Plasma Adrenomedullin Levels in Patients with Type I Diabetes Mellitus, Relationship to Microvascular Complications

Thesis

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By

Hala Rabie Mahmoud Afifi

M.B., B. Ch.

Supervised by

Prof. Dr. Safinaz Adel El-Habashy

Professor of Pediatrics

Faculty of Medicine – Ain Shams University

Assist Prof. Dr. Randa Mahmoud Matter

Assistant Professor of Pediatrics

Faculty of Medicine – Ain Shams University

Dr. Iman Saleh El-Hadidi

Lecturer of Clinical Pathology

Faculty of Medicine – Ain Shams University

Faculty of Medicine

Ain Shams University

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Contents

Page

Introduction

Diabetes is characterized by long-term complications including nephropathy, retinopathy and neuropathy, all of which are closely related to vascular damage ***(Martinez et al., ١٩٩٦)***.

Well-controlled diabetes prevents the occurrence of microvascular complications & decreases the formation of macrovascular complications ***(DCCT Research Group, ١٩٩٣)***.

Adrenomedullin (AM) is a novel ٥٢ amino acid peptide hormone, originally isolated from human pheochromocytoma. It acts as a local autocrine and/or Paracrine vasoactive hormone, and has a vasodilator and blood pressure lowering properties ***(Ruzicska et al., ٢٠٠١)***. AM is implicated in blood pressure regulation and in the pathophysiology of several diseases such as hypertension, cancer, diabetes, and renal disorders, becoming an interesting new target for the development of drugs ***(Garcia et al., ٢٠٠٥)***.

The major source of circulating adrenomedullin is considered to be the vasculature ***(Kinoshita et al., ٢٠٠٠)***. Adrenomedullin is a hypotensive peptide involved in insulin regulatory system ***(Di-Iorio et al., ٢٠٠١)***. Insulin secretion from pancreas is inhibited by adrenomedullin and i.v. injection of which reduces the plasma insulin concentration ***(Martinez et al., ١٩٩٦)***.

Aim of the Work

Assessment of plasma adrenomedullin levels in patients with type I diabetes mellitus (D.M) and correlation of these levels with metabolic control and diabetic microangiopathy.

Diabetes Mellitus

Definition:

Diabetes mellitus (DM) 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, ٢٠٠٥a)***.

Classification:

Both etiological classification and staging of pathophysiology by the degree of deficiency of insulin effect need to be considered. The etiological classification of diabetes and related disorders of glycemia includes, (I) type ١; (II) type ٢; (III) those due to specific mechanisms and diseases; and (IV) gestational diabetes mellitus. Destructive lesions of pancreatic β cells characterize type ١ either by an autoimmune mechanism or of unknown cause. Type ٢ diabetes is characterized by combination of decreased insulin secretion and decreased insulin sensitivity (insulin resistance). Category (III) includes two subgroups; subgroup A is diabetes in which specific mutations have been identified as a cause of genetic susceptibility, while subgroup B is diabetes associated with other pathologic conditions or diseases ***(Kuzuya et al., ٢٠٠٢)***.

In ١٩٩٨, WHO proposed a classification of diabetes

mellitus (DM) that encompasses both clinical stages and etiological types of DM. (table ١ and ٢) & figure (١).

Table (١): Etiological classification of disorders of glycemia:

Type ١ (β-cell destruction, usually leading to absolute insulin deficiency)

- Autoimmune.
- Idiopathic.

Type ٢ (may range from predominately insulin resistance with relative insulin deficiency to a predominately secretory defect with or without insulin resistance).

Other specific types

- Genetic defects of β-cell function.
- Genetic defects in insulin action.
- Diseases of the exocrine pancreas.
- Endocrinopathies.
- Drug-or chemical induced.
- Infections.
- Uncommon forms of immune-mediated diabetes.
- Other genetic syndromes sometimes associated with diabetes.

Gestational diabetes

(Alberti and Zimmet, ١٩٩٨).

Table (٢): Other specific types of diabetes:

Genetic defects of β-cell function:
- Chromosome ٢٠, HNF٤α (MODY ١).
- Chromosome ٧, glucokinase (MODY ٢).
- Chromosome ١٢, HNF١α (MODY ٣).
- Chromosome DNA, ٣٢٤٣ mutation.
- Others.

Genetic defects in insulin action:
- Type A insulin resistance.
- Leprechaunism.
- Rabson-Mendenhall syndrome.
- Lipoatrophic diabetes.
- Others.

Diseases of the exocrine pancreas:
- Fibrocalculous pancreatopathy.
- Pancreatitis.
- Trauma/pancreatectomy.
- Neoplasia.
- Cystic fibrosis.
- Hemochromatosis.
- Others.

