INTRODUCTION

Type 1 diabetes is a disorder of glucose metabolism that results from insulin deficiency secondary to altered immune system (autoimmune) destruction of the pancreatic β-cell ***(Dejkhamron et al., 2007).***

Liver disease among diabetic patients may be attributed to diverse pathologies ***(Tolman et al., 2007)***. It may be attributed to fatty liver and hepatic glycogenosis ***(Lin et al., 2012).*** Hepatitis C virus (HCV) infection in diabetic children is also considered a health-related infection ***(Cadranel et al., 2008)*** due to repeated hospitalization, insulin injections, shared insulin vials and shared spring-triggered devices for capillary blood glucose monitoring as type 1 is more common in pediatric patients which commonly presents or become complicated by diabetic ketoacidosis ***(Sangiorgio et al., 2000; Atabek et al., 2003).*** While in adults, diabetes mellitus is considered as an extrahepatic manifestation of HCV infection ***(Sim et al., 1996; Mason et al., 1999).***

Moreover, it is believed that patients of type 1 diabetes are liable for autoimmune hepatitis which is believed to a part of the autoimmune process that lead to destruction of beta cells of the pancreas that lead to the development of type 1 diabetes ***(Al-Hussaini et al., 2014)***. The reported association between autoimmune hepatitis and diabetes is 1-10% **(*Wong et al., 2015).***

The pediatric literature about type 1 diabetes– related liver disease is largely limited to small case series or case reports for children presenting with symptomatic hepatic dysfunction during metabolic decompensation and ketosis ***(Al-Hussaini et al., 2012)***.

Fibrosis prediction is an essential part of the management of patients with chronic liver disease. Liver biopsy is currently considered the gold standard for assessing hepatic fibrosis. However, it is an invasive and painful procedure ***(Cadranel et al., 2000)*** with rare but potential life threatening complications limiting its acceptance and repetition in usually asymptomatic patients ***(Bravo et al., 2001).*** In addition, the accuracy of liver biopsy in assessing fibrosis may be questioned because of sampling error and interobserver variability, which may lead to understaging of cirrhosis ***(Regev et al., 2002; Bedossa et al., 2003; Colloredo et al., 2003).*** Thus there is a need to develop and validate non-invasive tests that can accurately reflect the full spectrum of hepatic fibrosis, cirrhosis, and its severity in liver diseases ***(Adam, 2011)***.

One of those non invasive tests are serum biomarkers for predicting liver fibrosis. Biomarkers offer a number of advantages over the traditional standard of fibrosis assessment of liver biopsy, including safety, cost-savings and wide spread accessibility. Current biomarker algorithms include indirect surrogate measures of fibrosis, including aminotransaminases and platelet count, or direct measures of fibrinogenesis or

fibrinolysis such as hyaluronic acid and tissue inhibitor of metalloproteinase-1 ***(Adam, 2011)***.

Current limitations of biomarker models include a significant indeterminate range, and a predictive ability that is limited to only a few stages of fibrosis. Utilization of these biomarker models requires knowledge of patient co-morbidities which may produce false positive or negative results in a small proportion of individuals. Furthermore, knowledge of the underlying prevalence of fibrosis in the patient population is required for interpretation of the positive or negative predictive values of a test result ***(Adam, 2011)***.

Other non invasive tests have been developed as an alternative for liver biopsy, to evaluate liver fibrosis. One of those methods is FibroScan or Transient Elastography (TE) which is a non-invasive method for the diagnosis of liver fibrosis. TE has been validated in different chronic liver diseases, including chronic viral hepatitis, non-alcoholic steatohepatitis (NASH), autoimmune hepatitis, primary biliary cirrhosis ***(Sandrin et al., 2003; Ziol et al., 2005; Mirault et al., 2008; Sporea and Sirli, 2012).***

Aim of the Work

The aim of this study was to identify the effect induced by hepatopathies of different etiologies among children and adolescents with T1DM using liver stiffness by TE as a non-invasive assessment tool and its relation to clinical and laboratory parameters including glycemic control.

