indicate that the duodenum should be considered a therapeutic target for the inflammatory processes that occur in autoimmune diseases. Increased intestinal permeability is regarded as a potential mediator of the occurrence of T1DM and may be altered by restoring the normal microbiome [81]. The consumed food, and more precisely its nutrients such as sugars, fiber, resistant starch, fats and proteins, affects the type of gut microbiome. Artificial sweeteners are among the ingredients that can negatively influence not only the microbiota but also blood glucose levels [82]. It has been observed in people with known insulin resistance that the plasma metabolome is high in branched-chain amino acids (BCAAs) and in the gut microbes that synthesize them [83]. This may be an important issue for people with newly diagnosed T1DM because a significant relationship has been demonstrated between high consumption of BCAAs and omega-3 fatty acids and the maintenance of β cell function [84].

4.2.5. Pharmacological Support

There is little evidence for pharmacological support, mainly small studies on the use of metformin and dapagliflozin. In the case of the former drug, according to a systematic review by Al Khalifah et al., a small but statistically significant decrease in body weight (−1.46 kg; $p < 0.01$), BMI Z-score by 0.1 ($p < 0.05$), and insulin requirements (−0.16 units/kg/day; $p < 0.0001$) have been observed. There were no significant changes in HbA1c [85]. As for dapagliflozin, which is an inhibitor of sodium-glucose co-transporter 2 (SGLT2-I), one conference report examined its effect at a dose of 10 mg/day for 12 months in three girls with T1DM aged 15 ± 2 years. After 6 months, there was a reduction in the insulin dose (from 58 ± 16 to 35 ± 7 U/day), glucose level (from 191 ± 24 to 171 ± 34 mg/dL), and BMI (from 1.42 ± 0.7 to 0.75 ± 0.8 SDS), but HbA1c did not change. After another 6 months of observation, the above parameters abruptly rose in spite of the initial drop (51 ± 6 U/day; 177 ± 22 mg/dL; 0.86 SDS, respectively). It was also reported that the side effects of the drugs included euglycemic ketosis and hand tremor, and the need for randomized controlled trials was emphasized [86]. In the group of adults with T1DM, a randomized double-blind study was conducted with a dose of 5 and 10 mg/day. After 24 weeks of research, positive results were obtained in the form of an improvement in HbA1c results and weight loss without an increased number of hypoglycemic episodes [87]. However, further testing of this drug is still required, especially in the pediatric group.

4.2.6. Bariatric Surgery

Bariatric surgery, undertaken only in specific cases (especially severe obesity), is one of the most invasive types of treatment for MetS. A study was conducted on a group of 13 obese T1DM patients with average age of 39 years, who had undergone surgery using gastric bypass ($n = 6$) and sleeve gastrectomy ($n = 7$). Comparable benefits were demonstrated in all comparator groups (T1DM, T2DM, control). After 12 months, the median HbA1c decreased (8.3% vs. 7.6%), and the mean insulin dose was reduced (0.8 vs. 0.45 U/kg/day) [88]. Data from scientific publications discussing the use of bariatric surgery concern mainly teenagers. Inge et al. investigated the changes occurring within 5 years after surgery in a larger group, including 161 adolescents. It was observed that 60% of participants

maintained weight loss of above 20%. At the beginning, T2DM was present in 14% patients, and almost 90% were taking medications for DM; a year after the surgery, these percentages decreased, and 4 years later, DM was observed only in 2% and none of the people was taking any medications anymore. Furthermore, there were reductions in the incidence of arterial hypertension (30% vs. 15%) and the percentage of people taking antihypertensive drugs (57% vs. 11%). The proportion of patients with hypertriglyceridemia and low HDL cholesterol (36% vs. 6%; 53% vs. 13%) was lower. Death occurred in 3 adolescents (one—3 years after surgery probably from sepsis after a hypoglycemic episode, and two—4 years after surgery due to drug overdose) [89]. However, this method should be a definitive approach, considered and supported by rational arguments and only as a last resort.

4.2.7. Strength and Limitations

The strength of this systematic review is that it identifies gaps in the literature regarding the increasing prevalence of MetS even in children with T1DM. The results of this review have revealed that there is a need for further research in this area. Many studies assess the prevalence of overweight and obesity as well as various blood parameters of people with T1DM, especially in the adult population. However, only in a few studies they are all analyzed together and considered in terms of MetS.

There are also some limitations that should be mentioned. Despite the great efforts of the authors to perform a reliable manual search of databases and literature reference lists, it is possible that some studies that could be included in the review were omitted. Additionally, the fact that this work consists of cross-sectional studies may potentially cause a risk of bias, due to the small number of publications that met the inclusion criteria. In addition, most of the included studies were carried out on populations of European and Middle Eastern descent, which may have an impact on the range of results, due to the different national standards set in the countries of study.

The consequences of obesity, MetS and T1DM are closely related so it is sometimes difficult to distinguish between them. Excessive body weight significantly affects the course of DM, resulting in deterioration of insulin sensitivity and metabolic control. Entering adult life with such a burden may mean increased CVD risk and faster development of diabetic complications.

5. Conclusions

The above review indicates that currently one of the important issues is not only the increasing percentage of overweight and obese children and adolescents with T1DM, but also the new additional problem of increased MetS incidence. Research is required to investigate this problem in more depth and on much larger diabetic populations. Analysis of relevant studies may be helpful in developing new guidelines that are effective in reducing the occurrence of MetS among children with T1DM, who may face a range of complications in adulthood.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/nu13061782/s1, Table S1. MeSH terms; Table S2. The assessment of methodological quality included studies.

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Supplementary Material

Prevalence of Metabolic Syndrome in Children and Adolescents with Type 1 Diabetes Mellitus and Possibilities of Prevention and Treatment: A Systematic Review

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Table S1 MeSH terms.

Search: (((((((diabetes type 1) OR (T1DM)) OR (T1D)) AND (children)) OR (adolescents)) OR (youth)) OR (teenagers)) AND (metabolic syndrome)
((("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields] OR "diabetes type 1"[All Fields] OR "T1DM"[All Fields] OR "T1D"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields])) OR ("adolescences"[All Fields] OR "adolescency"[All Fields] OR "adolescent"[MeSH Terms] OR "adolescent"[All Fields] OR "adolescence"[All Fields] OR "adolescents"[All Fields] OR "adolescent s"[All Fields]) OR ("adolescent"[MeSH Terms] OR "adolescent"[All Fields] OR "youth"[All Fields] OR "youths"[All Fields] OR "youth s"[All Fields]) OR ("adolescent"[MeSH Terms] OR "adolescent"[All Fields] OR "teenage"[All Fields] OR "teenager"[All Fields] OR "teenagers"[All Fields] OR "teenaged"[All Fields] OR "teenager s"[All Fields] OR "teenages"[All Fields])) AND ("metabolic syndrome"[MeSH Terms] OR ("metabolic"[All Fields] AND "syndrome"[All Fields]) OR "metabolic syndrome"[All Fields])
Translations
diabetes type 1: "diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields] OR "diabetes type 1"[All Fields]
children: "child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child's"[All Fields] OR "children's"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields]
adolescents: "adolescences"[All Fields] OR "adolescency"[All Fields] OR "adolescent"[MeSH Terms] OR "adolescent"[All Fields] OR "adolescence"[All Fields] OR "adolescents"[All Fields] OR "adolescent's"[All Fields]
youth: "adolescent"[MeSH Terms] OR "adolescent"[All Fields] OR "youth"[All Fields] OR "youths"[All Fields] OR "youth's"[All Fields]
teenagers: "adolescent"[MeSH Terms] OR "adolescent"[All Fields] OR "teenage"[All Fields] OR "teenager"[All Fields] OR "teenagers"[All Fields] OR "teenaged"[All Fields] OR "teenager's"[All Fields] OR "teenages"[All Fields]
metabolic syndrome: "metabolic syndrome"[MeSH Terms] OR ("metabolic"[All Fields] AND "syndrome"[All Fields]) OR "metabolic syndrome"[All Fields]

Table S2 The assessment of methodological quality included studies.

Question number	Criteria	Castro-Correia [14]	Köken [15]	Łuczyński [16]	Saki [17]	Saki [18]	Soliman [19]	Szadkowska [20]	Valerio [21]	Van Vliet [22]
1.	Research question	yes	yes	yes	yes	yes	yes	yes	yes	yes
2.	Study population	yes	c/d	yes	yes	yes	yes	yes	yes	yes
3.	Participation rate	no	n/r	n/r	n/r	n/r	n/r	n/r	yes	n/r
4.	Groups recruited from the same population and uniform eligibility criteria	yes	yes	yes	yes	yes	yes	yes	yes	yes
5.	Sample size justification	no	no	no	yes	yes	no	no	no	no
6.	Exposure assessed prior to outcome measurement	no	no	no	no	no	no	no	no	no
7.	Sufficient timeframe of effect	no	no	no	no	no	no	no	no	no
8.	Different levels of the exposure of interest	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
9.	Exposure measures and assessment	yes	yes	yes	yes	yes	yes	yes	yes	yes
10.	Repeated exposure assessment	no	no	no	no	no	no	no	no	no
11.	Outcome measures	yes	yes	yes	yes	yes	yes	yes	yes	yes
12.	Blinding	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
13.	Follow-up rate	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
14.	Confounding	n/r	n/r	yes	n/r	n/r	no	no	yes	yes
	Quality category	**fair**	**fair**	**good**	**good**	**good**	**fair**	**fair**	**good**	**good**

Each question could be answered with yes (the item scored 1 points), no or other (c/d, cannot determine; n/a, not applicable; n/r, not reported.

Rozdział 9. Prevalence of Metabolic Syndrome in Relation to Cardiovascular Biomarkers and Dietary Factors among Adolescents with Type 1 Diabetes Mellitus

nutrients

MDPI

Article

Prevalence of Metabolic Syndrome in Relation to Cardiovascular Biomarkers and Dietary Factors among Adolescents with Type 1 Diabetes Mellitus

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Abstract: The occurrence of metabolic syndrome (MetS) significantly affects the course of diabetes mellitus (DM), resulting in deterioration of insulin sensitivity and metabolic control, as well as many cardiometabolic complications. The aim of the study was to investigate the relationships between cardiovascular biomarkers, nutritional status, dietary factors and the occurrence of MetS among 120 participants from northeast Poland (adolescents with type 1 DM and healthy peers). MetS was assessed using several criteria: nutritional status by anthropometric measurements, body composition analysis by bioelectrical impedance, and diet using a food diary and questionnaire. MetS was diagnosed in every third diabetic. Compared to healthy peers, MetS patients had higher total body fat (26% vs. 14%, $p < 0.001$) and visceral fat (77 cm^2 vs. 35 cm^2, $p < 0.001$), and lower total antioxidant status (1.249 mmol/L vs. 1.579 mmol/L, $p < 0.001$). Additionally, their diet was rich in saturated fatty acids, but low in dietary fiber as well as mono- and polyunsaturated fatty acids. The group of diabetics reported many inappropriate eating behaviors. The combination of those with the presence of an excessive content of visceral fat tissue and abnormal values of MetS components may negatively affect metabolic control, thus accelerating the development of cardiometabolic complications.

Keywords: diabetes type 1; adolescents; metabolic syndrome; obesity; insulin therapy; nutritional status; nutrients intake; antioxidant status; body composition; continuous glucose monitoring

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1. Introduction

Diabetes mellitus (DM) has become one of the most common chronic diseases of the 21st century [1]. Type 1 diabetes mellitus (T1DM) is an autoimmune disease in which the body attacks the beta cells of the pancreas, which produce insulin. As a result, insufficient amounts of insulin are secreted. The disease is most common in children and adolescents [2]. In 2021, the worldwide incidence of DM reached the level of 1.2 million children and adolescents up to the age of 19, exceeding 180,000 new diagnoses annually [1]. Patients need daily insulin injections to keep their blood glucose levels within the proper range. Intensive insulin therapy can be performed by means of continuous subcutaneous insulin infusion (CSII) with an insulin pump or multiple daily insulin-pen injections (MDI) [2]. Flash (FGM) or continuous (CGM) glucose-monitoring systems are becoming increasingly popular methods of monitoring blood glucose levels. They are designed to facilitate

everyday life and reduce the number of punctures of fingertips, as well as the number of hypo- and hyperglycaemic incidents [3].

Increasingly, overweight and obesity are being diagnosed as resulting from poor eating habits and low physical activity [4,5]. In combination, they can significantly worsen metabolic management, contributing to the development of metabolic syndrome (MetS) defined as a set of multiple biochemical, metabolic, and physiological factors that increase the risk of many cardiometabolic complications [6].

The most common diagnostic criteria used by researchers are created by the International Diabetes Federation (IDF) [7], the National Cholesterol Education Program Adult Treatment Panel III (ATP) [8], and the World Health Organization (WHO) [9]. Depending on the selection, estimates are quite divergent (between 3% and 30% of the pediatric population has T1DM). Although adult T1DM is widely covered by the literature, there is little research on this disease among children and adolescents, especially in conjunction with the analysis of their nutritional status and diet. Guidelines use different values of the criteria with different degrees of severity for the individual components of MetS. In addition, some of the criteria do not take age into account and, therefore, often differ from the national standards for the physical development of the pediatric population. Moreover, there is a dearth of studies that include comparative analyses of control groups [10].

The aim of the study was to investigate the relationships between the occurrence of MetS and cardiovascular biomarkers, nutritional status, and dietary factors among adolescents with T1DM, in comparison to healthy peers.

2. Materials and Methods

2.1. Study Group

The case-control study was conducted among 120 Polish patients with T1DM and healthy adolescents aged 10–17 years between March 2020 and July 2021. The T1DM group (n = 60) contained adolescents with T1DM from the Clinic of Pediatrics, Endocrinology, Diabetology with Subdivision of Cardiology, in the Children's University Clinical Hospital in Białystok, while the group without T1DM (n = 60) consisted of adolescents who reported directly to the Department of Bromatology, in the Medical University of Białystok. The recruitment process for the control group involved an interview to verify that they had no symptoms indicating the possibility of diabetes or other chronic diseases. In addition, the questionnaire included a screening question about the presence of various chronic diseases. The inclusion process is illustrated in Figure 1. The main study-inclusion criteria were: age between 10 and 17 years as well as T1DM and diabetes lasting for more than two years, without remission. The diagnosis of T1DM was confirmed according to the guidelines of the American Diabetes Association, with consideration of the frequent presence of autoantibodies (glutamic acid decarboxylase, islet cell antibodies, and insulin autoantibodies) in blood samples [11]. Written consent of the participants' parents and the bioethics committee (No. R-I-002/587/2019) were obtained to perform the study.

2.2. Blood Samples Analysis of Cardiovascular Biomarkers

Blood samples were drawn from participants using vacutainer-system tubes containing clot activator + gel or anticoagulant K2EDTA (Becton Dickinson, France). The material was appropriately prepared and tested shortly after collection (total cholesterol (TC), low-density lipoprotein cholesterol (LDL-ch), high-density lipoprotein cholesterol (HDL-ch), triglycerides (TG), fasting glucose level (FGL), and glycated hemoglobin (HbA1c)). The remainder of the serum material, after it had been centrifuged (10 min and approximately 2000 rpm), and the supernatant was removed, was transferred to the tubes and stored at −80 °C. TC, LDL-ch, HDL-ch, TG, and FGL were assayed using an enzymatic colorimetric method on an Alinity c analyzer (Abbott Laboratories, Lake Bluff, IL, USA). Glycated hemoglobin (HbA1c) was measured by the ion-exchange high-performance liquid-chromatography method using a D-10™ Dual Program Reorder Pack (Bio-Rad, Hercules, CA, USA). Total Antioxidant Status (TAS) was determined using a reagent kit for the

spectrophotometric method (Randox Laboratories, Crumlin, County Antrim, UK). This parameter informs about the amount of antioxidants in a sample and is related to the fact that ABTS (2,2'-Azino-di-[3-ethylbenzothiazoline sulfonate]), incubated with peroxidase (metmyoglobin) and H_2O_2, results in the formation of the radical cation $ABTS^+$, which has a relatively stable blue-green coloration that can be measured at 600 nm. The presence of antioxidants in a sample causes suppression of dye production, which is proportional to their concentration. Units are expressed in an mmol Trolox equivalent/L, used as a standard to calculate antioxidant levels in the samples [12]. Control of the accuracy of the applied methods of determination was verified on the certified reference materials dedicated to each set. In both groups, all determinations were made, except for: FGL (T1DM group) and HbA1c (control group). The eGDR (estimated glucose-disposal rate) index takes into account waist circumference (WC), HbA1c, and the presence of hypertension (HT). Its formula is as follows: $21.158 - (0.090 \times WC) - (3.407 \times HT) - (0.551 \times HbA1c)$. The value of WC is expressed in cm, HT as a dichotomous value (1 if present), and HbA1c in %. As eGDR decreases, insulin resistance (IR) increases [13]. It shows a strong correlation with IR based on euglycemic-hyperinsulinemic clamp and is associated with the occurrence of diabetic complications [13,14]. Our cut-off point was 8 mg/kg/min, selected on the basis of validation in adolescents with T1DM (76% sensitivity and 92% specificity) [15].

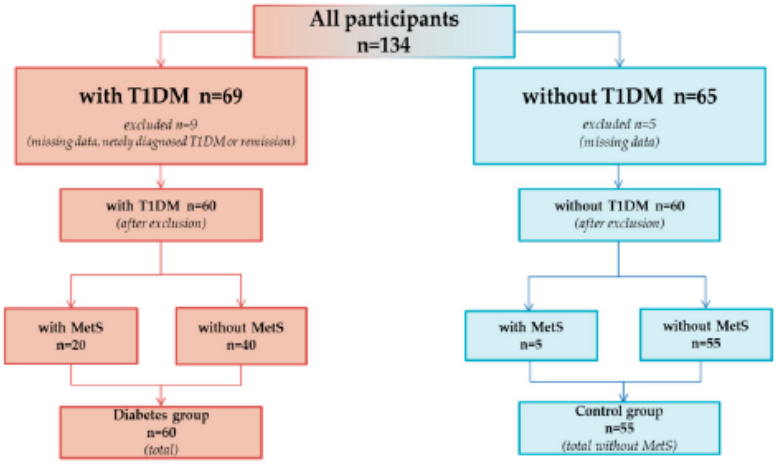

Figure 1. Flowchart of the inclusion process in the study.

2.3. Nutritional Status and Nutrients Intake

Our assessment of the subjects' nutritional status was based on anthropometric measurements (height, body weight, and circumference of the waist and hips). An analysis of the body composition was carried out by means of the bioelectric impedance method, using the professional medical analyzer Inbody 720 (Inbody, Cerritos, CA, USA). A detailed description of the measurement procedure and the devices used was extensively described in the previous study [4]. Blood pressure (BP) was measured at the beginning of the visit with a validated arm-pressure device, based on the oscillometric technique. Each participant was individually interviewed and asked to respond to a detailed 24 h nutritional intake survey about the day before their arrival at the clinic (T1DM group) or the Department of Bromatology (control group). The subjects were then given a food diary to record the food they ate for the next two days after the test (control group) or after leaving the hospital (T1DM group). Additionally, they were asked to complete a dietary questionnaire that included questions about the frequency of consumption of selected food groups [16]. The children and parents had been instructed on how to complete the document. In order to avoid discrepancies in the conducted interviews as well as in the

anthropometric measurements, the examination was performed by the same dietitian. The "Dieta 6" program, which uses Polish databases of nutritional values of food products, was used to assess the consumption of nutrients from the diet. The obtained values were compared to the Polish nutritional standards for healthy children and adolescents [17], and in the case of the diabetics, according to Diabetes Poland guidelines [18] and the guidelines of the International Society for Pediatric and Adolescent Diabetes (ISPAD) [19]. The nutritional standards used in the publication are presented in Table 1.

Table 1. Nutritional standards for children and adolescents.

Nutrients	Polish Standards for Healthy Children [17]	Diabetes Poland Standards [18]	ISPAD Standards [19]
Protein	10–20%	15–20%	15–20%
Carbohydrates	45–65%	45% (up to 60% if low-GI, high-fiber food)	45–50%
Fat	20–35%	25–40%	up to 30–35%
SFA	as low as possible	<10%	<10%
MUFA	-	<20%	-
PUFA	-	6–10%	-
EPA + DHA	250 mg	-	-
ALA	0.5%	-	-
LA	4%	-	-
Dietary fiber	19 g (10–15 y), 21 g (16–18 y)	>25 g or 15 g/1000 kcal	Age (y) + 5 g

Percentage values are expressed as total daily energy intake. Abbreviations: alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), glycemic index (GI), International Society for Pediatric and Adolescent Diabetes (ISPAD), linoleic acid (LA), monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), saturated fatty acids (SFA), years (y).

2.4. Metabolic Syndrome Diagnosis

Each person was diagnosed for MetS using the four main criteria (Figure 2) proposed by the IDF, ATP, WHO, and Weiss et al. (modified) [7–9,20]. The MetS+ group included respondents who met at least one of the above-mentioned criteria. The rest of the diabetics were classified as the MetS− group. Standards for the pediatric population were used. Polish percentile grids were employed to evaluate the parameters expressed in percentiles [21,22]. For the purposes of this research, we modified the guidelines of Weiss et al., due to the lack of percentile grids for HDL-ch and TG [23].

2.5. Statistical Analysis

Statistical analysis of the results was performed with Statistica software (version 13 PL; TIBCO Software Inc., Palo Alto, CA, USA). Normal distribution of the variables was tested using the Shapiro–Wilk, Kolmogorov–Smirnov, and Lilliefors tests. Due to abnormal distribution, the data were presented in the form of medians and quartile ranges. In the case of quantitative variables, the Mann–Whitney U and Kruskal–Wallis ANOVA tests with post-hoc analysis were conducted. To assess the significance of the relationships between the qualitative variables, the chi-squared test of independence was used. If necessary, an additional V-square test and Yates correction were applied. Multiple correspondence analysis (MCA) is one of the exploratory statistical techniques that was used to detect all the common characteristics among individuals with T1DM who had MetS. The analyzed data were presented in a Burt's matrix. Then, to determine the number of dimensions that the search space should have, a scree plot was used. p values < 0.05 were considered statistically significant. The study meets the assumptions of the minimum required sample size, assuming the maximum error value (10%) with a set confidence level (95%), which was calculated during study design, where we were guided by data on the estimated number of children and adolescents with T1DM in Poland [24].

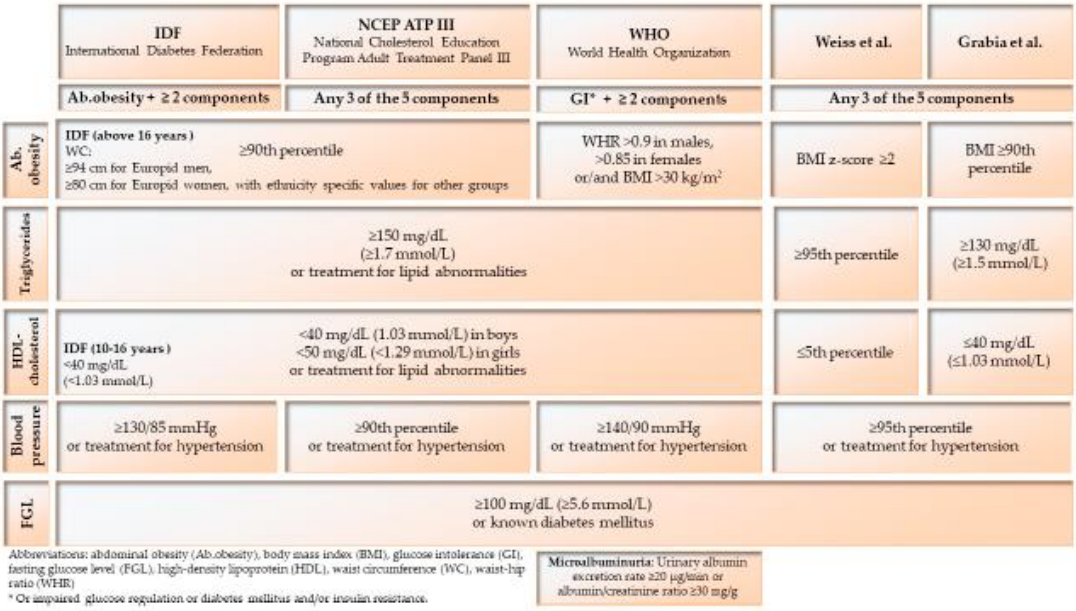

Figure 2. Criteria of metabolic syndrome (MetS) diagnosis in children and adolescents [7–9,14].

3. Results

3.1. Study Characteristic

The characteristics of the population studied, along with information on the disease, type of insulin therapy, and the use of modern techniques of glycemic monitoring (GM) are presented in Table 2.

Table 2. Characteristics of the study cohort.

Parameter	Participants	
	with T1DM (n = 60)	without T1DM (n = 60)
	Me ± IQR	
Age (years)	14 (12–16)	15 (13–16)
Body height (cm)	166 (156–173)	168 (162–176)
Body weight (kg)	54 (45–66)	58 (47–69)
Age of diagnosis (years)	9 (7–11)	
Diabetes duration (years)	5 (2–7)	
HbA1c (%)	7.6 (6.6–10.2)	
	n (%)	
Gender (girls/boys)	27 (45%)/33 (55%)	16 (27%)/44 (73%)
Type of insulin therapy (MDI/CSII)	23 (38%)/37 (52%)	
Type of glucose-monitoring system (FGM/CGM)	18 (70%)/8 (30%)	

Values are expressed as median and interquartile range (Me (Q_1–Q_3) or number and percentage of respondents (n (%)). Abbreviations: continuous glucose monitoring (CGM), continuous subcutaneous insulin infusion (CSII), flash glucose monitoring (FGM), multiple daily injections (MDI), type 1 diabetes mellitus (T1DM).

3.2. Prevalence of Metabolic Syndrome

Table 3 shows the percentage of respondents who met the individual criteria for the diagnosis of MetS. The syndrome was found in 33% of the diabetics—21% of the boys and 48% of the girls (some patients met more than one criterion), including 65%—CSII, 35%—MDI, and 30%—FGM or CGM; the remaining individuals (70%) did not use any modern GM support. In the healthy group, only 8% (n = 5) of adolescents had MetS. They were excluded from further comparative analysis.

