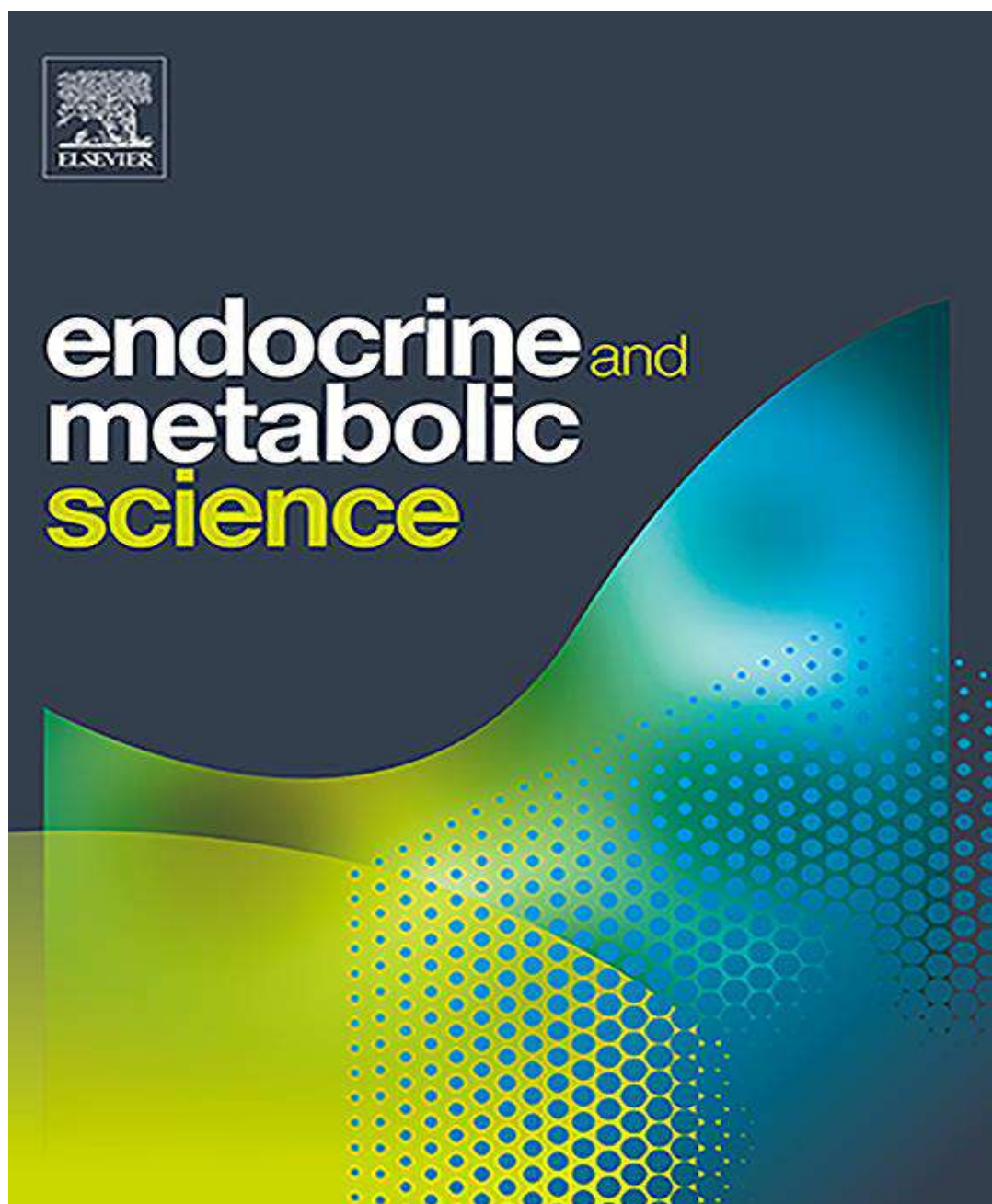


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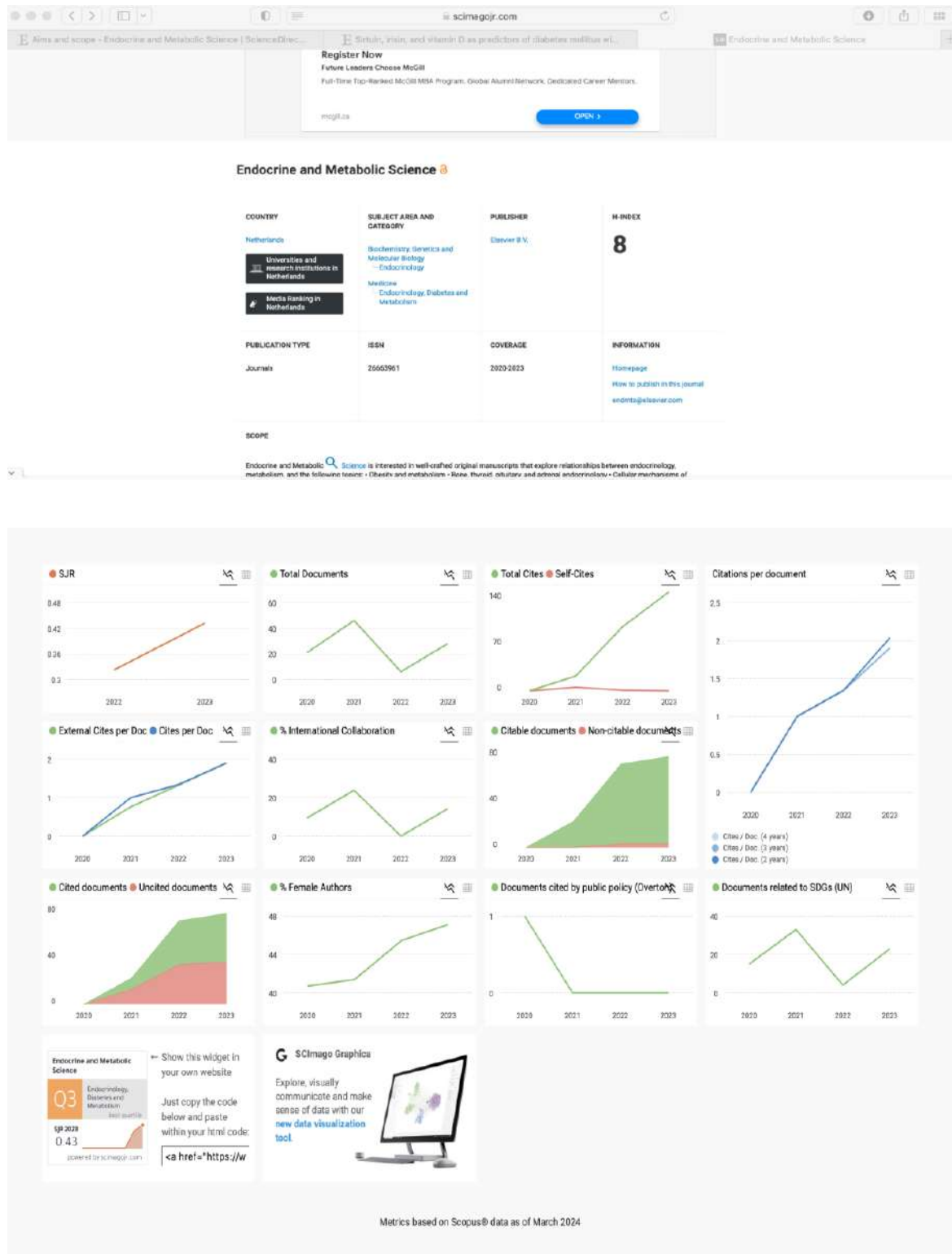
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## Full length article

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

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## 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  $\beta$ -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  $\beta$ -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

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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  $\beta$ -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 PPAR $\gamma$  1  $\alpha$  (PGC1- $\alpha$ ). 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)- $\gamma$  coactivator (PGC1- $\alpha$ ) PPAR- $\alpha$  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 ( $\mu$ IU/mL)  $\times$  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 inter-quartile 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 step-wise 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

