Assessment of Serum Level of Soluble Leptin Receptors and Cardiovascular Changes in Pubertal Type 1 Diabetic Patients

Thesis

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By

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Introduction

Diabetes Mellitus describes a collection of chronic disorders in which insulin production is insufficient to maintain normal glucose homeostasis. Whether insulin insufficiency is due to loss of pancreatic islet beta cells or resistance to insulin action, the end result is chronic elevation of systemic glucose levels ***(Moore et al., 2009).***

Puberty is a period of rapid and radical physical, psychological and social changes during which a child becomes an adult capable of reproduction ***(Tfayli and Arslanian, 2007).*** During the first 2 decades of life, insulin resistance and metabolic syndrome factors are influenced by significant developmental changes mediated by puberty and growth ***(Moran et al., 2008).*** In the context of type 1 Diabetes Mellitus (type 1 DM), many adolescents experience deterioration in metabolic control leading to greater insulin resistance ***(Court et al., 2008).*** The original observation of pubertal insulin resistance was reported in 1987, when Amiel et al showed insulin-stimulated glucose metabolism was ~ 30% lower in a sample of children at Tanner stages 2-4 compared with children at Tanner stage 1 or adults ***(Goran and Gower, 2001).***

Type 1 DM continues to carry a long term burden of increased microvascular and macrovascular complications and mortality risk ***(Krishanan and Short, 2009).*** The presence of insulin resistance has been described in patients with type 1 DM and may contribute to the elevated risk of cardiovascular

diseases seen in this patient population ***(Rodrigues et al., 2010).*** Moreover, alterations in diastolic function are frequently observed in asymptomatic individuals with type 1 DM and it has been described as an early sign of diabetic heart muscle disease preceding the systolic damage ***(Cosson and Kevorkian, 2003; Young, 2004).*** Primary diabetic Cardiomyopathy is suggested to be responsible for all the adverse cardiac events ***(Gul et al., 2009)***, and the possible pathogenetic mechanisms for this cardiomyopathy include abnormalities of small intramural coronary vessels, deposition of collagen, and lipids and metabolic derangements ***(Didangelos et al., 2003).***

Leptin, the *ob* gene product, is secreted by adipocytes ***(Lahlou et al., 2000).*** The biological effects of leptin include suppression of food intake, increase of energy expenditure, regulation of body weight and influence sexual progression through puberty ***(Kratzsch et al., 2004).*** The major leptin binding protein in plasma is the soluble leptin receptors (sOB-R); this binding protein may act as regulator of leptin physiologic effects ***(Hamnvik et al., 2010).*** Type 1 DM may lead to increased serum levels of the sOB-R which may contribute to leptin insensitivity in these patients which leads to weight gain and decrease energy consumption, where there is an association between weight gain and hyperinsulinemia reflected by correlations between insulin dose and the frequency of insulin injections ***(Kratzsch et al., 2004; Kratzsch et al., 2006).***

Aim of the work

This study aims to assess changes occurring during puberty in type 1 Diabetic patients regarding insulin resistance and cardiovascular complications.

Type 1 Diabetes Mellitus

Definition:

Diabetes mellitus (DM) is a metabolic disease characterized by absolute insulin deficiency, or relative insulin deficiency when insulin secretion is inadequate to overcome co-existent resistance to insulin action on carbohydrate, protein or fat metabolism ***(Dejkhamron et al., 2007).***

The epidemic of diabetes is a serious and growing public health problem that results in reduced life expectancy and increased morbidity due to disease-specific vascular complications ***(Ceriello et al., 2009).***

Classification:

Table (1): Etiological Classification of Disorders of Glycaemia (modified ADA and WHO) ***(American Diabetes Association, 2008):***

I. Type 1

β-cell destruction, usually leading to absolute insulin deficiency

a. Autoimmune

b. Idiopathic

II. Type 2

May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance

III. Other specific types

A. Mongenic defects of β-cell function

1. HNF-1α MODY (MODY 3),
2. Glucokinase MODY (MODY 2)
3. HNF-4 α MODY (MODY 1),
4. HNF-1β MODY (MODY 4)
5. WFS1 Wolfram syndrome
6. Neonatal diabetes
7. Other MODY

B. Mitochondrial diabetes

C. Genetic defects in insulin action

1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipoatrophic diabetes
5. Others

D. Diseases of the exocrine pancreas

1. Fibrocalculous pancreatopathy
2. Pancreatitis
3. Trauma / pancreatectomy
4. Neoplasia
5. Cystic fibrosis
6. Haemochromatosis
7. Others

