وزارة التعليم العالي والبحث العلمي
جامعـــــة ديـــــــالـى
كليـــــة العلـــــوم
قســـــم الكيميـــاء

تقييم الايريسين في مصل المرضى الذين يعانون من داء السكري من النوع 1

رسالة مقدمه الى
مجلس كلية العلوم - جامعة ديالى
كجزء من متطلبات نيل درجه الماجستير
في علوم الكيمياء

من قبل

ضفاف عبد العظيم عبد العباس

بكالوريوس في علوم الكيمياء التطبيقية 2010

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هجرية 1445 **ميلادية 2024**

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Evaluation Serum Irisin In Patients With Type 1 Diabetes Mellitus

A Thesis

Submitted to Council of College of Science - University of Diyala as a Partial Fulfillment of the Requirements for the Master's Degree of Sciences in Chemistry

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2024 AD **1445AH**

Summary

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease that progresses with pancreatic β-cell destruction and insulin dependence. Irisin is produce among other sources by skeletal muscle and is involved in the induction of the process of converting white adipose tissue (WAT) into brown adipose tissue (BAT). The precursor for this myokine is transmembrane protein FNDC5 (fibronectin type III domain containing 5).The purpose of this study was to measure the blood levels of irisin in T1DM patients and compare them to serum levels of irisin in healthy individuals. Additionally, it sought to determine the relationship between irisin levels and T1DM as well as the connections between irisin levels in newly diagnoses, and previously diagnosis T1DM. The enzyme-linked immune sorbent assay (ELISA) was used to determine the levels of serum irisin. Fasting blood sugar (FBS), lipid profile and urea were determined by enzymatic methods, glycated hemoglobin (HbA1c) was measured by (HPLC), and Creatinine (by kinetic method).

The study was conducted at National Center of Diabetes (AL- Mustansiria University) on 120 subjects divided into two groups according to Insulin therapy: newly diagnosed T1DM [group I (n= 37)] and those who previously diagnosed [group II (n= 53)]. 30 healthy: subject aged 18 to 30 years were examined as control group.

The results of the current study were summarized to:

1. Parametric BMI and age showed non-significant ($p>0.05$) in patient groups in compared to control group.
2. The results of the present study referred to significant increase ($p\leq0.05$)in metabolic factors (FSG and HbA1c) in patients groups as compare to control.
3. The comparison of (FSG and HbA1c) according to gender showed non- significant in the two groups of patients and control.

4. Lipid profile (TG, TC, LDL, and VLDL) levels were altered between groups. Significant increase ($p \leq 0.05$) were observed when compared with control group, whereas, HDL showed non-significant ($p>0.05$) in two group compared with control.
5. Lipid profile (TG, TC, LDL, and VLDL) according to gender the change was significant in newly diagnosis and non-significant in previously diagnosis HDL showed a non-significant in the two groups, compared to control.
6. Serum levels of irisin were significantly lower ($p \leq 0.01$), in patients as compared to the control group. In addition, irisin level was significantly lower in-group I compared to group II.
7. Serum irisin has been correlated negatively to fasting serum glucose, and glycated hemoglobin, whereas it positively correlated to serum lipid profile.
8. The receiver operating characteristic curve (ROC) analysis has done to
9. identify the cut off value for the parameters. There are two cut off in newly diagnosis The Irisin cutoff value was > 7.02 with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Area under curve of 97.3 %, 96.7 %, 97.3 %, 96.7% and 0.996 (0.989- 1.000). The Irisin cutoff value in previously diagnosis was > 8.74 with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Area under curve of 94.3 %, 96.7 %, 98.0 %, 90.6% and 0.969 (0.936- 1.000). The present results indicates that Irisin considered as an excellent diagnostic marker.

Conclusion: According to the results obtained in this study, it can been concluded that lower irisin levels were determined in T1DM patients compared to the control group. The association of highest irisin amounts to an insulin therapy and a better glycaemic control. May suggest that insulin therapy can be effective in the synthesis of irisin. Furthermore, the measurement of serum irisin levels could also be useful as laboratory marker to monitor T1DM severity and therapy response.

CHAPTER ONE

(INTRODUCTION & PREVIOUS STUDIES)

1.1 Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease often diagnosed in childhood that progresses with pancreatic β-cell destruction and life-long insulin dependence. Type 1 diabetes mellitus susceptibility involves a complex interplay between genetic and environmental factors and with the participation of adaptive immunity, although there is now growing evidence for the role of innate inflammation [(1)].

