INTRODUCTION

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by T-cell mediated destruction of the pancreatic beta cells, resulting in insulin deficiency and elevated blood glucose levels ***(Daneman, 2006)***. Around 490,100 children live with the disease worldwide, with incidence estimated to be increasing in children less than 15 years by 2.8% per year ***(Catanzariti et al., 2009)***.

Diabetic peripheral neuropathy is the most common chronic complication of diabetes mellitus, with an incidence rate of about 50% ***(Shi et al., 2013; Galuppo et al., 2014; Zhong et al., 2014)***. Diabetic peripheral neuropathy commonly develops insidiously, with various clinical manifestations. In the early stages, diagnosis is difficult as there are no symptoms ***(Kuntzer et al., 2012; Mete et al., 2013).*** Once symptoms appear, there are few effective therapeutic strategies ***(Won et al., 2014)***. Therefore, early discovery and diagnosis are extremely important ***(Zhang et al., 2014)***.

Fortunately, increasing use of electrophysiological techniques that allow the identification of sub-clinical pathological changes has made early diagnosis of diabetic peripheral neuropathy possible ***(Balbinot et al., 2012; Calvet et al., 2013; Sun et al., 2013; Gordon Smith et al., 2014).*** Nerve conduction studies are the most common method for diagnosis

of peripheral neuropathy ***(Morimoto et al., 2012; Joa and Kim, 2013; Chiles et al., 2014)***.

The cross talk between oxidative stress and inflammation mediates endothelial dysfunction, altered nitric oxide levels, and macrophage migration. These all culminate in the production of proinflammatory cytokines which are responsible for nerve tissue damage and debilitating neuropathies ***(Sandireddy et al., 2014)***.

Neopterin, a pyrazino-pyrimidine compound, is synthesized by monocytes and macrophages in response to Interferon (IFN-γ) produced by activated T cells. Neopterin levels are elevated in conditions of T-cell or macrophages activation ***(Huber et al., 1984; Werner et al., 1993).*** It enhances macrophage cytotoxicity through its interactions with reactive oxygen, nitrogen, and chloride species ***(Hoffmann et al., 2003)***.

Neopterin is a marker of inflammation and cellular immune response ***(Lhee et al., 2006).*** Its levels are elevated in several conditions including autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis ***(Aulitzky et al., 1988)***, infections such as hepatitis, human immunodeficiency virus, and cytomegalovirus ***(Fahey et al., 1990; Halota et al., 2002)***, cancers like hepatocellular, gastric, and urothelial carcinomas ***(Aulitzky et al., 1985)***, congestive heart failure; coronary artery disease, myocardial infarction,

transplant rejection ***(Alber et al., 2009; Chin et al., 2008)***, pulmonary tuberculosis with more extensive radiological changes ***(Eisenhut, 2013; El-Shimy et al., 2016)*** and Gaucher disease ***(Drugan et al., 2016)***.

Neopterin has emerged as a novel independent predictor of fatal ischemic heart disease in type 2 diabetes mellitus ***(Vengen et al., 2009)***. Neopterin levels were also elevated in gestational diabetes mellitus ***(Ipekci et al., 2015)***. Moreover, high levels of serum or CSF neopterin were found in neurological diseases ***(Hall et al., 2016)***. Although neopterin has been reported as a marker of disease progression and complication in diabetes ***(Weiss et al., 1998)***, its clinical relevance and relation to diabetic neuropathy remains largely unknown.

AIM OF THE WORK

The aim of this study was to measure serum neopterin level in children and adolescents with type 1 diabetes mellitus and to assess its relation to glycemic control as well as its possible association with peripheral neuropathy and nerve conduction studies.

Chapter 1
TYPE 1 DIABETES MELLITUS

Definition:

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defect 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, kidney, nerves, heart, and blood vessels ***(ISPAD, 2014a).*** The vast majorities of cases with diabetes fall into two etiopathogenetic categories; type 1 and type 2 diabetes mellitus ***(ISPAD, 2014a).***

The classical symptoms of diabetes are polyuria, polydepsia, and polyphagia ***(Cooke and Plotnick, 2008).*** The major forms of diabetes are divided into those caused by deficiency of insulin secretion due to pancreatic Beta-cell damage (type 1 DM), and those that are consequence of insulin resistance occurring at the level of skeletal muscles, liver, and adipose tissue with various degrees of Beta-cell impairment (type 2 DM) ***(Alemzadeh and Ali, 2011).***

Prevalence and incidence of T1DM:

WHO estimates that more than 180 million people worldwide have diabetes mellitus and this number is likely to be more than double by 2030; about 10% have T1DM ***(Jensen et al., 2011).*** There are approximately 500, 000 children aged

under 15 with type 1 diabetes in the world ***(Patterson et al., 2014)***. The International Diabetes Federation estimates that 79, 000 children developed type 1 diabetes in 2013 ***(IDF Diabetes Atlas, 2015)***.

