INTRODUCTION

Diabetes exerts a heavy toll on the vascular system. Vessels of all sizes are affected, from the aorta down to the smallest arterioles and capillaries. Gangrene of the lower extremities, as a result of advanced vascular disease, is about 100 times more common in diabetic persons than in the general population ***(Crawford et al., 2003).***

Diabetes is a risk factor for both PAD and PAD-associated mortality, emphasizing the critical need to detect and monitor PAD in diabetic patients***(Leibson et al., 2004).***

In patients with peripheral arterial disease, diabetic patients have worse arterial disease and a poorer outcome than nondiabetic patients ***(Jude et al., 2001).***

Peripheral arterial disease (PAD) is defined as obstruction of blood flow into an arterial tree excluding the intracranial or coronary circulations. PAD is mostly silent in its early stages, but when lesion obstruction exceeds 50%, it may cause intermittent claudication with ambulation. Further disease progression typically leads to rest pain or frank tissue loss. However, some patients may remain asymptomatic with severe disease because of extensive collateralization in the lower extremity. Estimates of the prevalence of intermittent claudication varyby population**,** from 0.6% to nearly 10%; the rate increases dramatically with age. Approximately 20% to 25% of patients will require revascularization, while fewer than

5% will progress to critical limb ischemia. Limb loss, although rare, is associated with severe disability and an overall poor prognosis, with 30% to 40% mortality in the first 24 months after limb loss. As with coronary artery disease, the most common cause of symptomatic obstruction in the peripheral arterial tree is atherosclerosis, a systemic inflammatory process in whichcholesterol-laden plaque builds up in the artery and eventually blocks the lumen. Typical risk factors include age, gender, diabetes, tobacco abuse, hypertension, and hyperlip-idemia ***(Garcia, 2006).***

Fetuins are blood proteins made in the liver more abundant in fetal blood hence its name. Fetuin A is regarded as an inhibitor of systemic calcification ***(Schafer et al., 2003).***

Researches were made to detect the relationship between fetuin A levels and peripheral vascular disease in diabetics stating that their study then high lightened the importance of further prospective studies and animal model systems to evaluate the role of serum fetuin A in the early development and progression of peripheral vascular disease in subjects with type2 DM***(Eraso et al., 2010).***

AIM OF THE WORK

To assess the relationship between plasma fetuin-A levels and peripheral vascular disease in type2 diabetes mellitus.

Chapter (1)

DIABETES MELLITUS

Definition

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 ***(American Diabetes Association., 2012).***

Pathophysiology of Diabetes mellitus

Since the availability of insulin and antibiotics, the number of deaths from acute metabolic complications has decreased, and disability and death in both insulin dependent diabetes mellitus (IDDM) and non-insulindependent diabetes mellitus (NIDDM) usually result from the degenerative complications of the disease ***(Williams et al., 2010)***.

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. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of

hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia***(Dejkhamron et al., 2007).***

Classification systems should reflect new understanding of the etiology and pathophysiology of disease.Thus, there is new etiology-based classification is timely and appropriate. The new classification is a big step away from the older clinical or "treatment-based" system toward a completely etiologic classification, such as exists for many other diseases ***(American Diabetes Association, 2012).***

- **The classification of diabetes includes:**

A- Clinical Classification:*(American Diabetes Association, 2012).*

1. Type- 1 -diabetes (results from **-β** –cell destruction, usually leading to absolute insulin deficiency).
2. Type -2- diabetes (results from a progressive insulin secretory defect on the background of insulin resistance).
3. Other specific types of diabetes due to other causes, e.g., genetic defects in -β-cell function, genetic defects in insulin action,diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical induced (such as in the treatment of HIV/AIDS or after organ transplantation).

4. Gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancythat is not clearly overt diabetes).

    - Some patients cannot be clearly classified as having type 1 or type 2 diabetes.

B- Etiologic classification of diabetes mellitus: *(The American Diabetes Association 2012, Expert Committee)*

I. Type-1-diabetes (**β**-cell destruction, usually leading to absolute insulin deficiency).

1.A. Immune mediated.

1.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- β-cell function

1. Chromosome 12, HNF-1_ (MODY3)
2. Chromosome 7, glucokinase (MODY2)
3. Chromosome 20, HNF-4_ (MODY1)
4. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
5. Chromosome 17, HNF-1_ (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. Fibrocalculouspancreatopathy
7. Others.

