Introduction

Type 2 diabetes is typically a chronic disease, associated with a ten years shorter life expectancy. This is partly due to a number of complications with which it is associated including: two to four times the risk of cardiovascular disease and stroke, a 20 fold increase in lower limb amputations, and increased rates of hospitalizations ***(Ripsin et al., 2009).***

In the developed world, and increasingly elsewhere, type 2 diabetes is the largest cause of non-traumatic blindness and kidney failure. It has been associated with an increased risk of cognitive dysfunction and dementia through disease processes such as Alzheimer's disease and vascular dementia ***(Pasquier, 2010).***

Since the 1950s, kidney disease has been clearly recognized as a common complication of diabetes mellitus (DM), with as many as 50% of patients with DM of more than 20 years' duration having this complication ***(Rosolowsky et al., 2011).***

Diabetic nephropathy (*nephropatiadiabetica*), also known as Kimmelstiel-Wilson syndrome, or nodular diabetic glomerulosclerosis and intercapillary glomerulonephritis, is a progressive kidney disease caused by angiopathy of capillaries in the kidney glomeruli, and is a prime indication for dialysis in many Western countries ***(Yusuf et al., 2008).***

Fatty acid-binding protein 1 (FABP1) also known as liver-type fatty acid-binding protein (L-FABP) is a protein that in humans is encoded by the FABP1 gene. Fatty acid binding proteins are a family of small, highly conserved, cytoplasmic proteins that bind long-chain fatty acids and other hydrophobic ligands. FABP1 and FABP6 (the ileal fatty acid binding protein) are also able to bind bile acids. It is thought that FABPs roles include fatty acid uptake, transport, and metabolism ***(Weickert et al., 2007).***

FABPs may also have a role in the reduction of cellular oxidative stress. The putative antioxidant properties of FABPs have stimulated interest in these proteins as potential tissue-specific markers of injury. Liver-type FABP (L-FABP) was initially identified in hepatocytes and later found to be expressed in the human renal proximal tubule epithelium. Urinary L-FABP levels may reflect the stress induced by FFA to the proximal tubules, leading to severe tubulointerstitial damage to investigate the associations of urinary free fatty acid (FFA) levels with tubulointerstitial damage, and to determine the clinical significance of urinary liver-type fatty acid binding protein (L-FABP) in diabetic nephropathy ***(Kamijo-lkemoi et al., 2011).***

Aim of the Work

To evaluate the relationship between urinary L-FABP and the severity of Diabetic nephropathy in type 2 DM.

Chapter (1): Diabetes Mellitus

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs especially the eyes, kidneys, nerves, heart and blood vessels. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat and protein metabolism in diabetes is deficient action of insulin on target tissues ***(American Diabetes Association, 2013).***

This hyperglycemia produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger) ***(Smyth and Heron, 2006).***

Diabetes is a chronic illness that requires continuing medical care and ongoing patient self management education and support to prevent acute complications and to reduce the risk of long-term complications ***(American Diabetes Association, 2010).***

Epidemiology of diabetes mellitus:

Diabetes mellitus remains one of the most challenging diseases for workers in the medical field. Its prevalence in adults worldwide was estimated to be 221 million in 2007 and it's expected to rise to reach 380 million by the year 2025. In 2007, 308 million people had impaired glucose tolerance (IGT), by 2025 this number will increase to 418 million. According to WHO, 130 million individual in China and India will have diabetes by 2025. These individuals are expected to consume about 40% of their country's health care budget, and may also reduce productivity and hinder economic growth. Type 1 DM makes up about 5% of diabetic cases. It is a condition of absolute insulin deficiency that results from B cell destruction. Type 2 makes up about 90% of the cases ***(William and Robert, 2014).***

Table (1): Countries with the Greatest Increase in the Number of Patients with Diabetes, 2011-2030.

Rank	Country	2011		2030		2030 minus 2011	
		T2D population*	Prevalence	T2D population*	Prevalence	Δ in T2D population*	Δ inT2D Prevalence
1	India	61.3	8.3%	101.2	9.9%	39.9	1.6%
2	China	90.0	9.3%	129.7	12.1%	39.7	2.8%
3	Bangladesh	8.4	9.6%	16.8	13.3%	8.4	3.7%
4	Brazil	12.4	9.7%	19.6	12.3%	7.2	2.6%
5	Mexico	10.3	14.8%	16.4	17.6%	6.1	2.8%
6	USA	23.7	10.9%	29.6	11.8%	5.9	0.9%
7	Pakistan	6.3	6.7%	11.4	7.8%	5.1	1.0%
8	Egypt	7.3	15.2%	12.4	17.8%	5.1	2.7%
9	Indonesia	7.3	4.7%	11.8	5.9%	4.5	1.2%
10	Iran	4.7	9.3%	8.4	13.1%	3.7	3.8%

* In millions

(International Diabetes Federation, 2012).

