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Serum Irisin In Individuals with Type 2 Diabetes Mellitus and Prediabetes in Duhok City

Ibrahim Hasan Ibrahim[1], Sherwan Ferman Salih[2]

[1]*Department of medical laboratory technology, College of Health and medical technology, Shekhan, Duhok polytechnic university Kurdistan Region, Iraq. (ibrahim.ibrahim@dpu.edu.krd)*

[2]*Department of medical chemistry, Duhok University, College of Medicine, Kurdistan Region, Iraq. (sherwan.salih@uod.ac)*

[*]Correspondence: *sherwan.salih@uod.ac*

Abstract

Type 2 diabetes mellitus is one of the most common chronic metabolic diseases characterized by hyperglycemia, with either lack of insulin secretion or decreased sensitivity to insulin metabolic effects. Prediabetes is an intermediate stage between normal glucose metabolism and diabetes mellitus with high prevalence rate of diabetes mellitus developments. We aimed in this study to evaluate serum irisin level among patients with type 2 diabetes mellitus and individuals with prediabetes. A cross-sectional study was done on 214 participants, who were attend to the Azadi Teaching Hospital, Diabetic unit at Duhok city between October 2021 and April 2022. The participants were classified to three groups; 94 patients with type 2 diabetes mellitus, 60 prediabetic individuals and 60 apparently healthy control. We collected blood samples in the morning after overnight fasting from all participants. All parameters were measured by cobas 6000 (Hitachi, Roche) and including glucose, insulin, total cholesterol, triglyceride, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol and blood HbA1c% except serum irisin that was measured by ELISA instrument. Serum irisin levels was lower in type 2 diabetic patients and prediabetic individuals compared to healthy control (P<0.001). There was a negative relation between serum irisin and total cholesterol, triglyceride, low-density lipoprotein-cholesterol, poor glycemic control and atherogenic indices, with positive relation of serum irisin with high-density lipoprotein-cholesterol -c. We found lower level of circulating serum irisin in type 2 diabetic patients and prediabetic individuals compared to healthy controls.

Keywords: *Irisin, Type 2 Diabetes Mellitus, Prediabetes, HbA1c%, HOMA-IR.*

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I. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most common chronic metabolic diseases characterized by impaired carbohydrates metabolism (hyperglycemia), with either lack of insulin secretion (pancreatic β-cell dysfunction) or decreased sensitivity to insulin metabolic effects (insulin resistance) (Motahari-Tabari *et al*., 2014). T2DM prevalence is high worldwide; about 1 in 11 people are currently diagnosed with diabetes mellitus, and it is expected that diabetic patients will increase to 552 million by 2030 (Aune *et al*., 2015). Prediabetes indicates the earliest stage of impaired glucose metabolism characterized by plasma glucose levels between those of normal glucose tolerance and diabetes mellitus. Diabetes mellitus development is associated with prevalence rate of prediabetes (Tabák *et al*., 2012), therefore; modifiable risk factors in prediabetes, such as obesity, physical inactivity and diet high energy, can be targeted in prediabetes to delay or prevent T2DM development (Williamson, 2018).

Irisin is a peptide that has important roles in both human health and illness. It is a myokine; muscles and subcutaneous fat are responsible for its release, influenced by nutritional status and physical activity, and metabolic pathways influenced by it, like the metabolism of lipids and glucose. Human obesity and insulin resistance have both been linked to irisin (Boström *et al*., 2012), since it produces browning of white adipose tissue and enhances energy expenditure via rising uncoupling protein 1 levels that reduce body weight and improve insulin resistance (Huh *et al*., 2012).

Irisin's exact role is still unclear in T2DM and prediabetes, with controversial relation with glycemic indices and lipid profile (Mahmoodnia *et al*., 2017), therefore; in this study, we aimed to evaluate serum irisin levels among T2DM patients and prediabetic individuals, ascertain the association of serum irisin with lipid profile and atherogenic indices in

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T2DM patients and prediabetic individuals, and in T2DM to estimate serum irisin relation with glycemic control.

