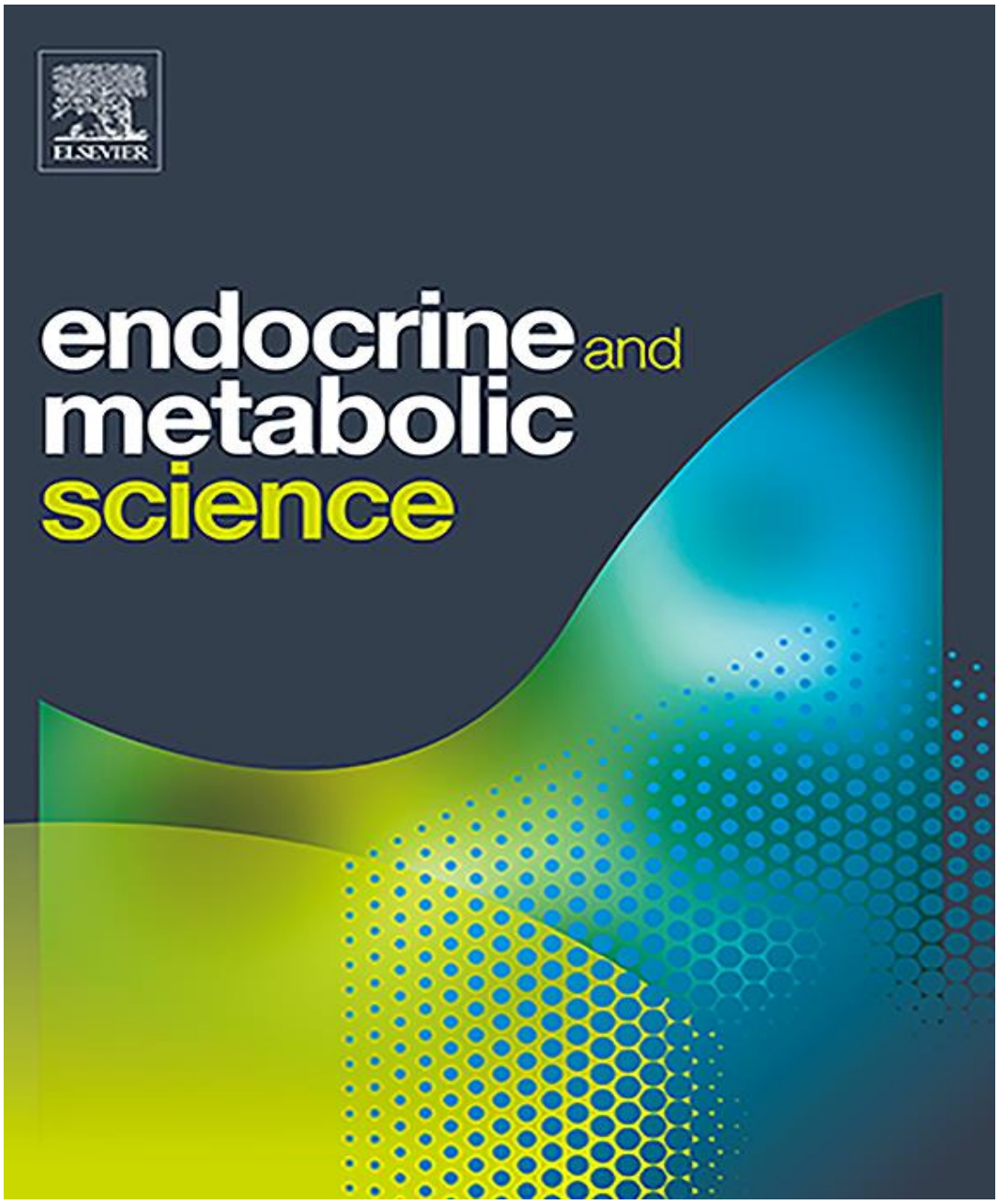
COVER JURNAL

Laman Jurnal: https://www.sciencedirect.com/journal/endocrine-and-metabolic-science



EDITORIAL BOARD

Laman: https://www.sciencedirect.com/journal/endocrine-and-metabolic-science/about/editorial-board

Editors-in-Chief

Andre van Wijnen, PhD

University of Vermont, Burlington, Vermont, United States of America

Areas of expertise - Stem cells, Epigenetics, Regenerative Medicine, Orthopedic research, Bone, Cancer, Chromatin

View full biography

Associate Editor

Hongshuai Li, MD PhD

The University of Iowa Roy J and Lucille A Carver College of Medicine, Iowa City, Iowa, United States of America

Skeletal Muscle-Bone Interaction, Stem Cells, Regenerative Medicine, Muscular Dystrophy, Osteoporosis, Osteoarthritis, Bone Marrow Adiposity

View full biography

Editorial Board Members

Jerzy Adamski, PhD

Helmholtz Zentrum München, Molecular Endocrinology and Metabolism, German Res. Centre for Environmental Health (GmbH), Neuherberg, Germany

Areas of Expertise - Steroid metabolism, Lipid metabolism, Metabolomics, Molecular endocrinology, Diabetes Type 2

Zaid Amso, PhD

The Scripps Research Institute, La Jolla, California, United States of America

Areas of expertise - Peptide and Protein Drug Discovery, GPCR agonists, Translational Science, Chemical Biology, Preclinical Drug Development

Annabel Berthon, PhD

Cochin Institute Department of Endocrinology Métabolism and Diabetes, Paris, France

Areas of Expertise - Adrenal gland, Physio-pathology, Adrenal tumors, Cortisol, Mouse models

View full biography

Carmine Cardillo, M.D.

Catholic University of the Sacred Heart, Milano, Italy

Areas of expertise - Hypertension, Obesity, Vascular function

Alicia Diaz-Thomas, MD, MPH

The University of Tennessee Health Science Center Department of Pediatrics, Memphis, Tennessee, United States of America

Areas of Expertise - General pediatric endocrinology, Intersex/DSD/CAH, Pediatric bone health, Health disparities in endocrinology

Gustavo Duque, MD, PhD

Research Institute of the McGill University Health Centre, Montréal, Quebec, Canada

Osteoporosis, Aging, Sarcopenia, Frailty, Vitamin D, Mesenchymal stem cells, Osteosarcopenia, Muscle, Bone, Falls, Fractures, Bone Marrow Adiposity

View full biography

Nada El Ghorayeb, MD

Saint Joseph University of Beirut, Beirut, Lebanon

Areas of Expertise - Molecular mechanisms of adrenal tumors, Aberrant hormone receptors in adrenal tumors and hyperplasia, New therapies for pituitary and adrenal tumors

Patricia V. Elizalde, PhD

Institute of Biology and Experimental Medicine, Buenos Aires, Argentina

Areas of Expertise - Breast cancer, Steroid hormone receptors, specifically progesterone receptor and estrogen receptor, ErbB family of receptor tyrosine kinases

Marina Fernandez, PhD

Institute of Diversity and Animal Ecology (CONICET-UNC), Bird Ecology Lab, Córdoba, Argentina

Areas of expertise - Endocrine Disrupting Chemicals, Metabolism, Neuroendocrinology, Neuroinflammation, Nuclear receptors, Reproduction

View full biography

Daniel Frigo, PhD

The University of Texas MD Anderson Cancer Center, Houston, Texas, United States of America

Areas of Expertise - Prostate cancer, Nuclear receptors, Androgens, Molecular endocrinology, Metabolism

Fady Hannah-Shmouni, MD, DABIM, AHSCP, FRCPC

The University of British Columbia, Vancouver, British Columbia, Canada

Areas of Expertise - Internal Medicine-Endocrinology, Hypertension, Metabolic Genetics

View full biography

John Hawse, PhD

Mayo Clinic in Rochester, Rochester, Minnesota, United States of America

Estrogen receptor, Hormone signaling, Breast cancer, Ovarian cancer, Transcriptional regulation

View full biography

Oto-Obong Idah, BSc, MSc

University of Jos, Department of Human Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Jos, Nigeria

Areas of expertise - Thyroid physiology, Endocrine physiology, Blood physiology

Michal Inbar-Feigenberg, MD, FCCMG

The Hospital for Sick Children Clinical and Metabolic Genetics, Toronto, Ontario, Canada

Areas of Expertise - Metabolic Genetics, Organelle related disorders, Disorders of carbohydrate metabolism, Disorders of amino acids metabolism, Disorders of energy metabolism, Inborn errors of metabolism in pediatric population

Sina Jasim, MD, MPH

Washington University in St Louis Division of Endocrinology Metabolism & Lipid Research, Saint Louis, Missouri, United States

Areas of Expertise - Thyroid diseases and thyroid cancer, Adrenal tumors, Endocrine tumors

Carolyn M. Klinge, PhD

University of Louisville Department of Biochemistry and Molecular Biology, Louisville, Kentucky, United States

Areas of expertise - Biochemistry, Molecular Biology, Endocrinology, Estrogen receptor, Breast cancer, Endocrine therapies, miRNAs, ncRNAs, Epitranscriptomics, Liver, NAFLD, Endocrine disrupting chemicals, Metabolism disturping chemicals

View full biography

Enzo Lalli, MD

French National Centre for Scientific Research (CNRS), Institute of Molecular and Cellular Pharmacology (IPMC), Paris, France

Areas of Expertise - Endocrinology, Oncology, Transcriptional regulation, Adrenal gland

View full biography

Dolores J. Lamb, PhD

Weill Cornell Medicine Department of Urology, New York, New York, United States of America

Areas of expertise - Genetics, genomics, Steroid receptor sanction, Steroids, Genitourinary birth defects, Male infertility, Men's health

Carol A. Lange, PhD

University of Minnesota Twin Cities, Minneapolis, Minnesota, United States of America

Areas of expertise - Steroid hormone receptors/hormone action, Signal transduction/stress signaling, Breast and ovarian cancer, Breast cancer stem cell biology, Cell cycle/cell fate control

Vincent Laudet, PhD

Okinawa Institute of Science and Technology Graduate University, Kunigami-gun, Japan

Areas of Expertise - Metamorphosis, Thyroid Hormones, Endocrine Disruptors, Fish, Evolutionary developmental biology

Ross Laybutt, PhD

Westmead Institute for Medical Research, Westmead, New South Wales, Australia

Areas of Expertise - Type 2 diabetes, Islet biology, Insulin secretion, Beta cells

Edra London, PhD, MSc

National Institute of Child Health and Human Development, Bethesda, Maryland, United States of America

Areas of Expertise - Obesity, Metabolism, Neuroscience, Nutrition, Adipose tissue biology

Stéphanie Lucas, PhD

Marrow Adiposity & Bone Lab, Boulogne-sur-Mer, France

Bone Marrow Adiposity, osteoporosis associated with menopause and metabolic disturbances, Pathophysiology of obesity and type 2 diabetes, Bone biology, Adipose tissues

View full biography

Zeynep Madak-Erdogan, PhD

University of Illinois Urbana-Champaign Department of Food Science and Human Nutrition, Urbana, Illinois, United States of America

Areas of expertise - Estrogen receptors, Breast Cancer, Menopause, Metabolic syndrome, Liver, System's biology, Genomics, Metabolomics, Transcriptomics

View full biography

Ozgur Mete, MD, FRCPC

University Health Network Toronto General Hospital Department of Pathology, Toronto, Canada

Areas of Expertise - Endocrine pathology, Pituitary pathology, Neuroendocrine neoplasms, Paraganglioma, Genotype-phenotype correlations in endocrine neoplasia

Julien Paccou, MD, PhD

Lille University Hospital, Lille, France

Osteoporosis, other bone diseases, bone marrow adipose tissue, bone impairment following intentional weight loss, epidemiology, clinical and translational research

View full biography

Rimesh Pal, MD, DM

Post Graduate Institute of Medical Education and Research, Chandigarh, India

Areas of Expertise - Metabolic bone disease, Osteoporosis, Osteomalacia, Diabetes mellitus, Sarcopenia, Metabolic Bone Disorders

View full biography

Juilee Rege, PhD

University of Michigan, Ann Arbor, Michigan, United States of America

Areas of expertise - Adrenal gland, Primary aldosteronism, Cushing syndrome, Adrenarche, Adrenal androgens

Rebecca B. Riggins, PhD

Georgetown Lombardi Comprehensive Cancer Center, Washington, District of Columbia, United States

Areas of Expertise - Orphan nuclear receptors, Steroid hormone receptors, Nuclear receptor signaling, Invasive lobular breast cancer, Cell and molecular biology, Breast cancer

Erica L. Scheller, DDS PhD

Washington University in St Louis School of Medicine, Saint Louis, Missouri, United States

Bone biology, Diabetes, Neuroscience, Adipose tissues

Ayesha Shajahan-Haq, PhD

Georgetown University Medical Center Lombardi Comprehensive Cancer Center Dept. of Oncology, Washington, District of Columbia, United States

Areas of Expertise - Cellular metabolic changes in drug resistance, Cell death pathways

Matthew J. Sikora, PhD

University of Colorado Anschutz Medical Campus Department of Pathology, Aurora, Colorado, United States

Areas of expertise - Breast cancer, Invasive lobular carcinoma of the breast, Hormone-dependent cancers, Steroid hormones, Estrogen receptor, Nuclear receptors, Estrogen and anti-estrogen pharmacology

Rita Strakovsky, Ph.D., R.D.

Michigan State University, East Lansing, Michigan, United States of America

Areas of Expertise - Pregnancy, Women's health, Obesity, Endocrine disrupting chemicals, Epidemiology, Nutrition, Fetal development

Constantine A. Stratakis, MD, DMedSci

National Institute of Child Health and Human Development, Bethesda, Maryland, United States of America

Amit Tirosh, MD

Chaim Sheba Medical Center The Endocrinology and Diabetes Research Center, Tel Aviv, Israel

Areas of Expertise - Neuroendocrine Tumors, Pituitary neoplasms, Hereditary endocrine multi-neoplasia syndromes, MEN-1, von Hippel-Lindau Disease, Cancer genetics and epigenetics, Cancer bioinformatics

Lindsey S. Treviño, PhD

City of Hope Beckman Research Institute, Duarte, California, United States of America

Areas of expertise - Hormone-dependent cancers, Endocrine-disrupting chemicals, Steroid hormone receptors, Epigenomics, Health disparities, Breast and ovarian cancer

Drenka Trivanovic

University of Belgrade, Institute for Medical Research, Belgrade, Serbia

Adipose tissue stem cells, Bone marrow adiposity, Cancer, Bone regeneration, Hematopoiesis, Obesity

View full biography

Adina Turcu, MD, MS

University of Michigan, Ann Arbor, Michigan, United States of America

Areas of expertise - Adrenal physiology, Adrenal disorders, Steroid biology, Mass spectrometry, Androgens

Jun Yang, MBBS (Hon), FRACP, PhD

Hudson Institute of Medical Research Endocrine Hypertension Research Group, Clayton, Australia

Areas of expertise - Mineralocorticoid receptor biology, Endocrine hypertension, Adrenal biology, Primary aldosteronism

View full biography

Mihail Zilbermint, MD

The Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America

Areas of Expertise - Diabetes, Hospital medicine, Adrenal diseases, Quality improvement, Business of medicine

All members of the Editorial Board have identified their affiliated institutions or organizations, along with the corresponding country or geographic region. Elsevier remains neutral with regard to any jurisdictional claims.

DAFTAR ISI

Laman : https://www.sciencedirect.com/journal/endocrine-and-metabolic-science/vol/17/suppl/C

Volume 17

In progress (March 2025)
This issue is in progress but contains articles that are final and fully citable.