Type 1 diabetes mellitus T1DM, in the early stage of the disease, is characterized by chronic inflammation that involves pancreatic islet degeneration. The maintenance activation of the innate immune system impairs insulin secretion and action, and inflammation contributes to diabetes complications, such as diabetic retinopathy and nephropathy. Prior to the manifestation of the disease, a pre-diabetic period may last several years and characterized by the detection of circulating autoantibodies against beta-cell antigens [(2)].

Symptoms of T1DM relatively develop suddenly over short period, even though β-cell destruction may begin years earlier [(3)]. The pancreas houses the β cells, which are sensitive to high glucose levels and produce insulin, a strong hormone able to reduce hyperglycemia. This regulation is not possible in T1DM. The body destroys the insulin-producing cells in the pancreas, and is the more aggressive form of the disease in this autoimmune disease. Patients with T1DM do not produce any insulin and must inject this hormone exogenously or wear an insulin pump to reduce their glucose levels [(4)]. Therefore, the objectives of diabetes management include maintaining homeostasis and blood glucose near normal levels, and avoiding hypoglycemia and ketoacidosis as well as other long-term complications (e.g., cardiovascular diseases, etc.) [(5)].

In recent years, irisin has been of great interest; it is produce among other sources by skeletal muscle and is involved in the induction of the process of converting white adipose tissue (WAT) into brown adipose tissue (BAT). The precursor for this myokine is transmembrane protein FNDC5 (fibronectin type III domain containing 5), from which irisin is detached under the influence of a specific protease, which then enters the circulation [(6)]. It works by increasing expression in the uncoupling protein 1 (UCP-1) in mitochondria, and this leads to the conversion of white to brown fat tissue [(7)]. White adipose tissue is a supply of lipids for the body — it is rich in triglycerides and free fatty acids and has a low number of mitochondria. Due to the large number of mitochondria, brown adipose tissue plays a major role in energy expenditure and is responsible for thermogenesis [(8)]. Irisin seems to play a pleiotropic role especially in type 2 diabetes. Browning of white adipose tissue under the influence of irisin may be associated with beneficial effects of weight loss, on glucose and lipid homeostasis and endothelium. Irisin also acts as the inhibitor of lipogenesis and gluconeogenesis via the AMPK **(**Adenosine Monophosphate-activated Protein Kinase) pathway, which has recently shown in mice [(9)], and it might be a protective antidiabetic factor. It has also shown that recombinant irisin has an antiapoptotic impact on pancreatic beta cells of humans and rodents — it stimulates their proliferation, insulin synthesis, and secretion. Its action seems to be similar to those of glucagon like peptide (1GLP-1) agonists and probably acts via special receptor for irisin, which has not yet found on beta cells [(10)]. This myokine also has a positive impact on bone mineral density [(11)], which often reduced in type1 diabetic patients with long-lasting disease. Factors that affect irisin levels include physical activity, obesity, and diet [(12)]. There are not many scientific papers on the evaluation of irisin in adults with type 1 diabetes

Studies are continuing on diabetes, and recent studies included the effect of the hormones of diabetics one of the recent discovered hormone is irsin. There are many research of the effect of irsin on type 2 diabetes but fewer in type 1. In this study, we

will discuss the first study in iraq on the effect of irsin on type 1 diabetes mellitus patients.

1.2. Previous studies

Names of researchers	Study year	Biological object	Number of subject	Conclusion
Yeon-Kyung Choi, Mi-Kyung Kim, Kwi Hyun Bae, Jung-Guk Kim, In-Kyu Lee, Keun-Gyu Park[18]	2013	human	104 subjects with NGT and 104 subjects with new-onset T2DM	Previously they found that serum irisin levels were decreased in T2DM patients and inversely associated with newly diagnosed T2DM, suggesting that irisin may play a crucial role in glucose intolerance and T2DM.
Ming-Shien Wen ,Chao-Yung Wang,Shuei-Liong Lin,Kuo-Chun Hung[19]	2013	human	38 consecutive patients with stage 5 CKD (52.6% female; mean age, 57.4±2.5 years)	summarizes the characteristics of the study patients. Patients with CKD had higher blood urea nitrogen (BUN) and creatinine levels and blood pressure, and lower hemoglobin and high-density lipoprotein (HDL) cholesterol levels than did normal controls. Additionally, because this study excluded patients with diabetes mellitus and severe hyperlipidemia, CKD patients did not significantly differ from normal subjects