Table 3. Prevalence of metabolic syndrome, based on various criteria.

Criteria	T1DM Group (n = 60)		Patients without T1DM (n = 60)	
	Total	Girls/Boys	Total	Girls/Boys
ATP	15 (25%)	11 (41%)/4 (12%)	3 (5%)	1 (6%)/2 (5%)
IDF	5 (8%)	3 (11%)/2 (6%)	3 (5%)	0/3 (7%)
WHO	8 (13%)	4 (15%)/4 (12%)	1 (2%)	0/1 (2%)
Grabia et al. (modified Weiss et al.)	11 (18%)	9 (33%)/2 (6%)	1 (2%)	0/1 (2%)

Values are expressed as a number and percentage of respondents (n (%)). Abbreviations: National Cholesterol Education Program Adult Treatment Panel III (ATP), International Diabetes Federation (IDF), type 1 diabetes mellitus (T1DM), World Health Organization (WHO).

Table 4 shows the parameters that have an impact on increased cardiovascular risk and some that are taken into account in the diagnosis of MetS. These results were also compared to those of a control group of healthy peers. Statistically significant differences in the medians of WHtR, BMI, HbA1c, eGDR, LDL-ch, HDL-ch, TG, and DBP were demonstrated.

Table 4. Comparison of cardiovascular biomarkers.

Parameter	MetS+ (n = 20)	MetS− (n = 40)	Control Group (n = 55)	p-Value	
		Me ± IQR		MetS+ vs. MetS−	MetS+ vs. Control
WC (cm)	73 (69–78)	66 (62–70)	70 (67–74)	<0.001	N/S
WHR	0.87 (0.84–0.9)	0.87 (0.81–0.91)	0.88 (0.85–0.92)	N/S	N/S
WHtR	0.40 (0.39–0.42)	0.40 (0.38–0.42)	0.44 (0.42–0.48)	<0.001	<0.001
BMI (kg/m^2)	22.6 (19.9–24.5)	19.8 (17.9–21.2)	20.3 (18.6–22.0)	<0.01	<0.5
FGL (mg/dL)	-	-	98 (93–103)	-	-
HbA1c (%)	8.9 (7.4–11.4)	6.9 (6.4–9.2)	-	<0.001	-
eGDR (mg/kg/min)	8.0 (6.3–10.0)	10.8 (8.8–11.6)	-	<0.001	-
TC (mg/dL)	157 (124–187)	148 (123–170)	143 (131–187)	N/S	N/S
LDL-ch (mg/dL)	102 (74–111)	80 (66–101)	86 (76–110)	<0.5	N/S
HDL-ch (mg/dL)	44.5 (34.5–57.5)	59 (48–71)	57 (52–64)	<0.001	<0.001
TG (mg/dL)	101 (67–143)	60 (47–91)	59 (45–76)	<0.001	<0.001
SBP (mmHg)	120 (110–128)	114 (109–118)	118 (110–125)	<0.5	N/S
DBP (mmHg)	74 (70–80)	70 (66–73)	70 (65–74)	<0.01	<0.5

Values are expressed as median and interquartile range (Me (Q_1–Q_3). Statistically significant differences between the medians were detected by the Mann–Whitney U test. Abbreviations: National Cholesterol Education Program Adult Treatment Panel III (ATP), body mass index (BMI), diastolic blood pressure (DBP), estimated glucose disposal resistance (eGDR), fasting glucose level (FGL), high-density lipoprotein cholesterol (HDL-ch), glycated hemoglobin (HbA1c), International Diabetes Federation (IDF), low-density lipoprotein cholesterol (LDL-ch), metabolic syndrome (MetS), systolic blood pressure (SBP), total cholesterol (TC), triglycerides (TG), waist circumference (WC), waist–hip ratio (WHR), waist-to-height ratio (WHtR), World Health Organization (WHO).

The parameters that most frequently exceeded the norm were those related to dyslipidaemia (Figure 3). However, a noteworthy observation is the large disproportion between the percentages of persons above normal SBP or DBP by numerical values and in terms of percentiles, e.g., 5% of patients with elevated DBP (in mmHg), as well as 70% and 45% of patients with DBP, were above the 90th and 95th percentiles, respectively.

It was observed that MetS+ patients had statistically significantly higher HbA1c values than those without MetS (8.9% vs. 6.9%, $p < 0.01$) (Table 5). MetS was found in almost half of the respondents, with values above 7%. Additionally, the concentration of TAS was measured and was statistically significantly lower in patients with MetS than in healthy volunteers (1.249 mmol/L vs. 1.578 mmol/L, $p < 0.001$).

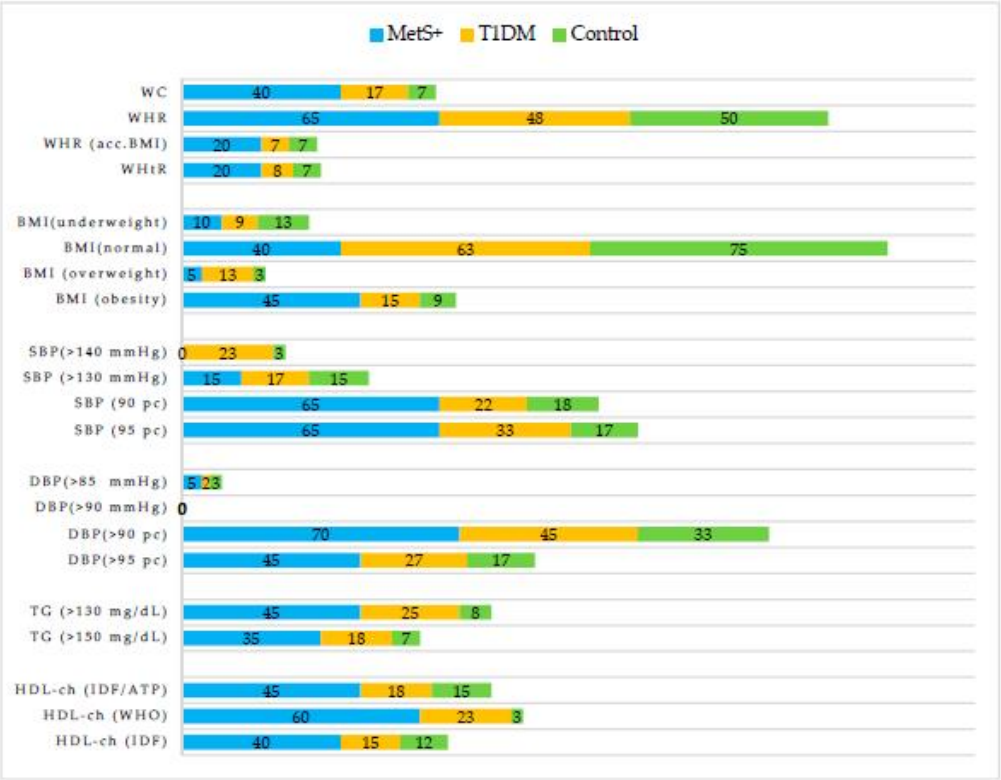

Figure 3. Percentage of participants meeting the metabolic syndrome components. Values are expressed as percentage of respondents (%). WHR (acc.BMI) includes the percentage of persons who are overweight or obese and, additionally, have a WHR above normal. BMI classifications for underweight, overweight, and obesity in the pediatric population correspond to the 10th, 85th, and 97th percentiles, respectively. Abbreviations: National Cholesterol Education Program Adult Treatment Panel III (ATP), body mass index (BMI), diastolic blood pressure (DBP), high-density lipoprotein cholesterol (HDL-ch), International Diabetes Federation (IDF), metabolic syndrome (MetS), systolic blood pressure (SBP), type 1 diabetes mellitus (T1DM), triglycerides (TG), waist circumference (WC), World Health Organization (WHO), waist–hip ratio (WHR), waist-to-height ratio (WHtR).

3.3. Nutritional Status

Comparative analysis of body composition parameters (Table 6) showed statistically significant ($p < 0.001$) differences in the medians of percent body fat (PBF) and visceral fat area (VFA) between both the control and the MetS− groupsand MetS+ group.

3.4. Nutrients Intake

In comparison with the diets of their healthy peers, the diets of persons with T1DM and MetS+ (Table 7) were higher in saturated fatty acids (SFA: 17.6 g vs. 16.0 g, $p < 0.01$) and lower in products rich in mono- and polyunsaturated fatty acids (MUFA, PUFA): oleic acid (12.3 g vs. 21.4 g, $p < 0.001$), ω-3 (0.831 g vs. 1.3 g, $p < 0.001$), and ω-6 (4.9 g vs. 7.6 g, $p < 0.001$), as well as dietary fiber (18.1 g vs. 19.6 g). Although healthy volunteers declared high total fat intakes (28.1 g), the majority of the fats they consumed came from MUFA (24.6 g) and PUFA (9.8 g), not SFA (16.0 g). The MetS+ group also proved to have higher saccharose intakes than MetS− subjects (39.5 g vs. 33 g).

Table 5. HbA1c and TAS values, depending on metabolic control.

Study Group	HbA1c (%)	TAS (mmol/L)	*p*-Value	HbA1c Group	HbA1c	*p*-Value	HbA1c (%)	*p*-Value	TAS (mmol/L)	*p*-Value
	Me ± IQR				*n*(%)		Me ± IQR		Me ± IQR	
MetS+ (n = 20)	8.9 (7.4–11.4)	1.249 (1.054–1.322)	MetS+ vs. MetS− <0.01$^{HbA1c, TAS}$	(<7%)	3 (12%)	<0.01	6.7 (6.2–7.0)	<0.001	1.230 (1.212–1.382)	MetS+$^{HbA1c>7\%}$ vs. MetS−$^{HbA1c>7\%}$ <0.01
				(>7%)	17 (49%)		9.9 (7.7–12.2)		1.243 (1.041–1.314)	
MetS− (n = 40)	6.9 (6.4–9.2)	1.394 (1.225–1.595)	MetS+ vs. Control MetS− vs. Control <0.001^{TAS}	(<7%)	22 (88%)		6.4 (6.0–6.7)	<0.001	1.403 (1.206–1.533)	
				(>7%)	18 (51%)		9.7 (7.8–12.1)		1.370 (1.256–1.655)	
Control group (n = 55)	-	1.579 (1.457–1.799)					-			

Values are expressed as median and interquartile range (Me (Q_1–Q_3) or number and percentage of respondents (n (%)). Statistically significant differences between the medians or percentages were detected by the Mann–Whitney U or the chi-squared test, respectively. Abbreviations: glycated hemoglobin (HbA1c), metabolic syndrome (MetS), total antioxidant status (TAS).

Table 6. Comparison of body-composition analysis parameters.

Parameter	MetS+ (n = 20)	MetS− (n = 40)	Control Group (n = 55)	p-Value	
	Me ± IQR			MetS+ vs. MetS−	MetS+ vs. Control
Body weight (kg)	64 (52–73)	52 (43–59)	58 (48–68)	<0.5	NS
Body height (cm)	167 (156–173)	164 (155–173)	169 (163–176)	NS	NS
TBW (L)	33 (28–38)	30 (26–38)	37 (31–41)	NS	NS
SMM (kg)	24 (21–29)	22 (19–29)	24 (18–30)	NS	NS
Protein (kg)	8.6 (7.6–10.2)	8.1 (6.9–10.2)	9.1 (7.9–10.5)	NS	NS
Minerals (kg)	3.3 (2.7–3.6)	2.9 (2.5–3.5)	3.2 (2.8–3.9)	NS	NS
PBF (%)	26 (21–33)	16 (12–23)	14 (12–16)	<0.001	<0.001
VFA (cm^2)	77 (54–100)	42 (28–48)	35 (26–44)	<0.001	<0.001

Values are expressed as median and interquartile range (Me (Q_1–Q_3). Statistically significant differences between the medians were detected by the Mann–Whitney U test. Abbreviations: metabolic syndrome (MetS), percentage body fat (PBF), skeletal muscle mass (SMM), total body water (TBW), visceral fat area (VFA).

Table 7. Consumption of selected nutrients with the diet.

Nutrient	MetS+ (n = 20)	MetS− (n = 40)	Control Group (n = 55)	p-Value (MetS+ vs. Control)
	Me ± IQR			
Main nutrients				
Energy (kcal)	1760 (1697–1924)	1803 (1574–1916)	1859 (1735–1935)	N/S
Protein (%TDEE)	20.0 (16.4–20.8)	18.1 (15.8–20.6)	16.4 (13.1–18.6)	<0.01
Carbohydrate (%TDEE)	56.5 (50.8–59.9)	54.8 (50.6–59.5)	55.4 (51.5–61.1)	N/S
Fat (%TDEE)	22.8 (20.0–28.1)	24.3 (21.2–29.1)	28.1 (23.7–32.4)	<0.01
Fatty acids				
SFA (g)	17.6 (14.3–20.7)	16.4 (15.3–17.5)	16.0 (15.1–17.9)	N/S
Palmitic acid (g)	10.4 (9.4–11.4)	10.1 (8.9–11.6)	9.8(8.6–10.8)	N/S
MUFA (g)	14.2 (11.9–17.7)	14.2 (11.2–19.2)	24.6 (20.5–28.5)	<0.001
Oleic acid (g)	12.3 (10.6–14.8)	13.1 (10.8–16.3)	21.4 (16.6–25.4)	<0.001
PUFA (g)	5.8 (5.0–7.1)	6.2 (4.6–8.1)	9.8 (7.4–11.6)	<0.001
LC-PUFA (g)	0.069 (0.036–0.205)	0.069 (0.04–0.093)	0.093 (0.06–0.231)	<0.05
ω-3 (g)	0.831 (0.569–1.178)	0.688 (0.554–1.28)	1.3 (0.948–1.6)	<0.001
ALA (g)	0.688 (0.524–0.817)	0.554 (0.478–0.879)	1.2 (0.822–1.4)	<0.001
EPA (g)	0.014 (0.006–0.045)	0.012 (0.007–0.017)	0.024 (0.008–0.052)	N/S
DHA (g)	0.039 (0.024–0.148)	0.038 (0.022–0.066)	0.066 (0.038–0.137)	<0.001
ω-6 (g)	4.9 (4.2–5.9)	5.5 (3.9–6.5)	7.6 (6.1–9.6)	<0.001
LA (g)	4.8 (4.1–5.9)	5.5 (3.8–6.4)	7.3 (6.0–9.4)	<0.001
AA (g)	0.048 (0.032–0.151)	0.048 (0.031–0.096)	0.111 (0.073–0.181)	<0.05
Carbohydrates				
Glucose (g)	8.1 (4.0–9.6)	4.8 (2.6–6.5)	6.8 (5.1–8.1)	N/S
Fructose (g)	10.1 (4.6–12.9)	7.3 (4.2–11.1)	8.3 (6.5–11.0)	N/S
Saccharose (g)	39.5 (30.2–54.8)	33.1 (13.7–45.0)	44.1 (35.1–51.6)	N/S
Dietary fiber (g)	18.1 (16.6–21.4)	18.0 (13.8–20.8)	19.6 (16.0–23.0)	N/S

Values are expressed as median and interquartile range (Me (Q_1–Q_3). Statistically significant differences between the medians were detected by the Mann–Whitney U test. Abbreviations: arachidonic acid (AA), alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), fatty acids (FA), linoleic acid (LA), long-chain polyunsaturated fatty acids (LC-PUFA), metabolic syndrome (MetS), monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), saturated fatty acids (SFA), total daily energy expenditure (TDEE).

It was shown that, compared to persons with normal values, volunteers who had lower HDL-ch levels not only consumed large amounts of SFA relative to total daily energy expenditure (TDEE) (8.4% vs. 8.2%TDEE) but also reported statistically significantly lower consumption of MUFA (7.6% vs. 10% TDEE, $p < 0.05$), oleic acid (13.1 g vs. 16.6 g, $p < 0.05$), LA (4.7 g vs. 6.2 g, $p < 0.05$), anddietary fiber (17.4 g vs. 18.7 g, $p < 0.05$). Additionally, differences were observed in the intake of PUFA (6.2 g vs. 7.8 g) from the ω-3 family: ALA (626 mg vs. 824 mg), EPA + DHA (57 mg vs. 71 mg), and ω-6 (4.8 g vs. 6.2 g). Subjects with higher TG levels consumed statistically significantly more SFA (9.1% vs. 8.1% TDEE, $p < 0.05$) but less oleic acid (13.5 g vs. 16.6 g, $p < 0.05$). As well, differences were noted in the intake of PUFA (6.4 g vs. 7.7 g), EPA + DHA (60 mg vs. 71 mg), LA (5.6 g vs. 6.1 g), and dietary fiber (16.9 g vs. 18.9 g). Participants with high BP consumed high amounts of salt

(8.6 g vs. 9.64 g, $p < 0.05$) but lower quantities of oleic acid (15 g vs. 16.5 g) and EPA + DHA (57 mg vs. 71 mg).

Table 8 shows the percentages of subjects who met the nutritional standards for selected nutrients. The vast majority of participants met the standard for basic nutrients, such as protein, fat, or carbohydrates. A statistically significant relationship was observed between the control group and MetS+ in the distribution of the percentage of nutritional norms for MUFA and LA ($p < 0.001$) as well asALA ($p < 0.01$). It was found that every third diabetic with MetS consumed more than 10% TDEE of SFA, and more than 90% and 75% of the patients failed to meet PUFA and MUFA recommendations, respectively.

Table 8. Implementation of nutritional standards for selected nutrients.

Nutrient	Recommendation	MetS+ (n = 20)	MetS− (n = 40)	Control Group (n = 55)	p-Value (MetS+ vs. Control)
Main nutrients					
Protein	<10% 10–20% >20%	0 (0%) 15 (75%) 5 (25%)	0 (0%) 33 (83%) 7 (17%)	3 (5%) 49 (90%) 3 (5%)	<0.05
Protein PolDiab	<15% 15–20% >20%	2 (10%) 13 (65%) 5 (25%)	6 (15%) 27 (68%) 7 (17%)	21 (38%) 31 (56%) 3 (6%)	<0.01
Fat	<20% 20–35% >35%	5 (25%) 15 (75%) 0 (0%)	6 (15%) 33 (83%) 1 (2%)	4 (7%) 47 (86%) 4 (7%)	<0.05
Fat PolDiab	<25% 25–40% >40%	14 (70%) 6 (30%) 0 (0%)	23 (58%) 17 (43%) 0 (0%)	20 (36%) 35 (64%) 0 (0%)	<0.01
Carbohydrates	<45% 45–65% >65%	0 (0%) 18 (90%) 2 (10%)	2 (5%) 37 (93%) 1 (2%)	2 (3%) 52 (95%) 1 (2%)	N/S
Carbohydrates PolDiab	<45% 45–60% >60%	0 (0%) 16 (80%) 4 (20%)	2 (5%) 31 (78%) 7 (17%)	2 (4%) 39 (71%) 14 (25%)	N/S
Carbohydrates ISPAD	<45% 45–50% >50%	0 (0%) 5 (25%) 15 (75%)	2 (5%) 9 (22%) 29 (73%)	2 (4%) 9 (16%) 44 (80%)	N/S
Fatty acids					
SFA	<10% ≥10%	13 (65%) 7 (35%)	29 (73%) 11 (27%)	49 (89%) 6 (11%)	<0.05
MUFA	<10% 10–20% >20%	15 (75%) 5 (25%) 0 (0%)	29 (73%) 11 (27%) 0 (0%)	15 (27%) 38 (69%) 2 (4%)	<0.001
LA	<3.5% 3.5–4.5% >4.5%	19 (95%) 1 (5%) 0 (0%)	31 (78%) 7 (18%) 2 (4%)	26 (47%) 16 (29%) 13 (24%)	<0.001
ALA	≤0.5% >0.5%	17 (85%) 3 (15%)	33 (83%) 7 (17%)	23 (42%) 32 (58%)	<0.01
EPA + DHA	≤250 mg >250 mg	17 (85%) 3 (15%)	37 (93%) 7 (3%)	44 (80%) 11 (20%)	N/S
PUFA	<6% 6–10% >10%	18 (90%) 2 (10%) 0 (0%)	39 (97%) 1 (2%) 0 (0%)	45 (82%) 9 (16%) 1 (2%)	N/S

Table 8. *Cont.*

Nutrient	Recommendation	MetS+ (n = 20)	MetS− (n = 40)	Control Group (n = 55)	p-Value (MetS+ vs. Control)
		Carbohydrates			
Saccharose	≤10% >10%	12 (60%) 8 (40%)	30 (75%) 10 (25%)	30 (55%) 25 (45%)	N/S
Dietary fiber	>19 g ≥19 g	13 (65%) 7 (35%)	27 (68%) 13 (32%)	26 (47%) 29 (53%)	N/S
Dietary fiber [PolDiab]	<25 g ≥25 g	18 (90%) 2 (10%)	39 (98%) 1 (2%)	46 (83%) 9 (17%)	N/S

The standards used refer to the Polish guidelines for the general population [17], unless there are separate recommendations for patients with diabetes mellitus (PolDiab—Polish guidelines for diabetics [18], ISPAD—international guidelines for young diabetics [19]). Values are expressed as number and percentage of respondents (n (%)). Statistically significant relationships between the numbers were detected by the chi-squared test. The data in the "Recommendation" column refer to the percentage of total daily energy expenditure. Abbreviations: alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), linoleic acid (LA), metabolic syndrome (MetS), monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), saturated fatty acids (SFA).

3.5. Nutritional Habits

Compared to their healthy peers (Table 9), members of the MetS+ group chose wheat bread (90% vs. 78%) more frequently (from several times a week to several times a day) than wholemeal bread (45% vs. 73%). They were also more likely to eat potatoes (100% vs. 56%) than groats and pastas (40% vs. 53%). Over 35% consumed fast-food products at least once to several times a week, and 80% ate fried foods. It has been observed that only 60% chose white meat and more than 90% ate red meat at least once or several times a week. Only 50% ate vegetables at least once a day, while 65% ate fruit. As many as 60% drank products containing sweeteners once or several times a week.

3.6. Insulin Therapy and Modern Glucose-Monitoring Systems

Comparative analyses of obtained results of cardiovascular biomarkers, body composition analysis, antioxidant status, metabolic management, and dietary nutrient intake in relation to insulin therapy and modern glycemic-monitoring systems are included in the Supplementary materials (Supplementary Tables S1–S5). It was shown that the largest subgroup of patients with MetS were participants who used CSII without the support of modern GM. Their HbA1c (8.3%), eGDR (8.7 mg/kg/min), and TAS (1.099 mmol/L) were worse than the levels of these indicators in those MetS patients who used CSII and CGM (7.9%, 6.5 mg/kg/min, 1.259 mmol/L). Similar observations were noted in the MDI group (Tables S1 and S2). Based on Table S3, it was found that there were statistically significant differences in median TG levels between insulin therapies (CSII vs. MDI: 60 mg/dL vs. 99 mg/dL, $p < 0.02$) and between groups using FGM or CGM and those not using either system (FGM/CGM vs. no GM: 63/54 mg/dL vs. 80 mg/dL, $p < 0.05$). It was also noted that participants supported with any of the systems had a statistically significantly lower HbA1c than those who did not use any modern support (6.8%/6.7% vs. 8.1%, $p < 0.001$). Table S4 contains the results of the body-composition analysis, which showed that the CSII group had a lower VFA than MDI (46 cm^2 vs. 52 cm^2), which was also observed in the modern GM participants (FGM/CGM vs. no GM: 46 cm^2/44 cm^2 vs. 49 cm^2).

Table 9. Frequency of consumption of selected groups of food products.

Food Products		Never	1–3 Times a Month	Once a Week	Several Times a Week	Once a Day	Several Times a Day
Wheat bread	MetS+	0 (0%)	1 (5%)	1 (5%)	5 (25%)	5 (25%)	8 (40%)
	MetS−	2 (5%)	2 (5%)	3 (8%)	8 (20%)	6 (15%)	19 (47%)
	Control	6 (11%)	2 (4%)	4 (7%)	21 (38%)	15 (27%)	7 (13%)
Wholemeal bread	MetS+	2 (10%)	3 (15%)	6 (30%)	5 (25%)	1 (5%)	3 (15%)
	MetS−	3 (8%)	2 (5%)	8 (20%)	11 (27%)	10 (25%)	6 (15%)
	Control	6 (11%)	3 (5%)	6 (11%)	25 (45%)	12 (22%)	3 (6%)
Groats, pasta, rice	MetS+	0 (0%)	2 (10%)	10 (50%)	7 (35%)	1 (5%)	0 (0%)
	MetS−	0 (0%)	7 (17%)	12 (30%)	20 (50%)	1 (3%)	0 (0%)
	Control	0 (0%)	8 (15%)	9 (16%)	35 (63%)	2 (4%)	1 (2%)
Potatoes	MetS+	0 (0%)	0 (0%)	0 (0%)	9 (45%)	11 (55%)	0 (0%)
	MetS−	0 (0%)	2 (5%)	2 (5%)	21 (52%)	15 (38%)	0 (0%)
	Control	0 (0%)	11 (20%)	13 (23%)	25 (46%)	4 (7%)	2 (4%)
Red meat	MetS+	1 (5%)	7 (35%)	6 (30%)	6 (30%)	0 (0%)	0 (0%)
	MetS−	6 (15%)	6 (15%)	5 (12%)	19 (48%)	2 (5%)	2 (5%)
	Control	3 (5%)	5 (9%)	15 (27%)	30 (55%)	2 (4%)	0 (0%)
White meat	MetS+	0 (0%)	2 (10%)	6 (30%)	11 (55%)	1 (5%)	0 (0%)
	MetS−	1 (2%)	3 (7%)	5 (13%)	27 (68%)	2 (5%)	2 (5%)
	Control	0 (0%)	2 (4%)	7 (13%)	43 (78%)	3 (5%)	0 (0%)
Fried products	MetS+	1 (5%)	3 (15%)	6 (30%)	5 (25%)	5 (25%)	0 (0%)
	MetS−	1 (3%)	4 (10%)	16 (40%)	18 (44%)	0 (0%)	1 (3%)
	Control	1 (2%)	6 (11%)	14 (25%)	30 (55%)	4 (7%)	0 (0%)
Fast-food	MetS+	2 (10%)	11 (55%)	5 (25%)	2 (10%)	0 (0%)	0 (0%)
	MetS−	4 (10%)	25 (63%)	10 (25%)	1 (2%)	0 (0%)	0 (0%)
	Control	9 (16%)	37 (67%)	8 (15%)	1 (2%)	0 (0%)	0 (0%)
Fruit	MetS+	0 (0%)	0 (0%)	1 (5%)	6 (30%)	9 (45%)	4 (20%)
	MetS−	0 (0%)	3 (8%)	0 (0%)	13 (32%)	11 (28%)	13 (32%)
	Control	0 (0%)	0 (0%)	2 (3%)	18 (33%)	17 (31%)	18 (33%)
Vegetables	MetS+	0 (0%)	0 (0%)	2 (10%)	8 (40%)	5 (25%)	5 (25%)
	MetS−	0 (0%)	0 (0%)	2 (5%)	13 (33%)	8 (20%)	17 (42%)
	Control	0 (0%)	0 (0%)	3 (6%)	17 (31%)	19 (35%)	16 (28%)
Beverages with sweeteners	MetS+	2 (10%)	3 (15%)	3 (15%)	10 (50%)	2 (10%)	0 (0%)
	MetS−	9 (22%)	4 (10%)	12 (30%)	9 (22%)	5 (13%)	1 (3%)
	Control	13 (24%)	8 (14%)	11 (20%)	12 (22%)	10 (18%)	1 (2%)
Energy drink	MetS+	13 (65%)	2 (10%)	4 (20%)	1 (5%)	0 (0%)	0 (0%)
	MetS−	30 (75%)	3 (7%)	6 (15%)	1 (3%)	0 (0%)	0 (0%)
	Control	47 (85%)	5 (9%)	3 (6%)	0 (0%)	0 (0%)	0 (0%)

Abbreviation: metabolic syndrome (MetS).