II. Materials And Methods

A. Population

We recruited 214 participants who attended to Azadi Teaching Hospital, Diabetic unit in Duhok city, between October 2021 and April 2022 in a cross-sectional study. The participants were classified into three groups; 94 T2DM patients, 60 prediabetic individuals and 60 apparently healthy as control.

The exclusion criteria include disorders affecting irisin level, including thyroid dysfunction, anaemia, cancer and renal diseases. We collected the clinical and demographic characteristics of the participants, including name, age, contact details, diabetes family history and gender. We obtained waist circumference, height and weight using a standard balance beam scale. The body mass index calculated as the body weight (kg)/height (m^2), and categorized from 18.5 kg/m2 to 24.9 kg/m^2 as normal weight, 25 kg/m^2 to 29.9 kg/m^2 overweight and 30 kg/m^2 and above for obese (Casadei *et al*., 2019). By using Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), we estimate Insulin resistance, HOMA-IR equation= fasting glucose (mg/dL) X fasting insulin (µU/mL) / 405 (Nuttall, 2015), and less than 3.0 was regarded as normal.

B. Blood collection

We collected blood samples in the morning after 12 hours overnight fasting from all participants. EDTA tube were used to collect blood for HbA1c analysis and gel tube for analysis of serum irisin, fasting glucose sugar, cholesterol, triglyceride, LDL-c, and HDL-c. Tests kit used in this study were from Germany. All tests were done daily except irisin, serum was frozen at minus 80 cellulose degree and analyzed at the end of blood collection.

C. Biochemical profile

All parameters were measured by Cobas 6000 (Hitachi, Roche) depending on different principles. HbA1c% based on the turbidimetric inhibition immunoassay for hemolyzed whole blood. Enzymatic, colorimetric method was used to measure concentration of serum glucose, serum cholesterol, triglyceride, low density lipoprotein-cholesterol and high-density lipoprotein-cholesterol. Plasma irisin was measured by using an enzyme-linked immunosorbent assay (ELISA) kit (Bioassay technology Laboratory, Zhejiang, China). Normal values of lipid profile depending on National Lipid Association (Jacobson *et al*., 2015).

Electrochemiluminescence method was used for serum insulin measurement. Atherogenic indices have been calculated as follows: total cholesterol/HDL-c ratio (less than 4.5 as normal range), triglyceride/HDL-c ratio less than 3.0 as normal range, less than 2.5 for LDL-c/HDL-c ratio as normal range and less than 130 mg/dl as normal range for non-HDL-c = total cholesterol- HDL-c (Hussain *et al*., 2020), The study was approved by the Research Ethics Committee of the General Directorate of Health at Duhok City (18 August 2021) and registered by reference number: 18082021-8-23.

D. Statistics

Statistical analyses were done using the SPSS Version 25.0 program (IBM). To compare baseline differences between groups continuous variables analysis of variance and participant's t-tests were used. For categorical variables, the chi-squared ($\chi 2$) test was used. Multiple linear regression analysis was used to look at the relationship between cognitive function and the concentration of irisin in circulation, as well as demographic and clinical factors. Statistical significance at $p< 0.05$.

III. Results

In this study, 214 individuals were recruited, 94 type 2 diabetic patients, 60 prediabetic individuals and 60 were apparently healthy controls. Mean age of T2DM patients was significantly higher than prediabetic individuals and healthy controls individuals. Majority of T2DM patients (87, 92.6%) and prediabetic individual (52, 86.7%) were equal to or more than 40 years old.

T2DM patients' females were predominant (53, 56.4%). Anthropometric measurements such as body mass index and waist circumference showed statistically significant difference among studied groups, with higher mean ±SD among patients with T2DM (30.22±4.32) and prediabetic individuals (27.76±3.18) as shown in Table 1.

Table 1. General characteristics of T2DM patients, prediabetic individuals and healthy controls.