Total prevalence of diabetes

Under 20 years of age: 215,000, or 0.26% of all people in this age group have diabetes. About 1 in every 400 children and adolescents has diabetes. Age 20 years or older: 25.6 million, or 11.3% of all people in this age group have diabetes. Age 65 years or older: 10.9 million, or 26.9% of all people in this age group have diabetes.

Men: 13.0 million, or 11.8% of all men aged 20 years or older have diabetes. Women: 12.6 million, or 10.8% of all women aged 20 years or older have diabetes ***(Zinman et al., 2014).***

Race and ethnic differences in prevalence of diagnosed diabetes:

After national survey data for people diagnosed with diabetes, aged 20 years or older include the following prevalence by race/ethnicity: 7.1% of non-Hispanic whites. 8.4% of Asian Americans. 12.6% of non-Hispanic blacks. 11.8% of Hispanics. Among Hispanics rates were: 7.6% for Cubans. 13.3% for Mexican Americans. 13.8% for Puerto Ricans ***(Nathan, 2014).***

Morbidity and Mortality:

Diabetes was listed as the underlying cause on 71,382 death certificates and was listed as a contributing factor on an additional 160,022 death certificates. This means that diabetes contributed to a total of 231,404 deaths.

Complications: Heart disease and stroke: Heart disease was noted on 68% of diabetes-related death certificates among people aged 65 years or older. Stroke was noted on 16% of diabetes-related death certificates among people aged 65 years or older. Adults aged 20 years or older with self-reported diabetes, 67% had blood pressure greater than or equal to 140/90 mmHg or used prescription medications for hypertension. Blindness: Diabetes is the leading cause of new cases of blindness among adults aged 20–74 years. Diabetes is the leading cause of kidney failure, accounting for 44% of new cases: About 60% to 70% of people with diabetes have mild to severe forms of nervous system damage. Amputation: More than 60% of nontraumatic lower-limb amputations occur in people with diabetes. Total costs of diagnosed diabetes in the United States in 2013. $176 billion for direct medical costs. $69 billion in reduced productivity ***(Gubitosi-Klug, 2014).***

Classification of Diabetes Mellitus:

Improved understanding of the origin and pathogenesis of diabetes has made it possible to revise the classification of diabetes mellitus. This revision contrasts with the previous classification, which was based mainly on therapeutic requirements: insulin-dependent diabetes (IDDM) and non-insulin-dependent diabetes (NIDDM), terms that have been eliminated. Any patient with diabetes may require insulin therapy at some stage of the disease,

irrespective of the classification. So the recent classification of diabetes depends on the etiology not the pharmacological treatments of the attained types ***(Philip et al., 2006).***

Diabetes mellitus is classified into four broad categories: type 1, type 2, gestational diabetes and "other specific types" ***(Vinay et al., 2005).*** The term "type 1 diabetes" has replaced several former terms, including childhood-onset diabetes, juvenile diabetes, and insulin-dependent diabetes mellitus (IDDM). Likewise, the term "type 2 diabetes" has replaced several former terms, including adult-onset mellitus (NIDDM) ***(Shoback et al., 2011).***

Etiologic Classification of Diabetes Mellitus

I. **Type 1 diabetes** (beta 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 beta-cell function

- Chromosome 20, HNF-4alpha (MODY1)
- Chromosome 7, glucokinase (MODY2)
- Chromosome 12, HNF-1alpha (MODY3)
- Chromosome 13, IPF-1 (MODY4)

- Chromosome 17, HNF-1beta (MODY5)
- Chromosome 2, NeuroD1 (MODY6)
- Chromosome 2, KLF11 (MODY7)
- Chromosome 9, CEL (MODY8)
- Chromosome 7, PAX4 (MODY9)
- Chromosome 11, INS (MODY10)
- Chromosome 8, BLK (MODY11)
- Mitochondrial DNA
- Permanent neonatal diabetes
- Transient neonatal diabetes
- Others

B-Genetic defects in insulin action

- Leprechaunism
- Lipoatrophic diabetes
- Rabson-Mendenhall syndrome
- Type A insulin resistance
- Others

C-Diseases of the exocrine pancreas

- Cystic fibrosis
- Fibrocalculouspancreatopathy
- Hemochromatosis
- Neoplasia
- Pancreatitis
- Trauma/pancreatectomy
- Others

D-Endocrinopathies

- Acromegaly
- Aldosteronoma
- Cushing's syndrome
- Glucagonoma
- Hyperthyroidism
- Pheochromocytoma
- Somatostatinoma
- Others

E-Drug- or chemical-induced

- Alpha-interferon
- Atypical antipsychotics
- Beta-adrenergic agonists
- Diazoxide
- Dilantin
- Glucocorticoids
- Highly Active Antiretroviral Therapy (HAART)
- HMG CoA reductase inhibitors (statins)
- Nicotinic acid
- Pentamidine
- Thiazides
- Thyroid hormone
- Vacor (rodenticide)
- Others

F-Infections

- Congenital rubella
- Cytomegalovirus
- Coxsackie B.