Download full issue

Previous vol/issue

Next vol/issue

Actions for selected articles

Select all / Deselect all
Download PDFsExport citations

Show all article previewsShow all article previews

Receive an update when the latest issues in this journal are published

Set up journal alerts

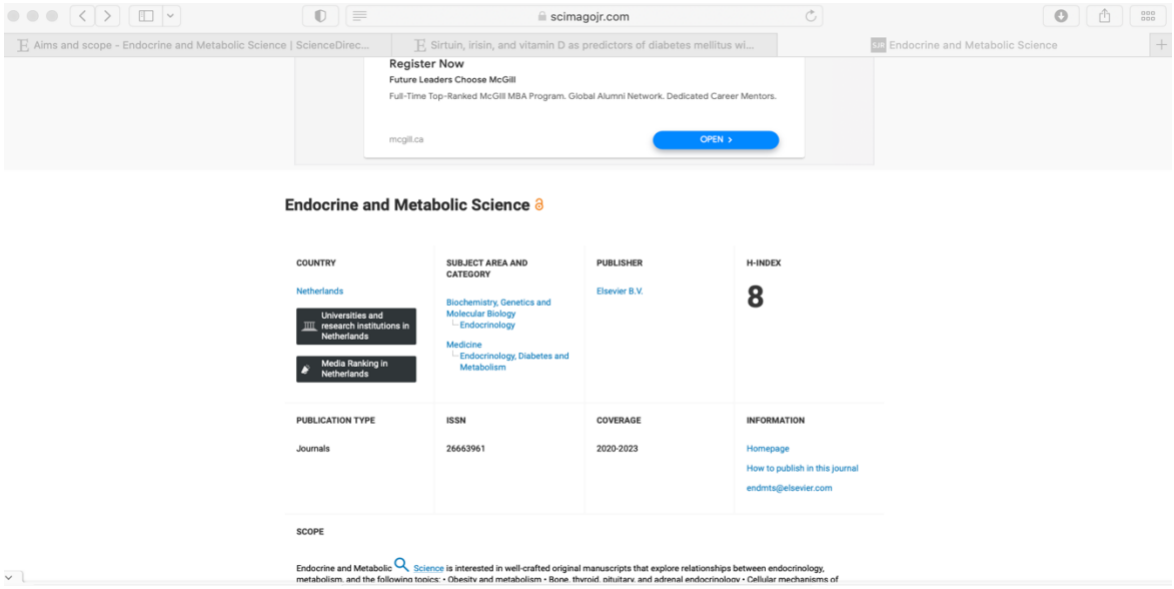
1. select article Mitochondrial dynamics, biogenesis, mitophagy and oxidative stress in gestational obesity: A review
   Review article*Open access*
   Mitochondrial dynamics, biogenesis, mitophagy and oxidative stress in gestational obesity: A review
   Karenth Milena Rodríguez-Córdoba, Sofia Agreda Soto, Jenniffer Alejandra Castellanos Garzón, Maria Carolina Pustovrh-Ramos
   Article 100205
   View PDF
   Article preview
2. select article CtBP: A mediator of a metabolic switch from homeostasis to carcinogenesis
   Review article*Open access*
   CtBP: A mediator of a metabolic switch from homeostasis to carcinogenesis
   Saumya Shukla, Raghvendra Singh
   Article 100208
   View PDF
   Article preview
3. select article Harnessing nanoscale innovations for enhanced healing of diabetic foot ulcers
   Short communication*Open access*
   Harnessing nanoscale innovations for enhanced healing of diabetic foot ulcers
   Marwan Al-Raeei

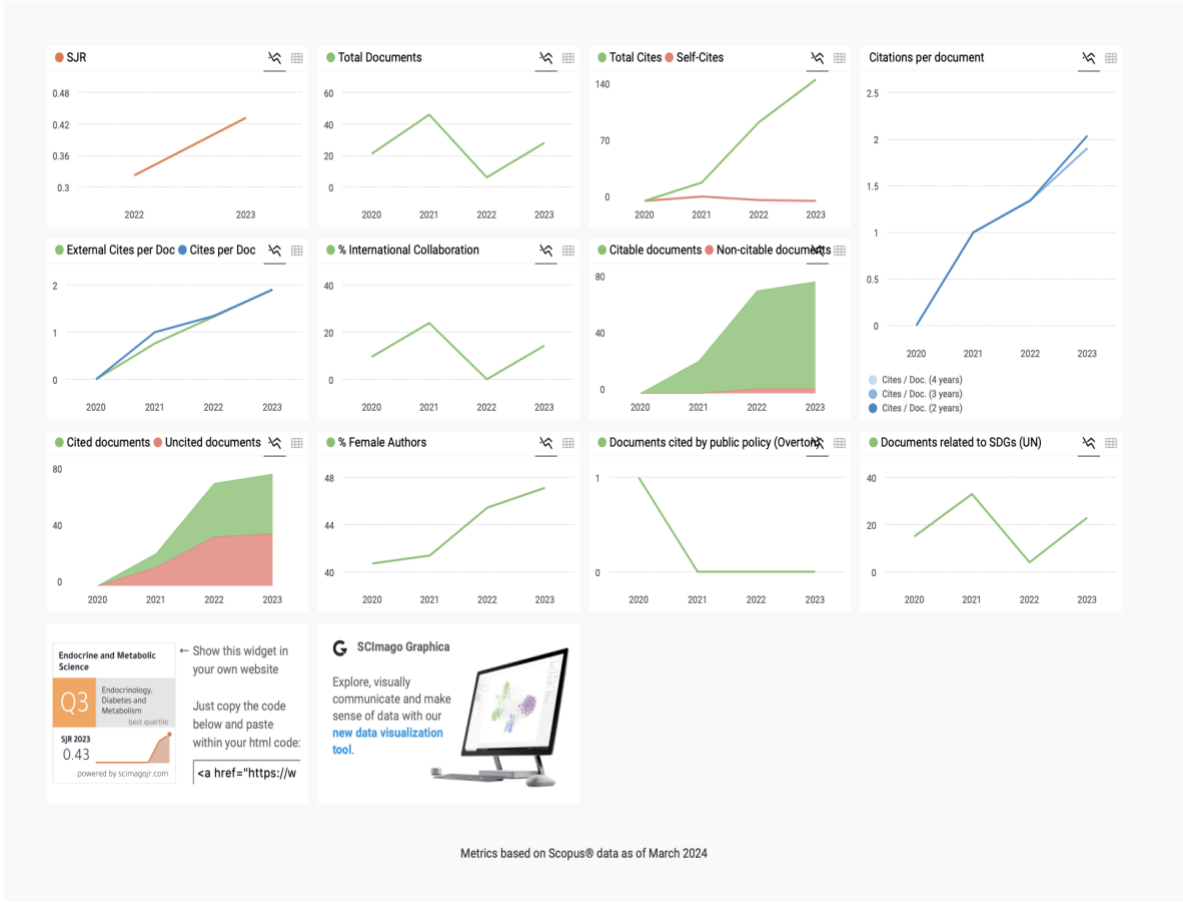
Article 100210
View PDF
Article preview

4. select article Systemic and meta-analyses of diabetic retinopathy and its care-related predictors after diabetic mellitus treatment initiation in Ethiopia
Review article*Open access*
Systemic and meta-analyses of diabetic retinopathy and its care-related predictors after diabetic mellitus treatment initiation in Ethiopia
Aboma Motuma, Abdi Birhanu, Lemma Demissie Regassa, Sina Tolera, ... Ibsa Mussa
Article 100209
View PDF
Article preview
5. select article Investigating the synergistic effects of gamma-glutamyl transferase with homocysteine, ferritin, and uric acid in patients with type II diabetes mellitus
Research article*Open access*
Investigating the synergistic effects of gamma-glutamyl transferase with homocysteine, ferritin, and uric acid in patients with type II diabetes mellitus
Simin Shirvani, Masomeh Halvaeezade, Maryam Avazzade, Morteza Golbashirzadeh, Atousa Moradzadegan
Article 100211
View PDF
Article preview
6. select article Etiopathogenesis and management updates on the comorbidity depression – Diabetes: A review of literature
Review article*Open access*
Etiopathogenesis and management updates on the comorbidity depression – Diabetes: A review of literature
Roland Muyisa Muhindo
Article 100213
View PDF
Article preview
7. select article Enhancing diabetes risk assessment through Bayesian networks: An in-depth study on the Pima Indian population
Research article*Open access*
Enhancing diabetes risk assessment through Bayesian networks: An in-depth study on the Pima Indian population
Xiaoling Liang, Wenhao Song, Weibing Yang, Zhenhua Yue
Article 100212
View PDF
Article preview
8. select article Sirtuin, irisin, and vitamin D as predictors of diabetes mellitus with uncontrolled glycemia in Indonesian patients
Research article*Open access*
Sirtuin, irisin, and vitamin D as predictors of diabetes mellitus with uncontrolled glycemia in Indonesian patients
Elly Herwana, Yenny, Alvina, Kurniasari, ... Pusparini
Article 100214
View PDF

SCIMAGO/SCOPUS

LAMAN: https://www.scimagojr.com/journalsearch.php?q=21101079112&tip=sid&clean=0





Endocrine and Metabolic Science 17 (2025) 100214

Contents lists available at ScienceDirect

Endocrine and Metabolic Science

journal homepage: www.elsevier.com/locate/endmts

Full length article

Sirtuin, irisin, and vitamin D as predictors of diabetes mellitus with uncontrolled glycemia in Indonesian patients

Elly Herwana [a,*], Yenny [a], Alvina [b], Kurniasari [a], Clarissa Asha Febinia [c], Pusparini [b]

[a] Department of Pharmacology and Pharmacy, Faculty of Medicine, Universitas Trisakti, Jakarta 11440, Indonesia
[b] Department of Clinical Pathology, Faculty of Medicine, Universitas Trisakti, Jakarta 11440, Indonesia
[c] Division of Biological Anthropology, Department of Archaeology, University of Cambridge, Cambridge CB2 1TN, United Kingdom

ARTICLE INFO

Keywords:
Insulin resistance
Sirtuin
Irisin
Vitamin D
HbA1c

ABSTRACT

The incidence of type 2 diabetes mellitus is increasing in developing countries, including Indonesia. Insulin resistance is a significant contributor to elevated blood glucose levels in type-2 diabetes patients. Low levels of serum sirtuin-1, irisin, and vitamin D have been linked to insulin resistance. This study aimed to identify risk factors that could predict uncontrolled glycemia and insulin resistance in Indonesian type-2 diabetes patients. We conducted a cross-sectional study with 73 adults from South Jakarta, Indonesia, in which we examined type-2 diabetes risk factors and biomarkers, including sex, age, body mass index, waist circumference, waist–to–hip ratio, fasting blood glucose (FBG) levels, fasting insulin, sirtuin-1, irisin, and vitamin D levels. The subjects were categorized into two groups based on their glycated hemoglobin (HbA1c) level and homeostatic model assessment for insulin resistance (HOMA-IR) index to assess glycemic control and insulin resistance, respectively. We compared risk factor profiles between groups and analyzed multivariate relationships with logistic regression. Our findings revealed that 54 % of the subjects had uncontrolled glycemia, whereas only 11 % had insulin resistance. There was a significant association between uncontrolled glycemia and reduced sirtuin-1 levels (odds ratio = 4.07; $p = 0.03$), which was confirmed in the multivariate analysis (beta = 5.41, $p = 0.014$) along with FBG (beta = 36.88, $p = 0.001$). Irisin showed a marginal association with insulin resistance in both univariate (odds ratio = 0.12; $p = 0.027$) and multivariate analyses (beta = 0.09; $p = 0.049$). In conclusion, sirtuin-1, in addition to FBG, is a potential marker for assessing glycemic control in type-2 diabetes patients.

1. Introduction

Diabetes mellitus is a chronic disease with a high global prevalence that continues to rise. The International Diabetes Federation reported an increase in the prevalence of diabetes from 9 % (463 million) in 2019 to 10.5 % (536.6 million) in 2021 (Sun et al., 2022). The prevalence of diabetes in Indonesia is estimated to double by 2045, reaching 16.09 % (40.7 million) compared with 9.19 % (18.69 million) in 2020 (Wahidin et al., 2024). Thus, there are public, academic, and government demands for intervention programs to manage diabetes risk factors.

The clinical manifestations of type 2 diabetes are heterogeneous, resulting in diverse progression to chronic complications. Hyperglycemia is the main sign of type-2 diabetes and is defined by high fasting blood glucose (FBG) levels. Glycemic levels in type-2 diabetes patients are also assessed by glycosylated hemoglobin (HbA1c) (American Diabetes Association, 2021). The pathogenesis and progression of diabetes are associated with a decreased number and function of pancreatic cells that secrete insulin, accompanied by reduced insulin sensitivity in the tissue. Insulin resistance is characterized by a failure to respond to insulin stimulation in various tissues caused by decreased sensitivity of insulin receptors (American Diabetes Association, 2021). The homeostatic model assessment for insulin resistance (HOMA-IR), developed by Matthews et al., quantifies insulin resistance and pancreatic β-cell function by considering plasma insulin levels and FBG (Matthews et al., 1985). Insulin resistance can affect the liver, skeletal muscle, and adipose tissues (Lee et al., 2021). The manifestation of insulin resistance in type-2 diabetes patients occurs due to the failure of pancreatic β-cells to compensate for the increased insulin secretion required at high blood sugar levels, resulting in impaired glucose tolerance.

The mechanisms underlying type-2 diabetes are not fully understood due to the polygenic nature of type-2 diabetes, which involves various physiological systems and is affected by environmental and dietary

* Corresponding author at: Jl. Letjen S. Parman No.260, Kampus B, RT.5/RW.9, Grogol, Jakarta Barat, DKI Jakarta 11440, Indonesia.
E-mail address: elly.herwana@trisakti.ac.id (E. Herwana).

https://doi.org/10.1016/j.endmts.2024.100214
Received 26 July 2024; Received in revised form 11 December 2024; Accepted 21 December 2024
Available online 24 December 2024

factors. New clinical and environmental risk factors, such as dietary and regulatory proteins, are continuously reported and have been established in recent years. Many of these newly proposed risk factors remain unconfirmed in populations in the Global South. In this study, we are particularly interested in risk factors that could predict glycemic control and insulin resistance in patients with confirmed type-2 diabetes in Indonesia. The chiefs among these factors were serum vitamin D, sirtuin-1, and irisin.

Recent studies have highlighted the role of vitamin D in the pathogenesis of type-2 diabetes. Vitamin D deficiency was found to be more prevalent among individuals with type-2 diabetes (Nasr et al., 2022). The pathogenesis of insulin resistance in the patients, such as pancreatic dysfunction and decreased β-cell mass, is associated with various risk factors, including vitamin D deficiency. Serum vitamin D levels are negatively associated with HbA1c (Buhary et al., 2017; Jha et al., 2020; Nasr et al., 2022), whereas vitamin D supplementation reduces HbA1c (Buhary et al., 2017; Mirhosseini et al., 2018; Safarpour et al., 2020) and HOMA-IR (Lei et al., 2023; Talaei et al., 2013; Xu et al., 2022). Safarpour et al. reported that, compared with placebo, vitamin D supplementation for six months significantly reduced HbA1c and increased sirtuin-1 and irisin levels; however, although there was a significant change in HOMA-IR after supplementation, it was not significantly different from that in the placebo group (Safarpour et al., 2020).

Sirtuins are a family of proteins involved in the regulation of various biological processes, including metabolic regulation, mitochondrial homeostasis, oxidative stress, inflammation, autophagy, and apoptosis. Sirtuin-1 is more widely studied compared to the other six sirtuins in mammals, particularly because of its regulatory role in aging, obesity, type-2 diabetes, cardiovascular diseases, neurodegenerative diseases, and cancer (Zhou et al., 2018). Sirtuin-1 is known to be negatively correlated with type-2 diabetes. A comparative study by Rahimi et al. revealed that sirtuin-1 levels were lower in individuals with uncontrolled glycemia than in those with controlled glycemia and healthy individuals (Rahimi et al., 2020).

Irisin is a novel myokine, a polypeptide secreted by an unknown protease protein containing a fibronectin type III domain (FNDC5), which is a membrane protein expressed in skeletal muscle, heart, liver, and adipose tissue (Akyuz et al., 2021). Irisin is a proteolytic cleavage product of FNDC5, whose expression is induced by the coactivator PPARγ 1 alpha (PGC1-α). Physical activity and exercise induce the expression of this gene, leading to the release of irisin into the circulation. This process increases energy expenditure and thermogenesis by increasing the levels of uncoupling protein 1 (UCP1) through the stimulation of peroxisome proliferator-activated receptor (PPAR)-γ coactivator (PGC-1α) PPAR-α expression in white adipose tissue (Moreno et al., 2015). Lower levels of irisin were reported in individuals with type-2 diabetes compared to those without type-2 diabetes (Choi et al., 2013; Moreno et al., 2015). Circulating irisin in blood was found to be associated with IR, as were age, sex, body mass index (BMI), and physical activity (Moreno et al., 2015). Taken together, these findings suggest that irisin might improve hyperglycemia by increasing energy expenditure, improving glucose homeostasis, and reducing insulin resistance.

Central to the pathophysiology of type 2 diabetes is systemic chronic inflammation, which leads to metabolic dysregulation, insulin resistance, and hyperglycemia (Ellulu and Samouda, 2022; Wu and Ballantyne, 2020). Vitamin D, sirtuin-1, and irisin possess anti-inflammatory properties; and vitamin D may support the functions of sirtuin-1 and irisin (Safarpour et al., 2020). The interplay of all three has the potential to mitigate the development of insulin resistance. Additionally, vitamin D is stored in adipose tissues, the liver, and muscle—where irisin is most highly expressed. This suggests a potential interplay between irisin and vitamin D that may enhance energy expenditure and adipose thermogenesis, both of which are crucial for maintaining metabolic homeostasis.

In this study, we measured the serum sirtuin-1, irisin, and vitamin D levels in Indonesian patients diagnosed with type-2 diabetes and investigated their associations with common type-2 diabetes risk factors, such as anthropometry and FBG. Furthermore, we established cutoff values for sirtuin-1 and irisin specific to type-2 diabetes within the population. Finally, we assessed the potential of sirtuin-1 and irisin as biomarkers for predicting uncontrolled glycemia and insulin resistance in type-2 diabetes patients.

2. Material and methods

2.1. Study design and subjects

This is a cross-sectional study with a targeted sampling strategy. Our study subjects were recruited through a community engagement activity with residents of the Mampang Prapatan district in South Jakarta, Indonesia, between June and November 2022. We enrolled men or women over 21 years of age who had been diagnosed with type-2 diabetes by a doctor and individuals with FBG $\geq$ 126 mg/dL without prior diagnosis of diabetes. Individuals with a history of kidney or liver dysfunction were excluded. Subjects were enrolled with informed consent. For the enrolled subjects with a history of diabetes, we recorded the time from their first diagnosis (in months) and the type of ongoing oral antidiabetic drug (OAD) treatment.

2.2. Sample and data collection

Venous blood samples were taken in the morning after the subjects had fasted for 10–12 h. The blood was used to measure FBG, HbA1c, insulin, vitamin D, sirtuin-1, irisin, alanine aminotransferase (ALT), creatinine, and albumin. To exclude patients with liver and kidney dysfunction, we used cutoff values of ALT >40 U/L, creatinine >1.1 mg/dL, and albumin <3.5 g/dL.

Interviews were conducted to obtain age and sex information. Body weight and height were measured, and BMI was calculated as body weight (kg) per square meter of height (m^2). Subjects with a BMI $\geq$ 25 kg/m^2 were categorized as obese. Waist circumference and hip circumference were measured in centimeters. We defined central obesity with cutoff points of 90 cm for waist circumference and 0.8 for the waist-to-hip ratio (World Health Organization, 2008). We also measured systolic and diastolic blood pressure (mmHg). Hypertension was determined on the basis of a systolic blood pressure $\geq$ 140 mmHg.