3.7. Multiple Correspondence Analysis

MCA was used to identify the structure of associations between metabolic control, antioxidant status, visceral fat and the occurrence of MetS, taking into account insulin therapy and the usage of modern glycemic monitoring. A prepared scree plot suggested adoption of two-dimensional space for analysis. After determining the number of dimensions in the next step, the coordinates of the column profiles were calculated in the new orthonormal framework. Figure 4 shows the results of the MCA. The two-dimensional plot explains 51% of the total variability, which allows us to distinguish the following three groups:

(1) The first quadrant contained participants with MetS, characterized by poor metabolic management (HbA1c > 7%), low eGDR (<8 mg/kg/min), low TAS (<1.3 mmol/L), and medium (>50 cm^2) to high (>100 cm^2) VFA, was not supported by FGM or CGM.
(2) The opposite (III) and side quadrant (II) included healthy peers with moderate (1.3–1.8 mmol/L) to high (>1.8 mmol/L) TAS and normal VFA (<50 cm^2).
(3) The last quadrant (IV) included individuals without MetS with optimal metabolic control (HbA1c < 7%) and high eGDR (>8 mg/kg/min), who were using CSII or MDI and FGM or CGM.

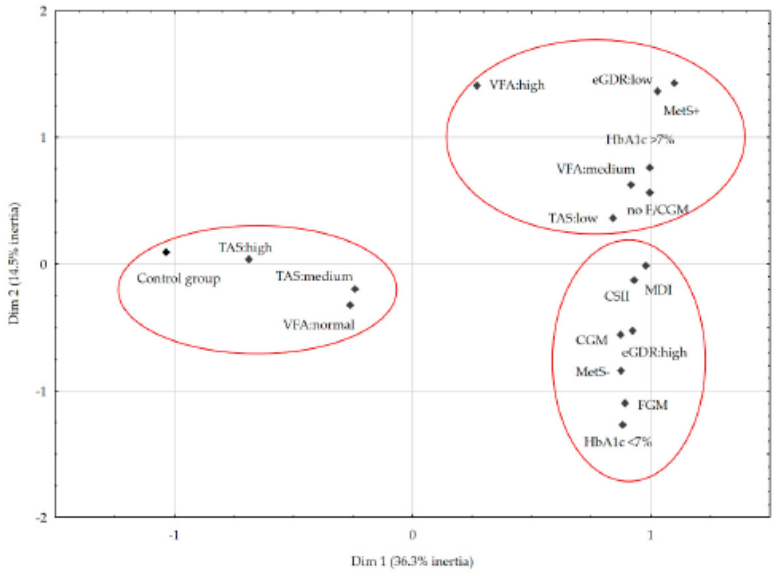

Figure 4. Multivariate correspondence analysis coordinate plot. Abbreviations: continuous glucose monitoring (CGM), continuous subcutaneous insulin infusion (CSII), dimension (dim), estimated glucose-disposal resistance (eGDR), flash glucose monitoring (FGM), glucose monitoring (GM), glycated hemoglobin (HbA1c), multiple daily injections (MDI), metabolic syndrome (MetS), total antioxidant status (TAS), visceral fat area (VFA).

4. Discussion

A previously published systematic review [10] showed that nearly 30% of diabetics were diagnosed with metabolic syndrome. Our study confirmed this: 33% of the diabetics had MetS. However, this was the case among girls (48%) more often than boys (21%), which has also been noted by other authors, e.g., Köken et al. (12% vs. 10%), Soliman et al. (18% vs. 8%), Szadkowska et al. (11% vs. 7%), and Valerio et al. (16% vs. 4%). In our study, most diagnoses of MetS were found based on the ATP criteria (25%), which is consistent with the literature data: 14% [25], 30% [26], and the lowest according to the IDF (8%), as well as in other authors from 3% [27] up to 13% [28], with the exception of the furthest outlier, 24% [29]. This is due to the different intensity of the components included in the criteria—the ATP allows for selecting three components out of five, while the IDF places diagnosed abdominal obesity as the first one, ahead of the other components. The second fundamental difference regards the values of the cut-off points used—mainly numerical values, rarely percentiles. When national percentile grids were used (according to the modified criteria of Weiss et al.), the percentage of MetS diagnoses fell to 13%. Another interesting thing is that when we used cut-off points from the percentile grids for SBP and DBP from the rarely recognized elevated BP (above 130/85 mmHg) and almost-never recognized high BP (above 140/90 mmHg), these percentages as much as doubled. In the case of the HDL-ch parameter, the percentage of non-compliant persons had a considerable discrepancy: 40%, 45%, and 60% according to the criteria of the IDF, ATP, and WHO, respectively. Therefore, it would be worthwhile to consider modifying the numerical values of some MetS components to those related to national percentile grids.

Due to the production of large amounts of oxygen free radicals and/or reduced antioxidant defense, oxidative stress has a significant impact on the development of insulin resistance and most diabetic complications [30]. Long-term high glycemia promotes over-

production of oxygen free radicals. In the presence of low antioxidant activity, beta cells are more susceptible to the adverse effects of oxidative stress and their destruction is exacerbated [31]. In our study, subjects with T1DM as well as with MetS had statistically significantly lower TAS values than the control group. Similar results were obtained by other authors [32,33].

Our investigation showed that MetS subjects had a statistically significantly higher VFA compared to the MetS− group. The same was seen in patients with MDI and CSII, as well as non-users of modern GM systems and those supporting themselves with FGM or CGM. Many studies confirmed that individuals with high VFA considerable risk of developing cardiometabolic complications and a number of related diseases [34]. Therefore, it is particularly threatening for individuals with T1DM.

Our study proved that MetS patients had much lower eGDR levels, which could be related to the occurrence of high IR. Similar results were observed by Köken et al. [15]. Moreover, during our analysis in different subgroups, the index increased depending on the insulin therapy and modern GM systems used. In combination with its high specificity and negative predictive value [15] for excluding the diagnosis of MetS, it should be considered as one of the components of MetS. An additional advantage is that it can be calculated quickly using the results obtained during routine follow ups, and its numerous correlations make it easily applicable in clinical practice.

It was shown that the average BMI value in young diabetics without MetS (19.8 kg/m^2) did not differ from the results reported by our previous study (19.2 kg/m^2) [4] or other authors conducting research in similar age groups—19.5 kg/m^2 [35], 21.3 kg/m^2 [36] and 21.5 kg/m^2 [37,38]. The percentage of fat mass in our study was 16%, while the other authors reported different outcomes—18.5% [35], 19.1% [4], 21.9% [38] and 22.4% [37].

Lifestyle medicine is a key element in the prevention and treatment of metabolic disorders. The most important role is played by modification of eating habits and physical activity [10,37,38].

Diabetics without MetS consumed protein at 18.1% TDEE. Similar results were obtained by other authors: 16.9% TDEE [39] and 16% TDEE [40,41]. Regarding consumption of SFA (16.4 g, 8.8% TDEE), MUFA (14.2 g, 7.5% TDEE), and PUFA (6.2 g, 10.3% TDEE), our results differed from those reported by Katz et al. (SFA 12.4% TDEE) [41] and Thomson et al. (37.4 g, 33.2 g, and 11.2 g, respectively) [42].

Our study found disturbing results suggesting inadequate nutrient intakes in patients with abnormal HDL-ch, TG, and BP levels. Participants with low HDL-ch levels consumed high amounts of SFA (8.4% TDEE) but low quantities of MUFA (7.6% TDEE), EPA + DHA (57 mg), and LA (4.7 g), which had the strongest influence in this case. We observed similar results in patients with high TG levels, who had a lot of products rich in SFA (9.1% TDEE) in their diet, and too few foods that were high in EPA + DHA (60 mg) and LA (5.6 g). Patients with high BP consumed large amounts of salt (8.4 g) and low amounts of oleic acid (15 g) and EPA + DHA (57 mg). An adequate quantity of HDL-ch has a beneficial anti-atherosclerotic effect, which is related primarily to its participation in cholesterol retransport. It has been shown that its concentration is increased by 0.4 mg/dL for each kilogram of body-weight loss and by 6 mg/dL as a consequence of moderate-intensity physical activity (approx. 300 min a week) [43]. However, the best results can be achieved by reducing trans fats and carbohydrates in the diet in favor of unsaturated FA [44]. If a nutritional intervention is aimed at lowering TG, a significant role is played by the reduction in body weight and the consumption of simple carbohydrates as well as by replacing SFA with PUFA and introducing regular physical activity. This improves tissue insulin sensitivity, which influences the TG level [44–46]. The consumption of ω-3 FA (approx. 2–4 g/day) favors the reduction in TG by about 25–30%, but also, importantly, has a beneficial effect on inflammatory markers [47]. The inclusion of products with a low glycemic index and load in the diet efficiently lowers the concentration of TG; then, such foods that have a low plasma glucose-absorption profile allow for its gradual release during intestinal transit [48]. Non-pharmacological treatment of arterial hypertension

should include: normalization of body weight, reduction in SFA and salt intake, increased consumption of vegetables and fruit, and systematic physical activity [49]. A meta-analysis by Aburto et al. showed that reducing sodium intake causes a decrease of 3.4/1.5 mmHg in SBP/DBP [50]. By monitoring its consumption, it is also possible to reduce the number and doses of antihypertensive drugs as well as the risk of cardiovascular events [49].

Lifestyle changes should be promoted in all patient groups and must become an integral part of the treatment of metabolic disorders.

Our study has several strengths and weaknesses. Firstly, some of the nutrient intake data were retrospectively collected, which could have influenced the results by underestimating or overestimating these parameters. Secondly, the size of the groups is not too large. However, compared to other studies, this group of patients maintained an appropriate test power, at about 90%. However, an extremely large advantage of the present study over others is the very extensive and comprehensive screening of participants in terms of the various criteria of MetS definition, cardiovascular biomarkers, nutrients intake, eating habits, and nutritional status, including a comparison of the type of insulin therapy and modern GM used. An additional advantage is the inclusion of a control group of healthy children, which enabled comparative analysis.

5. Conclusions

The study found that a high percentage of young diabetics had MetS. These participants displayed many inappropriate eating behaviors (meaning a diet low in mono- and polyunsaturated fatty acids and rich in saturated fatty acids). This long-term presence in combination with an excessive content of fat tissue, especially visceral, as well as incorrect results of laboratory tests (cardiovascular biomarkers) and confirmed low antioxidant status, may result in difficulty in maintaining metabolic control, which, in turn, may lead to faster development of diabetic complications.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/nu14122435/s1; Table S1: HbA1c, eGDR, and TAS values depending on insulin therapy and modern GM systems used, Table S2: TAS, HbA1c, and eGDR values depending on insulin therapy and modern GM systems used, Table S3: Comparison of cardiovascular biomarkers depending on insulin therapy and modern GM systems used, Table S4: Comparison of body-composition analysis parameters depending on insulin therapy and modern GM systems used, Table S5: Consumption of the selected nutrients with diet depending on insulin therapy and modern GM systems used.

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Informed Consent Statement: Written informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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nutrients

MDPI

Supplementary Material

Prevalence of Metabolic Syndrome in Relation to Cardiovascular Biomarkers and Dietary Factors among Adolescents with Type 1 Diabetes Mellitus

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Table S1. HbA1c, eGDR and TAS values depending on insulin therapy and modern GM systems used.

Group	Insulin therapy	GM systems	n (%)	HbA1c (%)	eGDR (mg/kg/min)	TAS (mmol/L)
MetS+	CSII	**Total**	**13**	**7.9 (7.6-9.9)**	**8.0 (6.5-10.4)**	**1.173 (1.04-1.259)**
		No GM	10 (77%)	8.3 (7.6-9.9)	8.7 (6.7-10.4)	1.099 (1.021-1.259)
		CGM	3 (23%)	7.9 (7.2-10.5)	6.5 (6.2-10.6)	1.259 (1.173-1.307)
	MDI	**Total**	**7**	**12.2 (6.7-13.2)**	**8.0 (6.1-9.4)**	**1.304 (1.211-1.367)**
		No GM	4 (57%)	12.7 (9.2-14.6)	7.9 (5.3-9.7)	1.257 (1.002-1.335)
		FGM	3 (43%)	10.1 (6.7-12.6)	8.7 (6.1-9.4)	1.336 (1.228-2.130)
MetS-	CSII	**Total**	**24**	**6.8 (6.2-8.1)**	**11.2 (9.6-11.7)**	**1.446 (1.213-1.644)**
		No GM	9 (38%)	7.8 (6.5-8.3)	10.8 (10.2-11.4)	1.414 (1.272-1.490)
		FGM	10 (42%)	6.9 (6.2-8.7)	11.5 (8.7-11.7)	1.596 (1.115-1.695)
		CGM	5 (20%)	6.4 (5.8-6.6)	11.7 (11.0-12.2)	1.419 (1.304-1.445)
	MDI	**Total**	**16**	**7.1 (6.6-11.6)**	**10.5 (7.7-11.0)**	**1.308 (1.225-1.455)**
		No GM	11 (69%)	11.2 (6.7-12.5)	10.4 (8.0-11.0)	1.322 (1.199-1.406)
		FGM	16 (31%)	6.6 (6.4-6.8)	10.8 (7.5-11.0)	1.294 (1.265-1.636)

Values are expressed as median and interquartile range (Me (Q_1-Q_3). Abbreviations: estimated glucose disposal resistance (eGDR), glucose monitoring (GM), glycated hemoglobin (HbA1c), continuous glucose monitoring (CGM), continuous subcutaneous insulin infusion (CSII), flash glucose monitoring (FGM), multiple daily injections (MDI), metabolic syndrome (MetS), total antioxidant status (TAS).

Table S2. TAS, HbA1c and eGDR values depending on insulin therapy and modern GM systems used.

Subgroup/ Category	CSII (n=37)	MDI (n=23)	No GM (n=34)	FGM (n=18)	CGM (n=8)
TAS					
low	18 (62%)	11 (38%)	19 (66%)	7 (24%)	3 (10%)
medium	17 (63%)	10 (37%)	14 (52%)	8 (30%)	5 (18%)
high	2 (50%)	2 (50%)	1 (25%)	3 (75%)	0 (0%)
HbA1c					
HbA1c ≤7%	15 (60%)	10 (40%)	8 (32%)	12 (48%)	5 (20%)
HbA1c >7%	22 (63%)	13 (37%)	26 (74%)	6 (17%)	3 (9%)
eGDR					
≤8mg/min/kg	7 (50%)	7 (50%)	9 (64%)	3 (21%)	2 (15%)
>8mg/min/kg	15 (35%)	30 (65%)	25 (54%)	15 (33%)	6 (13%)

Values are expressed as number and percentage of respondents (n(%)). Abbreviations: estimated glucose disposal resistance (eGDR), glucose monitoring (GM), glycated hemoglobin (HbA1c), continuous glucose monitoring (CGM), continuous subcutaneous insulin infusion (CSII), flash glucose monitoring (FGM), multiple daily injections (MDI), metabolic syndrome (MetS), total antioxidant status (TAS).

Table S3. Comparison of cardiovascular biomarkers depending on insulin therapy and modern GM systems used.

Subgroup/ Parameter	CSII (n=37)	MDI (n=23)	No GM (n=34)	FGM (n=18)	CGM (n=8)	p-value
WC (cm)	66 (62-73)	69 (66-74)	69 (62-74)	67 (64-74)	66 (62-71)	-
WHR	0.88 (0.81-0.91)	0.88 (0.84-0.91)	0.88 (0.83-0.92)	0.87 (0.81-0.9)	0.88 (0.84-0.9)	-
WHtR	0.42 (0.39-0.45)	0.42 (0.39-0.44)	0.42 (0.39-0.45)	0.42 (0.38-0.44)	0.42 (0.4-0.42)	-
BMI (kg/m^2)	20 (18-22)	21 (18-22)	20 (18-22)	20 (19-22)	20 (18-22)	-
HbA1c (%)	7.5 (6.5-8.8)	7.7 (6.6-12.5)	8.11 (7.12-11.24)	6.8 (6.31-8.65)	6.65 (6.1-7.54)	<0.001 F/CGM vs. no GM
eGDR (mg/kg/min)	9.4 (7.5-11)	10.5 (8.6-11.6)	10 (7.9-11)	10.7 (8.6-11.6)	10.8 (7.5-11.9)	-
TC (mg/dL)	151 (123-176)	144 (124-170)	142 (123-175)	156 (140-185)	152 (123-172)	-
LDL-ch (mg/dL)	83 (67-108)	90 (70-101)	83 (68-105)	85 (68-102)	92 (70-109)	-
HDL-ch (mg/dL)	56 (48-67)	48 (39-68)	50 (44-60)	63 (48-74)	59 (52-70)	<0.05 F/CGM vs. no GM
TG (mg/dL)	60 (49-81)	99 (56-119)	80 (58-117)	62 (52-99)	54 (46-78)	<0.05 MDI vs. CSII, F/CGM vs. no GM
SBP (mmHg)	116 (112-120)	113 (108-125)	114 (109-121)	117 (114-125)	114 (112-120)	-
DBP (mmHg)	71 (66-74)	72 (69-75)	72 (69-75)	72 (66-74)	69 (65-74)	-

Values are expressed as median and interquartile range (Me (Q_1-Q_3). Abbreviations: continuous glucose monitoring (CGM), continuous subcutaneous insulin infusion (CSII), diastolic blood pressure (DBP), estimated glucose disposal resistance (eGDR), flash glucose monitoring (FGM), high density lipoprotein cholesterol (HDL-ch), glucose monitoring (GM), glycated hemoglobin (HbA1c), low density lipoprotein cholesterol (LDL-ch), multiple daily injections (MDI), metabolic syndrome (MetS), systolic blood pressure (SBP), total cholesterol (TC), triglycerides (TG), waist circumference (WC), waist-hip ratio (WHR), waist-to-height ratio (WHtR).

Table S4. Comparison of body composition analysis parameters depending on insulin therapy and modern GM systems used.

Subgroup/ Parameter	CSII (n=37)	MDI (n=23)	No GM (n=34)	FGM (n=18)	CGM (n=8)
Body weight (kg)	53 (42-67)	56 (47-61)	56 (46-66)	53 (44-72)	51 (39-61)
Body height (cm)	164 (157-172)	168 (156-176)	167 (157-172)	163 (157-176)	158 (153-164)
TBW (L)	31 (27-35)	31 (27-39)	32 (28-38)	31 (27-42)	29 (24-31)
SMM (kg)	23 (19-26)	23 (20-30)	23 (20-29)	23 (20-32)	22 (17-23)
Protein (kg)	8 (7-9)	8 (7-11)	8 (7-10)	8 (7-11)	8 (6-8)
Minerals (kg)	3 (3-4)	3 (3-4)	3 (3-4)	3 (3-4)	3 (2-3)
PBF (%)	20 (14-29)	20 (12-26)	21 (15-29)	19 (12-26)	19 (14-26)
VFA (cm^2)	46 (30-67)	52 (35-76)	49 (35-76)	46 (26-59)	44 (32-62)

Values are expressed as median and interquartile range (Me (Q_1-Q_3). Statistically significant differences between the medians were not detected. Abbreviations: continuous glucose monitoring (CGM), continuous subcutaneous insulin infusion (CSII), flash glucose monitoring (FGM), glucose monitoring (GM), multiple daily injections (MDI), metabolic syndrome (MetS), percent body fat (PBF), skeletal muscle mass (SMM), total body water (TBW), visceral fat area (VFA).

Table S5. Consumption of the selected nutrients with diet depending on insulin therapy and modern GM systems used.

Nutrient	CSII (n=37)	MDI (n=23)	No GM (n=34)	FGM (n=18)	CGM (n=8)
	Me ± IQR				
Main nutrients					
Energy (kcal)[A*]	1803 (1685-1944)	1793 (1631-1904)	1804 (1631-1927)	1831 (1726-1934)	1740 (1533-1809)
Protein (%TDEE)	18 (16-21)	19 (18-21)	19 (17-21)	16 (15-18)	21 (20-22)
Carbohydrate (%TDEE)	57 (51-61)	54 (51-56)	54 (50-59)	58 (53-61)	55 (52-57)
Fat (%TDEE)	22 (20-28)	25 (22-29)	25 (21-30)	22 (21-29)	23 (21-25)
Fatty acids					
SFA (g)	17 (15-20)	16 (14-18)	16 (15-20)	17 (15-19)	17 (15-18)
Palmitic FA (g)	10 (9-11)	11 (9-12)	10 (9-11)	10 (9-12)	11 (10-12)
MUFA (g) [B*]	13 (11-18)	16 (13-22)	14 (12-20)	16 (11-23)	11 (8-14)
Oleic FA (g)	13 (10-14)	14 (12-17)	13 (11-17)	14 (11-15)	13 (9-13)
PUFA (g)	5 (4-8)	6 (6-8)	6 (5-8)	6 (4-9)	5 (3-6)
LC-PUFA (g)	0.052 (0.039-0.090)	0.069 (0.052-0.159)	0.066 (0.031-0.104)	0.054 (0.039-0.09)	0.069 (0.045-0.217)
ω-3 (g) [B*]	0.688 (0.554-0.975)	0.789 (0.566-1.336)	0.785 (0.573-1.173)	0.693 (0.535-1.399)	0.688 (0.565-1.162)
ALA (g)	0.554 (0.469-0.788)	0.607 (0.505-1.03)	0.626 (0.484-0.851)	0.544 (0.442-1.03)	0.55 (0.339-0.635)
EPA (g)	0.012 (0.004-0.016)	0.015 (0.009-0.04)	0.012 (0.004-0.026)	0.012 (0.01-0.015)	0.012 (0.011-0.041)
DHA (g)	0.029 (0.021-0.061)	0.038 (0.025-0.101)	0.037 (0.018-0.067)	0.034 (0.021-0.067)	0.039 (0.026-0.144)
ω-6 (g)	5 (4-6)	6 (5-7)	5 (4-6)	6 (4-7)	4 (3-5)
LA (g) [B*]	5 (4-6)	5 (4-7)	5 (4-6)	6 (4-7)	4 (3-5)
AA (g)	0.042 (0.031-0.08)	0.054 (0.034-0.153)	0.045 (0.03-0.141)	0.051 (0.034-0.083)	0.044 (0.033-0.157)
Carbohydrates					
Glucose (g)	5 (3-9)	5 (3-7)	4 (3-6)	5 (5-8)	8 (2-11)
Fructose (g)	8 (4-12)	7 (5-11)	6 (4-12)	8 (6-13)	11 (3-13)
Saccharose (g)	34 (15-51)	33 (14-47)	34 (13-54)	33 (17-47)	34 (20-36)
Dietary fiber (g) [A,B**]	18 (13-21)	17 (14-22)	17 (13-20)	21 (18-23)	13 (12-17)

Values are expressed as median and interquartile range (Me (Q_1-Q_3). Statistically significant differences (*p<0.05, **p<0.001) between the medians were marked as "A" (FGM vs. no GM) or "B" (CGM vs. no GM). Abbreviations: arachidonic acid (AA), alpha-linolenic acid (ALA), continuous glucose monitoring (CGM), continuous subcutaneous insulin infusion (CSII), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), fatty acids (FA), flash glucose monitoring (FGM), glucose monitoring (GM), linoleic acid (LA), multiple daily injections (MDI), long-chain polyunsaturated fatty acids (LC-PUFA), metabolic syndrome (MetS), monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), saturated fatty acids (SFA), total daily energy expenditure (TDEE).