**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 $\geq 25$ kg/m <sup>2</sup> ) | 48        | 65.8           |
| Nonobese (BMI $< 25$ kg/m <sup>2</sup> ) | 25        | 34.2           |
| Waist circumference                      |           |                |
| High ( $\geq 90$ cm)                     | 60        | 83.6           |
| Normal ( $< 90$ cm)                      | 12        | 16.4           |
| Waist-to-hip ratio                       |           |                |
| High ( $\geq 0.8$ )                      | 68        | 93.2           |
| Normal ( $< 0.8$ )                       | 5         | 6.8            |
| Systolic blood pressure                  |           |                |
| Hypertension ( $\geq 140$ mmHg)          | 46        | 63.0           |
| Normal ( $< 140$ mmHg)                   | 27        | 37.0           |
| Fasting blood glucose                    |           |                |
| High ( $\geq 140$ mg/dL)                 | 35        | 47.9           |
| Normal ( $< 140$ mg/dL)                  | 38        | 52.1           |
| Vitamin D                                |           |                |
| Insufficient ( $< 20$ ng/mL)             | 67        | 91.8           |
| Sufficient ( $\geq 20$ ng/mL)            | 6         | 8.2            |
| HOMA-IR                                  |           |                |
| Insulin resistant ( $\geq 3.75$ )        | 8         | 11.0           |
| Insulin responsive ( $< 3.75$ )          | 65        | 89.0           |
| HbA1c                                    |           |                |
| Uncontrolled glycemia ( $\geq 7$ %)      | 54        | 74.0           |
| Controlled glycemia ( $< 7$ %)           | 19        | 26.0           |
| Diabetes duration                        |           |                |
| $\leq 12$ 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            |
| Metformin + Glimepiride                  | 2         | 2.7            |

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

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  $\geq 90$  cm) and 93.2 % (waist-to-hip ratio  $\geq 0.8$ ) of the subjects. Systolic hypertension ( $\geq 140$  mmHg) was present in 63 % of the subjects. A total of 47.9 % of the subjects had high FBG ( $\geq 140$  mg/dL). Vitamin D deficiency ( $< 20$  ng/mL) was found in 91.8 % of the subjects. High HOMA-IR ( $\geq 3.75$ ) was a minority at 11.0 %, whereas the HbA1c level was high ( $\geq 7$  %) 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).

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  $\mu$ g/mL and IQR of 17.5–30.0  $\mu$ g/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  $\geq 7$  %, 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)  $\mu$ g/mL in patients with uncontrolled glycemia, which is comparable to the range of 28.9 (22.3–30.0)  $\mu$ g/mL reported in patients with controlled glycemia.

