Study of measuring Serum OPG in diabetic patients with peripheral arterial disease

Thesis

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Abbreviations

ABI .....Ankle-Brachial Index.

AGE .....Advanced Glycation End Products

ALT .....Alanine Transaminase

ARB .....Angiotensin Receptor Blocker

BAP .....Bone specific Alkaline Phosphatase

BMP .....Bone Morphogenic Protein

BMI .....Body Mass Index

CAC..... Calcifying vascular cells.

CHF .....Chronic Heart Failure

CKD .....Chronic Kidney Disease

CLI ..... Critical limb ischemia.

CRP .....C - reactive protein

CVC .....Calcifying Vascular Cells

CVD .....Cardiovascular Disease

DM .....Diabetes Mellitus

DN .....Diabetic Nephropathy

DV .....Diabetic Vasculopathy

EC .....Endothelial Cell

ECD .....Endothelial Cell Dysfunction

ECM ..... Extra cellular matrix.

EDHF ....Endothelium Derived Hyperpolarizing factor

ELISA ...Enzyme Linked Immunosorbent Assay

EPO .....Erythropoietin

EPOR ....Erythropoietin Receptor

ESRD .....End Stage Renal Disease

ET .....Endothelin

FFA..... Free fatty acids.

GDM .....Gestational Diabetes Mellitus

GGT .....Gamma Glutamyl Transferase

GFR .....Glomerular Filtration Rate

Hcy..... Homocysteine.

HIF .....Hypoxia Inducible Factor

HLA .....Human Leucocyte Antigen

HRE .....Hypoxia Responsible Element

IC..... Intermittent claudication.

ICAM ....Intercellular Adhesion Molecule

IDDM ....Insulin Dependent Diabetes Mellitus

IFG .....Impaired Fasting Glucose

IGT .....Impaired Glucose Tolerance

IL .....Interleukin

IR .....Insulin Resistance

MA..... Micro-albuminuria.

MAC .....Medial Arterial Calcification

MHC..... Major histocompitability complex.

MI .....Myocardial Infarction

MODY ...Maturity Onset Diabetes of the Young

MRDM ..Malnutrition Related Diabetes Mellitus

Msx2 .....Homeobox, msh-like 2 gene

NAG .....N - acetyl-β-D-glucosaminidase

NIDDM .Non Insulin Dependent Diabetes Mellitus

NO .....Nitric Oxide

Ntx .....N- linked telopeptide of Collagen

OCIF ..... Osteoclastin inhibitory factor.

OPG .....Osteoprotegerin

PAI .....Plasminogen activator inhibitor.

RAS ..... Renin angiotensin system.

PDGF ....Platelet Derived Growth Factor

PPi .....Inorganic pyrophosphate

PTC .....Peritubular Capillaries

PTH .....Parathyroid Hormone

PVD .....Peripheral Vascular Disease

RAGE ....Receptor for Advanced Glycation End Products

RANKL .Receptor Activator for nuclear factor kappa B ligand

RAS .....Renin Angiotensin System

RBC .....Red Blood Cells

RBP .....Retinol Binding Protein

ROS .....Reactive Oxygen Species

TACT ..... Therapeutic angiogenisis by cell transplantation trail

TGF-β .... Transforming Growth Factor Beta

TNF .....Tumour Necrosis Factor

TRAIL ...TNF - related apoptosis inducing ligand

VC .....Vascular Calcification

VCAM ...Vascular Adhesion Molecule

VDR .....Vitamin D Receptor

VEGF ....Vascular Endothelial Growth Factor

VSMC ....Vascular Smooth Muscle Cells

vWF .....Von Willebrand Factor

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DIABETES MELLITUS AND ITS COMPLICATIONS

Introduction

Diabetes Mellitus (DM) is a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.

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)**

DM has been known to physicians since antiquity. Initially, the disease was described as Diabetes (greek- syphon) literally meaning passing huge amounts of water, by Aretaeus, the Greek physician. Mellitus (latin- honey) was added by Thomas Willis, an English physician, to signify 'sweet urine' passed by these patients. **(Alberti and Zimmet, 1998)**

With increased understanding of the pathophysiology of DM, new variants of the disease were noticed over time. To

incorporate the new understanding about the disease and to overcome the chaotic situation about classification, the World Health Organisation (WHO) proposed and published the first widely accepted classification of DM in 1980 **(World Health Organ Tech Rep Ser 1980)** and, in modified form, in 1985 **(WHO Study Group. Geneva 1985)**.