Characters	T2DM (No, %) No=94	Prediabetes (No, %) No=60	Control (No, %) No=60	P- value
Gender				
Male	41(43.6%)	33(55%)	39(65%)	0.032
Female	53(56.4%)	27(45%)	21(35%)	
Age (years)	52.17±8.21	48.9±10.4	46.08±10.85	<0.001
<40	7(7.4%)	8(13.3%)	20(33.3%)	
≥40	87(92.6%)	52(86.7%)	40(66.7%)	<0.001
BMI (kg/m^2)	30.22±4.32	27.76±3.18	25.22±2.46	<0.001
Normal	15(16%)	12(20%)	36(60%)	<0.001
Overweight	27(28.7%)	35(58.3%)	23(38.3%)	<0.001
Obese	52(55.3%)	13(21.7%)	1(1.7%)	<0.001
W.C (cm)	99.52±11.63	93.13±7.34	83.23±5.08	<0.001
Male				
<102	27(28.7%)	27(45%)	39(65%)	<0.001
≥102	14(14.9%)	6(10%)	0(0%)	
Female				
<88	6(6.4%)	6(10%)	20(33.3%)	<0.001
≥88	47(50%)	21(35%)	1(1.7%)	

The biochemical analysis of the studied group was shown in table 2. Serum glucose, Insulin, HbA1c% and HOMA-IR in T2DM patients and prediabetic individuals were significantly higher than healthy controls $p<0.001$. Moreover, in T2DM

patients and prediabetic individual's, serum cholesterol, triglyceride and LDL-c were higher than in healthy control, while HDL-c had lower values in patients of T2DM and prediabetic individuals compared to healthy controls. Mean ±SD of irisin in T2DM patients was (7.67±1.57 ng/ml) and in prediabetic individuals (8.5±1.74ng/ml) that were lower than the mean level of controls (9.01±2.36 ng/ml) and the difference was statistically significant (P <0.001).

Table 2. biochemical parameters of T2DM patients, prediabetic individuals and healthy controls.

Parameters	T2DM Mean ±SD No=94	Pre-DM Mean ±SD No=60	Control Mean ±SD No=60	P-value
Glucose (mg/dl)	189.04±78.3	105.32±10.1	95.63±8.29	<0.001
Cholesterol (mg/dl)	191.61±39.86	169.9±34.51	167.78±18.71	<0.001
Triglyceride (mg/dl)	163.36±41.31	133.5±38.27	128.47±22.74	<0.001
HDL-c (mg/dl)	43.94±9.04	45.13±7.91	47.47±7.3	0.037
LDL-c (mg/dl)	111.47±30.84	98.43±27.42	93.42±16.34	<0.001
HbA1c%	9.06±2.15	5.99±0.3	5.28±0.59	<0.001
Insulin (µIU/ml)	18.5±16.93	14.86±10.31	11.28±4.19	<0.001
Irisin (ng/ml)	7.67±1.57	8.5±1.74	9.01±2.36	<0.001
HOMA-IR	8.5±7.43	3.88±2.78	2.66±1.05	<0.001

HDL-c, high density lipoprotein-cholesterol; LDL-c, Low-density lipoprotein-cholesterol; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance.

Atherogenic indices association between studied groups were shown in table 3. Differences found between mean ±SD of atherogenic indices among studied groups were statistically significant; patients of T2DM and prediabetic individuals had higher mean ±SD of atherogenic indices than healthy control.

Table 3. Atherogenic indices of T2DM patients, prediabetic individuals and healthy controls.

Atherogenic indices	T2DM patients	Prediabetic individuals	Healthy controls	P-value
CHO/HDL-c	4.49±1.15	3.89±1.12	3.61±0.69	<0.001
TG/HDL-c	3.91±1.38	3.11±1.26	2.79±0.71	<0.001
LDL-c/HDL-c	2.63±0.913	2.28±0.85	2.03±0.55	<0.001
non-HDL-c (mg/dl)	147.67±37.84	124.77±35.11	120.32±20.7	<0.001

The mean level of irisin with different levels of biochemical parameters was shown in table 4. In patients of T2DM, there were statistically significant lower levels of mean irisin with poor glycemic controls. Moreover, there was an insignificant low level of irisin among patients with T2DM and prediabetic individuals with abnormally high cholesterol, triglyceride and HOMA-IR.

