INTRODUCTION

Studies have shown a decreased bone formation and an increased risk of fractures in diabetic patients on thiazolidinediones (TZD). Changes in bone strength from glycation of collagen and negative calcium balance from calcium loss in the urine due to hyperglycaemia may also be seen. The thiazolidinediones affect bone turnover by increasing the formation of adipocytes instead of the bone-forming osteoblasts from the common mesenchymal stem cell***(Vertergaard et al., 2006).***

Vitamin D insufficiency contributes to osteoporosis by decreasing intestinal calcium absorption ***(Heaney, 2003).*** Treatment of vitamin D deficiency has been shown to improve bone mineral density ***(Harwood et al., 2004).*** An analysis of the Third National Health and Nutrition Examination Survey (NHANES III) demonstrated a positive correlation between circulating 25-hydroxy vitamin D (25OHD) levels and bone mineral density ***(Bischoff-Ferrari et al., 2004).***

25-hydroxy vitamin D3 insufficiency has been linked to obesity, whether obesity is assessed by body mass index (BMI) or waist circumference (waist). Central obesity, using waist as the surrogate, is associated with the metabolic syndrome, insulin resistance, type2 DM and atherosclerotic cardiovascular disease (CVD)***(Anne et al., 2008).***

Vitamin D insufficiency may increase the risk for type I and type II diabetes mellitus ***(Mathieu et al., 2005).*** In NHANES III, lower vitamin D status was associated with higher fasting glucose and 2-hour glucose after an oral glucose tolerance test ***(Scragg et al., 2007).***

The link between hypovitaminosis D3 and metabolic disorders, including obesity, Metabolic Syndrome, type 2 DM and CVD requires further investigation, particularly for those most at risk of these combined conditions ***(Vieth et al.,2007).***

AIM OF THE WORK

The aim of the study is to evaluate vitamin D level in Type 2 diabetic patients before and after three month of treatment with pioglitazone and assess any possible relationship in type 2 diabetic patients who are pioglitazone naïve.

Chapter One

DIABETES MELLITUS (DM)

History of diabetes:

Historical reviews report that the first mention of diabetes as a condition causing ‘polyuria' was first made about 1500 B.C. in Papyrus Eber's found at Luxor in Egypt ***(Bilous and Donnelly, 2010).***

A report from China indicated that the urine of diabetic patients was so sweet that dogs were attracted to it and a little later, around 400 B.C., the sweetness was referred to as "honey urine". Around the sixth century A.D, the association between excessive indulgence in food and drinks and the development of diabetes led to its description as the "disease of the rich" ***(El-Hazmi et al., 1995).***

Diabetes mellitus:

Diabetes mellitus is a syndrome consisting of metabolic, vascular, and neuropathic components that are interrelated***(Paddison, 2006).***

It 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 ***(ADA, 2012).***

The resulting hyperglycemia is associated with disorder of carbohydrate, fat, and protein metabolism and can lead to long term organ dysfunction ***(Michael and McDermott, 2009).***

The high prevalence of diabetes alone represents significant directhealth costs associated with screening and diagnosis, preventive education and counseling programs, and managing the disease and its shorthand long-term complications. Indirect costs include pain, suffering, and the effects of diabetes on the individual's physical and psychological well-being that profoundly affect his or her quality of life***(Dunning and Ward, 2008).***

Diabetes is an expensive disease. About 75% of the direct costs are absorbed by the long - term complications, rather than the management of diabetes itself. In the US in 2002, the annual economic burden of diabetes was estimated at $132 billion (accounting for >10% of total US healthcare expenditure). About 75% of the direct costs are attributable to managing the long-term vascular complications of diabetes, and 90% of resources are spent on T2DM. In terms of the costs of managing hyperglycemia, self - monitoring of blood glucose concentrations is the single biggest item ***(Bilous and Donnelly, 2010).***

In 2012, more than 471 billion USD were spent due to diabetes ***(IDF,2012).***

Diabetes mellitus type 1 (Type 1 diabetes, IDDM, or, formerly, autoimmune destruction of insulin-producing beta cells of the pancreas. The subsequent lack of insulin leads to increased blood and urine glucose***(Cooke and Plotnick, 2008).***

In this form of diabetes, the rate of β-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Still others, particularly adults, may retain residual β-cell function sufficient for many years***(ADA,2012).***

Type 1 diabetes is fatal unless treated with insulin. Injection is the most common method of administering insulin; insulin pumps and inhaledinsulin have been available at various times. Pancreatic transplants and pancreatic islet cell transplantation have been used to treat type 1 diabetes; however, pancreatic islet cell transplantation is still viewed as experimental, although utilization of the procedure is growing***(Santaguida et al., 2008)***.

