Uniwersytet Medyczny
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Zaburzenia gospodarki węglowodanowej w polskiej grupie uczestników Prospektywnego Badania Epidemiologicznego Ludności Miejskiej i Wiejskiej (PURE)

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lek. Agnieszka Święcicka-Klama

Promotor: dr hab. n. med. Katarzyna Zatońska, prof. UMW

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Niniejsza dysertacja doktorska jest owocem pracy wielu osób, którym pragnę serdecznie podziękować.

Mojej Pani Promotor dr hab. n. med. Katarzynie Zatońskiej, prof. UMW za opiekę merytoryczną, cenne uwagi, sugestie oraz za nieocenioną cierpliwość, zrozumienie i pomoc na każdym etapie realizacji pracy doktorskiej.

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Moim kolegom z pracy oraz pozostałym osobom napotkanym na drodze naukowej za wszelką pomoc.

Szczególne podziękowania chciałabym wyrazić moim Najbliższym
- Mężowi, Synkowi, Rodzicom, którzy gorąco mnie wspierali przez cały okres pisania pracy, byli dla mnie bardzo cierpliwi i wyrozumiali i bez których dysertacja nie mogłaby powstać.

Spis treści

1. Wprowadzenie

Zaburzenia gospodarki węglowodanowej, na które składają się cukrzyca oraz stan przedcukrzycowy (*prediabetes*), stanowią obecnie ogromny problem epidemiologiczny, zdrowotny, jak i ekonomiczny. Stan przedcukrzycowy obejmuje dwa podobnie brzmiące zaburzenia, lecz odmienne pod względem mechanizmu powstawania i przebiegu: nieprawidłową glikemię na czczo (IFG, ang. *impaired fasting glucose*) oraz nieprawidłową tolerancję glukozy (IGT, ang. *impaired glucose tolerance*). Nieprawidłowa glikemia na czczo jest definiowana przez Międzynarodowy Komitet Ekspertów (IEC, ang. *International Expert Committee*), Amerykańskie Towarzystwo Diabetologiczne (ADA, ang. *American Diabetes Association*), inne towarzystwa, w tym Polskie Towarzystwo Diabetologiczne (PTD) jako podwyższone stężenie glukozy w osoczu na czczo w zakresie 100-125 mg/dl (5,6–6,9 mmol/l) [1,2,3]. Zgodnie z kryteriami Światowej Organizacji Zdrowia (WHO, ang. *World Health Organization*) i Międzynarodowej Federacji Diabetologicznej (IDF, ang. *International Diabetes Federation*) dolna granica normy znajduje się na nieco wyższym poziomie 110 mg/dl (6,1 mmol/l), przy czym górna granica – pozostaje bez zmian [4].

Nieprawidłowa glikemia na czczo jest częstym zaburzeniem, które dotyka około 8,4% Europejczyków, znacznie częściej – mężczyzn niż kobiet [5]. Wciąż brakuje weryfikowalnych danych dotyczących rozpowszechnienia na świecie nieprawidłowej glikemii na czczo [6]. Na podstawie dwóch badań epidemiologicznych przeprowadzonych w Polsce, tj. Prospektywnego Badania Ludności Miejskiej i Wiejskiej (PURE, ang. *Prospective Urban and Rural Epidemiology*) i Polsko-Norweskiego Badania PONS (ang. *Polish-Norwegian Study*), częstość występowania IFG szacuje się na niespełna 30% (odpowiednio 28% i 29%). Liczby te mogą być nawet niedoszacowane, ponieważ wiele osób nie jest diagnozowanych w kierunku wczesnych zaburzeń gospodarki węglowodanowej lub nie jest świadomych tego, że ma stan przedcukrzycowy [7,8].

Szacuje się, że osoby z *prediabetes* mają 3-10-krotnie wyższe ryzyko rozwoju cukrzycy typu 2 (T2DM, ang. *type 2 diabetes mellitus*) w porównaniu z populacją ogólną [9]. Analiza danych z polskiej kohorty badania PURE wykazała, iż pacjenci z IFG mieli 2,7-krotnie większe ryzyko rozwoju T2DM niż osoby z normoglikemią [10].

Istotny klinicznie jest też fakt, iż długotrwale podwyższony poziom glikemii sprzyja rozwojowi i progresji miażdżycy. Istnieją dowody na to, że procesy miażdżycowe, zwłaszcza przewlekle toczący się proces zapalny i uszkodzenie śródbłonka, rozpoczynają się na wiele lat przed rozpoznaniem cukrzycy [11,12,13]. Zatem, pacjenci z IFG są obciążeni nie tylko większym ryzykiem rozwoju zarówno cukrzycy, ale też powikłań sercowo-naczyniowych spowodowanych miażdżycą, zwłaszcza choroby wieńcowej [14,15,16,17,18].

Wprawdzie dotychczas ukazało się wiele prac naukowych na temat czynników ryzyka rozwoju cukrzycy, jednakże wciąż trudno opisać typowy przebieg IFG. Przebieg tego zaburzenia jest bardzo zróżnicowany, ponieważ jest stopniowym i złożonym procesem, zależnym od wielu czynników. Znaczna część osób powraca do normoglikemii lub pozostaje u nich rozpoznana nieprawidłowa glikemia na czczo [19]. U pozostałych pacjentów, wartość glikemii stopniowo wzrasta w czasie, aż do rozwoju pełnoobjawowej cukrzycy typu 2 [20]. Skumulowaną 9-letnią zapadalność na T2DM szacuje się na 38% (95% CI 10-70%) u osób z izolowaną nieprawidłową glikemią na czczo i 84% (95% CI 74-91%) u pacjentów ze współistniejącą nieprawidłową tolerancją glukozy. W tym samym czasie, 17% osób (95% CI 14-22%) powróciło ze stanu przedcukrzycowego do normoglikemii [21].

Wciąż brakuje danych dotyczących długoterminowego ryzyka progresji *prediabetes,* zwłaszcza IFG, do cukrzycy oraz wpływu poszczególnych czynników ryzyka na ten proces. Zauważa sią także niespójność istniejących już danych. Fakt ten wynika z tego, iż w dotychczasowych badaniach stosowano różne kryteria diagnostyczne, kryteria włączenia do badania oraz metodologię o rożnej dokładności i powtarzalności. Co więcej, kohorty pacjentów były często niejednorodne, bez wyraźnego rozróżnienia między poszczególnymi rodzajami *prediabetes,* takimi jak izolowane IFG, izolowane IGT lub współistniejące IFG z IGT.

Potencjalnymi czynnikami zwiększającymi ryzyko rozwoju cukrzycy i występującymi powszechnie w populacji wydają się wskaźniki otyłości brzusznej oraz czynniki ryzyka sercowo-naczyniowego [22,23,24]. Szacuje się, że wraz ze starzeniem się społeczeństwa, zmianą stylu życia, obejmującą m.in. zmniejszoną aktywność fizyczną oraz wysoko przetworzoną dietę wysokoenergetyczną, ich rozpowszechnienie będzie coraz częstsze [25,26]. Wyżej wymienione czynniki znacząco przyczyniają się do pogorszenia stanu zdrowia społeczeństwa i stanowią różnorakie problemy: epidemiologiczny, zdrowotny, społeczny czy ekonomiczny (z uwagi na koszty leczenia i rehabilitacji osób dotkniętych powikłaniami). Stąd,

właśnie na wskaźnikach otyłości brzusznej i czynnikach ryzyka choroby wieńcowej, zawartych w skali Framingham, chciałabym się skupić w mojej dysertacji doktorskiej.

Na podstawie przeglądu aktualnego piśmiennictwa można stwierdzić, iż nadal istnieje potrzeba lepszego poznania etiopatogenezy IFG, jak i czynników wpływających na rozwój cukrzycy. Wczesne wykrycie zaburzeń metabolizmu glukozy może zapobiec lub opóźnić rozwój cukrzycy typu 2 i jej powikłań, dlatego nadrzędną rolę należy przypisać szeroko pojętej profilaktyce. Działania profilaktyczne mają na celu nie tylko wczesne wykrywanie i leczenie zaburzeń gospodarki węglowodanowej, ale także – identyfikację i eliminację czynników ryzyka. Wiedza ta może przyczynić się do zaprojektowania, udoskonalenia i wdrożenia strategii prewencyjnych dla osób z nieprawidłową glikemią na czczo i wysokim ryzykiem rozwoju cukrzycy.

2. Cele pracy naukowej

Rozprawę doktorską pt.: „***Zaburzenia gospodarki węglowodanowej w polskiej grupie uczestników Prospektywnego Badania Epidemiologicznego Ludności Miejskiej i Wiejskiej (PURE)”*** stanowi cykl autorskich publikacji – przegląd literatury odnośnie przebiegu IFG oraz analiza danych zebranych w ramach badania PURE na temat rozwoju cukrzycy typu 2 z nieprawidłowej glikemii na czczo. Celem mojej pracy było podsumowanie i pogłębienie wiedzy na temat nieprawidłowej glikemii na czczo oraz analiza wpływu wybranych czynników ryzyka na jej progresję do cukrzycy typu 2.

Celem pierwszej pracy pt.: „***The Natural Course of Impaired Fasting Glucose”*** było usystematyzowanie i przegląd dotychczasowego stanu wiedzy z zakresu etiopatogenezy, epidemiologii i przebiegu stanu przedcukrzycowego, ze szczególnym uwzględnieniem nieprawidłowej glikemii na czczo oraz czynników ryzyka przejścia IFG w cukrzycę typu 2.

Celem drugiej pracy pt.: „***Anthropometric Indices as Long-Term Predictors of Diabetes in Impaired Fasting Glucose Metabolism: Findings in the PURE Study in Poland”*** była ocena wpływu parametrów antropometrycznych na progresję IFG do cukrzycy w subpopulacji polskiej międzynarodowego badania PURE, na przestrzeni 9 lat. W niniejszym artykule skupiłam się na wartości predykcyjnej najczęściej stosowanych wskaźników otyłości brzusznej dla rozwoju cukrzycy typu 2 w populacji osób z IFG.

Celem trzeciej pracy pt.: „***Cardiovascular Risk Factors Drive Impaired Fasting Glucose to Type 2 Diabetes: Findings After a 9-Year Follow-Up in the PURE Study in Poland”*** była analiza wpływu czynników ryzyka sercowo-naczyniowego, uwzględnionych w skali Framingham, na rozwój cukrzycy u pacjentów z nieprawidłową glikemią na czczo, na podstawie 9-letniej obserwacji (ang. *follow-up*) badania PURE Polska.

Niniejszy cykl prac może w przyszłości pomóc w spersonalizowaniu programu profilaktycznego cukrzycy, który będzie efektywnie identyfikował osoby z nieprawidłową glikemią na czczo i wysokim ryzykiem progresji do cukrzycy typu 2.

3. Materiał i metody

3.1. Projekt i przebieg badania

Prace badawcze włączone do rozprawy doktorskiej zostały przeprowadzone na podstawie bazy danych zebranej w ramach międzynarodowego badania PURE (Prospektywnego Badania Epidemiologicznego Ludności Miejskiej i Wiejskiej, ang. *Prospective Urban and Rural Epidemiological Study*). Polską kohortę badania stanowi 2036 osób, w tym 1210 mieszkańców Wrocławia oraz 826 osób z terenów wiejskich (gmina Żórawina), w wieku od 30 do 85 lat. Rekrutacja do badania odbywała się w latach 2007-2010 (ang. *baseline*). Następnie, po zebraniu pierwszych danych z *baseline*, co roku był przeprowadzany wywiad telefoniczny odnośnie nowych zachorowań i pobytów w szpitalu. Ponadto, cyklicznie co 3 lata odbywają się bardziej szczegółowe wywiad i badanie kontrolne (ang. *follow-up).* Badanie PURE jest wciąż kontynuowane i obecnie trwa 12. *follow-up*.

Badanie zostało zaprojektowane i przeprowadzone zgodnie z międzynarodowym protokołem projektu PURE [25,27]. Polskie badanie PURE uzyskało pozytywną opinię Komisji Bioetycznej Uniwersytetu Medycznego im. Jana Mikulicza-Radeckiego we Wrocławiu (nr KB-443/2006).

Protokół badania zawiera standaryzowane do danego kraju kwestionariusze dotyczące danych socjodemograficznych, stanu zdrowia, aktywności fizycznej, nawyków żywieniowych, jak i warunków socjalnych. Na podstawie wywiadu i dostarczonej dokumentacji medycznej zostały zebrane informacje odnośnie przebytych i aktualnych chorób oraz przyjmowanych leków przez pacjenta. Przeprowadzany był szereg badań, m.in. dwukrotny pomiar ciśnienia tętniczego, badania antropometryczne (wzrost, masa ciała, obwody: bioder, talii, ramienia, grubość fałdu skórnego) oraz laboratoryjne, takie jak glikemia na czczo, lipidogram, badanie ogólne moczu [28].

W moich pracach, do badań zostało włączonych 283 osoby z nieprawidłową glikemią na czczo, u których w badaniu referencyjnym (ang. *baseline*) poziom glikemii na czczo (tj. upłynęło co najmniej 8 godzin od ostatniego posiłku) znajdował się w przedziale od 100 mg/dl do 125 mg/dl (5,6 - 6,9 mmol/l). Warunkiem włączenia pacjenta do analizy był komplet danych

z *baseline* oraz po 9 latach obserwacji (ang. *9 years of follow-up*). Z badania zostały wykluczone następujące osoby:

- u których wcześniej rozpoznano cukrzycę;
- którzy przyjmowali jakiekolwiek leki regulujące poziom glikemii;
- u których glikemia na czczo przekraczała 125 mg/dl (6,9 mmol/l) we wstępnym badaniu przesiewowym.

W publikacji pt.: „***Anthropometric Indices as Long-Term Predictors of Diabetes in Impaired Fasting Glucose Metabolism: Findings in the PURE Study in Poland"*** na podstawie zmierzonego wzrostu, masy ciała, obwodu talii (WC, ang. *waist circumference*), obwodu bioder (HC, ang. *hip circumference*) obliczono następujące wskaźniki antropometryczne:

- wskaźnik masy ciała (BMI, ang. *body mass index)*: masa ciała (kg) / wzrost^2 (m^2);
- stosunek obwodu talii do obwodu bioder (WHR, ang. *waist-to-hip ratio)*: WC (cm) / HC (cm);
- wskaźnik talia-wzrost tj. stosunek obwodu talii do wzrostu (WHtR, ang. *waist-to-height ratio*): WC (cm) / wzrost (cm);
- wskaźnik otyłości ciała (BAI, ang. *body adiposity index*): obwód bioder (cm) / [wzrost^{1,5} (m) - 18] [29].

Otyłość została zdefiniowana w następujący sposób:

- WC ≥ 80 cm u kobiet i ≥ 94 cm u mężczyzn, zgodnie z kryteriami WHO i IDF dla rasy białej [31,30];
- WHR ≥ 0,85 u kobiet i ≥ 0,9 u mężczyzn [30];
- WHtR ≥ 0,58 u kobiet i ≥ 0,63 u mężczyzn [33,32];
- BMI ≥ 30 kg/m2 [34].

W publikacji pt.: ***„Cardiovascular Risk Factors Drive Impaired Fasting Glucose to Type 2 Diabetes: Findings After a 9-Year Follow-Up in the PURE Study in Poland***" analizowano czynniki ryzyka choroby wieńcowej (CHD, ang. *coronary heart disease*) zawarte w skali Framingham:

— wiek;
— płeć;
— palenie tytoniu;
— skurczowe ciśnienie krwi lub leczenie hipotensyjne;
— poziom cholesterolu całkowitego (TC) i cholesterolu lipoprotein o dużej gęstości (HDL-C).

Punktację w skali Framingham (FRS, ang. *Framingham Risk Score*) obliczono przy użyciu zwalidowanego modelu predykcyjnego. 10-letnie ryzyko CHD zostało sklasyfikowane jako niskie (<10%), pośrednie (10-20%) i wysokie (>20%) [35,36]. Nikotynizm czynny zdefiniowano jako spożywanie co najmniej jednego wyrobu tytoniowego dziennie. Ciśnienie krwi mierzono dwukrotnie za pomocą automatycznego ciśnieniomierza naramiennego (Omron Corporation, Tokio, Japonia). Każdy pomiar wykonywano w pozycji siedzącej po co najmniej 5-minutowym odpoczynku, następnie wynik uśredniono. Nadciśnienie tętnicze definiowano jako średnie ciśnienie skurczowe (SBP, ang. *systolic blood pressure*) ≥ 140 mmHg, ciśnienie rozkurczowe (DBP, ang. *diastolic blood pressure*) ≥ 90 mmHg, rozpoznaną w przeszłości chorobę nadciśnieniową lub przyjmowanie leków hipotensyjnych. W celu bardziej szczegółowego przedstawienia wyników średnich wartości ciśnienia tętniczego wykorzystano klasyfikację ESH-ESC [37]:

— prawidłowe:
  - optymalne < 120/80 mmHg,
  - prawidłowe < 130/85 mmHg,
  - wysokie prawidłowe < 140/90 mmHg;

— nieprawidłowe:
  - nadciśnienie 1 stopnia ≥ 140/90 mmHg i <160/100 mmHg,
  - nadciśnienie 2 stopnia ≥ 160/100 mmHg i < 180/110 mmHg,
  - nadciśnienie 3 stopnia ≥180/110 mmHg,
  - izolowane nadciśnienie skurczowe SBP ≥ 140 mmHg i DBP <90 mmHg.