Rozdział 10. Determinants Related to Oxidative Stress Parameters in Pediatric Patients with Type 1 Diabetes Mellitus

nutrients

MDPI

Article

Determinants Related to Oxidative Stress Parameters in Pediatric Patients with Type 1 Diabetes Mellitus

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Abstract: Adequate glycemic management is one of the main goals in treating type 1 diabetes mellitus (T1DM) and preventing the early onset of diabetic complications. Improperly controlled diabetes mellitus (DM) will result in oxidative stress (OS) and lead to further related health issues. Therefore, the aim of this study was to evaluate the body's ability to defend against OS depending on the duration of T1DM, metabolic management, antioxidant intake and modern glycemic monitoring systems (GMS). The study included 103 adolescents with T1DM aged 10–17 years. The control group consisted of 65 healthy peers. The patients' blood was assayed for antioxidant enzymes, minerals and toxic elements. In addition, their dietary intake of antioxidant components was assessed. The T1DM group had higher total oxidant status, oxidative stress index and Cu/Zn ratio values, higher concentrations of malondialdehyde and lower total antioxidant status (TAS) and chromium, zinc, superoxide dismutase and catalase levels than their healthy peers. The comparison between GMS types revealed favorable changes in OS parameters for the flash and continuous systems. Furthermore, an effect of vitamin A and C dietary intake on serum TAS concentrations was detected. More than 82% of the patients with high TAS fulfilled the estimated average requirement norm for vitamin A, and more than 60% fulfilled the vitamin C requirement. In youths with T1DM, it is advisable to observe the antioxidant activity of the body to prevent the accelerated development of diabetic complications.

Keywords: oxidative stress; diabetes mellitus type 1; adolescents; minerals; toxic elements; antioxidant intake; metabolic management; continuous glucose monitoring systems

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1. Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease that involves insufficient insulin secretion caused by the destruction of pancreatic islet β cells [1]. The primary method of treatment is intensive insulin therapy, adjusted to the individual patient according to their lifestyle and nutrition. Multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII) are typically administered [2,3]. Flash glucose monitoring (FGM) or continuous glucose monitoring (CGM) systems are becoming widely available modern approaches to monitoring blood glucose levels. In addition to improving the quality of life, they also reduce the number of hypo- and hyperglycemic incidents, which has a positive effect on the body [1,3,4]. Proper glycemic control is one of the key elements of preventing the progression of diabetic complications, which affects the antioxidant defense (AOD) system [5]. The body has developed a protective system against reactive oxygen species (ROS) in the form of enzymatic and non-enzymatic systems to guard against the deleterious effects of oxygen metabolism. The former relies on the cooperation of enzymes (including superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx))

to neutralize ROS, preventing damage to vital cellular structures. Additional, but certainly key, compounds that significantly affect this antioxidant potential of the body include dietary antioxidant nutrients (vitamins E and C, β-carotene, copper (Cu), zinc (Zn) and selenium (Se)) [6,7]. Other factors that influence the burden on the AOD system and cause oxidative damage to the above-mentioned enzymes and lipids (enhanced malondialdehyde (MDA) production) include exposure to arsenic (As), cadmium (Cd), mercury (Hg) and lead (Pb) [8,9]. Although the interest in oxidative stress in diabetes has been growing in recent years [5,10–12], there is a lack of research in the scientific world regarding a comprehensive approach in adolescents with T1DM that uses the dietary intake of nutrients with antioxidant potential and considers other possible contributors of oxidative stress (OS).

These mechanisms contributed to the aim of this study, which is to evaluate the body's antioxidant capabilities in relation to T1DM duration, metabolic management, antioxidant intake and modern glucose monitoring systems.

2. Materials and Methods

2.1. Study Group

This case–control study involved 168 patients with T1DM and healthy peers aged 10–17 years. The participants in the T1DM group (n = 103) were under the care of the Department of Paediatrics, Endocrinology and Diabetology with the Subdivision of Cardiology of the Children's University Clinical Hospital in Białystok, Poland, between March 2020 and September 2022. The diagnosis of T1DM was performed by doctors in the field of diabetology under the standards of the frequent presence of autoantibodies [1]. The inclusion criteria were an age of 10 to 17 years, a diagnosis of T1DM and the willingness to take part in the study. We excluded patients who had other types of diabetes mellitus (DM) or severe chronic diseases (e.g., cancer, hepatic disease and cardiac disease). The control group consisted of 65 individuals who volunteered at the Department of Bromatology of the Medical University of Białystok and declared no history of symptoms that would indicate the presence of DM or other chronic diseases at the time of recruitment. The Bioethics Committee's approval (No. R-I-002/587/2019) was obtained to carry out the research. The consent of the participants' guardian was required for participation.

2.2. Blood Sample Analysis of Selected Biomarkers

Vacutainer tubes containing a clot activator and gel or anticoagulant K2EDTA (Becton Dickinson, France) were used to collect fasting blood samples. After centrifugation (Centrifuge M-diagnostic, MPW, Warsaw, Poland) of the blood (10 min at about 2000 rpm), the serum was transferred into tubes and stored at −20 °C (to determine the elements) and at −80 °C (to measure the antioxidant defense and oxidative stress parameters). To prepare samples for the determination of Cu, chromium (Cr), Zn, As, Cd and Pb, the material was deproteinized (1 mol/L nitric acid, Suprapur, Merck, Darmstadt, Germany) and a surfactant was used (1% Triton X-100, Sigma-Aldrich, St Louis, MO, USA). The material was centrifuged for 10 min at about 6000 rpm (Centrifuge IKA mini G, IKA, Staufen im Breisgau, Germany). Zn, Cr, As and Pb were measured in the supernatant, while Cu and Cd were measured in a sample further diluted with 0.1 mol/L nitric acid. Shortly before the Se assay, the serum was diluted with 0.2% Triton X-100. Calibration curves were made using stock solutions (Merck, Darmstadt, Germany).

The concentrations of mineral components were measured using atomic absorption spectrometry (AAS) with Zeeman background correction (Z-2000, Hitachi, Japan). An acetylene/air flame atomization technique was used to measure Zn, and electrothermal atomization in a graphite cuvette was used for Cu, Se, Cr, Cd and Pb. Inductively coupled plasma mass spectrometry (ICP-MS, NexION300D, PerkinElmer, Waltham, MA, USA) with a kinetic energy discrimination chamber (KED) was used to determine As in whole blood. Hg was assayed directly in the material through AAS using the amalgamation technique (AMA-254, Leco Corp., Altec Ltd., Prague, Czechia). Moreover, a molar ratio was computed between Cu and Zn. The detection limits of the methods were 0.011 µg/L

(As), 0.08 µg/L (Cd), 0.0005 mg/L (Cu), 0.12 µg/L (Cr), 0.003 µg/L (Hg), 0.97 µg/L (Pb), 1.44 µg/L (Se) and 0.02 mg/L (Zn). A spectrophotometry technique via a microplate reader (Infinite M200 Pro Tecan, Männedorf, Switzerland) was used to assay oxidative stress parameters such as total oxidant status (TOS; according to the methodology described by Erel et al. [13]), total antioxidant status (TAS) and GPx (with reagent kits from Randox Laboratories, Crumlin, County Antrim, UK) and MDA, CAT and SOD (with reagent kits from Cayman Chemical Company, Ann Arbor, MI, USA). Table 1 provides details of the determination. The oxidative stress index (OSI) is expressed as the ratio of TAS to TOS. Categories were defined for each level of TAS, TOS, OSI and Cu/Zn parameters to present the results in a transparent form. To classify the outcomes in the 'low' and 'high' categories, a reference range for a given parameter was defined and named as 'medium', which covered the tolerable normal values including the margin of error. The ranges were 1.2–1.45 mmol/L for TAS, 5–8 µmol H_2O_2 Equiv./L for TOS, 0.3–0.6 for OSI and 0.6–1.0 for Cu/Zn ratio. Glycated hemoglobin (HbA1c) was determined through ion exchange high-performance liquid chromatography using a Bio-Rad D-10TM system (Bio-Rad, Hercules, CA, USA). Certified materials specified for each kit were used to control the accuracy of the determination methods used (Seronorm Trace Elements Whole Blood L-2; Seronorm Trace Elements Serum L-1, Sero AS, Norway; Quality Control Randox; Catalase Control CaymanChem).

Table 1. Detailed specifications for the elements, antioxidant defense markers and oxidative stress markers measured.

Parameter	Unit	Wavelength	Material
Cu	mg/L	324.8 nm	Serum
Cr	µg/L	359.3 nm	Serum
Se	µg/L	196 nm	Serum
Zn	mg/L	213.9 nm	Serum
TAS	mmol/L	600 nm	Serum
SOD	U/mL	450 nm	Serum
CAT	n/mol/min	540 nm	Serum
GPx	U/L whole blood	340 nm	Whole blood
TOS	µmol H_2O_2 equiv./L	560/800 nm	Serum
MDA	µmol/L	535 nm	Serum
As	µg/L	As^{75} 74.92 U *	Whole blood
Cd	µg/L	228.8 nm	Whole blood
Hg	µg/L	254 nm	Whole blood
Pb	µg/L	283.3 nm	Whole blood

* Isotope mass. Abbreviations: arsenic (As), catalase (CAT), cadmium (Cd), copper (Cu), chromium (Cr), glutathione peroxidase (GPx), mercury (Hg), malondialdehyde (MDA), lead (Pb), selenium (Se), superoxide dismutase (SOD), total antioxidant status (TAS), total oxidant status (TOS), zinc (Zn).

2.3. Nutritional Status and Nutrient Intake

Basic anthropometric measurements (body height and weight) were taken in order to assess the nutritional status. A questionnaire covering general information, medical history, insulin therapy and dietary habits was conducted with each patient. To estimate the precise dietary intake of nutrients with antioxidant potential, a nutritional interview was additionally performed, the detailed process of which was described in a previous publication [14].

2.4. Statistical Analysis

Statistical analysis of the data was carried out in the software program Statistica (version 13 PL; TIBCO Software Inc., Palo Alto, CA, USA). In order to determine the normality of the variables' distribution so as to appropriately present the data and select adequate statistical tests, the Shapiro–Wilk, Kolmogorov–Smirnov and Lilliefors tests were performed. For quantitative variables, the Mann–Whitney U test and Kruskal–Wallis ANOVA test with post hoc analysis were applied. Correlations between parameters were

checked with Spearman's correlation coefficient. Multiple correspondence analysis (MCA) was used to detect all common features among individuals according to their antioxidant status and insulin therapy, along with the use of modern GMS and the duration of T1DM. The number of dimensions reliably representing the data was determined using a scree plot; the data were then analyzed and presented as a Burt matrix. Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic utility of antioxidant defense and oxidative stress markers. The overall efficacy of the indicator was expressed by the area under the ROC curve (AUC) with 95% confidence intervals (CI) and *p*-values. Cut-off values, sensitivity and specificity, the Youden index and positive and negative likelihood ratios were calculated. *p*-values of < 0.05 were recognized as statistically significant.

3. Results

Table 2 provides information on the research participants. For those with T1DM, details of the treatment are additionally included. Table 3 shows a comparison of the median concentrations of parameters in the blood between adolescents with T1DM and healthy peers. Among diabetics, statistically significantly higher values were found for Cu/Zn ($p < 0.05$), MDA ($p < 0.01$), TOS and OSI ($p < 0.001$), while lower values were found for Cr, Zn, TAS and SOD ($p < 0.001$), and CAT ($p < 0.01$). Only for MDA were there statistically significant differences between boys and girls in the T1DM group (3.863 µmol/L vs. 4.159 µmol/L, $p < 0.05$). Concerning the comparison between genders in the control group, discrepancies were found for Cd (0.728 µg/L vs. 1.173 µg/L, $p < 0.05$, respectively) and GPx (2160 U/L vs. 1206 U/L, $p < 0.05$, respectively). For the other parameters in Table 3 and for the dietary intake of nutrients with antioxidant potential, no such changes were observed.

Table 2. Characteristics of the study cohort.

Parameter		T1DM Group (n = 103)	Control Group (n = 65)
Age (years)	Me (Q_1–Q_3)	13 (11–15)	15 (14–15)
Height (cm)		164 (155–173)	167 (158–178)
Body weight (kg)		57 (46–67)	56 (48–67)
HbA1c (%)		8 (6–10)	–
Age at diagnosis (years)		9 (6–11)	–
T1DM duration (years)		4 (1–7)	–
Gender (girls/boys)	%	51/49	38/62
Newly diagnosed (<2 years)		27	–
Type of insulin therapy (MDI/CSII)		41/59	–
Type of glucose monitoring system (Glucometer only/FGM/CGM)		29/41/30	–

Values are expressed as median and interquartile range (Me (Q_1–Q_3)) or percentage of subjects (%). Abbreviations: continuous glucose monitoring (CGM), continuous subcutaneous insulin infusion (CSII), flash glucose monitoring (FGM), glycated hemoglobin (HbA1c), multiple daily injections (MDI), type 1 diabetes mellitus (T1DM).

Comparing those with newly diagnosed T1DM and those with the disease for more than two years (Table S1), the former group showed lower median Cd (0.629 µg/L vs. 0.784 µg/L, $p < 0.01$) and MDA (3.341 µmol/L vs. 4.171 µmol/L, $p < 0.05$) values, and higher Hg (0.680 µg/L vs. 0.391 µg/L, $p < 0.01$) and SOD (1.678 U/mL vs. 1.396 U/mL, $p < 0.01$) values. No differences were found between insulin therapies, while some were observed between individuals using modern GMS compared to traditional glucometers (Table S2). The participants using a CGM rather than a glucometer demonstrated higher TAS values (1.419 mmol/L vs. 1.236 mmol/L, respectively, $p < 0.05$) and lower OSI values (0.552 vs. 0.706, respectively, $p < 0.01$). Table S3 presents the concentrations of the markers in relation to the range in HbA1c values. Higher TAS levels were recorded in diabetics with an HbA1c level below 7% than in those with a level ranging from 7% to 9.9% (1.432 mmol/L vs. 1.259 mmol/L, $p < 0.01$) or above 10% (1.432 mmol/L vs. 1.299 mmol/L,

$p < 0.01$). Similarly, OSI was noted to be significantly higher in patients with poor metabolic management (<7% vs. 7–9.9%: 0.470 vs. 0.631, $p < 0.001$; <7% vs. ≥10%: 0.470 vs. 0.739, $p < 0.001$). Furthermore, statistically significantly higher TOS and lower Cu values were found in individuals with elevated HbA1c.

Table 3. Comparison of elements, antioxidant defense and oxidative stress markers between T1DM and control group.

Parameter	T1DM (n = 103)	Control (n = 65)	p-Value (T1DM vs. Control)
Cu (mg/L)	0.874 (0.724–1.154)	0.903 (0.706–1.130)	NS
Cu/Zn ratio	1.057 (0.842–1.458)	0.981 (0.669–1.179)	<0.05
Cr (µg/L)	0.648 (0.568–0.960)	1.530 (1.088–1.809)	<0.001
Se (µg/L)	60.9 (50.2–69.8)	61.4 (51.1–69.0)	NS
Zn (mg/L)	0.891 (0.796–1.020)	0.979 (0.898–1.119)	<0.001
TAS (mmol/L)	1.304 (1.173–1.525)	1.580 (1.476–1.761)	<0.001
SOD (U/mL)	1.470 (1.068–2.049)	2.114 (1.676–2.356)	<0.001
CAT (n/mol/min)	43.2 (27.7–72.4)	58.3 (48.2–75.2)	<0.01
GPx (U/L)	1329 (756–2168)	1749 (967–3049)	NS
TOS (µmol H_2O_2 Equiv./L)	7.568 (6.0–9.295)	4.847 (3.851–5.839)	<0.001
OSI	0.575 (0.439–0.771)	0.284 (0.241–0.382)	<0.001
MDA (µmol/L)	3.912 (2.512–5.312)	2.520 (1.690–4.950)	<0.01
As (µg/L)	0.593 (0.385–0.766)	0.581 (0.480–0.658)	NS
Cd (µg/L)	0.696 (0.577–1.330)	0.862 (0.569–1.650)	NS
Hg (µg/L)	0.456 (0.246–0.767)	0.344 (0.243–0.562)	NS
Pb (µg/L)	22.9 (15.2–32.6)	27.1 (20.1–31.5)	NS

Values are expressed as median and interquartile range (Me (Q_1–Q_3)). Statistically significant differences between the medians were detected using the Mann–Whitney U test. Abbreviations: arsenic (As), catalase (CAT), cadmium (Cd), chromium (Cr), copper (Cu), glutathione peroxidase (GPx), mercury (Hg), malondialdehyde (MDA), non-significant (NS), oxidative stress index (OSI), lead (Pb), selenium (Se), superoxide dismutase (SOD), type 1 diabetes mellitus (T1DM), total antioxidant status (TAS), total oxidant status (TOS), zinc (Zn).

The participants with T1DM were classified as having low, medium and high serum OS marker concentrations. Table 4 shows the medians of HbA1c values by category. There was a statistically significant difference between the HbA1c of diabetics with low and high TAS (9.0% vs. 6.9%, $p < 0.01$), as well as between those with low and medium TOS (6.6% vs. 7.7%, $p < 0.05$) and low and high TOS (6.6% vs. 8.1%, $p < 0.05$). The vast majority were classified as having medium TAS (41%), TOS (47%) and OSI (41%) values. More than half (52%) had a high Cu/Zn ratio, and only 28% had a high TAS. However, just 11% had a low TOS score, while 27% had a low OSI and 13% a low Cu/Zn ratio.

Table 4. The level of HbA1c and the percentage of individuals with T1DM classified into each group according to the level (low, medium and high) of each AOD and OS parameter (TAS, TOS, OSI and Cu/Zn).

Parameter	Low		Medium		High		p-Value	
	%	Me (Q_1–Q_3)	%	Me (Q_1–Q_3)	%	Me (Q_1–Q_3)	Low vs. Medium	Low vs. High
TAS	31	9.0 (7.4–10.7)	41	7.8 (6.6–9.8)	28	6.9 (6.3–8.7)	NS	<0.01
TOS	11	6.6 (6.1–7.9)	47	7.7 (6.8–9.8)	43	8.1 (7.0–10.6)	<0.05	<0.05
OSI	27	7.5 (6.6–9.8)	41	7.8 (6.6–10.8)	32	8.2 (7.3–9.8)	NS	NS
Cu/Zn	13	7.5 (6.73–10.5)	35	7.6 (6.6–9.7)	52	8.1. (6.7–9.9)	NS	NS

Values are expressed as median and interquartile range (Me (Q_1–Q_3)) or percentage of subjects (%). Statistically significant differences between the medians were detected using Kruskal–Wallis ANOVA tests with post hoc analysis. Abbreviations: antioxidant defense (AOD), copper (Cu), glycated hemoglobin (HbA1c), non-significant (NS), oxidative stress (OS), oxidative stress index (OSI), type 1 diabetes mellitus (T1DM), total antioxidant status (TAS), total oxidant status (TOS), zinc (Zn).

Table 5 shows the dietary intakes and percentages of individuals fulfilling the antioxidant nutrient dietary norms. Diabetics, compared to healthy peers, showed a statistically

significantly lower intake of vitamin A (722 µg vs. 882 µg, $p < 0.01$) and β-carotene (2574 µg vs. 3522 µg, $p < 0.01$). The highest percentages of participants with intake below the norm were observed for vitamin E (T1DM: 88%; control: 85%), vitamin C (42% and 38%, respectively), zinc and vitamin A (23% each in T1DM and 26% and 14% in the control group). A small percentage of individuals consumed zinc and vitamin A above the upper tolerable intake level. Furthermore, a relationship between dietary intake of vitamin A and C and serum TAS concentrations was noted. More than 82% of the patients with high TAS fulfilled the estimated average requirement (EAR) for vitamin A, and 62% reached the EAR for vitamin C. These percentages were substantially lower in the other (low and medium) TAS categories.

Table 5. Dietary intake of antioxidants and percentages of participants whose diets were in compliance with nutritional standards.

Parameter	T1DM (n = 103)				Control (n = 65)			p-Value (T1DM vs. Control)
	Me (Q_1–Q_3)	Percentage of Subjects (%)			Me (Q_1–Q_3)	Percentage of Subjects (%)		
		Type of Norm	Norm	Below (Above *) Norm		Norm	Below (Above *) Norm	
Cu (mg)	0.97 (0.77–1.1)	EAR	87	13	1.0 (0.88–1.3)	97	3	NS
Mn (mg)	3.4 (2.3–4.4)	AI	97	3	3.1 (2.8–4.4)	98	2	NS
Zn (mg)	9.0 (7.6–11)	EAR UL	77 97	23 2 *	9.6 (8.2–12)	74 92	26 8 *	NS
Vitamin A (µg)	722 (568–899)	EAR UL	77 88	23 12 *	882 (689–1184)	86 85	14 15 *	<0.01
Retinol (µg)	260 (197–367)	n/d	–	–	280 (215–340)	–	–	NS
β-carotene (µg)	2574 (1754–3594)	n/d	–	–	3522 (2479–5178)	–	–	<0.01
Vitamin C (mg)	65 (37–108)	EAR	58	42	70 (48–110)	62	38	NS
Vitamin E (mg)	5.5 (4.3–6.8)	AI	12	88	6.1 (4.5–7.9)	15	85	NS

Values are expressed as median and interquartile range (Me (Q_1–Q_3)) or percentage of subjects (%). Statistically significant differences between the medians were detected using the Mann–Whitney U test. Abbreviations: adequate intake (AI), copper (Cu), estimated average requirement (EAR), manganese (Mn), no data (n/d), non-significant (NS), type 1 diabetes mellitus (T1DM), tolerable upper intake level (UL), zinc (Zn).

A correlation was observed between selected parameters in the blood and also the intake of nutrients with antioxidant properties among diabetics (Table 6). A statistically significant positive association was found between HbA1c and OSI, and there was a negative one with TAS. Moreover, there was also a statistically significant positive correlation between Se and the dietary intake of vitamin A and β-carotene, as well as serum levels of TAS and CAT. In contrast, a statistically significant correlation was observed between the Cu/Zn ratio and the dietary intake of Zn, Cu, Mn, retinol and vitamin E.

The MCA helped describe the relation between the body's antioxidant capabilities and insulin therapy with a modern GMS (Figure 1A) and the duration of T1DM (Figure 1B). Figure 1A,B depict the MCA results in bivariate form, which explains more than half of the total variation. For Figure 1A, the following three groups were identified:

(1) The first and fourth quadrants represent healthy peers with an above-average TAS range and low TOS.
(2) The second quadrant includes diabetics with low TAS and high TOS who were not supported by FGM or CGM or who used MDI.
(3) The final quadrant (III) consists of individuals with T1DM, who had medium TAS and TOS and who used FGM or CGM and CSII.

Table 6. Correlations between blood parameters and dietary intake of nutrients among patients with T1DM.

Parameter 1	Parameter 2	R	*p*-Value
HbA1c	TAS	−0.3	<0.01
	OSI	0.3	<0.001
Zn	Cu	0.2	<0.05
Cu	Hg	0.3	<0.01
Cu/Zn ratio	Hg	0.2	<0.01
	Dietary Zn	−0.3	<0.001
	Dietary Cu	−0.3	<0.001
	Dietary Mn	−0.3	<0.001
	Dietary retinol	−0.3	<0.01
	Dietary vitamin E	−0.2	<0.05
Se	TAS	0.4	<0.001
	CAT	0.2	<0.01
	Dietary vitamin A	0.2	<0.01
	Dietary β-carotene	0.3	<0.01
TAS	Cd	−0.3	<0.01
	CAT	0.2	<0.01
	SOD	0.2	<0.05
Cd	OSI	0.2	<0.05
	MDA	0.3	<0.01
	GPx	−0.3	<0.01
CAT	SOD	0.4	<0.001

Statistically significant correlations were detected using Spearman's correlation coefficient. Repeated correlations between parameters were removed from the table. Abbreviations: catalase (CAT), cadmium (Cd), copper (Cu), glutathione peroxidase (GPx), glycated hemoglobin (HbA1c), mercury (Hg), malondialdehyde (MDA), manganese (Mn), oxidative stress index (OSI), selenium (Se), superoxide dismutase (SOD), type 1 diabetes mellitus (T1DM), total antioxidant status (TAS), zinc (Zn).

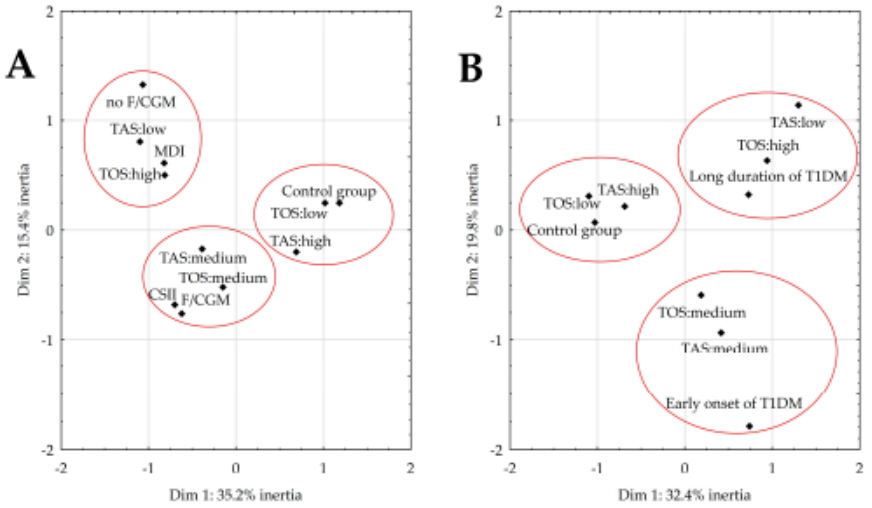

Figure 1. Multivariate correspondence analysis coordinate plot of total antioxidant and oxidant status, as well as insulin therapy with modern glycemic monitoring (**A**) and the duration of T1DM (**B**). Abbreviations: continuous glucose monitoring (CGM), continuous subcutaneous insulin infusion (CSII), flash glucose monitoring (FGM), multiple daily injections (MDI), type 1 diabetes mellitus (T1DM), total antioxidant status (TAS), total oxidant status (TOS).

Figure 1B illustrates the following:

(1) In the first quadrant are individuals who have had T1DM for more than 2 years, with low TAS and high TOS.
(2) The second quadrant classifies healthy participants with an above-normal TAS and low TOS.
(3) The last quadrant (IV) contains recently diagnosed patients with medium TAS and TOS.