Chapter 1
TYPE 1 DIABETES MELLITUS

Definition and Description

Diabetes Mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action, or both ***(International Society of Pediatric and Adolescent Diabetes ISPAD, 2014).*** The chronic hyperglycemia of diabetes is associated with relatively specific long term microvascular complications affecting the eyes, kidneys and nerves, as well as an increased risk for cardiovascular disease (CVD) ***(American Diabetes Association, 2012).***

Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss. In its most severe forms, ketoacidosis or a non-ketotic hyperosmolar state may develop and lead to stupor, coma and, in absence of effective treatment, death. Often symptoms are not severe, or may be absent, and consequently hyperglycemia sufficient to cause pathological and functional changes may be present for a long time before the diagnosis is made ***(World Health Organization, 1999).***

Several pathogenic processes are involved in the development of diabetes. These include processes which destroy the beta cells of the pancreas with consequent insulin deficiency, and others that result in resistance to insulin action.

The abnormalities of carbohydrate, fat and protein metabolism are due to deficient action of insulin on target tissues resulting from insensitivity or lack of insulin ***(World Health Organization, 1999)***.

The long-term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation, Charcot joints, and features of autonomic dysfunction, including sexual dysfunction. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease ***(McCance et al., 1994)***.

Global burden

Diabetes in all its forms imposes unacceptably high human, social and economic costs on countries at all income levels:

- There are 320.5 million people of working age (20-64 years) with diabetes and 94.2 million people aged 65-79 with diabetes by 2040 this will rise to 441.3 million of working age (20-64 years) and 200.5 million people aged 65-79 (Table 1).
- The number of people with type 2 diabetes is increasing in every country.
- 80% of people with diabetes live in low- and middle-income countries.

- The greatest number of people with diabetes is between 40 and 59 years of age.
- 193 million people with diabetes are undiagnosed.
- Approximately 5.0 million people aged between 20 and 79 years died from diabetes in 2015, equivalent to one death every six seconds.
- For the first time, the estimated number of children living with type 1 diabetes (542,000) exceeds half a million.
- The incidence of type 1 diabetes among children is increasing in many countries, particularly in children under the age of 15 years.

(IDF Diabetes Atlas, 2015)

Table (1): Top 10 countries/ territories for number of people with diabetes (20-79 years), 2015 and 2040

Rank	Country/territory	Number of people with diabetes	Rank	Country/territory	Number of people with diabetes
1	China	109.6 million (9.6-133.4)	1	China	150.7 million (138.0-179.4)
2	India	69.2 million (56.2-84.8)	2	India	123.5 million (99.1-150.3)
3	United States of America	29.3 million (27.6-30.9)	3	United States of America	35.1 million (33.0-37.2)
4	Brazil	14.3 million (12.9-15.8)	4	Brazil	23.3 million (21.0-25.9)
5	Russian Federation	12.1 million (6.2-17.0)	5	Mexico	20.6 million (11.4-24.7)
6	Mexico	11.5 million (6.2-13.7)	6	Indonesia	16.2 million (14.3-17.7)
7	Indonesia	10.0 million (8.7-10.9)	7	Egypt	15.1 million (7.3-17.3)
8	Egypt	7.8 million (3.8-9.0)	8	Pakistan	14.4 million (10.6-20.4)
9	Japan	7.2 million (6.1-9.6)	9	Bangladesh	13.6 million (10.7-24.6)
10	Bangladesh	7.1 million (5.3-12.0)	10	Russian Federation	12.4 million (6.4-17.1)

(IDF Diabetes Atlas, 2015)

Incidence and Prevalence in Egypt

The incidence of type 1 diabetes mellitus (T1DM) is increasing in all population at a rate of approximately 3% per year and the onset of the condition is occurring at younger age. Its incidence varies dramatically between populations and even within the same population, much of this variation is due to genetic defect. 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 varies between 1/100 000 per year (Pakistan) and 8/100 000 per year (Egypt) in children under the age of 15 years ***(Soltèsz et al., 2006).***

An Egyptian study of incidence and prevalence of T1DM in children and adolescents in four Egyptian Governorates (Fayoum, Minofeya, North Sainai and Sues) was held by ***Salem et al. (2007)***, showing a prevalence rate of 0.7/1000 and an incidence rate of 4.01/100.000.

