INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disorder in carbohydrate, protein and lipids metabolism characterized by chronic hyperglycemia resulting from the deficiency in insulin secretion ***(Piero et al., 2015).*** This high blood sugar result in the symptoms of frequent urination, increased hunger, and increased thirst ***(Begum et al., 2014).***

There are 2 types of diabetes type 1 and type 2, usually type 1 occur with children and type 2 with adults, type 1 which is known as juvenile onset diabetes or insulin dependent diabetes mellitus is an autoimmune disorder that involves the destruction of the β cells by activated CD4+ and CD8+ T cells and macrophages infiltrating the pancreatic islets, While Type 2 DM is characterized by deficiency in the synthesis of insulin and its secretion, secondary to insulin resistance ***(Maraschin, 2013)***. The incidence of type 1 diabetes is increased in many countries and that challenges health systems because the disease is currently incurable and has no known way of prevention, This is worrying because type 1 diabetes increases mortality and morbidity population-wide ***(James et al., 2014).***

The chronic hyperglycemia of diabetes is accompanied with long-term damage, failure, and dysfunction of many organs, particularly the kidneys, nerves, eyes, blood, and heart. Promotion of vascular damage and oxidative stress occurs due to prolonged hyperglycemia and dyslipidemia which also

accelerates endothelial dysfunction which is associated with macro vascular and micro vascular complications.

The micro vascular complications of diabetes mellitus leads to substantial morbidity and impair quality of life of the patient ***(Brown, 2008).***

Glucose overload may damage the cells through oxidative stress, clinical and experimental studies showed that oxidative stress plays a main role in the pathogenesis of type 1 and type 2 diabetes mellitus. Free radicals are formed excessively in diabetes by glucose oxidation, the subsequent oxidative degradation of glycated proteins and the non-enzymatic glycation of proteins ***(Rajendran et al., 2014).***

Carnosine (β-alanyl-L-histidine) which is a natural polypeptide found in skeletal muscle, cardiac muscle, and brain ***(Tan et al., 1998).*** Carnosine has antiglycating and antioxidant properties in addition to heavy metal sequestering and pH-buffering action which makes carnosine an important issue for preventing neurodegeneration and accumulation of aging features. Also, carnosine is recommended for patients under oxidative stress as an effective natural therapy that has no side effects ***(Boldyrev et al., 2010).***

Furthermore, carnosine has nephroprotective properties and has a role concerning kidney diseases and diabetic nephropathy ***(Prokopieva et al., 2016).***

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 ***(Piero et al., 2015).*** The symptoms for Type 1 DM include polyuria, polyphagia and polydipsia, weight loss, fatigue, and weakness. Additionally, patients with Type 2 DM could suffer from blurred vision, sluggish sores healing, irritability, tingling in hands or feet and recurrent infections of bladder, skin, and vagina ***(Kaul et al., 2013).*** Type 1 DM is an autoimmune disorder characterized by the destruction of insulin-producing pancreatic β-cells. Like many other immune-mediated diseases, Type 1 DM shows heterogeneity in relation to age of onset, severity of autoimmune response, and efficacy of therapy ***(Zaccardi et al., 2016).***

Global burden

Diabetes costs is considered high socially and economically on countries at all income levels, the annual increase in incidence has been reported to be approximately 3.0% worldwide ***(Helminen et al., 2015).***

Diabetes mellitus is the fifth leading cause of death in the world, accounting for 5.2% of all deaths ***(Domingueti et al., 2016).***

There are 320.5 million person within the age of (20-64 years) with diabetes and 94.2 million person within the age of 65-79 with diabetes by 2040 this will rise to 441.3 million within the age of (20-64 years) and 200.5 million person within the age of 65-79 (Table 1**)** ***(IDF Diabetes Atlas, 2015)***.

More than 80% of people with Type 2 DM live in low- and middle-income countries and their number increasing in every country. The majority of people with diabetes are among 40 and 59 years of age. 193 million diabetic are undiagnosed ***(IDF Diabetes Atlas, 2015)***.

Approximately 5.0 million people within the age of 20 and 79 years died from diabetes in 2015, which is equal to one death every six seconds. The probable number of children living with type 1 diabetes (542, 000) exceeds half a million ***(IDF Diabetes Atlas, 2015)***.