2.3. Laboratory measurements

HbA1c was measured with high-performance liquid chromatography (HPLC), and FBG was measured with the hexokinase enzymatic method. HbA1c and FBG values were used to differentiate controlled glycemia (HbA1c < 7 %; FBG < 140 mg/dL) from uncontrolled glycemia (HbA1c $\geq$ 7 %; FBG > 140 mg/dL). The HOMA-IR index was calculated as described in a previous study with the following formula: insulin level (μIU/mL) × FBG (mg/dL) / 405; individuals with a HOMA-IR value of $\geq$3.75 were categorized as insulin resistant (Kurniawan et al., 2018). Vitamin D levels were assessed with direct competitive chemiluminescent microparticle immunoassay (CMIA). Patients' vitamin D status was classified as either low if <20 ng/mL or sufficient if $\geq$20 ng/mL (Talaei et al., 2012). Human sirtuin-1 levels were determined with the Invitrogen Human SIRT1 ELISA Kit (catalog number EH427RB), and serum irisin levels were assessed with the Irisin ELISA Kit (BioVendor R&D; catalog number RAG018R). The assessments were performed following the manufacturers' protocol.

2.4. Statistical analysis

Numerical data were assessed for normality of distribution with the Shapiro–Wilk test. Owing to their nonnormal distributions, sirtuin-1, irisin, vitamin D, HbA1c, and HOMA-IR levels are reported as

medians, and the data ranges are expressed as the first and third interquartile ranges (IQRs). These parameters were compared between patients with uncontrolled glycemia and insulin-resistant patients with the Mann–Whitney U (MWU) test. Receiver operating characteristic (ROC) curves were generated to evaluate sirtuin-1 and irisin levels, as insulin-resistant patients had high HbA1c levels. The area under the curve (AUC) and optimal cutoff points for predicting HbA1c using sirtuin-1 and irisin were determined on the basis of the largest sum of sensitivity and specificity. Multivariate relationships between risk factors of uncontrolled glycemia and insulin resistance were assessed with logistic regression analysis, incorporating FBG, vitamin D, sirtuin-1, irisin levels, age, gender, BMI, waist circumference, waist-to-hip ratio, systolic blood pressure, and OAD consumption. We also applied a bi-directional stepwise model selection process to determine the combination of predictors for HbA1C and HOMA-IR status, selecting the model with the lowest Akaike Information Criterion (AIC) value as the optimal choice. All the statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 20.0 and R version 1.4.1. Statistical significance was considered at $p < 0.05$.

3. Results

3.1. Subject characteristics

Seventy-three out of eighty subjects fulfilled the inclusion and exclusion criteria. Table 1 describes the distribution of their characteristics at the time of enrollment. The majority of the subjects were women, with a male-to-female ratio of 1:4. Nearly 65 % of the sample was 60 years of age or younger. Obesity was observed in 65.8 % of the subjects, whereas central obesity was observed in 83.6 % (waist circumference ≥ 90 cm) and 93.2 % (waist-to-hip ratio ≥ 0.8) of the subjects. Systolic hypertension (≥140 mmHg) was present in 63 % of the subjects. A total of 47.9 % of the subjects had high FBG (≥140 mg/dL). Vitamin D deficiency (<20 ng/mL) was found in 91.8 % of the subjects. High HOMA-IR (≥3.75) was a minority at 11.0 %, whereas the HbA1c level was high (≥7 %) in most subjects at 74 %. Most subjects were recently diagnosed with diabetes within the last 12 months (46, 63 %), while the rest (27, 37 %) had been diagnosed between 13 and 36 months. Participants with a prior diagnosis (45 subjects) had been treated with OAD, with metformin being the most commonly prescribed, in line with the country's standard (53 %). Other reported OADs included glimepiride (1 subject), glibenclamide (3 subjects), and a combination therapy of metformin and glimepiride (2 subjects).

Table 1
Demography and clinical characteristics of the studied subjects.

Variables	Frequency	Percentage (%)
Sex		
Male	15	20.5
Female	58	79.5
Age group		
61–80 years old	26	35.6
35–60 years old	47	64.4
Obesity		
Obese (BMI ≥ 25 kg/m^2)	48	65.8
Nonobese (BMI < 25 kg/m^2)	25	34.2
Waist circumference		
High (≥90 cm)	60	83.6
Normal (<90 cm)	12	16.4
Waist-to-hip ratio		
High (≥0.8)	68	93.2
Normal (<0.8)	5	6.8
Systolic blood pressure		
Hypertension (≥140 mmHg)	46	63.0
Normal (<140 mmHg)	27	37.0
Fasting blood glucose		
High (≥140 mg/dL)	35	47.9
Normal (<140 mg/dL)	38	52.1
Vitamin D		
Insufficient (<20 ng/mL)	67	91.8
Sufficient (≥20 ng/mL)	6	8.2
HOMA-IR		
Insulin resistant (≥3.75)	8	11.0
Insulin responsive (<3.75)	65	89.0
HbA1c		
Uncontrolled glycemia (≥7 %)	54	74.0
Controlled glycemia (<7 %)	19	26.0
Diabetes duration		
≤12 months	46	63.0
>13 months	27	37.0
Antidiabetic treatment		
No OAD	28	38.4
Metformin	39	53.4
Glimepiride	1	1.4
Glibenclamide	3	4.1
Metfromin + Glimepiride	2	2.7

Abbreviations: BMI = body mass index; HOMA-IR = homeostatic model assessment for insulin resistance; HbA1c = glycosylated hemoglobin; OAD = oral antidiabetic drug.

3.2. Sirtuin-1 and irisin cutoff values in type-2 diabetes patients

Across 73 subjects, we observed that the median HbA1c level was 9.1 %, and the IQR was 6.8–11.0 %. The median HOMA-IR value was 1.12, and IQR of 0.33–2.09. Serum sirtuin-1 and irisin values had non-normal distributions (Shapiro-Wilk test, $p < 0.05$). Sirtuin-1 levels had a median of 0.45 ng/mL and IQR of 0.36–0.56 ng/mL. Irisin levels had a median of 28 μg/mL and IQR of 17.5–30.0 μg/mL.

We further investigated whether sirtuin-1 and irisin levels are different in our subjects with abnormal HbA1c levels. There was a significant difference in sirtuin-1 levels (MWU test, $p = 0.050$) between subjects with uncontrolled glycemia (HbA1c ≥ 7 %, 54 subjects) and those with normal glycemia (HbA1c < 7 %, 19 subjects). The median and IQR of sirtuin-1 levels were 0.39 (0.36–0.52) ng/mL in patients with uncontrolled glycemia and 0.55 (0.37–0.62) ng/mL in patients with controlled glycemia. In contrast, the irisin levels were not significantly different (MWU test, $p = 0.128$). Irisin levels had a median and IQR of 27.9 (15.6–30.0) μg/mL in patients with uncontrolled glycemia, which is comparable to the range of 28.9 (22.3–30.0) μg/mL reported in patients with controlled glycemia.

In addition, we investigated whether sirtuin-1 and irisin levels differ between subjects with insulin resistance. We found no difference in the circulating levels of sirtuin-1 (MWU test, $p = 0.219$) or irisin (MWU test, $p = 0.314$) between the insulin-resistant group (HOMA-IR ≥ 3.75, 8 subjects) and the insulin-responsive group (HOMA-IR < 3.75, 65 subjects).

Compared with the insulin-responsive group, the insulin-resistant group presented a modestly elevated median and IQR of 0.59 (0.36–0.98) ng/mL, whereas the insulin-responsive group presented 0.44 (0.36–0.55) ng/mL. The median and IQR of irisin concentration was 21.44 (17.9–26.7) μg/mL in the insulin-resistant group, which is lower compared to 28.9 (17.2–30.0) μg/mL in the insulin-responsive group. Owing to the low prevalence of insulin resistance in our data, we refrained from determining cutoff points for HOMA-IR.

To determine cutoff points for sirtuin-1 and irisin for patients with uncontrolled glycemia, we performed receiver ROC analysis. ROC analysis of sirtuin-1 revealed an area under the curve of 0.652, with a 95 % confidence interval ranging 0.501–0.893 (Fig. 1a). These values suggest that the role of sirtuin-1 in determining uncontrolled glycemia is weak (between 0.6 and 0.7). The optimal cutoff point for sirtuin-1 levels in our data was 0.49 ng/mL, with a sensitivity of 70.4 % and a specificity of 63.2 % for detecting uncontrolled glycemia in patients (Fig. 1b).

Although there was no significant difference in irisin levels between the uncontrolled and controlled glycemia groups, ROC analysis revealed an area under the curve value of 0.578, with a 95 % confidence interval ranging from 0.445 to 0.712 (Fig. 1c). This value indicates that irisin levels do not play a significant role in determining uncontrolled glycemia. The optimal cutoff point for irisin was 28.385 μg/mL, with a

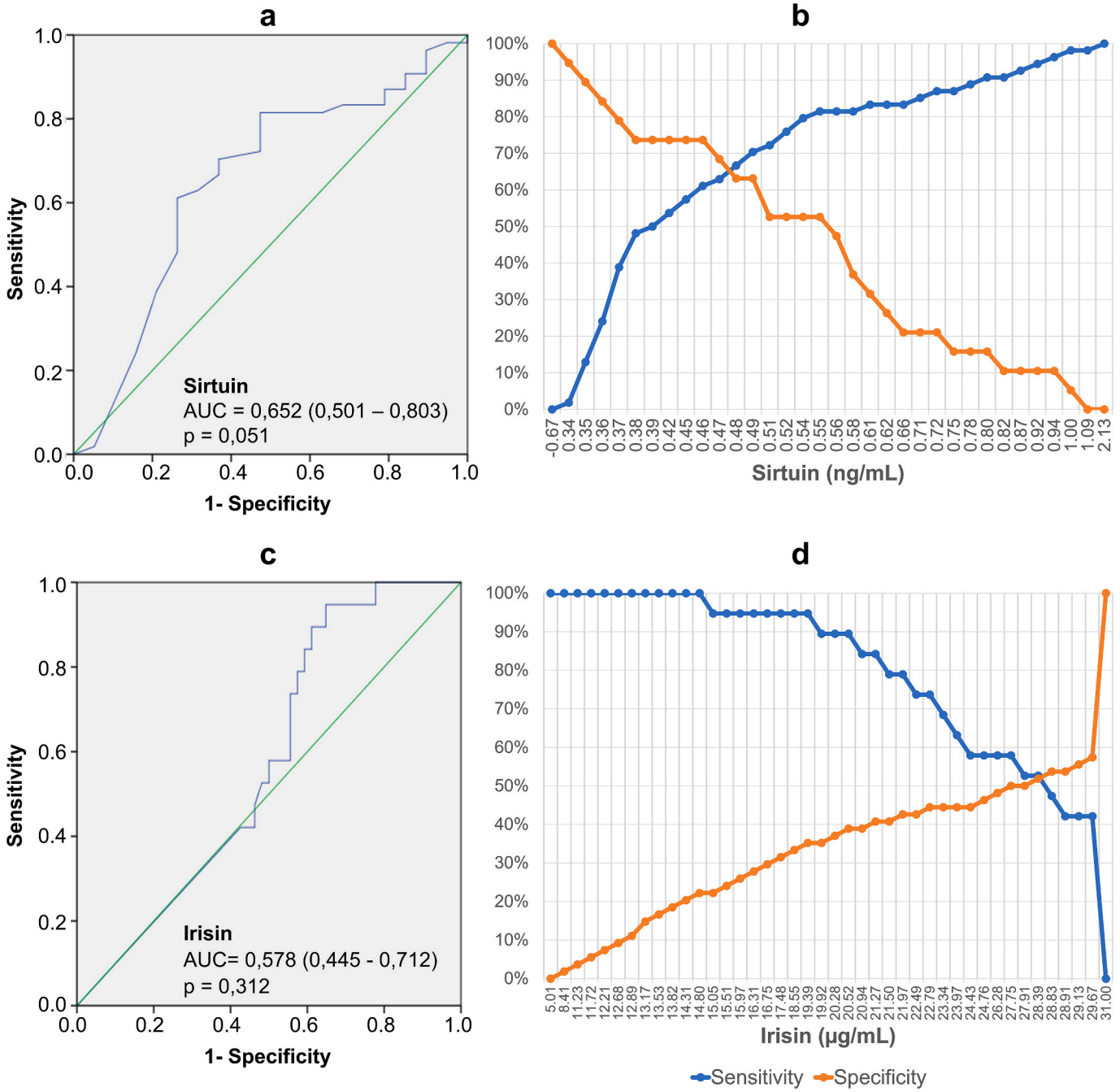


Fig. 1. Determination of cutoff points for sirtuin-1 and irisin in type-2 diabetes patients with uncontrolled glycemia; a, ROC curve for sirtuin-1; diagonal segments are produced by ties; b, sensitivity and specificity curves for sirtuin-1; c, ROC curve for irisin; d, sensitivity and specificity curves for irisin.

sensitivity and specificity of 51.9 % (Fig. 1d).

3.3. Associations of HbA1c and HOMA-IR with type-2 diabetes risk factors

We examined the relationships between various risk factors and uncontrolled glycemia. We found that high FBG, vitamin D deficiency, and low sirtuin-1 levels were associated with a high risk for uncontrolled glycemia (Table 2). As expected, patients with FBG levels above 140 mg/dL have a 30.6 times greater risk than those with lower blood sugar levels; the association is strongly significant, with a 95 % confidence interval (95 % CI) between 3.79 and 246.9 times greater. Patients with vitamin D deficiency had a 6.93-fold greater risk, with a 95 % CI between 1.16 and 41.6. Patients with low sirtuin-1 levels (<0.49 ng/mL) have a 4.07-fold greater risk for uncontrolled glycemic condition, with a 95 % CI between 1.36 and 12.23. On the other hand, we found no associations between HOMA-IR score and risk factors, except for irisin (Table 2). An elevated irisin was significantly associated with a lower risk for insulin resistance, but the decrease in odds was negligible (0.12 times).

Significant differences in both HbA1C and HOMA-IR were observed between subjects who consumed OADs, highlighting the impact of OAD consumption on diabetes phenotypes (Table 2). We further performed MWU tests to assess if sirtuin-1 and irisin levels were affected by OAD consumption, but we found no significant difference (all $p > 0.05$).

Table 2
HbA1c and HOMA-IR associations with sirtuin-1, irisin, and T2DM factors.

Risk factor	HbA1c (%)						HOMA-IR					
	≥7	<7	*p*	OR	95 % CI		≥3.75	<3.75	*p*	OR	95 % CI	
					Low	High					Low	High
Sex												
Male	11	4	1.000	0.96	0.27	3.47	1	14	0.956	0.52	0.06	4.59
Female	43	15					7	51				
Age group												
61–80-year-old	17	9	0.214	0.51	0.18	1.49	2	24	0.809	0.57	0.11	3.05
35–60-year-old	37	10					6	41				
BMI												
≥25 kg/m^2	34	14	0.397	0.61	0.19	1.94	5	43	1.000	0.85	0.19	3.90
<25 kg/m^2	20	5					3	22				
Waist circumference												
≥90 cm	44	17	0.680	0.52	0.11	2.61	7	54	1.000	1.43	0.16	12.78
<90 cm	10	2					1	11				
Waist-to-hip ratio												
≥0.8	50	18	1.000	0.69	0.07	6.63	8	60	1.000	1.55	0.54	4.42
<0.8	4	1					0	5				
Fasting blood glucose												
≥140 mg/dL	34	1	**<0.001*****	30.60	3.79	246.9	2	36	0.211	0.27	0,05	1.43
<140 mg/dL	20	18					6	29				
Vitamin D levels												
<20 ng/mL	52	15	**0.073**^	6.93	1.16	41.6	8	59	1.000	1.86	0.48	7.18
≥20 ng/mL	2	4					0	6				
Sirtuin-1 levels												
≤0.49 ng/mL	38	7	**0.010***	4.07	1.36	12.23	1	18	0.656	0.37	0.04	3.25
>0.49 ng/mL	16	12					7	47				
Irisin levels												
≥28.375 μg/mL	26	10	0.737	0.840	0.290	2.38	1	35	**0.027***	0.12	0.01	1.05
<28.375 μg/mL	28	9					7	30				
Antidiabetic treatment												
No OAD	15	13	**0.002****	0.18	0.06	0.55	0	28	**0.02***	0.08	0.01	0.65
OAD	39	6					8	37				

OR = odds ratio; OAD = oral antidiabetic drug. OR and *p*-value, obtained from Fisher Exact test for count data. Significant values are marked as ^ for $p < 0.1$ (marginal), * for $p < 0.05$; ** for $p < 0.01$, and *** for $p < 0.001$.

3.4. Predictors of HbA1c and HOMA-IR in type-2 diabetes patients

To further understand the relationship between risk factors in our data, we conducted a multivariate logistic regression analysis incorporating sirtuin-1, irisin, FBG, and vitamin D levels, along with age, sex, BMI, waist circumference, waist-to-hip ratio, systolic blood pressure, and OAD consumption. Furthermore, we used a bi-directional stepwise model selection process to identify the optimal combination of HbA1C and HOMA-IR status predictors. The model with the smallest Akaike Information Criterion (AIC) value was selected as the most suitable.

The result showed that sirtuin-1 was positively associated with HbA1C in both the full model and the optimal model, although the strength of the association was lower (6.8-fold reduction) than that of FBG (Table 3). On the other hand, irisin showed a weak and marginal association with HOMA-IR. HOMA-IR was also linked to OAD consumption, although these relationships were not statistically significant. Interestingly, we found no significant association between HbA1C and vitamin D level in the multivariate analysis, despite observing a marginal correlation in the univariate analysis (Table 2).