Classification

The American diabetes association (ADA) classification of DM encompasses 4 groups: Type 1, Type 2, other specific types of diabetes, and gestational diabetes. Type 1 DM is further subclassified into Type 1A which is associated with the presence of islet cell autoantibodies, and Type 1B characterized by the absence of such antibodies ***(Sperling, 2002; Devendra et al., 2004)***. A classification of diabetes is presented in Table 2.

Table (2): Etiological classification of diabetes mellitus

I. Type I-DM: (B-cell destruction, usually leading to absolute insulin deficiency) A. Immune mediated. B. Idiopathic.	**II. Type II-DM:** (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. MODY3 (Chromosome 12, HNF1α) 2. MODY1 (Chromosome 20 HNF4α) 3. MODY2 (Chromosome7glucokinase) 4. Other very rare forms of MODY (e.g. MODY4: Chromosome 13, insulin Promoter factor-1, MODY6: Chromosome9, carboxyl ester lipase) 5. Transient neonatal diabetes 6. Permanent neonatal diabetes 7. Mitochondrial DNA 8. Others	**B. Genetic defect in insulin action** 1.Type A insulin resistance 2.Leprechaunism 3.Rabson-Mendenhall syndrome 4.Others
B. Diseases of exocrine pancreas 1.Pancreatitis 2.Truama/ pancreatectomy 3.Neoplasia 4.Cystic fibrosis 5.Haemochromatosis 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. Drugs or chemical- induced 1.Vacor 2.Pentamidine 3.Nictotinic acid 4.Glucocorticoids 5.Thyroid hormone 6.Diazoxide 7.B-adrenegic agonist 8.Thiazides 9.Dilantin 10.γ-interferon 11.Others	**F. Infections** 1.Congenital rubella 2.cytomegalo virus 3.Others
G. Uncommon forms of immune-mediated Diabetes 1."Stiff-man" syndrome 2.Anti-insulin receptor antibodies 4.Others	**H. Other genetic syndromes sometimes Associated with diabetes** 1.Down syndrome 2.Klinfelter syndrome 3.Turner syndrome 4.Wolfram syndrome 5.Friedreich's ataxia 6.Huntington's chorea 7.Laurence-Moon-Biedle syndrome 8.Myotonic dystrophy 9.Porphyria 10.Prader-Willi syndrome 11.Others
IV. Gestational diabetes.	

(ISPAD, 2014)

MODY: Maturity onset diabetes of the young, **HNF-4α:** Hepatocyte Nuclear Factor, **NeuroD1:** Neurogenic differentiation.

Although the vast majority of children and young people with diabetes in the UK have type 1 diabetes, an increasing number are diagnosed with type 2 diabetes, recently reported at around 2% ***(Shepherd and Cropper, 2013).*** Other causes of childhood diabetes include neonatal diabetes, maturity-onset diabetes of the young (MODY), secondary diabetes and syndromic diabetes ***(Royal College of Pediatrics and Child Health, 2009).*** However, the correct classification of pediatric diabetes can be challenging (table 4); there may be confusion between the presenting features of different types of diabetes, which can lead to erroneous diagnosis ***(Ehtisham et al., 2004).***

Monogenic diabetes results from mutations in single genes that regulate beta-cell function, but is commonly misdiagnosed as type 1 or type 2 diabetes ***(Lambert et al., 2003; Shepherd, 2008)***, and only a minority of estimated cases have been confirmed by genetic testing in the UK ***(Shields et al., 2010).*** Individuals with monogenic diabetes do not need to be insulin resistent or obese to develop diabetes ***(Ehtisham et al., 2004).***

Guidelines have been developed to highlight when a diagnosis of monogenic diabetes should be considered in children (table 3) and when to suspect that a diagnosis of type 1 or type 2 diabetes is not correct ***(Hattersley et al., 2006).*** The approaches are separated into:

Those diagnosed less than 6 months of age (indicating neonatal diabetes).

Those who may otherwise have been labeled as having type 1 diabetes (a child with diabetes has an affected parent and evidence of endogenous insulin production outside the honeymoon period).