Age:

Diabetes is one of the most common diseases in school-aged children. According to the 2011 National Diabetes Fact sheet, about 215, 000 young people in the US under age of 20 had diabetes in 2010. This represents 0.26 percent of all people in this age group ***(National Diabetes Fact sheet, 2011).***

Peaks of presentation occur in 2 age groups: at 5-7 years old age and at the time of puberty. The first peak may correspond to the time of increased exposure to infectious agents coincident with the beginning of school; the second peak may correspond to the pubertal growth hormone secretion (which antagonize insulin) ***(Alemzadeh and Ali, 2011).***

Sex:

Girls and boys are almost equally affected but there is a modest female preponderance in some low-risk populations (e.g., the Japanese); there is no apparent correlation with socioeconomic status ***(Alemzadeh and Ali, 2011).***

Race:

Type 1 diabetes is more common among non-Hispanic whites, followed by African Americans and Hispanic Americans, it is comparatively uncommon among Asian ***(Lal et al., 2011).***

Pathogenesis of T 1 DM:

Genetic susceptibility:

The genetics of Type 1 DM cannot be classified according to specific model of inheritance. The most important genes are located within the Major Histocompatibility Complex (MHC) Human Leukocyte Antigen (HLA) class II region on chromosome 6p21, formally termed Insulin Dependent Diabetes Mellitus (IDDM), accounting for about 60% genetic susceptibility for the disease; their specific contribution to the pathogenesis of type 1 DM remains unclear ***(Alemzadeh and Wyatt, 2008).***

Autoimmunity:

In T1DM, a genetically susceptible host develops autoimmunity against his or her own Beta-cells. What triggers this autoimmune response remains unclear at this time. In some (but not all) patients, this autoimmune process results in progressive destruction of beta-cells until a critical mass of beta-cells is lost and insulin deficiency develops. Insulin deficiency in turn leads to the onset of clinical signs and

symptoms of T1DM. At the time of diagnosis, some viable Beta-cells are still present and these may produce enough insulin to lead a partial remission of the disease (honeymoon period) but over time, almost all Beta-cells are destroyed and the patient becomes totally dependent on exogenous insulin for survival (Figure 1) ***(Alemzadeh and Ali, 2011)***.

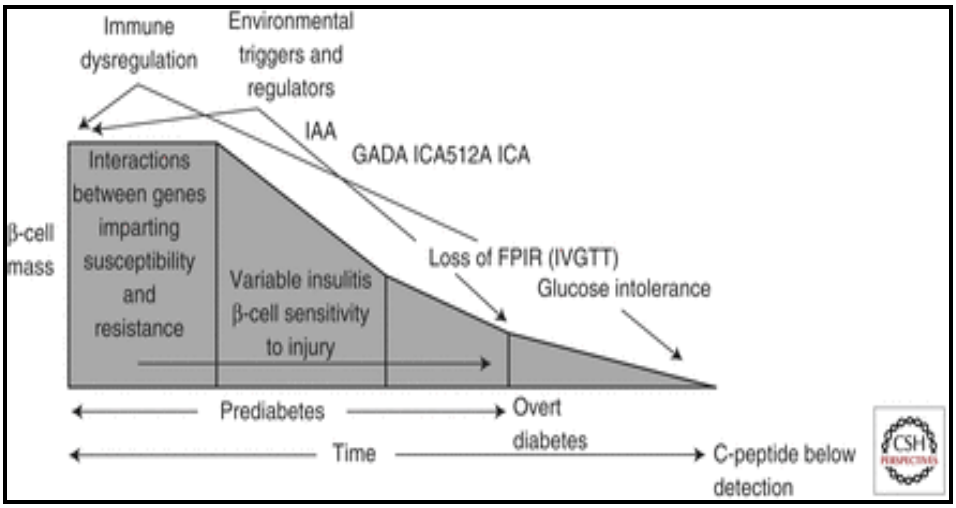

Figure (1): Proposed model of the pathogenesis and natural history of type 1 diabetes mellitus. IAA, insulin autoantibodies; GADA, glutamic acid decarboxylase antibody; ICA, islet cell antibody; IVGTT, intravenous glucose tolerance test ***(Alemzadeh and Ali, 2011).***

Environmental factors:

Environmental factors are important because even identical twins have only a 30-60% concordance for type 1 diabetes, and because incidence rates vary in genetically similar populations under different living conditions. No signals factor has been identified, but infections and diet are considered the two most likely environmental candidates ***(Lamb, 2011).***

Phases of T1DM:

Type 1 diabetes in childhood and adolescents is characterized by the following phases: (Figure 2)

- Preclinical diabetes.
- Presentation of diabetes.
- Partial remission phase.
- Chronic phase of lifelong dependency on administered insulin.

