Introduction

Selective IgA deficiency (SIgAD) constitutes the most frequent primary immunodeficiency (PID) ***(Geha et al., 2007).***

The prevalence of SIgAD is of different distribution worldwide, varying from 1:143 in Arabian Peninsula to 1:18 500 in Japan ***(Yel, 2010).***

SIgAD is defined based on IgA value <0.07 g/L, with normal immunoglobulin M (IgM) and immunoglobulin G (IgG) levels, in individuals >4 years of age, in accordance with the recommendations of the International Union of Immunological Societies Expert Committee on Primary Immunodeficiencies ***(Notarangelo et al., 2009).***

There is a wide clinical spectrum of SIgAD varying from asymptomatic (85%-90%) to recurrent infections (otitis media, upper respiratory tract infections, bronchitis, pneumonia, chronic diarrhea, urinary tract infections, and skin infections), allergy (allergic rhinitis/conjunctivitis, asthma, atopic dermatitis, urticaria, drug allergy, and food allergy), and autoimmune diseases (type 1 diabetes mellitus (T1DM), juvenile rheumatoid arthritis, systemic lupus erythematosus, Hashimoto thyroiditis, celiac disease (CD),

idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia) occurring more often ***(Yel L, 2010).***

T1DM is a chronic autoimmune disorder characterized by destruction of insulin producing beta cells of pancreatic islets by CD8+ cytotoxic T lymphocytes with the contribution of CD4+ helper T lymphocytes, while antibody-producing B cells play a role in the initial immunological events ***(Shkalim et al., 2010).***

Pancreatic β-cells are the target of an autoimmune assault in T1DM, with invasion of the islets by mononuclear cells in an inflammatory reaction termed "insulitis," leading to loss of most β-cells after prolonged periods of disease. β-Cell death in the course of insulitis is probably caused by direct contact with activated macrophages and T-cells, and/or exposure to soluble mediators secreted by these cells, including cytokines, nitric oxide (NO) and oxygen free radicals ***(Eizirik and Mandrup-Poulsen, 2001).***

Glycation of immunoglobulin occurs in patients with diabetes in proportion with the increase in HbA1c, and this may harm the biological function of the antibodies. However, the clinical relevance of these observations is not clear, since the response of antibodies after vaccination and to common

infections is adequate in persons with DM ***(Peleg et al., 2007).***

There is no way to prevent T1DM. Treatment with insulin is typically required for survival. Untreated, diabetes can cause many complications .Complications of relatively rapid onset include diabetic ketoacidosis (DKA) and non ketotic hyperosmolar coma ***(Chiang et al., 2014)*** Long-term complications include heart disease, stroke, kidney failure, foot ulcers and damage to the eyes ***(Sarwar et al., 2010)*** Furthermore, complications may arise from low blood sugar caused by excessive insulin treatment ***(Chiang et al., 2014).***

Several immunological mechanisms have been suggested in the development of autoimmunity in SIgAD patients. Secretory IgA has an important role in the protection of mucosal surfaces, as environmental antigens can easily penetrate the mucosa in the absence IgA. Molecular mimicry and cross-reaction with self-antigens might cause the formation of auto-reactive antibodies, ***(Stiehm, 2008)*** as an increase in autoantibody levels has been shown in patients with SIgAD ***(Jacob et al., 2008)*** The association between SIgAD and abnormal T-cell regulation, especially in CD4+CD25+Foxp3+ regulatory T-

cells (Treg) could also explain the association between SIgAD and autoimmunity due to the breakdown of immune tolerance. ***(Soheili et al., 2012)*** Researchers suggest that there is a complex association between genetic susceptibility and development of SIgAD and autoimmune diseases, as it has been reported an association between certain human leukocyte antigen (HLA) haplotypes especially HLA-A1, -B8, -DR3 and DQ2 and manifestation of SIgAD ***(Wang et al., 2011).***

Associations between SIgAD and certain major histocompatibility complex (MHC) class I, II and III haplotypes have been proposed. In SIgAD and T1DM, HLA-B8 frequency was found to be increased in earlier studies. HLA-B8 frequency was also higher in SIgAD and autoimmune disorders ***(Concha et al., 2002).***

Although an association of SIgAD with T1DM has been reported, the exact prevalence of SIgAD in Egyptian adults with T1DM is not known.

Aim of the Work

The aim of this work is to measure IgA level in serum among patients with T1DM as compared to healthy controls.