Those who may otherwise have been labeled as having type 2 diabetes that are not markedly obese, do not have acanthosis nigricans or other evidence of insulin resistance and are from a low-prevalence ethnic group ***(Hattersley et al., 2006).***

These guidelines should be used in the clinical setting to identify cases of atypical type 1 diabetes or type 2 diabetes, which warrant further investigation.

Table (3): Criteria to consider monogenic diabetes in children

When to consider monogenic diabetes in children
Diabetes diagnosed below the age of 6 months (neonatal diabetes)
Family history of diabetes with an affected parent
Mild fasting hyperglycemia (5.2-8 mmol/L), especially if young or familial
Diabetes associated with extra-pancreatic features

(Hattersley et al., 2006)

Table (4): Characteristic Phenotypes of the commonly encountered diabetes subtypes, illustrating the clinically useful differences between type 1 and type 2 diabetes, and monogenic forms of diabetes

Features associated with diabetes	Type 1 diabetes	Young onset Type 2 diabetes	Monogenic diabetes					
			GCK*	HNF1A#	HNF4A#	HNF1B#	Neonatal diabetes	MIDD≠
DKA	Yes	No	No	No ∞	No ∞	No	Yes	Yes/No
Parent affected	2%-4%	Yes	Yes	Yes	Yes	Yes	Variable	Mother
Age of onset	6 months to adulthood	Adolescence and young adulthood	Birth	Teens to young adulthood	Teens to young adulthood	Teens to young adulthood	< 6 months	Young adulthood
Obesity	Population frequency	Increased Frequency	Population frequency	Population frequency	Population frequency	Population frequency	Population frequency	Rare
Glycaemic pattern	Acute General hyperglycemia	Progressive hyperglycemia	Stable, mild fasting glycemia	Post-prandial, 12nitially progressing to general hyperglycemia	Post-prandial, 12nitially progressing to general hyperglycemia	Post-prandial, 12nitially progressing to general hyperglycemia	Acute General hyperglycemia	Variable dysglycaemic pattern either acute or slowly progressive
B cell antibodies±	Yes	**No**	**No**	**No**	No	No	No	No
C-peptide¥	**Very low/Absent (< 5 years)**	**Raised/ Normal**	**Normal**	**Low but detectable**	**Low but detectable**	**Low but detectable**	Absent but detectable once treated with SU	**Low but detectable**
hsCRP	Normal	**High/ High normal**	Normal	**Very low**	Normal	Normal	Normal	Normal
Additional clinical features	**Other autoimmune disease (Thyroid, celiac, etc.**	**Dyslipidaemia, PCOS, Hypertension, Acanthosis nigricans**	**Absence of microvascular and macrovascular complications**	**Low renal threshold for glucose in early stages of diabetes**	Macrosomia and transient neonatal hypoglycemia	High renal involvement e.g., cysts, etc,	Transient in 50% of cases although may relapse	Deafness, short stature, macular dystrophy

(Carroll & Murphy, 2013)

*= Glucokinase, #= Hepatocyte nuclear factor, ≠ = Mitochondrial diabetes and deafness, ∞= Excellent responses to sulfonylurea therapy are commonly noted

Type 1 Diabetes Mellitus

Type 1 diabetes is a disorder that arises following the autoimmune destruction of insulin-producing pancreatic Beta cells ***(Atkinson, 2001; Bluestone et al., 2010)***. The disease is most often diagnosed in children and adolescents, usually presenting with a classic trio of symptoms (i.e., polydypsia, polyphagia, polyuria) alongside of overt hyperglycemia, positing the immediate need for exogenous insulin replacement-a medicinal introduction to the disorder whose therapeutic practice lasts a lifetime ***(Thunandera et al., 2008).***

Classification of type 1 diabetes

Type 1 diabetes may be subdivided in three groups from the etiological point of view: autoimmune, idiopathic and double. The autoimmune group is represented by: type 1A, which is polygenic and it is the most frequent type of this disease, corresponding to approximately 80-90% of all T1DM cases ***(Daneman, 2006).***

The other subtype of this group is the latent autoimmune diabetes in adults (LADA) ***(Fourlanos et al., 2006)***, which appears after the age of 35 and is frequently associated with other autoimmune endocrine diseases.