Po 9 latach obserwacji, u wszystkich uczestników grupy badanej ponownie wykonano pomiar glikemii na czczo z krwi żylnej (FPG, ang. *fasting plasma glucose*). Na podstawie wyników oraz przeprowadzonego wywiadu dokonano stratyfikacji pacjentów na trzy grupy, różniące się między sobą pod względem metabolizmu glukozy w ciągu 9 lat obserwacji:

— Grupę A z normoglikemią stanowili pacjenci bez rozpoznanej dotychczas cukrzycy, nie przyjmujący leków hipoglikemizujących i po 9 latach wykazujący poziom FPG poniżej 100 mg/dl (5,6 mmol/l);
— Grupę B z przetrwałą nieprawidłową glikemią na czczo stanowili pacjenci bez rozpoznanej cukrzycy, nie przyjmujący leków hipoglikemizujących i po 9 latach wykazujący poziom FPG w zakresie 100-125 mg/dl (5,6–6,9 mmol/l);
— Grupę C z rozpoznaniem T2DM stanowili pacjenci z cukrzycą w wywiadzie, przyjmujący leki hipoglikemizujące lub po 9 latach wykazujący FPG powyżej 125 mg/dl (6,9 mmol/l).

Do analizy charakterystyki każdej z grup wykorzystano dane z *baseline*, które stanowiły podstawę do badań czynników ryzyka progresji IFG do cukrzycy. Pierwszorzędowym punktem końcowym była wartość FPG po 9 latach, stąd pozwolono sobie pominąć wszelkie inne zmiany, w tym parametrów antropometrycznych, profilu lipidowego czy kontroli ciśnienia tętniczego.

3.2. Analiza statystyczna

Zmienne jakościowe nominalne i porządkowe przedstawiono w tabelach jako liczebności (*n*) i proporcje (%). Istotność związków między dwiema zmiennymi jakościowymi weryfikowano za pomocą testów niezależności Chi-kwadrat Pearsona.

Dla zmiennych ilościowych obliczono podstawowe statystyki opisowe (średnią, odchylenie standardowe, wartość minimalną i wartość maksymalną). Zgodność ich rozkładów z teoretycznym rozkładem normalnym (Gaussa) sprawdzono za pomocą testów Kołmogorowa-Smirnowa oraz Shapiro-Wilka. Istotność różnic wartości średnich zmiennych ilościowych o rozkładzie zbliżonym do normalnego i o jednorodnych wariancjach w dwóch grupach niezależnych oceniano za pomocą testu t-Studenta. W przypadku większej ilości grup niezależnych, przeprowadzono analizę wariancji (ANOVA) i porównania wielokrotne (testy *post hoc* Tukeya). Siłę i kierunek współzależności między dwiema zmiennymi ilościowymi badano za pomocą współczynnika korelacji *r* Pearsona.

Na podstawie analizy krzywych ROC (ang. *receiver operating characteristic curves*) dla poszczególnych zmiennych ilościowych, określono wartość odcinającą (*cut-off*), czułość (*sensitivity*), swoistość (*specificity*), pole pod krzywą ROC (AUC*, ang. area under curve*) i jego 95% przedział ufności (CI 95%), celem predykcji ryzyka rozwoju cukrzycy typu 2 z IFG w przeciągu 9 lat. Dla powyższych czynników ryzyka obliczono także iloraz szans (OR, ang. *odds ratio*) oraz współczynnik ryzyka (HR, ang. *hazard ratio*).

Analizy statystyczne przeprowadzono przy użyciu programu STATISTICA v. 13.3 (StatSoft). Wynik uznano za istotny statystycznie, gdy wartość *p* wynosiła poniżej 0,05.

4. Publikacje naukowe

4.1. Wykaz publikacji naukowych włączonych do rozprawy doktorskiej

Agnieszka Święcicka-Klama

Cykl prac stanowiących rozprawę doktorską

Lp.	Tytuł, autorzy, źródło	IF	PK
1.	**The natural course of impaired fasting glucose.** [AUT. KORESP.] AGNIESZKA ŚWIĘCICKA-KLAMA, [AUT.] KATARZYNA POŁTYN-ZARADNA, ANDRZEJ SZUBA, KATARZYNA ZATOŃSKA. Adv.Exp.Med.Biol. 2021 Vol.1324: Medical Research and Innovation s.41-50, Publikacja w serii wydawnictwa Springer. DOI: 10.1007/5584_2020_571	2,622	20,00
2.	**Anthropometric Indices as Long-Term Predictors of Diabetes in Impaired Fasting Glucose Metabolism: Findings in the PURE Study in Poland.** [AUT. KORESP.] AGNIESZKA ŚWIĘCICKA-KLAMA, [AUT.] KATARZYNA POŁTYN-ZARADNA MARIA WOŁYNIEC, ANDRZEJ SZUBAKA, KATARZYNA ZATOŃSKA. Adv.Exp.Med.Biol. [2022] Publikacja w serii wydawnictwa Springer. DOI: 10.1007/5584_2021_681 [Ahead of print]	2,622*	20,00
3.	**Cardiovascular Risk Factors Drive Impaired Fasting Glucose to Type 2 Diabetes: Findings After a 9-Year Follow-Up in the PURE Study in Poland.** [AUT. KORESP.] AGNIESZKA ŚWIĘCICKA-KLAMA, [AUT.] KATARZYNA POŁTYN-ZARADNA MARIA WOŁYNIEC, ANDRZEJ SZUBA, KATARZYNA ZATOŃSKA. Adv.Exp.Med.Biol. [2022] Publikacja w serii wydawnictwa Springer. DOI: 10.1007/5584_2021_701 [Ahead of print]	2,622*	20,00
Suma:		**7,866**	**60,00**

* IF 2021

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Agnieszka Święcicka-Klama, Katarzyna Połtyn-Zaradna,
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„The Natural Course of Impaired Fasting Glucose”

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The Natural Course of Impaired Fasting Glucose

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Abstract

Impaired glucose regulation, including diabetes and prediabetes, poses a huge global problem not only in health but also in the epidemiological and economic areas. These disorders are often detected too late or remain unrecognized. The article aims to provide a review of the prevalence, etiology, and natural history of impaired fasting glucose (IFG). We focus on the progression of isolated IFG to full-fledged type 2 diabetes and the factors conducive to the development of diabetes. The knowledge about it could help design an optimal management program for the prevention of diabetes in patients with IFG; a program that would be patient-tailored and based on the underlying pathophysiology.

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Keywords

Diabetes · Impaired fasting glucose · Prediabetes · Prevention · Public health

1 Introduction

Carbohydrate metabolism disorders, including type 2 diabetes mellitus and prediabetes, pose a huge global problem not only in health but also in the epidemiological and economic areas. These abnormalities are often detected too late or remain unrecognized. Prediabetes is defined as an intermediate state between normal blood glucose levels and diabetes. The term includes such disorders as impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or raised glycated hemoglobin (HbA1c), each different in the underlying pathophysiology but each associated with a higher risk of developing diabetes. It is estimated that the presence of a prediabetic state increases the average risk for the future development of type 2 diabetes by threefold to tenfold (Garber et al. 2008). Early detection of prediabetes may prevent or delay the development of diabetes and its complications.

Risk factors for the development of type 2 diabetes are established. Nonetheless, it is hard to describe the natural course of prediabetes. Data on the long-term risk of progression from prediabetes, particularly IFG, to full-fledged diabetes and the associated risk factors are still lacking or

inconsistent. The inconsistency results from a variety of inclusion criteria and methodologies used in the available studies. Moreover, the patient cohorts often are highly heterogeneous, with no clear distinction between each prediabetic state, such as isolated IFG, IGT, or both combined. Based on a review of the current literature (Wen et al. 2017; Buysschaert et al. 2016; Chan et al. 2009; Toshihiro et al. 2008; Abdul-Ghani et al. 2006; DeFronzo 2004), it seems there is a need for a better savvy of the etiopathogenesis of IFG and the identification of factors bearing on the progression to diabetes.

2 Definitions and Diagnosis

In 1997, the American Diabetes Association (ADA) defined IFG as an elevated fasting plasma glucose (FPG) level 6.1–6.9 mmol/L (110–125 mg/dL). Six years later, the cutoff level for IFG was lowered to 5.6 mmol/L (100 mg/dL) by the ADA (Nathan et al. 2007) and the International Expert Committee (Gillett 2009; Forouhi et al. 2006), to maximize sensitivity and specificity for predicting diabetes mellitus. Nonetheless, the WHO and the International Diabetes Federation still uphold the 6.1–6.9 mmol/L cutoff glucose recommendation (WHO 2006). In isolated IFG, a 2-h post-load glucose level in the 75 g oral glucose tolerance test (OGTT) is within the normal range (below 7.8 mmol/L), in contrast to IGT, where the 2-h plasma glucose is in a range of 7.8–11.0 mmol/L (140–199 mg/dL) during OGTT.

Prediabetic diagnostic threshold and its verifying tools are still discussed (Huang et al. 2016; Buysschaert et al. 2016). Generally, FPG is used as a screening test for diabetes. OGTT is recommended in patients with a high risk of developing type 2 diabetes mellitus. Elevated HbA1c can be used as another tool for diagnosing prediabetes and diabetes, without distinction between IFG and IGT. According to the ADA guidelines, HbA1c in a range of 5.7–6.4% (39–47 mmol/mol) is considered as prediabetes (ADA 2020), whereas Canadian (Diabetes Canada Clinical Practice Guidelines Expert Committee et al. 2018), British guidelines (Chatterton et al. 2012) have established a higher cutoff point of 6.0 to 6.4% *(*42–47 mmol/mol*)*. The WHO has not approved the HbA1c as a diagnostic screening tool for prediabetes (WHO 2011).

3 Epidemiology

According to the last report of the Centers for Disease Control and Prevention, one in three American adults has prediabetes, mostly men, which approximates 88 M people as of 2018. The prevalence rises with age, reaching nearly 50% in those over 65 years of age. There is no significant difference between races and ethnicities (CDC 2020). The National Health and Nutrition Examination Surveys (NHANES) reported that the overall prediabetes prevalence, based on the FPG and HbA1c, increased from 27.4% in 1999–2002 to 34.1% in 2007–2010. On the other side, the prevalence of IFG remained a little changed amounting to 23.9–26.6% in 1999–2010 (Bullard et al. 2013) and 28.3% in 2011–2014 (Menke et al. 2018). The FPG above the threshold occurred more frequently in men than women, in non-Hispanic whites than in non-Hispanic blacks, and in obese subjects.

Statistically, IFG (defined as FPG 6.1–6.9 mmol/L) is rarer than IGT. In epidemiological studies in different adult populations, the prevalence of IFG ranged widely from 4.7% in Pima Indian adults (Gabir et al. 2000a) to 12.2% in Mexican-Americans (Harris et al. 1998), whereas IGT was prevalent from 11.1% in the Australian population (Dunstan et al. 2002) to 19.4% in Mexican-Americans. Based on the DE CODE Study Group (2003) and Qiao et al. (2003) studies, tallying data from 13 European and 11 Asian studies performed in subjects aged 30–89, IFG appeared more often in men than in women, mostly in young and middle-aged men, whereas IGT was common particularly in women and elderly subjects above 70 years of age. The prevalence of IFG reached a plateau in middle-aged subjects (40–50 years) in most populations. Conversely, the 2 h FPG concentration and, thus,

the prevalence of IGT increased linearly with age (DECODE Study Group 2003; Unwin et al. 2002). Notably, IFG was defined as FPG 6.1–6.9 mmol/L in all the studies above outlined.

A twofold to fourfold increase in IFG prevalence, the larger increases in younger age-groups, has been reported after the redefinition of IFG by ADA, compared with the WHO recommendations (Pankow et al. 2007; Forouhi et al. 2006; WHO 2006). A lowering of the cutoff point for IFG resulted in a nearly 20% increase in the prevalence of isolated IFG and a notable decrease in the prevalence of the isolated IGT. Thus, isolated IFG has become the most common form of a prediabetic state in both Caucasian and Asian cohorts. According to both 1999 WHO and 2003 ADA classifications, the prevalence of isolated IFG is significantly higher in Caucasians than in Asians. As a possible reason, the authors indicate a western-type diet rich in fats and meals with a high glycemic index, but this notion remains to be verified (Yip et al. 2017). In a recent meta-analysis of 46 studies performed in the general population of developed European countries, the overall prevalence of impaired glucose regulation was rated at 22.3%, and the mean prevalence of IGT was 11.4%, with no clear gender differences. In contrast, IFG occurred more frequently in men than in women, with a mean prevalence of 8.4% (Eades et al. 2016).

4 Differences Between Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT) Resulting from Pathophysiology

The IFG and IGT have a significantly different pathophysiologic background. Subjects with isolated IFG have moderate insulin resistance in the liver, disturbed first-phase insulin secretion, and normal muscle insulin sensitivity. The hepatic insulin resistance leads to excessive fasting glucose production and impaired suppression of liver glucose output, resulting in basal hyperinsulinemia. In comparison, individuals with isolated IGT have moderate or severe muscle insulin resistance, impaired first- and second-phase insulin secretion, and reduced β-cell sensitivity to glucose. The muscle insulin resistance results in disturbed glucose uptake after a meal rich in carbohydrates, leading to postprandial hyperglycemia (Wilson 2017; Buysschaert et al. 2016; DeFronzo and Abdul-Ghani 2011; Abdul-Ghani et al. 2006; DeFronzo 2004). Waist circumference (>102 cm for men and > 88 cm for women) and triglyceride/HDL-C ratio (>3.5 for men and > 2.5 for women) are useful indirect indices to identify prediabetic insulin resistance (Gagliardino et al. 2018; Salazar et al. 2013; Alberti et al. 2009).

Interestingly, increased glucose level, reduced insulin sensitivity, and defects in insulin secretion might be seen as early as 13 years before the development of type 2 diabetes (Tabák et al. 2012; Tabák et al. 2009). β-cell dysfunction is also observed, even when FPG remains within a normal range (Kahn et al. 2006; WHO 2006). Given the discordant findings in autopsy (Wen et al. 2017; Butler et al. 2003) and hyperinsulinemic-euglycemic clamp studies (Basu et al. 2013; Perreault et al. 2008), the clinical relevance of these results needs further elucidation. As the categories of impaired glucose regulation often coexist to an extent (DeFronzo and Abdul-Ghani 2011; DeFronzo 2004), we can distinguish isolated IFG, isolated IGT, and a combination of the two. The DECODE and DECODA studies show that a third of the European and Asian populations with IFG, defined according to the current ADA definition as FPG 6.1–6.9 mmol/L, have the coexisting IGT (DECODE Study Group 2003; Qiao et al. 2003). This less restrictive cutoff level of FPG brought about a decrease in the proportion of people with IFG combined with IGT, but it increased the proportion of IGT combined with IFG (WHO 2006). In the Atherosclerosis Risk in Communities (ARIC) Study, isolated IFG was more common in men and black women. Persons with isolated IFG were statistically younger, current smokers, and alcohol consumers than those with IGT. They also had a higher BMI, waist circumference, increased fasting insulin level, higher LDL cholesterol, and a lower content of HDL cholesterol. In contrast,

higher triglyceride content, systolic blood pressure, and leukocyte count were more commonly noticed in persons with isolated IGT (Pankow et al. 2007).