4. Discussion

This study investigated key risk factors for predicting uncontrolled glycemia and insulin resistance in type-2 diabetes patients in Indonesia. We assessed sirtuin-1, irisin, and vitamin D levels and their relationships with typical type-2 diabetes risk factors, including anthropometric parameters, FBG, HbA1c, and the HOMA-IR index. We established specific cutoff values for sirtuin-1 and irisin and evaluated these markers as potential glycemic control and insulin resistance predictors in Indonesian type-2 diabetes patients.

The use of HbA1c and HOMA-IR for classifying type-2 diabetes patients has been considered in clinical settings. While a recent systematic review reported that HbA1c is a reliable marker with high specificity for type-2 diabetes (Butler et al., 2021), there is a lack of consensus on the HOMA-IR reference value. Studies have shown that HOMA-IR values differ by ethnicity, age, and sex. For example, South Asians, particularly first-generation migrants, exhibit higher HOMA-IR values than European and African Caribbean populations (Molinari et al., 2021). Similarly, research indicates that Hispanic populations have higher HOMA-IR values than Caucasians (Wallace et al., 2004). The reported HOMA-IR values across different ethnicities were 2.29 for Caucasians, 3.80 for middle-aged Mexican Americans (Qu et al., 2011), 2.3 for elderly Taiwanese individuals (Cheng et al., 2017), and 3.63 for middle-aged individuals in the Czech Republic (Horáková et al., 2019).

We found a low incidence of insulin resistance based on HOMA-IR in confirmed type-2 diabetes patients despite the use of a cutoff value for HOMA-IR specific to our studied population and a high incidence of uncontrolled glycemia (HbA1c over 7 %). The incidence of uncontrolled glycemia was five times greater than the incidence of insulin resistance. This finding suggests that the association between HbA1c and HOMA-IR is not linear, possibly due to varying manifestations, antidiabetic medications, or confounding factors related to population bias. Furthermore, the majority of our subjects (61.6 %) had received diabetes medication prior to enrollment and, therefore, may also have reduced insulin levels, affecting the baseline for HOMA-IR scoring.

Furthermore, we found no significant correlation between HOMA-IR and anthropometric risk factors (*i.e.*, body mass index, waist circumference, and waist-to-hip ratio). There were also no significant associations between anthropometric factors and HbA1c. HOMA-IR has established associations with obesity, waist circumference, body fat, and visceral fat (Cheng et al., 2017; Kurniawan et al., 2018). Saravia et al. reported a significant difference in HOMA-IR and HbA1c when

Table 3
Multivariate associations of HbA1C and HOMA-IR with T2DM risk factors.

Covariates	HbA1C				HOMA-IR			
	Full model		Optimal model		Full model		Optimal model	
	beta	*p*	beta	*p*	beta	*p*	beta	*p*
Sirtuin								
1: >0.49 ng/mL	5.38	**0.037***	5.41	**0.014***	0.18	0.144	0.21	0.105
0: ≤0.49 ng/mL								
Irisin								
1: >28.375 μg/mL	1.36	0.697	–	–	0.05	**0.065^**	0.09	**0.049***
0: ≤28.375 μg/mL								
Fasting blood glucose								
1: ≥140 mg/dL	16.87	**0.028***	36.88	**0.001****	1.07	0.959	–	–
0: <140 mg/dL								
Vitamin D level								
1: ≥20 ng/mL	−1.86	0.211	–	–	−16.56	0.998	–	–
0: <20 ng/mL								
Age								
1: ≥61 years old	0.1	0.906	–	–	−0.73	0.636	–	–
0: <61 years old								
Body mass index								
1: ≥25 kg/m^2	−0.83	0.427	–	–	0.47	0.783	–	–
0: <25 kg/m^2								
Waist circumference								
1: M ≥ 90 cm; F ≥ 80 cm	0.94	0.585	–	–	−2.69	0.297	–	–
0: M < 90 cm; F < 80 cm								
Waist-to-hip ratio								
1: ≥0.8	0.21	0.913	–	–	14.22	0.998	–	–
0: <0.8								
Systolic hypertension								
1: ≥140 mmHg	0.17	0.833	–	–	−0.09	0.935	–	–
0: <140 mmHg								
Sex								
0: Female	0.15	0.893	–	–	−1.47	0.38	–	–
1: Male								
Antidiabetic treatment								
Metformin	1.12	0.15	–	–	19.15	0.995	19.05	0.995
Glimepiride	14.54	0.998			42.03	0.998	41.08	0.998
Glibenclamide	16.74	0.996			−0.6	1	−0.38	1
Metformin+Glimepiride	15.64	0.997			−1.64	1	0.7	1

Beta and *p*-value were obtained from logistic regression analysis. Significant values are marked as ^ for $p < 0.1$ (marginal), * for $p < 0.05$, and ** for $p < 0.01$. The optimum model was selected based on the lowest Akaike Information Criteria in a bi-directional step-wise selection method.

comparing groups with and without metabolic syndrome (Saravia et al., 2015). Importantly, the majority of our studied subjects were obese according to the WHO Asia Pacific standards. Therefore, there were minimal variations in BMI, waist circumference, body fat, and visceral fat between the groups in our data.

We also did not find that HOMA-IR was associated with serum FBG or vitamin D levels. In the univariate analysis, we observed a marginal association between vitamin D and HbA1C. However, this association was not significant in the multivariate analysis, which accounted for other phenotypic risk factors (age, gender, obesity, hypertension) and diabetes medications as cofactors. A clinical trial previously reported that Vitamin D supplementation reduced HbA1c and increased HOMA-IR, although the change in HOMA-IR was not significant compared with that of the placebo (Safarpour et al., 2020). Other studies, however, have reported a negative vitamin D correlation with both HbA1c (Buhary et al., 2017; Jha et al., 2020) and insulin resistance (Xu et al., 2022). Talei et al. reported that vitamin D supplementation led to lower levels of FBG and HOMA-IR (Talaei et al., 2013). Mirhosseini et al. also demonstrated that vitamin D supplementation improved FBG, glycemic control, and insulin resistance in individuals with prediabetes and a high risk of type-2 diabetes (Mirhosseini et al., 2018). We acknowledge that the low incidence of insulin resistance in our data might limit the robustness of the association analyses for HOMA-IR.

We found a strong association between HbA1c and sirtuin-1. Our data suggest an optimal cutoff value for predicting HbA1c using sirtuin-1 at 0.49 ng/mL, although the effect size, sensitivity, and specificity are modest. Rahimi et al. also reported significant differences in sirtuin-1 levels among individuals with uncontrolled diabetes, individuals with controlled diabetes, and healthy controls and reported a negative correlation between sirtuin-1 levels and HbA1c, and also with FBG (Rahimi et al., 2020). Curiously, we found no association between the serum irisin level and the HbA1c level. This contradicts the findings of a recent meta-analysis that revealed a significant difference in irisin levels between individuals with diabetes and those without diabetes (Song et al., 2021). Our data does not support the negative correlations between irisin levels and hyperglycemia (Ahmed et al., 2023; Khajebishak et al., 2023). Furthermore, we could not confirm the associations of HOMA-IR with sirtuin-1 and irisin in type-2 diabetes patients in Indonesia. The lack of associations may be attributed to the low incidence of insulin resistance in our study.

Our multivariate logistic regression analysis demonstrated that sirtuin-1 levels are associated with HbA1c levels, concurrently with FBG. Although FBG emerged as the strongest predictor, with an effect approximately seven times larger than that of sirtuin-1, this was expected. Our model only partially supports the results of Safarpour et al., who demonstrated that vitamin D supplementation also improved diabetic risk factors, accompanied by elevated sirtuin-1 and irisin levels (Safarpour et al., 2020). We recommend further investigations into the roles of sirtuin-1 and irisin in glycemic control, insulin resistance, and the management of patients with type-2 diabetes.

Our subjects reported using three types of OADs: metformin, glimepiride, and glibenclamide. Metformin, a biguanide, reduces glucose production in the liver and enhances insulin sensitivity in muscle and adipose tissue without stimulating insulin secretion. In contrast,

glibenclamide and glimepiride, which belong to the sulfonylurea class, act as insulin secretagogues, stimulating insulin secretion in the pancreas. Only six subjects (8 %) in this study reported using these drugs, while the majority used metformin. These OADs were significantly associated with both HbA1C levels and HOMA-IR values in the univariate analyses, but not in the multivariate.

OAD consumption did not significantly impact the association between sirtuin-1 and HbA1C in this study. However, there is some evidence that the role of sirtuin-1 in glucose control and insulin signaling is affected by hyperglycemic and insulin-resistant conditions *in vitro* (Jeon et al., 2019; Tu et al., 2021). Given that OADs are used to manage hyperglycemia and insulin resistance, their impact on these conditions could potentially influence sirtuin-1 expression and activity, which may, in turn, affect glucose metabolism and insulin sensitivity. Thus, further research is needed to understand how OAD consumption interacts with sirtuin-1.

We acknowledge several limitations in this study. The relatively small sample size of type-2 diabetes patients with elevated HOMA-IR may reduce the robustness of our association analyses for insulin resistance. Lifestyle factors, such as physical activity, nutritional status, and consumption of other medications, may impact the expression of sirtuin-1 and irisin. The cross-sectional design restricts our ability to establish causal relationships between risk factors, glycemic control, and insulin resistance. The relatively young age of our subjects raises the possibility of atypical diabetes types, such as maturity-onset diabetes of the young (MODY), which may have different clinical manifestations from typical type-2 diabetes. Lastly, considering the influence of environmental and genetic factors in the complex pathophysiology of type-2 diabetes, our findings—based on a specific community in Indonesia—should be validated in other populations.

5. Conclusion

Our study contributes valuable insights into potential predictors and biomarkers for managing type-2 diabetes. We evaluated the associations between glycemic control, insulin resistance, and several risk factors in patients with type-2 diabetes. Among these factors, sirtuin-1 has a significant association with uncontrolled glycemia, along with FBG, in type-2 diabetes patients. On the other hand, vitamin D and irisin were not strongly associated with either glycemic control or insulin resistance. Further multicenter studies with larger cohorts are recommended to gain a more comprehensive understanding of the role of sirtuin-1, irisin, and vitamin D in glycemic control, insulin resistance, and the pathogenesis of type-2 diabetes in Indonesia. Although the predictive roles of sirtuin-1 and irisin for diabetic phenotypes appear modest in our study and may not yet support their use in current clinical practice, we believe these biomarkers warrant further investigation as potential tools for diabetes sub-classification, as assessment markers for treatment effectiveness, and as new therapeutic targets.

Abbreviations

FBG	fasting blood glucose
HOMA-IR	homeostatic model assessment for insulin resistance
BMI	body mass index
OAD	oral antidiabetic drug
ALT	alanine aminotransferase
IQR	interquartile range
MWU	Mann-Whitney U
ROC	receiver operating characteristic
AUC	area under the curve
CI	confidence interval
OR	odds ratio

CRediT authorship contribution statement

Elly Herwana: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Conceptualization. **Yenny:** Writing – review & editing, Methodology. **Alvina:** Writing – review & editing, Methodology. **Kurniasari:** Writing – review & editing, Methodology. **Clarissa Asha Febinia:** Writing – review & editing, Writing – original draft, Visualization. **Pusparini:** Writing – review & editing, Methodology.

Ethical considerations

This study was reviewed by the ethics committee at the Faculty of Medicine, Universitas Trisakti and adhered to World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subject. The ethics permission was received ethical clearance (No: 183/KER/VI/2022). All procedures were performed in compliance with relevant laws and institutional guidelines. The subjects were thoroughly informed about the research and were required to sign a consent form to participate. Research data were anonymized to protect patients' names, initials, hospital numbers, dates of birth, and any other personal or identifying information.

Funding sources

This study was funded by an internal grant from the Universitas Trisakti research funds.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Elly Herwana reports financial support and article publishing charges were provided by Trisakti University. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors thank all the study participants, laboratory personnel, and funding institution (Faculty of Medicine, Universitas Trisakti).

Data availability

Data will be made available on request.

References

Ahmed, T.M., Nassar, M., Mohamed, H.A.A., Elhadidy, K.E., Farhan, H.M., El Basset, A.S. A., Elmessiery, R.M., Kamel, M.F., 2023. Evaluation of serum levels of Irisin as a marker of endothelial dysfunction in patients with type 2 diabetes mellitus. Endocrinol. Diabetes Metab. 6, e403. https://doi.org/10.1002/edm2.403.

Akyuz, A., Mert, B., Ozkaramanli Gur, D., Mucip Efe, M., Aykac, H., Alpsoy, S., Guzel, S., 2021. Association of lower serum irisin levels with diabetes mellitus: irrespective of coronary collateral circulation, and syntax score. North. Clin. Istanb. 8, 607–614. https://doi.org/10.14744/nci.2021.73669.

American Diabetes Association, 2021. Professional practice committee: standards of medical care in diabetes—2022. Diabetes Care 45, S3. https://doi.org/10.2337/dc22-Sppc.

Buhary, B.M., Almohareb, O., Aljohani, N., Alrajhi, S., Elkaissi, S., Sherbeeni, S., Almaghamsi, A., Khan, S.A., Almalki, M.H., 2017. Association of glycosylated hemoglobin levels with vitamin D status. J. Clin. Med. Res. 9, 1013–1018. https://doi.org/10.14740/jocmr3227w.

Butler, A.E., English, E., Kilpatrick, E.S., Östlundh, L., Chemaitelly, H.S., Abu-Raddad, L. J., Alberti, K.G.M.M., Atkin, S.L., John, W.G., 2021. Diagnosing type 2 diabetes using Hemoglobin A1c: a systematic review and meta-analysis of the diagnostic cutpoint based on microvascular complications. Acta Diabetol. 58, 279–300. https://doi.org/10.1007/s00592-020-01606-5.

Cheng, Y.-H., Tsao, Y.-C., Tzeng, I.-S., Chuang, H.-H., Li, W.-C., Tung, T.-H., Chen, J.-Y., 2017. Body mass index and waist circumference are better predictors of insulin

