Studying the relationship between Dipeptidyl peptidase-4 enzyme level, Tumor necrosis factor alpha enzyme level, and insulin resistance in type 1 Diabetes Mellitus patients

Submitted for Partial Fulfillment of Master Degree in

Endocrinology & Metabolism

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2018

Special dedication to Professor Dr/Maram Maher for her endless support in reviewing the material

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List of abbreviations

T1DM	Type 1 Diabetes Mellitus
IR	Insulin resistance
TNFα	Tumor necrosis factor alpha
DPP-4	Dipeptidyl peptidase-4
eGDR	estimated glucose disposal rate

WHR	waist to hip ratio

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(*Introduction*)

Type 1 diabetes mellitus (T1DM) is an inflammatory disease of the pancreatic islets that results in absolute insulin deficiency and the consecutive hyperglycemia due to immune-mediated beta cell destruction **(Burrack et al, 2017)**.

Throughout the globe, the incidence of T1DM is increasing at 3% to 5% per year.

Although beta cell death is the pathophysiological core of T1DM, recent data suggest that the disease associated metabolic disturbances, represent a common feature of autoimmunity and insulin resistance (IR) caused by Adipocyte derived pro-inflammatory factors, chronic activation of innate immune system, and low-grade inflammation **(Gerich et al, 2000)**.

Out of recently identified adipocytokines, dipeptidyl peptidase-4 (DPP-4) and tumor necrosis factor-alpha (TNF a) appear to be important in the pathogenesis of IR **(Famulla et al, 2011)**

Insulin resistance is traditionally related to type 2 diabetes (T2DM), but its association with T1DM is also well documented **(Kilpatrick et al, 2007)**

TNFα is closely related to metabolic disorders and diabetes. It was originally identified as cytokine associated with weight loss, hyper metabolism, and energy expenditure in infectious diseases or malignancies.

The observation that visceral adipocytes of obese animals overexpress TNF a provided evidence that it might be involved in the pathogenesis of IR **(Beutler et al, 1989)**.

Dipeptidyl peptidase 4 plays a major role in glucose metabolism. It is responsible for the degradation of incretins such as GLP-1

(*Barnett* et al, *2006*)

Recent data suggest that DPP-4 activity is higher in patients with T1DM compared to healthy controls independently of islet cell antibody status, C-peptide concentration, and disease duration or glycated hemoglobin (HbA1c) level and in an inverse correlation

with body mass index (BMI) and insulin sensitivity **(Blaslov et al, 2015)**

The estimated glucose disposal rate (eGDR) can be calculated using routine clinical measures: glycosylated hemoglobin (HbA1c), presence of hypertension, and waist circumference. **(Nyström et al, 2006)**

The eGDR shows good correlation with IR and has been validated for the estimation of insulin sensitivity in individuals with type 1 diabetes

(Aim of the study)

To study the relationship between DPP-4 serum level, TNF a concentration measurements, and insulin sensitivity in T1DM patient

Type 1 Diabetes Mellitus

DEFINITION

Type 1 diabetes mellitus (DM) is a multisystem disease with both biochemical and anatomic/structural consequences. It is a chronic disease of carbohydrate, fat, and protein metabolism caused by the lack of insulin, which results from the marked and progressive inability of the pancreas to secrete insulin because of autoimmune destruction of the beta cells ***(ADA, 2018)***.

