INTRODUCTION

Diabetes 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 different organs, especially the eyes, kidneys, nerves, heart, and blood vessels ***(American Diabetes Association, 2013).***

Regarding Egyptian society nowadays, Diabetes is widespread in many families, nearly 10.4% of the Egyptian population (aged 10-79 years) have Diabetes as it is mainly inherited in Egyptian families, moreover Egyptians unhealthy diet may contribute to Diabetes' spread too ***(Soliman, 2013).***

Diabetes has been associated with sexual dysfunction both in men and in women. Diabetes is an established risk factor for sexual dysfunction in men; a threefold increased risk of erectile dysfunction (ED) was documented in diabetic compared with non-diabetic men. Among women, the evidence regarding the association between diabetes and sexual dysfunction is less conclusive, although most studies have reported a higher prevalence of female sexual dysfunction (FSD) in diabetic women as compared with non-diabetic women and it includes disorders of sexual desire, arousal, orgasm, and pain ***(Maiorino et al., 2014).***

Male sexual dysfunction (SD) includes erectile, ejaculatory and orgasmic dysfunctions and decreased libido

(termed as hypoactive sexual desire disorder (HSDD). The prevalence of ejaculatory dysfunction seems to be increased in diabetic patients and includes premature ejaculation (PE), delayed ejaculation (DE), anejaculation (AE) and retrograde ejaculation (RE) ***(Isidro, 2012).***

Retrograde ejaculation and failure of emission are the two disorders of ejaculatory function which result in anejaculation and infertility. Retrograde ejaculation is the flow of semen into the bladder due to an incompletely closed bladder neck. In two large series of azoospermic men, retrograde ejaculation was the observed cause in 18%, although as a source of infertility, it was only implicated in 0.7%. Additionally, it has been noted the incidence is likely rising as a consequence increasing rates of diabetes ***(Revenig et al., 2014 and Mcmahon CG et al., 2004).***

Retrograde ejaculation can occur as a result of congenital abnormality, spinal trauma, retroperitoneal lymph node dissection, diabetes mellitus, and bladder neck surgery or can be idiopathic ***(Jefferys et al., 2012).***

A detailed pharmacologic, sexual, medical, and surgical history will all aid in the correct diagnosis. Sign and symptoms of hypogonadism (i.e., low energy, low libido), erectile dysfunction, diabetes (i.e., polyuria), psychiatric illness (i.e., depression), and neurological disease (i.e., sensory abnormalities, bowel or bladder dysfunction) may aid in the diagnosis of ejaculatory dysfunction ***(Revenig et al., 2014).***

Postejaculatory urine analysis (PEU) has been routinely used for the diagnosis of retrograde ejaculation. Nevertheless, the interpretation of a positive PEU remains complex. The authors propose a retrograde ejaculation index that takes into account the total number of sperm in the semen and urine to diagnose retrograde ejaculation**.**

$$\text{Volume of semen lost in urine (mL)} = \frac{\text{total urine sperm count (millions)}}{\text{Semen sperm density (millions=mL)}}$$

(Mehta et al., 2012).

In diabetic men with partial or complete RE, two small uncontrolled studies suggested that medical treatment with sympathomimetics (imipramine and pseudoephedrine, can offer improvement or conversion to antegrade ejaculation. Fertility problems associated with ejaculatory failure can be overcome with assisted reproductive techniques ***(Isidro, 2012 and Arafa, 2008).***

Most studies of SD in diabetic men have focused on erectile dysfunction (ED), and so the prevalence, risk factors and pathophysiology of other forms of SD are not well known. Most physicians do not address sexual issues and few diabetic men with SD are diagnosed and treated ***(Isidro, 2012).***

Aim of the work

The aim of this thesis is to determine the prevalence of retrograde ejaculation among Egyptian diabetic patients attending the diabetes clinic in Ain-Shams University hospital through complete clinical assessment and laboratory investigations.