5 Course and Adverse Outcomes

As subjects with IFG are a heterogeneous group, frequently with other concomitant disorders of glucose metabolism, the risk of progression to diabetes widely varies. Nonetheless, IFG should be seen as a risk factor for diabetes and adverse outcomes (WHO 2006). The development of diabetes and its complications is a gradual and complex process. The blood glucose level gradually increases over time until it exceeds the diagnostic criteria for diabetes (Færch et al. 2013). The progression of IFG to diabetes is not a must. A significant proportion of people revert to normoglycemia, or the process halts at the prediabetic stage (Diabetes Canada Clinical Practice Guidelines Expert Committee et al. 2018). Approximately, a third of the subjects with IFG will develop diabetes within 5–7 years (Unwin et al. 2002). Many factors, inter alia, nonuniform inclusion criteria in various studies, different definitions, different diagnostic tests for confirmation of IFG and diabetes, and a wide range of observation and follow-up periods result in significant differences in the findings. For instance, data from the Hoorn Study indicate that 33% of the people with isolated IFG and 64.5% with both IFG and IGT develop diabetes during a mean follow-up of 6.4 years, in comparison with 4.5% of those with normal glucose regulation at baseline. The survey was conducted among nondiabetic Caucasian residents of Hoorn in the Netherlands, aged 50–75 years, from 1989 to 1998 (de Vegt et al. 1998, 2001). An Italian study conducted among telephone company employees aged 40–59 years reported a much lower number of people with isolated IFG and with combined IFG and IGT who progressed to full-fledged type 2 diabetes. The proportion was just 9.1% and 44.4% after 11.5 years of the follow-up period, respectively. That study, however, raises methodological misgivings as there was only one person with isolated IFG and nine persons with both IFG and IGT. The odds ratios were 10.3 (95% confidence interval (CI) 2.2–46.8) and 1.2 (95% CI 0.3–10.2), respectively (Nichols et al. 2007; Vaccaro et al. 1999).

In the multiethnic Mauritius population, where the incidence of diabetes is high, the findings in people, aged 25–79, with IFG observed for 11 years were as follows: 38% (95% CI 28.5–47.5) reverted to normoglycemia, 7% (95% CI 2.0–12.0) retained IFG, 17% (95% CI 9.6–24.4) developed IGT, and 38% (95% CI 28.5–47.5) progressed to diabetes (Soderberg et al. 2004). In a study among Pima Indians, who have the highest prevalence of type 2 diabetes in the world, the risk of progression of prediabetes to diabetes is considerably higher in IFG than that in IGT. The 5-year cumulative incidence of type 2 diabetes in people with normal glucose regulation, isolated IGT, isolated IFG, and IFG/IGT combined was 3.6%, 19.9%, 31.0%, and 41.2%, respectively (Gabir et al. 2000b). In a Hong Kong study, 30.9% (n = 17) persons with IFG reverted to normoglycemia, 43.6% (n = 24) sustained the IFG status, and 25.5% (n = 14) progressed to diabetes after a median follow-up period of 1.12 years. It should be underlined that this study group was small (n = 55) and young (mean age 37.4 ± 9.3 years) but had a high risk of diabetes, including a family history of diabetes or gestational diabetes, overweight, and hypertension. Also, the period of observation was rather short (Ko et al. 2001).

In the Toranomon Hospital Health Management Center Study 3 (TOPICS 3), conducted in 6,241 Japanese participants, aged 24–82, without diabetes at baseline, prediabetes was newly diagnosed in 1,682 subjects. The prediabetic subjects were divided into three groups: 1/ isolated IFG (HbA1c <5.7% and FPG 5.6–6.9 mmol/L), 2/ isolated elevated HbA1c (HbA1c 5.7–6.4% and FPG <5.6 mmol/L), and 3/both HbA1c 5.7–6.4% and FPG 5.6–6.9 mmol/L. The groups consisted of 20.3% (n = 1,270), 6.6% (n = 412), and 6.6% (n = 410) subjects, respectively. Over the mean 4.7 year-long follow-up, diabetes (FPG >7.0 mmol/L, HbA1c >6.5%)

was diagnosed in 6.4% (n = 108), 1.8% (n = 30), and 9.2% (n = 154) of the subjects, respectively (Wilson 2017). According to the Toranomon Hospital Health Management Center Study 4 (TOPICS 4), conducted in a similar cohort with a 5-year follow-up, normoglycemia (neither HbA1c nor FPG elevated) was achieved by 20.5–32.0% of the participants diagnosed as having prediabetes at baseline, based on any one of the four criteria FPG 5.6–6.9 mmol/L, FPG 6.1–6.9 mmol/L, HbA1c 5.7–6.4%, or HbA1c 6.0–6.4% (Heianza et al. 2012).

A meta-analysis of multiple cohort studies shows the absolute annualized risk of progression of impaired glucose metabolism to full-fledged diabetes of 5–10%. The relative risk was 4.66 (95% CI 2.47–6.85) for IFG and 7.54 (95% CI 4.63–10.45) for isolated IFG. For comparison, in subjects with IGT and isolated IGT, the risk ratio was 6.35 (95% CI 4.87–7.82) and 5.52 (95% CI 3.13–7.91), respectively. The highest relative risk was 12.13 (95% CI 4.27–20.00) in a population with both IFG and IGT (Gerstein et al. 2007). These studies show that people with IFG and coexisting other glycemic disorders (IGT, elevated HbA1c, etc.) have a substantially increased risk of developing diabetes. Some authors indicate that all subjects with both FPG 6.1–6.9 mmol/L and HbA1c 6.0–6.4% develop diabetes over 5 years (Diabetes Canada Clinical Practice Guidelines Expert Committee et al. 2018; Heianza et al. 2012). Divergent results concerning the rate at which diabetes mellitus would like to develop stem from the unknown duration of impaired glucose regulations. The only study that traced the development of type 2 diabetes from the onset of abnormal glucose regulation is the Baltimore Longitudinal Study of Aging (Nichols et al. 2007). Of 488 participants with normal glucose regulation, aged 20–89 years, 14% progressed to IFG and 48% developed IGT after 10 years. In the same period, 8% of the participants with IFG and 27% with IGT developed diabetes. The lowest progression rate to diabetes is in the persons with an isolated elevation of FPG (Meigs et al. 2003).

The ADDITION-Denmark study reported that the overall incidence of diabetes is 3.51 (95% CI 3.32–3.72) *per* 1,000 person-years. In comparison with a low-risk reference group, the incidence in persons with prediabetes was significantly higher, amounting to 14.61 (95% CI 11.28–18.92), 21.83 (17.08–27.89), and 40.81 (95% CI 32.19–51.74) for isolated IFG, isolated IGT, and combined IFG and IGT, respectively. The pattern profile of the incidence of diabetes over a 10-year-long follow-up also was different. For the groups of persons with impaired glucose regulation outlined above, the incidence rate peaked during the first 2 years after the baseline tests, whereas it remained at a constant level during the first 6 years in the low-risk persons (Rasmussen et al. 2016).

As discussed above, the progression from prediabetes to diabetes depends on the spate of risk factors. The most frequently mentioned are the following: age; genetic factors including race and ethnicity, family history of diabetes, gestational diabetes, obesity (particularly central obesity), dyslipidemia, hypertension, high FPG, and plasma insulin levels; poor β-cell function; smoking; and sedentary lifestyle (Fonseca 2009; Levitzky et al. 2008). Stratton et al. (2000) reported that the higher the average blood glucose level, the greater is the risk of progression to diabetes and its micro- and macrovascular complications. The American College of Endocrinology and the American Association of Clinical Endocrinologists suggest that the diagnosis of metabolic syndrome is equivalent to a prediabetic state (Garber et al. 2008). Additionally, there are novel risk factors that are conducive to the development of diabetes such environmental contaminants, depression, vitamin D and K deficiency, and iron overload (Wolf et al. 2019; Chatterjee et al. 2015; Wu et al. 2014; Chan et al. 2009). Toshihiro et al. (2008) have also described the potential influence of psychosocial risk factors such as night work shifts, daily life stress, and holding a high administrative post, whereas being a nonsmoker, having a white-collar job, and a low serum alanine aminotransferase (ALT) are mentioned as possible protective factors against the development of diabetes. Nonetheless, there is limited and rather inconsistent knowledge of the factors influencing the

transition from isolated IFG to full-fledged diabetes (Meigs et al. 2003).

Most pro-diabetic factors are also associated with risk for cardiovascular diseases (CVD). Thus, people with prediabetes could benefit from cardiovascular risk factor modifications (Yeboah et al. 2011). Conversely, the risk of isolated IFG for fatal and nonfatal cardiovascular events also is considered. Isolated IGT might be a particularly strong contributor to CVD (Pankow et al. 2007; DECODE Study Group 2003; Unwin et al. 2002). Persons with combined IFG and IGT are at risk of worse cardiovascular outcomes (Diabetes Canada Clinical Practice Guidelines Expert Committee et al. 2018; Buysschaert et al. 2016). Studies indicate that the overlap of IFG and CVD risks decreases when the new IFG definition by ADA is employed (Abraham and Fox 2013; Soulimane et al. 2012; WHO 2006). Current guidelines for the prevention of type 2 diabetes recommend lifestyle interventions as fundamental management. Patients diagnosed with dysglycemia should be counseled to achieve and maintain a 7% body weight reduction and to enhance moderate-intensity physical activity to at least 150 min *per* week (American Diabetes Association 2020). Disappointingly, most people with prediabetes are undiagnosed and untreated. Statistics are alarming. According to the National Health and Nutrition Examination Survey (NHANES) performed in the US adult population in 2005/2006, solely 3.4% of persons with IFG and/or IGT reported that their physicians diagnosed them as being at the prediabetic stage. Only was a third of them counseled on physical activity and diet. Of those who reported performing physical exercise, only did half fulfill the then ADA recommendations to this end (Karve and Hayward 2010).

There is strong evidence that lifestyle modifications are effective in people with IGT. Most studies have been performed in persons with isolated IGT or combined IFG and IGT, such as the Finnish Diabetes Prevention Study (Toumilehto et al. 2013), the Diabetes Prevention Program Outcomes Study (Knowler et al. 2009), the Indian Diabetes Prevention Program (Ramachandran et al. 2006), the Diabetes Prevention Program Research Group (Knowler et al. 2002), and the Da Qing IGT and Diabetes Study (Pan et al. 1997). It remains unclear whether a similar effect is attainable in a group with isolated IFG (Huang et al. 2016; Rasmussen et al. 2016; Saito et al. 2011). Studies primarily focus on weight loss and increasing physical activity. There is a need to better understand how food and diet influence β-cell function and insulin sensitivity (Guess 2018). Preventive pharmacotherapy should be considered in people with dysglycemia, particularly in those with obesity, under 60 years of age, and in women with a history of gestational diabetes (ADA 2020). Out of the several drugs that could prevent or delay the onset of diabetes, such as metformin (Knowler et al. 2009; Knowler et al. 2002), glucagon-like peptide-1 receptor agonist (Kim et al. 2013), thiazolidinedione (DeFronzo et al. 2013; Hanley et al. 2010; DREAM et al. 2006), α-glucosidase inhibitors (Chiasson et al. 2002), or orlistat (Torgerson et al. 2004), only has metformin been approved for diabetes prevention (American Diabetes Association 2020).

6 Conclusions

In conclusion, the progression of impaired fasting glucose to full-fledged diabetes mellitus is not inevitable. Impaired fasting glucose and impaired glucose tolerance differ in the prevalence, underlying pathophysiology, risk of conversion to diabetes, mortality, and cardiovascular outcomes. Risks are substantially higher when impaired fasting glucose coincides with impaired glucose tolerance. Further studies are needed for a better understanding of how to delay or prevent the progression of isolated impaired fasting glucose to diabetes, regarding lifestyle, dietary, and pharmacological interventions. Individually tailored interventions based on the underlying pathophysiology should be performed in the optimal management program for diabetes prevention in patients with impaired glucose regulation.

Conflicts of Interest The authors declare no conflict of interest concerning this article.

Ethical Approval This review article does not contain any studies with human participants or animals directly performed by any of the authors.

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4.3. Publikacja nr 2

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„Anthropometric Indices as Long-Term Predictors of Diabetes in Impaired Fasting Glucose Metabolism: Findings in the PURE Study in Poland”

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Impaired Fasting Glucose and Progression to Type 2 Diabetes: Prediction Based on Anthropometric Measurements and Findings After 9 Years of Follow-Up in the PURE Study in Poland

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Abstract

This study aimed to assess the predictive value of anthropometric measurements in impaired fasting glucose progression to type 2 diabetes (T2DM) after 9 years of follow-up of the Prospective Urban and Rural Epidemiology (PURE) study run in Poland. The study group consisted of 283 patients aged 54.3 ± 8.9 years who had impaired fasting glucose at baseline and completed a 9-year-long follow-up. We analyzed body weight, height, waist (WC) and hip (HC) circumferences, waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), body mass index (BMI), and body adiposity index (BAI). Most individuals were overweight or obese according to BMI. Obesity occurred more often in men than women. The analysis highlighted the following three anthropometric parameters WHtR, BMI, and WC, each having equally good predictive power concerning the development of full-fledged T2DM in people with impaired fasting glucose. In conclusion, we confirmed the distinct harmfulness of obesity and pointed out the potential of easy-measured anthropometric parameters to self-control the risk of passing the impaired fasting glucose into T2DM.

Keywords

Anthropometry · Diabetes · Impaired fasting glucose · Obesity · Prediabetes · PURE study

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1 Introduction

Impaired fasting glucose is a disorder of glucose metabolism. It is defined as the elevated fasting plasma glucose level of 5.6–6.9 mmol/L (100–125 mg/dL) by the American Diabetes Association and the International Expert Committee. According to the WHO and International Diabetes Federation's (IDF) criteria, the cutoff is at a slightly higher level of 6.1 mmol/L (110 mg/dL), but the upper limit remains the same (WHO 2000; IDF 2019). People with impaired fasting glucose are referred to as having prediabetes, indicating an increased risk for the future development of type 2 diabetes (T2DM). It is estimated that prediabetics have a three- to tenfold higher risk of developing full-fledged T2DM when compared to the general population (Garber et al. 2008). In the Polish ramification of the international Prospective Urban and Rural Epidemiology (PURE) study, patients with impaired fasting glucose had a 2.7-fold increased risk of T2DM than normoglycemic ones (Zatońska et al. 2020).

The course of impaired fasting glucose varies widely because it is a gradual and complex process dependent on several factors. A considerable proportion of individuals revert to normoglycemia or retain impaired fasting glucose. In others, the blood glucose level gradually increases over time until full-fledged T2DM develops (Święcicka-Klama et al. 2021; Færch et al. 2013). A 9-year cumulative incidence of T2DM is estimated at 38% (95% CI 10–70%) in individuals with isolated impaired fasting glucose and 84% (95% CI 74–91%) in those with combined impaired fasting glucose and impaired glucose tolerance. After the same time, 17% (95% CI 14–22%) reverted from prediabetes to normoglycemia (Richter et al. 2018).

The impaired fasting glucose is a common disorder that affects approximately 8.4% of Europeans, significantly more often males than females (Eades et al. 2016). However, verifiable data on the worldwide prevalence of impaired fasting glucose are still lacking. In the PURE study and the Polish-Norwegian study (PONS), two cohort studies performed in Poland, the prevalence rates of impaired fasting glucose are as high as 28% and 29%, respectively. These figures might even be underestimated because many people are undiagnosed or unaware of the condition (Zatońska et al. 2017; Zatońska et al. 2011). There are remarkable differences in both studies in the mean body weight and fat distribution among individuals with normoglycemia, impaired fasting glucose, and T2DM. The risk of T2DM is increased in people with abdominal obesity.

Several indicators define obesity. The most commonly used one is body mass index (BMI) recommended by the WHO (WHO 2000). However, BMI does not provide any information about the regional fat distribution in the body. The amount of abdominal fat may considerably vary over a narrow range of BMI. There are two types of obesity depending on the location of adipose tissue: abdominal also called android or central obesity and gluteal-femoral, called gynoid obesity. The main indicators of abdominal obesity are waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR). The body adiposity index (BAI) has been designed to assess body composition (Bergman et al. 2011). This study aimed to assess the influence of the anthropometric indicators outlined above on the progression of impaired fasting glucose to full-fledged T2DM in the Polish cohort of the PURE study after 9 years of follow-up.

2 Methods

2.1 Study Design

The PURE study is an epidemiological prospective cohort study involving over 20 countries of diverse socioeconomic levels. This global research aims to investigate the influence of economic and urbanization changes on community health. It is focused on the environmental risk factors such as diet, physical activity, tobacco, alcohol consumption, and others in the development of chronic non-communicable diseases, notably, T2DM, obesity, and cardiovascular

diseases. The Polish ramification of the PURE study involved the urban and rural residents, aged 30–85, from the city of Wroclaw and its surroundings in the province of Lower Silesia. The study was designed and conducted according to the international PURE project protocol (Corsi et al. 2013; Teo et al. 2009). Briefly, baseline data were collected by trained staff between 2007 and 2010. At the onset, patients completed standardized questionnaires on the characteristics of household (family structure, income, and living conditions), health-related habits (smoking, alcohol consumption, physical activity, and diet pattern), and physical and mental health (stress, anxiety, and depression). Health status data reported by patients were counter compared with the available medical records. Then, patients underwent blood tests and blood pressure and standardized anthropometric measurements.