CLASSIFICATION

T1D may be classified into two main types:

1- type 1A immune-mediated
2- type 1B idiopathic(~10% of patients)

Unlike immune-mediated T1AD, T1BD is not associated with islet autoantibodies or HLA, although both forms can involve ketoacidosis **(Jonsdottir et al, 2015)**

EPIDEMIOLOGY

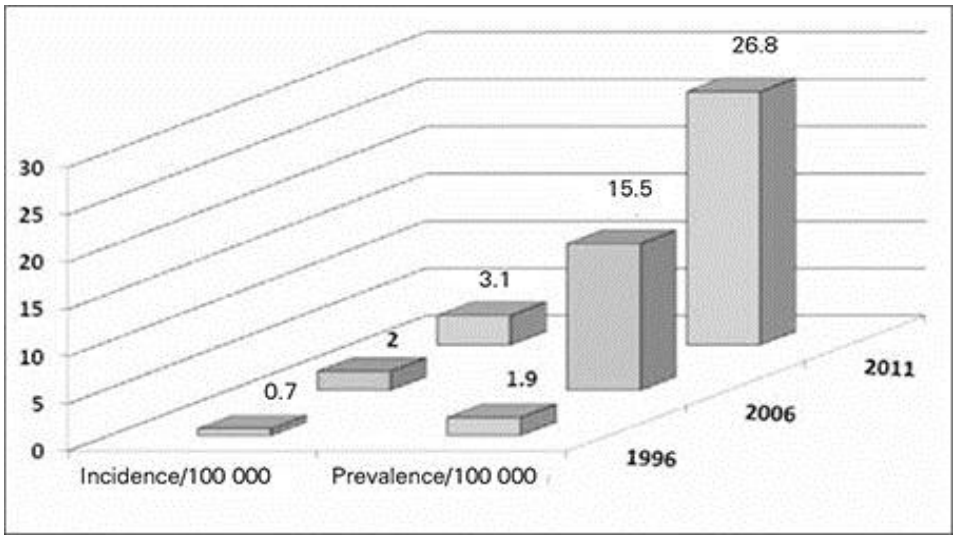
Prevalence

The prevalence of T1D is low compared with that of T2D. Among individuals 30 years of age or younger, the prevalence of T1D does not usually exceed about 0.3%, compared with prevalence rates for T2D of 4.2% worldwide populations and nearly 25% in certain high-risk populations. While current attention is directed toward the trends of the "epidemic" of T2D, epidemiological data suggest that there is a "parallel rise" in the incidence rates of both T1DM and T2DM **(Ankolekar et al, 2015)**

Prevalence of type 1 Diabetes in Egypt:

Among Eastern Mediterranean and Middle Eastern countries, the largest contribution to the total number of estimated childhood T1DM cases comes from Egypt which accounts for about a quarter of the region's total. The incidence is 8/100 000 per year (Egypt) in children under the age of 15 years ***(El-Ziny et al 2014).***

Figure (1): ***Calculated age-adjusted incidence and prevalence rates of type 1 diabetes mellitus (T1DM)/100 000 Egyptian children aged 0-18 years in 1996, 2006 and 2011:***



(El-Ziny *et al* ***2014)***

Incidence

Incidence is the rate at which new cases of disease appear in the population and is usually expressed as the annual number of new cases per 100,000 persons. Globally, the current rise in incidence rates by 3% (2% to 5%) is expected to increase 40% higher in 2010 Compared to figures from 1998. It was estimated that more than 70,000 new patients are diagnosed each year worldwide **(klonoff et al, 2009)**

Age related demographics:

Previously referred to as juvenile-onset diabetes, type 1 DM is typically diagnosed in childhood, adolescence, or early adulthood. Although the onset of type 1 DM often occurs early in life, 50% of patients with new-onset type 1 DM are older than 20 years of age.

Type 1 DM usually starts in children aged 4 years or older, appearing fairly abruptly, with the peak incidence of onset at age 11-13 years (i.e., in early adolescence and puberty). There is also a relatively high incidence in people in their late 30s and early 40s, in whom the disease tends to present less aggressively (i.e., with early hyperglycemia without ketoacidosis and gradual onset of ketosis). This slower-onset adult form of type 1 DM is referred to as latent autoimmune diabetes of the adult (LADA) (**Laugesen et al, 2015*).***

The risk of development of antibodies (anti-islet) in relatives of patients with type 1 DM decreases with increasing age. This finding supports annual screening for antibodies in relatives younger than 10 years and 1 additional screening during adolescence ***(Vehik 2011).***

Sex and race demographics:

Type 1 DM is more common in males than in females. In populations of European origin, the male-to-female ratio is greater than 1.5:1Type 1 DM is most common among non-Hispanic whites, followed by African Americans and Hispanic Americans. It is comparatively uncommon among Asians ***(CDC, 2011)***

Etiology:

1. Type 1A DM results from autoimmune destruction of the beta cells of the pancreas and involves both genetic predisposition and an environmental component.
2. Idiopathic.

