INTRODUCTION

Diabetic nephropathy is one of the commonest and most important microvascular complications in all types of diabetes especially type 1. It is associated with high incidence of morbidity up to end stage renal disease (ESRD) and also high mortality rate if left without proper management ***(Tesch, 2010).***

Diabetic nephropathy is classically defined by the presence of proteinuria, in the absence of other renal disease. It is a common problem that is most likely to occur in patients who have poor glycemic control, hypertension, glomerular hyperfiltration, or a genetic predisposition. The lifetime risk of nephropathy is estimated to be equivalent in type 1 and type 2 diabetes (***Ritz and Orth, 2011)***.

With early intervention and treatment, progression of this complication can be stopped to save a lot of patients. So, finding an ideal predictor for early detection of diabetic renal affection is a goal of many studies ***(ADA, 2017).***

Since long time it was proved that microalbuminuria (MA) is the only approved early marker of diabetic nephropathy. Microalbuminuria precedes the development of macroalbuminuria and is a predictive of future nephropathy ***(de Boer et al., 2011).***

However, MA is affected by many other factors such as exercise and urinary tract infection. Also, MA which results

from glomerular renal affection may be preceded by the earlier tubular affection. So, there is a strong need of finding a new earlier marker for diabetic nephropathy ***(ISPAD, 2009).***

Cystatin C a cystatin protease inhibitor is a novel biomarker of renal damage. One study from Zucker Diabetic fattu (ZDF) rats indicated that urinary Cystatin C was increased in ZDF rats where renal damage was not observed by histopathological assessment, and its levels in urine increased with the progression of renal damage, demonstrating the usefulness of early detection and accurate assessment of diabetic kidney damage in animals ***(Togashi and Miyarnoto ., 2012).***

Some studies pointed out that urinary Cystatin C is considered a good marker of kidney function as it is filtered solely by the glomerulus, is not handled by the renal tubules, and is generated at a constant rate by all cells in the body ***(Bashier et al., 2015).***

Two meta-analysis concerning study of serum Cystatin C concluded that it is superior to serum creatinine as a marker of kidney function ***(Dharnidharka et al., 2002; Roos et al., 2007).***

Cystatin C may detect mild to moderate decreases in GFR that are not evident with serum creatinine based measurements ***(Jerums et al., 2008).***

AIM OF THE WORK

The aim of the present study was to assess urinary Cystatin C in type 1 diabetic children and to evaluate it as an early marker of type 1 diabetic nephropathy and its relation to the diabetes control.

Chapter I

DIABETES MELLITUS

Diabetes mellitus is a common group of metabolic disorders that share the phenotype of hyperglycemia resulting from diminished and / or ineffective insulin action. The metabolic dysregulation associated with diabetes leads to secondary pathophysiological changes in multiple organs and systems which result in different complications. The disease needs continuous medical care and ongoing patient self management, education and support to prevent morbidities and mortalities from its complications ***(Gupta et al., 2016).***

Diabetes mellitus is a chronic illness with interrupted metabolic, vascular and neuropathic components. The chronic hyperglycemia is associated with long term dysfunction and failure of different organs especially the kidneys, eyes, nerves, heart and blood vessels ***(Expert Committee of the Diagnosis and Classification of DM, 2002 and ADA, 2013).***

Etiologic Classification:

It has been centuries since diabetes mellitus (DM) was recognized. The initial observation that diabetes is a syndrome and not a single disorder was made by two Indian physicians. In the 20th century the screening programs for DM commenced, it became apparent that the term DM covers a wide spectrum of disease, the different types of diabetes are shown in the following table: ***(ADA, 2013)***