resistance than total body fat percentage in middle-aged and elderly Taiwanese. Medicine 96, e8126. https://doi.org/10.1097/MD.0000000000008126.
Choi, Y.-K., Kim, M.-K., Bae, K.H., Seo, H.-A., Jeong, J.-Y., Lee, W.-K., Kim, J.-G., Lee, I.-K., Park, K.-G., 2013. Serum irisin levels in new-onset type 2 diabetes. Diabetes Res. Clin. Pract. 100, 96–101. https://doi.org/10.1016/j.diabres.2013.01.007.
Ellulu, M.S., Samouda, H., 2022. Clinical and biological risk factors associated with inflammation in patients with type 2 diabetes mellitus. BMC Endocr. Disord. 22, 16. https://doi.org/10.1186/s12902-021-00925-0.
Horáková, D., Štěpánek, Ladislav, Janout, V., Janoutová, J., Pastucha, D., Kollárová, H., Petráková, A., Štěpánek, Lubomír, Husár, R., Martiník, K., 2019. Optimal homeostasis model assessment of insulin resistance (HOMA-IR) cut-offs: a cross-sectional study in the Czech population. Medicina 55, 158. https://doi.org/10.3390/medicina55050158.
Jeon, J.Y., Choi, S.-E., Ha, E.S., Lee, H.B., Kim, T.H., Han, S.J., Kim, H.J., Kim, D.J., Kang, Y., Lee, K.-W., 2019. GLP-1 improves palmitate-induced insulin resistance in human skeletal muscle via SIRT1 activity. Int. J. Mol. Med. 44, 1161–1171. https://doi.org/10.3892/ijmm.2019.4272.
Jha, S.C., Kumar, H., Faisal, S.Y., 2020. Correlation between vitamin D and HbA1c in type 2 diabetic patients. Acad. J. Med. 3, 4–10.
Khajebishak, Y., Faghfouri, A.H., Soleimani, A., Peyrovi, S., Payahoo, L., 2023. The potential relationship between serum Irisin concentration with inflammatory cytokines, oxidative stress biomarkers, glycemic indices and lipid profiles in obese patients with type 2 diabetes mellitus: a pilot study. J. ASEAN Fed. Endocr. Soc. 38, 45–51. https://doi.org/10.15605/jafes.038.01.13.
Kurniawan, L.B., Bahrun, U., Hatta, M., Arif, M., 2018. Body mass, total body fat percentage, and visceral fat level predict insulin resistance better than waist circumference and body mass index in healthy young male adults in Indonesia. J. Clin. Med. 7, 96. https://doi.org/10.3390/jcm7050096.
Lee, S.-H., Park, S.-Y., Choi, C.S., 2021. Insulin resistance: from mechanisms to therapeutic strategies. Diabetes Metab. J. 46, 15–37. https://doi.org/10.4093/dmj.2021.0280.
Lei, X., Zhou, Q., Wang, Y., Fu, S., Li, Z., Chen, Q., 2023. Serum and supplemental vitamin D levels and insulin resistance in T2DM populations: a meta-analysis and systematic review. Sci. Rep. 13, 12343. https://doi.org/10.1038/s41598-023-39469-9.
Matthews, D.R., Hosker, J.P., Rudenski, A.S., Naylor, B.A., Treacher, D.F., Turner, R.C., 1985. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28, 412–419. https://doi.org/10.1007/BF00280883.
Mirhosseini, N., Vatanparast, H., Mazidi, M., Kimball, S.M., 2018. Vitamin D supplementation, glycemic control, and insulin resistance in prediabetics: a meta-analysis. J. Endocr. Soc. 2, 687–709. https://doi.org/10.1210/js.2017-00472.
Molinari, M., de Iorio, M., Chaturvedi, N., Hughes, A., Tillin, T., 2021. Modelling ethnic differences in the distribution of insulin resistance via Bayesian nonparametric processes: an application to the SABRE cohort study. Int. J. Biostat. 17, 153–164. https://doi.org/10.1515/ijb-2019-0108.
Moreno, M., Moreno-Navarrete, J.M., Serrano, M., Ortega, F., Delgado, E., Sanchez-Ragnarsson, C., Valdés, S., Botas, P., Ricart, W., Fernández-Real, J.M., 2015. Circulating Irisin levels are positively associated with metabolic risk factors in sedentary subjects. PLoS ONE 10, e0124100. https://doi.org/10.1371/journal.pone.0124100.
Nasr, M.H., Hassan, B.A.R., Othman, N., Karuppannan, M., Abdulaziz, N.B., Mohammed, A.H., Alsarani, M.A., Eskembaji, M.H., Aman, A.M., Othman, G., 2022. Prevalence of vitamin D deficiency between type 2 diabetes mellitus patients and non-diabetics in the Arab gulf. Diabetes Metab. Syndr. Obes. 15, 647–657. https://doi.org/10.2147/DMSO.S350626.
Qu, H.-Q., Li, Q., Rentfro, A.R., Fisher-Hoch, S.P., McCormick, J.B., 2011. The definition of insulin resistance using HOMA-IR for Americans of Mexican descent using machine learning. PLoS ONE 6, e21041. https://doi.org/10.1371/journal.pone.0021041.
Rahimi, M., Ghanbari, S., Khazaei, M., Niroman, E., 2020. Comparison of sirtuin 1 level and related blood factors in diabetic and healthy subjects. Pediatr. Endocrinol. Diabetes Metab. 26, 17–21. https://doi.org/10.5114/pedm.2020.94392.
Safarpour, P., Daneshi-Maskooni, M., Vafa, M., Nourbakhsh, M., Janani, L., Maddah, M., Amiri, F.-S., Mohammadi, F., Sadeghi, H., 2020. Vitamin D supplementation improves SIRT1, Irisin, and glucose indices in overweight or obese type 2 diabetic patients: a double-blind randomized placebo-controlled clinical trial. BMC Fam. Pract. 21, 26. https://doi.org/10.1186/s12875-020-1096-3.
Saravia, G., Civeira, F., Hurtado-Roca, Y., Andres, E., Leon, M., Pocovi, M., Ordovas, J., Guallar, E., Fernandez-Ortiz, A., Casasnovas, J.A., Laclaustra, M., 2015. Glycated hemoglobin, fasting insulin and the metabolic syndrome in males. Cross-sectional analyses of the Aragon Workers' Health Study Baseline. PLoS ONE 10, e0132244. https://doi.org/10.1371/journal.pone.0132244.
Song, R., Zhao, X., Zhang, D.-Q., Wang, R., Feng, Y., 2021. Lower levels of irisin in patients with type 2 diabetes mellitus: a meta-analysis. Diabetes Res. Clin. Pract. 175, 108788. https://doi.org/10.1016/j.diabres.2021.108788.
Sun, H., Saeedi, P., Karuranga, S., Pinkepank, M., Ogurtsova, K., Duncan, B.B., Stein, C., Basit, A., Chan, J.C.N., Mbanya, J.C., Pavkov, M.E., Ramachandaran, A., Wild, S.H., James, S., Herman, W.H., Zhang, P., Bommer, C., Kuo, S., Boyko, E.J., Magliano, D. J., 2022. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res. Clin. Pract. 183, 109119. https://doi.org/10.1016/j.diabres.2021.109119.
Talaei, A., Yadegari, N., Rafee, M., Rezvanfar, M.R., Moini, A., 2012. Prevalence and cut-off point of vitamin D deficiency among secondary students of Arak, Iran in 2010. Indian J. Endocrinol. Metab. 16, 786. https://doi.org/10.4103/2230-8210.100676.
Talaei, A., Mohamadi, M., Adgi, Z., 2013. The effect of vitamin D on insulin resistance in patients with type 2 diabetes. Diabetol. Metab. Syndr. 5, 8. https://doi.org/10.1186/1758-5996-5-8.
Tu, Q., Wang, J., Xie, H., Zhao, Q., Fu, J., Xu, H., Cao, Z., 2021. Up-regulation of GLP-1R improved the dysfunction of late EPCs under hyperglycemia by regulating SIRT1 expression. Mol. Cell. Endocrinol. 538, 111455. https://doi.org/10.1016/j.mce.2021.111455.
Wahidin, M., Achadi, A., Besral, B., Kosen, S., Nadjib, M., Nurwahyuni, A., Ronoatmodjo, S., Rahajeng, E., Pane, M., Kusuma, D., 2024. Projection of diabetes morbidity and mortality till 2045 in Indonesia based on risk factors and NCD prevention and control programs. Sci. Rep. 14, 5424. https://doi.org/10.1038/s41598-024-54563-2.
Wallace, T.M., Levy, J.C., Matthews, D.R., 2004. Use and abuse of HOMA modeling. Diabetes Care 27, 1487–1495. https://doi.org/10.2337/diacare.27.6.1487.
World Health Organization, 2008. Waist Circumference and Waist-hip Ratio: Report of a WHO Expert Consultation. World Health Organization, Geneva.
Wu, H., Ballantyne, C.M., 2020. Metabolic inflammation and insulin resistance in obesity. Circ. Res. 126, 1549–1564. https://doi.org/10.1161/CIRCRESAHA.119.315896.
Xu, Z., Gong, R., Luo, G., Wang, M., Li, D., Chen, Y., Shen, X., Wei, X., Feng, N., Wang, S., 2022. Association between vitamin D3 levels and insulin resistance: a large sample cross-sectional study. Sci. Rep. 12, 119. https://doi.org/10.1038/s41598-021-04109-7.
Zhou, S., Tang, X., Chen, H.-Z., 2018. Sirtuins and insulin resistance. Front. Endocrinol. 9. https://doi.org/10.3389/fendo.2018.00748.

Glossary

Anthropometry: the measurement of the size, shape, and composition of the human body.
Glycemia: the concentration of glucose in the blood. Controlled glycemia refers to maintaining blood glucose levels within a target range to avoid complications associated with diabetes.
Insulin resistance: a condition where the body's cells become less responsive to insulin, leading to elevated blood glucose levels.

Sirtuin, irisin, and vitamin D as predictors of diabetes mellitus with uncontrolled glycemia in Indonesian patients

By Elly Herwana

WORD COUNT 7724
TIME SUBMITTED 06-JAN-2025 10:57AM
PAPER ID 113879362

Endocrine and Metabolic Science 17 (2025) 100214

Contents lists available at ScienceDirect

Endocrine and Metabolic Science

journal homepage: www.elsevier.com/locate/endmts

Full length article

Sirtuin, irisin, and vitamin D as predictors of diabetes mellitus with uncontrolled glycemia in Indonesian patients

Elly Herwana [a,*], Yenny [a], Alvina [b], Kurniasari [a], Clarissa Asha Febinia [c], Pusparini [b]

[a] Department of Pharmacology and Pharmacy, Faculty of Medicine, Universitas Trisakti, Jakarta 11440, Indonesia
[b] Department of Clinical Pathology, Faculty of Medicine, Universitas Trisakti, Jakarta 11440, Indonesia
[c] Division of Biological Anthropology, Department of Archaeology, University of Cambridge, Cambridge CB2 1TN, United Kingdom

ARTICLE INFO

Keywords:
Insulin resistance
Sirtuin
Irisin
Vitamin D
HbA1c

ABSTRACT

The incidence of type 2 diabetes mellitus is increasing in developing countries, including Indonesia. Insulin resistance is a significant contributor to elevated blood glucose levels in type-2 diabetes patients. Low levels of serum sirtuin-1, irisin, and vitamin D have been linked to insulin resistance. This study aimed to identify risk factors that could predict uncontrolled glycemia and insulin resistance in Indonesian type-2 diabetes patients. We conducted a cross-sectional study with 73 adults from South Jakarta, Indonesia, in which we examined type-2 diabetes risk factors and biomarkers, including sex, age, body mass index, waist circumference, waist-to-hip ratio, fasting blood glucose (FBG) levels, fasting insulin, sirtuin-1, irisin, and vitamin D levels. The subjects were categorized into two groups based on their glycated hemoglobin (HbA1c) level and homeostatic model assessment for insulin resistance (HOMA-IR) index to assess glycemic control and insulin resistance, respectively. We compared risk factor profiles between groups and analyzed multivariate relationships with logistic regression. Our findings revealed that 54 % of the subjects had uncontrolled glycemia, whereas only 11 % had insulin resistance. There was a significant association between uncontrolled glycemia and reduced sirtuin-1 levels (odds ratio = 4.07; $p = 0.03$), which was confirmed in the multivariate analysis (beta = 5.41, $p = 0.04$) along with FBG (beta = 36.88, $p = 0.001$). Irisin showed a marginal association with insulin resistance in both univariate (odds ratio = 0.12; $p = 0.027$) and multivariate analyses (beta = 0.09; $p = 0.049$). In conclusion, sirtuin-1, in addition to FBG, is a potential marker for assessing glycemic control in type-2 diabetes patients.

1. Introduction

Diabetes mellitus is a chronic disease with a high global prevalence that continues to rise. The International Diabetes Federation reported an increase in the prevalence of diabetes from 9 % (463 million) in 2019 to 10.5 % (536.6 million) in 2021 (Sun et al., 2022). The prevalence of diabetes in Indonesia is estimated to double by 2045, reaching 16.09 % (40.7 million) compared with 9.19 % (18.69 million) in 2020 (Wahidin et al., 2024). Thus, there are public, academic, and government demands for intervention programs to manage diabetes risk factors.

The clinical manifestations of type 2 diabetes are heterogeneous, resulting in diverse progression to chronic complications. Hyperglycemia is the main sign of type-2 diabetes and is defined by high fasting blood glucose (FBG) levels. Glycemic levels in type-2 diabetes patients are also assessed by glycosylated hemoglobin (HbA1c) (American Diabetes Association, 2021). The pathogenesis and progression of diabetes are associated with a decreased number and function of pancreatic cells that secrete insulin, accompanied by reduced insulin sensitivity in the tissue. Insulin resistance is characterized by a failure to respond to insulin stimulation in various tissues caused by decreased sensitivity of insulin receptors (American Diabetes Association, 2021). The homeostatic model assessment for insulin resistance (HOMA-IR), developed by Matthews et al., quantifies insulin resistance and pancreatic β-cell function by considering plasma insulin levels and FBG (Matthews et al., 1985). Insulin resistance can affect the liver, skeletal muscle, and adipose tissues (Lee et al., 2021). The manifestation of insulin resistance in type-2 diabetes patients occurs due to the failure of pancreatic β-cells to compensate the increased insulin secretion required at high blood sugar levels, resulting in impaired glucose tolerance.

The mechanisms underlying type-2 diabetes are not fully understood due to the polygenic nature of type-2 diabetes, which involves various physiological systems and is affected by environmental and dietary

* Corresponding author at: Jl. Letjen S. Parman No.260, Kampus B, RT.5/RW.9, Grogol, Jakarta Barat, DKI Jakarta 11440, Indonesia.
E-mail address: elly.herwana@trisakti.ac.id (E. Herwana).

https://doi.org/10.1016/j.endmts.2024.100214
Received 26 July 2024; Received in revised form 11 December 2024; Accepted 21 December 2024
Available online 24 December 2024

factors. New clinical and environmental risk factors, such as dietary and regulatory proteins, are continuously reported and have been established in recent years. Many of these newly proposed risk factors remain unconfirmed in populations in the Global South. In this study, we are particularly interested in risk factors that could predict glycemic control and insulin resistance in patients with confirmed type-2 diabetes in Indonesia. The chiefs among these factors were serum vitamin D, sirtuin-1, and irisin.

Recent studies have highlighted the role of vitamin D in the pathogenesis of type-2 diabetes. Vitamin D deficiency was found to be more prevalent among individuals with type-2 diabetes (Nasr et al., 2022). The pathogenesis of insulin resistance in the patient such as pancreatic dysfunction and decreased β-cell mass, is associated with various risk factors, including vitamin D deficiency. Serum vitamin D levels are negatively associated with HbA1c (Buhary et al., 2017; Jha et al., 2020; Nasr et al., 2022), whereas vitamin D supplementation reduces HbA1c (Buhary et al., 2017; Mirhosseini et al., 2018; Safarpour et al., 2020) and HOMA-IR (Lei et al., 2023; Talaei et al., 2013; Xu et al., 2022). Safarpour et al. reported that, compared with placebo, vitamin D supplementation for six months significantly reduced HbA1c and increased sirtuin-1 and irisin levels; however, although there was a significant change in HOMA-IR after supplementation, it was not significantly different from that in the placebo group (Safarpour et al., 2020).

Sirtuins are a family of proteins involved in the regulation of various biological processes, including metabolic regulation, mitochondrial homeostasis, oxidative stress, inflammation, autophagy, and apoptosis. Sirtuin-1 is more widely studied compared to the other six sirtuins in mammals, particularly because of its regulatory role in aging, obesity, type-2 diabetes, cardiovascular diseases, neurodegenerative diseases, and cancer (Zhou et al., 2018). Sirtuin-1 is known to be negatively correlated with type-2 diabetes. A comparative study by Rahimi et al. revealed that sirtuin-1 levels were lower in individuals with uncontrolled glycemia than in those with controlled glycemia and healthy individuals (Rahimi et al., 2020).

Irisin is a novel myokine, a polypeptide secreted by an unknown protease protein containing a fibronectin type III domain (FNDC5), which is a membrane protein expressed in skeletal muscle, heart, liver, and adipose tissue (Akyuz et al., 2021). Irisin is a proteolytic cleavage product of FNDC5, whose expression is induced by the coactivator PPARγ 1 alpha (PGC1-α). Physical activity and exercise induce the expression of this gene, leading to the release of irisin into the circulation. This process increases energy expenditure and thermogenesis by increasing the levels of uncoupling protein 1 (UCP1) through the stimulation of peroxisome proliferator-activated receptor (PPAR)-γ coactivator (PGC-1α) PPAR-α expression in white adipose tissue (Moreno et al., 2015). Lower levels of irisin were reported in individuals with type-2 diabetes compared to those without type-2 diabetes (Choi et al., 2013; Moreno et al., 2015). Circulating irisin in blood was found to be associated with IR, as well as age, sex, body mass index (BMI), and physical activity (Moreno et al., 2015). Taken together, these findings suggest that irisin might improve hyperglycemia by increasing energy expenditure, improving glucose homeostasis, and reducing insulin resistance.

Central to the pathophysiology of type 2 diabetes is systemic chronic inflammation, which leads to metabolic dysregulation, insulin resistance, and hyperglycemia (Ellulu and Samouda, 2022; Wu and Ballantyne, 2020). Vitamin D, sirtuin-1, and irisin possess anti-inflammatory properties; and vitamin D may support the functions of sirtuin-1 and irisin (Safarpour et al., 2020). The interplay of all three has the potential to mitigate the development of insulin resistance. Additionally, vitamin D is stored in adipose tissues, the liver, and muscle—where irisin is most highly expressed. This suggests a potential interplay between irisin and vitamin D that may enhance energy expenditure and adipose thermogenesis, both of which are crucial for maintaining metabolic homeostasis.

In this study, we measured the serum sirtuin-1, irisin, and vitamin D levels in Indonesian patients diagnosed with type-2 diabetes and investigated their associations with common type-2 diabetes risk factors, such as anthropometry and FBG. Furthermore, we established cutoff values for sirtuin-1 and irisin specific to type-2 diabetes within the population. Finally, we assessed the potential of sirtuin-1 and irisin as biomarkers for predicting uncontrolled glycemia and insulin resistance in type-2 diabetes patients.

2. Material and methods

2.1. Study design and subjects

This is a cross-sectional study with a targeted sampling strategy. Our study subjects were recruited through a community engagement activity with residents of the Mampang Prapatan district in South Jakarta, Indonesia, between June and November 2022. We enrolled men or women over 21 years of age who had been diagnosed with type-2 diabetes by a doctor and individuals with FBG ≥ 126 mg/dL without prior diagnosis of diabetes. Individuals with a history of kidney or liver dysfunction were excluded. Subjects were enrolled with informed consent. For the enrolled subjects with a history of diabetes, we recorded the time from their first diagnosis (in months) and the type of ongoing oral antidiabetic drug (OAD) treatment.

2.2. Sample and data collection

Venous blood samples were taken in the morning after the subjects had fasted for 10–12 h. The blood was used to measure FBG, HbA1c, insulin, vitamin D, sirtuin-1, irisin, alanine aminotransferase (ALT), creatinine, and albumin. To exclude patients with liver and kidney dysfunction, we used cutoff values of ALT >40 U/L, creatinine >1.1 mg/dL, and albumin <3.5 g/dL.

Interviews were conducted to obtain age and sex information. Body weight and height were measured, and BMI was calculated as body weight (kg) per square meter of height (m^2). Subjects with a BMI ≥ 25 kg/m^2 were categorized as obese. Waist circumference and hip circumference were measured in centimeters. We defined central obesity with cutoff points of 90 cm for waist circumference and 0.8 for the waist-hip ratio (World Health Organization, 2008). We also measured systolic and diastolic blood pressure (mmHg). Hypertension was determined on the basis of a systolic blood pressure ≥ 140 mmHg.