There is an increase in the incidence of type 1 diabetes between children in many countries, mainly in children below the age of 15 years ***(IDF Diabetes Atlas, 2015)***.

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

(IDF Diabetes Atlas, 2015)

Rank	Country/territory	2015 Number of people with diabetes
1	China	109.6 million (99.6-133.4)
2	India	69.2 million (56.2-84.8)
3	United States of America	29.3 million (27.6-30.9)
4	Brazil	14.3 million (12.9-15.8)
5	Russian Federation	12.1 million (6.2-17.0)
6	Mexico	11.5 million (6.2-13.7)
7	Indonesia	10.0 million (8.7-10.9)
8	Egypt	7.8 million (3.8-9.0)
9	Japan	7.2 million (6.1-9.6)
10	Bangladesh	7.1 million (5.3-12.0)

Rank	Country/territory	2040 Number of people with diabetes
1	China	150.7 million (138.0-179.4)
2	India	123.5 million (99.1-150.3)
3	United States of America	35.1 million (33.0-37.2)
4	Brazil	23.3 million (21.0-25.9)
5	Mexico	20.6 million (11.4-24.7)
6	Indonesia	16.2 million (14.3-17.7)
7	Egypt	15.1 million (7.3-17.3)
8	Pakistan	14.4 million (10.6-20.4)
9	Bangladesh	13.6 million (10.7-24.6)
10	Russian Federation	12.4 million (6.4-17.1)

Incidence and Prevalence in Egypt

Type1 DM incidence is growing in all population at a rate of nearly 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 ***(IDF Diabetes Atlas, 2015).***

The biggest contribution to the overall number of estimated childhood type 1DM cases comes from Egypt between Eastern Mediterranean and Middle Eastern countries which accounts for about a quarter of the region's total. The incidence fluctuates between 7/1000 in Egypt ***(IDF Diabetes Atlas, 2015).***

Table (2): Incidence of diabetes in Egypt ***(IDF Diabetes Atlas, 2015)***

Adult population (20-79) in 1000s	52, 587
Diabetes expenditure/person with diabetes	218.8
Diabetes cases (20-79) in 1000s	7, 809
Diabetes-related deaths (20-79)	78, 184
Diabetes prevalence in adults (%)	14.9
Number of people with undiagnosed diabetes (20-79) in 1000s	3, 217.8

Classification

The American diabetes association (ADA) grouping of DM includes 4 groups: Type 1, Type 2, other specific types of diabetes, and gestational diabetes. Type 1 DM is more sub classified into Type 1A which is accompanied by islet cell autoantibodies, and Type 1B which described by the absence of such antibodies. A classification of diabetes is presented in Table 3 ***(Maraschin, 2013)***.

Table (3): Etiological classification of diabetes mellitus

(Wolfsdorf et al., 2014; ISPAD, 2014)

A. I. Type 1DM: (B-cell destruction, usually leading to absolute insulin deficiency) Immune-mediated. Idiopathic.	II. Type 2 DM: (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance).
III. other specific types	
B. Genetic defects of β-cell function: 1. MODY3 (Chromosome 12, HNF1α) 2. MODY1 (Chromosome 20 HNF4α) 3.MODY2(Chromosome 7 glucokinase) 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	Genetic defect in insulin action 1.Type A insulin resistance 2.Leprechaunism 3.Rabson-Mendenhall syndrome 4.Others
C. Diseases of exocrine pancreas 1.Pancreatitis 2.Trauma/ pancreatectomy 3.Neoplasia 4.Cystic fibrosis 5.Haemochromatosis 6.Fibrocalculous pancreatopathy 7.Other	D. Endocrinopathies 1. Acromegaly 2.Cushing's syndrome 3. Glucagonoma 4. Pheochromocytoma 5. Hyperthyroidism 6.Somatostatinoma 7.Aldosteronoma 8.Others

Classification of type 1 diabetes

Type 1DM is subdivided by etiology into autoimmune, idiopathic. The autoimmune type is denoted by type 1A, which is polygenic and it is the most common form of the disease, approximately 80-90% of all Type 1 DM cases ***(Maraschin, 2013)***. The latent autoimmune diabetes in adults is the other subtype of this group is which is an autoimmune diabetes defined by adult-onset, occurrence of diabetes accompanied by autoantibodies, and no insulin therapy is required for a period after diagnosis ***(Laugesen et al., 2015).***