Table 4. Association of serum irisin mean level with abnormal biochemical parameters of T2DM patients, prediabetes individuals and healthy controls.

Parameters	Irisin in T2DM No= 94		Irisin in Pre-DM No=60		Irisin in Control No=60	
	Mean±SD	P- value	Mean±SD	P- value	Mean ± SD	P-value
Glucose(mg/dl) <100 >=100	 7.90±1.79 7.66±1.55	0.688	 8.57±0.61 8.50±1.80	0.933	9.01±2.36	NA*
Cholesterol (mg/dl) < 200 >=200	 7.80±1.58 7.48±1.53	0.230	 8.61±1.86 7.85±0.59	0.325	9.01±2.36	NA
Triglyceride (mg/dl) <150 >=150	 7.69±1.12 7.67±1.74	0.940	 8.63±1.98 8.28±1.26	0.467	9.01±2.29 9.00±2.84	0.990
HDL-c (mg/dl) Male ≥40 < 40 Female ≥50 < 50	 7.80±1.51 7.60±1.90 7.75±1.63 7.51±1.28	 0.700 0.571	 9.03±2.48 8.21±0.89 8.21±1.14 8.18±1.53	 0.178 0.956	 11.67±1.16 8.67±2.40 9.36±2.82 8.78±1.51	 0.020 0.561
LDL-c (mg/dl) <130 ≥130	 7.80±1.53 7.32±1.59	0.186	 8.63±1.80 7.49±0.58	0.103	9.10±2.43 8.08±1.03	0.365
HbA1c% <6.5 >=6.5	 8.44±0.30 7.63±1.59	0.001	8.5±1.74	NA	9.01±2.36	NA
Insulin (µIU/ml) 2-20 >=20	 7.68±1.64 7.67±1.42	0.975	 8.60±1.83 8.11±1.32	0.391	9.11±2.43 7.89±0.76	0.273
HOMA-IR <3.0 >=3.0	 7.91±1.81 7.63±1.53	0.526	 8.68±1.76 8.31±1.73	0.426	9.01±2.38 8.69	0.893

*NA, no association

In relation to all abnormal levels of atherogenic indices, the mean level of irisin was lower in patients of T2DM and prediabetic individuals than apparently healthy controls, and they were statistically insignificant, as shown in table 5.

Table 5. Association of irisin with abnormal atherogenic indices of T2DM patients, prediabetes individuals and healthy controls.

Parameters		Irisin in T2DM No=94		Irisin in Pre-DM No=60		Irisin in Control No=60	
		Mean±SD	P-value	Mean±SD	P-value	Mean± SD	P-value
LDL-c/HDL-c	<2.5	7.61±1.68	0.697	8.46±1.92	0.825	8.92±2.30	0.551
	>=2.5	7.74±1.48		8.56±1.47		9.40±2.69	
CHO/HDL-c	<4.5	7.62±1.65	0.718	8.57±1.90	0.566	8.90±2.24	0.326
	>=4.5	7.74±1.47		8.26±1.12		9.84±3.22	
TG/HDL-c	<3.0	7.58±1.45	0.718	8.68±2.02	0.387	9.13±2.45	0.637
	>=3.0	7.71±1.63		8.28±1.34		8.84±2.28	
non-HDL-c mg/dl	< 130	7.47±1.53	0.360	8.68±1.96	0.483	9.07±2.50	0.794
	>=130	7.78±1.60		8.36±1.58		8.91±2.17	