The ROC curve analysis revealed that TAS, TOS and OSI may be good predictors of oxidative stress for T1DM (Table 7). The calculated cut-off values corresponded to the highest accuracy of the markers, revealing a significant diagnostic potential for OSI (AUC: 0.87, $p < 0.001$) and TOS (AUC: 0.83, $p < 0.001$) and TAS (AUC: 0.77, $p < 0.001$). Comparative analysis between individuals with T1DM and the control group showed a significantly higher percentage of adolescents with elevated TOS (78% vs. 23%) and OSI (88% vs. 26%), as well as lower TAS (30% vs. 77%).

Table 7. Assessment of TAS, TOS and OSI as possible indicators of oxidative stress in T1DM.

Parameter	TAS	TOS	OSI
AUC (CI)	0.77 (0.7–0.84)	0.83 (0.77–0.90)	0.87 (0.82–0.93)
p-Value AUC	<0.001	<0.001	<0.001
Cut-off point	1.450	5.892	0.375
Sensitivity	72%	79%	89%
Specificity	77%	77%	74%
Youden index	0.488	0.556	0.632
+LR	0.231	0.231	0.262
−LR	0.282	0.214	0.107

Abbreviations: area under curve (AUC), confidence interval (CI), positive likelihood ratios (+LR), negative likelihood ratios (−LR), oxidative stress index (OSI), type 1 diabetes mellitus (T1DM), total antioxidant status (TAS), total oxidant status (TOS).

4. Discussion

Our study showed that adolescents with T1DM had lower levels of Zn (0.891 mg/L vs. 0.979 mg/L, $p < 0.001$) and Cu (0.874 mg/L vs. 0.903 mg/L, $p > 0.05$), but higher Cu/Zn ratios (1.057 vs. 0.981, $p < 0.05$) compared to their healthy peers. Similar results of Zn and higher Cu concentration in young diabetics were obtained by Salmonowicz et al. [11] (Zn: 0.88 mg/L; Cu: 1.26 mg/L) and Rychter-Stoś et al. [15] (0.946 mg/L and 1.333 mg/L, respectively). This finding is important for this population because of the functions that these elements are involved in. Zn is stored with insulin in the secretory vesicles of pancreatic islet β cells, and is responsible for the normal synthesis and secretion of insulin and glucagon [16]. Similarly, Cu is crucial for the normal activity of antioxidant enzymes such as SOD. Nevertheless, its homeostasis needs to be controlled, not only at the cellular level, but also in organs and tissues [17]. Although these values are within the reference range, a higher Cu/Zn ratio may indicate the possibility of oxidative stress in the body. Excessively high concentrations will lead to the formation of ROS and associated damage.

The above-mentioned elements are the main ones included in the active center of SOD, one of the most effective enzymes for neutralizing superoxide anions. Along with CAT, both are crucial enzymes of the AOD system. There is a significant rise in CAT activity at the onset of T1DM and a decline as it progresses. The opposite trend was observed for metabolic management: with higher HbA1c values, CAT levels increased [10]. Much the same was observed in our study. In addition, CAT positively correlated with Se, TAS and SOD levels. The concentrations of SOD were statistically significantly lower in diabetics than in healthy peers, and declined with the duration of T1DM. This lower activity level may also have been caused by diminished levels of Zn and Cu, which are embedded in the active center of this enzyme. More importantly, Zn is responsible for insulin synthesis in cells that are degraded in T1DM [16].

Selenium has a strong antioxidant potential that affects the antioxidant balance in the body [18]. In the current study, we found no differences in Se concentrations between adolescents with T1DM and healthy peers, similarly to Salmonowicz et al. [11]. However, they were within the reference range. One of the most important selenoenzymes is GPx. Its key function is to reduce hydrogen peroxide to water [18]. Darenskaya [19] reported a decrease in GPx activity among diabetics, which we also found in this study. Moreover, in our participants, it was about 20% lower in patients with long duration of T1DM as compared to the early onset group. This finding may be due to low glutathione levels or inactivation of the enzyme as a result of intense oxidative stress [20].

Even in low amounts, Pb may affect attention and concentration, and may cause irritability [9]. We reported lower levels of Pb in adolescents with T1DM than in the control group. Likewise, Forte et al. [21] observed that low concentrations of Zn, Pb, Cr, Mn and Ni were associated with T1DM. Similarly, in the case of the other elements we measured (Hg, Cd and As), no significant differences were found; the only exception was the statistically significant two-fold lower Cr values among diabetics. Low concentrations of Cr, as compared to a control group, were also observed by Lin et al. [22]. This is a disturbing sign, since Cr is involved in regulating glucose metabolism [23]. Furthermore, in a study on umbilical cord blood from babies, it was shown that the blood of patients who developed T1DM later in life had higher concentrations of Hg and As than a control group. One theory is that exposure to toxic metals during pregnancy may be one of many environmental factors that contributes to the future disease process [24].

Some of the by-products of lipid peroxidation are thiobarbituric acid reactive substances (TBARS). Using the thiobarbituric acid reagent, it is possible to measure MDA, a reactive aldehyde produced during the peroxidation of polyunsaturated fatty acids [25]. Diabetic patients were shown to be more susceptible to this production, further compounded by chronic hyperglycemia, which results in elevated production of free radicals and other ROS [12]. Similar findings were observed in our study. More importantly, MDA levels were higher in diabetics with an HbA1c level above 10% than in those with a level below 7%. A similar pattern was noted when individuals with T1DM for more than 2 years were compared to those with recently diagnosed T1DM.

The above-mentioned outcomes suggest the possibility of oxidative stress. For a comprehensive view, TAS and TOS were also determined, and their ratio, i.e., OSI, was calculated. Lower TAS and higher TOS and OSI indicate an oxidant–antioxidant imbalance through an endogenous antioxidant exhaustion, which leads to the manifestation of oxidative stress among young diabetics [14]. We observed this phenomenon, and it was particularly associated with deteriorated metabolic management measured via HbA1c, but also among individuals not using FGM or CGM. Moreover, considering their concentrations the highest oxidative stress was detected in pediatric participants at the initial stage of T1DM; this decreased amongst those with T1DM for more than 2 years.

It is also necessary to evaluate this study for its weaknesses and strengths. The type of research introduces a limitation, which is the inability to determine the exact causes of correlations and statistical significance; we can only identify them and make their presence known. The findings demonstrate that there is a strong need for research that can identify cause-and-effect relationships. It should be emphasized that a major strength of this study is the extensive comparison of the data regarding data classification, type of insulin therapy and use of modern FCM and CGM. Another advantage is the inclusion of a control group as part of the study, which made the comparative analysis possible and reliable.

5. Conclusions

Based on the findings of our research, it can be concluded that a low defense potential of the antioxidant system leading to high oxidative stress occurs among young diabetics and is present even at the onset of T1DM. In addition, there was a similar tendency in relation to deteriorating metabolic management, but not in patients supported by FGM or CGM. All these findings highlight the importance of monitoring the undesirable changes

associated with high oxidant levels at T1DM onset, as they interfere with treatment and can lead to earlier progression of diabetic complications.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/nu15092084/s1, Table S1. Comparison of antioxidant defense and oxidative stress parameters regarding duration of T1DM; Table S2. Comparison of antioxidant defense and oxidative stress parameters regarding insulin therapy and glucose monitoring systems; Table S3. Comparison of antioxidant defense and oxidative stress parameters regarding classification of HbA1c levels among T1DM patients.

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nutrients

MDPI

Supplementary Material

Determinants Related to Oxidative Stress Parameters in Pediatric Patients with Type 1 Diabetes Mellitus

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Table S1. Comparison of antioxidant defense and oxidative stress parameters regarding duration of T1DM.

Parameter	Early onset of T1DM (n=28)	Long duration of T1DM (n=75)	*p*-Value
Cu (mg/L)	0.920 (0.731-1.532)	0.874 (0.724-1.079)	NS
Cu/Zn ratio	1.111 (0.884-1.632)	1.016 (0.821-1.420)	NS
Cr (µg/L)	0.634 (0.564-0.895)	0.652 (0.576-0.965)	NS
Se (µg/L)	62.5 (54.5-70.6)	60.3 (47.1-69.8)	NS
Zn (mg/L)	0.921 (0.803-1.059)	0.890 (0.796-1.008)	NS
TAS (mmol/L)	1.292 (1.157-1.400)	1.321 (1.173-1.567)	NS
SOD (U/ml)	1.678 (1.327-2.657)	1.396 (1.032-1.855)	<0.01
CAT (n/mol/min)	44.0 (28.3-80.0)	43.2 (27.8-64.8)	NS
GPx (U/L)	1601 (627-2514)	1285 (803-2072)	NS
TOS (µmol H_2O_2 Equiv./L)	8.033 (6.189-10.5)	7.500 (5.897-9.189)	NS
OSI	0.652 (0.416-0.862)	0.552 (0.450-0.713)	NS
MDA (µmol/L)	3.341 (1.712-4.549)	4.171 (2.771-5.688)	<0.05
As (µg/L)	0.593 (0.385-0.762)	0.593 (0.358-0.766)	NS
Cd (µg/L)	0.629 (0.445-0.729)	0.784 (0.601-1.558)	<0.01
Hg (µg/L)	0.680 (0.350-0.983)	0.391 (0.185-0.744)	<0.01
Pb (µg/L)	20.8 (15.0-30.8)	23.1 (15.2-34.4)	NS

Values are expressed as median and interquartile range (Me (Q_1–Q_3). Statistically significant differences between the medians were detected by the Mann–Whitney U test. Abbreviations: arsenic (As), catalase (CAT), cadmium (Cd), chromium (Cr), copper (Cu), glutathione peroxidase (GPx), mercury (Hg), malondialdehyde (MDA), non-significant (NS), oxidative stress index (OSI), lead (Pb), selenium (Se), superoxide dismutase (SOD), type 1 diabetes mellitus (T1DM), total antioxidant status (TAS), total oxidant status (TOS), zinc (Zn).

Table S2. Comparison of antioxidant defense and oxidative stress parameters regarding insulin therapy and glucose monitoring systems.

Parameter	Insulin therapy		Glucose monitoring systems				*p*-Value
	MDI (n=42)	CSII (n=61)	Glucometer only (n=30)	FGM (n=42)	CGM (n=31)	F/CGM (n=73)	
Cu (mg/L)	0.816 (0.695-1.114)	0.906 (0.784-1.230)	0.831 (0.724-1.049)	0.862 (0.709-1.404)	0.905 (0.792-1.079)	0.898 (0.737-1.230)	NS
Cu/Zn ratio	0.941 (0.735-1.474)	1.161 (0.890-1.447)	0.984 (0.821-1.447)	1.072 (0.752-1.590)	1.141 (0.920-1.420)	1.141 (0.886-1.464)	NS
Cr (µg/L)	0.652 (0.576-0.960)	0.643 (0.568-0.946)	0.678 (0.624-0.946)	0.633 (0.514-1.120)	0.638 (0.564-0.803)	0.636 (0.564-0.960)	NS
Se (µg/L)	61.9 (54.3-70.8)	60.3 (46.0-69.3)	61.2 (47.1-70.8)	61.1 (56.0-70.8)	60.3 (45.6-69.0)	60.9 (50.5-69.8)	NS
Zn (mg/L)	0.912 (0.825-1.026)	0.890 (0.733-0.960)	0.923 (0.821-1.037)	0.901 (0.825-1.020)	0.854 (0.711-0.954)	0.890 (0.784-1.008)	NS
TAS (mmol/L)	1.302 (1.154-1.407)	1.321 (1.174-1.596)	1.236 (1.068-1.367)	1.304 (1.220-1.553)	1.419 (1.201-1.691)	1.336 (1.213-1.602)	<0.05 [A] <0.01 [B,C]
SOD (U/ml)	1.608 (1.215-2.174)	1.363 (1.032-1.855)	1.514 (1.120-2.690)	1.460 (1.056-1.869)	1.413 (1.068-2.161)	1.450 (1.068-1.885)	NS
CAT (n/mol/min)	50.7 (29.2-73.7)	42.1 (26.6-64.8)	44.5 (30.7-84.8)	39.9 (27.5-63.4)	53.3 (23.3-73.7)	42.6 (26.6-66.8)	NS
GPx (U/L)	1438 (756-2491)	1285 (817-2071)	1163 (629-2119)	1401 (728-2256)	1420 (904-2305)	1420 (849-2256)	NS
TOS (µmol H_2O_2 Equiv./L)	7.847 (5.892-9.216)	7.500 (6.189-9.295)	4.035 (3.323-5.382)	7.160 (5.676-8.865)	7.945 (5.9-10.1)	7.500 (5.841-9.514)	NS
OSI	0.575 (0.450-0.787)	0.586 (0.431-0.745)	0.706 (0.491-0.904	0.520 (0.388-0.652)	0.552 (0.412-0.713)	0.533 (0.411-0.659)	<0.01 [A,C]
MDA (µmol/L)	4.206 (2.877-5.300)	3.632 (2.265-5.335)	4.035 (3.324-5.382)	3.839 (2.559-4.759)	4.220 (1.841-5.594)	3.862 (2.241-5.276)	NS
As (µg/L)	0.593 (0.356-0.766)	0.593 (0.385-0.741)	0.593 (0.415-0.736)	0.595 (0.296-0.808)	0.596 (0.385-0.820)	0.596 (0.356-0.808)	NS
Cd (µg/L)	0.671 (0.559-1.454)	0.722 (0.59-1.078)	0.751 (0.571-1.893)	0.656 (0.581-0.926)	0.777 (0.585-0.969)	0.696 (0.585-0.964)	NS
Hg (µg/L)	0.576 (0.317-0.767)	0.363 (0.218-0.751)	0.636 (0.218-1.002)	0.570 (0.317-0.964)	0.342 (0.177-0.536)	0.421 (0.248-0.701)	NS
Pb (µg/L)	25.7 (14.6-32.6)	21.8 (16.2-31.3)	22.3 (16.2-47.5)	24.0 (14.6-32.6)	21.8 (15.2-28.6)	23.0 (15.2-31.0)	NS

Values are expressed as median and interquartile range (Me (Q_1–Q_3). Statistically significant differences between the medians (A – glucometer vs. FGM; B – glucometer vs. CGM; C – glucometer vs. FGM&CGM) were detected by the Mann–Whitney U test and Kruskal–Wallis ANOVA test with post-hoc analysis. Abbreviations: arsenic (As), catalase (CAT), cadmium (Cd), continuous glucose monitoring (CGM), chromium (Cr), continuous subcutaneous insulin infusion (CSII), copper (Cu), flash glucose monitoring (FGM), glutathione peroxidase (GPx), mercury (Hg), malondialdehyde (MDA), multiple daily injections (MDI), non-significant (NS), oxidative stress index (OSI), lead (Pb), selenium (Se), superoxide dismutase (SOD), total antioxidant status (TAS), total oxidant status (TOS), zinc (Zn).

Table S3. Comparison of antioxidant defense and oxidative stress parameters regarding classification of HbA1c levels among T1DM patients.

Parameter	HbA1c ≤ 7% (n=34)	HbA1c 7.1-9.9% (n=44)	HbA1c ≥ 10% (n=25)	*p*-Value
Cu (mg/L)	0.876 (0.724-1.150)	0.918 (0.797-1.329)	0.779 (0.635-1.012)	<0.05 [B]
Cu/Zn ratio	0.971 (0.745-1.474)	1.134 (0.911-1.470)	1.014 (0.882-1.377)	NS
Cr (µg/L)	0.676 (0.596-1.120)	0.636 (0.538-1.043)	0.624 (0.592-0.803)	NS
Se (µg/L)	63.6 (50.5-69.7)	59.9 (50.1-70.6)	61.6 (50.4-70.8)	NS
Zn (mg/L)	0.908 (0.840-1.030)	0.891 (0.776-1.035)	0.848 (0.671-0.960)	NS
TAS (mmol/L)	1.432 (1.279-1.648)	1.259 (1.142-1.417)	1.299 (0.923-1.394)	<0.01 [A, C]
SOD (U/ml)	1.475 (1.154-1.885)	1.386 (0.947-1.769)	1.564 (1.159-2.356)	NS
CAT (n/mol/min)	37.4 (26.6-66.8)	48.2 (29.6-78.2)	45.8 (27.5-63.8)	NS
GPx (U/L)	1351 (908-2168)	1259 (645-2092)	1606 (675-2258)	NS
TOS (µmol H_2O_2 Equiv./L)	6.657 (5.270-9.027)	7.870 (6.890-9.635)	8.135 (6.243-9.351)	<0.01 [A]
OSI	0.470 (0.376-0.574)	0.631 (0.508-0.784)	0.739 (0.467-0.936)	<0.001 [A, C]
MDA (µmol/L)	4.132 (2.323-4.700)	3.590 (1.805-5.294)	4.524 (3.323-6.465)	NS
As (µg/L)	0.597 (0.385-0.817)	0.593 (0.341-0.779)	0.593 (0.385-0.661)	NS
Cd (µg/L)	0.637 (0.494-1.124)	0.772 (0.645-1.351)	0.601 (0.564-1.302)	NS
Hg (µg/L)	0.488 (0.177-0.751)	0.404 (0.248-0.756)	0.513 (0.332-0.964)	NS
Pb (µg/L)	20.6 (16.2-27.2)	22.8 (14.2-31.3)	25.8 (17-35.2)	NS

Values are expressed as median and interquartile range (Me (Q_1–Q_3). Statistically significant differences between the medians (A – HbA1c ≤ 7% vs. 7.1-9.9%; B – HbA1c 7.1-9.9% vs. ≥ 10%; C – HbA1c ≤ 7% vs. ≥ 10%) were detected by the Kruskal–Wallis ANOVA test with post-hoc analysis. Abbreviations: arsenic (As), catalase (CAT), cadmium (Cd), chromium (Cr), copper (Cu), glutathione peroxidase (GPx), glycated hemoglobin (HbA1c), mercury (Hg), malondialdehyde (MDA), non-significant (NS), oxidative stress index (OSI), lead (Pb), selenium (Se), superoxide dismutase (SOD), type 1 diabetes mellitus (T1DM), total antioxidant status (TAS), total oxidant status (TOS), zinc (Zn).

Rozdział 11. Metabolic Syndrome as a Factor of Impairment of Antioxidant Defense System in Youth with T1DM

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Article

Metabolic Syndrome as a Factor of Impairment of Antioxidant Defense System in Youth with T1DM

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Abstract: Research indicates that adolescents with type 1 diabetes mellitus (T1DM) may develop both metabolic syndrome (MetS) and oxidative stress. The purpose of this study was to test the hypothesis that MetS could potentially affect antioxidant defense parameters. The study recruited adolescents aged 10–17 who had been diagnosed with T1DM, and divided them into two groups: "MetS+" (n = 22), who had been diagnosed with MetS, and "MetS−" (n = 81), who did not have metabolic syndrome. A control group consisting of 60 healthy peers without T1DM was included for comparison. The study examined cardiovascular parameters, such as complete lipid profile and estimated glucose disposal rate (eGDR), as well as markers of antioxidant defense. The results revealed a statistically significant difference between the MetS+ and the MetS− group in terms of total antioxidant status (TAS) (1.186 mmol/L vs. 1.330 mmol/L), and oxidative stress index (OSI) levels (0.666 vs. 0.533). Furthermore, multivariate correspondence analysis identified individuals with HbA1c < 8%; eGDR > 8 mg/kg/min, using either flash or continuous glucose monitoring systems, as MetS− patients. The study also found that eGDR (AUC 0.85, $p < 0.001$), OSI and HbA1c (AUC 0.71, $p < 0.001$) markers may be useful for diagnosing the onset of MetS in adolescents with T1DM.

Keywords: adolescents; diabetes mellitus type 1; metabolic syndrome; antioxidant enzymes; antioxidant status; dyslipidemia; hypertension; obesity; continuous glucose monitoring; biomarkers

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1. Introduction

The most commonly diagnosed type of diabetes mellitus (DM) among children and adolescents is type 1 (T1DM), which is an autoimmune disease. There is a reduction in insulin production due to the degradation of pancreatic islet β cells, making it necessary for such patients to be treated with intensive insulin therapy for the rest of their lives [1–3]. Recent years of research have shown that an increasing number of adolescents are overweight [4]. It is also observed that the pediatric diabetic population is beginning to exhibit a similar trend of being overweight [5]. Most importantly, research suggests that the issue of concern is not limited to overweight or obesity, but also encompasses metabolic syndrome (MetS), which is beginning to emerge [6]. MetS is a set of factors whose presence reflects an increased risk of cardiometabolic complications [7]. Our previous study indicated that approximately 30% of patients with T1DM had MetS. Those individuals had excessive visceral fat, consumed low amounts of monounsaturated fatty acids and high quantities saturated fatty acids. What is more concerning, they also had low total antioxidant status (TAS) and poorly controlled T1DM [8]. This is particularly important because maintaining proper glycemic control is essential in preventing the disorders associated with the antioxidant defense system (AOD) through the accumulation of reactive oxygen species (ROS). Considering previous findings, it is possible that oxidative stress (OS) is a factor which could contribute to the accelerated progression of diabetes complications [8,9].

The purpose of this study was to investigate the presence of oxidative stress in adolescents with T1DM who developed MetS.

2. Results

Table 1 presents basic information that characterizes the study participants based on their MetS diagnosis. The data showed that 21% of diabetic participants met the diagnostic criteria for MetS: they had a statistically significantly higher ($p < 0.05$) body weight compared to those in the MetS− group. Additionally, there was a higher prevalence of MetS among adolescents with a T1DM duration exceeding 2 years ($p < 0.001$). Moreover, it was more common among individuals who solely relied on a glucometer instead of modern glucose monitoring systems (GMS) ($p < 0.001$) and those using CSII ($p < 0.001$).

Table 1. Characteristics of the study cohort.

Parameter		MetS+ (n = 22)	MetS− (n = 81)	Control Group (n = 60)
Age (years)	Me (Q_1–Q_3)	13 (11–15)	14 (11–15)	15 (14–16)
Body height (cm)		167 (157–172)	163 (155–173)	167 (157–178)
Body weight (kg)		67 (58–71)	54 (45–66)	56 (47–67)
Age of diagnosis (years)		10 (7–11)	9 (6–11)	-
T1DM duration (years)		4 (1–6)	4 (1–7)	-
Gender (girls/boys)	%	68/32	47/53	40/60
Newly diagnosed (<2 years)		28	27	-
Type of insulin therapy (MDI/CSII)		27/73	44/56	-
Type of GMS (glucometer/FGM/CGM)		50/23/27	23/46/31	-

Values are expressed as median and interquartile range (Me (Q_1–Q_3) or percentage of respondents (%). Abbreviations: continuous glucose monitoring (CGM), continuous subcutaneous insulin infusion (CSII), flash glucose monitoring (FGM), glucose monitoring system (GMS), multiple daily injections (MDI), type 1 diabetes mellitus (T1DM).

The study findings indicated that there were significant differences in all cardiovascular markers between the MetS+ and MetS− groups, as well as between the MetS+ group and healthy peers, except for low-density lipoprotein (LDL) (Table 2). It was observed that MetS+ diabetic patients had statistically significantly lower TAS (MetS+ vs. MetS−: 1.186 mmol/L vs. 1.330 mmol/L, $p < 0.05$) and higher levels of oxidative stress index (OSI) (0.666 vs. 0.533, respectively, $p < 0.01$). No statistically significant differences were observed between boys and girls in MetS+, as well as MetS− group for all the parameters included in this table.

Table 2. Comparison of cardiovascular, antioxidant defense, and oxidative stress parameters between MetS+ and MetS− patients, as well as the control group.

Parameter	MetS+ (n = 22)	MetS− (n = 81)	Control Group (n = 60)	*p*-Value (MetS+ vs. MetS−)	*p*-Value (MetS+ vs. Control)
Cardiovascular markers					
TC (mg/dL)	181 (169–197)	154 (128–175)	151 (127–172)	<0.001	<0.001
LDL (mg/dL)	103 (91–109)	83 (68–105)	87 (76–110)	<0.01	N/S
HDL (mg/dL)	45 (38–51)	57 (49–69)	57 (53–65)	<0.001	<0.001
TG (mg/dL)	122 (105–151)	66 (52–88)	59 (46–75)	<0.001	<0.001
SBP (mmHg)	122 (116–129)	114 (109–120)	118 (110–124)	<0.001	<0.05
DBP (mmHg)	79 (72–84)	71 (66–74)	71 (65–75)	<0.001	<0.001
BMI (kg/m^2)	23.7 (20.8–25.2)	20.3 (18.4–21.9)	20.2 (18.6–21.8)	<0.001	<0.001
FGL (mg/dL)	-	-	99 (94–103)	-	-
HbA1c (%)	9.9 (7.9–11.2)	7.6 (6.6–9.1)	-	<0.01	-
eGDR (mg/kg/min)	4.4 (3.9–6.2)	7.5 (6.6–9.9)	-	<0.001	-

Table 2. *Cont.*

Parameter	MetS+ (n = 22)	MetS− (n = 81)	Control Group (n = 60)	*p*-Value (MetS+ vs. MetS−)	*p*-Value (MetS+ vs. Control)
Antioxidant defense and oxidative stress markers					
Cu (mg/L)	0.914 (0.695–1.392)	0.863 (0.731–1.124)	0.935 (0.697–1.143)	N/S	N/S
Zn (mg/L)	0.875 (0.724–0.959)	0.896 (0.821–1.030)	0.976 (0.905–1.116)	N/S	<0.01
Cu/Zn ratio	1.113 (0.974–1.568)	0.995 (0.798–1.447)	0.978 (0.650–1.206)	N/S	<0.05
Se (µg/L)	57.0 (45.6–68.2)	61.3 (51.5–69.8)	61.4 (51.5–69.2)	N/S	N/S
TAS (mmol/L)	1.186 (1.040–1.336)	1.330 (1.201–1.540)	1.605 (1.477–1.766)	<0.05	<0.001
SOD (U/mL)	1.165 (0.960–1.716)	1.519 (1.154–2.100)	2.101 (1.699–2.298)	N/S	<0.001
CAT (n/mol/min)	49.1 (35.1–68.4)	42.1 (26.0–72.4)	57.7 (48.2–75.1)	N/S	<0.01
GPx (U/L)	1378 (908–2258)	1320 (728–2119)	1669 (987–3072)	N/S	N/S
TOS (µmol H_2O_2 equiv./L)	8.176 (7.456–10.295)	7.432 (5.892–9.189)	4.937 (3.920–5.857)	N/S	<0.001
OSI	0.666 (0.575–0.965)	0.533 (0.412–0.713)	0.284 (0.243–0.386)	<0.01	<0.001

Values are expressed as median and interquartile range (Me (Q_1–Q_3)). Statistically significant differences between the medians were detected by the Kruskal–Wallis ANOVA test with post-hoc analysis. Abbreviations: body mass index (BMI), catalase (CAT), copper (Cu), diastolic blood pressure (DBP), estimated glucose-disposal rate (eGDR), fasting glucose level (FGL), glutathione peroxidase (GPx), glycated hemoglobin (HbA1c), high-density lipoprotein (HDL), low-density lipoprotein (LDL), metabolic syndrome (MetS), oxidative stress index (OSI), systolic blood pressure (SBP), selenium (Se), superoxide dismutase (SOD), total antioxidant status (TAS), total cholesterol (TC), triglycerides (TG), total oxidant status (TOS), zinc (Zn).