E. Endocrinopathies

1. Acromegaly
2. Cushing syndrome
3. Glucagonoma
4. Phaeochromocytoma
5. Hyperthyroidism
6. Somatostatinoma
7. Others

F. Drug- or chemical-induced

1. Glucocorticoids
2. Vacor
3. Pentamidine
4. Nicotinic acid
5. Thyroid hormone
6. Diazoxide
7. β-adrenergic agonists
8. Thiazides
9. Dilantin
10. α-Interferon
11. Others

G. Infections

1. Congenital rubella
2. Cytomegalovirus
3. Others

H. Uncommon forms of immune-mediated diabetes

1. Insulin autoimmune syndrome (antibodies not insulin)
2. Anti-insulin receptor antibodies
3. "Stiff-man" syndrome
4. Others

I. Other genetic syndromes sometimes associated with diabetes

1. Down syndrome
2. Klinefelter's syndrome
3. Turner syndrome
4. Friedreich's ataxia
5. Huntington's chorea
6. Laurence-Moon-Biedl syndrome
7. Myotonic dystrophy
8. Porphyria
9. Prader-Willi syndrome
10. Others

IV. Gestational diabetes

Incidence and complications:

Despite recent progress in understanding the genetics and immunology of the disease, its incidence continues to increase by3-5% per year. The high and increasing incidence, associated severe morbidity, mortality and enormous health care expenditures, makes T1DM a prime target for prevention ***(Majeed-and Hassan, 2011).***

Diabetes prevalence in some Eastern Mediterranean countries is among the highest in the world. The highest rates are reported in Egypt, Kuwait, Lebanon, Oman and Qatar where the incidence of type 1 diabetes is reported to be 8-10 per 100 000 population per year in children aged <15 years ***(WHO. Guidelines for the prevention, management and care of diabetes mellitus, 2006).***

The estimated prevalence of type 1 Diabetes Mellitus in children and adolescents is 0.38/1000 in Egypt. The prevalence of type 1 Diabetes Mellitus is 0.27/1000 in Fayoum, 0.17/1000 in Menofia, 0.8/1000 in Suez, and 0.3/1000 in North Sinai. The overall incidence is 3.5/100000 ***(Salem et al., 2010).***

Patients with type 1 diabetes mellitus (DM) represent 10%of the DM patients. However, DM's micro and micro vascular complications present high prevalence in this group of patients ***(Rodrigues et al., 2010).***

Since the discovery of insulin enormous strides in T1DM treatment has resulted in improved quality of life for patients

diagnosed with this chronic disorder. However, T1DM continues to carry a long term burden of increased micro vascular and macro vascular complications and mortality risk ***(Krishnan and Short, 2009).***

Pathophysiology and etiology:

Type 1 diabetes mellitus (T1DM) results from the interaction of genetic and environmental factors that alter the immune system and culminate in destruction of the pancreatic beta cell. The 30 to 50 percent concordance rate in monozygotic twin reflects the role of genetic factors in the etiology of T1DM ***(Haller et al., 2005).***

Association studies exploiting unbiased genome-wide analyses have identified a defined number of loci *(IDDM1-18)* that are linked to the causation of T1DM. The most significant susceptibility locus (*IDDM1* locus) is in the HLA class II gene located at 6p21.3. The *HLA-DR* and *HLA-DQ* loci in the class II region have the strongest influence on T1DM risk ***(Dejkhamron et al., 2007).***

Since HLA class II molecules participate in antigen presentation, the mechanism of HLA-influenced susceptibility inT1DM is believed to involve antigen presentation toCD4+ cell, thymic selection, and immune responsiveness ***(Kim and Polychronakos, 2005).***

The 50 per cent discordance rate for the development of T1DM in identical twins reflects the role of environmental factors and their interactions with the immune system.

Environmental factors such as virus, dietary factors, and pollutants are implicated in disease pathogenesis ***(Dejkhamron et al., 2007).***

Several viruses have been identified to be associated with the development ofT1DM with the strongest evidence linking the rubella virus. Individuals with congenital rubella have a20 per cent likelihood to develop T1DM in later life ***(Lammi et al., 2005).***

Infection with enterovirus, cytomegalovirus, coxsackie virus, parvovirus B19, and rotavirus insusceptible individuals have also been implicated to play a role in the causation of T1DM ***(Roivainen, 2006).***

Vascular complications and its risk factors:

Type 1 diabetes is a chronic disease that is frequently associated with severe vascular complications .Importantly, diabetic complications account for the major morbidity and mortality associated with the disease ***(Daneman, 2006).***

Hyperglycemia and hypertension are the main risk factors for the development of DM's chronic complications. Lipid profile is also considered a risk factor for micro vascular complications, in addition to its traditional association with macro vascular complications, as seen in the population with no DM ***(Rodrigues et al., 2010).***