The third subtype includes called "monogenic" T1DM. They correspond to T1DM of the autoimmune polyglandular syndrome type 1A ***(Su and Anderson, 2004)*** and of IPEX

syndrome (Immune Dysfunction, Polyendocrinopathy, Enteropathy, X-linked) ***(Wildin and Freitas, 2005)***.

Type 1B, also called idiopathic, has all the clinical features of type 1A, but the autoimmune component is not detected ***(American Diabetes association, 2008).*** Another 1B subtype is the fulminant diabetes most described in Asian peoples, mainly Japan, China and Korea, characterized by a short clinical history, before to the first acute metabolic decompensation, presents the impairment of beta and alpha cells of the pancreatic islet and no autoimmune etiology ***(Imagawa et al., 2000)***.

Finally, the denomination of mixed, 1.5 or double (type 1 plus type 2) diabetes has been proposed when we have the type 1A (autoimmunity) plus type 2 (obesity, insulin resistance, dyslipidemia) diabetes characteristics in the same individual ***(Libman and Becker, 2003).***

Etiology of type 1 diabetes

The etiology of type 1 diabetes remains poorly understood, but it is likely that an environmental factor triggers an autoimmune process in a predisposed individual (figure 1). Although the genetic susceptibility to type 1 diabetes is inherited, only 12–15% of type 1 diabetes occurs in families. Twin studies have shown that the concordance rate for type 1 diabetes in monozygotic twins is around 20–30% ***(Holt, 2004).***

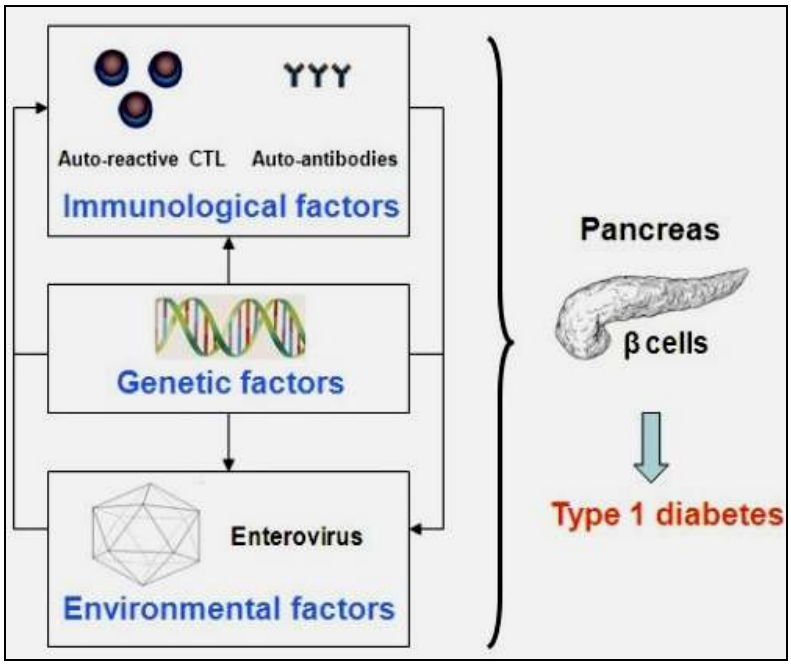

Figure (1): Types 1 diabetes and environmental factors. Type 1 diabetes is the result of interactions between immunological, genetic, and environmental factors, especially viruses mainly represented by enteroviruses ***(www.discoverymedicine.com /enteroviral pathogenesis-of-type-1-diabetes).***

Studies indicate that genetic factors do not account entirely for the development of type 1 diabetes, and several environmental triggers, including viral infections, nutritional factors, parental age and low birth weight, have been implicated ***(Akerblom et al., 2002).***

1. Genetics of type 1 diabetes

Despite being strongly influenced by genetic factors, type 1 DM does not fit any simple pattern of inheritance and is considered a complex, multifactorial disease ***(Noble and***