				in terms of fasting glucose, high-sensitivity C-reactive protein (hs-CRP), total cholesterol, triglyceride,low-density lipoprotein (LDL) cholesterol, and uric acid levels.
MohammadReda Halawa1, Manal M. AbuShady1,Mohammad AbdelFattah Mahmoud2 and Mohammad Hasan Ibrahim[20]	2015	human	60 T2DM subjects and 30 Healthy controls.	they found that serum irisin levels were decreased in T2DM. Lower irisin level may be associated with peripheral neuropathy. Irisin levels associated inversely with insulin resistance.
Huh, Ji Hye MD; Ahn, Song Vogue MD, PhD; Choi, Jung Hye MD; Koh, Sang Baek MD, PhD; Chung, Choon Hee MD, PhD[21]	2016	human	3500 participants were enrolled in this study	this study is the first longitudinal design study to investigate the association between higher circulating irisin levels and development of DM in a relatively healthy rural population The results of this study demonstrate that irisin itself is associated with incident DM, independently of insulin resistance, physical activity, and BMI. These results suggest that irisin may play a possible role in the regulation of glucose metabolism. In addition, we

				also presented evidence that circulating the irisin level may be a predictive marker for high risk of DM Further studies with larger sample sizes in various conditions and populations are warranted to elucidate the mechanism for the role of irisin in incident DM.
Karan S. Rana , Chathyan Pararasa, Islam Afzal, David A. Nagel, Eric J. Hill, Clifford J. Bailey, Helen R. Griffiths, Ioannis Kyrou Harpal S. Randeva Srikanth Bellary and James E. Brown[22]	2017	human	79(42 males, 37 females; mean BMI 31.5 ± 5.4 kg/m2)	These data suggested that elevated plasma irisin in T2DM is associated with indices of adiposity, and that irisin may be involved in pro-atherogenic endothelial disturbances that accompany obesity and T2DM. Accordingly, irisin may constitute a potentially novel therapeutic opportunity in the field of obesity and cardiovascular diabetology
Maria Felicia Faienza Giacomina Brunetti , Lorenzo Sanesi , Graziana Colaianni , Monica Celi , Laura Piacente , Gabriele D'Amato , Ernestina Schipani , Silvia	2018	human	Ninety-six T1DM subjects (12.2 + 4 years), 56 on multiple daily injections(MDI), 40on continuous subcutaneous insulin infusion	They demonstrated high irisin levels in T1DM children and the association of highest irisin amounts to a better glycaemic control and bone health in TDM1 subjects on CSII.

Colucci , Maria Grano[13]			(CSII), and 34 controls	
Hemmat El Haddad, Heba Sedrak, Mervat Naguib,Elham,Yousief, Dalia R. Ibrahim, Rasha M. Abdel Samie & Ahmed Hamdy[23]	2019	human	60 T2DM patients and 30 healthy controls	In T2DM patients, negative correlations between irisin and HbA1C, urinary albumin, and CIMT were found. Moreover, patients with diabetic neuropathy had lower irisin levels.
panelZahra Mazloum Khorasani, Ramin Khameneh Bagheri, Mohammad Ali Yaghoubi, Saeed Chobkar, Monavvar Afzal Aghaee, Mohammad Reza Abbaszadegan f, Amirhossein Sahebkar[24]	2019	human	30 diabetic subjects with angiographically defined CAD were compared with 30 age- and sex-matched diabetic subjects without CAD	Serum irisin levels were lower in the diabetic patients with cardiovascular complication compared with the uncomplicated diabetic patients. Therefore, additional larger scale studies are needed to determine the role of irisin in monitoring CAD in diabetic patients.
Irina AlKhairi ,Preethi Cherian ,Mohamed Abu-Farha ,Ashraf Al Madhoun ,Rasheeba Nizam ,Motasem Melhem ,Mohamed Jamal ,Suleiman Al-Sabah ,Hamad Ali ,Jaakko Tuomilehto ,Fahd Al-Mulla and Jehad Abubaker [25]	2019	human	228 Arab adult men and women with and without T2DM (124 non-diabetic [73 non-obese and 51 obese] and 104 T2DM [38 non-obese and 66 obese]) individuals	the study confirms an increased expression level of both irisin and METRNL proteins in obesity and T2DM. In addition, both proteins demonstrated a strong positive correlation with each other,suggesting a possible relationship between them. Further studies are needed to

				elucidate the role of these proteins, their interplay, and their mechanistic significance in the pathophysiology of T2DM and obesity. Also to better understand their ethnic and gender specific variations.
James J. McCormick1 , Sean R. Notley , Jane E. Yardley Ronald J. Sigal and Glen P. Kenny[14]	2020	human	Twenty-two habitually active young adults (aged 22-37 years) with (8 men, 3 women) and without (9 men, 2 women; control)	irisin concentrations did not change in response to exercise in a hot environment in young adults with T1DM compared to controls without diabetes. Further, our findings could suggest that blood glucose concentrations do not influence circulating irisin levels during exercise. Given our limited understanding of irisin in T1DM, it is hoped the outcomes from this preliminary study can be used to generate hypotheses that direct future research. More studies are necessary to examine the impact of higher exercise intensities and the effect of acute irisin release during exercise on health in individuals with T1DM.