2.3. Laboratory measurements

HbA1c was measured with high-performance liquid chromatography (HPLC), and FBG was measured with the hexokinase enzymatic method. HbA1c and FBG values were used to differentiate controlled glycemia (HbA1c < 7 %; FBG < 140 mg/dL) from uncontrolled glycemia (HbA1c ≥ 7 %; FBG > 140 mg/dL). The HOMA-IR index was calculated as described in a previous study with the following formula: insulin level (μIU/mL) × FBG (mg/dL) / 405; individuals with a HOMA-IR value of ≥3.75 were categorized as insulin resistant (Kurniawan et al., 2018). Vitamin D levels were assessed with direct competitive chemiluminescent microparticle immunoassay (CMIA). Patients' vitamin D status was classified as either low if <20 ng/mL or sufficient if ≥20 ng/mL (Talaei et al., 2012). Human sirtuin-1 levels were determined with the Invitrogen Human SIRT1 ELISA Kit (catalog number EH427RB), and serum irisin levels were assessed with the Irisin ELISA Kit (BioVendor R&D; catalog number RAG018R). The assessments were performed following the manufacturers' protocol.

2.4. Statistical analysis

Numerical data were assessed for normality of distribution with the Shapiro–Wilk test. Owing to their nonnormal distributions, sirtuin-1, irisin, vitamin D, HbA1c, and HOMA-IR levels are reported as

medians, and the data ranges are expressed as the first and third interquartile ranges (IQRs). These parameters were compared between patients with uncontrolled glycemia and insulin-resistant patients with the Mann–Whitney U (MWU) test. Receiver operating characteristic (ROC) curves were generated to evaluate sirtuin-1 and irisin levels, as insulin-resistant patients had high HbA1c levels. The area under the curve (AUC) and optimal cutoff points for predicting HbA1c using sirtuin-1 and irisin were determined on the basis of the largest sum of sensitivity and specificity. Multivariate relationships between risk factors of uncontrolled glycemia and insulin resistance were assessed with logistic regression analysis, incorporating FBG, vitamin D, sirtuin-1, irisin levels, age, gender, BMI, waist circumference, waist-to-hip ratio, systolic blood pressure, and OAD consumption. We also applied a bi-directional stepwise model selection process to determine the combination of predictors for HbA1C and HOMA-IR status, selecting the model with the lowest Akaike Information Criterion (AIC) value as the optimal choice. All the statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 20.0 and R version 1.4.1. Statistical significance was considered at $p < 0.05$.

3. Results

3.1. Subject characteristics

Seventy-three out of eighty subjects fulfilled the inclusion and exclusion criteria. Table 1 describes the distribution of their characteristics at the time of enrollment. The majority of the subjects were women, with a male-to-female ratio of 1:4. Nearly 65 % of the sample was 60 years of age or younger. Obesity was observed in 65.8 % of the subjects, whereas central obesity was observed in 83.6 % (waist circumference ≥ 90 cm) and 93.2 % (waist-to-hip ratio ≥ 0.8) of the subjects. Systolic hypertension (≥140 mmHg) was present in 63 % of the subjects. A total of 47.9 % of the subjects had high FBG (≥140 mg/dL). Vitamin D deficiency (<20 ng/mL) was found in 91.8 % of the subjects. High HOMA-IR (≥3.75) was a minority at 11.0 %, whereas the HbA1c level was high (≥7 %) in most subjects at 74 %. Most subjects were recently diagnosed with diabetes within the last 12 months (46, 63 %), while the rest (27, 37 %) had been diagnosed between 13 and 36 months. Participants with a prior diagnosis (45 subjects) had been treated with OAD, with metformin being the most commonly prescribed, in line with the country's standard (53 %). Other reported OADs included glimepiride (1 subject), glibenclamide (3 subjects), and a combination therapy of metformin and glimepiride (2 subjects).

Table 1
Demography and clinical characteristics of the studied subjects.

Variables	Frequency	Percentage (%)
Sex		
Male	15	20.5
Female	58	79.5
Age group		
61–80 years old	26	35.6
25–60 years old	47	64.4
Obesity		
Obese (BMI ≥ 25 kg/m^2)	48	65.8
Nonobese (BMI < 25 kg/m^2)	25	34.2
Waist circumference		
High (≥90 cm)	60	83.6
Normal (<90 cm)	12	16.4
Waist-to-hip ratio		
High (≥0.8)	68	93.2
Normal (<0.8)	5	6.8
Systolic blood pressure		
Hypertension (≥140 mmHg)	46	63.0
Normal (<140 mmHg)	27	37.0
Fasting blood glucose		
High (≥140 mg/dL)	35	47.9
Normal (<140 mg/dL)	38	52.1
Vitamin D		
Insufficient (<20 ng/mL)	67	91.8
Sufficient (≥20 ng/mL)	6	8.2
HOMA-IR		
Insulin resistant (≥3.75)	8	11.0
Insulin responsive (<3.75)	65	89.0
HbA1c		
Uncontrolled glycemia (≥7 %)	54	74.0
Controlled glycemia (<7 %)	19	26.0
Diabetes duration		
≤12 months	46	63.0
>13 months	27	37.0
Antidiabetic treatment		
No OAD	28	38.4
Metformin	39	53.4
Glimepiride	1	1.4
Glibenclamide	3	4.1
Metfromin + Glimepiride	2	2.7

Abbreviations: BMI = body mass index; HOMA-IR = homeostatic model assessment for insulin resistance; HbA1c = glycosylated hemoglobin; OAD = oral antidiabetic drug.

3.2. Sirtuin-1 and irisin cutoff values in type-2 diabetes patients

Across 73 subjects, we observed that the median HbA1c level was 9.1 %, and the IQR was 6.8–11.0 %. The median HOMA-IR value was 1.12, and IQR of 0.33–2.09. Serum sirtuin-1 and irisin values had non-normal distributions (Shapiro-Wilk test, $p < 0.05$). Sirtuin-1 levels had a median of 0.45 ng/mL and IQR of 0.36–0.56 ng/mL. Irisin levels had a median of 28 μg/mL and IQR of 17.5–30.0 μg/mL.

We further investigated whether sirtuin-1 and irisin levels are different in our subjects with abnormal HbA1c levels. There was a significant difference in sirtuin-1 levels (MWU test, $p = 0.050$) between subjects with uncontrolled glycemia (HbA1c ≥ 7 %, 54 subjects) and those with normal glycemia (HbA1c < 7 %, 19 subjects). The median and IQR of sirtuin-1 levels were 0.39 (0.36–0.52) ng/mL in patients with uncontrolled glycemia and 0.55 (0.37–0.62) ng/mL in patients with controlled glycemia. In contrast, the irisin levels were not significantly different (MWU test, $p = 0.128$). Irisin levels had a median and IQR of 27.9 (15.6–30.0) μg/mL in patients with uncontrolled glycemia, which is comparable to the range of 28.9 (22.3–30.0) μg/mL reported in patients with controlled glycemia.

In addition, we investigated whether sirtuin-1 and irisin levels differ between subjects with insulin resistance. We found no difference in the circulating levels of sirtuin-1 (MWU test, $p = 0.219$) or irisin (MWU test, $p = 0.314$) between the insulin-resistant group (HOMA-IR ≥ 3.75, 8 subjects) and the insulin-responsive group (HOMA-IR < 3.75, 65 subjects). Compared with the insulin-responsive group, the insulin-resistant group presented a modestly elevated median and IQR of 0.59 (0.36–0.98) ng/mL, whereas the insulin-responsive group presented 0.44 (0.36–0.55) ng/mL. The median and IQR of irisin concentration was 21.44 (17.9–26.7) μg/mL in the insulin-resistant group, which is lower compared to 28.9 (17.2–30.0) μg/mL in the insulin-responsive group. Owing to the low prevalence of insulin resistance in our data, we refrained from determining cutoff points for HOMA-IR.

To determine cutoff points for sirtuin-1 and irisin for patients with uncontrolled glycemia, we performed receiver ROC analysis. ROC analysis of sirtuin-1 revealed an area under the curve of 0.652, with a 95 % confidence interval ranging 0.501–0.893 (Fig. 1a). These values suggest that the role of sirtuin-1 in determining uncontrolled glycemia is weak (between 0.6 and 0.7). The optimal cutoff point for sirtuin-1 levels in our data was 0.49 ng/mL, with a sensitivity of 70.4 % and a specificity of 63.2 % for detecting uncontrolled glycemia in patients (Fig. 1b).

Although there was no significant difference in irisin levels between the uncontrolled and controlled glycemia groups, ROC analysis revealed an area under the curve value of 0.578, with a 95 % confidence interval ranging from 0.445 to 0.712 (Fig. 1c). This value indicates that irisin levels do not play a significant role in determining uncontrolled glycemia. The optimal cutoff point for irisin was 28.385 μg/mL, with a

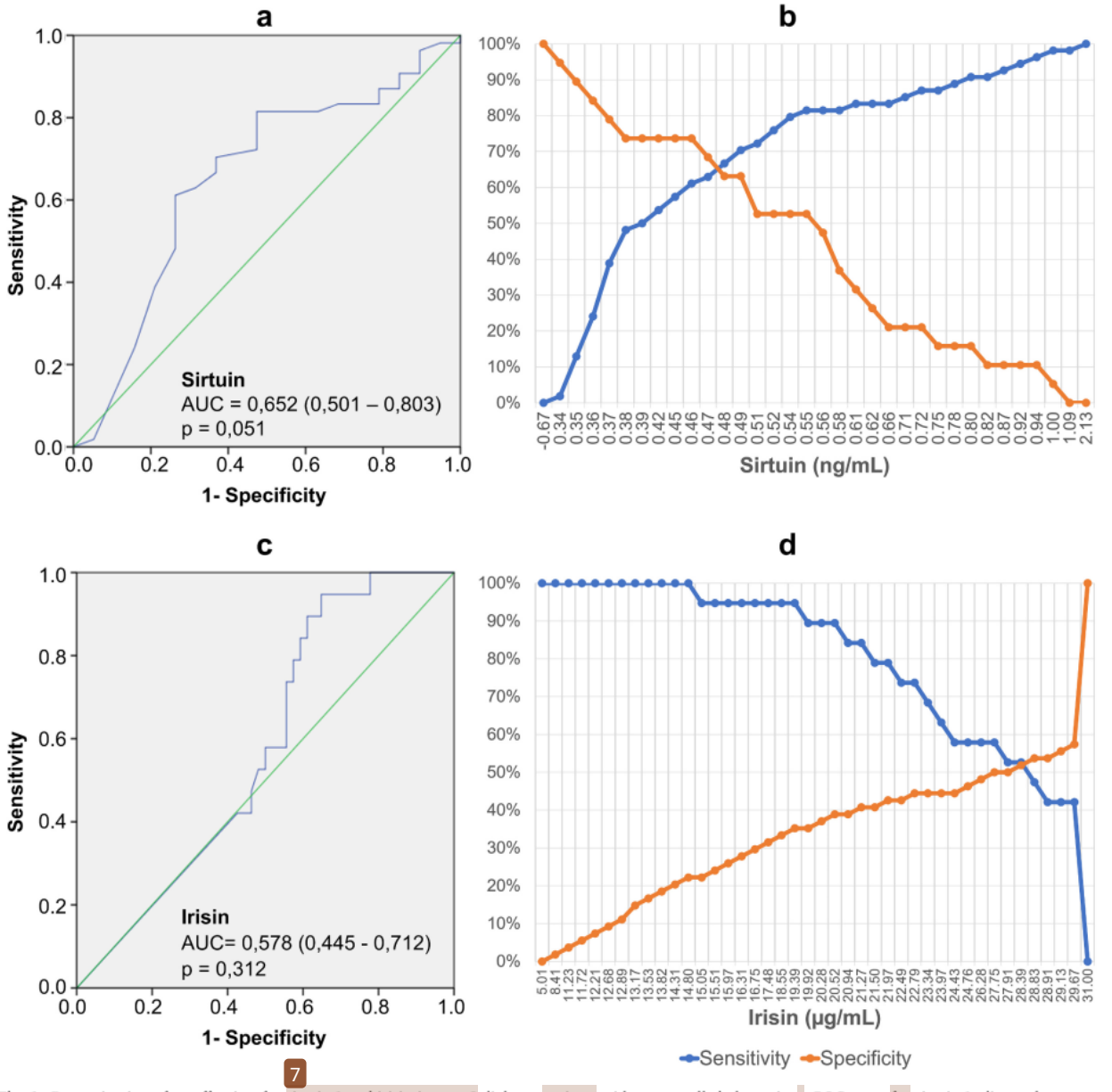


Fig. 1. Determination of cutoff points for sirtuin-1 and irisin in type-2 diabetes patients with uncontrolled glycemia; a, ROC curve for sirtuin-1; diagonal segments are produced by ties; b, sensitivity and specificity curves for sirtuin-1; c, ROC curve for irisin; d, sensitivity and specificity curves for irisin.

sensitivity and specificity of 51.9 % (Fig. 1d).

3.3. *Associations of HbA1c and HOMA-IR with type-2 diabetes risk factors*

We examined the relationships between various risk factors and uncontrolled glycemia. We found that high FBG, vitamin D deficiency, and low sirtuin-1 levels were associated with a high risk for uncontrolled glycemia (Table 2). As expected, patients with FBG levels above 140 mg/dL have a 30.6 times greater risk than those with lower blood sugar levels; the association is strongly significant, with a 95 % confidence interval (95 % CI) between 3.79 and 246.9 times greater. Patients with vitamin D deficiency had a 6.93-fold greater risk, with a 95 % CI between 1.16 and 41.6. Patients with low sirtuin-1 levels (<0.49 ng/mL) have a 4.07-fold greater risk for uncontrolled glycemic condition, with a 95 % CI between 1.36 and 12.23. On the other hand, we found no associations between HOMA-IR score and risk factors, except for irisin (Table 2). An elevated irisin was significantly associated with a lower risk for insulin resistance, but the decrease in odds was negligible (0.12 times).

Significant differences in both HbA1C and HOMA-IR were observed between subjects who consumed OADs, highlighting the impact of OAD consumption on diabetes phenotypes (Table 2). We further performed MWU tests to assess if sirtuin-1 and irisin levels were affected by OAD consumption, but we found no significant difference (all $p > 0.05$).

Table 2
HbA1c and HOMA-IR associations with sirtuin-1, irisin, and T2DM factors.

Risk factor	HbA1c (%)						HOMA-IR					
	≥7	<7	*p*	OR	95 % CI		≥3.75	<3.75	*p*	OR	95 % CI	
					Low	High					Low	High
Sex												
Male	11	4	1.000	0.96	0.27	3.47	1	14	0.956	0.52	0.06	4.59
Female	43	15					7	51				
Age group												
61–80-year-old	17	9	0.214	0.51	0.18	1.49	2	24	0.809	0.57	0.11	3.05
35–60-year-old	37	10					6	41				
BMI												
≥25 kg/m^2	34	14	0.397	0.61	0.19	1.94	5	43	1.000	0.85	0.19	3.90
<25 kg/m^2	20	5					3	22				
Waist circumference												
≥90 cm	44	17	0.680	0.52	0.11	2.61	7	54	1.000	1.43	0.16	12.78
<90 cm	10	2					1	11				
Waist-to-hip ratio												
≥0.8	50	18	1.000	0.69	0.07	6.63	8	60	1.000	1.55	0.54	4.42
<0.8	4	1					0	5				
Fasting blood glucose												
≥140 mg/dL	34	1	**<0.001*****	30.60	3.79	246.9	2	36	0.211	0.27	0,05	1.43
<140 mg/dL	20	18					6	29				
Vitamin D levels												
<20 ng/mL	52	15	**0.073**^	6.93	1.16	41.6	8	59	1.000	1.86	0.48	7.18
≥20 ng/mL	2	4					0	6				
Sirtuin-1 levels												
≤0.49 ng/mL	38	7	**0.010***	4.07	1.36	12.23	1	18	0.656	0.37	0.04	3.25
>0.49 ng/mL	16	12					7	47				
Irisin levels												
≥28.375 μg/mL	26	10	0.737	0.840	0.290	2.38	1	35	**0.027***	0.12	0.01	1.05
<28.375 μg/mL	28	9					7	30				
Antidiabetic treatment												
No OAD	15	13	**0.002****	0.18	0.06	0.55	0	28	**0.02***	0.08	0.01	0.65
OAD	39	6					8	37				

OR = odds ratio; OAD = oral antidiabetic drug. OR and *p*-value, obtained from Fisher Exact test for count data. Significant values are marked as ^ for $p < 0.1$ (marginal), * for $p < 0.05$; ** for $p < 0.01$, and *** for $p < 0.001$.

3.4. Predictors of HbA1c and HOMA-IR in type-2 diabetes patients

To further understand the relationship between risk factors in our data, we conducted a multivariate logistic regression analysis incorporating sirtuin-1, irisin, FBG, and vitamin D levels, along with age, sex, BMI, waist circumference, waist-to-hip ratio, systolic blood pressure, and OAD consumption. Furthermore, we used a bi-directional stepwise model selection process to identify the optimal combination of HbA1C and HOMA-IR status predictors. The model with the smallest Akaike Information Criterion (AIC) value was selected as the most suitable.

The result showed that sirtuin-1 was positively associated with HbA1C in both the full model and the optimal model, although the strength of the association was lower (6.8-fold reduction) than that of FBG (Table 3). On the other hand, irisin showed a weak and marginal association with HOMA-IR. HOMA-IR was also linked to OAD consumption, although these relationships were not statistically significant. Interestingly, we found no significant association between HbA1C and vitamin D level in the multivariate analysis, despite observing a marginal correlation in the univariate analysis (Table 2).

4. Discussion

This study investigated key risk factors for predicting uncontrolled glycemia and insulin resistance in type-2 diabetes patients in Indonesia. We assessed sirtuin-1, irisin, and vitamin D levels and their relationships with typical type-2 diabetes risk factors, including anthropometric parameters, FBG, HbA1c, and the HOMA-IR index. We established specific cutoff values for sirtuin-1 and irisin and evaluated these markers as potential glycemic control and insulin resistance predictors in Indonesian type-2 diabetes patients.