2.2 Participants and Measurements

Baseline cohort consisted of 2,036 participants from both urban and rural areas. Out of this cohort, 283 patients of the mean age of 54.3 ± 8.9(SD) years (F/M – 186/97) who had impaired fasting glucose metabolism were eligible for inclusion in the present study. The impairment was defined as the mean fasting plasma glucose level of 5.99 ± 0.38 mmol/L (range of 5.6 to 6.9 mmol/L). The patients were interrogated over the phone about morbidity and hospitalizations on the yearly basis and were invited for an office examination every 3 years. The patients who were diagnosed with diabetes in the past, taking glycemia-lowering medications, had the fasting plasma glucose level exceeding 6.9 mmol/L at the initial screening, or those failing to complete examinations after 9 years of follow-up were excluded.

Venous blood samples were taken after an overnight 8-h-long fast. The fasting plasma glucose level was assessed by an enzymatic method. The following anthropometric indices were calculated:

- Body mass index (BMI; kg/m^2).
- Waist-to-hip ratio (WHR; cm/cm.
- Waist-to-height ratio (WHtR; cm/cm).
- Body adiposity index (BAI): hip circumference (cm)/[height (m)$^{1.5}$ – 18] (Bergman et al. 2011).

Obesity was defined as follows:

- WC ≥80 cm in women and ≥ 94 cm in men, according to the WHO and IDF's criteria for Caucasians (WHO 2000; IDF 2019; Alberti et al. 2006)· and WHR ≥0.85 in women and ≥0.9 in men (WHO 2008).
- WHtR ≥0.58 in women and ≥ 0.63 in men, which are the cutoff levels for abdominal obesity (Ashwell and Gibson 2014; Ashwell et al. 2012).
- BMI ≥ 30 kg/m^2 (WHO 2000).

2.3 Statistical Analysis

Quantitative data distribution was checked using the Kolmogorov-Smirnov and the Shapiro-Wilk tests. The significance of differences between independent groups was evaluated using one-way ANOVA, Tukey's HSD post hoc test, and a *t*-test. The Pearson chi-square test was used for the evaluation of associations between qualitative variables. For the risk prediction of the progression of impaired fasting glucose into T2DM, receiver operating characteristic (ROC) curves were performed. The influence of risk factors after 9 years of follow-up was determined by calculating odds ratios (OR) and hazard ratios (HR). A p-value <0.05 defined statistically significant differences. Analyses were performed using a commercial Statistica v13.3 package (StatSoft Inc.; Tulsa, OK).

3 Results

The socio-demographic characteristics of the study cohort at baseline are presented in Table 1. There were similar about 50% proportions of urban and rural residents.

t.1 **Table 1** Baseline demographics of study patients ($n = 283$)

t.2		*n* (%)
t.3	Age 54.3 ± 8.9; range 32–79 years	
t.4	Place of residence:	
t.5	Urban	148 (52.3)
t.6	Rural	135 (47.7)
t.7	Sex:	
t.8	Women	186 (65.7)
t.9	Men	97 (34.3)
t.10	Age group:	
t.11	Under 45 years	41 (14.5)
t.12	45–64 years	209 (73.9)
t.13	Over 64 years	33 (11.7)

Baseline anthropometric measurements are presented in Table 2. WC, weight, and height differed significantly between men and women. Men were more likely to have central obesity based on WHR (87.6% vs. 46.8%; $p < 0.001$). Most patients (71.4%) were obese, regardless of gender, according to WC. Most (74.2%) were also classified as overweight or obese according to BMI score, with the mean BMI of 28.8 ± 5.2 kg/m^2 ranging widely from 18.1 to 47.0 kg/m^2. A significant sex difference was observed in BAI. The mean BAI value was higher in women than men (34.1 ± 6.0 vs. 27.1 ± 2.9, respectively). Similar obesity rates were obtained using either BMI or WHtR. However, the rate of obesity was highest using WC and lowest using BAI assessments. Abdominal obesity was present in 39.2% to 71.4% of all patients, depending on the indicator applied.

The baseline data outlined above were the foundation on which the stratification of patients into normoglycemic, persisting impaired fasting glucose, and full-fledged T2DM was based according to the development of differential changes in glucose metabolism after 9 years of follow-up. The stratification was referenced to these baseline data, which was the core rationale of the PURE study aimed at sorting out the most meaningful anthropometric indicators for the prediction of the development of diabetes over time. The anthropometric indicators, including sex differences, were relatively stable over the observation time. Any endpoint changes in the indicators would have been inconsistent with the project rationale consisting of the prediction of diabetes development based on the size of these indicators assessed at baseline. Thus, any such changes were not considered the primary outcomes and were not evaluated in this report.

After 9 years of follow-up, the study patients underwent medical check-ups, including face-to-face interviews, anthropometric measurements, arterial blood pressure measurements, and fasting plasma glucose tests. They were classified into three groups based on the fasting plasma glucose level: Group A, normoglycemia (<5.6 mmol/L); Group B, persistently impaired fasting glucose (5.6–6.9 mmol/L); and Group C, diagnosed with T2DM irrespective of the need to use hypoglycemic medications (>6.9 mmol/L). During the observation period, 138 patients (49%) reverted to normoglycemia, 86 (30%) remained with impaired fasting glucose, and 59 (21%) progressed to T2DM. Hypoglycemic medications were regularly taken by 55 (93.2%) patients with T2DM. Those who developed diabetes were 4.9 years and 3.6 years senior to those from the normoglycemic and impaired fasting glucose groups, respectively ($p < 002$). There were no significant inter-group differences in the place of residence or sex (Table 3).

Further, we found significant differences between the prediabetic patients who progressed to T2DM and the other two groups concerning all the anthropometric parameters investigated except for height. Most patients in Group C (91.5%) had WC and BMI above normal

t.1 **Table 2** Anthropometric data of the study cohort at baseline

t.2		All patients ($n = 283$)	Women ($n = 186$)	Men ($n = 97$)	p
t.3	Waist circumference (WC; cm)	94.4 ± 14.1 (62–135)	91.1 ± 14 (62–127)	100.7 ± 11.6 (78–135)	
t.4	*Patient stratification*	*n (%)*	*n (%)*	*n (%)*	0.300
t.5	Normal weight	81 (28.6)	49 (26.3)	32 (33.0)	
t.6	Abdominal obesity	202 (71.4)	137 (73.7)	65 (67.0)	
t.7	Hip circumference (HC; cm):	105.4 ± 10.3 (83–152)	106.1 ± 11.5 (83–152)	104.2 ± 7.4 (90–127)	0.145
t.8	Waist-to-hip ratio (WHR)	0.89 ± 0.09 (0.69–1.21)	0.86 ± 0.08 (0.69–1.12)	0.97 ± 0.07 (0.80–1.21)	<0.001
t.9	*Patient stratification*	*n (%)*	*n (%)*	*n (%) %*	<0.001
t.10	Normal weight	111 (39.2)	99 (53.2)	12 (12.4)	
t.11	Abdominal obesity	172 (60.8)	87 (46.8)	85 (87.6)	
t.12	Height (cm):	165.6 ± 8.9 (143–193)	160.8 ± 5.7 (143–176)	174.9 ± 6.1 (160–193)	<0.001
t.13	Waist-to-height ratio (WHtR)	0.57 ± 0.08 (0.37–0.85)	0.57 ± 0.09 (0.37–0.85)	0.58 ± 0.06 (0.43–0.75)	0.415
t.14	*Patient stratification*	*n (%)*	*n (%)*	*n (%)*	0.244
t.15	Normal weight	172 (60.8)	108 (58.1)	64 (66.0)	
t.16	Abdominal obesity	111 (39.2)	78 (41.9)	33(34.0)	
t.17	Body adiposity index (BAI; %)	31.7 ± 6.1 (20.1–60.0)	34.1 ± 6.0 (20.8–60.0)	27.1 ± 2.9 (20.1–34.7)	<0.001
t.18	Body weight (kg):	79.3 ± 16.9 (44–145)	74.2 ± 15.1 (44–128)	89.2 ± 15.8 (59–145)	<0.001
t.19	Body mass index (BMI; kg/m^2)	28.8 ± 5.2 (18.1–47.0)	28.71 ± 5.65 (18.1–47.0)	29.08 ± 4.30 (21.4–40.5)	0.577
t.20	*Patient stratification*	*n (%)*	*n (%)*	*n (%)*	0.278
t.21	Underweight	2 (0.7)	2 (1.1)	0 (9.0)	
t.22	Normal weight	71 (25.1)	51 (27.4)	20 (20.6)	
t.23	Overweight	102 (36.0)	61 (32.8)	41 (42.3) 42.3%	
t.24	Obesity	108 (38.2)	72 (38.7)	36 (37.1) 37.1%	

t.25 Continuous data are means ±SD (min-max); discrete data are counts (%); p-value denotes the significance of differences between sexes

t.1 **Table 3** Demographics of patients stratified into three groups based on the level of blood glucose after 9 years of follow-up

	Group A	Group B	Group C	
t.3	Normoglycemia	IFG	Diabetes	
t.4	($n = 138$)	($n = 86$)	($n = 59$)	p
t.5	Age (years):	52.9 ± 9.7 (33–75)	54.2 ± 8.4 (32–79)	57.8 ± 6.7 (45–77)	0.002
t.6	Place of residence	*n (%)*	*n (%)*	*n (%)*	0.159
t.7	Urban	58 (42.0)	47 (54.7)	30 (50.8)	
t.8	Rural	80 (58.0)	39 (45.3)	29 (49.2)	
t.9	Sex	*n (%)*	*n (%)*	*n (%)*	0.062
t.10	Females	100 (72.5)	50 (58.1)	36 (61.0)	
t.11	Males	38 (27.5)	36 (41.9)	23 (39.0)	

t.12 Continuous data are means ±SD (min-max); discrete data are counts (%). *IFG,* impaired fasting glucose; p-value denotes significant age differences between Group A and both Group B and Group C

(91.5% and 98.3%, respectively). Only two patients were underweight, and both were normoglycemic after 9 years of follow-up (Group A). The BMI was lower than that at baseline in Group A, remained about the same in Group B, and was higher in Group C. Similar trends were noticeable concerning body weight, WC, WHR, and WHtR (Table 4).

t.1 **Table 4** Anthropometric data of the study cohort stratified into three groups based on the level of blood glucose after 9 years of follow-up

	Group A	Group B	Group C	
	Normoglycemia	IFG	Diabetes	
	(*n = 138*)	(*n = 86*)	(*n = 59*)	*p*
Waist circumference (WC; cm)	89.4 ± 13.6 (62–126)	95.9 ± 12.3 (71–127)	104.0 ± 12.7 (67–135)	<0.001
Patient stratification	*n (%)*	*n (%)*	*n (%)*	<0.001
Normal weight	57 (41.3)	19 (22.1)	5 (8.5)	
Abdominal obesity	81 (58.7)	67 (77.9)	54 (91.5)	
Hip circumference (HC; cm)	103.2 ± 10.3 (83–152)	105.1 ± 8.4 (90–130)	111.0 ± 10.9 (85–139)	<0.001
Waist-to-hip ratio (WHR)	0.86 ± 0.09 (0.69–1.19)	0.91 ± 0.08 (0.74–1.11)	0.94 ± 0.09 (0.77–1.21)	<0.001
Patient stratification	*n (%)*	*n (%)*	*n (%)*	<0.001
Normal weight	73 (52.9)	26 (30.2)	12 (20.3)	
Abdominal obesity	65 (47.1)	60 (69.8)	47 (79.7)	
Height (cm):	165.0 ± 8.5 (150–193)	166.9 ± 9.0 (149–187)	165.0 ± 9.6 (143–188)	0.263
Waist-to-height ratio (WHtR)	0.54 ± 0.08 (0.37–0.76)	0.58 ± 0.07 (0.43–0.85)	0.63 ± 0.08 (0.43–0.78)	<0.001
Patient stratification	*n (%)*	*n (%)*	*n (%)*	<0.001
Normal weight	102 (73.9)	49 (57.0)	21 (35.6)	
Abdominal obesity	36 (26.1)	37 (43.0)	38 (64.4)	
Body adiposity index (BAI; %)	30.9 ± 5.9 (20.8–60.0)	31.0 ± 5.4 (20.1–46.2)	34.7 ± 6.9 (23.7–54.6)	<0.001
Body weight (kg)	74.2 ± 16.3 (44–145)	81.1 ± 15.1 (56–113)	88.9 ± 16.4 (47–136)	<0.001
Body mass index (BMI; kg/m^2)	27.1 ± 5.0 (18.1–46.2)	29.0 ± 4.4 (20.9–41.4)	32.6 ± 5.0 (19.6–47.0)	<0.001
Patient stratification	*n (%)*	*n (%)*	*n (%)*	<0.001
Underweight	2 (1.4)	0 (0.0)	0 (0.0)	
Normal weight	50 (36.2)	20 (23.3)	1 (1.7)	
Overweight	55 (39.9)	29 (33.7)	18 (30.5)	
Obesity	31 (22.5)	37 (43.0)	40 (67.8)	

t.27 Continuous data are means ±SD (min-max); discrete data are counts (%). *IFG,* impaired fasting glucose; p-value denotes significant age differences between Group A and both Group B and Group C

The ROC curves showed that BMI and age had the highest sensitivity of 96.6% but lowest specificity of 45.1% and 26.8%, respectively. The highest specificity was observed for WHtR and WC (87.1% and 81.2%, respectively). The best parameters for the prediction of progression of impaired fasting glucose to T2DM over 9 years were the following in the descending order: WHtR (AUC 0.757; 95% CI 0.69–0.83), BMI (AUC 0.755; 95% CI 0.69–0.82), and WC (AUC 0.750; 95% CI 0.68–0.82). Odds ratios and hazard ratios were calculated for all independent risk factors, after calculating the cutoff values for each of them. The hazard ratios for the development of diabetes were highest for the BMI >26.9 kg/m^2, WC >104 cm, and WHtR >0.64 amounting to 16.56, 4.34, and 4.11, respectively. These results are shown in detail in Table 5 (Fig. 1).

4 Discussion

The present study investigated the contribution of anthropometric indicators to the risk prediction for the development of T2DM in people with impaired fasting glucose. People who developed full-fledged T2DM after 9 years of follow-up had a larger body mass than those who returned to normoglycemia or in whom impaired fasting

t.1 **Table 5** Risk prediction of progression of impaired fasting glucose to full-fledged type 2 diabetes after 9 years of follow-up

t.2	Risk factor	Cutoff value	Sensitivity (%)	Specificity (%)	AUC (95% CI)	Odds ratio (95% CI)	Hazard ratio (95% CI)
t.3	WHtR	> 0.64	52.5	87.1	0.757 (0.69–0.83)	7.44 (3.91–14.16)	4.11 (2.47–6.86)
t.4	BMI	> 26.9 kg/m^2	96.6	45.5	0.755 (0.69–0.82)	23.83 (5.68–100.00)	16.56 (4.04–67.80)
t.5	WC	> 104 cm	62.7	81.3	0.750 (0.68–0.82)	7.29 (3.90–13.60)	4.34 (2.56–7.36)
t.6	Body weight	> 83 kg	64.4	70.1	0.711 (0.64–0.78)	4.24 (2.32–7.76)	3.07 (1.80–5.22)
t.7	HC	> 104 cm	76.3	55.8	0.700 (0.63–0.77)	4.06 (2.11–7.81)	3.10 (1.70–5.65)
t.8	WHR	> 0.95	49.2	77.7	0.669 (0.59–0.74)	3.36 (1.85–6.13)	2.50 (1.50–4.16)
t.9	BAI	> 30.5%	74.6	54.5	0.660 (0.58–0.74)	3.51 (1.85–6.67)	2.75 (1.53–4.95)
t.10	Age	> 49 years	96.6%	26.8%	0.638 (0.57–0.71)	10.4 (2.47–44.0)	7.99 (1.95–32.70)

t.11 *WHtR* waist-to-hip ratio, *BMI* body mass index, *WC* waist circumference, *HC* hip circumference; *WHR* waist-to-hip ratio, *BAI* body adiposity index

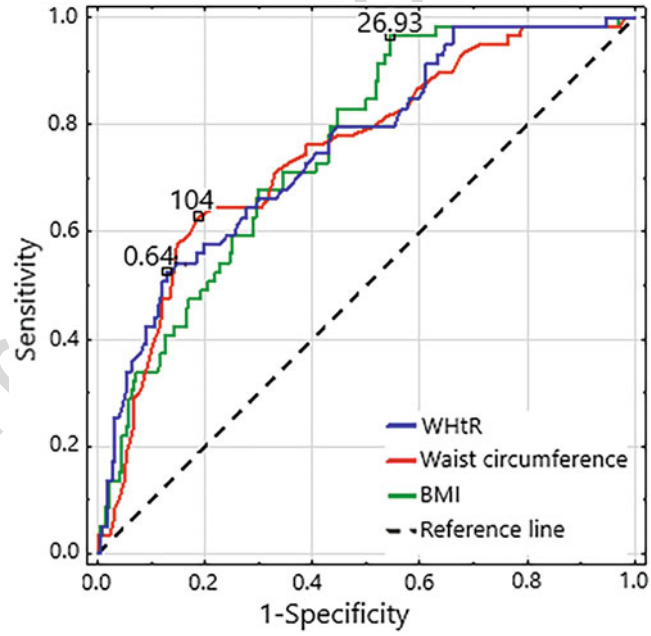

Fig. 1 Receiver operating characteristic (ROC) curves of waist-to-hip ratio (WHtR), body mass index (BMI), and waist circumference for the prediction of type 2 diabetes development after 9 years of follow-up

glucose remained unchanged. Significant contributions were noticed for all obesity-related parameters, except for body height that does not directly associate with obesity. Of note, almost all people (98.3%) with impaired fasting glucose who progressed to T2DM were overweight or obese according to the BMI classification. These findings are consistent with the evidence that excess body weight is a major risk factor for the development of diabetes (WHO 2000).