- Mumps
- Adenovirus
- Others

G-Uncommon forms of immune-mediated diabetes

- Anti-insulin receptor antibodies
- "Stiff-man" syndrome
- Others

H- Other genetic syndromes sometimes associated with diabetes

- Down syndrome
- Friedreich ataxia
- Huntington chorea
- Klinefelter syndrome
- Laurence-Moon-Bardet-Biedl syndrome
- Myotonic dystrophy
- Porphyria
- Prader-Willi syndrome
- Turner syndrome
- Wolfram syndrome
- Others

IV. Gestational diabetes mellitus

(American Diabetes Association, 2012).

Diagnosis (Table 2,3)

Prediabetes is a condition when blood glucose is higher than normal but not high enough to be diabetes. This condition at risk for developing type 2 diabetes. Random (also called Casual) Plasma Glucose Test. This test is a blood check at any time of the day, when there are severe diabetes symptoms. Diabetes is diagnosed at: Blood glucose ≥200 mg/dl ***(American Diabetes Association, 2013).***

Diabetes is diagnosed at:

Table (2): Fasting plasma glucose test

Plasma Glucose Result (mg/dL)	Diagnosis
99 and below	Normal
100 to 125	Prediabetes (impaired fasting glucose)
126 and above	Diabetes*

* Confirmed by repeating the test on a different day

Table (3): Plasma A1C% test

Plasma A1C %	Diagnosis
5.6% and below	Normal
5.7% to 6.4%	Prediabetes (impaired fasting glucose)
6.5% and above	Diabetes*

(American Diabetes Association, 2013).

Table (4): Factors interfering with chromatographic measurement of glycohemoglobins ***(Selvin et al., 2010).***

Substances causing falsely high values:
Prehemoglobin A_{1C} (reversible aldimine intermediate)
Carbamoylated hemoglobin (uremia)
Hemoglobin F
Conditions causing falsely low values:
Hemoglobinopathies (hemoglobins C, D and S)
Reduced span of erythrocytes[1]
Hemorrhage or therapeutic phlebotomies
Hemolytic disorders

This causes falsely low values of *all* methods used to measure HbA_{1C}.

Pathogenesis of type 2 diabetes:

It was previously called (NIDDM) or adult-onset diabetes this form of diabetes accounts from 90-95% of those with diabetes. It is characterized by disorder of insulin action and insulin secretions either of which may be predominant feature ***(American Diabetes Association, 2009).***

Type 2 frequently goes undiagnosed for many years because the hyperglycemia develops gradually and at earlier stages is often not severe enough for the patient to notice any of the classic symptoms of diabetes. Ketoacidosis Seldom occurs spontaneously in this form of diabetes when seen it usually arises in association with the stress of another illness such as infection ***(Goldberg and Mather, 2012).***

Type 2 diabetes mellitus is characterized by insulin resistance (IR) in peripheral tissue and an insulin secretory defect of the beta cell. This is the most common form of diabetes mellitus and is highly associated with a family history of diabetes, older age, obesity and lack of exercise. It is more common in women, especially women with a history of gestational diabetes, and in blacks, Hispanics and Native Americans. Insulin resistance and hyperinsulinemia eventually lead to impaired glucose tolerance. Defective beta cells become exhausted, further fueling the cycle of glucose intolerance and hyperglycemia ***(Esposito et al., 2009).***

Persons with type 2 diabetes consistently demonstrate three cardinal abnormalities:

I. Defective insulin secretion, particularly in response to glucose stimulus (β-cell dysfunction).

II. Increased glucose production by the liver.

III. Resistance to the action of insulin in peripheral tissues, particularly muscle, fat and also the liver (Insulin resistance).

I- β-cell dysfunction:

β-cell dysfunction is the result of chronic exposure to hyperglycemia, chronic exposure to free fatty acid, from reduced insulin mediated inhibition of lipolysis, which elevates the levels of free fatty acids, further comprise β-cell sensitivity and function or both ***(Banting and Best, 2007).***

Insulin secretion and sensitivity are inter-related. In type 2 diabetes mellitus, insulin secretion initially increases in response to insulin resistance in order to maintain normal glucose tolerance. Initially, the insulin secretory defect is mild and selectively involves glucose-stimulated insulin secretion, but the response to other non glucose secretagogues, such as arginine, is preserved ***(Sattar et al., 2008).***

Amylin, a 37-amino acid polypeptide, has been identified as the major protein component of pancreatic amyloid deposits in patients with type 2 diabetes mellitus. Amylin is stored and released together with insulin and has been proposed to play a major role in the pathogenesis of type 2 diabetes mellitus. Islet amyloid deposition is a pathogenic feature of type 2 diabetes, and these deposits contain the unique amyloidogenic peptide islet amyloid polypeptide. Autopsy studies in humans have demonstrated that islet amyloid is associated with loss of β-cell mass. Furthermore, the extent of amyloid deposition is associated with both loss of β-cell mass and impairment in insulin secretion and glucose metabolism, suggestive role for islet amyloid in islet lesion of type 2 diabetes. Increase of islet amyloid deposition with increase formation and secretion from obesity and/or insulin resistance ***(Herder and Roden, 2011).***