Table (1): Etiologic classification of diabetes mellitus

I. Type 1 diabetes (B-cell destruction 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 secretary defect with insulin resistance)	
III. Other specific types	
A. Genetic defects of B-cell function 1.Chromosome 12, HNF-1a (MODY3) 2.Chromosome 7, glucokinase (MODY2) 3. Chromosome 20, HNF-4a (MODY1) 4.Chromosome 13, insulin promoter factor- (IPF-1;MODY4) 5.Chromosome 17, HNF-1B-(MODY5) 6.Chromosome 2, NeuroD1 (MODY6) 7.Mitochondrial DNA mutation 8.Chromosome 7, KCNJ11 (Kir6.2) 9. Others	**E. Drug- or chemical-induced** 1. Vacor 2. Pentamidine 3. Nicotinic acid 4. Glucocorticoids 5. Thyroid hormone 6. Diaz oxide 7. B-adrenergic agonists 8. Thiazides 9. Dilantin 10. Y-Interferon 11. Others
B. Genetic defects in insulin action 1. Type A insulin resistance 2. Leprechaunism 3. Rabson-Mendenhall syndrome 4. Lipoatrophic diabetes 5. Others	**F. Infections** 1. Congenital rubella 2. Cytomegalovirus 3. Others
C. Diseases of the exocrine pancreas 1. Pancreatitis 2. Trauma / pancreatectomy 3. Neoplasia 4. Cystic fibrosis 5. Haemochromatosis 6. Fibrocalculous pancreatopathy 7. Others	**G. Uncommon forms of immune-mediated diabetes** 1."Stiff-man" syndrome 2. Anti-insulin receptor antibodies 3. Others – polyendocrine autoimmune Deficiencies APS I and II
D. Endocrinopathies 1. Acromegaly 2. Cushing syndrome 3. Glucagonoma 4. Phaeochromocytoma 5. Hyperthyroidism 6. Somatostatinoma 7. Aldosteronoma 8. Others	**H. Other genetic syndromes sometimes associated with diabetes** 1. Down's syndrome 2.Klinefelter's syndrome 3. Turner's syndrome 4. Wolfram's syndrome 5. Friedreich's ataxia 6. Huntington's chorea 7. Laurence-Moon-Biedl syndrome 8. Myotonic dystrophy 9. Porphyria 10. Prader- Willi syndrome 11. Others
IV. Gestational diabetes	

(Modified From ADA and WHO, 2013)

An exciting point to be considered in classifying the patients is that some patients cannot be clearly diagnosed as having type 1 or type 2 diabetes. Clinical presentation and disease progression vary considerably in both types of diabetes. Occasionally, patients with type 1 may have a late onset and slow progression of disease despite having features of autoimmune disease, similarly patients who otherwise have type2 diabetes may present with ketoacidosis. Such difficulties in diagnosis may occur in different age groups. The true diagnosis becomes clear over time ***(ADA, 2013).***

The differentiation between different types of diabetes is crucial for both therapeutic and educational aspects. Characteristics of the main types of diabetes are listed in the following table (Table 2)

Table (2): Characteristic features of youth onset type 1 diabetes in comparison with type2 diabetes and monogenic diabetes:

Characteristic	Type 1	Type 2	Monogenic
Genetics	**Polygenic**	**Polygenic**	**Monogenic**
Age of onset	6 months to young adulthood	Usually pubertal (or later)	Often post pubertal except glucokinase and neonatal diabetes.
Clinical presentation	Most often acute, rapid	Variable; from slow; mild (often insidious) to severe.	Variable (may be incidental in glucokinase).
Associations	Yes	No	No
Ketosis	Common	Uncommon	Common in neonatal diabetes rare in other forms
Obesity	Population frequency	Increased frequency	Population frequency
Acanthosis nigricans	No	Yes	No
Frequency % of all diabetes in young people	Usually 90%+	Most countries <10% /Japan 60-80%)	71.3%
Parent with diabetes	2-4%	80%	90%

(Criag et al., 2009)

Type1 Diabetes mellitus

Diabetes mellitus is considered as the most common endocrinal and metabolic disease in children, which affects mainly children and adolescents below 30 years of age.

However, it can also develop in adults as late autoimmune diabetes of adulthood (LADA) which often initially appears to be type 2 DM ***(Kishore, 2013).***

It comprises 5% - 15% of all diabetics all over the world. Increased incidence and earlier onset of type 1 DM have been realized in the last few years and this increases the burden on young patients, their families and society by increasing early occurrence of complications such as blindness, kidney and cardiac disease as well as medical costs ***(Angeli et al., 2010).***

Incidence and prevalence of DM.

The International Diabetes Federation (IDF) estimated that in year 2013, the five countries with the largest numbers of people with diabetes were China, India, the United States of America, Russia and Brazil. The IDF also reported that in 2013 the five countries with the highest diabetes prevalence in the adult population were Kiribati, Marshall Islands, Kuwait, Nauru and Lebanon ***(IDF, 2013).***

Low and middle income countries face the greatest burden of diabetes ***(IDF, 2013)***.

There are approximately 500000 children below 15 years age with type1 diabetes in the world ***(Patterson et al., 2014)***.