The third subtype includes called "monogenic" Type 1 DM which is produced due to unusual single-gene defect, Monogenic diabetes includes a broad spectrum of clinically and genetically greatly heterogeneous forms of non-autoimmune diabetes, which are mainly characterized by insulin deficiency and medium to extreme hyperglycemia early in life due to functional defects of pancreatic β-cells ***(Vaxillaire et al., 2016).***

Finally, mixed, double or 1.5 (type 1 plus type 2) diabetes is found when we have the type 1A (autoimmunity) and family history and type 2 (insulin resistance, obesity, dyslipidemia) diabetes characteristics in the same individual ***(Cleland et al., 2013).***

Pathogenesis of type 1 diabetes:

The hyperglycemia and the loss of functional β cell results from a combination of environmental and genetic factors. Together the innate and the adaptive immunity are implicated in the development of T1D ***(Tai et al., 2016)***. Many studies showed that T cells play an important in the autoimmune attack of β-cells. Anti-islet T cells, both CD4 and CD8 T cells, have been recognized in type 1 diabetic patients ***(Lehuen et al., 2010)***.

Phases of pathogenesis of type 1 DM (Figure 1)

The starting phase of type 1 diabetes occurs in the pancreas, where conventional dendritic cells (cDCs) release and process β-cell antigens. Natural apoptosis or a viral infection leads to β-cell damage. Plasmacytoid DCs (pDCs) and invariant natural killer T (iNKT) cells control viral replication, preventing consequent inflammation and type 1 DM. Activated cDCs leads to pathogenic islet antigen-specific T cells then it migrates to the draining lymph node, and macrophages stimulate this activation through the secretion of interleukin-12 (IL-12). β-cell antigen is presented to diabetogenic T cells and produce autoantibodies ***(Lehuen et al., 2010)***.

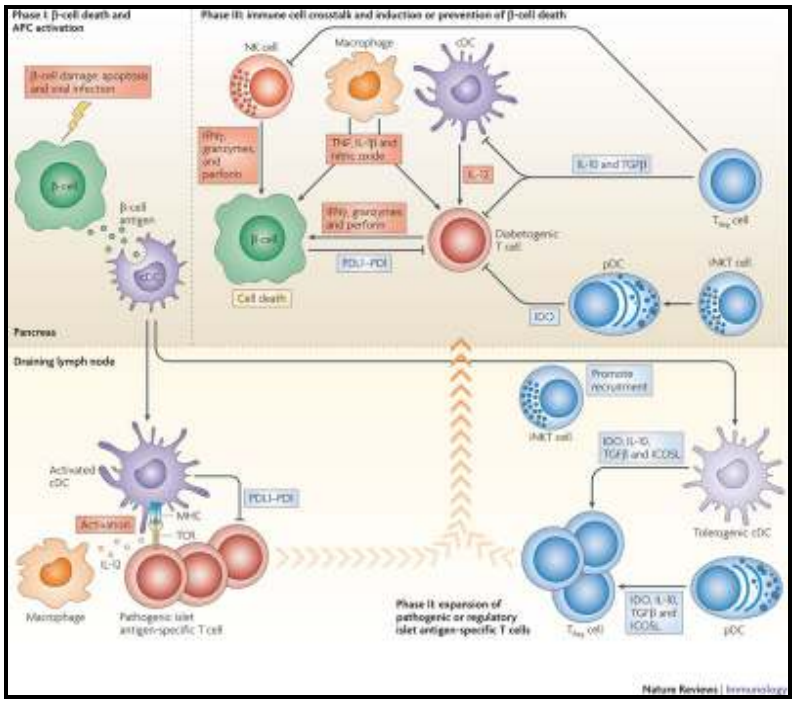

Figure (1): Cellular and molecular mechanisms in the development or prevention of type 1 diabetes ***(Lehuen et al., 2010).***

In the pancreas, β-cells that express MHC class I could be directly killed by CD8 T cells. CD4 T cells that distinguish peptides expressed by MHC class II molecules usually contribute in β-cell destruction directly by producing of IFN-γ and indirectly by the activation of local innate cells as dendritic cells and macrophages ***(Herold et al., 2013)***. Our recognition about the pathogenesis of type 1 diabetes comes from examination of patient's pancreatic specimens, peripheral-blood lymphocytes, and serum. Studies showed that defects in the immune system, thymus, bone marrow and β cells contribute to pathophysiology type 1 diabetes pathophysiology ***(Atkinson, 2014).***

Diagnosis of diabetes in childhood and adolescence

Early aggressive treatment and improvement in glycemic control of children and adolescents will postpone or prevent the onset and progression of microvascular complications (nephropathy, retinopathy, neuropathy) and macrovascular complications (coronary heart disease) ***(Donaghue et al., 2014)***.

