Study of Serum Irisin in patients with Thyroid Dysfunction

Thesis

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Mohamed Samir Mohamed

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List of Abbreviations

Abb.	Full term
AACE	*American Association of Clinical Endocrinologists*
ACE	*Angiotensin-converting enzyme*
Ach	*Acetylcholine*
AHEI	*Alternate Healthy Eating Index*
AMED	*Alternate Mediterranean Diet Score*
Anti TPO	*Thyroid peroxidise antibody*
ATP	*Adenosine triphosphate*
BMI	*Body mass index*
CIPD	*Chronic Inflammatory Demyelinating Polyradiculoneuropathy*
CIPN	*Chemotherapy induced peripheral neuropathy*
CK	*Creatine kinase*
CKD	*Chronic kidney disease*
CMAP	*Compound muscle action potential*
CRP	*C-reactive protein*
CYP3A4	*Cytochrome P450 3A4*
EE	*Energy expenditure*
ELISA	*Enzyme Linked-Immunosorbent Assay*
EMG	*Electromyography*
FDA	*Food and drug administration*
FNDC5	*Fibronectin type III domain-containing protein 5*
FNIII	*Fibronectin III*
G-CSF	*Granulocyte colony-stimulating factor*
GEO	*Gene Expression Omnibus*
HIV	*Human immunodeficiency virus*
HOMA-IR	*Homeostatic model assessment insulin resistance*
IGF-1	*Insulin growth factor-1*
LDH	*Lactate dehydrogenase*

List of Abbreviations (Cont...)

Abb.	Full term
MEP	*Motor end plate*
NAFLD	*Non alcoholic fatty liver*
NAP	*Propagated nerve action potential*
NASH	*Non alcoholic steatohepatitis*
NCV	*Nerve conduction velocity*
OGTT	*Oral glucose tolerance test*
Pcos	*Polycystic ovarian syndrome*
PPAR	*Peroxisome proliferator-activated receptor- α*
PPT	*Post partum thyroiditis*
RA	*Reumatoid arthritis*
ROC	*Receiver-operating characteristic*
SCH	*Subclinical hypothyroidism*
SLE	*Systemic lupus erythematosus*
SSKI	*Saturated solution of potassium iodide*
SST	*Serum separator tube*
SVR	*Visceral fat area ratio*
T3	*Triiodothyronine*
T4	*Thyroxin*
TM	*Thyrotoxic myopathy*
TMS	*Transcutaneous magnetic stimulation*
TRH	*Thyrotropin-releasing hormone*
TSH	*Thyroid stimulating hormone*
Ucp1	*Uncoupling protein1*

INTRODUCTION

Irisin is a newly discovered adipo-myokin, which is reported to have a significant influence on the body metabolism and thermogenesis. Other influencing factors on metabolic state are thyroid hormones, which increase heat production and control the energy balance. Due to numerous similarities in action it seems imperative to explore these substances' potential mutual influence on the body ***(Ruchal et al., 2014).***

Thyroid hormone signalling regulates crucial biological functions, including energy expenditure, thermogenesis, development and growth. The skeletal muscle is a major target of thyroid hormone signalling. Regulation of the expression and activity of deiodinases constitutes a cell-autonomous, pre-receptor mechanism for controlling the intracellular concentration of T_3. This local control of T_3 activity is crucial during the various phases of myogenesis ***(Salvatore et al., 2014).***

Hypothyroidism is the most common endocrinal disorder. The variety of end-organ effects and wide range of disease severity; from entirely asymptomatic individuals to patients in coma with multisystem failure, can make hypothyroidism an elusive clinical entity. Peripheral neuropathy occurs early in hypothyroidism even before other symptoms occur. Hence early detection of peripheral neuropathy in hypothyroidism is necessary for early diagnosis and treatment ***(Waghmare et al., 2015).***

Both hypothyroidism and hyperthyroidism may cause signs and symptoms of neuromuscular dysfunction. Hypothyroidism has been associated with the clinical features of myopathy (for example, proximal muscle weakness) mononeuropathy, and sensorimotor axonal polyneuropathy. Hyperthyroidism may cause myopathy and possibly also polyneuropathy. The reported prevalence of these signs and symptoms is variable. In hyperthyroid patients 67% had neuromuscular symptoms, 62% had clinical weakness in at least one muscle group that correlated with FT4 concentrations ***(Duffy et al., 2000)***.