Type 1 diabetes is 2-3 times more common in the offspring of diabetic men (3.6-8.5%) compared with diabetic women (1.3-3.6%) ***(Steck et al.,2004).***

Epidemiology:(Figure 1&2)

The IDF states that in 2012, more than 371 million people worldwide had diabetes***(IDF, 2012).***

In 2012, more than4.8 million people died due to diabetes half of them are under 60 ***(IDF, 2012).***

WHO projects that diabetes deaths will double between 2005 and 2030.More than 80% of diabetes deaths occur in low- and middle-income countries***(WHO, 2011).***

According to WHO, The anticipated number of diabetics in 2025 is 380 million ***(IDF, 2009).***

The anticipated number of diabetics in 2030 (20-79 yrs) is 438.7 million ***(IDF,2012).***

T2DM prevalence is estimated to rise to 439 million, or 7.7% of the world population ***(Nicholas et al., 2013)***.

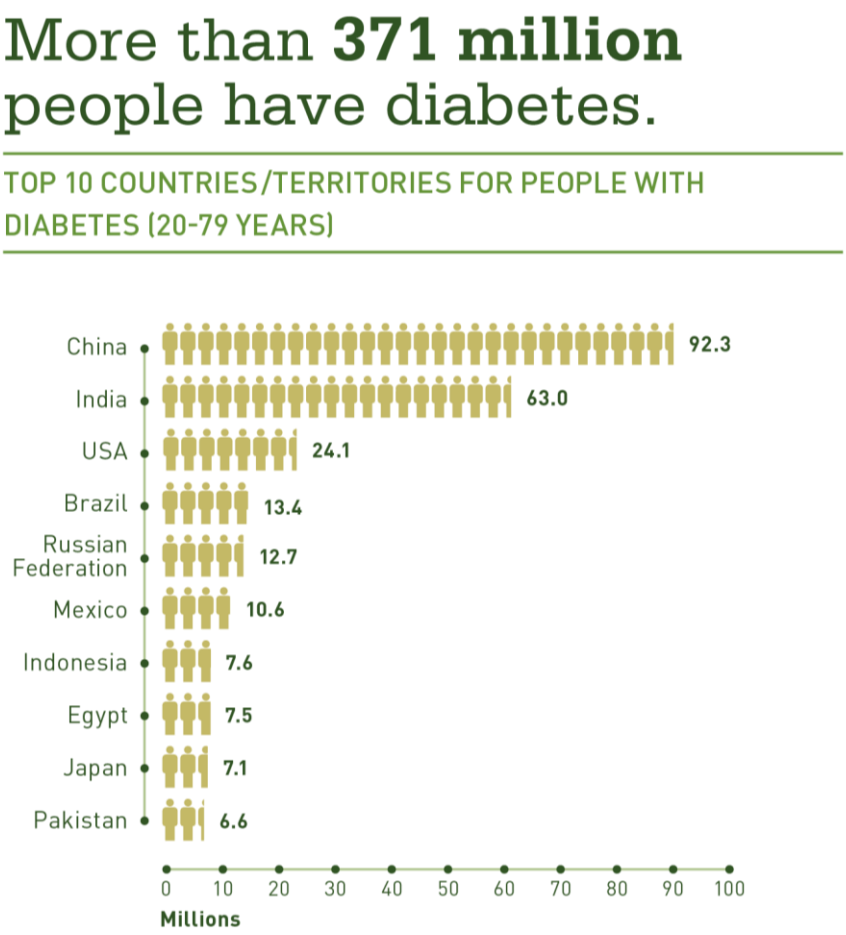

Figure (1): Top countries for people with diabetes (20-79 yrs).