Accurate diagnosis of this condition is critical for ideal care and to avoid complications, and the diagnosis of diabetic ketoacidosis of type 1 disease represents the clue for survival ***(Atkinson, 2014).*** Diabetic children present with signs and symptoms of lack of insulin and hyperglycemia (weight loss, polydipsia, polyuria, visual change, and raised glycosylated hemoglobin A1c levels) or more severe metabolic disorder such as ketoacidosis ***(Herold et al., 2013).***

The diagnosis is confirmed by blood glucose measurements in most patients without delay, and treatment is started immediately, usually as a life saving measure. An OGTT is neither essential nor appropriate for diagnosis in such conditions. OGTT may be required for diagnosis by a small number of children who present with less severe symptoms ***(Alberti et al., 1998)***.

Diagnostic criteria

Table (4): Criteria for the diagnosis of diabetes mellitus*
(ISPAD, 2014)

i. Symptoms of diabetes plus casual plasma glucose concentration ≥ 11.1 mmol/l (200 mg/dl)*. Casual is defined as any time of day without regard to time since last meal.
OR
ii. Fasting plasma glucose ≥ 7.0 mmol/l (≥ 126 mg/dl) †. Fasting is defined as no caloric intake for at least 8 hours.
OR
iii. Two-hour postload glucose ≥ 11.1 mmol/l (≥ 200 mg/dl) during an OGTT. The test should be performed as described by WHO, 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.
iv. HbA1c ≥ 6.5. However, there are difficulties with assay standardization and individual variation in the relationship between blood glucose and HbA1c, which may outweigh the convenience of this test.

* Corresponding values are ≥ 10.0 mmol/l for venous whole blood and ≥ 11.1 mmol/l for capillary whole blood

† ≥ 6.3 mmol/l for both venous and capillary whole blood

Prediabetes includes Impaired Glucose Tolerance (IGT) and Impaired Fasting Glycaemia (IFG)

IGT: 2 hour postload plasma glucose 7.8-11.1 mmol/l (140-199 mg/dl)

IFG: plasma glucose 5.6-6.9 mmol/l (100-125 mg/dl)

Complications of Type 1 diabetes

Acute and chronic complications of type 1 DM has been the reason of the high mortality reported for individuals with type 1 diabetes (Table 5). As recently developed from a huge population-based cohort with type 1 diabetes mellitus, throughout the first decade of diabetes acute complications,

such as hypoglycemia and diabetic ketoacidosis, are the major causes of death, it is responsible for 73% of the cases, whereas during later decades renal diseases and cardiovascular (CVD) become the leading causes of mortality ***(Washington et al., 2014).***

Table (5): Overview of diabetes-related complications

(White, 2015)

Short-term Complications
Diabetic ketoacidosis
Hypoglycemia
Visual
Psychosocial
Long-term Complications
Microvascular
Nephropathy
Retinopathy
Neuropathy
-Autonomic
-Peripheral
Macrovascular
Cerebrovascular disease
Coronary artery disease
Peripheral vascular disease

A- Acute complications

I- Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) is an acute complication of diabetes mellitus, associated with significant morbidity mortality ***(Misra et al., 2015)***, it may lead to diabetic coma, cerebral edema if not cured, death. DKA may happen in anybody with diabetes. However, about Two-thirds of DKA patients were having type 1

diabetes and 34% were having type 2 diabetes ***(Kitabchi et al., 2009)***.

Definition of Diabetic Ketoacidosis (DKA)

The biochemical criteria for DKA contain the following triad ***(Gosmanov et al., 2014)*** **(Figure 2)**:

- Hyperglycemia (blood glucose >250 mg/dL)
- Bicarbonate level of ≤18 mEq/L
- Arterial pH of ≤7.30
- Ketonemia and ketonuria.
- Adjusted albumin anion gap of 10–12.