1. Diabetes Mellitus

DM 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. It is the most common endocrine-metabolic disorder of childhood and adolescence ***(ADA, 2013).***

DM makes up a group of hormonal diseases characterized by alterations in carbohydrate, protein, and lipid metabolism that results in elevated levels of blood glucose. More than 220 million people in the world have DM, and this number is expected to double by 2030**.** DM affects virtually all organs in the body, including the macrovascular system (heart) and the microvascular system (eyes, nerves, kidney, and the periodontium in the oral cavity). Cardiovascular complications of diabetes are common and are a leading cause of death in individuals with diabetes ***(Junttila et al., 2010).***

1.1 Classification:

WHO classified DM into clinical (normoglycemia, IGT/IFG, diabetes), and etiological types ***(ADA, 2012)*** as shown in table (1).

Table (1): Etiological classification of diabetes mellitus

1) Type 1 diabetes (ß-cell destruction, usually leading to absolute insulin deficiency)
    1. Immune mediated
    2. Idiopathic
2) Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
3) Other specific types
    1. Genetic defects of ß-cell function
    2. Genetic defects in insulin action
    3. Diseases of the exocrine pancreas
    4. Endocrinopathies
    5. Drug- or chemical-induced
    6. Infections
    7. Uncommon forms of immune-mediated diabetes
    8. Other genetic syndromes sometimes associated with diabetes

(ADA, 2013)

Patients with any form of diabetes may require insulin treatment at some stage of their disease. Such use of insulin does not, of itself, classify the patient ***(ADA, 2012).***

The vast majority of cases of diabetes fall into two broad etiopathogenetic categories as shown in table (2) ***(ADA, 2013).***

Table (2): Clinical characteristics of type 1 diabetes, type 2 diabetes

Characteristics	Type 1	Type 2
Age of onset	6 months to young adulthood	Usually older
Onset	Most often acute, rapid	Variable, from slow, mild to severe
Genetics	Polygenic	Polygenic
Clinical presentation	Most often acute, rapid	Variable; from slow (of insidious) to severe
Autoimmunity	Yes	No
Ketosis	Common	Uncommon
Glycemia	High	Variable
Obesity	Population frequency	Increased frequency
Frequency (% of all diabetes in young people)	Usually 90%+	Most countries <10% (Japan 60-80%)
Acanthosis Nigerians	No	Yes
Parent with diabetes	2-4%	80%

(ADA, 2013)

Type 1 diabetes accounts for only 5-10% of those with diabetes, previously encompassed by the terms insulin-dependent diabetes or juvenile-onset diabetes ***(ADA, 2012).*** Type 1 is further classified to the following subtypes:

1.1.1 Type Ia (The autoimmune form):

This form of diabetes, which accounts for only 5-10% of those with diabetes, previously encompassed by the terms insulin dependent diabetes, type 1 diabetes, or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of pancreatic ß-cells representing about 90% of type 1 cases in Europe. The presence of other autoimmune disorders is highly raised ***(ADA, 2012).***

1.1.2 Type Ib (The idiopathic form):

Smaller group of type 1 diabetic patients exhibit no evidence of autoimmunity and the cause of insulin deficiency remains undefined. This cases are categorized as type 1b diabetes or idiopathic type 1 DM and are relatively more common in African and Asian population. This category is heterogenous, and remain poorly understood at this time ***(Ali, 2010).***

1.2 Diagnosis of DM:

The Criteria for diagnosis of diabetes mellitus are shown in table (3). Three ways to diagnose diabetes are possible, and each in the absence of unequivocal hyperglycemia must be confirmed, on a subsequent day by any one of the three methods given in table (3).

Table (3): Criteria for diagnosis of diabetes mellitus and impaired glucose

Diabetes mellitus:

1) HbA1C>6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.
2) Symptoms of DM plus casual plasma glucose concentration ≥ 200 mg / dl (11.1 mmol / L). Casual is defined as any time of day without regard to time since last meal. The classic symptoms include polyuria, polydipsia or unexplained weight loss.