IV. DISCUSSION

The prevalence of diabetes mellitus is growing globally, and over 90% of patients with diabetes have T2DM (Holman *et al*., 2015). T2DM is associated with numerous complications,

including cardiovascular disease, which significantly contributes to the high mortality, morbidity, and socioeconomic burden associated with diabetes (Shah *et al*., 2018). Prediabetic individuals' risk for acquiring T2DM is high, as most T2DM patients have hyperglycemia for several years prior to its diagnosis, and it is associated with complications like cardiovascular disease (Aroda *et al*., 2008). Depending on American Diabetes Association, the following are the diagnostic criteria for type 2 diabetes mellitus and prediabetes (American Diabetes Association (ADA), 2021): For type 2 diabetes mellitus, HbA1c% level of 6.5% and higher, fasting plasma glucose level of 126 mg/dL (7.0 mmol/L) or higher, 2-hour plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher during 75-gram oral glucose tolerance test and a random plasma glucose of 200 mg/dL (11.1 mmol/L) or higher. For prediabetes: HbA1c% between 5.7%-6.4%, fasting plasma glucose level of 100-125 mg/dL (5.6-6.9 mmol/L) and 2-hour plasma glucose level of 144-199 mg/dL (7.8- 11mmol/L) during a 75-gram oral glucose tolerance test.

Irisin is a new myokine that plays a crucial function in energy balance, homeostasis and metabolism (Lv *et al*., 2015). Moreover, circulating irisin levels gradually decline as glucose tolerance deteriorates (Zhang *et al*., 2016).

Our study showed a higher mean of waist circumference and body mass index in patients with T2DM and prediabetic individuals than healthy controls with statistically significant ($P<0.001$). We found consistency with another study done in China that found T2DM patients and prediabetic individuals had higher waist circumference and body mass index (Sun *et al*., 2022). Obesity causes both insulin resistance and β-cell dysfunction, which are significant risk factors for acquiring T2DM and prediabetes.

In constituent and conflicting data were reported by different studies in a different area about the relation between the mean level of irisin among patients of T2DM and prediabetic individuals, and evaluate the involvement of irisin in the initiation as well as the evolution of diabetes mellitus and prediabetes (Park *et al*., 2020; Akour *et al*., 2017) We found that in patients with T2DM and prediabetes, the mean circulating levels of irisin was lower compared to healthy controls (7.67±1.57 ng/ml, 8.5±1.74 ng/ml and 9.01±2.36 ng/ml). Peroxisome proliferator-activated receptor gamma coactivator 1-alpha activity and expression were significantly downregulated in the skeletal muscle of T2DM patients and individuals with prediabetes, which plays an important role in glucose metabolism, insulin sensitivity and insulin secretion in muscle and liver, and this may explain the lower serum irisin levels as irisin is an exercise-induced myokine activated via the peroxisome proliferator-activated receptor gamma coactivator-1-α pathway (Soyal *et al*., 2006).

Some studies found a probable role of irisin in the homeostasis of fat metabolism or lipid abnormalities but still, the relation of the mean level of irisin with lipid profile was controversial (de la Iglesia *et al*., 2014). In our study, a statistically insignificant negative relation was found between mean level of serum irisin and serum cholesterol, triglyceride and LDL-c among patients with T2DM and prediabetic individuals, as a lower level of irisin was found with hypercholesterolemia and hypertriglyceridemia among T2DM patients and individuals with prediabetes. Moreover, we found a positive correlation between serum irisin level and HDL-c levels. Other studies discovered that circulating irisin levels were negatively associated to total cholesterol, triglyceride and LDL-c levels (Ebert *et al*., 2015; Duran *et al*., 2015) and positively with HDL-c (Akour *et al*., 2017; Wen *et al*., 2013). At the same time, we found lower circulating irisin levels in patients with T2DM and prediabetic individuals with highly abnormal atherogenic indices than apparently healthy controls. A study done in Iran showed no significant association between irisin and atherogenic indices (Ommati *et al*., 2019).