Obesity is a heterogeneous condition due to individual differences in the regional fat distribution, especially concerning the accumulation in intra-abdominal fat depots. An excess of adipose tissue in the abdominal cavity (visceral and/or subcutaneous fat) is associated with several metabolic disorders, including dyslipidemia, endothelial dysfunction, insulin resistance, hyperinsulinemia, glucose intolerance, or T2DM. The adipose tissue is a large endocrine organ synthesizing numerous

bioactive compounds that influence metabolic homeostasis. Particularly, peptide hormones, called adipocytokines, affect both glucose and lipid metabolism (Gastaldelli et al. 2017; Després 2012).

The present study focused on the indicators of central obesity, such as waist circumference, waist-to-hip ratio, and waist-to-height ratio. The percentage of people with android obesity ranged broadly from 39.2% to 71.4% depending on the parameter. The waist circumference was associated with a much higher rate of obesity (71.4%) than the other parameters were. However, all the parameters investigated significantly contributed to the progress of impaired fasting glucose to T2DM after 9 years of follow-up. The BAI was used to assess how the amount of adipose tissue could contribute to the development of diabetes in people with impaired fasting glucose. This index enables the calculation of the percentage of body fat using a formula that includes just the height and hip circumference. Bergman et al. (2011) have suggested that the index is superior to BMI because it correlates well with the assessment of body fat measured by the dual-energy X-ray absorptiometry (DEXA). In the present study, BAI was significantly higher in women than men (34.1 $\pm$ 6.0 vs. 27.1 $\pm$ 2.9, respectively), which contrasted with BMI. The difference between the two indicators could be caused by a higher percentage of body fat in women. After 9 years of follow-up, the percentage of body fat in the group of people who progressed to full-fledged T2DM was considerably higher than in the other groups ($p < 0.001$).

Although most obesity indicators contribute to the prediction of diabetes development, an ideal parameter determining the risk of progression of impaired fasting glucose to T2DM is yet to be found. In the present study, ROC curves were constructed attempting to identify people with impaired fasting glucose who could likely develop T2DM after 9 years of follow-up based on anthropometric parameters. The age and BMI showed the highest sensitivity to this end; however, the specificity of the two indicators was lowest. The cutoff point for BMI was slightly above the overweight threshold amounting to 26.9 kg/m^2. The low specificity might stem from the inability of BMI to provide information about body composition or fat distribution. BMI may spuriously indicate obesity in an athletically muscular young man. Okorodudu et al. (2010) have shown that BMI may misclassify above 50% of obese subjects as non-obese when compared to body fat percentage. BAI has been supposed to eliminate the limitations of BMI, but recent studies show no advantage of it over both BMI and basic measurements of abdominal obesity such as waist circumference or waist-to-hip ratio (Lam et al. 2015; Bennasar-Veny et al. 2013; Vinknes et al. 2013; Schulze et al. 2012). The present findings are in line with those showing no distinct superiority of BAI over other indicators. Based on the ROC curves, WHtR had the highest AUC of 0.757, being the best predictor of diabetes, followed by BMI with 0.755, and waist circumference with 0.750. WHtR, having the universal cutoff value of 0.5 irrespective of age, sex, or ethnicity and taking body height and waist circumference into account, might be a meaningful indicator of central obesity (Ashwell and Gibson 2014).

The waist circumference tends to be larger in tall people, including those with normal weight. Potential advantages of WHtR over the waist circumference, waist-to-hip ratio, and BMI have been suggested by previous studies (Dong et al. 2016; Bennasar-Veny et al. 2013), although some results are contentious making the issue unsettled (Lam et al. 2015). Currently, the WHO recommends the use of BMI and either waist circumference or waist-to-hip ratio whenever possible (WHO 2008). In people with BMI greater than 35 kg/m^2, the waist circumference measurement becomes meaningless (NIH 2000).

In the present study, the mean BMI in people with impaired fasting glucose was 28.8 kg/m^2 at baseline. This value was comparable to the 29.4 kg/m^2 in people with impaired fasting glucose in the PONS study (Zatońska et al. 2011) but somehow higher than the 27.1 kg/m^2 in the general population of the Multicenter National Population Health Examination Survey (WOBASZ II) (Stepaniak et al. 2016). We found that the prevalence of overweight and obesity was 36% and 38.2%, respectively, while the respective figures

were 36% and 24% in the WOBASZ II study. The abdominal overweight according to the IDF's (2019) criteria (waist circumference $\geq$ 94 cm in men and $\geq$ 80 cm in women) was observed in 67% of men and 73.7% of women in the present study. These figures were considerably higher than those in the general population in the WOBASZ II study (27.2% of men and 21.7% of women). The differences above outlined were due likely to a varying association of obesity with disorders of carbohydrate metabolism and other environmental determinants (Zdrojowy-Wełna et al. 2018).

In the present 9-year-long follow-up ramification of the PURE study, despite a significant proportion of obesity, a relatively high percentage of patients with impaired fasting glucose returned to normoglycemia (42%), and fewer people developed diabetes (21%). These findings are comparable with those of the 6-year-long PURE study where the reversion to normoglycemia was in 47% of people and another 23.8% developed T2DM (Zatońska et al. 2020).

This study has several limitations. It was a cross-sectional observational study with a significant majority of women and middle-aged people. Secondly, a single fasting blood glucose test was used to categorize patients into the normoglycemia, impaired fasting glucose, and diabetes groups. There was neither an oral glucose tolerance test nor a glycated hemoglobin test performed. This could result in misdiagnosis in some cases. However, the impaired glucose tolerance as an outstanding result is standardly used in epidemiological studies, including the PURE study worldwide (Dagenais et al. 2016).

In conclusion, obesity is strongly associated with an increased risk for the development of type 2 diabetes as a sequela of impaired fasting glucose. The obesity-related anthropometric indicators such as the waist-to-height ratio, body mass index, and waist circumference seem the best predictors of diabetes. Therefore, it is recommendable to introduce these simple measurements for self-assessment and control in people with impaired fasting glucose to help predict the potential development of diabetes. The calculated risk would allow taking appropriate preventive and anticipatory measures in prediabetic individuals.

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Conflicts of Interest The authors declare no conflicts of interest concerning this article.

Ethical Approval All procedures performed in studies involving human participants followed the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of Wroclaw Medical University (permit no. KB-443/2006).

Informed Consent Written informed consent was obtained from all individual participants included in the study.

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4.4. Publikacja nr 3

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"Cardiovascular Risk Factors Drive

Impaired Fasting Glucose to Type 2 Diabetes:

Findings After a 9-Year Follow-Up in the PURE Study in Poland"

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Cardiovascular Risk Factors Drive Impaired Fasting Glucose to Type 2 Diabetes: Findings After a 9-Year Follow-Up in the PURE Study in Poland

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Abstract

This study aimed to evaluate the role of risk factors included in the Framingham Risk Score for hard coronary heart disease (CHD) in the development of type 2 diabetes (DM) in patients with impaired fasting glycemia (IFG) after a 9-year follow-up. The research was part of the Polish insight into the international Prospective Urban and Rural Epidemiology (PURE) study. The cohort consisted of 283 subjects aged 54.3 ± 8.9 years who were diagnosed with IFG at baseline and then completed after a 9-year follow-up. The main risk factors for both CHD and DM evaluated were smoking, arterial hypertension, abnormal lipid profile, and family medical history. Most participants had both untreated or poorly controlled hypertension and dyslipidemia. Those who developed full-fledged DM over time were older and had significantly higher levels of fasting plasma glucose, lipid parameters, and mean blood pressure records. In conclusion, we confirmed that early diagnosis of dyslipidemia and hypertension, along with the treatment optimization of these conditions, could prevent or reduce the risk of DM and adverse cardiovascular outcomes. The study highlighted a large-scale problem of the modifiable risk factors that could jeopardize the health status in patients with IFG in the long range and pointed to targeted preventive measures.

Keywords

Coronary heart disease · Diabetes type 2 · Framingham Risk Score · Impaired fasting glucose · Prediabetes · PURE study

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1 Introduction

Diabetes mellitus type 2 (DM) and coronary heart disease (CHD) are two common and often coexisting pathologies. Chronically increased plasma glucose is conducive to atherosclerosis, a promotor of both diseases. There is evidence that atherosclerotic processes, notably chronic inflammation and endothelial injury, begin years before the diagnosis of DM, in the prediabetic stage (Poznyak et al. 2020; Funk et al. 2012; Aronson and Rayfield 2002). The Framingham Heart Study is the longest-running and most recognizable epidemiological study that investigates cardiovascular risk factors (Andersson et al. 2021). The main factors such as gender, age, cigarette smoking, high blood pressure, increased total cholesterol (TC), and decreased high-density lipoprotein cholesterol (HDL-C) were incorporated into the 10-year CHD risk calculator called the Framingham Risk Score (FRS) (Wilson et al. 1998). FRS has become a simple and useful clinical tool for the assessment of CHD risk and individualized treatment. It has been made for the American white population aged 30–79 primarily undiagnosed with CHD, DM, or intermittent claudication and then validated for other ethnicities and included in the recommendations of the National Cholesterol for Education Adult Treatment Panel III (Andersson et al. 2021; D'Agostino 2001). FRS has become so clinically useful that now it is evaluated in other pathologies like in metabolic disorders or frailty (Shi et al. 2021; Jahangiry et al. 2017).

Prediabetes and CHD share multiple risk factors, including smoking, obesity, abnormal lipids, hypertension, physical activity, and unhealthy dietary patterns. However, populations tend to develop these conditions more or less frequently, despite the similar occurrence of risk factors. The INTERHEART study investigated population differences depending on a country's level of development (Yusuf et al. 2004). The international Prospective Urban and Rural Epidemiology (PURE) study, which is a successor to the INTERHEART study, has been designed to investigate the influence of socioeconomic (urban transition), sociocultural (health behavior), and individual (psychosocial, genetic) factors on the development of chronic noncommunicable diseases (Teo et al. 2009).

The current study is part of the PURE study that includes the Polish population with impaired fasting glucose (IFG). There is strong evidence that individuals with IFG carry an increased risk of developing both DM and atherosclerotic cardiovascular disorders, notably CHD (Cai et al. 2020; Brannick and Dagogo-Jack 2018; DeFronzo and Abdul-Ghani 2011; Barr et al. 2007; Stratton et al. 2000). However, limited data are available that evaluate the influence of the risk factors included in the Framingham outcome model on the progression of IFG to full-fledged diabetes. These data would be significant because these risk factors often coexist with IFG, are common in the population, and appreciably contribute to the health hazard and adverse cardiovascular outcomes. A good understanding and practical knowledge of risk factors would enable to design and implement more effective preventive strategies both for DM and CHD. Therefore, the present study aims to evaluate the role of cardiovascular risk factors included in the Framingham Risk Score for the development of CHD and DM in patients with IFG after a 9-year follow-up.

2 Methods

2.1 Study Design and Participants

The PURE study is a large-scale international cohort study, engaging countries with different statuses of socioeconomic development. One of the aims of the study is to investigate the influence of biological, behavioral, social, and environmental risk factors (diet, physical activity, tobacco, alcohol, and the like) for chronic noncommunicable diseases, such as DM and CHD. The entire Polish cohort of the PURE study included 2036 participants. Out of this population, 283 (urban/rural, 148/135) inhabitants of the mean age of 54.3 ± 8.9 (range 32–79 years),

diagnosed with IFG (F/M, 186/97), from the city of Wroclaw and its surroundings in the Lower Silesia province were enrolled in the study. The study was conducted according to the international PURE project protocol (Corsi et al. 2013; Teo et al. 2009). This is a companion chapter to an earlier study performed on the same cohort of subjects, which concerned the probability of the development of full-fledged DM in patients with IFG based on the values of anthropometric parameters at the beginning of after a 9-year follow-up (Święcicka-Klama et al. 2021a, b). The present study evaluates the role of cardiovascular risk factors for the development of CHD and DM in patients with IFG and is reported as a separate ramification of the PURE project. Baseline data were collected by trained staff between 2007 and 2010. At first, participants completed standardized questionnaires: the Family Census Questionnaire (about the household, family, and demographic and socioeconomic status) and the Adult Questionnaire including questions about I NTERHEART risk factors (diabetes, indices of abdominal obesity, hypertension, lipids, dietary pattern, physical activity, smoking, consumption of alcohol, and psychosocial factors). Then, subjects underwent blood pressure measurements and blood collection.

2.2 Measurements

IFG was based on a clinical diagnosis by a doctor or fasting glucose level in a range of 100–125 mg/dL (5.6–6.9 mmol/L) untreated with hypoglycemic medications. Each year after recruitment, participants were interrogated over the phone about hospitalizations and morbidity. Every third year, they were invited for a health assessment. Those earlier diagnosed with DM, taking glucose-lowering agents, having FPG beyond the range of 100–125 mg/dL during screening, not fasting before the blood tests, and providing incomplete were excluded.

Current smoking was defined as consuming at least one tobacco product per day. Family medical history included parents and siblings. Blood pressure was measured twice with an automated oscillometric device (Omron Corporation, Tokyo, Japan). Each measurement was obtained in the sitting position after at least 5 min rest. Hypertensive was defined as having a mean systolic blood pressure above 140 mmHg and diastolic above 90 mmHg in medical diaries, the presence of an earlier diagnosis of hypertension, and taking antihypertensive agents (Szuba et al. 2016). Patients underwent venous blood tests that were carried out after an overnight fast. Fasting glucose levels and lipid panels were determined using standard enzymatic methods.

The Framingham Risk Score (FRS) was calculated using a validated prediction model. It is based on six risk factors: age, gender, smoking status, systolic blood pressure or antihypertensive treatment, and total cholesterol and high-density lipoprotein cholesterol (HDL-C) levels. A 10-year CHD risk was classified as low (<10%), intermediate (10–20%), and high (>20%) (D'Agostino Sr et al. 2001; Wilson et al. 1998). For the calculation of FRS, patients were stratified into five successive decade-old age groups (Table 1). Patients aged 50–69 were most numerous. Out of the 283 patients, every fifth (21.6%) was a current tobacco smoker, every third (32.9%) was a former smoker, and 45.6% never smoked.

Table 1 Age groups of study patients (n = 283)

Age (years)	n (%)
30–39	22 (7.8)
40–49	47 (16.6)
50–59	132 (46.6)
60–69	72 (25.4)
70–79	10 (3.6)

2.3 Statistical Analysis

Data distribution was checked using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The significance of differences between independent groups was assessed using a *t*-test and one-way analysis of variance (ANOVA) with post hoc Tukey's test. Relationships between pairs of variables were assessed using Pearson's correlation coefficient for quantitative variables and the Chi-square test for qualitative variables. A p-value <0.05 defined statistically significant differences. The analysis was performed using a commercial Statistica v13.3 package (StatSoft Inc.; Tulsa, OK).

3 Results

At the starting point of the study, cardiovascular diseases in the family were reported by every second person (54.4%), and a family history of diabetes was provided in the questionnaire by 28.6% of subjects. One-eighth (12.4%) of patients with IFG were diagnosed with cardiovascular disorders, including CHD with and without heart infarct, heart failure, or stroke. Arterial hypertension occurred in about two-thirds (68.2%) and dyslipidemia in 76.7% of patients. Most hypertensive patients (56.0%) admitted to not taking any blood pressure-lowering medications, and 26.9%, 11.4%, and 5.7% of them were treated with one, two, and three antihypertensive drugs, respectively. Likewise, just 12.0% of dyslipidemic patients were used to taking lipid-lowering drugs regularly. Detailed personal and family medical histories of the patients at baseline are shown in Table 2.