Micro vascular disease is a major complication of type 1 diabetes that results from—generalized micro vascular vasodilatation, mainly due to altered levels of vasoactive substances, chronic plasma volume expansion and tissue hypoxia. The generalized precapillary vasodilatation and increased micro vascular blood flow result in capillary hypertension and endothelial dysfunction, which in turn lead to vascular complications ***(Tibirica et al., 2009).***

Prevention of cardiovascular complications:

Patients with diabetes are also at increased risk to develop heart failure independent of having an underlying ischemic heart disease. It has been postulated that long standing hyperglycemia causes primary changes in the myocardium leading to heart failure though the exact molecular mechanism is still unclear ***(Krishnan and Short, 2009).***

Cardiovascular mortality affects the majority of diabetic patients, the relative risk as compared to a non-diabetic population is several fold higher ***(Skyler et al., 2009).***

Thus, the aims of long term management of T1DM are to avoid the development of chronic micro- and macro-vascular complications of DM ***(Dejkhamron et al., 2007).***

It was observed in several large scale clinical trials, that an intensive anti hyperglycemic treatment of diabetic patients, both in type 1 and 2, reduces the incidence of micro vascular complications ***(Holman et al., 2008).*** While achieving good

glycaemic control is important in all age groups, it is of particular importance in children with type 1 diabetes, as they face the longest duration of the disease ***(Aschner et al., 2010).***

A strong relationship was unequivocally established between the levels of HbA1c and the incidence of chronic micro vascular complications of T1DM, and thus the lower the HbA1c, the lower was the risk of developing chronic micro vascular complications of DM ***(Dejkhamron et al., 2007).***

Optimization of glycaemic control at an early stage of the disease is the most fundamental aspect of care in type 1 diabetes for preventing micro vascular and macro vascular complications ***(Aschneret al., 2010).***

It is well established that hyperglycemia mediates vascular changes through several pathways. These pathways are interconnected with each other and include the increased synthesis of sorbitol and hexosamines, glycosylation of proteins, synthesis of "advanced glycosylation end products" (AGE), and oxidative stress ***(Brownlee, 2001).*** The term "metabolic memory" implies that early glycaemic environment is "remembered" by target organs such as blood vessels, but also retina, heart, kidney, etc ***(Ceriello et al., 2009).***