D. Endocrinopathies:

1. Acromegaly.
2. Cushing's syndrome.
3. Glucagonoma.
4. Pheochromocytoma.
5. Hyperthyroidism.
6. Somatostatinoma.
7. Aldosteronoma.
8. Others.

E. Drug or chemical induced:

1. Vacor.
2. Pentamidine.

3. Nicotinic acid.
4. Glucocorticoids.
5. Thyroid hormone.
6. Diazoxide
7. Adrenergic agonists.
8. Thiazides.
9. Dilantin.
10. Interferon.
11. Others

F. Infections:

1. Congenital rubella.
2. Cytomegalovirus.
3. Others.

G. Uncommon forms of immune-mediated diabetes:

1. “Stiff-man” syndrome.
2. Anti-insulin receptor antibodies.
3. Others.

H. Other genetic syndromes sometimes associated with diabetes:

1. Down syndrome.
2. Klinefelter syndrome.
3. Turner syndrome.
4. Wolfram syndrome.
5. Friedreich ataxia.
6. Huntington chorea

7. Laurence-Moon-Biedl syndrome.
8. Myotonic dystrophy.
9. Porphyria.
10. Prader-Willi syndrome.
11. Others.

IV. Gestational diabetes mellitus.

The most important types of Diabetes mellitus include:

- **Type 1 diabetes (-β-cell destruction usually leading to absolute insulin deficiency) (Immune-mediated diabetes) (Type-1-A)*(American Diabetes Association, 2012).***

Immune-mediated diabetes. This form of diabetes which accounts for only5–10% of those with diabetes, previously encompassed by the terms insulin dependent diabetes, type 1 Diabetes, or juvenile-onset diabetes, results from a cellular-mediated auto immune destruction of the β-cells of the pancreas. Such individuals eventually become dependent on insulin for survival and are at risk of ketoacidosis. These patients are also prone to other autoimmune disorders such as Addison's disease, vitiligo, Graves'disease, Hashimoto's thyroiditis, celiac sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anemia ***(Haller et al., 2005).***

The more indolent adult-onset variety has been referred to as latent auto-immune diabetes in adults (LADA). Latent autoimmune diabetes in adults (LADA) is a disorder inwhich,

despite the presence of islet antibodies at diagnosisof diabetes, the progression of autoimmune ß cellfailure is slow. LADA patients are therefore not insulin requiring,at least during the first 6 months after diagnosis of diabetes.Among patients with phenotypic type 2 diabetes, LADA occursin 10% of individuals older than 35 years and in 25% below that age. Prospective studies of ß-cell function show thatLADA patients with multiple islet antibodies develop ß-cellfailure within 5 years, whereas those with only GAD antibodies(GADAs) or only islet cell antibodies (ICAs) mostly develop ß-cell failure after 5 years ***(Dejkhamron et al., 2007).*** Even though it may takeup to 12 years until ß-cell failure occurs in somepatients, Consequently, LADA is not a latent disease; therefore, autoimmunediabetes in adults with slowly progressive ß-cellfailure might be a more adequate concept. In agreement withproved impaired ß-cell function at diagnosis of diabetes,insulin is the treatment of choice***(Haller et al., 2005).***

- **Idiopathic diabetes (Type-1-B):**

Some forms of type 1diabetes have no known etiologies. Some of these patients have permanent insulinopenia and are prone to ketoacidosis,but have no evidence of auto immunity.Although only a minority of patients with type- 1-diabetes fall into this category,of those who do, most are of African or Asian ancestry***(Dejkhamron et al., 2007).***Individuals with this form of diabetes suffer from episodic ketoacidosisand exhibit varying degrees of insulin deficiency between episodes. This form of diabetes is strongly

inherited,lacks immunological evidence for-β-cell autoimmunity, and is not HLA associated. An absolute requirement for insulin replacement therapy in affected patients may come and go ***(AmericanDiabetes Association,2012).***

- **Type -2- diabetes (Ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance)** ***(American Diabetes Association, 2012).***

