Fibroblast growth factor 23 relation to peripheral arterial disease in type 2 diabetes mellitus

Thesis submitted by

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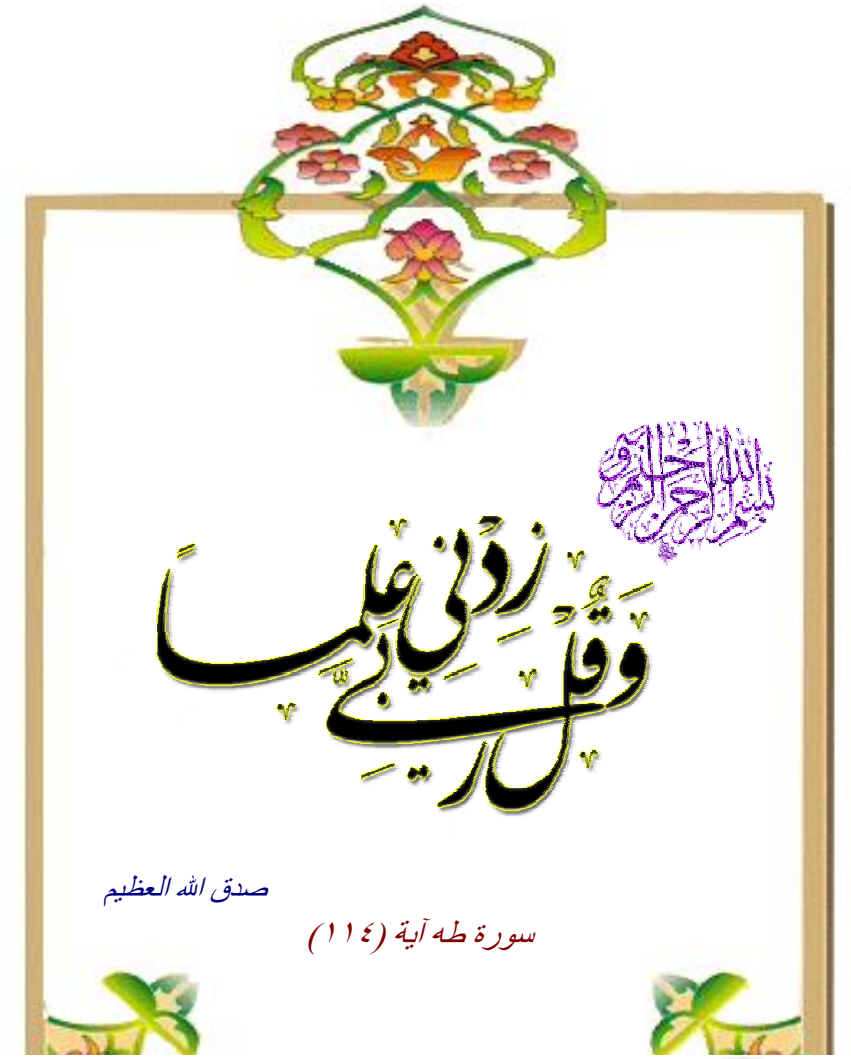
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Introduction

Egypt has been among the top ten countries for number of people with diabetes with 7.5 million expected to project to 13.1 million in 2035.Thiscarries a huge economic and social burden as people with diabetes are at risk of developing a number of disabiling and life threating health problem **(IDF, 2013).**

Cardiovascular disease is the most common cause of death and disability among people with diabetes. The Cardiovascular diseases that accompany diabetes include angina, myocardial infarction, stroke, peripheral arterial diseases and congestive heart failure **(IDF, 2013).**

Peripheral arterial disease (PAD) is a major vascular complication and the leading cause of amputation in people with diabetes**.** Diabetic foot complications are associated with a 15 fold increase for lower limb amputation **(Singh et al., 2011).** Typically, diabetes associated PAD affects the popliteal arteries **(Mukherjee, 2009).**

Fibroblast growth factor 23 (FGF23) is a recently discovered 30kDa secreted hormone glycoprotein that plays role in the complex and tightly regulated mechanisms of mineral metabolism. In healthy individuals, FGF23 is secreted from bone osteocytes in response to increase in

diatery phosphate. FGF23 acts through one of the FGF receptors, with klotho as coreceptor, to inhibit renal phosphorus reabsorption and decrease circulating levels of 1,25 (OH)2D and possibly inhibit parathyroid hormone (PTH) secretion by the parathyroid glands. Thus, its net effect is a reduction in serum phosphorus and 1,25 (OH)2D level which may result in hypocalcemia. Increase serum FGF23 concentration was independent predictor of coronary artery diseases in patient with mild chronic kidney disease and mortality in patients undergoing hemodialysis. Recently, FGF 23 has been found to be associated with total body atherosclerosis and vascular dysfunction **(Dalal et al., 2011)**.

No studies on relation between FGF23 and peripheral arterial diseases.

