INTRODUCTION

Fetuin-A was isolated from fetal calf serum. It has three carbohydrate units, which are present on a peptide chain linked with threonine and serine residues ***(Yang et al., 2008).***

Atherosclerosis demonstrated by the accumulation of lipids, connective tissue and inflammatory cells in the intima-media layer of the arterial wall. There are various factors that support the development of atherosclerosis: insulin resistance, hyperuricaemia, age, sex, lipid disturbances, hypoalbuminaemia, anaemia, hyperhomocysteinaemia ***(Luczak et al., 2011)***.

Hyperglycaemia produces various changes in the vascular tissue at the cellular level that accelerates the atherosclerosis ***(Aronson and Rayfield, 2002)***. There is a direct correlation among carotid arterial stiffness and the serum fetuin-A level. It is a calcium regulatory glycoprotein and inhibits vascular calcification, which is related to the inflammation ***(Stenvinkel et al., 2005).***

Fetuin -A is an inhibitor of ectopic calcification ***(Morik et al., 2007)***. Fetuin-A increases procalcific milieu and is associated with aortic stiffness ***(Smith et al., 2011).*** Fetuin-A is a marker of the inflammatory nutritional state and acts as a protective agent because it solubilizes the calcium phosphate salt ***(Coen et al., 2006***).

AIM OF THE WORK

To study the role of fetuin-A in atherosclerosis and its association with type 2 diabetes.

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 dependant diabetes mellitus(IDDM type1)and non insulin dependant diabetes mellitus (NIDDM type2) 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 pregnancy that is not clearly overt diabetes).

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

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

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

A. Immune mediated.

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. ***<u>Genetic defects of β-cell function:</u>***

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. <u>Genetic defects in insulin action:</u>

1. Type A insulin resistance.
2. Leprechaunism.
3. Rabson-Mendenhall syndrome.
4. Lipoatrophic diabetes.
5. Others.

C. <u>Diseases of the exocrine pancreas:</u>

1. Pancreatitis
2. Trauma/pancreatectomy
3. Neoplasia
4. Cystic fibrosis
5. Hemochromatosis
6. Fibrocalculous pancreatopathy
7. Others.

D. <u>Endocrinopathies:</u>

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 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 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 in which, despite the presence of islet antibodies at diagnosis of diabetes, the progression of autoimmune **ß-**cell failure 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 occurs in 10% of individuals older than 35 years and in 25% below that age. Prospective studies of ß-cell function show that LADA patients with multiple islet antibodies develop ß-cell failure 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 take up to 12 years until ß-cell failure occurs in some patients, Consequently, LADA is not a latent disease; therefore, autoimmune diabetes in adults with slowly progressive ß-cell failure might be a more adequate concept. In agreement with proved 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 ketoacidosis and 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 ***(American Diabetes 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 do not 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 associated with 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) ***(McCarthy and Frognel, 2002).***

They are referred to as maturity onset diabetes of 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 an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are exceeded:

- Fasting: _92 mg/dl (5.1 mmol/l).
- 1 h: 180 mg/dl (10.0 mmol/l).
- 2 h 153 mg/dl (8.5 mmol/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. <u>Medical history:</u>

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's 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.

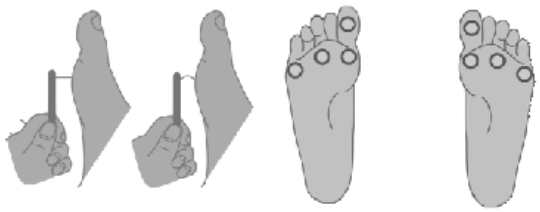
e- Other: psychosocial problems and dental disease.

2. <u>Physical examination:</u>

- Height, weight, BMI(body mass index).
- Blood pressure determination, including orthostatic measurements when indicated.
- Fundoscopic examination.
- Thyroid palpation.
- Skin examination (for acanthosis nigricans and insulin injection sites).
- ***Comprehensive foot examination:***
  - Inspection
  - Palpation of dorsalis pedis 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 force to 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.

(Boulton et al., 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.
- Serum creatinine and calculated GFR.
- Thyroid-stimulating hormone in type 1 diabetes dyslipidemia, or women overage 50 years.
- Family planning for women of reproductive age.
- Registered dietitian for MNT (Medical nutrition therapy).
- DMSE: Diabetes self management education.
- Dentist for comprehensive periodontal examination.
- Mental health professional, if needed.

4. Early detection of individuals with increased risk for diabetes (prediabetes):

In ***(1997 & 2003), The Expert Committee on Diagnosis and Classification of Diabetes Mellitus*** recognized an intermediate group of individuals whose glucose levels, although not meeting criteria for diabetes, are nevertheless too high to be considered normal. These persons were defined as having impaired fasting glucose (IFG) (FPG levels 100 mg/dL [5.6mmol/L] to 125 mg/dL [6.9 mmol/L]), or impaired glucose