Endocrinopathies:
- Cushing's syndrome.
- Acromegaly.
- Pheochromocytoma.
- Glucagonoma.
- Hyperthyroidism.
- Somatostatinoma.
- Others

Drug or chemical-induced

Infections :
- Congenital rubella.
- Cytomegalovirus.
- Others.

Uncommon forms of immune-mediated diabetes:
- Insulin autoimmune syndrome (antibodies to insulin)
- Anti-insulin receptor antibodies.
- 'Stiff man' syndrome.
- Others.

Other genetic syndromes sometimes associated with diabetes:

١. Down syndrome ٢. Klinefelter syndrome
٣. Laurence-Moon-Biedl Syndrome ٤. Prader-willi-syndrome

(Alberti and Zimmet, ١٩٩٨)

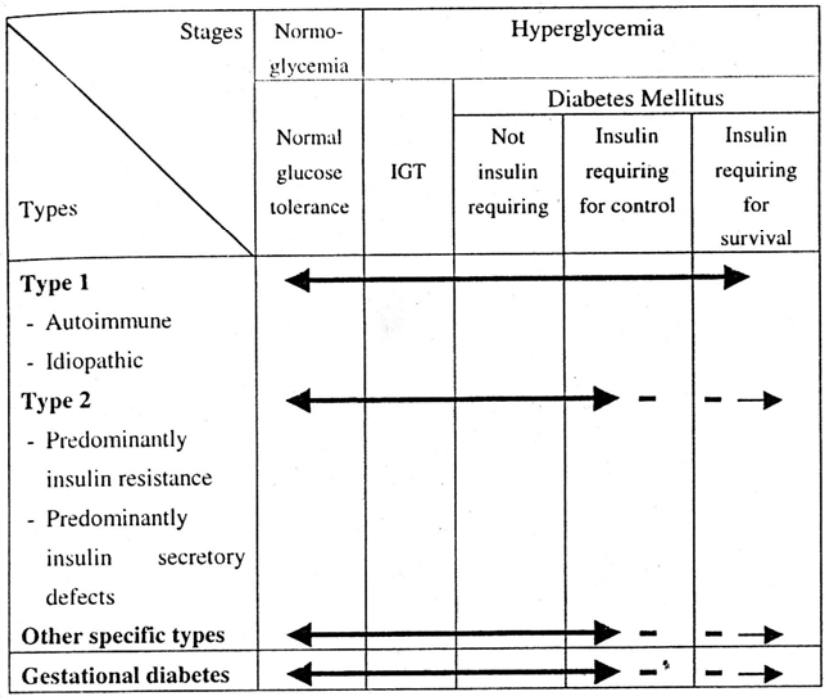

Figure (١): *Disorders of glycemia: etiological types and clinical stages* ***(Alberti & Zimmet, ١٩٩٨)***.

WHO classification has several applications:

The clinical staging reflects that DM, regardless of its etiology, progress through various degrees of hyperglycemia and individual subjects may move from one stage to another in either direction. The etiological classification reflects the fact that the defect or the process that may lead to DM, may be identified at any diabetic stage even in the stage of normoglycemia. Thus, the presence of islet cell antibodies in a normoglycemic individual makes it likely that this person will have type ١ DM ***(Alberti and Zimmet, ١٩٩٨).***

The term impaired glucose tolerance (IGT) is reclassified

as a stage of impaired glucose regulation, since it can be observed in any hyperglycemic disorder, and it is not diabetes ***(Alberti and Zimmet, ١٩٩٨)***.

Epidemiology of Type ١ diabetes:

Type ١ diabetes is the most common endocrine metabolic disorder of children and adolescents. During childhood, the incidence of type ١ diabetes increases steadily. Peaks of presentation occur in two age groups: at ٥-٧ years of age and at time of puberty. After the age of ٢٠ years, the incidence is probably constant at low level ***(Sperling, ٢٠٠٠)***.

Salem et al. (١٩٨٧) found that there is bimodal peak of incidence, the first around six years of age and the other around ten years of age.

There is marked geographical variability in the incidence of type ١ diabetes. The highest incidence is reported in Scandinavians, with Finland showing the highest rates (about ٤٠/١٠٠.٠٠٠/year), meanwhile Japanese and Oriental Population show the lowest rates (less than ١/١٠٠.٠٠٠/year) ***(Kocova et al., ١٩٩٣)***. Figure (٢).