Aim of the Work

To study possible relation of FGF23 with peripheral arterial disease in type 2 diabetic subjects with normal kidney function.

Diabetes Mellitus

Definition and descripition of Diabetes Mellitus

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 **(ADA, 2015).**

Diabetes Mellitus (DM) is now a recognized pandemic and treatment costs of DM and its complications are a major burden on healthcare systems throughout the world. Diabetic vasculopathy (DV) is the most important consequence of chronic hyperglycemia, in patients with DM **(Conte et al., 2015).**

Epidemiology of diabetes mellitus

Diabetes mellitus is one of the most challenging health problems in the 21st century. 366 million people around the world had diabetes in 2011, by 2030 this will have risen to 552 million. 80% of people with diabetes live in low- and middle-income countries **(IDF, 2013).**

The increase in rates in developing countries follows the trend of urbanization and lifestyle changes, Perhaps most importantly a "Western-style" diet. This has suggested an environmental effect **(Wild et al., 2004).**

DM 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).**

Just over 10% of all deaths in adults in the Middle East and North Africa are attributable to diabetes. Early death from diabetes may be a result of the rapidly changing environments and lifestyles of the region, late diagnosis, and health systems **(IDF, 2013).**

Prevalence (Worldwide prevalence)

Most regions have seen a continuous increase in diabetes. The heavily populated Western Pacific Region has 153 million adults with diabetes; substantially more than any other region. It is however, the North America and Caribbean Region which has the highest prevalence per capita with one out of eight adults with the disease. Europe has the highest number of children with type 1 diabetes; approximately 140,000, and faces an increase of around

21,600 new cases per year. In 2015, the top ten countries for number of adults with diabetes were China (109.6 millions), India (69.2 million), United States of America (29.3 million), Brazil (14.3 million), Russian Federation (12.1 million), Mexico (11.5 million), Indonesia (10.0 million), Egypt (7.8 million), Japan 7.2 million and Bangladesh (7.1 million) **(IDF, 2015).**

Classification of Diabetes Mellitus

Diabetes mellitus is classified into four broad categories: type 1, type 2, gestational diabetes, and "other specific types" **(Shoback et al., 2011).**

***Type 1diabetes mellitus* (T*1*DM)**

Previously called "insulin- dependent diabetes. It accounts for 5-10% of diabetes and is due to cellular mediated autoimmune destruction of the pancreatic B-cells **(Dabelea et al., 2014).**

Autoimmune markers include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to Glutamic Acid Decarboxylase (GAD) (GAD65), autoantibodies to the tyrosine phosphatases IA-2 and IA-2b, and autoantibodies to zinc transporter 8 (ZnT8). Type 1 DM is defined by the presence of one or more of these autoimmune markers **(Ziegler el al., 2013).**

The disease has strong human leukocyte antigen (HLA) associations, with linkage to the DQA and DQB genes. The rate of beta-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults) **(Sorensen et al., 2013).**

Children and adolescents may present with ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia rapidly change to severe hyperglycemia and/or ketoacidosis with infection or other stress. Adults may retain sufficient beta-cell function to prevent ketoacidosis for many years; such individuals eventually become dependent on insulin for survival and are at risk for ketoacidosis. At this latter stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide **(Sosenko et al., 2013).**

Type 2 diabetes mellitus (**T2DM)**

T2DM is the most common type **(Shoback et al., 2011).** T2DM accounts for the remaining 90–95 % of diabetes cases **(Noble et al., 2011).**

T2DM is heterogeneous disease as patients can range from those with predominantly an insulin resistance phenotype but with sufficient beta cell reserve to remain insulin independent to those who may require early insulin treatment during the course of their disease **.**Most patients with T2DM are overweight or obese. Obesity, physical inactivity, hypertension, certain ethnicities (e.g. Middle Eastern, South Asian and Hispanic) and dyslipidaemia are risk factors. There is often a family history of T2DM and several genetic risk markers have been propose **(ADA, 2014).**

Clinical studies suggest this broad category of β-cell failure is comprised of alterations in β-cell mass as well as insulin secretory function **(Meier and Bonadonna, 2013)**, while provocative new preclinical data suggest that alterations in β-cell identity may also play a role in the T2DM phenotype **(Talchai et al., 2012)**.

Table (1): Clinical features that commonly distinguish T1DM and T2DM

Clinical features	Type 1 diabetes mellitus	Type 2 diabetes mellitus
Age at onset (years)	Majority <25, but may occur at any age	Typically >25 but incidence is increasing in adolescents due to increasing rates of obesity in this age group
Symptoms at presentation	Polyuria, polydipsia, fatigue	Majority asymptomatic
Phenotype	Thin	>90 % overweight
Autoantibodies	Present	Absent
Insulin dependant	Yes	Not initially
Insulin sensitivity	Normal when controlled	Decreased
Family history of diabetes	Infrequent (5–10 %)	Frequent (75–90 %)
Risk of diabetic ketoacidosis	High	Low

(ADA, 2013)

There are several other less common forms of diabetes. Latent autoimmune diabetes of adults (LADA) is a term used to describe the development of diabetes-associated antibodies and diabetes onset in older adults. It is thought to account for 2–12 % of all diabetes cases **(Guglielmi et al., 2012)**.