(Atkinson and Skyler, 2012)

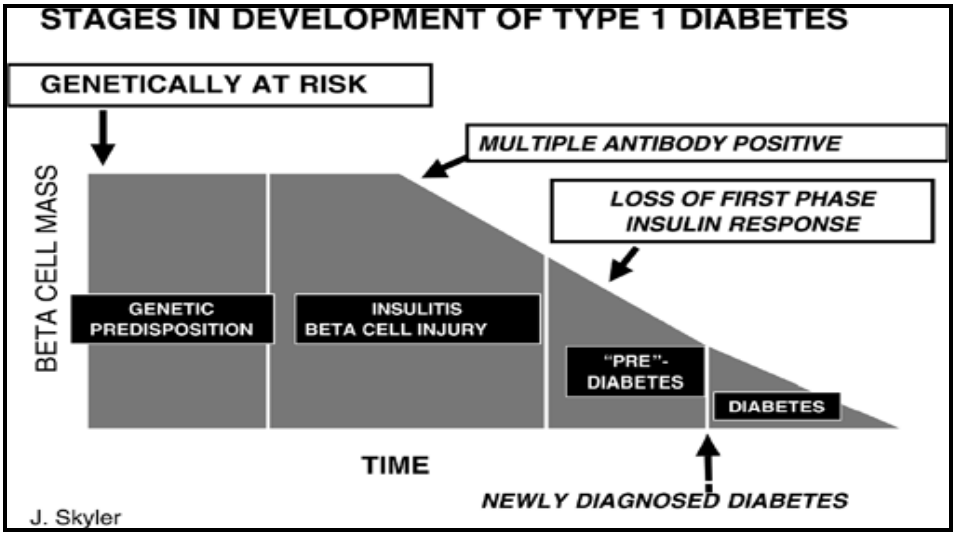

Figure (2): Phases of T1DM ***(Atkinson and Skyler, 2012).***

Clinical presentation of new onset diabetes:

- The presentation of new onset T1DM is distributed among three typical patterns: classic new onset diabetes, silent and diabetic ketoacidosis. Children who have classic new onset diabetes typically present with polydepsia, polyuria, polyphagia, enuresis in a previously toilet trained child and pyogenic skin infections and monilial vaginitis in teenage girls ***(International Society of Pediatrics and Adult Diabetes [ISPAD], 2014a).***
- Children with silent T1DM are typically diagnosed by families and physicians with high index of suspicion and they often require little insulin because they have greater residual cell mass ***(Haller et al., 2005).***
- Diabetic ketoacidosis (DKA) is the usual emergency presentation of type 1 diabetes. An explosive onset of symptoms in a young lean patient with ketoacidosis always has been considered diagnostic of type 1 DM ***(Lamb, 2011).***

Diagnosis of T1DM:

The diagnosis of diabetes should not be based on a single plasma glucose concentration. Diagnosis may require continued observation with fasting and/or 2 hour post-prandial blood glucose levels and/or an oral glucose tolerance test (OGTT). An OGTT should not be performed if diabetes can be diagnosed using fasting, random or post-prandial criteria as excessive hyperglycemia can result ***(Craig et al., 2009).*** Diagnostic criteria of T1DM are shown in Table (1).

Table (1): Criteria for diagnosis of diabetes

Classic symptoms of diabetes or hyperglycemic crisis, with plasma glucose concentration ≥ 11.1 mmol/L (200 mg/dL)
OR
Fasting plasma glucose ≥ 7.0 mmol/L (≥ 126 mg/dL). Fasting is defined as no caloric intake for at least 8 h*
OR
Two hour postload glucose ≥ 11.1 mmol/L (≥ 200 mg/dL) during an OGTT*.
The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g.
OR
HbA1c > 6.5%
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.

HbA1c, hemoglobin A1c; OGTT, oral glucose tolerance test

*In the absence of unequivocal hyperglycemia, the diagnosis of diabetes based on these criteria should be confirmed by repeat testing.

*A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests. The role of HbA1c alone in diagnosing type 1 diabetes in children is unclear.

(International Society of Pediatric and Adolescent Diabetes [ISPAD], 2014a)

Management of type 1 diabetes:

1- Medications:

Insulin therapy is recommended for most individuals with type 1 diabetes.

