ADRENOMEDULLIN LEVEL IN PATIENTS WITH TYPE ٢ DIABETES MELLITUS

Thesis

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Abstract :

The study of two population with type 2 diabetes showed that a subset of the patients had higher levels of adrenomedullin (ADM) than the rest of the diabetics. In this subset, physiological elevation of ADM might have triggered the disease in predisposed individuals. Diabetics showed higher levels of ADM than healthy controls. ADM is a circulating hormone and its plasma concentration is increased in various cardiorenal diseases such as hypertension, chronic renal failure and congestive heart failure.

Keywords :

Adrenomedullin, Type 2 Diabetes Mellitus.

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Contents

List of Abbreviations

ACEI	Angiotensin converting enzyme inhibitors
ACTH	Adreno corticotrophic hormone
ADM	Adrenomedullin
AG II	Angiotensin II
BMI	Body mass index
CAD	Coronary artery disease
CAMP	Cyclic adenosine 3` , 5` monophosphate
CGRP	Calcitonin gene related peptide
CRH	Corticotrophic releasing hormone
CRLR	Calcitionin receptor like receptor
CV	Coefficient variation
CVA	Cerebrovascular accident
DM	Diabetes mellitus
ET1	Endothelin 1
FFA	Free fatty acids
FPG	Fasting plasma glucose
GAD	Glutamic acid decarboxylase
GDM	Gestational diabetes mellitus
HBA1c	Hemoglobin A1c
HDL	High density lipoprotein
HLA	Human leukocyte antigen

HNF	Hepatocyte nuclear factor
HS	Highly significant
ICAS	Islet cell autoantibodies
IDDM	Insulin dependent diabetes mellitus
IL1	Interleukin 1
IPF	Insulin promoter factor
LDL	Low density lipoprotein
M	Mean
MODY	Maturity onset diabetes of the young
N	Number
NDDG	National diabetes data group
NIDDM	Non insulin dependent diabetes mellitus
NO	Nitric oxide
NS	Not significant
OGTT	Oral glucose tolerance test
PAI-1	Plasminogen activator inhibitor-1
PAMP	Proadrenomedullin N-terminal 20 peptide
PAV	Plasma arginine vasopressin
PGI2	Prostaglandin I 2
PKC	Protein kinase c
PRA	Plasma renin activity
RAMP	Receptor activation modification protein
rpm	Run per minute
S	Significant

SA-HRP	Streptavidin -horseradish peroxidase
SD	Standard Deviation
TG	Triglycerides
TMB	Tetramethyl -benzidine
TNF-α	Tumour necrosis factor - α
VIP	Vasoactive intestinal peptide
VSMCS	Vascular smooth muscle cells
WHO	World health organization

Introduction

Diabetes mellitus is a metabolic disorder 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, 2005**).

It is one of the most common reasons for patient contact with the physician and is a major cause of premature disability and mortality. It increased the risk of cardiac, cerebral and peripheral vascular diseases two – to – seven folds and is a major factor contributing to morbidity and mortality (**Sherwin, R.S, 2000**).

Adrenomedullin (ADM), a 52-amino acid ringed – structure peptide with c-terminal amidation, was originally isolated from human pheochromocytoma. Adrenomedullin mediates vaso-dilatory and natriuretic properties through the second messenger cyclic adenosine 3`,5`-monophosphate (CAMP), nitric oxide and the renal prostaglandin system. Adreno-medullin immunoreactivity and its gene are widely distributed in cardiovascular, pulmonary, renal, Gastrointestinal, cerebral and endocrine tissues. Adrenomedullin is also synthesized and Secreated from vascular endothelial and smooth muscle cells. In addition, ADM is a circulating hormone and its plasma concentration is increased in various cardiorenal diseases such as hyper-tension, chronic renal failure and congestive heart failure. Current evidence suggests that ADM plays an important role in fluid and electrolyte homeostasis and cardiorenal regulation (**Jougasaki M and Burnett JR JC.,**

2000). Recently it was found that ADM level increases in type II diabetes (**Martinez E, et al., 1999**). The plasma ADM increases in cases of diabetic nephropathy and retinopathy . Plasma level of ADM positively correlated with urinary execretion of protein. The increase in plasma adrenomedullin is closely related to diabetic complication (**Nakamura T, et al., 1998**).

Aim of the work

The aim of the present thesis is to study Adrenomedullin level in type 2 diabetes mellitus.