Further, the mean fasting blood glucose (FPG) was 107.9 ± 6.8 mg/dL. The mean values for TC, LDL-C, and non-HDL-C were elevated (201.9 mg/dL, 119.1 mg/dL, 145.8 mg/dL, respectively), while HDL-C was in the normal range (56.5 mg/dL). Blood pressure was measured twice in each patient, and the final value was averaged. Most patients (62.5%) were in the hypertensive range with systolic ≥140 and diastolic blood pressure levels greater than 140 mmHg and 90 mmHg, respectively. Grade I hypertension was most common. The optimal blood pressure, taken as <120/80 mmHg, was recorded only in 17 patients (6.0%). The mean FRS was 14.6 ± 9.2 points, ranging widely from 0.5 to 35.7 points. FRS did not differ significantly between urban and rural dwellers. These results were displayed in detail in Table 3. The youngest

Table 2 Personal and family medical history of patients at baseline (n = 283)

	n (%)
Family history	
Diabetes	81 (28.6)
CVD	154 (54.4)
Comorbidities and past CVD events	
Dyslipidemia	217 (76.7)
Treated dyslipidemia	26 (12.0)
Hypertension	193 (68.2)
Cardiovascular disorders:	
CHD with/without heart infarct	22 (7.8)
Heart failure	6 (2.1)
Stroke	7 (2.5)
Number of blood pressure-lowering medications	n (%) Hypertensive patients
0	108 (56.0)
1	52 (26.9)
2	22 (11.4)
3	11 (5.7)

CVD cardiovascular disorders, *CHD* coronary heart disease

t.1 **Table 3** Laboratory data in study patients (n = 283) at baseline

t.2	Variables	
t.3	FPG (mg/dL)	108 ± 7 (100–125)
t.4	TC (mg/dL)	202 ± 41 (116–360)
t.5	TG (mg/dL)	132 ± 73 (35–478)
t.6	LDL-C (mg/dL)	119 ± 35 (31–248)
t.7	HDL-C (mg/dL)	57 ± 15 (27–132)
t.8	Non-HDL-C (mg/dL)	146 ± 42 (46–309)
t.9	SBP (mmHg):	146 ± 0.4 (90–213)
t.10	DBP (mmHg):	87 ± 12 (60–130)
t.11	Blood pressure – Categories	n (%)
t.12	Optimal (<120/80 mmHg)	17 (6.0)
t.13	Normal (<130/85 mmHg)	39 (13.8)
t.14	High normal (<140/90 mmHg)	50 (17.7)
t.15	Isolated systolic hypertension	22 (7.8)
t.16	Grade I (<160/100 mmHg)	64 (22.6)
t.17	Grade II (<180/110 mmHg)	49 (17.3)
t.18	Grade III (≥180/110 mmHg)	42 (14.8)
t.19	Blood pressure – Assessment	
t.20	Normal	106 (37.5)
t.21	Abnormal	177 (62.5_
t.22	FRS	14.7 ± 9.2 (0.5–35.7)

t.23 Continuous data are means ±SD (min-max); discrete data are counts (%). *FPG* fasting plasma glucose, *TC* total serum cholesterol, *TG* triglycerides, *LDL-C* low-density cholesterol, *HDL-C* high-density cholesterol, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FRS* Framingham Risk Score.

patients up to the age of 49 years had a low 10-year CHD risk (FRS < 10%), while those over 60 years of age had a high CHD risk (FRS > 20%). There was a positive correlation between age and CHD risk determined by FRS (r = 0.66). With increasing age by 10, the FRS increased by 6.8% (Fig. 1).

After a 9-year follow-up, the patients were questioned about their health including morbidity and medication intake and lifestyle including smoking, alcohol use, diet, physical activity, using standardized questionnaires, and underwent blood pressure measurements and blood tests. Then, the patients were stratified into the following groups: (A) normoglycemia (FPG < 100 mg/dL), (B) persisting impaired fasting glucose (FPG 100–125 mg/dL), and (C) diabetes (FPG > 125 mg/dL) and/or treatment with glucose-lowering agents. The findings were that 49% (n = 138) of patients reverted to normoglycemia, 30% (n = 86) had persisting IFG, and 21% (n = 59) developed full-fledged diabetes. The mean age (range) of the patients in the respective groups was 52.9 ± 9.7 (33–75), 54.2 ± 8.4 (32–79), and 57.8 ± 6.7 (45–77) years. The patients who progressed to DM (Group C) were, on average, 4.9 years older than those who attained normoglycemia (Group A) (p = 0.002). There were no significant differences between the groups based on sex, place of residence, or smoking. The stratification of patients into the three groups was based on the changes in the glucose that occurred during a 9-year follow-up. Any changes in the medical status, including laboratory and blood pressure measurements, were not considered the primary outcomes, and therefore were not evaluated.

Further analysis included data taken from the initial baseline screening. Positive family history of diabetes or cardiovascular disorders went side by side. Almost all diabetic patients (94.9%) (Group C) suffered from dyslipidemia and most (83.1%) also were hypertensive. There were insignificant inter-group differences in the diagnosis of cardiovascular disorders (Table 4).

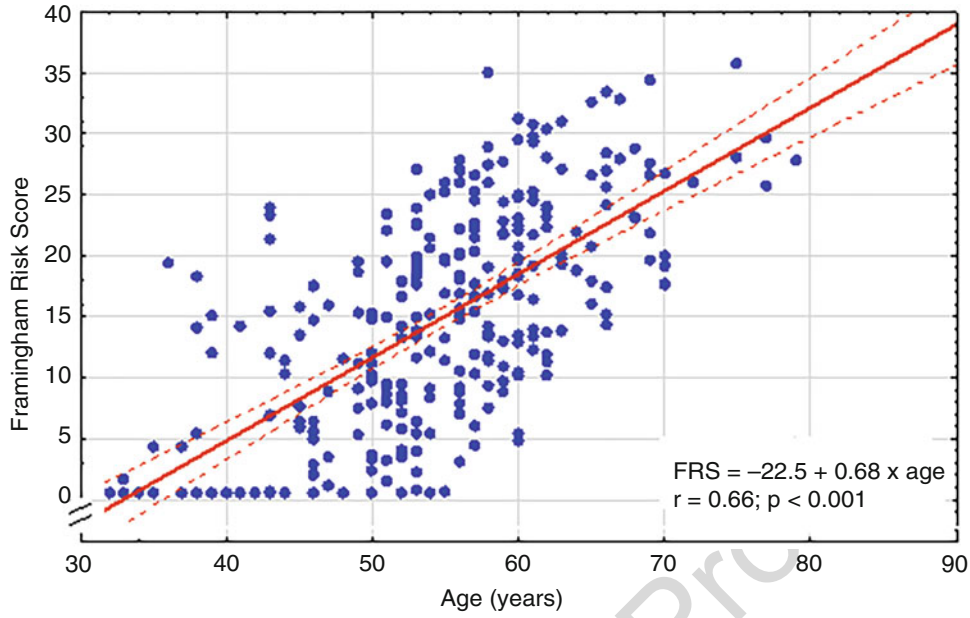

Fig. 1 Linear regression analysis of the relationship between the Framingham Risk Score (FRS) and age of patients with impaired fasting blood glucose at study baseline

t.1 **Table 4** Medical history collected at baseline in patients stratified by blood glucose level after a 9-year follow-up

	Group A	Group B	Group C	
t.3	Normoglycemia	IFG	Diabetes	
t.4	(*n* = 138)	(*n* = 86)	(*n* = 59)	p
t.5 Family history	*n (%)*	*n (%)*	*n (%)*	
t.6 Diabetes	39 (28.3)	26 (30.2)	16 (27.1)	0.912
t.7 Cardiovascular disorders	81 (58.7)	40 (46.5)	33 (55.9)	0.198
t.8 Co-morbidities and past events	*n (%)*	*n (%)*	*n (%)*	
t.9 Dyslipidemia	91 (65.9)	70 (81.4)	56 (94.9)	<0.001*
t.10 Arterial hypertension	77 (55.8)	67 (77.9)	49 (83.1)	<0.001*
t.11 Cardiovascular disorders				
t.12 CHD with/without heart infarct	3 (2.2)	3 (3.5)	0 (0.0)	0.358
t.13 Heart failure	9 (6.5)	6 (7.0)	7 (11.9)	0.416
t.14 Stroke	4 (2.9)	2 (2.3)	1 (1.7)	0.878

t.15 Continuous data are means ±SD (min-max); discrete data are counts (%). *IFG* impaired fasting glucose, *CHD* coronary heart disease, p-value denotes significant differences between Group A, Group B, and Group C; *Chi-square contingency table

Laboratory results, blood pressure measurements, and calculated FRS differed significantly between groups based on the blood glucose level. Fasting plasma glucose and lipids levels were higher in diabetics (Group C). These patients also had higher mean blood pressure. Most of them (49.1%) were at high risk, and a few (11.9%) were at low risk of CHD. In the normoglycemic patients (Group A), the proportions were inverse (22.5% and 44.9%, respectively). The mean FRS was significantly higher in Group C than in Groups A and B (19.8 vs. 12.1 and 15.3, respectively) (Table 5 and Fig. 2).

t.1 **Table 5** Laboratory data and measurements collected at baseline in patients stratified by the level of blood glucose after a 9-year follow-up

	Group A	Group B	Group C	
t.3	Normoglycemia	IFG	Diabetes	
t.4	(*n = 138*)	(*n = 86*)	(*n = 59*)	p
t.5 FPG (mg/dL)	107 ± 7 (100–125)	108 ± 7 (100–125)	110 ± 7 (100–125)	0.038**
t.6 TC (mg/dL)	196 ± 38 (116–333)	207 ± 41 (132–333)	210 ± 43 (147–360)	0.034**
t.7 TG (mg/dL)	119 ± 70 (35–478)	137 ± 74 (44–452)	155 ± 69 (53–345)	0.004**
t.8 HDL-C (mg/dL)	58 ± 14 (35–112)	56 ± 17 (35–132)	52 ± 14 (27–89)	0.038**
t.9 Non-HDL-C (mg/dL)	138 ± 41 (46–290)	151 ± 40 (74–263)	157 ± 43 (85–309)	0.003**
t.10 LDL-C (mg/dL)	113 ± 36 (31–240)	124 ± 35 (50–232)	127 ± 39 (62–248)	0.028**
t.11 SBP (mmHg)	143 ± 21 (90–194)	146 ± 8 (111–201)	154 ± 22 (113–213)	<0.001**
t.12 DBP (mmHg)	86 ± 12 (60–120)	88 ± 11 (62–120)	91 ± 12 (69–130)	0.006**
t.13 Patient stratification:	*n (%)*	*n (%)*	*n (%)*	0.008*
t.14 Normal blood pressure	64 (46.4)	27 (31.4)	15 (25.4)	
t.15 Abnormal blood pressure	74 (53.6)	59 (68.6)	44 (74.6)	
t.16 FRS:	12.1 ± 9.3 (1–34)	15.3 ± 8.5 (1–33)	19.8 ± 7.8 (2–36)	<0.001**
t.17 FRS – Categories	*n (%)*	*n (%)*	*n (%)*	<0.001*
t.18 <10	62 (44.9)	24 (27.9)	7 (11.9)	
t.19 10–20	45 (32.6)	36 (41.9)	23 (39.0)	
t.20 >20	31 (22.5)	26 (30.2)	29 (49.1)	

t.21 Continuous data are means ±SD (min-max); discrete data are counts (%). *IFG* impaired fasting glucose, *FPG* fasting blood glucose, *TC* total cholesterol, *TG* triglycerides, *HDL-C* high-density cholesterol, *LDL-C* low-density cholesterol, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FRS* Framingham Risk Score; p-values denote differences between Group A, Group B, and Group C; *Chi-square contingency table; **one-way ANOVA

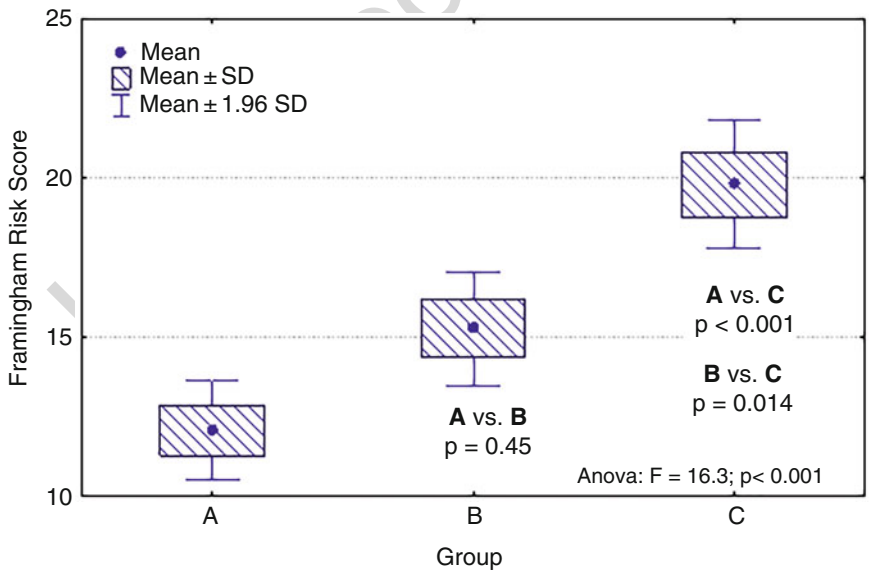

Fig. 2 Ten-year risk for coronary heart disease in patients stratified by the level of blood glucose after a 9-year follow-up; (**a**) normoglycemia, (**b**) impaired fasting glucose (IFG), (**c**) diabetes; p-values denote significant inter-group differences (one-way ANOVA with post hoc Tukey's test)

4 Discussion

This study assessed the influence of the main cardiovascular risk factors included in the Framingham Risk Score, such as age, smoking status, adverse lipid profile, and hypertension, on the progression of impaired fasting glucose to DM in the Polish cohort of the PURE study. The findings were that age significantly weight in on both the Framingham Risk Score for CHD and progression of IFG to full-fledged DM. The youngest patients aged under 49 were likely to have a low risk (FRS <10%), whereas those aged over 60 had an increased CHD risk (FRS > 20%). There was a strong positive correlation between FRS and age. With each decade of age, FRS increased by 6.8%. Patients who developed DM were, on average, 4.9 years older than those in the normoglycemic group ($p = 0.002$).

Laboratory tests performed at the baseline screening were essential for the assessment of DM development. Patients who developed DM over a 9-year follow-up showed higher fasting plasma glucose levels compared to those who remained normoglycemic. That could reflect the continuity of the process of DM development consisting of a gradual increase in the blood glucose level (Święcicka-Klama et al. 2021a, b; Færch et al. 2013). Chronic hyperglycemia enhances the atherogenic processes at almost every step. It leads to the accelerated development of cardiovascular disorders and their sequelae such as stroke, myocardial infarction, heart failure, macrovascular death, and all-cause mortality.

The role of lipids cannot be underestimated in the pathogenesis of atherosclerosis. Numerous biochemical pathways involving lipids have been proposed (Poznyak et al. 2020). Our study revealed a high prevalence of abnormal lipid profiles in the population sample (76.7%). The mean total cholesterol, LDL-C, and non-LDL-C levels exceeded the recommended standards, even those for individuals at low risk of cardiovascular disorders. It is disturbing that the regular intake of cholesterol-lowering medications was reported by only 26 patients (12.0%), with 24 of them treated with statins. In some cases, dyslipidemia was not earlier diagnosed, and in others, poor adherence to statin therapy was observed. There is evidence that statins reduce the 5-year risk of mortality from cardiovascular disorders by about 25% in patients earlier diagnosed with cardiovascular disorders (Collins et al. 2004). All lipid fractions in patients with sustained impaired fasting glucose and full-fledged DM after 9 years of follow-up were elevated. These findings are congruent with those of Gagliardino et al. (2018). According to recent studies, a low level of HDL is a stronger predictor of cardiovascular risk and worse outcome than LDL is (Skoczyńska et al. 2013; Després et al. 2000).

Most patients in this study (62.5%) had untreated or poorly controlled hypertension. The optimal blood pressure was recorded in just 17 patients (6.0%). Stage I hypertension was the most prevalent (22.6%). In a past PURE study performed on the Polish population, undiagnosed arterial hypertension occurred in nearly every second person (48.5%). In that study, the level of education played was a key element in improving hypertension prevention and treatment (Szuba et al. 2016). In the present paper, elevated either systolic or diastolic blood pressures were conducive to the progression of IFG to full-fledged DM. About three-fourths (74.6%) of diabetics required the optimization of hypertension treatment. Several eloquent studies have shown that the optimal control of blood pressure is beneficial in patients with carbohydrate metabolism disorders (Naha et al. 2021; Brannick and Dagogo-Jack 2018; The NAVIGATOR Study Group 2010; The DREAM Trial Investigators 2006; UK Prospective Diabetes Study Group 1998).