Genetic factors:

Although the genetic aspect of type 1 DM is complex, with multiple genes involved, there is a high sibling relative risk **.**Whereas dizygotic

twins have a 5-6% concordance rate for type 1 DM, monozygotic twins will share the diagnosis more than 50% of the time by the age of 40 years ***(Jerram* et al, *2017).***

For the child of a parent with type 1 DM, the risk varies according to whether the mother or the father has diabetes. Children whose mother has type 1 DM have a 2-3% risk of developing the disease, whereas those whose father has the disease have a 5-6% risk. When both parents are type 1 diabetic, the risk rises to almost 30%. In addition, the risk for children of parents with type 1 DM is slightly higher if onset of the disease occurred before age 11 years and slightly lower if the onset occurred after the parent's 11th birthday.

The genetic contribution to type 1 DM is also reflected in the significant variance in the frequency of the disease among different ethnic populations. Type 1 DM is most prevalent in European populations, with people from northern Europe more often affected than those from Mediterranean regions ***(***Yanling Wu***,*** 2014***).***The disease is least prevalent in East Asians ***(Diabetes Epidemiology Research International Group, 1988).***

Environmental factors:

Extra genetic factors also may contribute. Potential triggers for immunologically mediated destruction of the beta cells include viruses (e.g.: enterovirus ***(Petzold, 2015),*** mumps, rubella, and Coxsackie virus B4), toxic chemicals, exposure to cow's milk in infancy, and cytotoxins.

Combinations of factors may be involved***. Lempainen et al*** found that signs of an enterovirus infection by 12 months of age were associated with the appearance of type 1 DM–related autoimmunity among children who were exposed to cow's milk before 3 months of age. These results

suggest an interaction between the 2 factors and provide a possible explanation for the contradictory findings obtained in studies that examined these factors in isolation ***(Lempainen* et al*, 2012)*.**

One meta-analysis found a weak but significant linear increase in the risk of childhood type 1 DM with increasing maternal age**.** However, little evidence supports any substantial increase in childhood type 1 DM risk after pregnancy complicated by preeclampsia ***(*Svensson et al*, 2005)*.**

A study by ***Simpson et al*** found that neither vitamin D intake nor 25-hydroxyvitamin D levels throughout childhood were associated with islet autoimmunity nor progression to type 1 DM ***(Simpson* et al*, 2011)*.**

This study was based in Denver, Colorado, and has been following children at increased risk of diabetes since 1993.

Early upper respiratory infection may also be a risk factor for type 1 diabetes. In an analysis of data on 148 children considered genetically at risk for diabetes, upper respiratory infections in the first year of life were associated with an increased risk for type 1 diabetes. All children in the study who developed islet autoimmunity had at least 2 upper respiratory infections in the first year of life and at least 1 infection within 6 months before islet autoantibody seroconversion ***(Rewer* et al*, s 2017)***.

Children with respiratory infections in the first 6 months of life had the greatest increased hazard ratio (HR) for islet autoantibody seroconversion (HR = 2.27), and the risk was also increased in those with respiratory infections at ages 6 to almost 12 months (HR = 1.32). The rate of islet autoantibody seroconversion was highest among children with more than 5 respiratory infections in the first year of life. Respiratory infections in the second year of life were not related to increased risk ***(Ziegler* et al*, 2016)*.**