Study of irisin hormone level in type 2 Diabetic patients and patients with diabetic Nephropathy

Thesis

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Internal Medicine

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بسم الله الرحمن الرحيم

وقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ وَرَسُولُهُ والْمُؤْمِنُونَ

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Yasmeen Abd Almageed Mohamed

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List of Abbreviations

ACE	Angiotensin converting enzyme
ACR	Albumin creatinine ratio
ADA	American diabetic association
AER	Albumin excretion rate
AHEI	Alternate healthy eating index
AMED	Alterante Mediterranean deit score
AMPK	Activated monophosphate protein kinase
ARB	Angiotensin receptor blockers
BAT	Brown adipose tissue
CKD	Chronic kidney disease
CRP	C-Reactive Protein
DKD	Diabetic kidney disease
DNA	Deoxyribonucliec acid
ECM	Extracellular matrix
EE	Energy expenditure
ERK	Extacellular signal regulated kinase
ESRD	End stage renal disease
FN	Fibronectin
Fndc5	Fibronectin domain containing protein 5
GBM	Glomerular basement membrane
GBM	Glomerular basement membrane
GFP	Green fluroscent protein
GFR	Glomerular filteration rate
HLA	Human leukocyte Ag
HNF	Hepatocyte nuclear factor
IDNT	International diabetics and nutritional terminology
IL-15	Interleukin 15
IPF	Insulin Promotor Factor
Lrg1	Leucine rich glycoprotein 1
MESCS	Mouse empryonic stem cells
MODY	Maturity Onset Diabetes Of the young

List of Abbreviations (Cont.)

PGC1α	Peroxisome proliferator-activated receptor-8 coactivator 1 alpha
PPARα	Peroxisome proliferator activated receptor α
RENAAL	Reduction in endpoints with angiotensin antagonist losartan
SHARP	Study of heart and renal protection
STAT	Signal transducer and activator of transcription
TBM	Tubular basement membrane
TIMP4	Tissue inhibitor of metalloprotinases 4
tRNA	Transfer ribonucleic acid
UAE	Urinary albumin excretion
UCP1	Uncoupling protein 1
VEGFß	Vascular endothelial growth factor ß
WAT	White adipose tissue

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Introduction

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, hearts and blood vessels (**Genuth, 2003**).

Diabetic nephropathy is a leading cause of chronic kidney disease and one of the most significant long term complications in terms of morbidity and mortality for individual patients with diabetes.Diabetes is responsible for 30-40% of all end stage renal disease (**ESRD**) cases (**Burney Bo et al., 2009**)

In January 2012, Bostrom and colleagues identified a new muscle tissue secreted peptide, which they named IRISIN (referring to Greek messenger Goddess IRIS, to highlight its role as a messenger that comes from skeletal muscle to other parts of the body (**Bostrom, 2012**).

Irisin hormone is normally present as part of a larger protein Fibronectin domain-containing protein 5 (FNDC5) in a muscle cell's outer membrane, where it lies dormant and inactive. Exercise (and other unknown factors) cause this protein to be split, releasing irisin, which exits the muscle cell to other cells of the body causing conversion of some white fat cells to brown fat cells and islet cells of pancreas which are told to produce more insulin (A**ggarwal, 2012**).

There is controversy concerning irisin level in plasma that it is reduced in Type 2 Diabetic (T2D) by 50%. Some studies found that serum irisin levels were decreased in T2D patients and inversely associated with newly diagnosed T2D, suggesting that irisin may play a role in glucose intolerance

and T2D in presence of insulin resistance (**choi, 2013**). Although it is also reported that irisin hormone expression is not related to diabetes status in humans (**Timmons, 2012**).

Preliminary studies suggest that irisin is decreased in Type 2 diabetic patients with renal insufficiency (GFR<60ml/min/1.73m (2) **(Liu et al., 2014).**

However no studies evaluate irisin in type2 diabetic patients with Microalbuminuria.

Aim of The Work

The aim of this work is to study Irisin Hormone level in Type 2 diabetic patient. Also, to study the relation between Irisin Hormone level and diabetic nephropathy.

Chapter (I)
Diabetes mellitus

Definition of diabetes mellitus:

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both **(American Diabetic Association, 2014).**

Epidemiology:

Over the past three decades, the number of people with diabetes mellitus has more than doubled globally, making it one of the most important public health challenges to all nations. Type 2 diabetes mellitus and prediabetes are increasingly observed among children, adolescents and younger adults **(Chen et al., 2011).**

Diabetes can be found in every country in the world and without effective prevention and management programmes the burden will continue to increase globally. Type 2 diabetes makes up about 85 to 95% of all diabetes in high-income countries and may account for an even higher percentage in low- and middle-income countries.Type 2 diabetes is now a common and serious global health problem, which, for most countries, has developed together with rapid cultural and social changes, ageing populations, increasing urbanisation, dietary changes, reduced physical activity, and other unhealthy behaviours **(World Health Organization, 1994)**.

Rates of diabetes have increased markedly over the last 50 years in parallel with obesity. As of 2010 there are approximately 285 million people with the disease compared to around 30 million in 1985 **(Fasanmade et al., 2008).**

The global burden:

- **366 million** people have diabetes in 2011; by 2030 this will have risen to **552 million.**

- The number of people with type 2 **diabetes is increasing** in every country.
- **80%** of people with diabetes live in **low- and middle-income countries**.
- The **greatest number** of people with diabetes are between **40 to 59** years of age.
- **183 million** people (50%) with diabetes are**undiagnosed**
- Diabetes caused **4.6 million deaths** in 2011.
- Diabetes caused at least **USD 465 billion dollars** in healthcare expenditures in 2011; **11% of total healthcare expenditures** in adults (20-79 years).
- **78.000 children** develop **type 1 diabetes** every year.

(IDF, 2011)

Table (I): Prevelence of diabetes in 2011 and 2030

Year	Country/territory	Millions
2011	1- China	90.0
	2- India	61.30
	3- United States of America	23.70
	4- Russian Fedration	12.60
	5- Brazil	12.40
	6- Japan	10.70
	7- Mexico	10.30
	8- Bengladesh	8.40
	9- Egypt	7.30
	10- Indonesia	7.30
2030	1- China	129.70
	2- India	101.20
	3- United states of america	29.60
	4- Brazil	19.60
	5- Bengladesh	16.80
	6- Mexico	16.40
	7- Russian federation	14.10
	8- Egypt	12.40
	9- Indonesia	11.80
	10- Pakistan	11.40

(IDF Diabetes Atlas, 2011)

Pathogenesis:

Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the pancreatic β-cells with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia. A degree of hyperglycemia sufficient to cause pathologic and functional changes in various target tissues, but without clinical symptoms, may be present for a long period of time before diabetes is detected. During this asymptomatic period, it is possible to demonstrate an abnormality in carbohydrate metabolism by measurement of plasma glucose in the fasting state or after a challenge with an oral glucose load or by A1C **(Geiss et al., 2006).**

Symptoms of DM:

Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome **(Cooke and Plotinck, 2008).**

Classification of diabetes mellitus:

This classification has now replaced the earlier clinical classification into insulin dependent DM (IDDM) and non Insulin dependant DM (NIDDM) which was based on the need for insulin treatment at diagnosis **(Mirghani, 2012).**