The two most prevalent components of MetS were high diastolic blood pressure (DBP) and a body mass index (BMI) (Figure 1). In addition, statistically significant relationships were found between the intensity of antioxidant defense, oxidative stress parameters, and the presence of MetS (Figure 2). Compared to participants without MetS, the majority of MetS+ individuals had lower TAS levels (MetS+ vs. MetS−: 55% vs. 25%, $p < 0.001$), higher total oxidant status (TOS) (59% vs. 38%, $p < 0.01$), OSI (50% vs. 27%, $p < 0.001$), and a higher Cu/Zn ratio (64% vs. 49%, $p < 0.05$).

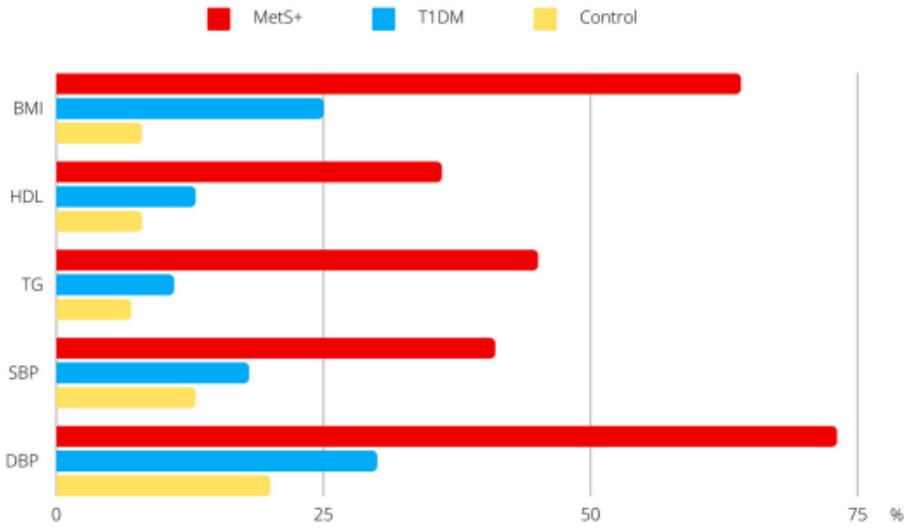

Figure 1. Percentage of participants meeting the components of MetS. Values are expressed as percentage of respondents (%). Abbreviations: body mass index (BMI), diastolic blood pressure (DBP), high-density lipoprotein (HDL), metabolic syndrome (MetS), systolic blood pressure (SBP), diabetes mellitus type 1 (T1DM), triglycerides (TG).

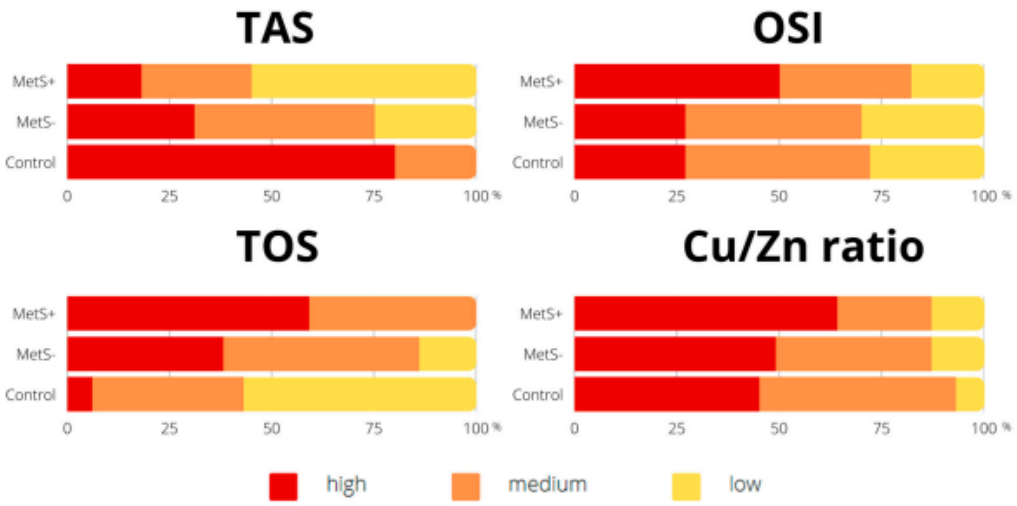

Figure 2. Percentage of participants according to the intensity of total antioxidant status and oxidative stress parameters. Values are expressed as percentage of respondents (%). Abbreviations: copper (Cu), metabolic syndrome (MetS), oxidative stress index (OSI), total antioxidant status (TAS), total oxidant status (TOS), zinc (Zn).

Table 3 displays statistically significant correlations among selected studied parameters in diabetics with MetS. Notably, there were high statistically significant correlations between glycated hemoglobin (HbA1c) and estimated glucose-disposal rate (eGDR) ($R = -0.8$, $p < 0.001$), triglycerides (TG) ($R = 0.6$, $p < 0.01$), systolic blood pressure (SBP) ($R = 0.5$, $p < 0.05$), and TAS ($R = -0.5$, $p < 0.05$). Additionally, as DBP increased, there was a decrease in eGDR ($R = -0.7$, $p < 0.001$), and an increase in BMI ($R = 0.6$, $p < 0.001$).

Table 3. Correlations between parameters among T1DM patients with MetS.

Parameter 1	Parameter 2	R	*p*-Value
HbA1c	TG	0.6	<0.01
	SBP	0.5	<0.05
	eGDR	−0.8	<0.001
	TAS	−0.5	<0.05
eGDR	TG	−0.5	<0.05
	SBP	−0.6	<0.01
DBP	eGDR	−0.7	<0.001
	BMI	0.6	<0.001
SOD	Zn	0.5	<0.05

Statistically significant correlations were detected using Spearman's correlation coefficient. Repeated correlations between parameters were removed from the table. Abbreviations: body mass index (BMI), diastolic blood pressure (DBP), estimated glucose-disposal rate (eGDR), glycated hemoglobin (HbA1c), metabolic syndrome (MetS), systolic blood pressure (SBP), superoxide dismutase (SOD), triglycerides (TG), type 1 diabetes mellitus (T1DM), total antioxidant status (TAS), zinc (Zn).

Multivariate correspondence analysis (MCA) was performed to investigate the relationships between the presence of MetS, metabolic management, and the use of modern GMS (Figure 3A), as well as the link between MetS and the body's AOD system (Figure 3B).

In Figure 3A:

(1) The first and fourth quadrants include MetS+ participants with poor metabolic management (HbA1c $\geq$ 8% and eGDR $\leq$ 8 mg/kg/min), using only glucometers without any modern GMS.

(2) The two left quadrants, II and III, consist of diabetic patients without MetS using either flash glucose monitoring (FGM) or continuous glucose monitoring (CGM), with better metabolic management (HbA1c < 8% and eGDR > 8 mg/kg/min).

Together, these quadrants accounted for 64% of the total variability in the data.

In Figure 3B:

(1) The second quadrant consists of diabetics without MetS characterized by moderate levels of TAS and TOS.

(2) The third quadrant contains individuals from the MetS+ group with low TAS and high TOS.

(3) The fourth quadrant (IV) consists of healthy peers with high TAS and low TOS.

Together, these quadrants accounted for 54% of the total variability in the data.

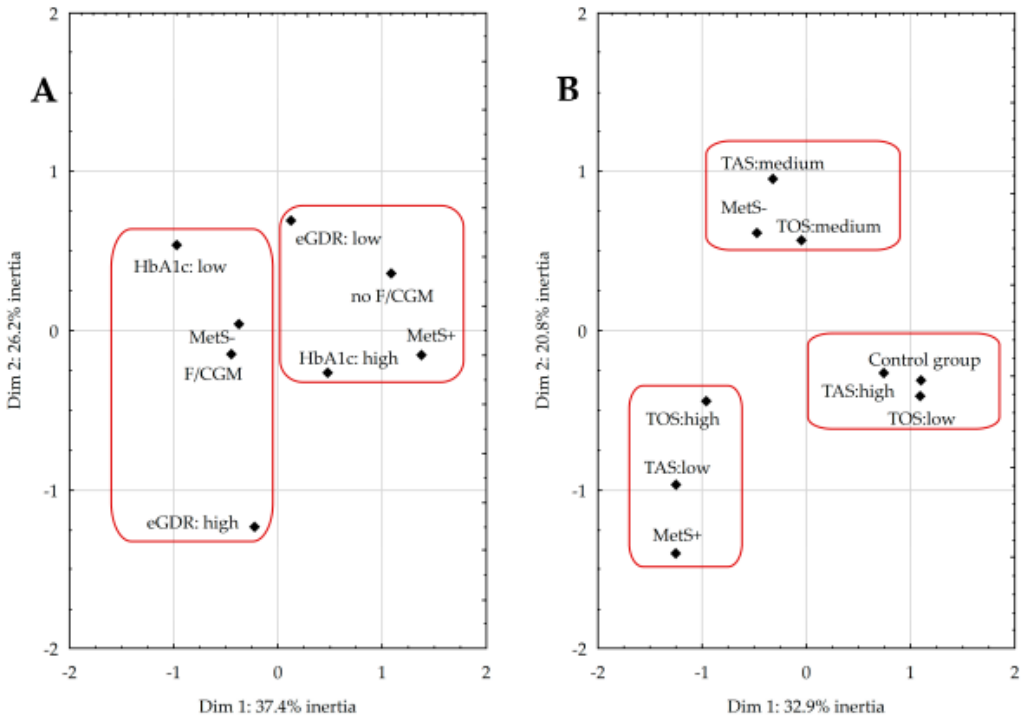

Figure 3. Coordinate plot for the multivariate correspondence analysis illustrating the relationship between metabolic management and the use of modern glucose monitoring systems (**A**) and the body's antioxidant–oxidant balance (**B**). Abbreviations: continuous glucose monitoring (CGM), estimated glucose-disposal rate (eGDR), flash glucose monitoring (FGM), glycated hemoglobin (HbA1c), metabolic syndrome (MetS), total antioxidant status (TAS), total oxidant status (TOS).

Table 4 presents the results of ROC analysis, which showed significant diagnostic value for eGDR (AUC 0.85, $p < 0.001$), OSI and HbA1c (AUC 0.71, $p < 0.001$), TAS (AUC 0.67, $p < 0.01$), and TOS (AUC 0.63, $p < 0.05$). The cutoff point for HbA1c identified 73% of those with MetS and 30% of those without MetS.

Table 4. Assessment of oxidative stress and metabolic management parameters as possible indicators of the presence of MetS in patients with T1DM.

Parameter	TAS	TOS	OSI	HbA1c	eGDR
AUC (95% CI)	0.67 (0.53–0.81)	0.63 (0.51–0.75)	0.71 (0.59–0.82)	0.71 (0.60–0.83)	0.85 (0.74–0.95)
p-Value AUC	<0.01	<0.05	<0.001	<0.001	<0.001
Cutoff point	1.213	6.973	0.575	8.67	6.41
Sensitivity	59%	86%	77%	73%	82%
Specificity	74%	44%	57%	70%	78%
Youden index	0.332	0.308	0.341	0.431	0.596
+LR	0.259	0.556	0.432	0.296	0.222
−LR	0.409	0.136	0.227	0.273	0.182

Abbreviations: area under curve (AUC), confidence interval (CI), estimated glucose-disposal rate (eGDR), glycated hemoglobin (HbA1c), positive likelihood ratios (+LR), negative likelihood ratios (−LR), metabolic syndrome (MetS), oxidative stress index (OSI), type 1 diabetes mellitus (T1DM), total antioxidant status (TAS), total oxidant status (TOS).

3. Discussion

Our study confirmed the hypothesis that diabetics with MetS experienced AOD impairment. In addition to observing low TAS and high OSI levels in this group of patients, we also demonstrated that improvements in their condition could be achieved through better metabolic control of the disease (HbA1c < 8%; eGDR > 8 mg/kg/min) and implementation of one of the F/CGM systems. These systems are becoming increasingly widespread, not only improving the quality of life of patients, but also helping maintain appropriate glycemic control, which is a key element of preventive OS [10,11].

Obesity is characterized by an excessive accumulation of body fat, especially visceral adipose tissue. Unfortunately, it continues to rise in the population and is a major contributor to the development of hypertension, or dyslipidemia, thereby increasing the risk of MetS [12]. Its progression, combined with the ongoing advancement of T1DM, has the potential to promote oxidative stress, which was found to be present among the examined patients in the current study. We have demonstrated that MetS+ patients had an impaired antioxidant defense system (Table 2), as evidenced by statistically significantly lower TAS and higher TOS levels, as well as low activity of superoxide dismutase (SOD) and catalase (CAT) when compared to the control group. In addition, among MetS+ patients, 73% had elevated DBP, and 64% had high BMI (Figure 1). Studies have suggested that ROS influence the regulation of endothelial function and vascular remodeling of their production, which may contribute to the development of hypertension [13]. Furthermore, excessive body weight is strongly associated with adipocyte dysfunction and the secretion of pro-inflammatory adipokines, which can lead to a depletion of AOD system reserves [8,14]. Among T1DM patients, especially those who are metabolically imbalanced, this process seems to be more compounded. The increase in HbA1c levels in our study participants was accompanied by a decrease in TAS (Table 3) which, according to other studies, further exacerbates the degradation of pancreatic islet β cells [15]. To prevent complications in T1DM, it is crucial to maintain normoglycemia. The presence of hyperglycemia, even for a short time, can lead to a phenomenon called "metabolic memory". This phenomenon induces irreversible changes in cellular function, involving the advanced glycation end products receptor and other factors, leading to a cascade of events associated with inflammation and OS progression. Despite subsequent return to an optimal state, these changes can persist and contribute to long-term complications [16]. In our study, we also observed that an increase in HbA1c marker was accompanied by a decline in eGDR and an increase in TG and SBP (Table 3).

Diabetes and obesity both promote glycoxidation, leading to enzymatic changes in the body by causing cell dysfunction, resulting in disruption of the AOD system [17]. In the MetS patients that we studied, both conditions occurred together, making it difficult to determine exactly which pathway is activated by which factor. Obesity and OS are closely related through maintenance mechanisms. OS can trigger obesity and also

be a consequence of it. Nutritional factors such as excessive eating, or high-fat as well as high-carbohydrate diets, can activate intracellular pathways, such as NOX, oxidative phosphorylation in mitochondria, or glycoxidation, thereby enhancing OS [17,18]. In the development of metabolic disorders, the proliferation of preadipocytes due to chronic adipocyte inflammation, fatty acid oxidation, or accumulation of cellular damage can trigger ROS. Furthermore, adiponectin promotes high LDL and low HDL concentrations and shows a negative association with BMI, but a positive association with pro-inflammatory cytokines, such as TNF-α and IL-6 [19–21]. The lipid profile results obtained in our study were similar to those reported by other Authors who also studied young individuals with T1DM [10,22,23].

One straightforward parameter to calculate as an indicator of insulin resistance (IR) is the eGDR (Table 2). It was significantly lower (4.4 mg/kg/min) in the MetS+ group in our study, compared to the result obtained by Köken et al. in a similar group (6.4 mg/kg/min) [24]. Köken et al. also suggested that eGDR could be a potential predictor for MetS in T1DM. We confirmed statistically significant diagnostic value of eGDR (Table 4). The presence of IR is associated with OS. To respond to insulin, the cell increases the expression of its main glucose transporter (GLUT 4), causing increased glucose uptake from the bloodstream. However, when insulin concentrations are excessively high, expression decreases, resulting in elevated blood glucose levels, so the pancreas continues to secrete insulin. The consequence is a deterioration of tissue sensitivity towards the hormone, leading to the development of hyperglycemia, hyperinsulinemia [25,26]. Such a condition in the body results in the activation of pathways that trigger stress transduction and increased glucose metabolism, which affects the appearance of ROS, resulting in the occurrence of intracellular OS [27]. In reaction to ROS, the organism inhibits phosphorylation of the tyrosine pathway and then blocks GLUT 4 translocation, all of which leads to a vicious cycle because it impairs glucose disposal and increases insulin secretion [25,26].

The most significant enzymes of the AOD system are SOD, CAT, and glutathione peroxidase (GPx). SOD is involved in removing superoxide ions and converting them into oxygen and less reactive hydrogen peroxides. Studies have shown that SOD may positively impact the implications of the production of ROS induced by hyperglycemia. Catalase, on the other hand, protects cells from the harmful effects of H_2O_2 by participating in its conversion to oxygen and water. Meanwhile, GPx is one of the primary enzymes that prevent the aggregation of intracellular H_2O_2 [28]. Based on the above findings, we detected high CAT activity and low SOD and GPx activity in diabetics with MetS when compared to the control group (Table 2). Similar observations were reported in other studies where the group consisted of diabetics with cardiovascular complications: a decrease in SOD and GPx was observed [29]. Furthermore, our ROC analysis (Table 4) also revealed that TAS (cutoff point 1.213 mmol/L), TOS (cutoff point 6.973 μmol H_2O_2 equiv./L), and OSI (cutoff point 0.575) could potentially serve as predictors of MetS and be used as one of the components.

Studies have reported that MetS can be prevented through reprogramming, even before the onset of symptoms. The suggested way to achieve this is by supporting impaired antioxidant defenses through antioxidant therapies that target various mechanisms, including enzymatic and non-enzymatic ones. The first approach offers the potential therapeutic effect of targeting individual components of MetS with SOD mimetics [30]. However, most of these studies have been conducted on animals and have relied primarily on supplementation, which makes it difficult to rank them in drug form. Therefore, evidence from ongoing clinical trials is necessary to validate their effectiveness [31]. Strategies involving vitamins and polyphenols, such as resveratrol, genistein, and curcumin have also been suggested as non-enzymatic mechanisms for reprogramming. However, more research is required in this case, taking into account the complexity and inter-individual variability of their pharmacokinetics, as well as their low bioavailability in vivo [30,32].

Despite the valuable insights provided by this study, as with any research, there are strengths and limitations to consider. Among the limitations is the fact that, due to

the study's design, it is not possible to establish causal relationships and measure the incidence of MetS directly. At this stage the study can only identify the presence of the problem. Nevertheless, it should be noted that our research addresses a gap in the scientific understanding, which has been repeatedly discussed in previous studies. Additionally research in this area among T1DM adolescents rarely involves a control group, which enhances the significance of our findings.

4. Materials and Methods

4.1. Study Group

The case-control study consisted of 163 participants aged 10–17 years. The T1DM group included 103 patients, of which 22 were diagnosed with MetS, while the remaining 81 did not have the condition. The diabetics were recruited between March 2020 and September 2022 from the Department of Pediatrics, Endocrinology, Diabetology with the Division of Cardiology at the University Children's Clinical Hospital in Bialystok. Only those who met the following criteria were eligible for participation: age between 10 and 17 years, presence of T1DM, absence of other types of DM and severe chronic diseases, as well as interest in participating in the study. The diagnosis of T1DM was based on the presence of autoantibodies, as determined by physicians specializing in diabetology [1]. The control group consisted of 60 healthy volunteers without a diagnosis of MetS who visited the Department of Bromatology at the Medical University of Bialystok. At the time of recruitment, they reported an absence of any history of symptoms suggesting the presence of DM or other chronic diseases. The permission of the Bioethics Committee (No. R-I-002/587/2019) had been obtained prior to the study, and the consent of each participant's guardian was required during the study.

4.2. Blood Samples Analysis

For the collection of fasting blood as material for analysis, Vacutainer tubes containing clot activator and gel or anticoagulant K2EDTA (Becton Dickinson, Pont de Claix, France) were used. After centrifuging the blood for 10 min at about 2000 rpm (Centrifuge M-diagnostic, MPW, Warsaw, Poland), the serum was moved into tubes and stored at −20 °C to be used for the determination of mineral elements and −80 °C to provide suitable conditions for subsequent measurement of antioxidant defense and oxidative stress parameters. To determine Cu and Zn contents, the serum was first deproteinized with 1 mol/L nitric acid (Suprapur, Merck, Darmstadt, Germany), and surfactant 1% Triton X-100 (Sigma-Aldrich, St. Louis, MO, USA) was added. The samples were then centrifuged for 10 min at about 6000 rpm (Centrifuge IKA mini G, IKA, Staufen im Breisgau, Germany). Zn was measured in the supernatant, and Cu was measured in a sample that had been additionally diluted with 0.1 mol/L nitric acid. Directly prior to the determination of Se, the material was diluted with 0.2% Triton X-100. Calibration curves were performed on standard solutions (Merck, Darmstadt, Germany). The study employed the Zeeman background-corrected atomic absorption spectrometry method (Z-2000, Hitachi, Tokyo, Japan) with an acetylene-air flame atomization technique for Zn, and a flameless technique with electrothermal atomization in a graphite cuvette for Cu and Se to measure mineral concentrations. In addition, the molar ratio between Cu and Zn was calculated. To determine oxidative stress parameters, a spectrophotometry technique was applied using a microplate reader (Infinite M200 Pro Tecan, Männedorf, Switzerland). The TOS measurement was conducted following the methodology proposed by Erel et al. [33]. TAS and GPx were assayed using Randox reagent kits (Randox Laboratories, Crumlin, County Antrim, UK). The OSI was determined as the ratio of TOS to TAS. CAT and SOD were detected via reagent sets from CaymanChem (Cayman Chemical Company, Ann Arbor, MI, USA). Table 5 provides detailed information about the methods employed in the study. The limits of detection for Cu, Se, and Zn were 0.0005 mg/L, 1.44 µg/L, and 0.02 mg/L, respectively. To facilitate the interpretation of the results, categories were established for each parameter, with "medium" representing the reference range and "low" and "high" indicating values outside this range. The reference

range for TAS was 1.2–1.45 mmol/L, for TOS it was 5–8 µmol H_2O_2 equiv./L, for OSI it was 0.3–0.6, and for the Cu/Zn ratio it was 0.6–1.0. The levels of total cholesterol (TC), TG, HDL, LDL and fasting glucose level were determined using the enzymatic colorimetric method on an Alinity c analyzer (Abbott Laboratories, Lake Bluff, IL, USA). To assess metabolic management, HbA1c was measured, and the eGDR was calculated, by means of ion-exchange high-performance liquid chromatography using a Bio-Rad D-10TM (Bio-Rad, Hercules, CA, USA). The calculation of eGDR was based on a formula that considered the value of BMI [34]. The decrease in this index reflects the increase in IR in the body. The accuracy of the methods was ensured by performing determinations with dedicated certified materials (Seronorm Trace Elements Serum L-1, Sero AS, Norway; Quality Control Randox; Catalase Control CaymanChem).

Table 5. Values of the determined antioxidant defense and oxidative stress markers.

Parameter	Units	Wavelengths	Material
Cu	mg/L	324.8 nm	Serum
Se	µg/L	196 nm	Serum
Zn	mg/L	213.9 nm	Serum
TAS	mmol/L	600 nm	Serum
SOD	U/mL	450 nm	Serum
CAT	n/mol/min	540 nm	Serum
GPx	U/L whole blood	340 nm	Whole blood
TOS	µmol H_2O_2 equiv./L	560/800 nm	Serum

Abbreviations: catalase (CAT), copper (Cu), glutathione peroxidase (GPx), selenium (Se), superoxide dismutase (SOD), total antioxidant status (TAS), total oxidant status (TOS), zinc (Zn).

4.3. Anthropometric Measurements

To perform an initial assessment of nutritional status, anthropometric measurements of body height and weight were obtained. Body height was measured in the Frankfort horizontal position, using a height meter with an accuracy of 0.1 cm. Body weight was taken using a calibrated medical instrument with an accuracy of 0.1 kg. Additionally, the body mass index was calculated using the following formula: body weight in kg divided by height in meters squared, which was referenced to national centile grids [35].

4.4. Metabolic Syndrome Diagnosis

The criteria for diagnosing MetS in each patient were based on those proposed in a previous publication. These criteria were modified based on other established ones, and the rationale for their use was extensively described in previous papers [6,8]. The MetS+ group included participants who met three out of the five components:

(1) BMI $\geq$ 95th percentile (based on Polish percentile grids [35]);
(2) TG $\geq$ 130 mg/dL (based on the norm for the pediatric population [36]);
(3) HDL $\leq$ 40 mg/dL (based on the norm for the pediatric population [36]);
(4) SBP/DBP $\geq$ 95th percentile (based on Polish percentile grids [37]);
(5) FGL $\geq$ 100 mg/dL or known DM.

4.5. Statistical Analysis

Statistica software (version 13 PL; TIBCO Software Inc., Palo Alto, CA, USA) was used for appropriate statistical processing of the data. To select adequate tests, normality of the distribution of variables was determined using the Shapiro–Wilk, Kolmogorov–Smirnov and Lilliefors tests. Kruskal–Wallis ANOVA test with post-hoc analysis was used to assess the significance of quantitative variables, and the chi-squared test of independence was applied to examine the relationships between qualitative variables. Spearman's correlation coefficient test was carried out to study correlations between parameters. A multiple correspondence analysis was performed in order to identify characteristics among individuals with MetS regarding their antioxidant–oxidant balance and metabolic management. A

scree plot was used to choose the number of dimensions reliably representing the data, which enabled us to analyze the variables and present them as a Burt matrix. In addition, to assess the suitability of the selected markers for MetS diagnosis, a receiver operating characteristic (ROC) analysis was conducted. The Youden index was used to calculate the cutoff points that provided the highest possible accuracy of the parameter. To express the overall efficacy, the area under the ROC curve with 95% CI was examined. Values of $p < 0.05$ were considered statistically significant.