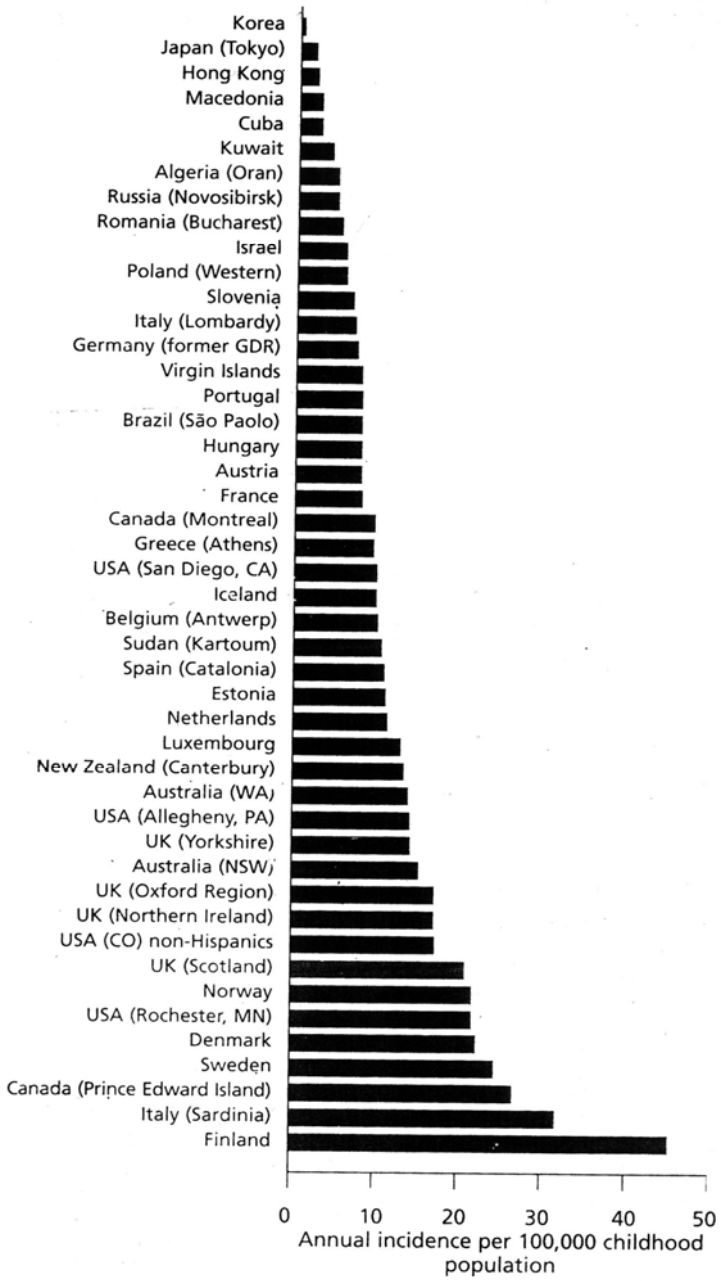

Figure (٢): *Annual incidence rates for childhood type ١ diabetes (٠- to ١٤-year age group) in different regions of the world.* ***(Source: Verge, Thesis, University of Sydney, ١٩٩٤)*** **[ISPAD, ٢٠٠٠]**.

In Egypt, ***Ghaly et al. (١٩٨٥)*** reported a prevalence rate of type ١ diabetes of ٠.٣٣/١٠٠٠ among school age children in Giza and Embaba. Also, ***Salem et al. (١٩٧٨); Salem et al., (١٩٩٠)*** reported that, the point prevalence rate of type ١ diabetes among school children in Heliopolis district in Cairo was ١.٠٩/١٠٠٠ with male predominance. In El-Mansura, a screening survey of school children (٥-١٥ years) revealed that the prevalence rate of type ١ diabetes was ٢/١٠٠٠ ***(Ali et al., ١٩٨٦)***.

Etiology and Pathogenesis:

Type ١ diabetes is usually due to autoimmune destruction of the β-cells of the islets of the Langerhans in individuals with genetic predisposition, when exposed to environmental factors, which are still poorly understood ***(Alberti and Zimmet, ١٩٩٨)***.

١- Genetic Factors:

There is no clear pattern of inheritance of childhood diabetes although there is a familial aggregation due to the association of type ١ diabetes with certain genetic markers. In the higher incidence countries the risk to relatives of developing the disease when a member of the family has type ١ diabetes are as follow:-

- Risk to child/adolescent of a father with type ١ DM ~ ٧%.
- Risk to child/adolescent of a mother with type ١ DM ~ ٢%.
- Risk to identical twin of a child with type ١ DM ~ ٣٥%.
- Risk to sibling of a child of type ١ DM ~ ٣-٦%.

(ISPAD, ٢٠٠٠).