Diabetes Mellitus

Definition:

Diabetes mellitus (D.M.) is a heterogeneous group of chronic metabolic diseases which are characterized by increase in blood sugar.***(Bluestone et al.,2010).*** T1DM is thought to occur due to autoimmune destruction of the beta cells of pancreas which produce insulin.***(Atkinson et al.,2014).***This destruction leads to insulin deficiency which leads to absolute need for exogenous insulin replacement ,it predominantly occurs in young people.***(Bluestone et al.,2010).***

Classification:

D.M.is classified to the following:

1. Type 1 D.M.

2. Type 2 D.M.

3. Other specific types

As shown in Table (1) ***(ADA 2018)***

Table (1): Classification of D.M. *(ADA, 2018)*

I. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
   A. Immune mediated
   B. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

III. Other specific types
   A. Genetic defects of β-cell function
      1. MODY 3 (Chromosome 12, HNF-1α)
      2. MODY 1 (Chromosome 20, HNF-4α)
      3. MODY 2 (Chromosome 7, glucokinase)
      4. Other very rare forms of MODY (e.g., MODY 4: Chromosome 13, insulin promoter factor-1; MODY 6: Chromosome 2, *NeuroD1*; MODY 7: Chromosome 9, carboxyl ester lipase)
      5. Transient neonatal diabetes (most commonly ZAC/HYAMI imprinting defect on 6q24)
      6. Permanent neonatal diabetes (most commonly KCNJ11 gene encoding Kir6.2 subunit of β-cell K_{ATP} channel)
      7. Mitochondrial DNA
      8. Others
   B. Genetic defects in insulin action
      1. Type A insulin resistance
      2. Leprechaunism
      3. Rabson-Mendenhall syndrome
      4. Lipoatrophic diabetes
      5. Others
   C. Diseases of the exocrine pancreas
      1. Pancreatitis
      2. Trauma/pancreatectomy
      3. Neoplasia
      4. Cystic fibrosis
      5. Hemochromatosis
      6. Fibrocalculous pancreatopathy
      7. Others
   D. Endocrinopathies
      1. Acromegaly
      2. Cushing's syndrome
      3. Glucagonoma
      4. Pheochromocytoma
      5. Hyperthyroidism
      6. Somatostatinoma
      7. Aldosteronoma
      8. Others
   E. Drug or chemical induced
      1. Vacor
      2. Pentamidine
      3. Nicotinic acid
      4. Glucocorticoids
      5. Thyroid hormone
      6. Diazoxide
      7. β-Adrenergic agonists
      8. Thiazides
      9. Dilantin
      10. γ-Interferon
      11. Others
   F. Infections
      1. Congenital rubella
      2. Cytomegalovirus
      3. Others
   G. Uncommon forms of immune-mediated diabetes
      1. Stiff-man syndrome
      2. Anti-insulin receptor antibodies
      3. Others
   H. Other genetic syndromes sometimes associated with diabetes
      1. Down syndrome
      2. Klinefelter syndrome
      3. Turner syndrome
      4. Wolfram syndrome
      5. Friedreich ataxia
      6. Huntington chorea
      7. Laurence-Moon-Biedl syndrome
      8. Myotonic dystrophy
      9. Porphyria
      10. Prader-Willi syndrome
      11. Others

IV. Gestational diabetes mellitus

Patients with any form of diabetes may require insulin treatment at some stage of their disease. Such use of insulin does not, of itself, classify the patient.

Diagnosis:

Criteria for the diagnosis of diabetes:

Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours

Or

2 hour postprandial glucose (2h PG) ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT)

The test should be performed as described by the WHO, (using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water)

In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing

Or

Hemoglobin A1c (HA1C) ≥6.5% (48 mmol/mol)

(The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes control and complications trial (DCCT) assay)

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L). ***(ADA 2016)***

Type 1 Diabetes Mellitus:

Epidemiology:

T1DM is considered one of the most common diseases of childhood, it can be diagnosed at any age but its peak presentation occurs between 5-7 years and at or near by puberty ***(Harjutsalo et al., 2008)***. The number of people affected all over the world is unknown, yet it is estimated that around 80,000 children develop the disease each year**.** ***(Chiang et al., 2014)***

Unlike most of autoimmune disorders, T1DM is more common in boys and men ***(Ostman et al., 2008).***

clinical presentation:

T1DM patients present with polyuria or polydipsia and approximately one-third present with DKA ***(Dabelea et al., 2014).***

Disease heterogeneity :

Most of T1DM cases represent features of immunologic contribution to the pathogenesis of the disease (eg, autoantibodies or genetic associations with genes that control the immune responses), however not all of them have these characteristic features leading to the following classifications:

Type 1A (autoimmune) diabetes: it represents around 70–90% of patients with T1DM and they have immunological, self-reactive autoantibodies ***(Eisenbarth et al., 2007)***

Type 1B (idiopathic) diabetes: it represents the remainder and it has unspecific pathogenesis ***(Gianani et al., 2010)***

Maturity onset diabetes of the young (MODY) type: it represent a subset from the latter group and it has a monogenic form of diabetes ***(Hattersley et al., 2009)***

Disease Pathogenesis:

T1DM is a chronic inflammatory disease which is caused by autoimmune destruction of the β cell of the pancreas ***(Atkinson MA et al, 2014)***. The presence of a chronic inflammatory infiltrate that affects pancreatic islets at

symptomatic onset of T1DM is the basis of this observation as shown in figure (1) ***(In't Veld,2011)***.

Islet inflammation is typically marked by infiltrating adaptive and innate immune effectors , insulitis progresses over time and when sufficient amount of the β cell mass become nonfunctional or destroyed, hyperglycemia occurs and diabetes clinically establish, so in patients with longstanding disease, the pancreas is found to be devoid of insulin-producing cells and the remaining β cells are incapable of regeneration. ***(Gregg et al., 2012)*** .

Recent data suggest that although most patients with longstanding T1DM have few β cells, if any, there is evidence for β-cell regeneration in infants and very young children (but not in adolescents or adults)**.** ***(Keenan et al., 2010)*** .

T1DM is viewed to be a T cell-driven autoimmune disease, particularly for the more prevalent and aggressive type of T1DM that develops in children and adolescents versus adults ***(Pugliese, 2017).*** There is also a T cell-independent subtype of T1DM, which is thought that is mediated by innate immune effectors ***(Skog et al., 2013)***. There are heterogeneous mechanisms that mediate autoimmunity against the β cells and

they are influenced by both genetic and environmental factors ***(Katsarou et al., 2017)***

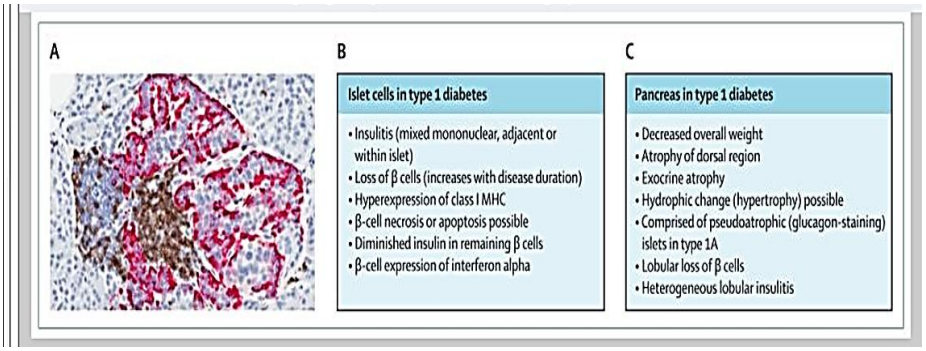

Figure (1): Pathological characteristics of the pancreas in T1D:

Figure (1) shows the following: (A) Islet infiltrate (ie, insulitis) seen in a patient with recent-onset T1DM. Immunohistochemistry shows the intra-islet presence of CD3-positive cells (brown) and glucagon-producing alpha cells (pink). Image courtesy of M Campbell Thompson, University of Florida, Gainsville, FL, USA. (B) Histological features of islets and (C) gross pathological characteristics of the pancreas associated with the natural history of T1DM (ie, preonset, onset, postonset). ***(In't Veld, 2011).***

Genetic factors:

T1DM is polygenic; there are more than 20 genetic loci that are identified to be associated with increased or decreased risk with T1DM. ***(Onengut-Gumuscu et al., 2015).***The human leukocyte antigen locus (HLA) (IDDM1) is considered the strongest genetic association, particularly class I and II

haplotypes (IDDM1), consistent with a key role for T cells in T1DM ***(Nerup et al., 1974)***.