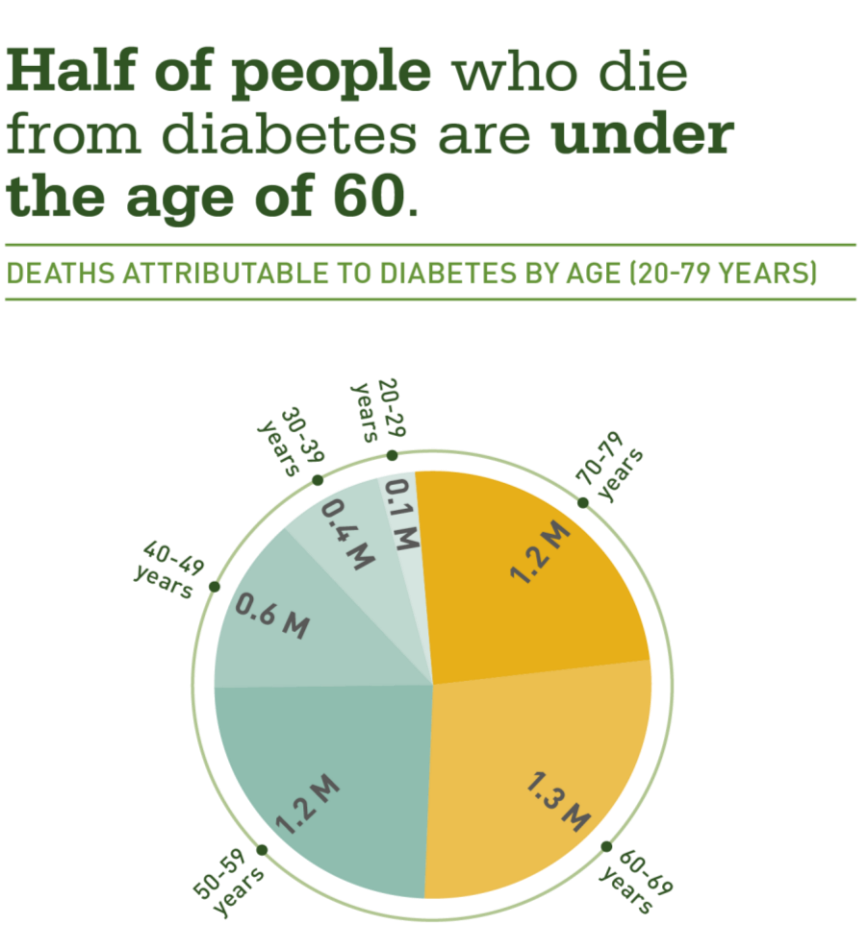

Figure (2): Deaths attributable to diabetes by age (20-79 yrs).

Egypt was in the world top 10 in terms of highest number of people with diabetes in 2012 (more than 7.5 million) ***(IDF, 2012).***

Egypt is expected to be among ten countries with the highest number of estimated cases of diabetes for 2030 ***(IDF, 2012).***

Diabetes is the eleventh most important cause of premature mortality in Egypt, and is responsible for 2.4% of all years of life lost. Similarly, diabetes is the sixth most important cause of disability burden in Egypt ***(Arafa and Amin, 2010).***

People of South Asian family origin living in the UK are up to six times more likely to have type 2 diabetes than the white population ***(Department of Health, 2001)*** andthey are also likely to develop type 2 diabetes 10 years earlier ***(Nicholl et al., 1986).***

People of African and African-Caribbean descent are threetimes more likely to have type 2 diabetes than the white population. Type 2 diabetes is also more common among Chinese and other non-white groups than among white European populations ***(Department of Health, 2001).***

The higher risk for South Asian people living in the UK is at least partly due to the fact that they may accumulate significantly more 'metabolically active' fat in the abdomen and around the waist than white European populations. (This is true even for those with a BMI in the 'healthy' range –that is, 18.5–24.9 kg/m^2) ***(Banerji et al., 1999).***

Diabetes mellitus (DM) occurs throughout the world, but is more common (especially type 2) in the more developed countries. The increase in incidence of diabetes in developing countries follows the trend of urbanization and life style

changes, perhaps most importantly a "western-style" diet. This has suggested an environmental (i.e., dietary) effect, but there is little understanding of the mechanism(s) at present ***(Wild et al., 2004).***