Patients and methods:

This study will include 50 persons, 40 type2 diabetic patients aged between 30 and 70 years, both sex (males and females) who will be subjected to analysis adrenomedullin level divided into 3 groups, group I 20 patients non complicated type 2 diabetes, group II 20 patients complicated type 2 diabetes with nephropathy, group III 10 control persons.

Exclusion criteria:

١. patient with heart failure.

٢. patient with ischaemic heart disease.

٣. patient with hypertension.

4-patient with chronic renal failure.

Diabetes mellitus (DM)

Diabetes mellitus "DM" is a metabolic disorder 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, 2005**).

Epidemiology of diabetes mellitus :

Diabetes mellitus remain one of the most challenging diseases for workers in the medical field. It's prevalence in adults worldwide was estimated to be 171 million in 2000 and it's expected to rise to 300 millions by the year 2025 and 371 millions in 2030. The prevalence is similar in men and women throughout most age ranges but is slightly greater in men>60 years (**Padwal M, et al., 2005**).

The incidence of both type 1 and type 2 DM has a considerable geographic variations; it is higher in developing countries than in developed countries. DM prevalence also varies among different ethnic populations within a given country. This variability is likely due to genetic, behavioral, and environmental factors (**Wild S, et al., 2004**).

Type 2 DM is the predominant form of diabetes world wide accounting for 90-95% of cases globally. The prevalence of type 2 DM is expected to rise more rapidly in the future because of increasing obesity and reduced activity levels (**Kasper, et al., 2005**).

Classification of Diabetes Mellitus :

Improved understanding of the origin and pathogenesis of diabetes has made it possible to revise the classification of diabetes mellitus. This revision contrasts with the previous classification, which was based mainly on therapeutic requirements: insulin-dependent diabetes (IDDM) and non-insulin-dependent diabetes (NIDDM), terms that have been eleminated. Any patient with diabetes may require insulin therapy at some stage of the disease, irrespective of the classification. So the recent classification of diabetes depends on the etiology not the pharmacological treatments of the attained types (**Philip B, et al., 2001**).

Etiologic classification of diabetes mellitus :

1- type 1 diabetes mellitus.

There is B-cell destruction usually which leads to absolute insulin deficiency. It is of two types :

A- Immune mediated.

B- Idiopathic.

2- Type 2 diabetes mellitus :

May range from predominantly insulin resistance with relative insulin deficiency to predominantly secretory defect with insulin resistance.

3- Other specific types :

A- Genetic defects of B-cell function:

Characterized by onset of hyperglycemia at an early age (generally before age 25 years). They are referred to as

maturity – onset diabetes of the young (MODY) and are characterized by impaired insulin secretion with minimal or no defect in insulin action. They are inherited in an autosomal dominant pattern. The most common form is associated with mutation on chromosome12 in hepatic transcription factor referred to as a hepatocyte nuclear factor (HNF). A second form is associated with mutation in the glucokinase gene on chromosome7 and insulin promoter factor (IPF)-1. Mutations in mitochondrial DNA have been found to be associated with diabetes mellitus.

١- Chromosome 12 HNF-1 α (MODY 3).

٢- Chromosome 7 glucokinase (MODY 2).

٣- Chromosome 20 HNF – 4 α (MODY 1).

٤- Mitochondrial DNA.

٥- Others.

B- Genetic defects in insulin action :

There are unusual causes of diabetes that results from genetically determined abnormalities of insulin action. The metabolic abnormalities associated with mutations of the insulin receptor may range from hyperinsulinemia and modest hyper-glycemia to sever diabetes.

١- Type A insulin resistance.

٢- Leprechaunism.

٣- Rabson- Mandenhall syndrome

٤- Lipoatrophic diabetes.

٥- Others.

Leprechaunism and the Rabson – Mendenhall syndromes are two pediatric syndromes that have mutation in the insulin receptor gene.

C- Diseases of exocrine pancrease :

١- Pancreatitis.

٢- Trauma / pancreatectomy.

٣- Neoplasia.

٤- Cystic fibrosis.

٥- Hemochromatosis.

٦- Fibrocalculous pancreatopathy.

٧- Others.

D- Endocrinopathies :

١- Acromegaly.

٢- Cushing's syndrome.

٣- Glucagonoma (α-cell tumours which are responsible for the syndrome of migratory necrolytic dermatitis, weight loss, diabetes mellitus, deep vein thrombosis, anaemia hypoalbuminemia).

٤- Pheochromocytoma.

٥- Hyperthyroidism.

٦- Somatostatinoma.

٧- Aldosteronoma.

٨- Others.