The use of HbA1c and HOMA-IR for classifying type-2 diabetes patients has been considered in clinical settings. While a recent systematic review reported that HbA1c is a reliable marker with high specificity for type-2 diabetes (Butler et al., 2021), there is a lack of consensus on the HOMA-IR reference value. Studies have shown that HOMA-IR values differ by ethnicity, age, and sex. For example, South Asians, particularly first-generation migrants, exhibit higher HOMA-IR values than European and African Caribbean populations (Molinari et al., 2021). Similarly, research indicates that Hispanic populations have higher HOMA-IR values than Caucasians (Wallace et al., 2004). The reported HOMA-IR values across different ethnicities were 2.29 for Caucasians, 3.80 for middle-aged Mexican Americans (Qu et al., 2011), 2.3 for elderly Taiwanese individuals (Cheng et al., 2017), and 3.63 for middle-aged individuals in the Czech Republic (Horáková et al., 2019).

We found a low incidence of insulin resistance based on HOMA-IR in confirmed type-2 diabetes patients despite the use of a cutoff value for HOMA-IR specific to our studied population and a high incidence of uncontrolled glycemia (HbA1c over 7 %). The incidence of uncontrolled glycemia was five times greater than the incidence of insulin resistance. This finding suggests that the association between HbA1c and HOMA-IR is not linear, possibly due to varying manifestations, antidiabetic medications, or confounding factors related to population bias. Furthermore, the majority of our subjects (61.6 %) had received diabetes medication prior to enrollment and, therefore, may also have reduced insulin levels, affecting the basis for HOMA-IR scoring.

Furthermore, we found no significant correlation between HOMA-IR and anthropometric risk factors (*i.e.*, body mass index, waist circumference, and waist-to-hip ratio). There were also no significant associations between anthropometric factors and HbA1c. HOMA-IR has established associations with obesity, waist circumference, body fat, and visceral fat (Cheng et al., 2017; Kurniawan et al., 2018). Saravia et al. reported a significant difference in HOMA-IR and HbA1c when

Table 3
Multivariate associations of HbA1C and HOMA-IR with T2DM risk factors.

Covariates	HbA1C				HOMA-IR			
	Full model		Optimal model		Full model		Optimal model	
	beta	*p*	beta	*p*	beta	*p*	beta	*p*
Sirtuin								
1: >0.49 ng/mL	5.38	**0.037***	5.41	**0.014***	0.18	0.144	0.21	0.105
0: ≤0.49 ng/mL								
Irisin								
1: >28.375 μg/mL	1.36	0.697	–	–	0.05	**0.065^**	0.09	**0.049***
0: ≤28.375 μg/mL								
Fasting blood glucose								
1: ≥140 mg/dL	16.87	**0.028***	36.88	**0.001****	1.07	0.959	–	–
0: <140 mg/dL								
Vitamin D level								
1: ≥20 ng/mL	−1.86	0.211	–	–	−16.56	0.998	–	–
0: <20 ng/mL								
Age								
1: ≥61 years old	0.1	0.906	–	–	−0.73	0.636	–	–
0: <61 years old								
Body mass index								
1: ≥25 kg/m^2	−0.83	0.427	–	–	0.47	0.783	–	–
0: <25 kg/m^2								
Waist circumference								
1: M ≥ 90 cm; F ≥ 80 cm	0.94	0.585	–	–	−2.69	0.297	–	–
0: M < 90 cm; F < 80 cm								
Waist-to-hip ratio								
1: ≥0.8	0.21	0.913	–	–	14.22	0.998	–	–
0: <0.8								
Systolic hypertension								
1: ≥140 mmHg	0.17	0.833	–	–	−0.09	0.935	–	–
0: <140 mmHg								
Sex								
0: Female	0.15	0.893	–	–	−1.47	0.38	–	–
1: Male								
Antidiabetic treatment								
Metformin	1.12	0.15	–	–	19.15	0.995	19.05	0.995
Glimepiride	14.54	0.998			42.03	0.998	41.08	0.998
Glibenclamide	16.74	0.996			−0.6	1	−0.38	1
Metformin+Glimepiride	15.64	0.997			−1.64	1	0.7	1

Beta and *p*-value were obtained from logistic regression analysis. Significant values are marked as ^ for $p < 0.1$ (marginal), * for $p < 0.05$, and ** for $p < 0.01$. The optimum model was selected based on the lowest Akaike Information Criteria in a bi-directional step-wise selection method.

comparing groups with and without metabolic syndrome (Saravia et al., 2015). Importantly, the majority of our studied subjects were obese according to the WHO Asia Pacific standards. Therefore, there were minimal variations in BMI, waist circumference, body fat, and visceral fat between the groups in our data.

We also did not find that HOMA-IR was associated with serum FBG or vitamin D levels. In the univariate analysis, we observed a marginal association between vitamin D and HbA1C. However, this association was not significant in the multivariate analysis, which accounted for other phenotypic risk factors (age, gender, obesity, hypertension) and diabetes medications as cofactors. A clinical trial previously reported that Vitamin D supplementation reduced HbA1c and increased HOMA-IR, although the change in HOMA-IR was not significant compared with that of the placebo (Safarpour et al., 2020). Other studies, however, have reported a negative vitamin D correlation with both HbA1c (Buhary et al., 2017; Jha et al., 2020) and insulin resistance (Xu et al., 2022). Talaei et al. reported that vitamin D supplementation led to lower levels of FBG and HOMA-IR (Talaei et al., 2013). Mirhosseini et al. also demonstrated that vitamin D supplementation improved FBG, glycemic control, and insulin resistance in individuals with prediabetes and a high risk of type-2 diabetes (Mirhosseini et al., 2018). We acknowledge that the low incidence of insulin resistance in our data might limit the robustness of the association analyses for HOMA-IR.

We found a strong association between HbA1c and sirtuin-1. Our data suggest an optimal cutoff value for predicting HbA1c using sirtuin-1 at 0.49 ng/mL, although the effect size, sensitivity, and specificity are modest. Rahimi et al. also reported significant differences in sirtuin-1 levels among individuals with uncontrolled diabetes, individuals with controlled diabetes, and healthy controls and reported a negative correlation between sirtuin-1 levels and HbA1c, and also with FBG (Rahimi et al., 2020). Curiously, we found no association between the serum irisin level and the HbA1c level. This contradicts the findings of a recent meta-analysis that revealed a significant difference in irisin levels between individuals with diabetes and those without diabetes (Song et al., 2021). Our data does not support the negative correlations between irisin levels and hyperglycemia (Ahmed et al., 2023; Khajebishak et al., 2023). Furthermore, we could not confirm the associations of HOMA-IR with sirtuin-1 and irisin in type-2 diabetes patients in Indonesia. The lack of associations may be attributed to the low incidence of insulin resistance in our study.

Our multivariate logistic regression analysis demonstrated that sirtuin-1 levels are associated with HbA1c levels, concurrently with FBG. Although FBG emerged as the strongest predictor, with an effect approximately seven times larger than that of sirtuin-1, this was expected. Our model only partially supports the results of Safarpour et al., who demonstrated that vitamin D supplementation also improved diabetic risk factors, accompanied by elevated sirtuin-1 and irisin levels (Safarpour et al., 2020). We recommend further investigations into the roles of sirtuin-1 and irisin in glycemic control, insulin resistance, and the management of patients with type-2 diabetes.

Our subjects reported using three types of OADs: metformin, glimepiride, and glibenclamide. Metformin, a biguanide, reduces glucose production in the liver and enhances insulin sensitivity in muscle and adipose tissue without stimulating insulin secretion. In contrast,

glibenclamide and glimepiride, which belong to the sulfonylurea class, act as insulin secretagogues, stimulating insulin secretion in the pancreas. Only six subjects (8 %) in this study reported using these drugs, while the majority used metformin. These OADs were significantly associated with both HbA1C levels and HOMA-IR values in the univariate analyses, but not in the multivariate.

OAD consumption did not significantly impact the association between sirtuin-1 and HbA1C in this study. However, there is some evidence that the role of sirtuin-1 in glucose control and insulin signaling is affected by hyperglycemic and insulin-resistant conditions *in vitro* (Jeon et al., 2019; Tu et al., 2021). Given that OADs are used to manage hyperglycemia and insulin resistance, their impact on these conditions could potentially influence sirtuin-1 expression and activity, which may, in turn, affect glucose metabolism and insulin sensitivity. Thus, further research is needed to understand how OAD consumption interacts with sirtuin-1.

We acknowledge several limitations in this study. The relatively small sample size of type-2 diabetes patients with elevated HOMA-IR may reduce the robustness of our association analyses for insulin resistance. Lifestyle factors, such as physical activity, nutritional status, and consumption of other medications, may impact the expression of sirtuin-1 and irisin. The cross-sectional design restricts our ability to establish causal relationships between risk factors, glycemic control, and insulin resistance. The relatively young age of our subjects raises the possibility of atypical diabetes types, such as maturity-onset diabetes of the young (MODY), which may have different clinical manifestations from typical type-2 diabetes. Lastly, considering the influence of environmental and genetic factors in the complex pathophysiology of type-2 diabetes, our findings—based on a specific community in Indonesia—should be validated in other populations.

5. Conclusion

Our study contributes valuable insights into potential predictors and biomarkers for managing type-2 diabetes. We evaluated the associations between glycemic control, insulin resistance, and several risk factors in patients with type-2 diabetes. Among these factors, sirtuin-1 has a significant association with uncontrolled glycemia, along with FBG, in type-2 diabetes patients. On the other hand, vitamin D and irisin were not strongly associated with either glycemic control or insulin resistance. Further multicenter studies with larger cohorts are recommended to gain a more comprehensive understanding of the role of sirtuin-1, irisin, and vitamin D in glycemic control, insulin resistance, and the pathogenesis of type-2 diabetes in Indonesia. Although the predictive roles of sirtuin-1 and irisin for diabetic phenotypes appear modest in our study and may not yet support their use in current clinical practice, we believe these biomarkers warrant further investigation as potential tools for diabetes sub-classification, as assessment markers for treatment effectiveness, and as new therapeutic targets.

Abbreviations

FBG	fasting blood glucose
HOMA-IR	homeostatic model assessment for insulin resistance
BMI	body mass index
OAD	oral antidiabetic drug
ALT	alanine aminotransferase
IQR	interquartile range
MWU	Mann-Whitney U
ROC	receiver operating characteristic
AUC	area under the curve
CI	confidence interval
OR	odds ratio

CRediT authorship contribution statement

Elly Herwana: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Conceptualization. **Yenny:** Writing – review & editing, Methodology. **Alvina:** Writing – review & editing, Methodology. **Kurniasari:** Writing – review & editing, Methodology. **Clarissa Asha Febinia:** Writing – review & editing, Writing – original draft, Visualization. **Pusparini:** Writing – review & editing, Methodology.

Ethical considerations

This study was reviewed by the ethics committee at the Faculty of Medicine, Universitas Trisakti and adhered to World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subject. The ethics permission was received ethical clearance (No: 183/KER/VI/2022). All procedures were performed in compliance with relevant laws and institutional guidelines. The subjects were thoroughly informed about the research and were required to sign a consent form to participate. Research data were anonymized to protect patients' names, initials, hospital numbers, dates of birth, and any other personal or identifying information.

Funding sources

This study was funded by an internal grant from the Universitas Trisakti research funds.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Elly Herwana reports financial support and article publishing charges were provided by Trisakti University. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors thank all the study participants, laboratory personnel, and funding institution (Faculty of Medicine, Universitas Trisakti).

Data availability

Data will be made available on request.

References

Ahmed, T.M., Nassar, M., Mohamed, H.A.A., Elhadidy, K.E., Farhan, H.M., El Basset, A.S. A., Elmessiery, R.M., Kamel, M.F., 2023. Evaluation of serum levels of Irisin as a marker of endothelial dysfunction in patients with type 2 diabetes mellitus. Endocrinol. Diabetes Metab. 6, e403. https://doi.org/10.1002/edm2.403.

Akyuz, A., Mert, B., Ozkaramanli Gur, D., Mucip Efe, M., Aykac, H., Alpsoy, S., Guzel, S., 2021. Association of lower serum irisin levels with diabetes mellitus: irrespective of coronary collateral circulation, and syntax score. North. Clin. Istanb. 8, 607–614. https://doi.org/10.14744/nci.2021.73669.

American Diabetes Association, 2021. Professional practice committee: standards of medical care in diabetes—2022. Diabetes Care 45, S3. https://doi.org/10.2337/dc22-Sppc.

Buhary, B.M., Almohareb, O., Aljohani, N., Alrajhi, S., Elkaissi, S., Sherbeeni, S., Almaghamsi, A., Khan, S.A., Almalki, M.H., 2017. Association of glycosylated hemoglobin levels with vitamin D status. J. Clin. Med. Res. 9, 1013–1018. https://doi.org/10.14740/jocmr3227w.

Butler, A.E., English, E., Kilpatrick, E.S., Östlundh, L., Chemaitelly, H.S., Abu-Raddad, L. J., Alberti, K.G.M.M., Atkin, S.L., John, W.G., 2021. Diagnosing type 2 diabetes using Hemoglobin A1c: a systematic review and meta-analysis of the diagnostic cutpoint based on microvascular complications. Acta Diabetol. 58, 279–300. https://doi.org/10.1007/s00592-020-01606-5.

Cheng, Y.-H., Tsao, Y.-C., Tzeng, I.-S., Chuang, H.-H., Li, W.-C., Tung, T.-H., Chen, J.-Y., 2017. Body mass index and waist circumference are better predictors of insulin