In the present study, the average calculated FRS for 10-year risk of CHD was 14.7 ± 9.2. This moderate-risk value could result from the fact that the most numerous patients were in the middle age range of 50–59 years. We noticed significant differences in risk between the groups with normoglycemia, IFG, and DM. The highest proportion of patients (49.1%) at high greater

than 20% risk of CHD was among diabetics. In this group, a low risk smaller than 10% of CHD was present in just 11.9% of patients. In patients who remained normoglycemic after a 9-year follow-up, these proportions tended to reverse, with 44.9% and 22.5%, respectively. These results well-illustrated how many risk factors DM shares with CHD. It is worth noting that IFG has been recognized as the highest-scoring risk factor in the diabetes risk calculator based on FRS (Wilson et al. 2007). The diabetes risk calculator also includes a family history of diabetes. In the present study, the family interview was positive in only 28.6% of patients and had no statistical significance for the development of diabetes in patients with IFG. Intriguingly, we also failed to show that current smoking would affect the progression of IFG to full-fledged DM.

Framingham Risk Score for CHD is valid for CHD-naive people. In the present study, the population sample size was similar to that in the primary Framingham Heart Study (Wilson et al. 1998) consisting of Caucasians aged 30–79. We did not exclude individuals with known CHD as the primary target was the evaluation of the contribution of individual factors included in FRS to the progression of IFG to DM, rather than a strict assessment of CHD risk. Coronary heart disease, past myocardial infarct, heart failure, and stroke did not reveal a statistical significance for the development of full-fledged DM. The reason might be a small number of such patients (31 patients, i.e., 11.0% of the entire cohort). Nonetheless, the Polish branch of the PURE study enabled the creation and evaluation of an outstanding epidemiologic database of risk factors leading to DM, expanding the past Framingham Heart Study and INTERHEART study (Yusuf et al. 2004; Wilson et al. 1998).

In conclusion, we confirmed that the basic CHD risk factors included in the Framingham Risk Score, such as age, dyslipidemia, and hypertension, have a significant contribution to the progression of impaired fasting glucose type 2 diabetes. In a large proportion of cases, impaired fasting glucose was accompanied by other disorders, such as abnormal lipid profile or hypertension, increasing the cardiovascular risk in patients with prediabetes. Assessing the scale of the problem in the Polish population and the influence of these factors on carbohydrate metabolism disorders may help improve both targeted primary and secondary prevention strategies. This work highlights the importance of controlling lipid disorders and blood pressure. We believe that this study may contribute to the earlier diagnosis of dyslipidemia and hypertension in prediabetic patients and reduce the prevalence of diabetes DM and adverse cardiovascular outcomes.

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Conflicts of Interest The authors declare no conflicts of interest concerning this chapter.

Ethical Approval All procedures performed in studies involving human participants followed the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of Wroclaw Medical University (permit no. KB-443/2006).

Informed Consent Written informed consent was obtained from all individual participants included in the study.

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5. Podsumowanie i wnioski

W publikacji pt.: ***„Anthropometric Indices as Long-Term Predictors of Diabetes in Impaired Fasting Glucose Metabolism: Findings in the PURE Study in Poland”*** zbadano udział wybranych wskaźników antropometrycznych w predykcji ryzyka rozwoju T2DM u osób z nieprawidłową glikemią na czczo. Pacjenci, u których rozwinęła się cukrzyca po 9 latach obserwacji, mieli istotnie statystyczną większą masę ciała niż ci, którzy powrócili do normoglikemii lub u których pozostała rozpoznana IFG. Istotny udział miały głównie parametry związane z otyłością. Prawie wszystkie osoby (98,3%) z nieprawidłową glikemią na czczo, u których doszło do progresji do T2DM, miały nadwagę lub otyłość według klasyfikacji BMI. Wyniki niniejszej pracy pokazują, iż nadmierna masa ciała ma istotne znaczenie w rozwoju cukrzycy typu 2 z nieprawidłowej glikemii na czczo oraz jest niezależnym czynnikiem ryzyka progresji IFG do cukrzycy.

Mimo że większość wskaźników otyłości przyczynia się do przewidywania rozwoju cukrzycy, wciąż nie znaleziono idealnego parametru określającego ryzyko progresji IFG do cukrzycy. Na podstawie analizy krzywych ROC dla poszczególnych czynników, największą czułość w predykcji ryzyka rozwoju T2DM z nieprawidłowej glikemii na czczo wykazały wiek i BMI, jednakże oba te parametry miały przy tym najniższą swoistość. Biorąc pod uwagę jednocześnie czułość i swoistość, najlepszymi predyktorami rozwoju cukrzycy po 9 latach u pacjentów z IFG były: wskaźnik talia-wzrost (WHtR), indeks masy ciała (BMI) oraz obwód talii (WC). Wszystkie te parametry są łatwe i tanie w zastosowaniu, wymagają wykonania zaledwie kilku prostych pomiarów, a mogą służyć zarówno do identyfikacji pacjentów z otyłością brzuszną, jak i tych z wysokim ryzykiem rozwoju cukrzycy z IFG.

Uważam, że warto zaimplementować te proste pomiary do samooceny i kontroli u osób z nieprawidłową glikemią na czczo do codziennej praktyki klinicznej, aby pomogły oszacować prawdopodobieństwo rozwoju cukrzycy. Obliczone ryzyko pozwoliłoby klinicystom podjąć odpowiednie działania prewencyjne, aby zapobiec rozwojowi T2DM oraz jej powikłaniom.

W pracy pt.: ***„Cardiovascular Risk Factors Drive Impaired Fasting Glucose to Type 2 Diabetes: Findings After a 9-Year Follow-Up in the PURE Study in Poland”*** analizowano wpływ głównych czynników ryzyka sercowo-naczyniowego, uwzględnionych w skali Framingham, takich jak wiek, palenie tytoniu, nadciśnienie tętnicze oraz niekorzystny profil

lipidowy na progresję IFG do cukrzycy w polskiej kohorcie badania PURE. Badanie wykazało, że wiek ma istotne znaczenie zarówno w ocenie ryzyka rozwoju choroby wieńcowej (CHD) według skali Framingham, jak i predykcji ryzyka rozwoju T2DM u chorych z nieprawidłową glikemią na czczo. Statystycznie, pacjenci w wieku poniżej 49 lat częściej wykazywali niskie ryzyko CHD (FRS < 10%), podczas gdy osoby powyżej 60 roku życia charakteryzowały się podwyższonym ryzykiem (FRS > 20%). Z każdą dekadą życia wynik FRS wzrastał o 6,8%. Pacjenci z grupy C, u których rozwinęła się cukrzyca, byli średnio o 4,9 roku starsi niż pacjenci w grupie A, w której po 9 latach uzyskali normoglikemię.

Istotne znaczenie dla oceny ryzyka progresji zaburzeń metabolizmu węglowodanów miały badania laboratoryjne wykonane w *baseline*. Już wówczas osoby, które później rozwinęły cukrzycę, wykazywały wyższe stężenie glukozy we krwi, w porównaniu z pacjentami, którzy powrócili do normoglikemii. Wynika to prawdopodobnie z tego, iż rozwój cukrzycy jest procesem ciągłym i polega na stopniowym wzroście glikemii, opisywanym szerzej w mojej pracy poglądowej pt.: ***„The Natural Course of Impaired Fasting Glucose”***.

Badanie ujawniło także wysoką częstość zaburzeń lipidowych w populacji. Średnie stężenie cholesterolu całkowitego, LDL i non-HDL wykraczało poza normy, nawet tych przyjętych dla zdrowych osób. Gdyby uwzględnić docelowe zalecane stężenia cholesterolu całkowitego, frakcji LDL oraz non-HDL, dostosowane do ryzyka sercowo-naczyniowego, wyniki jeszcze bardziej odbiegałyby od normy. Niepokojący jest też fakt, iż regularne przyjmowanie leków obniżających cholesterol zadeklarowało tylko 26 osób (12,0%), z czego 24 osoby były leczone statynami. W znacznej części dyslipidemia nie została wcześniej zdiagnozowana, w innych przypadkach było to spowodowane słabym *compliance*. Różnice między grupą osób, które rozwinęły cukrzycę a tą, w której pacjenci powrócili do normoglikemii były istotne statystycznie we wszystkich frakcjach profilu lipidowego.

U większości osób z grupy badanej (62,5%) stwierdzono także nieleczone lub źle kontrolowane nadciśnienie tętnicze. Optymalne wartości ciśnienia tętniczego zarejestrowano u zaledwie 17 osób (6,0%). Największy odsetek stanowiły osoby z nadciśnieniem tętniczym I stopnia (22,6%). W rozwoju cukrzycy z IFG istotne znaczenie miały wartości skurczowego, jak i rozkurczowego ciśnienia tętniczego. Około trzy czwarte (74,6%) osób z grupy C, w której po 9 latach obserwacji rozwinęli cukrzycę, wymagało optymalizacji leczenia nadciśnienia tętniczego.

Poszczególne grupy: z normoglikemią (A), utrzymującą się nieprawidłową glikemią na czczo (B) i cukrzycą typu 2 (C) po 9 latach różniły się między sobą również pod względem ryzyka CHD. Największy odsetek pacjentów (49,1%) z FRS powyżej 20% obserwowano wśród chorych w grupie C. Niskie ryzyko CHD, poniżej 10%, występowało tylko u 11,9% pacjentów z tej grupy. W grupie A tj. u pacjentów, którzy powrócili do normoglikemii, po 9-letniej obserwacji, proporcje te uległy odwróceniu, wynosiły odpowiednio 44,9% i 22,5%. Wyniki te świadczą o wielu wspólnych czynnikach ryzyka zarówno dla rozwoju chorób sercowo-naczyniowych, jak i cukrzycy typu 2.

W badaniu potwierdzono, że podstawowe czynniki ryzyka CHD uwzględnione w skali Framingham, takie jak wiek, dyslipidemia i nadciśnienie tętnicze, mają istotny udział w progresji zaburzeń gospodarki węglowodanowej u pacjentów z IFG. Nieprawidłowej glikemii na czczo towarzyszyły często inne zaburzenia, takie jak nieprawidłowy profil lipidowy czy nadciśnienie tętnicze. Ocena skali problemu w polskiej populacji oraz wpływu tych czynników na zaburzenia metabolizmu węglowodanów może pomóc w podjęciu efektywniejszych strategii profilaktyki pierwotnej, jak i wtórnej. Praca podkreśla znaczenie optymalizacji współistniejących chorób, szczególnie dyslipidemii i nadciśnienia tętniczego. Dzięki temu, że badanie PURE wciąż trwa, istnieje możliwość kontynuacji obserwacji po 12 oraz 15 latach.

6. Streszczenie w języku polskim

Wstęp: Zaburzenia gospodarki węglowodanowej, cukrzyca jak i stan przedcukrzycowy (*prediabetes*), stanowią znaczący problem epidemiologiczny, zdrowotny oraz ekonomiczny. Na podstawie przeglądu aktualnego piśmiennictwa można stwierdzić, iż nadal istnieje potrzeba lepszego poznania etiopatogenezy nieprawidłowej glikemii na czczo (IFG) oraz czynników wpływających na rozwój cukrzycy. Wczesne wykrycie zaburzeń metabolizmu glukozy może zapobiec lub opóźnić rozwój cukrzycy typu 2 i jej powikłań. Niniejszą rozprawę doktorską stanowi cykl autorskich publikacji – przegląd literatury odnośnie przebiegu IFG oraz analiza danych zebranych w ramach Prospektywnego Badania Epidemiologicznego Ludności Miejskiej i Wiejskiej (PURE, ang. *Prospective Urban and Rural Epidemiological Study*)**.**

Cele pracy: Celem niniejszej dysertacji było podsumowanie i pogłębienie wiedzy na temat nieprawidłowej glikemii na czczo oraz analiza wpływu wybranych czynników ryzyka na jej progresję do cukrzycy typu 2, na podstawie 9-letniej obserwacji polskiej kohorty badania PURE. Praca przeglądowa miała za zadanie usystematyzowanie oraz przegląd aktualnego stanu wiedzy z zakresu etiopatogenezy, epidemiologii i przebiegu *prediabetes*, ze szczególnym uwzględnieniem nieprawidłowej glikemii na czczo oraz czynników ryzyka przejścia IFG w cukrzycę typu 2. Celem drugiej pracy była analiza wartości predykcyjnej najczęściej stosowanych wskaźników otyłości brzusznej dla rozwoju cukrzycy typu 2 w populacji osób z IFG, w ciągu 9 lat obserwacji. W trzeciej publikacji oceniono wpływ czynników ryzyka sercowo-naczyniowego uwzględnionych w skali Framingham na rozwój cukrzycy u pacjentów z nieprawidłową glikemią na czczo, na podstawie 9-letniej obserwacji badania PURE Polska.

Materiał i metody: Prace badawcze włączone do rozprawy doktorskiej zostały przeprowadzone na podstawie bazy danych zebranej w ramach międzynarodowego badania PURE. Polską kohortę badania stanowiło 2036 osób, mieszkańców Wrocławia oraz pobliskiej gminy Żórawina, w wieku od 30 do 85 lat. Rekrutacja do badania odbywała się w latach 2007--2010. W moich pracach do badań zostało włączonych 283 osoby z nieprawidłową glikemią na czczo (glikemia na czczo mieściła się w przedziale od 100 mg/dl do 125 mg/dl), bez wcześniej rozpoznanej cukrzycy i nieprzyjmujący leków hipoglikemizujących. Warunkiem włączenia pacjenta do analizy był komplet danych z badania referencyjnego (ang. *baseline*) oraz po 9 latach. Na podstawie wyników glikemii na czczo po 9 latach obserwacji oraz przeprowadzonego wywiadu dokonano stratyfikacji pacjentów na trzy grupy: grupę A

z normoglikemią, grupę B z przetrwałą nieprawidłową glikemią na czczo i grupę C z rozpoznaniem cukrzycy. Podstawę do dalszej analizy stanowiły dane z *baseline*, na podstawie których można było przeanalizować różnice w metabolizmie gospodarki węglowodanowej w ciągu 9 lat, pomiędzy poszczególnymi grupami pacjentów.

Wyniki: Po 9 latach obserwacji, 49% (n = 138) pacjentów uzyskało normoglikemię, u 30% (n = 86) utrzymywała się nieprawidłowa glikemia na czczo, a 21% (n = 59) osób rozwinęło T2DM. Wśród parametrów otyłości, najlepszymi predyktorami rozwoju cukrzycy po 9 latach u pacjentów z IFG okazały się: wskaźnik talia-wzrost (WHtR), indeks masy ciała (BMI) oraz obwód talii (WC). W pracy potwierdzono, że podstawowe czynniki ryzyka sercowo-naczyniowego uwzględnione w skali Framingham, takie jak wiek, dyslipidemia i nadciśnienie tętnicze, mają istotny udział w progresji zaburzeń gospodarki węglowodanowej u pacjentów z IFG. Nieprawidłowej glikemii na czczo towarzyszyły często inne zaburzenia, takie jak nieprawidłowy profil lipidowy czy nadciśnienie tętnicze.

Wnioski: Trudno jest opisać typowy przebieg nieprawidłowej glikemii na czczo. Niemniej, można wskazać pewne czynniki zwiększające prawdopodobieństwo rozwoju cukrzycy. Nadmierna masa ciała jest silnie związana ze zwiększonym ryzykiem rozwoju cukrzycy typu 2 jako następstwa długotrwale podwyższonego stężenia glukozy na czczo. Wskaźniki antropometryczne związane z otyłością, takie jak stosunek talii do wzrostu, wskaźnik masy ciała i obwód talii wydają się najlepszymi predyktorami cukrzycy. Dlatego zaleca się wprowadzenie tych prostych pomiarów do oceny i samokontroli u osób z IFG w codziennej praktyce klinicznej, aby pomóc przewidzieć potencjalny rozwój cukrzycy. W stratyfikacji ryzyka rozwoju IFG do cukrzycy istotny udział mają także czynniki sercowo-naczyniowe. Wzięcie pod uwagę wieku pacjenta oraz optymalizacja współistniejących chorób, szczególnie dyslipidemii i nadciśnienia tętniczego, może zapobiec rozwojowi cukrzycy i jej powikłaniom.

Podsumowanie: Niniejszy cykl prac podkreśla fakt częstego współwystępowania otyłości, zaburzeń lipidowych i nadciśnienia tętniczego u osób z IFG w Polsce i ich znaczącego wpływu w rozwoju cukrzycy. Wiedza ta oraz ocena skali problemu w polskiej populacji może w przyszłości pomóc w spersonalizowaniu programu profilaktycznego cukrzycy, który będzie efektywnie identyfikował osoby z nieprawidłową glikemią na czczo i wysokim ryzykiem progresji do cukrzycy typu 2.

7. Streszczenie w języku angielskim (Abstract)

Introduction: Carbohydrate metabolism disorders, including diabetes and prediabetes, poses a significant epidemiological, health and economic problem. Based on a review of the current literature, it seems that there is still a need for a deeper understanding the etiopathogenesis of impaired fasting glucose (IFG) and the factors conducive to the development of type 2 diabetes (T2DM). Early detection of impaired glucose regulation may prevent or delay the development of T2DM and its complications. This doctoral dissertation was based on a series of three publications – a review of the literature on the natural course of IFG and an analysis of factors bearing on the progression to diabetes of the Prospective Urban and Rural Epidemiological Study (PURE) run in Poland.