Type 1 and Type 2:

For adults, we estimate that:

- Ten percent of people with diabetes have type1 diabetes.
- Ninety percent people with diabetes have type 2.
- If we include children, we estimate that:
- Fifteen percent of people with diabetes have type 1
- Eighty five percent of people with diabetes have type 2

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

Three hundred seventy eight million people have diabetes; by 2035 this will rise to **592 million.**

The number of people with type 2 **diabetes is increasing** in every country.

Eighty% of people with diabetes live in **low- and middle-income countries**.

The **greatest numbers** of people with diabetes are between **40 and 59** years of age.

One hundred seventy five million people with diabetes are **undiagnosed**.

Diabetes caused **4.9 million deaths** in 2014; every seven seconds a person dies from diabetes.

Diabetes caused at least **612 billion dollars** in health expenditure in 2014 – **11% of total spending** on adults.

More than **79,000 children** developed **type 1 diabetes** in 2013.

More than **21 million live births** were affected by diabetes during pregnancy in 2013. ***(IDF Diabetes Atlas, 2014)***

The IDF Diabetes Atlas, 2014 revealed the prevalence of diabetes in different countries of the world as shown in the following figure:

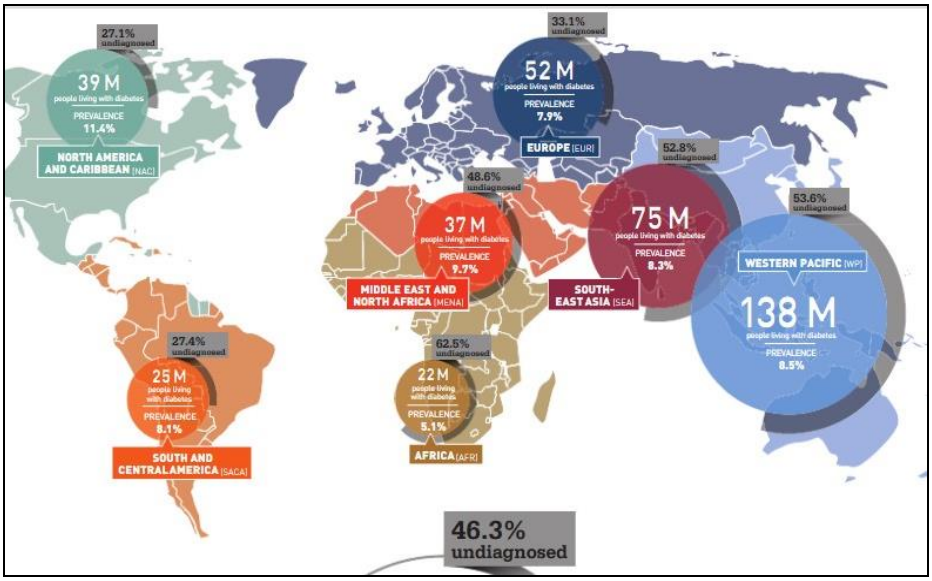

Fig. (1): Global diabetes prevalence ***(IDF Diabetes Atlas, 2014).***

Also, the following table reveals the top 10 countries in the number ofdiabetic patients in the world according to ***IDF (2013)***

Table (3): Top 10 countries/ territories for number of people with diabetes (20-79 years), 2013 and 2035

Country / territory	2013 Millions	Country / territory	2035 Millions
China	98.4	China	142.7
India	65.1	India	109.0
United States of America	24.4	United States of America	29.7
Brazil	11.9	Brazil	19.2
Russian Federation	110.9	Mexico	15.7
Mexico	8.7	Indonesia	14.1
Indonesia	8.5	Egypt	13.1
Germany	7.6	Pakistan	12.8
Egypt	7.5	Turkey	11.8
Japan	7.2	Russian Federation	11.2

(IDF Diabetes Atlas, 2013)

Clinical Diagnosis of Diabetes Mellitus

1- History:

The symptoms of diabetes may be noticed up to months before the diagnosis. Presentation of diabetes differs widely among patients.

It ranges from silent presentation with mild polyuria and polydypsia especially in type 2 diabetic patients or classic symptoms of presentation (polyuria, polydypsia, loss of weight)

or other symptoms as polyphagia or resistant infections up to acute life threatening diabetic coma either ketoacidotic in type 1 DM or non ketotic hypersomolar in type2 which is more severe and may cause rapid death with delay of treatment ***(ADA, 2013).***

So symptoms and signs of type 1 diabetes are summarized as: -

- ***Symptoms of hyperglycemia:***

Polyuria, nocturnal enuresis, polydypsia, dehydration, drowsiness and blurred vision.