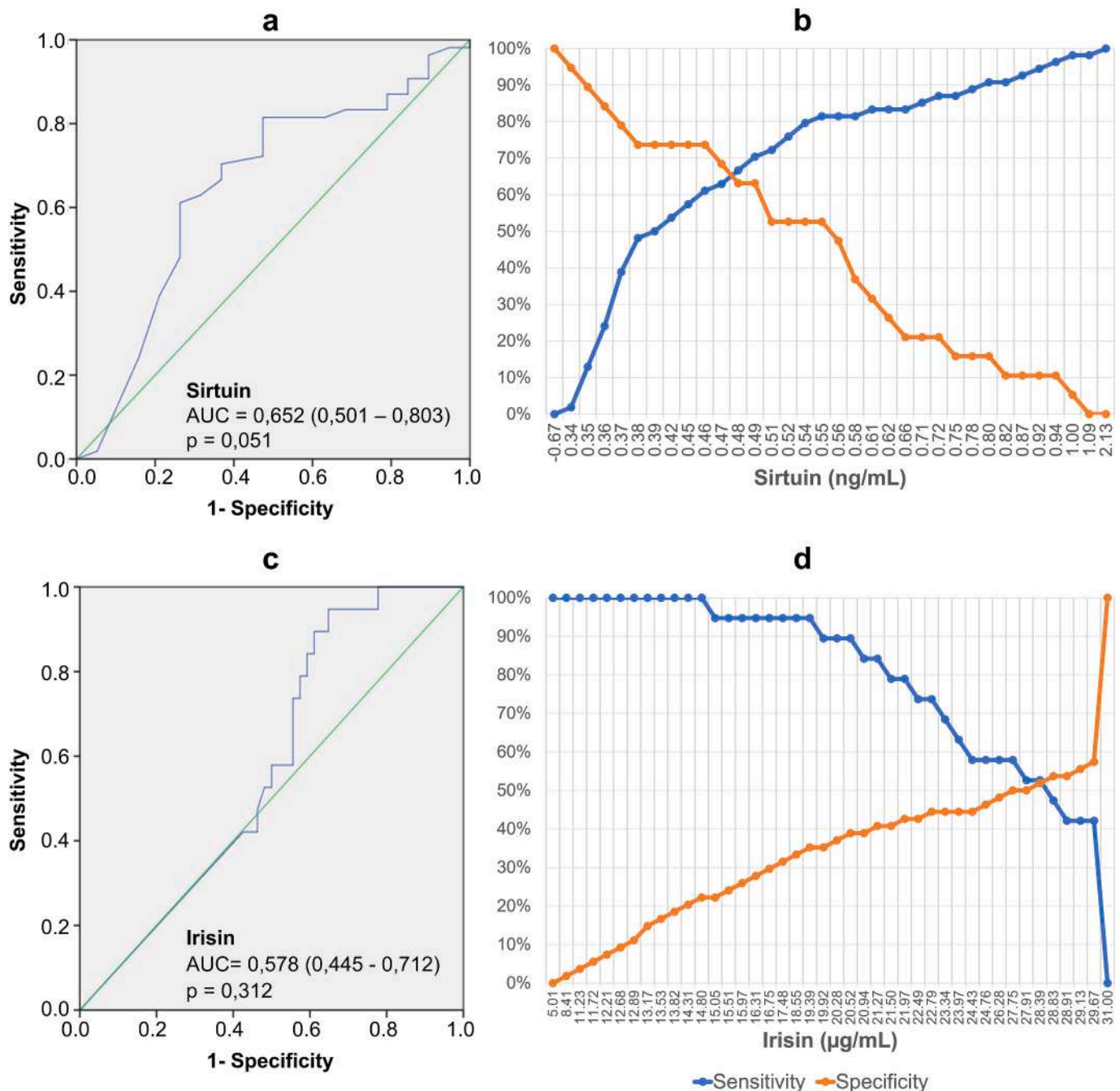
In addition, we investigated whether sirtuin-1 and irisin levels differ between subjects with insulin resistance. We found no difference in the circulating levels of sirtuin-1 (MWU test,  $p = 0.219$ ) or irisin (MWU test,  $p = 0.314$ ) between the insulin-resistant group (HOMA-IR  $\geq 3.75$ , 8 subjects) 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)  $\mu$ g/mL in the insulin-resistant group, which is lower compared to 28.9 (17.2–30.0)  $\mu$ g/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  $\mu$ g/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 <sup>2</sup>  | 34        | 14 | 0.397     | 0.61  | 0.19    | 1.94  | 5       | 43    | 1.000  | 0.85 | 0.19    | 3.90  |
| <25 kg/m <sup>2</sup>  | 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       | <b>0.037*</b> | 5.41          | <b>0.014*</b>  | 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       | <b>0.065*</b> | 0.09          | <b>0.049*</b> |
| 0: ≤28.375 µg/mL         |            |               |               |                |            |               |               |               |
| Fasting blood glucose    |            |               |               |                |            |               |               |               |
| 1: ≥140 mg/dL            | 16.87      | <b>0.028*</b> | 36.88         | <b>0.001**</b> | 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 <sup>2</sup> | –0.83      | 0.427         | –             | –              | 0.47       | 0.783         | –             | –             |
| 0: <25 kg/m <sup>2</sup> |            |               |               |                |            |               |               |               |
| 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 (Talaie 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.

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## 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.

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## Data availability

Data will be made available on request.