Or

1) FPG ≥ 126 mg / dL (7.0 mmol / L).
   Fasting is defined as no caloric intake for at least 8 hrs.

or

2) 2hrPPG ≥ 200 mg / dL (11.1 mmol / L) after a 75-g glucose load.

Impaired glucose homeostasis:

4) Impaired fasting glucose: FPG from 110 to <126 mg/dL (6.1 to 7.0 mmol / L).
5) Impaired glucose tolerance: 2hrPPG from 140 to < 200 mg/dL (7.75 to <1 1.1 mmol /L).

Normal:

1) FPG < 110 mg /dL (6.1 mmol /L).
2) 2hrPPG <140 mg / dL (7.75 mmol / L).

NGSP: National Glycohemoglobin Standardization Program

DCCT: Diabetes Control and Complications Trial

FPG: Fasting Blood Glucose

PPG: Postprandial Glucose

(ADA, 2013)

1.3 Complications of DM:

1.3.1 Acute metabolic complications:

Diabetic Ketoacidosis (DKA), hypoglycemia or infections, increased risk for infections and delayed wound healing are considered acute metabolic complications of DM ***(Baune et al., 2010)***.

1.3.1.1 Diabetic ketoacidosis:

Diabetic ketoacidosis is a metabolic derangement caused by the absolute or relative deficiency of the anabolic hormone insulin. Together with the major complication of cerebral edema, DKA is the most important cause of mortality and severe morbidity in children with diabetes, particularly at the time of first diagnosis. Early recognition and careful management are essential if death and disability are to be avoided ***(Yun and Xuefeng, 2013).***

DKA is biochemically defined as a venous pH <7.3 or serum bicarbonate concentration <15 mmol/L, serum glucose concentration >200 mg/dL (11 mmol/L) together with ketonemia, glucosuria, and ketonuria. The severity of DKA is determined by the degree of acidosis:

1.3.1.1.1 Mild: venous pH >7.2 and<7.3, bicarbonate <15 mmol/L

1.3.1.1.2 Moderate: venous pH >7.1 and <7.2, bicarbonate <10 mmol/L

1.3.1.1.3 Severe: venous pH <7.1, bicarbonate <5 mmol/L

(Rosenbloom, 2010)

1.3.1.2 Hypoglycemia:

Hypoglycemia is the commonest diabetic emergency and is associated with considerable morbidity and mortality. It is the most common acute complication associated with the treatment of T1DM ***(Bajwa et al., 2014).***

1.3.1.2.1 Hypoglycemic symptoms:

Shakiness, hunger, anxiety, palpitation, sweatiness, dizziness, irritability, crying, sleepiness, headache, mental confusion and the child appears pale.

1.3.1.2.1.1 Mild hypoglycemia: capillary blood glucose values between 70 and 55 mg/ dl.

1.3.1.2.1.2 Moderate hypoglycemia: BG <55 mg/dl without loss of consciousness.

1.3.1.2.1.3 Severe hypoglycemia: as any episode associated with loss of consciousness or seizures ***(Dendy et al., 2014).***

1.3.1.2.2 Management of hypoglycemia:

Mild or moderate hypoglycemia: provide glucose tablets (5g glucose each) or orange juice. Severe hypoglycemia: dextrose solution intravenous or SC glucagon or glucose gel into the cheek ***(Bajwa et al., 2014).***

1.3.1.3 Life quality impairment:

Nocturia, poor sleep, daytime tiredness, tooth and gum disease and cognitive impairment That can be severe and lead to decreased school performance in children, and decreased work performance in adults ***(Baune et al., 2010).***

1.3.2 Long term complications:

1.3.2.1 Microvascular complications:

Microangiopathy mainly affects vessels of the eyes, kidneys and nervous system causing respectively: diabetic retinopathy, diabetic nephropathy and diabetic neuropathy.