Maturity onset diabetes of the young (MODY) is a heterogeneous group of disorders caused by a mutation in one of the six genes essential for β-cell function and accounts for 1 % of diabetes cases presented in adolescence or young adulthood with mild asymptomatic hyperglycemia. It can be differentiated from T2D by the presence of a strong family history of diabetes with an apparent autosomal dominant pattern of inheritance, milder hyperglycemia, and often lack of obesity. Genetic testing should be performed in cases with a high index of suspicion **(Kavvoura and Owen, 2012)**.

Gestational diabetes mellitus (GDM)

(GDM) is defined as glucose intolerance with first onset or recognition during pregnancy due to inadequate β-cell reserve or capacity to compensate for the generalized state of pregnancy with insulin resistance **(Sacks et al., 2012).**

Diabetes may also occur secondary to other disease states, including lipodystrophy or cystic fibrosis-related diabetes (CFRD) **(Gorden et al., 2012)** or drug or chemical induced, resulting from a combination of glucose intolerance and/or β-cell dysfunction. The most common offending drugs are high-dose glucocorticoids, calcineurin

inhibitors used post- transplantation, and certain antiretrovirals used in the treatment of Human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) **(Rudich et al., 2005).**

Diagnosis of diabetes mellitus

Table (2): Criteria for diagnoses of diabetes

Criteria for Diabetes Diagnosis: 4 options
A1C ≥6.5%
FPG ≥126 mg/dL (7.0 mmol/L) Fasting defined as no caloric intake for ≥8 hrs
2-hr PG ≥200 mg/dL (11.1 mmol/L) during OGTT (75-g)* Performed as described by the WHO, using glucose load containing the equlivalent of 75g anhydrous glucose dissolved in water
Random PG ≥200 mg/dL (11.1 mmol/L) In persons with symptoms of hyperglycemia or hyperglycemic crisis
Point-of-care A1C testing allows for more timely treatment changes

(ADA, 2015)

Signs and symptoms

The classic symptoms of untreated diabetes are weight loss, polyuria, polydipsia, and polyphagia. Symptoms may develop rapidly (weeks or months) in type 1DM, while they usually develop much more slowly in type 2 DM **(Cooke and Plotnick, 2009).**

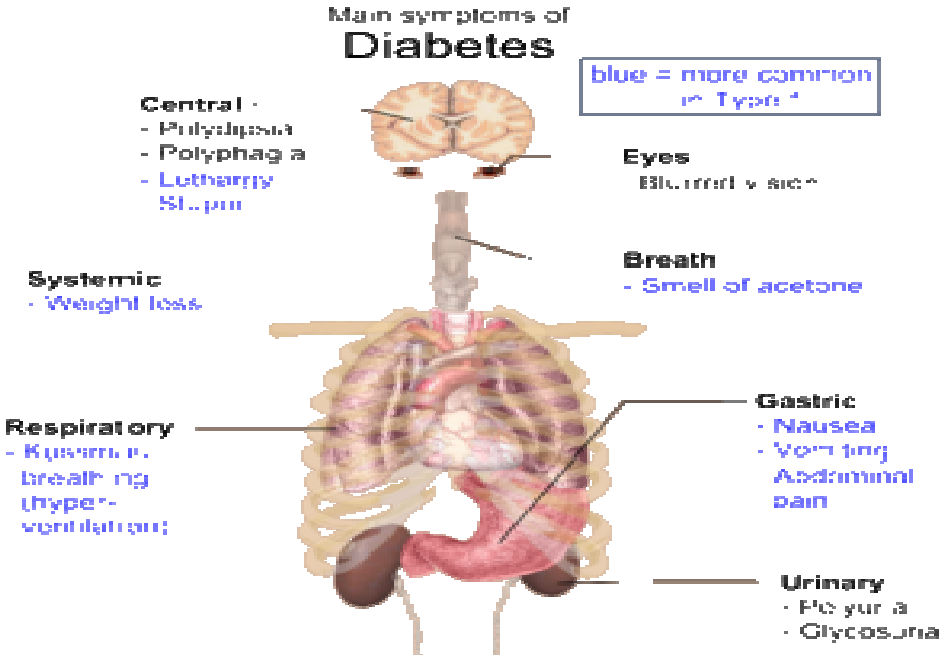

Figure (1): Overview of the most significant symptoms of diabetes.

Prediabetes

It is a state of defective glucose metabolism defined as impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). IGT is characterized by postprandial hyperglycemia and IFG is manifested by mild fasting hyperglycemia **(Khavandi et al., 2013)**.