It is well known that glycemic control is the cornerstone of managing T2DM and is essential for long-term diabetes complications prevention (Afroz *et al*., 2019). However, irisin and glycemic indices relationship in diabetes remain contradictory. As serum irisin levels were lower in patients of T2DM with poor glycemic control and higher glucose levels, as we established a negative correlation between irisin and glycemic control in these patients. Liu *et al*. found pancreatic β cell proliferation was promoted by irisin to protect cells from apoptosis as well as ameliorate glucose metabolism in skeletal muscle and liver cells (Liu *et al*., 2017; So *et al*., 2016). In other research's, irisin and serum glucose levels, insulin and HbA1c% were found to be negatively correlated in T2DM patients (Mehrabian *et al*.; 2016). Fibronectin type III domain-containing 5 is the protein precursor whose proteolytic cleavage generates irisin (Boström *et al*., 2012). Increased serum fibronectin type III domain containing 5 in T2DM is related to increased age and poor glycemic control (Mágero *et al*., 2021).

In this study, we found lipid profile in patients of T2DM and prediabetes were abnormal compared to healthy controls. Patients of T2DM and prediabetic individual's had higher serum cholesterol, triglyceride, and LDL-c mean levels than healthy controls, while HDL-c means level was lower in patients of T2DM and prediabetic groups than healthy controls, and the results were statistically significant. Studies done in Jordan and Bangladesh have shown the same results as ours (Bhowmik *et al*., 2018; Akour *et al*., 2017). An increase in blood glucose level will enhance acetyl CoA formation by activating of the Krebs cycle pathway that end ups with cholesterol synthesis (Krivoruchko *et al*., 2015). A decrease in the activity of insulin in patients of T2DM and prediabetic individuals' results in decrease in lipoprotein lipase and hepatic lipase activity, which lead to an increase in serum triglyceride concentration (ADA, 2003). Since the apoprotein B lysine residues become glycated as glycemia rises, the LDL receptor cannot identify it, which results in decreased LDL-c catabolism (Kim-Dorner *et al*., 2010).

Reduced blood HDL-c levels are caused by increased VLDL acted upon by cholesterol ester transfer protein to create small HDL-c, which is quickly removed from circulation (McLaughlin *et al*., 2005).

Diabetes related dyslipidemia is caused by a number of causes, including insulin's effects on the formation of apoproteins in the liver, and regulation of lipoprotein lipase, cholesteryl ester transfer protein actions, and the peripheral effects of insulin on muscle and adipose tissue (Goldberg, 2001). In patients with T2DM and prediabetic individuals, statistically significant results were found in our study for atherogenic indices compared to healthy controls with higher levels in patients of T2DM and prediabetic individuals.

V. Conclusion

In T2DM and prediabetes low mean level of serum irisin was found. Collectively low mean level of irisin, abnormal lipid profile and abnormally high atherogenic indices among patients with T2DM and prediabetes will enhance risks development for cardiovascular disease, therefore; early diagnosis and management of both are crucial as they associated with increased levels irisin and normalization of lipid profile, thus decreasing the risk of development of cardiovascular diseases.

References

Afroz, A., Ali, L., Karim, M., Alramadan, M.J., Alam, K., Magliano, D.J., and Billah, B. (2019). Glycaemic control for people with type 2 diabetes mellitus in Bangladesh-an urgent need for optimization of management plan. *Scientific Reports*, 9(1), 1-10.

Akour, A., Kasabri, V., Boulatova, N., Bustanji, Y., Naffa, R., Hyasat, D., Momani, M. (2017). Levels of metabolic markers in drug-naive prediabetic and type 2 diabetic patients. *Acta Diabetologica*, 54(2), 163-170.

American Diabetes Association. ADA. (2003). Management of dyslipidemia in adults with diabetes. *Diabetes care*, 26(suppl_1), s83-s86.

American Diabetes Association. ADA. Classification and Diagnosis of Diabetes: Standards of medical Care in Diabetes-2021. *Diabetes Care*. 2021 Jan .44 (Suppl 1); S15-S33.

Aroda, V.R., and Ratner, R. (2008). Approach to the patient with prediabetes. *The Journal of Clinical Endocrinology & Metabolism*, 93(9), 3259-3265.

Aune, D., Norat, T., Leitzmann, M., Tonstad, S., and Vatten, L.J. (2015). Physical activity and the risk of type 2 diabetes: a systematic review and dose–response meta-analysis. *European journal of epidemiology*, 30(7), 529-542.