resistance than total body fat percentage in middle-aged and elderly Taiwanese. Medicine 96, e8126. https://doi.org/10.1097/MD.0000000000008126.
Choi, Y.-K., Kim, M.-K., Bae, K.H., Seo, H.-A., Jeong, J.-Y., Lee, W.-K., Kim, J.-G., Lee, I.-K., Park, K.-G., 2013. Serum irisin levels in new-onset type 2 diabetes. Diabetes Res. Clin. Pract. 100, 96–101. https://doi.org/10.1016/j.diabres.2013.01.007.
Ellulu, M.S., Samouda, H., 2022. Clinical and biological risk factors associated with inflammation in patients with type 2 diabetes mellitus. BMC Endocr. Disord. 22, 16. https://doi.org/10.1186/s12902-021-00925-0.
Horáková, D., Štěpánek, Ladislav, Janout, V., Janoutová, J., Pastucha, D., Kollárová, H., Petráková, A., Štěpánek, Lubomír, Husár, R., Martiník, K., 2019. Optimal homeostasis model assessment of insulin resistance (HOMA-IR) cut-offs: a cross-sectional study in the Czech population. Medicina 55, 158. https://doi.org/10.3390/medicina55050158.
Jeon, J.Y., Choi, S.-E., Ha, E.S., Lee, H.B., Kim, T.H., Han, S.J., Kim, H.J., Kim, D.J., Kang, Y., Lee, K.-W., 2019. GLP-1 improves palmitate-induced insulin resistance in human skeletal muscle via SIRT1 activity. Int. J. Mol. Med. 44, 1161–1171. https://doi.org/10.3892/ijmm.2019.4272.
Jha, S.C., Kumar, H., Faisal, S.Y., 2020. Correlation between vitamin D and HbA1c in type 2 diabetic patients. Acad. J. Med. 3, 4–10.
Khajebishak, Y., Faghfouri, A.H., Soleimani, A., Peyrovi, S., Payahoo, L., 2023. The potential relationship between serum Irisin concentration with inflammatory cytokines, oxidative stress biomarkers, glycemic indices and lipid profiles in obese patients with type 2 diabetes mellitus: a pilot study. J. ASEAN Fed. Endocr. Soc. 38, 45–51. https://doi.org/10.15605/jafes.038.01.13.
Kurniawan, L.B., Bahrun, U., Hatta, M., Arif, M., 2018. Body mass, total body fat percentage, and visceral fat level predict insulin resistance better than waist circumference and body mass index in healthy young male adults in Indonesia. J. Clin. Med. 7, 96. https://doi.org/10.3390/jcm7050096.
Lee, S.-H., Park, S.-Y., Choi, C.S., 2021. Insulin resistance: from mechanisms to therapeutic strategies. Diabetes Metab. J. 46, 15–37. https://doi.org/10.4093/dmj.2021.0280.
Lei, X., Zhou, Q., Wang, Y., Fu, S., Li, Z., Chen, Q., 2023. Serum and supplemental vitamin D levels and insulin resistance in T2DM populations: a meta-analysis and systematic review. Sci. Rep. 13, 12343. https://doi.org/10.1038/s41598-023-39469-9.
Matthews, D.R., Hosker, J.P., Rudenski, A.S., Naylor, B.A., Treacher, D.F., Turner, R.C., 1985. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28, 412–419. https://doi.org/10.1007/BF00280883.
Mirhosseini, N., Vatanparast, H., Mazidi, M., Kimball, S.M., 2018. Vitamin D supplementation, glycemic control, and insulin resistance in prediabetics: a meta-analysis. J. Endocr. Soc. 2, 687–709. https://doi.org/10.1210/js.2017-00472.
Molinari, M., de Iorio, M., Chaturvedi, N., Hughes, A., Tillin, T., 2021. Modelling ethnic differences in the distribution of insulin resistance via Bayesian nonparametric processes: an application to the SABRE cohort study. Int. J. Biostat. 17, 153–164. https://doi.org/10.1515/ijb-2019-0108.
Moreno, M., Moreno-Navarrete, J.M., Serrano, M., Ortega, F., Delgado, E., Sanchez-Ragnarsson, C., Valdés, S., Botas, P., Ricart, W., Fernández-Real, J.M., 2015. Circulating Irisin levels are positively associated with metabolic risk factors in sedentary subjects. PLoS ONE 10, e0124100. https://doi.org/10.1371/journal.pone.0124100.
Nasr, M.H., Hassan, B.A.R., Othman, N., Karuppannan, M., Abdulaziz, N.B., Mohammed, A.H., Alsarani, M.A., Eskembaji, M.H., Aman, A.M., Othman, G., 2022. Prevalence of vitamin D deficiency between type 2 diabetes mellitus patients and non-diabetics in the Arab gulf. Diabetes Metab. Syndr. Obes. 15, 647–657. https://doi.org/10.2147/DMSO.S350626.
Qu, H.-Q., Li, Q., Rentfro, A.R., Fisher-Hoch, S.P., McCormick, J.B., 2011. The definition of insulin resistance using HOMA-IR for Americans of Mexican descent using machine learning. PLoS ONE 6, e21041. https://doi.org/10.1371/journal.pone.0021041.
Rahimi, M., Ghanbari, S., Khazaei, M., Niroman, E., 2020. Comparison of sirtuin 1 level and related blood factors in diabetic and healthy subjects. Pediatr. Endocrinol. Diabetes Metab. 26, 17–21. https://doi.org/10.5114/pedm.2020.94392.
Safarpour, P., Daneshi-Maskooni, M., Vafa, M., Nourbakhsh, M., Janani, L., Maddah, M., Amiri, F.-S., Mohammadi, F., Sadeghi, H., 2020. Vitamin D supplementation improves SIRT1, Irisin, and glucose indices in overweight or obese type 2 diabetic patients: a double-blind randomized placebo-controlled clinical trial. BMC Fam. Pract. 21, 26. https://doi.org/10.1186/s12875-020-1096-3.
Saravia, G., Civeira, F., Hurtado-Roca, Y., Andres, E., Leon, M., Pocovi, M., Ordovas, J., Guallar, E., Fernandez-Ortiz, A., Casasnovas, J.A., Laclaustra, M., 2015. Glycated hemoglobin, fasting insulin and the metabolic syndrome in males. Cross-sectional analyses of the Aragon Workers' Health Study Baseline. PLoS ONE 10, e0132244. https://doi.org/10.1371/journal.pone.0132244.
Song, R., Zhao, X., Zhang, D.-Q., Wang, R., Feng, Y., 2021. Lower levels of irisin in patients with type 2 diabetes mellitus: a meta-analysis. Diabetes Res. Clin. Pract. 175, 108788. https://doi.org/10.1016/j.diabres.2021.108788.
Sun, H., Saeedi, P., Karuranga, S., Pinkepank, M., Ogurtsova, K., Duncan, B.B., Stein, C., Basit, A., Chan, J.C.N., Mbanya, J.C., Pavkov, M.E., Ramachandaran, A., Wild, S.H., James, S., Herman, W.H., Zhang, P., Bommer, C., Kuo, S., Boyko, E.J., Magliano, D. J., 2022. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res. Clin. Pract. 183, 109119. https://doi.org/10.1016/j.diabres.2021.109119.
Talaei, A., Yadegari, N., Rafee, M., Rezvanfar, M.R., Moini, A., 2012. Prevalence and cut-off point of vitamin D deficiency among secondary students of Arak, Iran in 2010. Indian J. Endocrinol. Metab. 16, 786. https://doi.org/10.4103/2230-8210.100676.
Talaei, A., Mohamadi, M., Adgi, Z., 2013. The effect of vitamin D on insulin resistance in patients with type 2 diabetes. Diabetol. Metab. Syndr. 5, 8. https://doi.org/10.1186/1758-5996-5-8.
Tu, Q., Wang, J., Xie, H., Zhao, Q., Fu, J., Xu, H., Cao, Z., 2021. Up-regulation of GLP-1R improved the dysfunction of late EPCs under hyperglycemia by regulating SIRT1 expression. Mol. Cell. Endocrinol. 538, 111455. https://doi.org/10.1016/j.mce.2021.111455.
Wahidin, M., Achadi, A., Besral, B., Kosen, S., Nadjib, M., Nurwahyuni, A., Ronoatmodjo, S., Rahajeng, E., Pane, M., Kusuma, D., 2024. Projection of diabetes morbidity and mortality till 2045 in Indonesia based on risk factors and NCD prevention and control programs. Sci. Rep. 14, 5424. https://doi.org/10.1038/s41598-024-54563-2.
Wallace, T.M., Levy, J.C., Matthews, D.R., 2004. Use and abuse of HOMA modeling. Diabetes Care 27, 1487–1495. https://doi.org/10.2337/diacare.27.6.1487.
World Health Organization, 2008. Waist Circumference and Waist-hip Ratio: Report of a WHO Expert Consultation. World Health Organization, Geneva.
Wu, H., Ballantyne, C.M., 2020. Metabolic inflammation and insulin resistance in obesity. Circ. Res. 126, 1549–1564. https://doi.org/10.1161/CIRCRESAHA.119.315896.
Xu, Z., Gong, R., Luo, G., Wang, M., Li, D., Chen, Y., Shen, X., Wei, X., Feng, N., Wang, S., 2022. Association between vitamin D3 levels and insulin resistance: a large sample cross-sectional study. Sci. Rep. 12, 119. https://doi.org/10.1038/s41598-021-04109-7.
Zhou, S., Tang, X., Chen, H.-Z., 2018. Sirtuins and insulin resistance. Front. Endocrinol. 9. https://doi.org/10.3389/fendo.2018.00748.

Glossary

Anthropometry: the measurement of the size, shape, and composition of the human body.
Glycemia: the concentration of glucose in the blood. Controlled glycemia refers to maintaining blood glucose levels within a target range to avoid complications associated with diabetes.
Insulin resistance: a condition where the body's cells become less responsive to insulin, leading to elevated blood glucose levels.

Sirtuin, irisin, and vitamin D as predictors of diabetes mellitus with uncontrolled glycemia in Indonesian patients

ORIGINALITY REPORT

22%
SIMILARITY INDEX

PRIMARY SOURCES

1	www.frontiersin.org Internet	88 words — 1%
2	www.mdpi.com Internet	57 words — 1%
3	m3g.github.io Internet	36 words — 1%
4	diving-rov-specialists.com Internet	34 words — 1%
5	journals.lww.com Internet	31 words — < 1%
6	journals.plos.org Internet	27 words — < 1%
7	e-dmj.org Internet	26 words — < 1%
8	mdpi-res.com Internet	26 words — < 1%
9	research.thea.ie Internet	24 words — < 1%

10	www.researchgate.net Internet	24 words — < 1%
11	www.medrxiv.org Internet	23 words — < 1%
12	advances.umw.edu.pl Internet	22 words — < 1%
13	oa.las.ac.cn Internet	22 words — < 1%
14	vtimes.at Internet	22 words — < 1%
15	www.wjgnet.com Internet	22 words — < 1%
16	academic.oup.com Internet	21 words — < 1%
17	link.springer.com Internet	21 words — < 1%
18	www.resmedjournal.com Internet	21 words — < 1%
19	www2.mdpi.com Internet	20 words — < 1%
20	pure.eur.nl Internet	19 words — < 1%
21	www.spandidos-publications.com Internet	18 words — < 1%

22	Svanborg, A.. "Determination of unesterified fatty acids in normal human plasma", Clinica Chimica Acta, 195809 Crossref	17 words — < 1%
23	sbg.org.br Internet	17 words — < 1%
24	bmcgeriatr.biomedcentral.com Internet	15 words — < 1%
25	hull-repository.worktribe.com Internet	15 words — < 1%
26	www.ismni.org Internet	15 words — < 1%
27	Jian-Han Chen, Po-Jui Chi, Chung-Yen Chen, Chi-Ming Tai, Po-Jen Chen, Yu-Chieh Su, Hung-Yu Lin, Ming-Shiang Wu. "Three-Month Excessive Body Weight Loss < 37.7% as a Predictor of Mid-term Suboptimal Outcomes Postlaparoscopic Sleeve Gastrectomy: Risk Factors and the Impact of Neutrophil-to-Lymphocyte Ratio on Adipocyte Function", Obesity Surgery, 2024 Crossref	14 words — < 1%
28	d2v96fxpocvxx.cloudfront.net Internet	14 words — < 1%
29	lirias.kuleuven.be Internet	14 words — < 1%
30	www.zjyfyxzz.com Internet	14 words — < 1%
31	Adel A. Gomaa, Yasmin A. Abdel-Wadood, Romany H. Thabet, Ghada A. Gomaa.	13 words — < 1%

"Pharmacological evaluation of vitamin D in COVID-19 and long COVID-19: recent studies confirm clinical validation and highlight metformin to improve VDR sensitivity and efficacy", Inflammopharmacology, 2023
Crossref

32 Ying Zhang, Jianjun Du, Jinglu Wang, Liming Ma, Xianju Lu, Xiaodi Pan, Xinyu Guo, Chunjiang Zhao. "High-throughput micro-phenotyping measurements applied to assess stalk lodging in maize (Zea mays L.)", Biological Research, 2018 — 13 words — < 1%
Crossref

33 www.atlantis-press.com — 13 words — < 1%
Internet

34 Ranil Jayawardena, Piumika Sooriyaarachchi, Anoop Misra. "Abdominal obesity and metabolic syndrome in South Asians: prevention and management", Expert Review of Endocrinology & Metabolism, 2021 — 12 words — < 1%
Crossref

35 Tatsumi Moriya, Takahiro Yamagishi, Madoka Matsubara, Motoshi Ouchi. "Serial renal biopsies in normo- and microalbuminuric patients with type 2 diabetes demonstrate that loss of renal function is associated with a reduction in glomerular filtration surface secondary to mesangial expansion", Journal of Diabetes and its Complications, 2019 — 12 words — < 1%
Crossref

36 assets-eu.researchsquare.com — 12 words — < 1%
Internet

37 downloads.hindawi.com — 12 words — < 1%
Internet

38	res.mdpi.com Internet	12 words — < 1%
39	www.cisejournal.org Internet	12 words — < 1%
40	www.science.gov Internet	12 words — < 1%
41	www.withpower.com Internet	12 words — < 1%
42	dokumen.tips Internet	11 words — < 1%
43	efficientpapers.com Internet	11 words — < 1%
44	nicm.edu.au Internet	11 words — < 1%
45	ricerca.unich.it Internet	11 words — < 1%
46	unglueit-files.s3.amazonaws.com Internet	11 words — < 1%
47	www.myfoodresearch.com Internet	11 words — < 1%
48	www.targetedonc.com Internet	11 words — < 1%
49	Adrianne E. Hardman, David J. Stensel. "Physical Activity and Health - The Evidence Explained", Routledge, 2019 Publications	10 words — < 1%

50	Stefania Mai, Graziano Grugni, Chiara Mele, Roberta Vietti et al. "Irisin levels in genetic and essential obesity: clues for a potential dual role", Scientific Reports, 2020 Crossref	10 words — < 1%
51	care.diabetesjournals.org Internet	10 words — < 1%
52	image.hanspub.org Internet	10 words — < 1%
53	m.scirp.org Internet	10 words — < 1%
54	pure-oai.bham.ac.uk Internet	10 words — < 1%
55	repository.ush.edu.sd:8080 Internet	10 words — < 1%
56	uokerbala.edu.iq Internet	10 words — < 1%
57	www.dovepress.com Internet	10 words — < 1%
58	www.thieme-connect.com Internet	10 words — < 1%
59	Ai Guo, Kai Li, Qian Xiao. "Sarcopenic obesity: Myokines as potential diagnostic biomarkers and therapeutic targets?", Experimental Gerontology, 2020 Crossref	9 words — < 1%

60	Steven E. Mendonca, Carrie L. Tyler, Kristina M. Barclay, Lindsey R. Leighton. "Intrinsic factors affecting predator failure in crab-gastropod encounters and their implications for repair scar frequencies", Journal of Experimental Marine Biology and Ecology, 2025 Crossref	9 words — < 1%
61	napier-repository.worktribe.com Internet	9 words — < 1%
62	researchopenworld.com Internet	9 words — < 1%
63	www.aimspress.com Internet	9 words — < 1%
64	www.escardio.org Internet	9 words — < 1%
65	www.nature.com Internet	9 words — < 1%
66	www.redorbit.com Internet	9 words — < 1%
67	www.researchsquare.com Internet	9 words — < 1%
68	"Poster Session Clinical", European Journal of Heart Failure, 2013. Crossref	8 words — < 1%
69	"VIII Latin American Conference on Biomedical Engineering and XLII National Conference on Biomedical Engineering", Springer Science and Business Media LLC, 2020 Crossref	8 words — < 1%

70 Birhanu AlehegnAwoke, Mehretie Kokeb Alemu, Geta Bayu Genet, Addisu Ginbu Dubie, Biruk Fanta Alemayehu. "Prevalence and associated factors of psychiatric problems in children aged 6-18 years with type 1 diabetes mellitus in Gondar, Ethiopia: a cross-sectional study", Springer Science and Business Media LLC, 2024 — 8 words — < 1%
Crossref Posted Content

71 Casimir C. Akoh, Oi-Ming Lai. "Healthful Lipids", Routledge, 2019 — 8 words — < 1%
Publications

72 Daniel D. Lam, Lora K. Heisler. "Serotonin and energy balance: molecular mechanisms and implications for type 2 diabetes", Expert Reviews in Molecular Medicine, 2007 — 8 words — < 1%
Crossref

73 Dima Samer Ali, Samuel O. Sofela, Muhammedin Deliorman, Pavithra Sukumar et al. "OMEF biochip for evaluating red blood cell deformability using dielectrophoresis as a diagnostic tool for type 2 diabetes mellitus", Lab on a Chip, 2024 — 8 words — < 1%
Crossref

74 Hamse Mohamed Mohamoud, Md. Kamruzzaman, M. Mominul Islam, Anuwatchakij Klamrak, Shaikh Shahinur Rahman. "Body composition, nutritional status, and socio-demographic factors among university students and teachers in Bangladesh: A pilot study", Food and Humanity, 2024 — 8 words — < 1%
Crossref

75 J Wesseling, D Van Driel, M Smrkovsky, E Van der Veer, L.M Geven-Boere, P.J.J Sauer, B.C.L Touwen. "Neurological outcome in school-age children after in utero exposure to coumarins", Early Human Development, 2001 — 8 words — < 1%

Crossref

76 Leah Coles. "Clinical Nutrition - The Interface Between Metabolism, Diet, and Disease", Apple Academic Press, 2019 — 8 words — < 1%
Publications

77 Lotte Leick, Birgitte Lindegaard, Dorthe Stensvold, Peter Plomgaard, Bengt Saltin, Henriette Pilegaard. "Adipose Tissue Interleukin-18 mRNA and Plasma Interleukin-18: Effect of Obesity and Exercise*", Obesity, 2007 — 8 words — < 1%
Crossref

78 Maria Poliana Leite Galantini, Israel Souza Ribeiro, Caroline Vieira Gonçalves, Igor Pereira Ribeiro Muniz et al. "The sweet fuel of inflammation: New perspectives on the complex web that interconnects diabetes", Experimental Gerontology, 2022 — 8 words — < 1%
Crossref

79 Michał Kukla, Lubomir Skladany, Tomasz Menżyk, Aleksandra Derra et al. "Irisin in Liver Cirrhosis", Journal of Clinical Medicine, 2020 — 8 words — < 1%
Crossref

80 Murat Yilmaz, Mehmet Ali Ergün, Ayhan Karakoç, Erkan Yurtçu, Nuri Çakir, Metin Arslan. "Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-γ gene in women with polycystic ovary syndrome", Gynecological Endocrinology, 2009 — 8 words — < 1%
Crossref

81 Peter Piko, Tibor Jenei, Zsigmond Kosa, Janos Sandor, Nora Kovacs, Ildiko Seres, Gyorgy Paragh, Roza Adany. "Association of HDL Subfraction Profile with the Progression of Insulin Resistance", International Journal of Molecular Sciences, 2023 — 8 words — < 1%
Crossref

82	Sajal Chakraborti. "Handbook of Proteases in Cancer - Cellular and Molecular Aspects", CRC Press, 2024 Publications	8 words — < 1%
83	Stephanie T. Chung, Samantha T. Matta, Abby G. Meyers, Celeste K. Cravalho et al. "Nuclear Magnetic Resonance Derived Biomarkers for Evaluating Cardiometabolic Risk in Youth and Young Adults Across the Spectrum of Glucose Tolerance", Frontiers in Endocrinology, 2021 Crossref	8 words — < 1%
84	Vinicius J. B. Martins, Paula A. Martins, Janaína das Neves, Ana L. Sawaya. "Children recovered from malnutrition exhibit normal insulin production and sensitivity", British Journal of Nutrition, 2008 Crossref	8 words — < 1%
85	academicjournals.org Internet	8 words — < 1%
86	accjournal.org Internet	8 words — < 1%
87	dmsjournal.biomedcentral.com Internet	8 words — < 1%
88	file.scirp.org Internet	8 words — < 1%
89	ia904705.us.archive.org Internet	8 words — < 1%
90	jfmpc.com Internet	8 words — < 1%

91	m.moam.info Internet	8 words — < 1%
92	nrl.northumbria.ac.uk Internet	8 words — < 1%
93	public.pensoft.net Internet	8 words — < 1%
94	uwspace.uwaterloo.ca Internet	8 words — < 1%
95	worldwidescience.org Internet	8 words — < 1%
96	www.jtcm.org Internet	8 words — < 1%
97	www.omicsonline.org Internet	8 words — < 1%
98	www.physiology.org Internet	8 words — < 1%
99	www.springermedizin.de Internet	8 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 8 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 8 WORDS