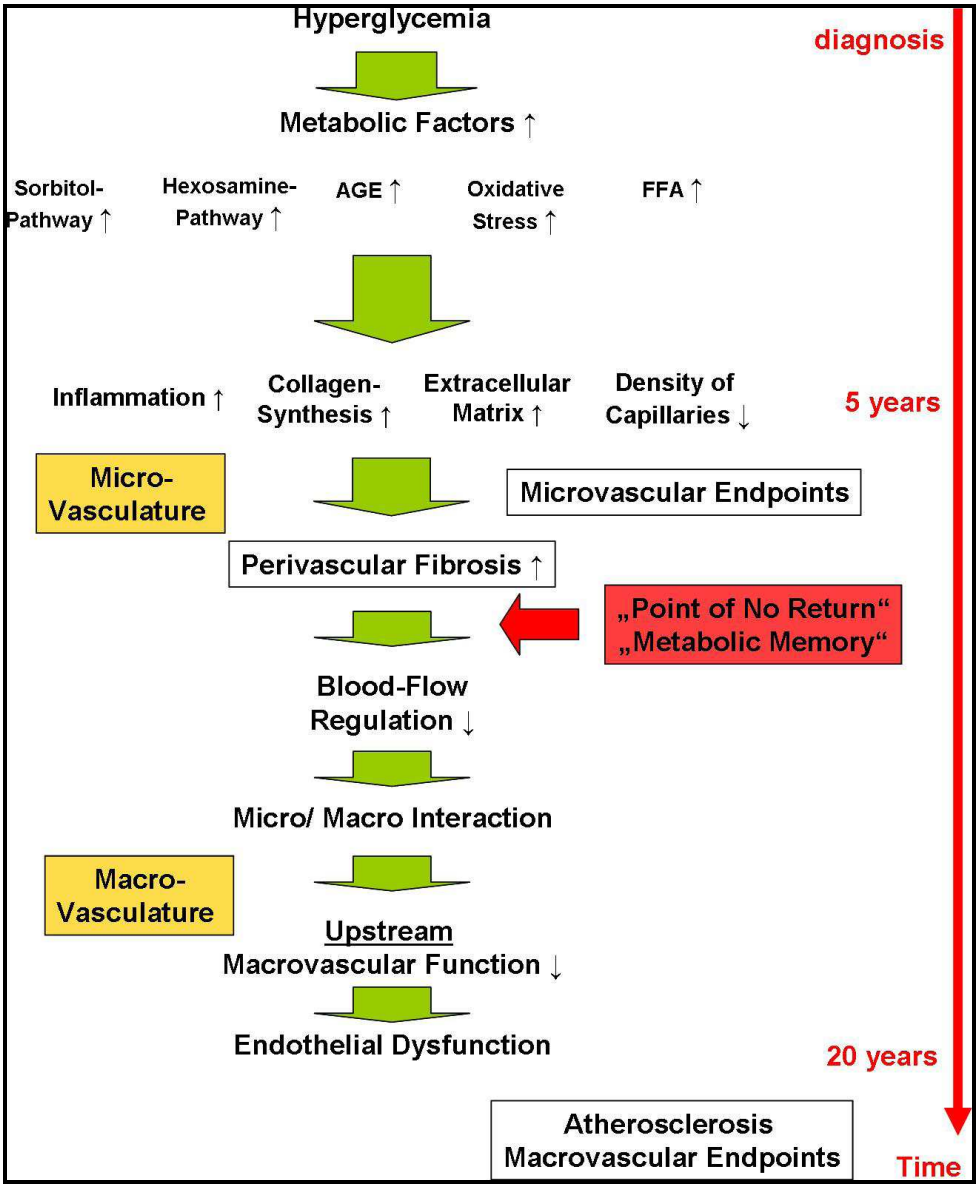

Figure (1): Showing effect of hyperglycemia on diabetic micro and macro vascular complications ***(Jax, 2010).***

Treatment:

Children with type 1 diabetes (DM1) require multiple daily injections of insulin to maintain good glycemic control. The Diabetes Control and Complications Trial (DCCT) has shown that intensive insulin treatment using at least three times daily (TID) injections achieves superior blood glucose control with decreased risk of long term complications than conventional insulin treatment using once daily or twice daily (BID) injections ***(Ho et al.,2011).***

Intensive insulin therapy using a basal-bolus approach, whether as multiple daily injections or pump therapy, is considered the best treatment for individuals with type 1 diabetes regardless of age ***(American Diabetes Association, 2009).***

This is because it provides greater glycemic control and has been shown to reduce the risk of complications compared with conventional fixed dose regimens ***(Nathan et al., 2005).***

Current strategies for the treatment of type 1 diabetes with insulin involve the use of basal‑bolus therapy to maintain near normoglycemia in order to prevent long‑term complications ***(Szypowska et al., 2011).***

Cardiovascular Complications and Insulin Resistance during Puberty in Diabetic Patients

Definition of puberty:

Puberty is a period of rapid and radical physical, psychological and social change during which a child, in physiological terms, becomes an adult capable of reproduction ***(Tfayli and Arslanian, 2007).***

Puberty is the end point of a complex series of developmental events, and identification of the triggers of pubertal onset has drawn considerable attention ***(Aksglaede et al., 2009).***

Physiology of puberty:

Pubertal development and fertility are determined by a multi-hormonal effect ***(El-Eshmawy et al., 2010).***

The pubertal system is active in utero and at birth, but within 4-6 months becomes suppressed. This suppression lasts throughout childhood until a (still unresolved) signal of maturation releases this inhibition and the child begins pubertal development ***(Curtis and Allen, 2011).***

The timing of the onset and progression through puberty is affected by genetic factors as well as environment. Worldwide, secular changes in the age of puberty, have occurred, likely related to availability of better nutrition,

increased body mass, less disease, and increased psychological stimulation ***(Curtis and Allen, 2011).***

Gonadotrophic gonadal axis role:

Onset of puberty occurs after reactivation of the hypothalamic Gonadotropin Releasing Hormone (GnRH) secretory system ***(Karapanou and Papadimitriou, 2010).***

Puberty is characterized by increasing concentrations of gonadal estradiol in girls and testosterone in boys, driven by increasing concentrations of pituitary gonadotrophins which are, in turn,regulated by gonadotrophin-releasing hormone (GnRH) released by hypothalamic neurons ***(El-Eshmawy et al., 2010).***

GnRH pulse generator is comprised by scattered neurons that are distributed in the arcuate nucleus of the medial basal hypothalamus and the preoptic area in the rostral region of the hypothalamus ***(Karapanou and Papadimitriou, 2010)***.

The GnRH pulsatile secretion is dependant on the coordinated action of the scattered GnRH neurons. The latter are controlled by trans-synaptic, stimulatory and inhibitory, and glia-to-neuron inputs***(Karapanou and Papadimitriou, 2010)*** .

Various neuropeptides and neurotransmitters have been shown to have stimulatory (e.g. glutamate, noradrenaline) or inhibitory (e.g. gamma-aminobutyric acid-GABA, endogenous opiates, NPY) role in the regulation of GnRH neurons. The