Irisin is a novel myokine that promote energy expenditure. It could act on adipocyte metabolism through a novel neural pathway and on the other hand irisin induces neural proliferation and adequate neural differentiation. Lower irisin level may be associated with peripheral neuropathy. Irisin levels associated inversely with insulin resistance ***(Halawa et al., 2015).***

Irisin, identified as a proteolytic cleavage product of the fibronectin type III domain-containing protein 5 (FNDC5), is a novel myokine secreted by contracting skeletal muscle, possibly mediating some exercise health benefits via 'browning' of white adipose tissue. Irisin can causes a significant increase in total body energy expenditure and resistance to obesity-associated insulin resistance in mice, while controversy still exists concerning irisin origin, regulation and function in humans ***(Yang et al., 2015).***

Aim of the Work

To study the relation of serum irisin level, muscle damage and neuropathy in patients with thyroid dysfunction (hypo and hyperthyroidism).

Chapter 1
IRISIN HORMONE

In January 2012, Boström 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 ***(Boström et al., 2012).***

Irisin is a hormone induced with exercise from the skeletal muscles in mice and humans, and mildly increased irisin levels in the blood cause an increase in energy expenditure with no changes in movement or food intake. This results in improvements in obesity and glucose homeostasis. The hormone has been found to act in two ways. It promotes the conversion of inert (white) yellow fat to the metabolically more active brown fat, and facilitates insulin action, thus decreasing blood glucose levels. While white fat is used to store energy (calories), brown fat seems to be more involved in burning it. The researchers found irisin to be present in the blood of human volunteers who had undergone 10 weeks of exercise ***(Aggarwal et al., 2012).***

It is unclear why exercise would stimulate irisin synthesis when conservation of calories to fuel exercise would seem paramount. One hypothesis suggests that irisin is released from shivering muscle to induce thermogenesis and prevent hypothermia ***(Boström et al., 2012).***

Furthermore, an additional contribution of fat to energy expenditure could be attributed to the adipokines leptin and adiponectin ***(Kaiyala et al., 2010).***

Irisin may play a role alongside leptin and adiponectin in the maintenance of lean and fat mass, and may well predict the efficacy of sustainable weight loss In addition to irisin's proposed role in energy balance it may also be involved in insulin resistance and type 2 diabetes ***(Hojlund et al., 2013).***

Irisin levels have been reported to increase with exercise and to be lower in patients with type 2 diabetes. A role for irisin in insulin action is supported by the report that two single nucleotide polymorphisms in the fibronectin domain containing protein 5 (FNDC5) gene have been associated with insulin sensitivity, as measured in vivo ***(Choi, 2013).***

Furthermore, irisin levels have been reported to correlate inversely with intrahepatic fat content in obese adults ***(Zhang et al., 2013).***

At this point, there are many unanswered questions, but it is important to determine whether irisin plays a role in mediating the beneficial effects of exercise on metabolism and energy expenditure. It is clear that obesity results in an increased risk of diabetes and metabolic diseases and that exercise increases insulin sensitivity and metabolic health. However, the exact mechanisms and physiological pathways

responsible are not clearly understood. The recently discovered myokine, irisin, may be an important link between exercise and its benefits on body weight, diabetes and metabolic health ***(Staiger et al., 2013).***

Several studies have investigated the relationship between circulating irisin and body mass index (BMI). Huh et al reported in a cross-sectional study of 117 healthy middle-aged women with BMI ranging from 20.0 to 47.7 kg/m2, circulating irisin had positive associations with fat-free mass and a positive trend with BMI. Stengel et al performed a study including anorexia nervosa patients, normal weight control subjects, and morbidly obese patients, providing a broad spectrum of body weights. They found that obese patients have higher circulating irisin levels compared with normal weight controls and anorexic patients, and irisin has a positive correlation with body weight and BMI. Similarly, Pardo et al reported that in 145 female patients, including anorexia nervosa patients, obese patients, and healthy normal weight subjects, the plasma irisin levels are significantly elevated in the obese patients compared with the anorexia nervosa patients and normal weight subjects, and irisin also positively correlated with body weight, BMI, and fat mass. Liu et al. found that in non-diabetic subjects, circulating irisin is correlated with BMI. Their group also reported that in patients with T2DM and renal insufficiency, irisin levels correlated with BMI, fat mass, and percentage of fat mass ***(Huang et al., 2015).***