A number of genes which regulate T, B, and innate cell immunobiology are linked to T1DM, as are genetic variants intrinsic to β cells, which affect the β cell function and/or responses to inflammation ***(Dooley et al., 2016).***

The inefficient negative selection of anti-self-single positive thymocytes (SP) that occurs in the thymus leads to generation of an autoreactive T cell receptor (TCR) in the periphery ***(Takaba and Takayanagi, 2017)***. Early in ontogeny negative selection is lax which results in increased escape of anti-self-SP ***(Guerau-de-Arellano et al., 2009).***

The temporal decrease in the negative selection and the elevation in survival of β cell-specific clonotypes may help in explaining the predominance of T1DM onset in childhood. By time, the thymic structural organization changes and there is maturation in the thymic antigen-presenting cells (APC) leading to more efficient negative selection and increased death of the autoreactive SP ***(He et al., 2013).***

In humans, the T1DM-associated variant of the protein tyrosine phosphatase non-receptor 22 (PTPN22) gene may limit the TCR signaling which is needed to drive the

apoptosis of β cell-specific SP , also the increased activity of the (PTPN22) may limit the thymic development of β cell-specific forkhead box P3 expressing regulatory CD4+ T cells (FOXP3+Treg), which is dependent on higher avidity/affinity of self-peptide recognition ***(Vang T et al., 2005).***

Environmental factors:

The role of the environmental factors in T1DM is not well understood .The most common hypothesis is that microbial infections initiate and/or exacerbate islet inflammation in individuals with genetics susceptibility ***(Op de Beeck and Eizirik, 2016).***

Sometimes it is associated with enteroviruses such as coxsackievirus B1 ***(Lin et al., 2015)***.

Viral infection may lead to cytolysis and /or produce local inflammation that initiates and/or drives autoimmunity ***(Krogvold et al., 2015).***

The gut microbiota also has a regulatory effect on the autoimmunity against the β cell of the pancreas ***(Knip and Siljander, 2016)***

Studies of these constituents suggest that a series of functional defects in the bone marrow, thymus, immune

system, and β cells collectively contribute to the pathophysiology of T1DM as shown in figure (2**).** ***(Roep and Peakman. 2011)***

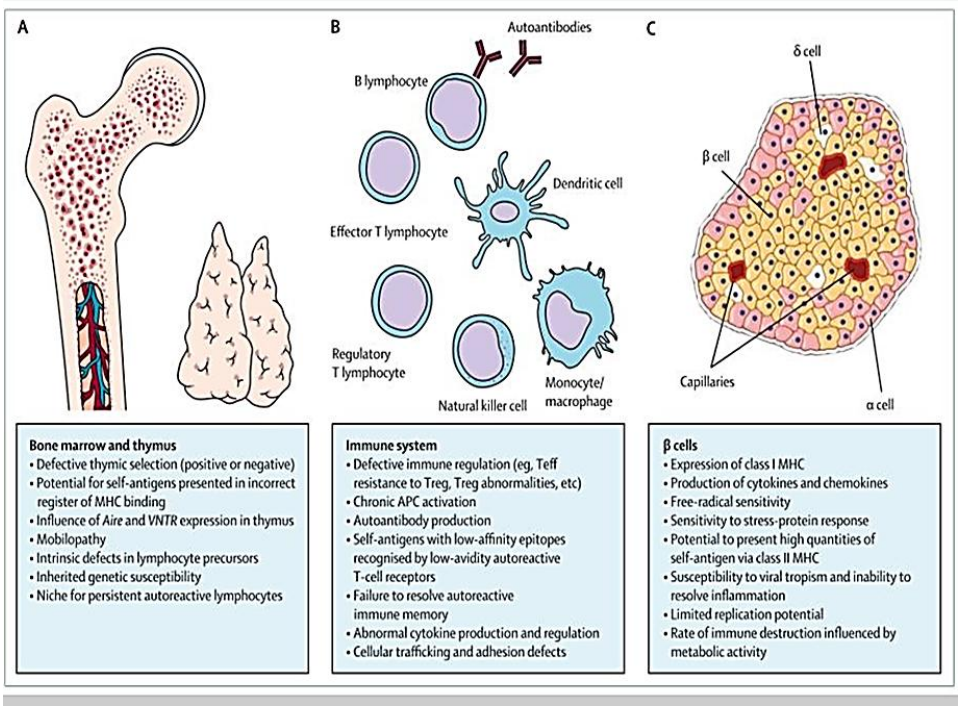

Figure (2): Physiological contributions to the pathogenic processes that underlieT1DM

Figure (2) shows: A series of defects emanating from (A) the bone marrow and thymus, (B) immune system, and (C) β cells collectively lead to loss of insulin production by autoimmune mechanisms. These actions are continuous throughout the natural history of type1 diabetes. Teff=effector T cell. Treg=regulatory T cell APC=anaphase-promoting complex ***(Roep and Peakman ,2011).***