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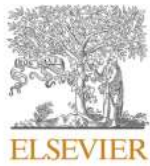
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## Glossary

- 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*



## Full length article

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

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## 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  $\beta$ -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  $\beta$ -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

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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  $\beta$ -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 type peptide 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 PPAR- $\gamma$  1 alpha (PGC1- $\alpha$ ). 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)- $\gamma$  coactivator (PGC1- $\alpha$ ) PPAR- $\alpha$  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  $\geq 126$  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-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 ( $\mu IU/mL$ )  $\times$  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 demographic and clinical characteristics of the studied 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           |
| <60 years old                            | 47        | 64.4           |
| Obesity                                  |           |                |
| Obese (BMI $\geq 25$ kg/m <sup>2</sup> ) | 48        | 65.8           |
| Nonobese (BMI < 25 kg/m <sup>2</sup> )   | 25        | 34.2           |
| Waist circumference                      |           |                |
| High ( $\geq 90$ cm)                     | 60        | 83.6           |
| Normal (<90 cm)                          | 12        | 16.4           |
| Waist-to-hip ratio                       |           |                |
| High ( $\geq 0.8$ )                      | 68        | 93.2           |
| Normal (<0.8)                            | 5         | 6.8            |
| Systolic blood pressure                  |           |                |
| Hypertension ( $\geq 140$ mmHg)          | 46        | 63.0           |
| Normal (<140 mmHg)                       | 27        | 37.0           |
| Fasting blood glucose                    |           |                |
| High ( $\geq 140$ mg/dL)                 | 35        | 47.9           |
| Normal (<140 mg/dL)                      | 38        | 52.1           |
| Vitamin D                                |           |                |
| Insufficient (<20 ng/mL)                 | 67        | 91.8           |
| Sufficient ( $\geq 20$ ng/mL)            | 6         | 8.2            |
| HOMA-IR                                  |           |                |
| Insulin resistant ( $\geq 3.75$ )        | 8         | 11.0           |
| Insulin responsive (<3.75)               | 65        | 89.0           |
| HbA1c                                    |           |                |
| Uncontrolled glycemia ( $\geq 7\%$ )     | 54        | 74.0           |
| Controlled glycemia (<7%)                | 19        | 26.0           |
| Diabetes duration                        |           |                |
| $\leq 12$ 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            |
| Metformin + glimepiride                  | 2         | 2.7            |

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

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  $\geq 90$  cm) and 93.2 % (waist-to-hip ratio  $\geq 0.8$ ) of the subjects. Systolic hypertension ( $\geq 140$  mmHg) was present in 63 % of the subjects. A total of 47.9 % of the subjects had high FBG ( $\geq 140$  mg/dL). Vitamin D deficiency (<20 ng/mL) was found in 91.8 % of the subjects. High HOMA-IR ( $\geq 3.75$ ) was a minority at 11.0 %, whereas the HbA1c level was high ( $\geq 7\%$ ) 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).