- Treat with multiple-dose insulin injections (3-4 injections/day of basal and prandial insulin) or continuous subcutaneous insulin infusion
- Match prandial insulin dose to carbohydrate intake, Premeal blood glucose, and anticipated activity
- Use insulin analogs to reduce risk of hypoglycemia
- Consider using sensor-augmented low glucose suspend threshold pump in patients with frequent nocturnal hypoglycemia and/or hypoglycemia unawareness

(ADA, 2015a)

Insulin regimen:

Table (2): Insulin types, preparations and suggested action profiles according to manufacturers

Insulin type	Onset of action (h)	Peak of action (h)	Duration of action (h)
Rapid-acting analogues			
(Aspart, Glulisine, and Lispro)	0.15–0.35	1–3	3–5
Regular/soluble (short acting)	0.5–1	2–4	5–8
Intermediate acting Semilente (pork)	1–2	4–10	8–16
NPH	2–4	4–12	12–24
IZS Lente type	3–4	6–15	18–24
Basal long-acting analogs			
Glargine	2–4	None	24*
Detemir	1–2	6–12	20–24
Long-acting			
Degludec †	0.5–1.5	None	>24
Ultralente type	4–8	12–24	20–30

NPH, Neutral Protamine Hagedorn insulin; **IZS**, insulin zinc suspension.

*The duration of action may be shorter than 24 h.

†Not yet approved worldwide.

(ISPAD, 2014b)

2- Diet:

One of the first steps in managing type 1 DM is diet control. Dietary treatment is based upon nutritional assessment and treatment goals. Dietary recommendations should take into account the patient's eating habits and lifestyle ***(Ahmedani et al., 2012).***

3- Education:

According to ***ISPAD Clinical Practice Consensus Guidelines 2014***, education is the key to successful management of diabetes. There is evidence that educational interventions in childhood and adolescent diabetes have a beneficial effect on glycemic control and on psychosocial outcomes.

4- Activity:

Exercise might greatly benefit many patients with diabetes by improving their metabolic profile, dyslipidemia, aiding in their weight loss and maintaining their blood pressure. Exercise improves glycemic control by reducing HbA1c values and is dispensable component in the medical treatment of patients with T1DM as it improves glycemic control and decreases cardiovascular risk factors among them ***(Salem et al., 2010).***

Complication of diabetes mellitus:

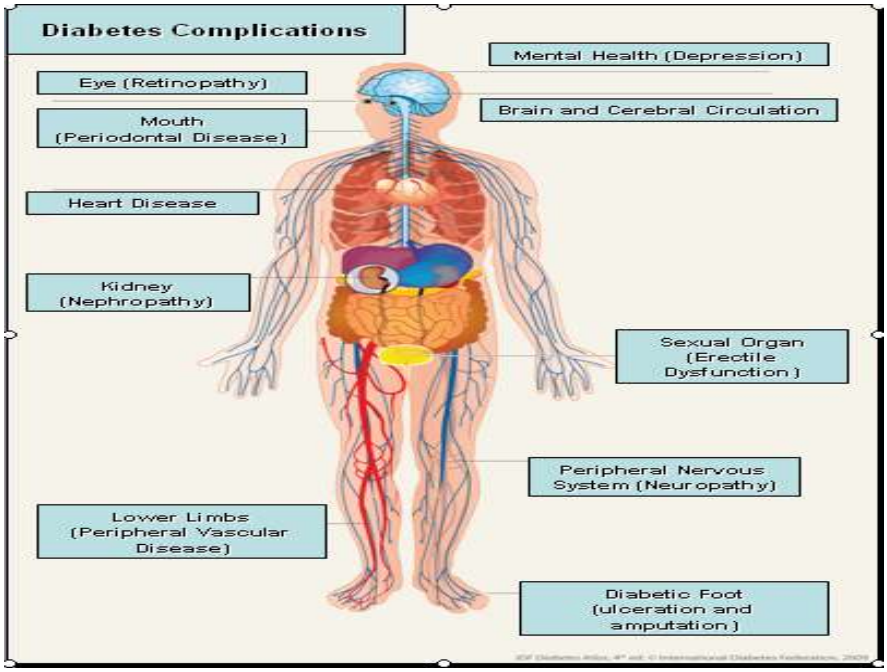

Figure (3): Diabetic complications ***(Bode, 2004).***

Complications can be acute or chronic:

1- Acute complications include the following:

A) Diabetic ketoacidosis (DKA)

Diabetic ketoacidosis (DKA) is a serious acute complication that may lead to cerebral edema, diabetic coma, and if not treated, death. Although DKA may occur in anyone with diabetes, it is far more common in patients with T1DM compared to those with T2DM ***(Kitabchi, 2012).***