5. Conclusions

The presence of OS was observed in diabetic patients with MetS compared to both those without MetS (high OSI and low TAS values) and the control group (low levels of Zn, TAS, SOD, CAT and high of Cu/Zn, TOS, OSI). Furthermore, it was shown that the MetS− group of patients included those with well-balanced T1DM and additionally using either FGM or CGM systems. The study also identified the potential diagnostic usefulness of eGDR, OSI and HbA1c markers for the presence of MetS in young patients with T1DM.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Medical University of Białystok (No. R-I-002/587/2019).

Informed Consent Statement: Written informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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Rozdział 12. Zgoda Komisji Bioetycznej

KOMISJA BIOETYCZNA
UNIWERSYTETU MEDYCZNEGO w BIAŁYMSTOKU
ul. Jana Kilińskiego 1
15-089 Białystok
tel. (085) 748 54 07, fax. (085) 748 55 08
prorektorkl@umb.edu.pl

Białystok, 19-12-2019

Uchwała nr: R-I-002/587/2019

Komisja Bioetyczna Uniwersytetu Medycznego w Białymstoku, po zapoznaniu się z projektem badania zgodnie z zasadami GCP/ Guidelines for Good Clinical Practice /- **w y r a ż a z g o d ę** na prowadzenie tematu badawczego: „Ocena sposobu żywienia i stanu odżywienia młodzieży z cukrzycą typu 1" przez mgr Monikę Grabia wraz z zespołem badawczym z UMB.

Przewodnicząca Komisji Bioetycznej UMB

prof. dr hab. Otylia Kowal-Bielecka

Rozdział 13. Oświadczenia autora rozprawy doktorskiej

Białystok, 01.06.2023r.

mgr Monika Grabia
Zakład Bromatologii
Wydział Farmaceutyczny
Z Oddziałem Medycyny Laboratoryjnej
Uniwersytet Medyczny w Białymstoku

Oświadczenie autora

Oświadczam, iż mój udział w przygotowaniu publikacji:

1. ***Grabia M**, Markiewicz-Żukowska R, Socha K. Prevalence of Metabolic Syndrome in Children and Adolescents with Type 1 Diabetes Mellitus and Possibilities of Prevention and Treatment: A Systematic Review. Nutrients 2021, 13, doi:10.3390/nu13061782*

wchodzącej w skład mojej rozprawy doktorskiej polegał na przeszukaniu baz naukowych pod kątem wyselekcjonowania publikacji spełniających kryteria włączenia do przeglądu systematycznego, przeprowadzeniu selekcji prac oraz ocenie ich wiarygodności zgodnie z zastosowanymi kryteriami, pozyskaniu niezbędnych danych z prac, zebraniu danych oraz opracowaniu w formie manuskryptu oraz udoskonaleniu pracy zgodnie z sugestiami recenzentów, co określam jako **85%** udziału w przygotowaniu wyżej wymienionej publikacji.

2. ***Grabia M**, Markiewicz-Żukowska R, Socha K, Polkowska A, Zasim A, Boruch K, Bossowski A. Prevalence of Metabolic Syndrome in Relation to Cardiovascular Biomarkers and Dietary Factors among Adolescents with Type 1 Diabetes Mellitus. Nutrients 2022, 14, 2435, doi:10.3390/nu14122435*

wchodzącej w skład mojej rozprawy doktorskiej polegał na zaplanowaniu badań, opracowaniu ich metodologii i przeprowadzeniu wszystkich analiz, rekrutowaniu pacjentów, ocenie sposobu żywienia, wykonywaniu analizy składu ciała, zebraniu pomiarów antropometrycznych, oznaczeniu całkowitego statusu antyoksydacyjnego we krwi, opracowaniu statystycznym i graficznym danych, przygotowaniu manuskryptu oraz udoskonaleniu go zgodnie z sugestiami recenzentów, co określam jako **77%** udziału w przygotowaniu wyżej wymienionej publikacji.

3. ***Grabia M,*** *Socha K, Soroczyńska J, Bossowski A, Markiewicz-Żukowska R. Determinants Related to Oxidative Stress Parameters in Pediatric Patients with Type 1 Diabetes Mellitus. Nutrients 2023, 15, 2084, doi:10.3390/nu15092084*

wchodzącej w skład mojej rozprawy doktorskiej polegał na zaplanowaniu badań, opracowaniu ich metodologii i przeprowadzeniu wszystkich analiz, rekrutowaniu pacjentów, ocenie sposobu żywienia, oznaczeniu pierwiastków, parametrów antyoksydacyjnych i markerów stresu oksydacyjnego i peroksydacji lipidów we krwi, opracowaniu statystycznym i graficznym danych, przygotowaniu manuskryptu oraz udoskonaleniu go zgodnie z sugestiami recenzentów, co określam jako **80%** udziału w przygotowaniu wyżej wymienionej publikacji.

4. *Grabia M,* ***Socha K****, Bossowski A, Markiewicz-Żukowska R. Metabolic Syndrome as a Factor of Impairment of Antioxidant Defense System in Youth with T1DM. Int J Mol Sci 2023, 24, 9428, doi:10.3390/ijms24119428*

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Grabia Monika

Podpis autora rozprawy doktorskiej (czytelny)

ADIUNKT
Zakładu Bromatologii
dr hab. n. farm. Renata Markiewicz-Żukowska

Podpis promotora (czytelny)

Rozdział 14. Oświadczenia współautorów rozprawy doktorskiej

Białystok, 01.06.2023r.

dr hab. Renata Markiewicz-Żukowska
Zakład Bromatologii
Wydział Farmaceutyczny z Oddziałem Medycyny Laboratoryjnej
Uniwersytet Medyczny w Białymstoku

Oświadczenie współautora

Oświadczam, iż mój udział w przygotowaniu publikacji:

1. *Grabia M, **Markiewicz-Żukowska R**, Socha K. Prevalence of Metabolic Syndrome in Children and Adolescents with Type 1 Diabetes Mellitus and Possibilities of Prevention and Treatment: A Systematic Review. Nutrients 2021, 13, doi:10.3390/nu13061782*

wchodzącej w skład rozprawy doktorskiej Pani mgr Moniki Grabia polegał na udziale w opracowaniu koncepcji pracy, weryfikacji dokładności stosowanych metod, pomocy przy analizie badań, nadzorowaniu przebiegu badań oraz udoskonalaniu pracy zgodnie z sugestiami recenzentów.

2. *Grabia M, **Markiewicz-Żukowska R,** Socha K, Polkowska A, Zasim A, Boruch K, Bossowski A. Prevalence of Metabolic Syndrome in Relation to Cardiovascular Biomarkers and Dietary Factors among Adolescents with Type 1 Diabetes Mellitus. Nutrients 2022, 14, 2435, doi:10.3390/nu14122435*

wchodzącej w skład rozprawy doktorskiej Pani mgr Moniki Grabia polegał na udziale w opracowaniu koncepcji pracy i metodologii, pomocy przy wykonywaniu badań oraz udoskonalaniu pracy zgodnie z sugestiami recenzentów.

3. *Grabia M, Socha K, Soroczyńska J, Bossowski A, **Markiewicz-Żukowska R.** Determinants Related to Oxidative Stress Parameters in Pediatric Patients with Type 1 Diabetes Mellitus. Nutrients 2023, 15, 2084, doi:10.3390/nu15092084*

wchodzącej w skład rozprawy doktorskiej Pani mgr Moniki Grabia polegał na udziale w opracowaniu koncepcji pracy, nadzorowaniu przebiegu badań i udoskonalaniu pracy zgodnie z sugestiami recenzentów.

4. *Grabia M, Socha K, Bossowski A, **Markiewicz-Żukowska R**. Metabolic Syndrome as a Factor of Impairment of Antioxidant Defense System in Youth with T1DM. Int J Mol Sci 2023, 24, 9428, doi:10.3390/ijms24119428*

wchodzącej w skład rozprawy doktorskiej Pani mgr Moniki Grabia polegał na nadzorowaniu przebiegu badań oraz udoskonalaniu pracy zgodnie z sugestiami recenzentów.

Jednocześnie wyrażam zgodę na przedłożenie wyżej wymienionych prac przez Panią mgr Monikę Grabia jako rozprawy doktorskiej w formie spójnego tematycznie cyklu prac opublikowanych w czasopismach naukowych.

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Oświadczenie współautora

Oświadczam, iż mój udział w przygotowaniu publikacji:

1. *Grabia M, Markiewicz-Żukowska R,* ***Socha K****. Prevalence of Metabolic Syndrome in Children and Adolescents with Type 1 Diabetes Mellitus and Possibilities of Prevention and Treatment: A Systematic Review. Nutrients 2021, 13, doi:10.3390/nu13061782*

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4. *Grabia M,* ***Socha K****, Bossowski A, Markiewicz-Żukowska R. Metabolic Syndrome as a Factor of Impairment of Antioxidant Defense System in Youth with T1DM. Int J Mol Sci 2023, 24, 9428, doi:10.3390/ijms24119428*

wchodzącej w skład rozprawy doktorskiej Pani mgr Moniki Grabia polegał na udziale w opracowaniu metodologii, weryfikacji dokładności stosowanych metod oraz pomocy przy oznaczeniach pierwiastków we krwi.

Jednocześnie wyrażam zgodę na przedłożenie wyżej wymienionych prac przez Panią mgr Monikę Grabia jako rozprawy doktorskiej w formie spójnego tematycznie cyklu prac opublikowanych w czasopismach naukowych.

Katarzyna Socha
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Oświadczenie współautora

Oświadczam, iż mój udział w przygotowaniu publikacji:

1. *Grabia M, Markiewicz-Żukowska R, Socha K, Polkowska A, Zasim A, Boruch K,* ***Bossowski A****. Prevalence of Metabolic Syndrome in Relation to Cardiovascular Biomarkers and Dietary Factors among Adolescents with Type 1 Diabetes Mellitus. Nutrients 2022, 14, 2435, doi:10.3390/nu14122435*

2. *Grabia M, Socha K, Soroczyńska J,* ***Bossowski A****, Markiewicz-Żukowska R. Determinants Related to Oxidative Stress Parameters in Pediatric Patients with Type 1 Diabetes Mellitus. Nutrients 2023, 15, 2084, doi:10.3390/nu15092084*

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wchodzących w skład rozprawy doktorskiej Pani mgr Moniki Grabia polegał na umożliwieniu pozyskania materiału badawczego oraz wsparciu merytorycznym badań.

Jednocześnie wyrażam zgodę na przedłożenie wyżej wymienionych prac przez Panią mgr Monikę Grabia jako część rozprawy doktorskiej w formie spójnego tematycznie cyklu prac opublikowanych w czasopismach naukowych.

KIEROWNIK
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prof. dr hab. n. med. Artur Bossowski

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Oświadczenie współautora

Oświadczam, iż mój udział w przygotowaniu publikacji:

1. *Grabia M, Socha K,* ***Soroczyńska J****, Bossowski A, Markiewicz-Żukowska R. Determinants Related to Oxidative Stress Parameters in Pediatric Patients with Type 1 Diabetes Mellitus. Nutrients 2023, 15, 2084, doi:10.3390/nu15092084*

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Jednocześnie wyrażam zgodę na przedłożenie wyżej wymienionej pracy przez Panią mgr Monikę Grabia jako część rozprawy doktorskiej w formie spójnego tematycznie cyklu prac opublikowanych w czasopismach naukowych.

Jolanta Soroczyńska
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Uniwersytecki Dziecięcy Szpital Kliniczny im. L. Zamenhofa w Białymstoku

Oświadczenie współautora

Oświadczam, iż mój udział w przygotowaniu publikacji:

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wchodzącej w skład rozprawy doktorskiej Pani mgr Moniki Grabia polegał na pomocy przy rekrutacji pacjentów.

Jednocześnie wyrażam zgodę na przedłożenie wyżej wymienionej pracy przez Panią mgr Monikę Grabia jako część rozprawy doktorskiej w formie spójnego tematycznie cyklu prac opublikowanych w czasopismach naukowych.

Agnieszka Polkowska
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lek. med. Aneta Zasim
Klinika Pediatrii, Endokrynologii, Diabetologii z Pododdziałem Kardiologii
Uniwersytecki Dziecięcy Szpital Kliniczny im. L. Zamenhofa w Białymstoku

Oświadczenie współautora

Oświadczam, iż mój udział w przygotowaniu publikacji:

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lek. Aneta Zasim
specjalista pediatrii, endokrynologii
i diabetologii dziecięcej
2348894

Aneta Zasim

Podpis (czytelny)

Białystok, 01.06.2023r.

mgr Karolina Boruch
Klinika Pediatrii, Reumatologii, Immunologii i Chorób Metabolicznych Kości
Uniwersytecki Dziecięcy Szpital Kliniczny im. L. Zamenhofa w Białymstoku

Oświadczenie współautora

Oświadczam, iż mój udział w przygotowaniu publikacji:

1. *Grabia M, Markiewicz-Żukowska R, Socha K, Polkowska A, Zasim A,* ***Boruch K,*** *Bossowski A. Prevalence of Metabolic Syndrome in Relation to Cardiovascular Biomarkers and Dietary Factors among Adolescents with Type 1 Diabetes Mellitus. Nutrients 2022, 14, 2435, doi:10.3390/nu14122435*

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Boruch Karolina

Podpis (czytelny)

Rozdział 15. Dorobek naukowy

Łączna wartość Impact Factor (IF) całego dorobku naukowego	**148,085**
Łączna wartość punktów Ministra Edukacji i Nauki (MEiN) całego dorobku naukowego	**2926**
Indeks Hirscha (według WoS i Scopus)	**7**
Liczba cytowań (według WoS/Scopus)	**128/148**

Wykaz publikacji stanowiących rozprawę doktorską

Łączna wartość Impact Factor (IF) dla cyklu publikacji (**P.1-P.4**)	**26,326**
Łączna wartość punktów Ministra Edukacji i Nauki (MEiN) dla cyklu publikacji (**P.1-P.4**)	**560**

1. **Grabia M**, Markiewicz-Żukowska R, Socha K. Prevalence of Metabolic Syndrome in Children and Adolescents with Type 1 Diabetes Mellitus and Possibilities of Prevention and Treatment: A Systematic Review. Nutrients 2021, 13, doi:10.3390/nu13061782
   IF= 6,706; MEiN= 140

2. **Grabia M**, Markiewicz-Żukowska R, Socha K, Polkowska A, Zasim A, Boruch K, Bossowski A. Prevalence of Metabolic Syndrome in Relation to Cardiovascular Biomarkers and Dietary Factors among Adolescents with Type 1 Diabetes Mellitus. Nutrients 2022, 14, 2435, doi:10.3390/nu14122435
   IF= 6,706; MEiN= 140

3. **Grabia M**, Socha K, Soroczyńska J, Bossowski A, Markiewicz-Żukowska R. Determinants Related to Oxidative Stress Parameters in Pediatric Patients with Type 1 Diabetes Mellitus. Nutrients 2023, 15, 2084, doi:10.3390/nu15092084
   IF= 6,706; MEiN= 140

4. **Grabia M**, Socha K, Bossowski A, Markiewicz-Żukowska R. Metabolic Syndrome as a Factor of Impairment of Antioxidant Defense System in Youth with T1DM. International Journal of Molecular Sciences 2023, 24, 9428, doi:10.3390/ijms24119428
   IF= 6,208; MEiN= 140

Wykaz innych publikacji naukowych

Łączna wartość Impact Factor (IF) innych publikacji	**121,753**
Łączna wartość punktów Ministra Edukacji i Nauki (MEiN) innych publikacji	**2366**

1. **Grabia M,** Markiewicz-Żukowska R, Bielecka J, Puścion-Jakubik A, Socha K. Effects of Dietary Intervention and Education on Selected Biochemical Parameters and Nutritional Habits of Young Soccer Players. Nutrients 2022, 14, 3681, doi:10.3390/nu14183681 (IF 6,706, 140 pkt. MEiN)
2. Mielcarek K, Nowakowski P, Puścion-Jakubik A, Gromkowska-Kępka K.J, Soroczyńska J, Markiewicz-Żukowska R, Naliwajko S, **Grabia M,** Bielecka J, Żmudzińska A, Moskwa J, Karpińska E, Socha K. Arsenic, Cadmium, Lead and Mercury Content and Health Risk Assessment of Consuming Freshwater Fish with Elements of Chemometric Analysis. Food Chemistry 2022, 379, 132167, doi:10.1016/j.foodchem.2022.132167 (IF 9,231, 200 pkt. MEiN)
3. Markiewicz-Żukowska R, Puścion-Jakubik A, **Grabia M**, Perkowski J, Nowakowski P, Bielecka J, Soroczyńska J, Kańgowski G, Bołtryk J, Socha, K. Nuts as a Dietary Enrichment with Selected Minerals – Content Assessment Supported by Chemometric Analysis. Foods 2022, 11, 3152, doi:10.3390/foods11203152 (IF 5,561, 100 pkt. MEiN)
4. Puścion-Jakubik A, Pienkiewicz M, Steckiewicz K, Stypułkowska A, **Grabia M**, Bielecka J, Markiewicz-Żukowska R, Socha K. Use of Hand Creams during the Period of Frequent Disinfection in COVID-19 Pandemic Preference Survey and Evaluation of Mercury Contamination. International Journal of Environmental Research and Public Health 2022, 19, 13025, doi:10.3390/ijerph192013025 (IF 4,614, 140 pkt. MEiN)
5. Puścion-Jakubik A, Bielecka J, **Grabia M**, Markiewicz-Żukowska R, Soroczyńska J, Teper D, Socha K. Comparative Analysis of Antioxidant Properties of Honey from Poland, Italy, and Spain Based on the Declarations of Producers and Their Results of Melissopalinological Analysis. Nutrients 2022, 14, 2694, doi:10.3390/nu14132694 (IF 6,706, 140 pkt. MEiN)
6. Bielecka J, Markiewicz-Żukowska R, Puścion-Jakubik A, **Grabia M**, Nowakowski P, Soroczyńska J, Socha K. Gluten-Free Cereals and Pseudocereals as a Potential Source of Exposure to Toxic Elements among Polish Residents. Nutrients 2022, 14, 2342, doi:10.3390/nu14112342 (IF 6,706, 140 pkt. MEiN)
7. Żmudzińska A, Puścion-Jakubik A, Bielecka J, **Grabia M**, Soroczyńska J, Mielcarek K, Socha K. Health Safety Assessment of Ready-to-Eat Products Consumed by Children Aged 0.5–3 Years on the Polish Market. Nutrients 2022, 14, 2325, doi:10.3390/nu14112325 (IF 6,706, 140 pkt. MEiN)
8. **Grabia M,** Puścion-Jakubik A, Markiewicz-Żukowska R, Bielecka J, Mielech A, Nowakowski P, Socha K. Adherence to Mediterranean Diet and Selected Lifestyle Elements among Young Women with Type 1 Diabetes Mellitus from Northeast Poland: A Case-Control COVID-19 Survey. Nutrients 2021, 13, 1173, doi:10.3390/nu13041173 (IF 6,706, 140 pkt. MEiN)
9. Gromkowska-Kępka KJ, Markiewicz-Żukowska R, Nowakowski P, Naliwajko SK, Moskwa J, Puścion-Jakubik A, Bielecka J, **Grabia M,** Mielcarek K, Soroczyńska J, Socha K. Chemical Composition and Protective Effect of Young Barley (Hordeum vulgare L.) Dietary Supplements Extracts on UV-Treated Human Skin Fibroblasts in In Vitro Studies. Antioxidants 2021, 10, 1402, doi:10.3390/antiox10091402 (IF 7,675, 100 pkt. MEiN)
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Skin Hydration and Lubrication in Young Women. Antioxidants 2021, 10, 1110, doi:10.3390/antiox10071110 (IF 7,675, 100 pkt. MEiN)

11. Nowakowski P, Markiewicz-Żukowska R, Gromkowska-Kępka K, Naliwajko S, Moskwa J, Bielecka J, **Grabia M**, Borawska M, Socha K. Mushrooms as potential therapeutic agents in the treatment of cancer: Evaluation of anti-glioma effects of Coprinus comatus, Cantharellus cibarius, Lycoperdon perlatum and Lactarius deliciosus extracts. Biomedicine & Pharmacotherapy 2021, 133, 111090, doi:10.1016/j.biopha.2020.111090 (IF 7,419, 100 pkt. MEiN)
12. Nowakowski P, Markiewicz-Żukowska R, Bielecka J, Mielcarek K, **Grabia M,** Socha K. Treasures from the Forest: Evaluation of Mushroom Extracts as Anti-Cancer Agents. Biomedicine & Pharmacotherapy 2021, 143, 112106, doi:10.1016/j.biopha.2021.112106 (IF 7,419, 100 pkt. MEiN)
13. **Grabia M**, Markiewicz-Żukowska R. Nutritional Status of Pediatric Patients with Type 1 Diabetes Mellitus from Northeast Poland: A Case-Control Study. Diabetes Therapy 2021, 12, 329-343, doi:10.1007/s13300-020-00972-1 (IF 3,595, 100 pkt. MEiN)
14. Bielecka J, Markiewicz-Żukowska R, Nowakowski P, Puścion-Jakubik A, **Grabia M**, Mielech A, Soroczyńska J, Socha K. Identifying the Food Sources of Selected Minerals for the Adult European Population among Rice and Rice Products. Foods 2021, 10, 1251, doi:10.3390/foods10061251 (IF 5,561, 100 pkt. MEiN)
15. Puścion-Jakubik A, Mielech A, Abramiuk D, Iwaniuk M, **Grabia M**, Bielecka J, Markiewicz-Żukowska R, Socha K. Mercury Content in Dietary Supplements From Poland Containing Ingredients of Plant Origin: A Safety Assessment. Frontiers in Pharmacology 2021, 12, doi:10.3389/fphar.2021.738549 (IF 5,988, 100 pkt. MEiN)
16. Bielecka J, Puścion-Jakubik A, Markiewicz-Żukowska R, Soroczyńska J, Nowakowski P, **Grabia M,** Mielcarek K, Przebierowska K, Kotowska K, Socha K. Assessment of the Safe Consumption of Nuts in Terms of the Content of Toxic Elements with Chemometric Analysis. Nutrients 2021, 13, 3606, doi:10.3390/nu13103606 (IF 6,706, 140 pkt. MEiN)
17. Puścion-Jakubik A, Bielecka J, **Grabia M**, Mielech A, Markiewicz-Żukowska R, Mielcarek K, Moskwa J, Naliwajko S, Soroczyńska J, Gromkowska-Kępka K, Nowakowski P, Socha K. Consumption of Food Supplements during the Three COVID-19 Waves in Poland-Focus on Zinc and Vitamin D. Nutrients 2021, 13, doi:10.3390/nu13103361. (IF 6,706, 140 pkt. MEiN)
18. **Grabia M**, Markiewicz-Żukowska R, Puścion-Jakubik A, Bielecka J, Nowakowski P, Gromkowska-Kępka K, Mielcarek K, Socha K. The Nutritional and Health Effects of the COVID-19 Pandemic on Patients with Diabetes Mellitus. Nutrients 2020, 12, 3013, doi:10.3390/nu12103013 (F 5,719, 140 pkt. MEiN)
19. Bielecka J, Markiewicz-Żukowska R, Nowakowski P, **Grabia M**, Puścion-Jakubik A, Mielcarek K, Gromkowska-Kępka K, Soroczyńska J, Socha K. Content of Toxic Elements in 12 Groups of Rice Products Available on Polish Market: Human Health Risk Assessment. Foods 2020, 9, 1906, doi:10.3390/foods9121906 (IF 4,350, 100 pkt. MEiN)
20. **Grabia M**, Naliwajko SK, Nowakowski P, Gromkowska-Kępka KJ, Puścion-Jakubik A, Markiewicz-Żukowska R. Wybrane Elementy Zachowań Żywieniowych w Grupie Uczniów w Wieku 11-14 lat. Bromatologia i Chemia Toksykologiczna 2018, 51, 187-191 (6 pkt. MNiSW)