#### 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  $\mu$ g/mL and IQR of 17.5–30.0  $\mu$ g/mL.

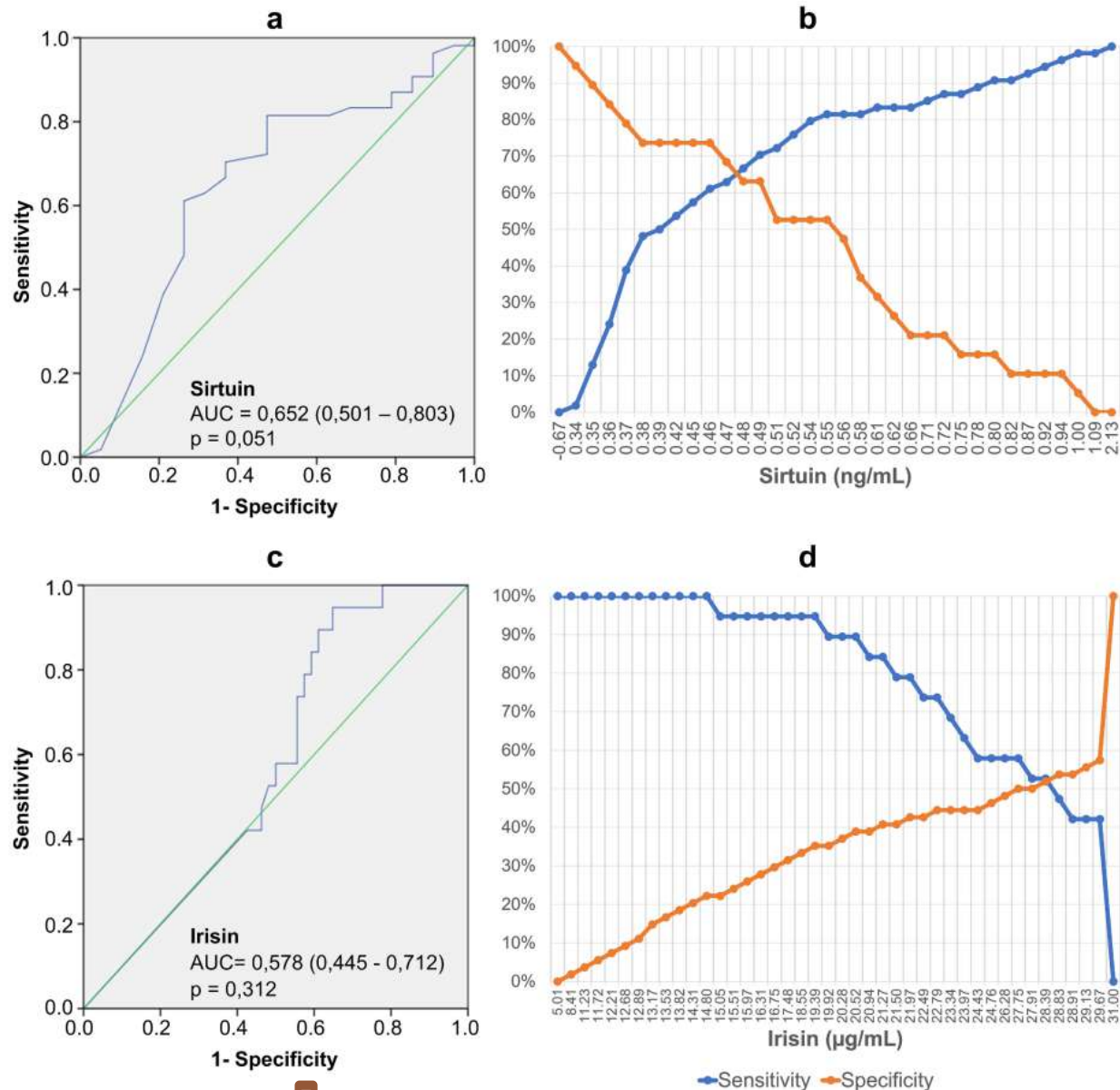
We further investigated whether sirtuin-1 and irisin levels are different in our subjects with abnormal HbA1c levels. There was a significant difference in sirtuin-1 levels (MWU test,  $p = 0.050$ ) between subjects with uncontrolled glycemia (HbA1c  $\geq 7\%$ , 54 subjects) and those with normal glycemia (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)  $\mu$ g/mL in patients with uncontrolled glycemia, which is comparable to the range of 28.9 (22.3–30.0)  $\mu$ g/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  $\geq 3.75$ , 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)  $\mu$ g/mL in the insulin-resistant group, which is lower compared to 28.9 (17.2–30.0)  $\mu$ g/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  $\mu$ g/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).

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### 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 <sup>2</sup>  | 34        | 14 | 0.397     | 0.61  | 0.19    | 1.94  | 5       | 43    | 1.000  | 0.85 | 0.19    | 3.90  |
| <25 kg/m <sup>2</sup>  | 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 results 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 |         | HOMA-IR |        | HOMA-IR |        |
|--------------------------|-------|--------|---------|---------|---------|--------|---------|--------|
|                          | 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 <sup>2</sup> | –0.83 | 0.427  | –       | –       | 0.47    | 0.783  | –       | –      |
| 0: <25 kg/m <sup>2</sup> |       |        |         |         |         |        |         |        |
| 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 reported that vitamin D supplementation led to lower levels of FBG and HOMA-IR (Talei 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, which 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                                 |
| Mann-Whitney U | 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.

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## 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.

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## Data availability

Data will be made available on request.

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## 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.



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