Bhowmik, B., Siddiquee, T., Mujumder, A., Afsana, F., Ahmed, T., Mdala, I.A., Omsland, T.K. (2018). Serum lipid profile and its association with diabetes and prediabetes in a rural Bangladeshi population. *International Journal of Environmental Research and Public Health*, 15(9), 1944.

Boström P., Wu, J., Jedrychowski, M.P., Korde, A., Ye, L., Lo, J.C., Rasbach, K.A., Boström, E.A., Choi, J.H., Long, J.Z. (2012) A PGC1 -α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*, 481(7382), 463-468, 2012.

Casadei, K., Kiel, J. (2021). Anthropometric Measurement In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing:30726000.

de la Iglesia, R., Lopez-Legarrea, P., Crujeiras, A.B., Pardo, M., Casanueva, F. F., Zulet, M.A., Martinez, J.A. (2014). Plasma irisin depletion under energy restriction is associated with improvements in lipid profile in metabolic syndrome patients. *Clinical Endocrinology*, 81(2), 306-311.

Duran, I.D., Gülçelik, N.E., Ünal, M., Topçuoğlu, C., Sezer, S., Tuna, M.M., Güler, S. (2015). Irisin levels in the progression of diabetes in sedentary women. *Clinical Biochemistry*, 48(18), 1268-1272.

Ebert, T., Kralisch, S., Wurst, U., Scholz, M., Stumvoll, M., Kovacs, P., Tönjes, A. (2016). Association of metabolic parameters and rs726344 in FNDC5 with serum irisin concentrations. *International Journal of* Obesity, 40(2), 260-265.

Goldberg, I.J. (2001). Diabetic dyslipidemia: causes and consequences. The Journal of Clinical Endocrinology and Metabolism, 86(3), 965-971.

Holman, N., Young, B., Gadsby, R. (2015). Current prevalence of Type 1 and Type 2 diabetes in adults and children in the UK. *Diabetic Medicine*, 9(32), 1119-1120.).

Huh, J.Y., Panagiotou, G., Mougios, V., Brinkoetter, M., Vamvini, M.T., Schneider B.E., Mantzoros, C.S. (2012). FNDC5 and irisin in humans: I. Predictors of circulating concentrations in serum and plasma and II. mRNA expression and circulating concentrations in response to weight loss and exercise. Metabolism. 61,1725–38.

Hussain, A., Ballantyne, C.M., Saeed, A., Virani, S.S. (2020). Triglycerides and ASCVD risk reduction: recent insights and future directions. Current Atherosclerosis Reports, 22(7), 1-10.

Jacobson, T.A., Ito, M.K., Maki, K.C., Orringer, C.E., Bays, H.E., Jones, P.H., Brown, W.V. (2015). National lipid association recommendations for patient-centered management of dyslipidemia: part 1—full report. *Journal of Clinical Lipidology*, 9(2), 129-169.

Kim-Dorner, S. J., Deuster, P. A., Zeno, S. A., Remaley, A. T., and Poth, M. (2010). Should triglycerides and the triglycerides to high-density lipoprotein cholesterol ratio be used as surrogates for insulin resistance?. *Metabolism*, 59(2), 299-304.

Krivoruchko, A., Zhang, Y., Siewers, V., Chen, Y., Nielsen, J. (2015). Microbial acetyl-CoA metabolism and metabolic engineering. *Metabolic engineering*, 28, 28-42.

Liu, S., Du, F., Li, X., Wang, M., Duan, R., Zhang, J., Zhang, Q. (2017). Effects and underlying mechanisms of irisin on the proliferation and apoptosis of pancreatic β cells. PloS one, 12(4), e0175498.

Lv, J., Pan, Y., Li, X., Cheng, D., Ju, H., Tian, J., Zhang, Y. (2015). Study on the distribution and elimination of the new hormone irisin in vivo: new discoveries regarding irisin. *Hormone and Metabolic Research*, 47(08), 591-595.