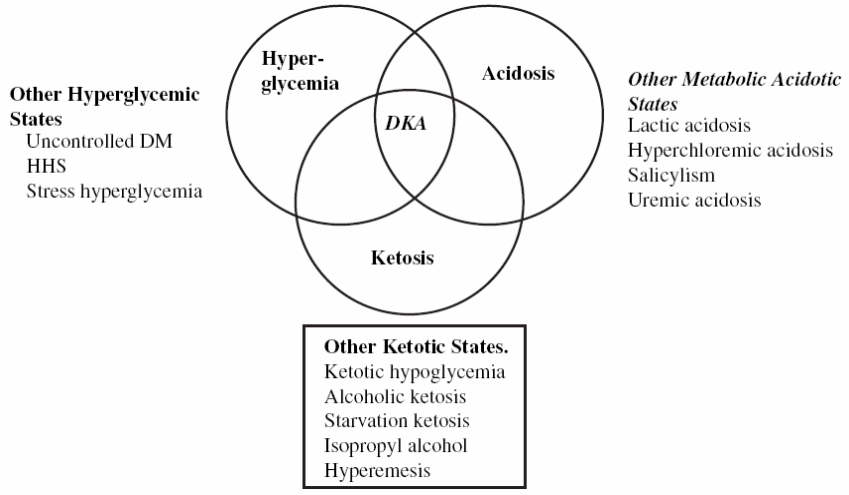

Figure (2): Differential diagnosis of DKA ***(Kitabchi et al., 2006)***.

Pathophysiology

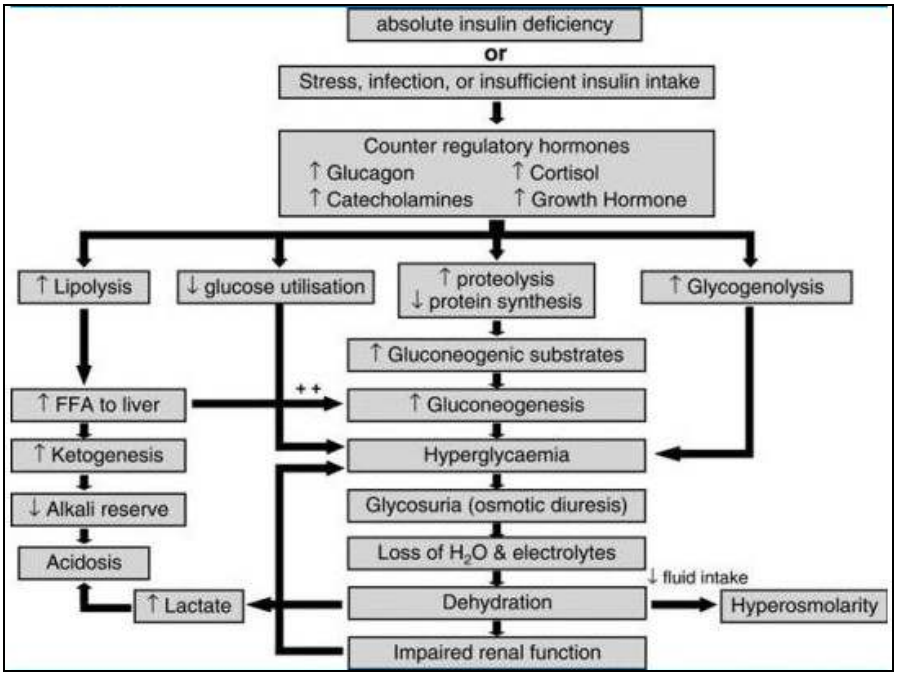

Figure (3): Pathophysiology of diabetic ketoacidosis
(Wolfsdorf et al., 2014).

II- Hyperosmolar hyperglycemic state (HHS)

It is a life threating complication of diabetes. It differs from DKA and it is important to distinguish them as the management significantly differs. Unlike to diabetic ketoacidosis, in HHS there is sufficient circulating insulin but it occurs due to sepsis or trauma resulting in increased hyperglycemia. Severe hyperglycemia raises the plasma osmolality in the extracellular fluid, which in turn results in the movement of the water from the intracellular to the extracellular space causing severe depletion of