This form of diabetes, which accounts for 90–95% of those with diabetes, previously referred to as non–insulin dependent diabetes, type 2 diabetes, or adult-onset diabetes, encompasses individuals who have insulin resistance and usually have relative (rather than absolute)insulin deficiency At least initially,and often throughout their lifetime, these individuals do not need insulin treatment to survive***(Defronzo, 1997).***

There are probably many different causes of this form of diabetes. Although the specific etiologies are not known, autoimmune destruction of-β cells does not occur, and patients don't have any of the other causes of diabetes listed above and Ketoacidosis seldom occurs spontaneously in this type of diabetes, when seen, it usually arises in association with the stress of another illness such as infection ***(American Diabetes Association, 2010).***

- **Maturity onset diabetes of the young**

These are genetic defects of the- **β** -cell. Several forms of diabetes are associatedwith monogenetic defects in – **β** -cell function.These forms of diabetes are frequently characterized by onset of hyperglycemia at an early age (generally before age 25 years)***(Mc Carthy and Frognel, 2002).***

They are referred to as maturity onset diabetesof the young (MODY) and are characterized by impaired insulin secretion with minimal or no defects in insulin action***(American Diabetes Association, 2012).***

- **Gestational Diabetes mellitus:GDM:*(Dejkhamron et al., 2007)***

Screening for and diagnosis of GDM .Perform a 75-g OGTT, with plasma glucose measurement fasting and at 1 and 2 h, at 24-28 of weeks gestation in women not previously diagnosed with overt diabetes.

The OGTT should be performed in the morning after anovernight fast of at least 8 h.

The diagnosis of GDM is made when any ofthe following plasma glucose values areexceeded:

- Fasting: _92 mg/dl (5.1 mmol/l)
- 1 h: _180 mg/dl (10.0 mmol/l)
- 2 h:_153 mg/dl (8.5mmol/l) ***(American Diabetes Association, 2012)***.

Symptoms of Diabetes mellitus:*(Dejkhamron et al., 2007).*

Diabetes may be Asymptomatic in early stages and symptomatic in chronic hyperglycemia including polyuria, polydypsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute life-threatening consequences of diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome***(American Diabetes Association,2012).***

Components of the comprehensive diabetes evaluation:*(American Diabetes Association, 2012)*.

1- Medical history

A. Diabetes education history,Review of previous treatment regimens and response to therapy (A1C records), Current treatment of diabetes, including medications and medication adherence,meal plan, physical activity patterns, and readiness for behavior change.

B. Results of glucose monitoring and patient are use of data.

C. DKA frequency, severity, and cause, hypoglycemic episodes Hypoglycemia awareness,and any severe hypoglycemia: frequency and cause.

D. History of diabetes-related complications:

- Microvascular: retinopathy, nephropathy, neuropathy (sensory, including historyof foot lesions; autonomic, including sexual dysfunction and gastroparesis)
- Macrovascular: CHD, cerebrovascular disease,peripheral arterial disease.

E. Other: psychosocial problems, dental disease

2- Physical examination:

- Height, weight, BMI(body mass index).
- Blood pressure determination, including orthostatic measurements when indicated.
- Fundoscopic examination.
- Thyroid palpation.
- Skin examination (for acanthosisnigricans and insulin injection sites).
- *Comprehensive foot examination:*
  - Inspection
  - Palpation of dorsalispedis and posterior tibial pulses.
  - Presence/absence of patellar and Achilles reflexes.
  - Determination of proprioception(monofilament sensation),and, vibration
  - Testing for proprioception monofilament sensation.

- Place patient in a supine position with his or her eyes closed.
- Ask the patient to respond “yes” when the filament is felt
- Test 4 sites on each foot in random sequence (the sites to be tested are indicated on the diagram)
- Apply the filament perpendicular to the surface of the skin and apply sufficient forceto form a C-shape for 1 second
- Do not allow the filament to slide across the skin or make repetitive contact at the test site
- Randomize the order and timing of successive tests.
- Do not apply to an ulcer site, callous, or scar – apply to adjacent tissue instead
- Mark in the patient chart areas positive or negative for sensation***(Boultonetal,2009).***

3- Laboratory evaluation:

- A1C, if results not available within past 2–3 months
- If not performed/available within past year:
- Fasting lipid profile, including total, LDL, and HDL cholesterol and triglycerides
- Liver function tests
- Test for UAE with spot urine albumin-to-creatinine ratio