Mahmoodnia, L., Sadoughi, M., Ahmadi, A., Kafeshani, M. (2017). Relationship between serum irisin, glycemic indices, and renal function in type 2 diabetic patients. Journal Of *Renal Injury Prevention*, 6(2), 88.

Mágero, F.R.L., Vasconcellos, L.F., Frazão, L., Bandeira, F. (2021). Irisin Precursor FNDC5 and Glycemic Control in Patients with Type 2 Diabetes. *Journal of the Endocrine Society*, 5(Suppl 1), A471.

McLaughlin, T., Reaven, G., Abbasi, F., Lamendola, C., Saad, M., Waters, D., Krauss, R.M. (2005). Is there a simple way to identify insulin-resistant individuals at increased risk of cardiovascular disease?. *The American Journal of Cardiology*, 96(3), 399-404.

Mehrabian, S., Taheri, E., Karkhaneh, M., Qorbani, M., Hosseini, S. (2015). Association of circulating irisin levels with normal weight obesity, glycemic and lipid profile. *Journal of Diabetes & Metabolic Disorders*, 15(1), 1-6.

Motahari-Tabari, N., Shirvani, M. A., Shirzad-e-Ahoodashty, M., Yousefi-Abdolmaleki, E., Teimourzadeh, M. (2015). The effect of 8 weeks aerobic exercise on insulin resistance in type 2 diabetes: a randomized clinical trial. *Global Journal of Health Science*, 7(1), 115.

Nuttall, F.Q. (2015). Body mass index: obesity, BMI, and health: a critical review. *Nutrition Today*, 50(3), 117.

Ommati, N., Nikniaz, L., Mandavi, R. (2019). Association of serum irisin levels with anthropometric, biochemical, and atherogenic indices in healthy adults. *Progress In Nutrition*, 21(1), 174-182.

Park, K., Ahn, C.W., Park, J.S., Kim, Y., Nam, J.S. (2020). Circulating myokine levels in different stages of glucose intolerance. *Medicine*, 99(8).

Shah, H.S., Morieri, M. L., Marcovina, S. M., Sigal, R.J., Gerstein, H.C., Wagner, M.J., Doria, A. (2018). Modulation of GLP-1 levels by a genetic variant that regulates the cardiovascular effects of intensive glycemic control in ACCORD. *Diabetes Care*, 41(2), 348-355.

So, W.Y., Leung, P.S. (2016). Irisin ameliorates hepatic glucose/lipid metabolism and enhances cell survival in insulin-resistant human HepG2 cells through adenosine monophosphate-activated protein kinase signaling. *The International Journal of Biochemistry & Cell Biology*, 78, 237-247.

Soyal, S., Krempler, F., Oberkofler, H., Patsch, W. (2006). PGC-1α: a potent transcriptional cofactor involved in the pathogenesis of type 2 diabetes. *Diabetologia*, 49(7), 1477-1488.

Sun, J., Liu, Z., Zhang, Z., Zeng, Z., Kang, W. (2022). The Correlation of Prediabetes and Type 2 Diabetes with Adiposity in Adults. *Frontiers in Nutrition*, 9, 818263.

Tabák, A.G., Herder, C., Rathmann, W., Brunner, E.J., Kivimäki, M. (2012). Prediabetes: a high-risk state for developing diabetes. *Lancet*, 379(9833), 2279.

Wen, M.S., Wang, C.Y., Lin, S.L., Hung, K.C. (2013). Decrease in irisin in patients with chronic kidney disease. *PloS one*, 8(5), e64025.

Williamson, D.A. (2018). Prevention of type 2 diabetes: what is the right target population?. *Expert Review of Endocrinology & Metabolism*, 13(6), 295-305.

Zhang, C., Ding, Z., Lv, G., Li, J., Zhou, P., Zhang, J. (2016). Lower irisin level in patients with type 2 diabetes mellitus: A case-control study and meta-analysis. *Journal of Diabetes*, 8(1), 56-62.