Wykaz doniesień zjazdowych

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2. Bielecka J, Markiewicz-Żukowska R, **Grabia M**, Soroczyńska J, Socha K. Zawartość cynku, miedzi i selenu w wybranych produktach zbożowych naturalnie bezglutenowych. II Ogólnopolska Konferencja Naukowa "Żywność i żywienie w pigułce", 22.04.2023r., Gdańsk
3. Kurzyńska K, **Grabia M**, Rytwińska T, Perkowski J, Socha K, Markiewicz-Żukowska R. Aktywność GPx-1 jako potencjalny biomarker w chorobie wieńcowej. 1st International Conference for Young Scientists "Biomarkers of Civilization Diseases", 21.04.2023r., Białystok
4. **Grabia M**, Markiewicz-Żukowska R, Bielecka J, Mielech A, Bossowski A, Socha K. Modern glycemic monitoring systems and prevalence of metabolic syndrome among adolescents with type 1 diabetes mellitus. 5th Edition of Innovations in Food Science and Human Nutrition, 20-21.09.2022r., Barcelona, Hiszpania
5. **Grabia M**, Markiewicz-Żukowska R, Socha K, Polkowska A, Zasim A, Bossowski A. Metabolic syndrome in children and adolescents with type 1 diabetes mellitus - is it a real problem in clinical practice? XXIII Zjazd Naukowy Polskiego Towarzystwa Diabetologicznego, 05-07.05.2022 r., Gdańsk
6. Mirończuk A, Kapica-Topczewska K, Socha K, Soroczyńska J, Jamiołkowski J, Czarnowska A, Tarasiuk J, Kulikowska J, Jakubowicz-Lachowska D, **Grabia M**, Kochanowicz J, Kułakowska A. Is the Cd/Zn molar ratio a potentially new diagnostic biomarker of carotid atherosclerosis in ischemic stroke patients? 8th Congress of the European Academy of Neurology, 25-28.06.2022r., Wiedeń, Austria
7. **Grabia M**, Markiewicz-Żukowska R, Socha K, Polkowska A, Zasim A, Bossowski A. Ocena wybranych czynników żywieniowych w kontekście występowania zespołu metabolicznego u młodych diabetyków. I Ogólnopolska Konferencja Naukowa „Żywność i żywienie w pigułce", Gdański Uniwersytety Medyczny, 09.04.2022r., Gdańsk
8. Falkowska M, **Grabia M**, Perkowski J, Markiewicz-Żukowska R, Socha K. Ocena stanu nawodnienia organizmu u młodych piłkarzy. I Ogólnopolska Konferencja Naukowa „Żywność i żywienie w pigułce", 09.04.2022r., Gdańsk
9. Perkowski J, **Grabia M**, Falkowska M, Markiewicz-Żukowska R, Socha K. Czy młodzi sportowcy narażeni są na wystąpienie niedokrwistości z niedoboru żelaza? I Ogólnopolska Konferencja Naukowa „Żywność i żywienie w pigułce", 09.04.2022r., Gdańsk
10. Markiewicz-Żukowska R, Bielecka J, Puścion-Jakubik A, Perkowski J, Iwaniuk M, **Grabia M**, Socha K. Ocena zawartości wybranych mikroelementów w jajach kurzych. XI Polska Konferencja Chemii Analitycznej "Quo vadis nauka, quo vadis analityka?", 19-23.06.2022r., Łódź.
11. Bielecka J, Markiewicz-Żukowska R, **Grabia M**, Puścion-Jakubik A, Nowakowski P, Soroczyńska J, Żmudzińska A, Socha K. Wykorzystanie metody ICP-MS w ocenie bezpieczeństwa spożycia produktów ryżowych. XVI Konwersatorium Absorpcji Atomowej. XI Konwersatorium Optycznej Spektrometrii Emisyjnej, VIII Konwersatorium Spektrometrii Mas, III Konwersatorium Rentgenowskiej Spektrometrii Fluorescencyjnej, 06-08.09.2021r., Białystok
12. Puścion-Jakubik A, Teper D, Markiewicz-Żukowska R, Soroczyńska J, Bielecka J, **Grabia M**, Mielech A, Moskwa J, Naliwajko S, Mielcarek K, Nowakowski P, Socha K. Zastosowanie ICP-MS i ASA z techniką amalgamacji do oceny bezpieczeństwa spożycia

miodów pszczelich pod względem zawartości pierwiastków toksycznych. XI Konwersatorium Optycznej Spektrometrii Emisyjnej, VIII Konwersatorium Spektrometrii Mas, III Konwersatorium Rentgenowskiej Spektrometrii Fluorescencyjnej. 06-08.09.2021r., Białystok

13. **Grabia M**, Markiewicz-Żukowska R, Puścion-Jakubik A, Bielecka J, Mielech A, Nowakowski P, Gromkowska-Kępka K, Mielcarek K, Socha K. Polypragmasy in the elderly and drug-food interactions. International Scientific Conference of the Polish Society of Nutritional Sciences of the "Dilemmas of Human Nutrition Sciences - Today and Tomorrow". Nutrition and Quality of Life of the Elderly. 23-24.06.2021r., Warszawa
14. Puścion-Jakubik A, Markiewicz-Żukowska R, Moskwa J, **Grabia M**, Gromkowska-Kępka K, Mielech A, Bielecka J, Naliwajko S, Mielcarek K, Nowakowski P, Borawska M, Socha K. Possibilities of using bee honey in the treatment of diseases of old age - a review of the literature. International Scientific Conference of the Polish Society of Nutritional Sciences of the "Dilemmas of Human Nutrition Sciences - Today and Tomorrow". Nutrition and Quality of Life of the Elderly. 23-24.06.2021r., Warszawa
15. Bielecka J, Markiewicz-Żukowska R, Nowakowski P, Puścion-Jakubik A, **Grabia M**, Mielech A, Gromkowska-Kępka K, Soroczyńska J, Socha K. Possibilities of using rice products as a source of essential elements in the diet of seniors. International Scientific Conference of the Polish Society of Nutritional Sciences of the "Dilemmas of Human Nutrition Sciences - Today and Tomorrow". Nutrition and Quality of Life of the Elderly. 23-24.06.2021r., Warszawa
16. Mielech A, Puścion-Jakubik A, Markiewicz-Żukowska R, Bielecka J, **Grabia M**, Gromkowska-Kępka K, Nowakowski P, Socha K. Vitamins in Alzheimer's Disease. International Scientific Conference of the Polish Society of Nutritional Sciences of the "Dilemmas of Human Nutrition Sciences - Today and Tomorrow". Nutrition and Quality of Life of the Elderly. 23-24.06.2021r., Warszawa
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18. Mielech A, Puścion-Jakubik A, Bielecka J, **Grabia M**, Socha K. Diagnostyka i dietoterapia insulinooporności w różnych grupach wiekowych. VII Ogólnopolska Konferencja Studentów Medycyny Laboratoryjnej i Młodych Diagnostów "Wschodząca Diagnostyka", 05.06.2021r., Białystok
19. **Grabia M**, Bielecka J, Mielech A, Markiewicz-Żukowska R. Problematyka diagnostyki zespołu metabolicznego u dzieci i młodzieży z cukrzycą typu 1. VII Ogólnopolska Konferencja Studentów Medycyny Laboratoryjnej i Młodych Diagnostów "Wschodząca Diagnostyka", 05.06.2021r., Białystok
20. **Grabia M**, Markiewicz-Żukowska R, Socha K, Soroczyńska J, Bielecka J, Puścion-Jakubik A, Żmudzińska A, Polkowska A, Zasim A, Bossowski A. Ocena parametrów związanych ze statusem antyoksydacyjnych u młodzieży z cukrzycą typu 1. XXIV Naukowy Zjazd Polskiego Towarzystwa Farmaceutycznego "Salus aegroti suprema lex", 22-24.09.2021r., Lublin
21. Żmudzińska A, Puścion-Jakubik A, Bielecka J, **Grabia M**, Mielcarek K, Nowakowski P, Socha K. Zawartość związków polifenolowych w produktach spożywanych przez dzieci w wieku 0,5-3 lat. XXIV Naukowy Zjazd Polskiego Towarzystwa Farmaceutycznego "Salus aegroti suprema lex", 22-24.09.2021r., Lublin
22. **Grabia M,** Markiewicz-Żukowska R, Bielecka J, Puścion-Jakubik A, Nowakowski P, Socha K. Czy problem nadwagi dotyczy dzieci i młodzieży z cukrzycą typu 1? XXVIII Ogólnopolskie Sympozjum Bromatologiczne. "Innowacyjne podejście do bezpiecznej żywności i racjonalnego

żywienia", 28-29.09.2020r. Gdańsk

23. Puścion-Jakubik A, Horyłek P, Gromkowska-Kępka K, Moskwa J, Markiewicz-Żukowska R, **Grabia M**, Mielcarek K, Nowakowski P, Socha K, Borawska M. Jakie warzywa mogą być bezpiecznie spożywane przez małe dzieci pod względem zawartości azotanów (V)? XXVIII Ogólnopolskie Sympozjum Bromatologiczne. "Innowacyjne podejście do bezpiecznej żywności i racjonalnego żywienia", 28-29.09.2020r. Gdańsk
24. Nowakowski P, Mielcarek K, Gromkowska-Kępka K, Naliwajko S, Moskwa J, Puścion-Jakubik A, **Grabia M**, Markiewicz-Żukowska R, Borawska M, Socha K. Ocena wpływu ekstraktów z czernidłaka kołpakowatego na komórki glejaka wielopostaciowego w badaniach *in vitro*. XXVIII Ogólnopolskie Sympozjum Bromatologiczne. "Innowacyjne podejście do bezpiecznej żywności i racjonalnego żywienia", 28-29.09.2020r. Gdańsk
25. Bielecka J, Markiewicz-Żukowska R, **Grabia M**, Gromkowska-Kępka K, Mielcarek K, Nowakowski P, Socha K. Ocena zawartości rtęci w wybranych produktach bezglutenowych. XXVIII Ogólnopolskie Sympozjum Bromatologiczne. "Innowacyjne podejście do bezpiecznej żywności i racjonalnego żywienia", 28-29.09.2020r. Gdańsk
26. **Grabia M,** Nowakowski P, Bielecka J, Naliwajko S, Puścion-Jakubik A, Markiewicz-Żukowska R. Ocena żywieniowych czynników ryzyka chorób sercowo-naczyniowych wśród studentek Uniwersytetu Medycznego w Białymstoku w odniesieniu do składu ciała. I Ogólnopolski Kongres Medycyny Stylu Życia, 21-22.04.2018 r., Warszawa
27. **Grabia M,** Nowakowski P, Bielecka J, Puścion-Jakubik A, Markiewicz-Żukowska R, Borawska M. Dietetyczne i farmakologiczne możliwości łagodzenia zaparć u osób w wieku podeszłym. Ogólnopolska Konferencja Naukowa Studenckiej Sekcji Polskiego Towarzystwa Farmaceutycznego "Postępy farmakoterapii personalizowanej seniorów", 25-26.05.2018r., Białystok
28. **Grabia M**, Gromkowska-Kępka K, Puścion-Jakubik A, Markiewicz-Żukowska R. Ocena spożycia wybranych składników mineralnych wpływających na wygląd skóry, włosów i paznokci wśród studentek kosmetologii Uniwersytetu Medycznego w Białymstoku. V Ogólnopolska Konferencja Naukowa "Nutrikosmetologia prozdrowotna", 12.05.2018r., Olsztyn
29. **Grabia M**, Puścion-Jakubik A, Markiewicz-Żukowska R. Wybrane elementy stylu życia młodzieży z cukrzycą typu 1 - badanie pilotażowe. V Ogólnopolska Konferencja Naukowa "Nutrikosmetologia prozdrowotna", 12.05.2018r., Olsztyn
30. Bielecka J, Gromkowska-Kępka K, **Grabia M**, Naliwajko S, Puścion-Jakubik A, Markiewicz-Żukowska R. Ocena spożycia wybranych składników mineralnych z dietą a stan mineralny kości. VIII Ogólnopolska Konferencja Dietetyki - Congressus Dietetica „Choroby autoimmunizacyjne i alergie towarzyszące", 06-07.04.2018r., Łódź
31. **Grabia M**, Naliwajko S, Nowakowski P, Gromkowska-Kępka K, Puścion-Jakubik A, Markiewicz-Żukowska R. Wybrane elementy zachowań żywieniowych w grupie uczniów w wieku 11-14 lat. XXVI Ogólnopolskie Sympozjum Bromatologiczne, "Żywność i żywienie człowieka - kierunki rozwoju", 13-15.09.2018r., Białystok
32. **Grabia M**, Bielecka J, Nowakowski P, Puścion-Jakubik A, Markiewicz-Żukowska R, Borawska M. Zaparcia u osób starszych - rola dietetyka i farmaceuty. XIII Zjazd Naukowy Polskiego Towarzystwa Gerontologicznego "Kobieta i Mężczyzna 65+", 17-18.11.2017r., Warszawa
33. Bielecka J, Nowakowski P, Naliwajko S, Puścion-Jakubik A, **Grabia M**, Markiewicz-Żukowska R, Borawska M. Znaczenie żywienia w terapii nadciśnienia tętniczego u osób starszych. XIII Zjazd Naukowy Polskiego Towarzystwa Gerontologicznego "Kobieta i Mężczyzna 65+", 17-18.11.2017r., Warszawa

Wykaz innych aktywności naukowych

Stypendia naukowe

1. Stypendium naukowe Rektora Uniwersytetu Medycznego w Białymstoku w roku akademickim 2021/2022 oraz 2022/2023

Granty zewnętrzne

1. Projekt naukowy w ramach grantu „Inkubator Innowacyjności 4.0" na badania przedwdrożeniowe „Żywność funkcjonalna dla osób z chorobą Hashimoto" Kierownik: dr hab. Sylwia Naliwajko. Współwykonawca: mgr Monika Grabia.
2. Projekt mający na celu m.in. opracowanie i zrealizowanie programu edukacyjnego o tematyce zdrowotno-żywieniowej dla seniorów w ramach projektu mobilności edukacyjnej Erasmus+ *„Broaden the Horizons of Knowledge"* (czerwiec 2022r., Ateny, Grecja). Kierownik: Polski Związek Emerytów, Rencistów i Inwalidów Oddział Olsztyn. Współwykonawca: mgr Monika Grabia.
3. Projekt naukowy w ramach grantu „Inkubator Innowacyjności 4.0" na badania przedwdrożeniowe „Przekąski dla insulinoopornych", które miały na celu opracowanie innowacyjnych receptur oraz wykonanie badań konsumenckich i klinicznych z udziałem najnowszych technologii kontroli glikemii. Kierownik: dr Anna Puścion- Jakubik. Współwykonawca: mgr Monika Grabia.

Granty wewnętrzne

1. Projekt naukowy z subwencji Uniwersytetu Medycznego w Białymstoku – B.SUB.23.133. Kierownik: mgr Martyna Falkowska. Współwykonawca: mgr Monika Grabia. Wpływ żywienia na całkowity status antyoksydacyjny (TAS) pacjentów z zaćmą.
2. Projekt naukowy z subwencji Uniwersytetu Medycznego w Białymstoku – B.SUB.23.406. Kierownik: dr hab. Renata Markiewicz-Żukowska. Współwykonawca: mgr Monika Grabia. Ocena bezpieczeństwa spożycia różnych rodzajów jaj w aspekcie narażenia na pierwiastki toksyczne.
3. Projekt naukowy z subwencji Uniwersytetu Medycznego w Białymstoku – B.SUB.23.407. Kierownik projektu: dr Anna Puścion-Jakubik. Współwykonawca: mgr Monika Grabia. Ocena zawartości soli w produktach przeznaczonych dla niemowląt i małych dzieci – opracowanie nowej metody oznaczania - kalibracji do metody NIR.
4. Projekt naukowy z subwencji Uniwersytetu Medycznego w Białymstoku – SUB/2/DN/22/005/2216. Kierownik: mgr Monika Grabia. Wpływ wysiłku fizycznego na potencjał antyoksydacyjny organizmu młodych sportowców.
5. Projekt naukowy z subwencji Uniwersytetu Medycznego w Białymstoku – SUB/3/DN/22/001/2216. Kierownik: mgr Joanna Bielecka. Współwykonawca: mgr Monika Grabia. Ocena zawartości kadmu i ołowiu w kakao i produktów wytwarzanych na bazie kakao dostępnych w sprzedaży detalicznej w Polsce.
6. Projekt naukowy z subwencji Uniwersytetu Medycznego w Białymstoku – SUB/2/DN/22/002/2216. Kierownik projektu: dr hab. Renata Markiewicz-Żukowska. Współwykonawca: mgr Monika Grabia. Ocena zawartości cynku, selenu i żelaza w różnych rodzajach jaj w aspekcie wykorzystania ich jako źródła składników mineralnych w diecie, z uwzględnieniem standardów żywieniowych.
7. Projekt naukowy z subwencji Uniwersytetu Medycznego w Białymstoku – SUB/2/DN/22/005/2216. Kierownik projektu: dr Anna Puścion-Jakubik. Współwykonawca:

mgr Monika Grabia. Ocena zawartości białka w produktach przeznaczonych dla niemowląt i małych dzieci – opracowanie nowej kalibracji do metody NIR.

8. Projekt naukowy z subwencji Uniwersytetu Medycznego w Białymstoku – SUB/2/DN/21/003/2216. Kierownik: mgr Monika Grabia. Wpływ interwencji i edukacji żywieniowej na stan odżywienia i markery ryzyka żywieniowego u młodych sportowców.
9. Projekt naukowy z subwencji Uniwersytetu Medycznego w Białymstoku – SUB/3/DN/21/001/2216. Kierownik: mgr Joanna Bielecka. Współwykonawca: mgr Monika Grabia. Całkowita zawartość polifenoli oraz pierwiastków antyoksydacyjnych w naturalnie bezglutenowych produktach zbożowych pochodzących z upraw konwencjonalnych oraz ekologicznych.
10. Projekt naukowy z subwencji Uniwersytetu Medycznego w Białymstoku – SUB/2/DN/21/004/2216. Kierownik projektu: dr hab. Renata Markiewicz-Żukowska. Współwykonawca: mgr Monika Grabia. Ocena możliwości wykorzystania grzybów jadalnych jako naturalnego źródła wybranych czynników immunomodulujących.
11. Projekt naukowy z subwencji Uniwersytetu Medycznego w Białymstoku – SUB/2/DN/20/002/2216. Kierownik: mgr Monika Grabia. Ocena stanu odżywienia, statusu redoks i sposobu żywienia u dzieci i młodzieży z cukrzycą typu 1.

Wygłoszone wykłady

1. „Żywieniowe i zdrowotne skutki pandemii COVID-19 u pacjentów z cukrzycą", podczas zebrania naukowego Oddziału Białostockiego Polskiego Towarzystwa Nauk Żywieniowych, 04.12.2020r., Białystok
2. „Zasady prawidłowego żywienia w okresie dojrzewania" w ramach projektu realizowanego przez Centrum Kompetencji BOF, 24.11.2020r., Białystok
3. „Rola farmaceuty w ocenie stanu odżywienia pacjentów" dla członków Polskiego Towarzystwa Studentów Farmacji, 20.11.2021r., Białystok
4. „Diagnostyka stanu odżywienia w chorobach cywilizacyjnych" podczas XVII Ogólnopolskiej Debaty Studentów Analityki Medycznej, 09.04.2022r., Białystok

Podnoszenie kompetencji specjalistycznych i naukowych

1. „Żywienie zbiorowe dzieci i młodzieży w placówkach oświatowych", EduPunkt, 22.03.2023r., Słupsk
2. „Zarządzanie projektami", Akademia PARP (Polskiej Agencji Rozwoju Przedsiębiorczości), 01.03.2023r., Warszawa
3. Warsztaty i szkolenie „Ars Mollis i szybkie randki naukowo-dziennikarskie" współfinansowane przez Ministerstwo Edukacji i Nauki, 17.11.2022r., Białystok
4. Otrzymanie tytułu *„Specjalisty Przyjaznego Dzieciom"* nadanego przez Uniwersytet Medyczny w Łodzi podczas II Kongresu Pediatryczno-Żywieniowego, 14.11.2020r. po zdaniu egzaminu certyfikacyjnego
5. Praktyczne szkolenie z zakresu cukrzycy typu 1, 11.07.2020r., Lublin
6. Otrzymanie tytułu *„Specjalisty Przyjaznego Insulinooopornym"* nadanego przez School of Insulinresistance Therapy, Fundacja „Insulinooporność", 05.06.2020r. po zdaniu egzaminu certyfikacyjnego
7. Nowoczesne techniki pomiarowe w procesie badania fenotypów, biochemii i oddziaływań komórkowych, Perkin Elmer, 21.05.2020r.
8. Podstawy i możliwości techniki ICP-MS, Perlan, 19.05.2020r.
9. Spektroskopia w przemyśle spożywczymi i paszowym, MS Spektrum, 13.05.2020r.

10. Warsztaty analityczne połączone z pokazami nowoczesnej aparatury badawczej, MS Spektrum, 26.11.2019r., Białystok

Nagrody i wyróżnienia

1. **Grabia M,** Markiewicz-Żukowska R, Socha K, Polkowska A, Zasim A, Bossowski A. Ocena wybranych czynników żywieniowych w kontekście występowania zespołu metabolicznego u młodych diabetyków. I Ogólnopolska Konferencja Naukowa „Żywność i żywienie w pigułce", Gdański Uniwersytety Medyczny, 09.04.2022r., Gdańsk *(wyróżnienie w sesji)*
2. Falkowska M, **Grabia M**, Perkowski J, Markiewicz-Żukowska R, Socha K. Ocena stanu nawodnienia organizmu u młodych piłkarzy. I Ogólnopolska Konferencja Naukowa „Żywność i żywienie w pigułce", 09.04.2022r., Gdańsk *(wyróżnienie w sesji)*
3. Perkowski J, **Grabia M**, Falkowska M, Markiewicz-Żukowska R, Socha K. Czy młodzi sportowcy narażeni są na wystąpienie niedokrwistości z niedoboru żelaza? I Ogólnopolska Konferencja Naukowa „Żywność i żywienie w pigułce", 09.04.2022r., Gdańsk *(wyróżnienie w sesji)*
4. **Grabia M**, Markiewicz-Żukowska R, Socha K, Polkowska A, Zasim A, Bossowski A. Całkowity status antyoksydacyjny, stężenie cynku, miedzi i selenu w surowicy krwi a spożycie składników antyoksydacyjnych wśród młodzieży z cukrzycą typu 1 w porównaniu do zdrowych rówieśników - badanie pilotażowe. VI Ogólnopolska Konferencja Naukowa "Dietoterapia Zaburzeń Metabolicznych" 12-13.06.2021, Poznań *(wyróżnienie)*
5. Mielech A, Puścion-Jakubik A, Bielecka J, **Grabia M**, Socha K. Diagnostyka i dietoterapia insulinooporności w różnych grupach wiekowych. VII Ogólnopolska Konferencja Studentów Medycyny Laboratoryjnej i Młodych Diagnostów "Wschodząca Diagnostyka", 05.06.2021, Białystok *(wyróżnienie)*
6. Nowakowski P, Mielcarek K, Gromkowska-Kępka K, Naliwajko S, Moskwa J, Puścion-Jakubik A, **Grabia M**, Markiewicz-Żukowska R, Borawska M, Socha K. Ocena wpływu ekstraktów z czernidłaka kołpakowatego na komórki glejaka wielopostaciowego w badaniach *in vitro*. XXVIII Ogólnopolskie Sympozjum Bromatologiczne. "Innowacyjne podejście do bezpiecznej żywności i racjonalnego żywienia", 28-29.09.2020r. Gdańsk *(I miejsce)*
7. **Grabia M**, Naliwajko S, Nowakowski P, Gromkowska-Kępka K, Puścion-Jakubik A, Markiewicz-Żukowska R. Wybrane elementy zachowań żywieniowych w grupie uczniów w wieku 11-14 lat. XXVI Ogólnopolskie Sympozjum Bromatologiczne, "Żywność i żywienie człowieka - kierunki rozwoju", 13-15.09.2018r., Białystok *(I miejsce)*

Wykaz aktywności popularyzatorskich, organizacyjnych i współprac z przedsiębiorcami

Popularyzacja nauki oraz Uniwersytetu Medycznego w Białymstoku

1. Projekt „Akademia Zdrowego Diabetyka" obejmujący działania edukacyjne zaplanowane na rok 2023, skierowane do pacjentów z cukrzycą oraz ich rodzin i opiekunów zamieszkujących województwo warmińsko-mazurskie, mające na celu ograniczenie powikłań cukrzycy oraz poprawę jakości i długości życia chorych. Projekt realizowany w ramach zadań Samorządu Województwa Warmińsko-Mazurskiego. Kierownik: mgr Monika Grabia
2. „Suplementy diety – fakty i mity" stworzenie scenariusza oraz wystąpienie w roli dietetyka w filmie stworzonym w ramach projektu „Teraz już wiem", 12.04.2022r., Białystok
3. „Wykrywanie jełczenia tłuszczów jadalnych" film promocyjny stworzony na potrzeby Pikniku Naukowego Polskiego Radia i Centrum Nauki Kopernik, 15.05.2021r., Warszawa
4. „Żywienie dzieci i młodzieży" w radiu Ortodoxia audycja radiowych w ramach cyklu „ Pytanie do specjalisty" 10.10.2020r., Białystok

Przeprowadzone warsztaty

1. "Wpływ niezdrowej żywności na organizm człowieka" Szkoła Podstawowa nr 13 w Białymstoku, 27.10.2022r.
2. "Co odżywia mózg?" – cykl letnich warsztatów dla dzieci (lipiec-sierpień 2022r.)
3. "Zdrowe żywienie" – cykl warsztatów edukacyjno-kulinarnych w szkołach podstawowych na zlecenie Krajowego Ośrodka Wsparcia Rolnictwa (kwiecień-czerwiec 2022r. i 2023r.)
4. „Wpływ żywienia na zdrowie człowieka" Liceum w Węgrowie (14.12.2021r.) i Augustowie (13.01.2022r.)
5. Program warsztatów edukacyjnych dla młodych piłkarzy w ramach interwencji żywieniowej finansowanej z subwencji Uniwersytetu Medycznego w Białymstoku
6. „Prawidłowe nawyki żywieniowe u młodych sportowców", Szkoła Podstawowa nr 5 w Białymstoku, 21.02.2020r.
7. „Jesteś tym, co jesz…, czyli o racjonalnym żywieniu", Szkoła Podstawowa w Choroszczy, 03.12.2019r.
8. "Zdrowe żywienie" cykl warsztatów edukacyjno-kulinarnych dla młodzieży i rodziców w ramach olsztyńskiego projektu realizowanego dla Angels Foundation, listopad 2019r.
9. "Zdrowe żywienie" zajęcia dla przedszkolaków z zespołem Downa w ramach Akademii Zdrowego Przedszkolaka 11.04.2018r., Białystok
10. "Co, ile i jak jeść" Szkoła Podstawowa i Gimnazjum w Gródku 22.01.2018r.

Organizacja Sympozjum Naukowego

1. Członek Komitetu Organizacyjnego XXVI Ogólnopolskiego Sympozjum Bromatologicznego w 2018r.

Przynależność do Towarzystwa Naukowego

1. Członek Polskiego Towarzystwa Nauk Żywieniowych

Współpraca z przedsiębiorcami

1. Badania komercyjne – Oznaczanie zawartości wybranych związków antyoksydacyjnych i składników mineralnych w produktach spożywczych dla dzieci na zlecenie firmy Purella Food Sp. z o.o. (2021r.)