The human leucocyte antigen (HLA) region on the short arm of chromosome ٦ is probably responsible for more than ٦٠% of the genetic susceptibility to type ١ diabetes, with the strongest association with HLA-class٢ antigens in the DR and DQ region. Inheritance of HLA-D٣ or D٤ antigens appear to confer two to three folds increased risk for the development of type ١ diabetes. When both D٣ and D٤ are inherited, the relative risk for the development of diabetes is increased by ٧ to ١٠ folds ***(Zimmet, ١٩٩٣).***

In Whites, at least one major susceptibility locus may reside in the DQB١ gene. The homogenous absence of aspartic acid at position ٥٧ of the HLA DQ-B chain (non Asp/non Asp) confers an approximately ١٠٠ folds relative risk for the development of type ١ diabetes. Those who are heterogeneous with a single Aspartic acid at position ٥٧ (non Asp/Asp) are less likely to acquire diabetes. Indeed, the incidence of type ١ diabetes in a given population appears to be proportional to the gene frequency of non Asp alleles in that population. In addition, Arginine at position ٥٢ of the DQB chain confers marked susceptibility to type ١ diabetes. In a region of variable number of tandem repeats in the region of the insulin gene on chromosome ١١ may account for about ١٠% of the genetic risk ***(Sperling ٢٠٠٠)***.

It is important to emphasize that there is no diabetes gene, but rather genetic alterations are associated with increased or decreased susceptibility for β cell damage, thus potentially leading to DM ***(Drash and Arsalanian, ١٩٩٠)***.

٢- Environmental Factors:

Environmental factors are important in the pathogenesis of type ١ DM, as they interact with, and influence the penetration of diabetes susceptibility genes. Likely agents include virus, dietary components and perhaps stress ***(Pickup and Williams, ٢٠٠٣a)***.

Neonatal infections and respiratory difficulties were important risk factors of developing type ١ diabetes. Exclusive breast feeding as the initial feeding method was significantly protective ***(McKinney et al., ١٩٩٩)***. Non-breast fed children have a higher risk of developing type ١ diabetes than those who were breast fed. Also, cow's milk consumption in particular may be a risk for the disease ***(Gerstein, ١٩٩٤)***.

Several observations have implicated bovine serum albumin (BSA), a constituent of cow's milk, as a trigger of type ١ diabetes in human. BSA can damage β cells through "Molecular Mimicry". An epitope of BSA, specifically ١٧-amino acid peptide has close homology with islet cell membrane. A high level of consumption of cow's milk (>٠.٥ liters/ day) increases the risk of type ١ diabetes ***(Virtanen et al.,***

٢٠٠٠).

Viruses:

Traditionally, it has been suspected that viruses may act as triggers for the initiation of the anti-immune event that eventually leads to diabetes ***(Yoon, ١٩٩٥; Devendra and Eisenbarth, ٢٠٠٤)***.

Certain viruses are known to be pancreotropic, among them mumps, coxackie B٤, other enteroviruses, retroviruses and others. Studies demonstrated evidence of enteroviral RNA sequences by polymerase chain reaction (PCR) in ٢٧% of newly diagnosed diabetics versus ٤.٩% of control subjects ***(Narin et al., ١٩٩٩)***.

Coxsackie B viruses may induce diabetes through strong cytolytic effect on β cells. Also, they can induce autoimmune destruction of islet cells through "Molecular Mimicry" as antibodies to viral antigen (P٢-C) may cross react with the β cell antigen, glutamic acid decarboxylase (GAD) especially in susceptible individuals. Moreover, infection with the virus increases expression of GAD by β cells ***(Sperling, ١٩٩٧)***.

Immunological factors

There is evidence that tissue-specific molecules are expressed in the thymus and peripheral lymphoid tissue by specialized antigen-presenting cells, and that such expression is critical for self-tolerance. Insulin, a key hormone exclusively

produced by pancreatic beta cells and a critical auto antigen in type ١ diabetes, provides an excellent example of a molecule with tissue-restricted expression that is ectopically expressed by antigen-presenting cells in both thymus and peripheral lymphoid tissues ***(Prabakar and Pugliese, ٢٠٠٤)***.

About ٨٠-٩٠% of newly diagnosed patients with type ١ diabetes have islet cell antibodies (ICAs) directed against cell surface or cytoplasmic determinants in their islet cells. The prevalence of these antibodies decreases with the duration of established disease, but persistence is associated with increased β cells destruction (low C-peptide and high insulin requirement) ***(Sperling, ١٩٩٧)***.

٣٠% of ICA-positive first degree relatives of type ١ diabetic patients later develop the disease ***(Pickup and Williams, ٢٠٠٣b)***.

Immunotherapy could be considered as the most satisfactory solution to the prevention and cure of type ١ diabetes ***(Chatenoud, ٢٠٠١; Singh, ٢٠٠٠)***.

Multiple islet autoantibody positivity is currently believed to best predict progression to type ١ diabetes ***(Decockez et al., ٢٠٠٠)***.

The type of autoantibody was found to be important to predict impending diabetes, positivity for IA-٢A seems to have a higher predictive value for impending clinical onset than other