- ***Symptoms of insulinemia (lack of insulin):***

Hyperglycemia with marked glucosuria, weight loss, easy fatigability, muscle wasting, ketosis and ketoacidosis.

- ***Symptoms of caloric defeciencies:***

Weight loss inspite of increased apetite (Polyphagia)

- ***Symptoms of immune system affection:***

Increased susceptibility and vaginal, genital and skin resistant infection.

The most common of the forementioned manifestations are:

- Polyuria
- Polydypsia

} Most Common

- Loss of weight
- Polyphagia or anorexia
- Lethargy and easy fatigue
- Increased susceptibility to infection such as oral and vaginal candidiasis.
- Diabetic ketoacidosis (vomiting and abdominal pain).
- Hypoglycemic attacks (rare may be due to insulin improper secretion in early stage of diabetes).

(ADA, 2013)

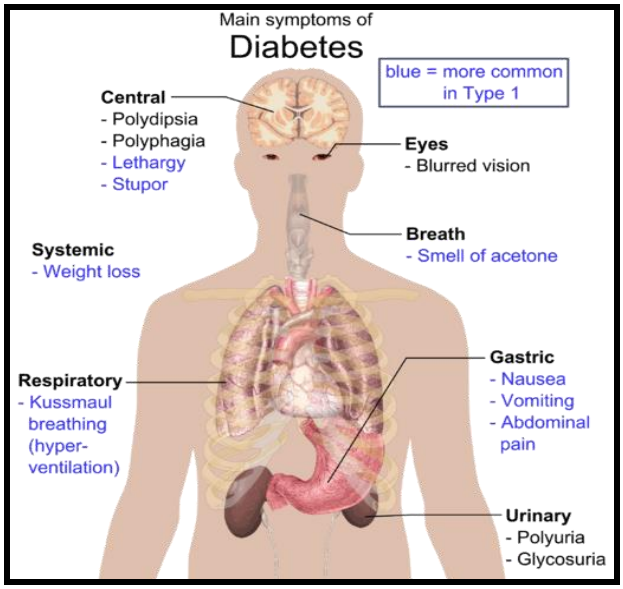

Fig. (2): Common symptoms of DM ***(ADA, 2013).***

2- Examination:

At diagnosis, approximately 75% of the patients will not have DKA, and may only have evidence of weight loss, or possibly, candida skin infection. At diagnosis most patients have ketonuria but the presence of an abnormally low pH is suggestive of DKA ***(Kitabchi and Razari, 2012).***

If the child is presenting with the signs and symptoms of DKA it will be managed as described later in the part of acute complications ***(ADA, 2007)***.

At diagnosis it is advisable to perform the following investigations: Plasma glucose concentration (interpretation of the results are shown in table 3), venous blood gas measurement, serum electrolytes, urea and creatinine concentrations, and Full blood count It's important to know that leukocytosis is common in DKA and does not necessary mean that an infection is present ***(Raghavan and Griffing, 2013).***

A few children will have signs of sepsis and need appropriate investigations (e.g. blood culture, chest radiograph, urine microscopy and culture)**.** The National Diabetes Data Group and World Health Organization "WHO" have implemented diagnostic criteria for DM.

These criteria which encourage the use of fasting blood glucose HbA1C or glucose Tolerance Test for diagnosis are enlisted in the following table. But it is important to focus on

the American Diabetes Association's definition of normal FBG blood glucose as less than 100 mg% and the persons with FBG values between this normal value and the diabetic level (126 mg%) are classified as prediabetics (Formerly named impaired glucose tolerance (IGT) ***(ADA, 2017).***

Table (4): Criteria for the diagnosis of diabetes.

▪ Symptoms of diabetes and a random plasma glucose ≥ 200 mg/dl (11.1mmol/l). Random is defined as any time of day regard less time that passed since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
OR
▪ FPG ≥ 126 mg/dl (7.0mmol/l). Fasting is defined as stopping caloric intake for at least 8 h.
OR
▪ 2-h plasma glucose ≥ 200 mg/dl (11.1mmol/l) during an oral glucose tolerance test OGTT. The test must be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water or 1.75 g/kg body wt. if weight is < 40 pounds (18 kg). **OR** ▪ $HbA_1c \geq 6.5\%$ in two tests.

(ADA, 2017)

These persons who are considered prediabetics are those who have glycated hemoglobin between 5.6: 6.5 or impaired fasting glucose (IFG) 100: 125 mg/dl (5.6 – 6.9 mmol/L) or impaired glucose tolerance (IGT) (2h values in OGTT between 140:199 mg/dl (7.8:11 mmol/L).