Proposed two major classes of DM and named them, insulin dependent diabetes mellitus (IDDM) or type 1 DM, and non-insulin dependent diabetes mellitus (NIDDM) or type 2 DM. In both the 1980 and 1985 reports other classes of DM included Other Types and Impaired Glucose Tolerance (IGT) as well as Gestational DM (GDM). The WHO classification of DM was further revised in 1997 by ADA (American Diabetes Association), The new classification incorporates both, the staging of DM based on clinical descriptive criteria and complementary aetiological criteria.

Etiologic classification of DM:

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

   A. Immune mediated

   B. 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***

A. Genetic defects of β-cell function

Chromosome 12, HNF-1α (MODY3)

Chromosome 7, glucokinase (MODY2)

Chromosome 20, HNF-4α (MODY1)

Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)

Chromosome 17, HNF-1β (MODY5)

Chromosome 2, *NeuroD1* (MODY6)

Mitochondrial DNA

Others

B. Genetic defects in insulin action

Type A insulin resistance

Leprechaunism Rabson-Mendenhall syndrome

Lipoatrophic diabetes

Others

C. Diseases of the exocrine pancreas

Pancreatitis

Trauma/pancreatectomy

Neoplasia

Cystic fibrosis

Hemochromatosis

Fibrocalculous pancreatopathy

Others

D. Endocrinopathies

Acromegaly Cushing's syndrome

Glucagonoma

Pheochromocytoma

Hyperthyroidism

Somatostatinoma

Aldosteronoma

Others

E. Drug- or chemical-induced

Vacor

Pentamidine

Nicotinic acid

Glucocorticoids

Thyroid hormone

Diazoxide

β-adrenergic agonists

Thiazides

Dilantin

α-Interferon

Others

F. Infections

Congenital rubella

Cytomegalovirus

G. Uncommon forms of immune-mediated diabetes

"Stiff-man" syndrome

Anti–insulin receptor antibodies

H. Other genetic syndromes sometimes associated with diabetes

Down's syndrome

Klinefelter's syndrome

Turner's syndrome

Wolfram's syndrome

Friedreich's ataxia

Huntington's chorea

Laurence-Moon-Biedl syndrome

Myotonic dystrophy

Porphyria

Prader-Willi syndrome

Gestational diabetes mellitus (GDM)

(Diabetes Care, 2011)

Type 1 Diabetes Mellitus

Type 1 DM, which was previously recognised as IDDM (insulin dependent diabetes mellitus), based on absolute insulin requirement for survival, is now classified on the basis of aetiopathogenesis of the disease. It is an autoimmune disorder characterized by loss of the insulin-producing beta cells in the islets of Langerhans, in the pancreas, resulting in deficiency of insulin. The autoimmune destruction of the beta cells is induced by CD4+ and CD8+ T cells and macrophages infiltrating the islets. **(Lancet, 2000)**

Type 1 DM patients may also have associated other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis and Addison's disease. **(Honeyman, 2000)**

Type 1 DM accounts for about 10% of the total occurrence of DM, while the majority of DM comprises of type 2 DM. It typically affects young children and generally manifests before the of age 40, although there may be exceptions. Due to the frequent occurrence in children, previously it was also termed as "juvenile diabetes", although the term is now obsolete. Among the various racial groups, type 1 DM is most common in caucasians.

Gillespie stated on 2006 that the overall incidence of type 1 DM is on a rise with current rate of 3% and is expected to be much higher in future. **(Gillespie KM, 2006)**

Autoimmunity is the predominant effector mechanism of T1D, but may not be its primary cause. T1D precipitates in genetically susceptible individuals, very likely as a result of an environmental trigger. Current genetic data point towards the following genes as susceptibility genes: HLA, insulin, IL2Ra (Interleukin 2 Receptor alpha gene.), and CTLA4 (Cytotoxic T-Lymphocyte associated protein 4). **(Tom et al., 2010)**

Type 1 diabetes was posed to be initiated by an ill-defined environmental attack resulting in the release of β-cell autoantigens Subsequently, those self-antigens were thought to be scavenged by macrophages, presented by major histocompatibility complex (MHC) class II molecules (i.e., HLA-DR), leading to the activation of helper T-cells, which would in turn activate B-cells to produce antibodies (e.g., islet cell cytoplasmic autoantibodies and complement-fixing autoantibodies) as well as activate killer cells and cytotoxic T-cells. **(Atkinson et al., 2011)**

Type 2 Diabetes Mellitus

This form, previously referred to as “noninsulin dependent diabetes” or “adult onset diabetes,” accounts for 90–95% of all diabetes. Type 2 DM encompasses individuals who have insulin resistance and usually relative (rather than absolute) insulin deficiency. At least initially, and often