Aleksandra Żebrowska , Marcin Sikora, Anna Konarska, Anna Zwierzchowska, Tomasz Kamiński, Anna Robins and Barbara Hall[15]	2020	human	A total of 14 individuals with T1DM (age: 28.7±7.3years) and 14 healthy adults (age: 27.1±3.9years)	The study results suggest that moderate intensity continuous Ex has beneficial effect on BDNF and IGF-1 levels. Ex in hypoxic conditions may be more effective in increasing availability of IGF-1. The alterations in the post-Ex irisin levels and IGF-1 system may be contributing to more effective glycaemia control in patients with T1DM.
Ruibin Zhang,Tingting Fu,Xin Zhao,Yao Qiu,Xiaolin Hu,Hongyan Shi &Xiao Yin [26]	2020	human	A total of 740 participants (374 males and 366 females)	this study confirmed that circulating irisin was associated with adiposity, glucose tolerance and insulin resistance status in a middle-aged Chinese population, the increase of irisin under conditions of obesity may indicate its physiological function to improve glucose tolerance which is often impaired in obese subjects, but this compensatory secretion of irisin seems likely to be progressing to a secretion failure once diabetes develops. Irisin may

				have potentially favorable effects on glucose homeostasis and insulin sensitivity, but the specific receptor and potential signal pathway through which irisin could protect against obesity needs to be further explored.
panelÖzlem Tok a, Savaş Volkan Kişioğlu , Halil Önder Ersöz , Bahittin Kahveci a, Zeynep Göktaş[27]	2021	human	A total of 60 subjects (BMI > 25.0 kg/m2) with IGM were recruited in this single-centered interventional study. Twelve subjects dropped out during the study and the study was completed with 48 patients.	These results demonstrate that serum irisin, FGF21, visfatin, and FSTL1 levels decreased in response to weight loss interventions. Weight loss induced by DI or DPA therapies had similar lowering effects on these proteins in subjects with IGM, and these myokines might be related to glucose metabolism biomarkers.
Marta Wróbel , Artur Gołaś , Dominika Rokicka , Łukasz Pyka , Marta Szewczyk , Tomasz Stołtny , Robert Roczniok , Mariusz Gąsior , Krzysztof Strojek[16]	2022	Human	Eleven type 1 male diabetic patients with low levels of physical activity were recruited, with mean age 38 ± 6 years, body mass index (BMI) 28.4 ± 2.6 kg/m2 , and diabetes	A 3-month resistance-training programmed in patients with long-term type 1 diabetes and low level of physical activity significantly affects their maximum strength level. This indicates that people with diabetes are more adaptive to additional loads,

			duration 23 ± 7 years.	which allows them to increase their load faster.
Evelyn Teo & Norasyikin Hassan & Wilson Tam & Serena Koh [17]	2022	human	Twenty-two studies, involving 2188 individuals with type 1 diabetes	Continuous Glucose Monitors (CGM) is superior to Self-monitoring of blood glucose (SMBG) in improving glycaemic control among individuals with type 1 diabetes in the community, especially in those with uncontrolled glycaemia. Individuals with type 1 diabetes with HbA1c >64 mmol/mol (>8%) are Most likely to benefit from CGM. Current findings could not confer a concrete conclusion on the effectiveness of CGM on DKA outcome as DKA incidences were rare. Current evidence is also limited to outpatient settings. Future research should evaluate the accuracy of CGM and the effectiveness of CGM across different age groups and insulin regimens as these remain unclear in this paper.

1.3. Aim of the present study

The aim of this work is to study the link between Irisin as marker and insulin treatment in diabetes mellitus type1 by the following means:

1. Measuring the level of serum irisin, lipid profile, FBS, blood urea, serum creatinine and HbA1c in sera of type1 diabetic patients and control group and find the correlation between these parameters in sera of control and diabetes mellitus type1 patient groups.
2. The receiver operating characteristic curve (ROC) analysis to specify the cutoff value for new markers.

CHAPTER TWO

(THEORETICAL PART)