The rising incidence of type 2 DM is associated with Obesity and weight gain dramatically increase the risk***(Frank et al., 2011)*** **also,** Physical inactivity further elevates the risk, independently of obesity ***(Hu et al., 1999)***

Cigarette smoking is associated with a small increase ***(Manson et al., 2000),*** while, moderate alcohol consumption with a decrease in the risk of diabetes***(Wei et al., 2000)***.In addition, a lowfiber diet with a high glycemic index has been associated with an increased risk of diabetes ***(Frank et al., 2001).***

Family history of type 2 diabetes,a history of gestational diabetes and age (being older than 40 or older than 25 for some black and minority ethnic groups) ***(NICE, 2011).***

In addition, people from the following communities are particularly at risk: those of South Asian,African-Caribbean, black African and Chinese descent and those from lower socioeconomicgroups ***(NICE, 2011).***

The more risk factors someone has, the more likely he can develop diabetes ***(Harding et al., 2006).***

Diabetes in the Eastern Mediterranean Region:

Diabetes mellitus is highly prevalent among both sexes in Member States of the Eastern Mediterranean Region. Its prevalence ranges from between 3.5% and 30.0% and is highest among member countries of the Gulf Cooperation Council (GCC) at a rate of 11.5% to 30.0%. Many countries in the Region are now reporting the onset of type 2 diabetes mellitus at an increasingly young age. This is due to increasinglysedentary lifestyles, higher life expectancy and obesity. High blood pressure and cardiovascular diseases are also on the rise ***(Khatib, 2006).***

In 2003, the five countries with the highest diabetes prevalence in the adult population were Nauru (30.2%), United Arab Emirates (20.1%), Qatar (16%), Bahrain (14.9%), and Kuwait (12.8%). By 2025, the number of people with diabetes is expected to be more than double in Africa, the Eastern Mediterranean and South-East Asia regions ***(International Diabetes Federation, 2003).***

Diagnosis of DM:

Criteria for the diagnosis of diabetes *(ADA, 2012):*

- A1C $\geq$ 6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay*.

*In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.

OR

- FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*

OR

- 2-h plasma glucose ≥200mg/dl (11.1mmol/l) during an OGTT. The test should be performed as described by the World HealthOrganization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l).

Classification of DM:(table 1)

The differentiation between type 1 and type 2 DM has important implications for both therapeutic decisions and educational approaches***(Silverstein et al., 2005).***

Assigning a type of diabetes to an individual often depends on the circumstances present at the time of diagnosis, and many diabetic individuals do not easily fit into a single class. For example, a person with gestational diabetes mellitus (GDM) may continue to be hyperglycemic after delivery and may be determined to have, in fact, type 2 diabetes. Alternatively, a person who acquires diabetes because of large

doses of exogenous steroids may become normoglycemic once the glucocorticoids are discontinued, but then may develop diabetes many years later after recurrent episodes of pancreatitis. Another example would be a person treated with thiazides who develops diabetes years later. Because thiazides in themselves seldomcause severe hyperglycemia, such individuals probably have type 2 diabetes that is exacerbated by the drug.Thus, for the clinician and patient, it is less important to label the particular type of diabetes than it is to understand the pathogenesis of the hyperglycemia and to treat it effectively***(ADA,2012).***

Aetiological classification of DM (ADA, 2012)

Table (1): Aetiological classification of diabetes.

I. Type 1 diabetes	II. Type 2 diabetes	III. Other specific types	IV. Gestational diabetes mellitus
A. Immune mediated B. Idiopathic	(may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)	**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-1 (IPF-1; MODY4) 5. Chromosome 17, HNF-1b (MODY5) 6. Chromosome 2, NeuroD1 (MODY6) 7. Mitochondrial DNA 8. Others. **B. Genetic defects in insulin action:** 1. Type A insulin resistance 2. Leprechaunism 3. Rabson-Mendenhall syndrome 4. Lipoatrophic diabetes 5. Others. **C. Diseases of the exocrine pancreas:** 1. Pancreatitis 2.Trauma/pancreatectomy 3. Neoplasia 4. Cystic fibrosis 5. Hemochromatosis 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.	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.