Aims of the study: The aim of this dissertation was to systematize and deepen the knowledge on impaired fasting glucose and to assess the role of selected risk factors in its progression to T2DM, based on the 9-year follow-up in the PURE study in Poland. The purpose of the review article was to evaluate the current state of knowledge on the etiology, prevalence, and typical course of prediabetes, with the main focus on isolated IFG and the risk factors of passing the disorder into diabetes. The second study aimed to assess the predictive value of the most commonly used abdominal obesity parameters for the development of T2DM in people with impaired fasting glucose, after a 9-year follow-up. At last, the aim of the third publication was to evaluate the influence of cardiovascular risk factors included in the Framingham Risk Score on the progression of IFG to diabetes, over 9 years of follow-up.

Material and methods: The research was based on a data collected within the Polish ramification of the international PURE study. The Polish cohort of the study consisted of 2036 people, residents of Wroclaw and the rural commune of Żórawina, aged 30 to 85 years. Recruitment for the study took place between 2007 and 2010. Out of this population, 283 subjects with IFG (fasting glycemia ranging from 100 mg/dL to 125 mg/dL), without previously diagnosed diabetes and not taking hypoglycemic drugs, with completed a 9-year follow-up, were enrolled in the studies described in the publications. Based on the fasting plasma glucose level after 9 years of follow-up and a medical interview, the patients were stratified into three groups: (A) normoglycemia (FPG < 100 mg/dL), (B) persisting impaired fasting glucose (FPG 100–125 mg/dL), and (C) diabetes (FPG > 125 mg/dL) and/or previously diagnosed T2DM. The baseline data were the foundation on which both the stratification and further

analysis were based according to the development of differential changes in carbohydrate metabolism after 9 years.

Results: Over 9 years of follow-up, 49% (n = 138) of patients reverted to normoglycemia, 30% (n = 86) had persisting IFG, and 21% (n = 59) developed full-fledged diabetes. Among the obesity parameters, the best predictors for developing diabetes after 9 years in patients with IFG were: waist-to-height ratio (WHtR), body mass index (BMI), and waist circumference (WC). The study confirmed that the main cardiovascular risk factors included in the Framingham Risk Score, such as age, dyslipidemia and hypertension, play a significant role in the progression of carbohydrate metabolism disorders in patients with IFG. Impaired fasting glycemia was often accompanied by other disorders, such as abnormal lipid profile or arterial hypertension.

Conclusions: It is hard to describe the typical course of impaired fasting glucose. Nevertheless, there are some factors that increase the risk of developing diabetes. Excess body weight is related to higher risk of diabetes as a result of increased fasting plasma glucose levels. Obesity parameters, such as waist-to-height ratio, body mass index, and waist circumference seems to be the best predictors of T2DM. Therefore, it is recommended to implement these simple measures into assessment and self-control the risk of passing IFG into diabetes. Cardiovascular factors also play a major role in the risk stratification. Taking into account patient's age and the treatment optimization of comorbidities, especially dyslipidemia and arterial hypertension, can prevent the development of diabetes and its complications.

Summary: This series of the publications highlights the frequent coexistence of obesity, lipid disorders and arterial hypertension in the Polish population with IFG and the significant contribution in the development of diabetes. The knowledge and the assessment of the scale of the problem in Poland could help to improve diabetes prevention approaches targeting patients with impaired fasting glycemia and an increased risk of progression to diabetes.

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9. Załączniki

9.1. Oświadczenia współautorów

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OŚWIADCZENIE

Oświadczam, że w pracy:

- Święcicka-Klama A., Połtyn-Zaradna K., Szuba A., Zatońska K. (2020) **The Natural Course of Impaired Fasting Glucose.** In: Pokorski M. (eds) Medical Research and Innovation. Advances in Experimental Medicine and Biology, vol 1324. Springer, Cham. https://doi.org/10.1007/5584_2020_571

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mój udział polegał na koncepcji pracy, analizie bazy danych, interpretacji wyników badań oraz redakcji artykułu;

- Święcicka-Klama A., Połtyn-Zaradna K., Wołyniec M., Szuba A., Zatońska K. (2022) **Cardiovascular Risk Factors Drive Impaired Fasting Glucose to Type 2 Diabetes: Findings After a 9-Year Follow-Up in the PURE Study in Poland.** In: Advances in Experimental Medicine and Biology. Springer, Cham. https://doi.org/10.1007/5584_2021_701

mój udział polegał na koncepcji pracy, analizie bazy danych, interpretacji wyników badań oraz redakcji artykułu.

Agnieszka Święcicka-Klama
lekarz
3131876

.....

(pieczątka i podpis)

Wrocław, 26.01.2022 r.

dr Katarzyna Połtyn-Zaradna
Katedra Zdrowia Populacyjnego
Uniwersytetu Medycznego we Wrocławiu
ul. Odona Bujwida 44, 50-345 Wrocław

OŚWIADCZENIE

Oświadczam, że w pracach:

- Święcicka-Klama A., Połtyn-Zaradna K., Szuba A., Zatońska K. (2020) **The Natural Course of Impaired Fasting Glucose.** In: Pokorski M. (eds) Medical Research and Innovation. Advances in Experimental Medicine and Biology, vol 1324. Springer, Cham. https://doi.org/10.1007/5584_2020_571
- Święcicka-Klama A., Połtyn-Zaradna K., Wołyniec M., Szuba A., Zatońska K. (2021) **Anthropometric Indices as Long-Term Predictors of Diabetes in Impaired Fasting Glucose Metabolism: Findings in the PURE Study in Poland.** In: Advances in Experimental Medicine and Biology. Springer, Cham. https://doi.org/10.1007/5584_2021_681
- Święcicka-Klama A., Połtyn-Zaradna K., Wołyniec M., Szuba A., Zatońska K. (2022) **Cardiovascular Risk Factors Drive Impaired Fasting Glucose to Type 2 Diabetes: Findings After a 9-Year Follow-Up in the PURE Study in Poland.** In: Advances in Experimental Medicine and Biology. Springer, Cham. https://doi.org/10.1007/5584_2021_701

mój udział polegał na nadzorowaniu badań oraz współredagowaniu merytorycznym publikacji.

Uniwersytet Medyczny we Wrocławiu
KATEDRA ZDROWIA POPULACYJNEGO
Zakład Badań Populacyjnych
i Profilaktyki Chorób Cywilizacyjnych
adiunkt
dr Katarzyna Połtyn-Zaradna

.....
(pieczątka i podpis)

Wrocław, 26.01.2022 r.

mgr Maria Wołyniec
Katedra Zdrowia Populacyjnego
Uniwersytetu Medycznego we Wrocławiu
ul. Odona Bujwida 44, 50-345 Wrocław

OŚWIADCZENIE

Oświadczam, że w pracach:

- Święcicka-Klama A., Połtyn-Zaradna K., Wołyniec M., Szuba A., Zatońska K. (2021) **Anthropometric Indices as Long-Term Predictors of Diabetes in Impaired Fasting Glucose Metabolism: Findings in the PURE Study in Poland.** In: Advances in Experimental Medicine and Biology. Springer, Cham. https://doi.org/10.1007/5584_2021_681
- Święcicka-Klama A., Połtyn-Zaradna K., Wołyniec M., Szuba A., Zatońska K. (2022) **Cardiovascular Risk Factors Drive Impaired Fasting Glucose to Type 2 Diabetes: Findings After a 9-Year Follow-Up in the PURE Study in Poland.** In: Advances in Experimental Medicine and Biology. Springer, Cham. https://doi.org/10.1007/5584_2021_701

mój udział polegał na zebraniu danych w ramach Prospektywnego Badania Epidemiologicznego Ludności Miejskiej i Wiejskiej (PURE).

Maria Wołyniec
.....
(podpis)

Wrocław, 01.02.2022 r.

prof. Andrzej Szuba
Katedra i Klinika Angiologii, Nadciśnienia
Tętniczego i Diabetologii
Uniwersytetu Medycznego we Wrocławiu
ul. Borowska 213, 50-556 Wrocław

OŚWIADCZENIE

Oświadczam, że w pracach:

- Święcicka-Klama A., Połtyn-Zaradna K., Szuba A., Zatońska K. (2020) **The Natural Course of Impaired Fasting Glucose.** In: Pokorski M. (eds) Medical Research and Innovation. Advances in Experimental Medicine and Biology, vol 1324. Springer, Cham. https://doi.org/10.1007/5584_2020_571
- Święcicka-Klama A., Połtyn-Zaradna K., Wołyniec M., Szuba A., Zatońska K. (2021) **Anthropometric Indices as Long-Term Predictors of Diabetes in Impaired Fasting Glucose Metabolism: Findings in the PURE Study in Poland.** In: Advances in Experimental Medicine and Biology. Springer, Cham. https://doi.org/10.1007/5584_2021_681
- Święcicka-Klama A., Połtyn-Zaradna K., Wołyniec M., Szuba A., Zatońska K. (2022) **Cardiovascular Risk Factors Drive Impaired Fasting Glucose to Type 2 Diabetes: Findings After a 9-Year Follow-Up in the PURE Study in Poland.** In: Advances in Experimental Medicine and Biology. Springer, Cham. https://doi.org/10.1007/5584_2021_701

mój udział polegał na projektowaniu, koordynacji i nadzorowaniu badań, interpretacji wyników badań oraz współredagowaniu merytorycznym publikacji.

Uniwersytet Medyczny we Wrocławiu
KATEDRA I KLINIKA ANGIOLOGII, NADCIŚNIENIA TĘTNICZEGO I DIABETOLOGII
Kierownik
prof. dr hab. n. med. Andrzej Szuba

(pieczątka i podpis)

Wrocław, 26.01.2022 r.

dr hab. Katarzyna Zatońska, prof. nadzw.
Katedra Zdrowia Populacyjnego
Uniwersytetu Medycznego we Wrocławiu
ul. Odona Bujwida 44, 50-345 Wrocław

OŚWIADCZENIE

Oświadczam, że w pracach:

- Święcicka-Klama A., Połtyn-Zaradna K., Szuba A., Zatońska K. (2020) **The Natural Course of Impaired Fasting Glucose.** In: Pokorski M. (eds) Medical Research and Innovation. Advances in Experimental Medicine and Biology, vol 1324. Springer, Cham. https://doi.org/10.1007/5584_2020_571
- Święcicka-Klama A., Połtyn-Zaradna K., Wołyniec M., Szuba A., Zatońska K. (2021) **Anthropometric Indices as Long-Term Predictors of Diabetes in Impaired Fasting Glucose Metabolism: Findings in the PURE Study in Poland.** In: Advances in Experimental Medicine and Biology. Springer, Cham. https://doi.org/10.1007/5584_2021_681
- Święcicka-Klama A., Połtyn-Zaradna K., Wołyniec M., Szuba A., Zatońska K. (2022) **Cardiovascular Risk Factors Drive Impaired Fasting Glucose to Type 2 Diabetes: Findings After a 9-Year Follow-Up in the PURE Study in Poland.** In: Advances in Experimental Medicine and Biology. Springer, Cham. https://doi.org/10.1007/5584_2021_701

mój udział polegał na opiece promotorskiej, pomocy w pisaniu prac, projektowaniu, koordynacji i nadzorowaniu badań, interpretacji wyników badań oraz współredagowaniu merytorycznym publikacji.

Uniwersytet Medyczny we Wrocławiu
Katedra Zdrowia Populacyjnego
ZAKŁAD BADAŃ POPULACYJNYCH
I PROFILAKTYKI CHORÓB CYWILIZACYJNYCH
p.o. kierownika
dr hab. Katarzyna Zatońska, prof. UMW

(pieczątka i podpis)

9.2. Zgoda Komisji Bioetycznej

KOMISJA BIOETYCZNA
przy
Akademii Medycznej
we Wrocławiu
ul. Pasteura 1; 50-367 WROCŁAW

OPINIA KOMISJI BIOETYCZNEJ Nr KB – 443/2006

Komisja Bioetyczna przy Akademii Medycznej we Wrocławiu, powołana zarządzeniem Rektora Akademii Medycznej we Wrocławiu nr 4XIII R/99 z dnia 27 września 1999 r., oraz działająca w trybie przewidzianym rozporządzeniem Ministra Zdrowia i Opieki Społecznej z dnia 12 maja 1999 r. (Dz. U. Nr 47, poz. 480) na podstawie ustawy o zawodzie lekarza z dnia 5 grudnia 1996 r. (Dz. U. Nr 28 z 1997 r. poz. 152 z późniejszymi zmianami) w składzie:

prof. dr hab. Karol BAL – filozof, profesor zwyczajny
Dyrektor Instytutu Filozofii Uniwersytetu Wrocławskiego,
prof. dr hab. Wiktor BEDNARZ – specjalista chirurg, profesor
i Katedra i Klinika Chirurgii Ogólnej, Gastroenterologicznej
i Endokrynologicznej Akademii Medycznej we Wrocławiu,
ks. dr Janusz CZARNY – teolog, adiunkt Papieskiego Fakultetu Teologicznego
we Wrocławiu,
dr Henryk KACZKOWSKI – chirurgia szczękowa, chirurgia stomatologiczna,
adiunkt Katedry i Kliniki Chirurgii Szczękowo-Twarzowej Akademii Medycznej
we Wrocławiu,
mgr Irena KNABEL-KRZYSZOWSKA – farmacja, przedstawiciel Dolnośląskiej
Izby Aptekarskiej,
prof. dr hab. Jan KOLASA - prawnik, profesor zwyczajny Uniwersytetu Wrocławskiego
prof. dr hab. Krystyna ORZECHOWSKA-JUZWENKO - farmakologia kliniczna,
choroby wewnętrzne, emerytowany profesor zwyczajny Akademii Medycznej,
prof. dr hab. Janusz PATKOWSKI – alergologia, choroby wewnętrzne, profesor
zwyczajny Katedra i Klinika Chorób Wewnętrznych i Alergologii Akademii
Medycznej,
prof. dr hab. Zbigniew RUDKOWSKI – pediatria, choroby zakaźne,
emerytowany profesor zwyczajny Akademii Medycznej we Wrocławiu,
dr hab. Sławomir SIDOROWICZ - specjalista psychiatra, Katedra Psychiatrii Akademii
Medycznej we Wrocławiu
Danuta TARKOWSKA – położna, emeryt,
dr Andrzej WOJNAR – patomorfologia, dermatologia, przedstawiciel Dolnośląskiej Izby
Lekarskiej.

pod przewodnictwem
prof. dr hab. Jana KORNAFELA – ginekologia i położnictwo, onkologia
profesor zwyczajny, Katedra Onkologii i Klinika Onkologii Ginekologicznej
Akademii Medycznej we Wrocławiu

Przestrzegając w działalności zasad Good Clinical Practice oraz zasad Deklaracji Helsińskiej, po zapoznaniu się z projektem badawczym pt.

„Epidemiologiczne badania prospektywne przeprowadzane wśród ludności miejskiej i wiejskiej (PURE)"

ZGODNOŚĆ Z ORYGINAŁEM

Uniwersytet Medyczny we Wrocławiu
KATEDRA I ZAKŁAD
MEDYCYNY SPOŁECZNEJ
kierownik
dr hab. n. med. Katarzyna Zatońska, prof. nadzw.

zgłoszonym przez **prof. dr hab. Ryszarda Andrzejaka** zatrudnionego w Katedrze i Klinice Chorób Wewnętrznych, Zawodowych i Nadciśnienia Tętniczego Akademii Medycznej we Wrocławiu oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła wyrazić zgodę na przeprowadzenie badania w mieście Wrocławiu, gminach: Boguszyce, Żurawina i inne oraz w Katedrze i Klinice Chorób Wewnętrznych, Zawodowych i Nadciśnienia Tętniczego; Katedrze i Zakładzie Bromatologii; Katedrze i Zakładzie Medycyny Społecznej Akademii Medycznej we Wrocławiu oraz w Fundacji „Promocja Zdrowia" .

Pouczenie: W ciągu 14 dni od otrzymania decyzji wnioskodawcy przysługuje prawo odwołania do Komisji Odwoławczej za pośrednictwem Komisji Bioetycznej AM we Wrocławiu
Opinia dotyczy: międzynarodowego badania epidemiologicznego

PRZEWODNICZĄCY KOMISJI

prof. dr hab. Jan Kornafel

Wrocław, dnia 6 października 2006 r.

ZGODNOŚĆ Z ORYGINAŁEM

Uniwersytet Medyczny we Wrocławiu
KATEDRA I ZAKŁAD
MEDYCYNY SPOŁECZNEJ
kierownik
dr hab. n. med. Katarzyna Zatońska, prof. nadzw.