Microvascular diabetic complications are the most common causes of morbidity and mortality of patients with diabetes ***(Exalto et al., 2012).***

The major mechanism of microvascular disease is the toxic effect of prolonged hyperglycemia. Screening for microvascular disease enables intervention at the earliest possible stage maximizing the effectiveness of treatment. Intensive control of blood glucose level prevents the development and /or progression of microvascular complications ***(Chatziralli et al., 2010).***

1.3.2.1.1 Risk factors for the development of microvascular complications:

Younger age at onset, longer duration of diabetes, poor glycemic control, family history of diabetic complications and higher blood pressure (not necessarily to hypertensive level) increase the risk for development of microvascular complications ***(Jisieike-Onuigbo et al., 2011).***

1.3.2.2 Macrovascular complications:

Atherosclerosis and its sequelae affect mainly coronary, cerebral and peripheral blood vessels ***(Jisieike-Onuigbo et al., 2011).***

1.3.2.1.2 Age of screening of diabetic microvascular complications:

1.3.2.1.2.1 Prepubertal onset of diabetes: 5 years after onset or age 11 years or at puberty (which earlier) and annually thereafter.

1.3.2.1.2.2 Pubertal onset of diabetes: 2 years after onset and annually thereafter ***(ADA, 2012).***

1.3.2.1.3 Diabetic Retinopathy:

Diabetic retinopathy is one of the most frequent complications of diabetes and the leading cause of acquired blindness in young adults. Male gender, coexistence of hypertension, long duration of DM and high HbA1c represent independent risk factors for severe diabetic retinopathy ***(Chatziralli et al., 2010).***

No RCT had adequately examined the role of vitamin C and superoxide dismutase supplementation in the treatment of diabetic retinopathy ***(Williams et al., 2013).***

1.3.2.1.4 Diabetic Nephropathy:

Diabetic nephropathy occurs in 20–40% of patients with diabetes and is the single leading cause of end-stage renal disease (ESRD). Persistent albuminuria in the range of 30–299 mg/24 h (microalbuminuria) has been shown to be the earliest stage of diabetic nephropathy in type 1 diabetes. Microalbuminuria is also a well-established marker of increased CVD risk. Patients with microalbuminuria who progress to macroalbuminuria (300 mg/24 h) are likely to progress to ESRD. Intensive management of diabetes with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to delay the onset of microalbuminuria and the progression of micro to macroalbuminuria in patients with type 1 diabetes ***(ADA, 2013).***

Diabetic nephropathy is characterized by persistent proteinuria >300 mg/24h, increased blood pressure and a progressive decline in renal function to end stage renal disease. Early stage of overt disease is preceded by a phase known as incipient nephropathy or microalbuminuria ***(Exalto et al., 2012).***

1.3.2.1.5 Diabetic Neuropathy:

Diabetic neuropathy (DN) refers to symptoms and signs of neuropathy in a patient with diabetes in whom other causes of neuropathy have been excluded (table 4) ***(Misra et al., 2014).***

Diabetes is usually associated with distal symmetrical poly-neuropathy, focal and multifocal neuropathy, the entrapment neuropathies are highly prevalent in the diabetic population ***(Mutagaywa et al., 2014).***

Table (4): Characteristics of diabetic autonomic neuropathy

Functions	Symptoms and signs
Cardiovascular	Fixed tachycardia Silent myocardial infarction Prolonged QT interval Orthostatic hypotension
Gastrointestinal	Dysphagia Burning pain Gastric fullness Nausea Vomiting Diarrhoea Stipsis
Genitourinary	Erectile dysfunction Retrograde ejaculation Increased interval between micturitions Hesitancy when micturating Urinary incontinence Urinary infections
Sudomotor	Distal hypoanhidrosis Upper hyperhidrosis Gustatory sweating
Thermoregulatory	Distal hypothermia Hyperthermia
Hormonal and metabolic	Postural hypotension Impaired glucose counter-regulation Hypoglycemia that the patient is unaware of

(Fatehi et al., 2013)

1.4 Management of DM:

1.4.1 Prediction and Prevention:

Type 1 diabetes mellitus is caused by autoimmune islet b-cell destruction with consequent severe insulin deficiency. We can now predict the development of T1DM by determining four biochemically characterized islet