Relation between Carotid Intima Media Thickness and Oxidative Stress in Type 1 Diabetic Children and Adolescents

Thesis

Submitted for partial Fulfillment of Master Degree
in Pediatrics

By

Nermeen Ahmed Kamal Abd Allah
M.B. BCh. – 2006
Faculty of Medicine, Ain Shams University

Under Supervision of

Prof. Dr. Mona Hussein El Samahy
Professor of Pediatrics
Faculty of Medicine -Ain Shams University

Prof. Dr. Randa Mahmoud Asaad Sayed Matter
Professor of Pediatrics
Faculty of Medicine -Ain Shams University

Dr. Omneya Ibrahim Youssef
Lecturer of Pediatrics
Faculty of Medicine -Ain Shams University

Faculty of Medicine
Ain Shams University
2012

Contents

List of Abbreviations

ACEIs	: Angiotensin converting enzyme inhibitors
ADP	: Adenosine diphosphate
AGE	: Advanced glycosylation end products
AR	: Aldose reductase
ARBs	: Angiotensin receptor blockers
ATRA	: All-trans retinoic acid
BG	: Blood glucose
BMI	: Body mass index (BMI)
CAC	: Coronary artery calcification
CCA	: Common carotid artery
CETP	: Cholesterol ester transfer protein
CHD	: Coronary heart disease
cIMT	: Carotid intima-media thickness
CSII	: Continuous subcutaneous insulin infusion
CT	: Computed tomography
CVD	: Cardiovascular disease
DCCT	: Diabetes control and complications trial
DCCT/EDIC	: Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications
DKA	: Diabetic keto-acidosis
DM	: Diabetes mellitus
ECM	: Extracellular matrix

EDNO : Endothelium derived nitric oxide

EDRF : Endothelium derived relaxing factor

eNOS : Endothelial nitric oxide synthase

ESRD : End-stage renal disease

GD : Gestational diabetes mellitus

GMP : Guanosine monophosphate

HBP : Hexosamine biosynthesis pathway

HNF : Hepatocyte nuclear factor

H_2O_2 : Hydrogen peroxide

ICA : Internal carotid artery

IDDM : Insulin-dependent diabetes mellitus'

IMT : Intima media thickness

LADA : Latent autoimmune diabetes of the adult

MODY : maturity-onset diabetes of the young

NAC : N-Acetyl-Cysteine

NADPH : Nicotinamide adenine dinucleotide phosphate

NO : Nitric oxide

PKC :Protien kinase C

RAGE : Receptor for advanced glycation end products

ROS : Reactive Oxygen Species

RNC : Reactive Nitrogen Species

SDH : Sorbitol dehdrogenase

SDS : Standard deviation score

SMBG : Self-monitoring of blood glucose

S1P :Sphingosine 1 phosphate

T1DM : Type 1 diabetes mellitus

TAC : Total Antioxidant Capacity

Th : T helper cell

tHcy : Total homocysteine

TG : Triglycerides

UDP-GlcNAc : UDP-Nacetylglucosamine

VSMC : Vascular smooth muscle cell

List of Tables

List of Figures

Introduction

Diabetes mellitus (DM) is a common chronic metabolic syndrome characterized by hyperglycemia as a cardinal biochemical feature.Type-1 D.M is the most common form of D.M in children and adolescents ***(Wyatt, 2008).***

The incidence of type 1 diabetes has been increasing by about 3% per year ***(Aanstoot et al., 2007).***

Diabetes mellitus type 1 is an important risk factor for the development of cardiovascular disease. Patients with diabetes show a 2- to 10-fold risk for developing atherosclerotic lesions compared with the normal population. Even if atherosclerotic complications become manifest in the adult diabetic patient, the process of vascular changes starts much earlier ***(Dalla Pozza et al., 2007)***.

There is a growing interest to prevent the cardiovascular disease risk factors early in the course of the disease, even at pediatric stages. It is necessary to identify children with type 1diabetes with the highest risk for CHD using objective and noninvasive studies ***(Rabago Rodriguez et al., 2007).***

Carotid artery intima thickness (IMT), as measurable by high-resolution B-mode ultrasonography, is a noninvasive marker of subclinical atherosclerosis. Recently, normative values for the IMT in children and adolescents have been published ***(Dalla Pozza et al., 2007).***

Diabetic patients are exposed to increased oxidative stress due to several mechanisms which include not only oxygen free radical generation due to non enzymatic glycosylation and oxidation of glycation products but also change in tissue content and activity of antioxidant defense system. Increased levels of the products of oxidative damage to lipids have been detected in serum of diabetic patients, and their presence correlates with the development of complications ***(Ramakrishna and Jaikhani, 2007).***

The role of oxidative stress in diabetes mellitus as a possible link between metabolic control and vascular complications have been subject of great interest ***(Vessebly et al., 2002)***.

Total Antioxidant Capacity (TAC) is found to be significantly lower in diabetic patients. Total Antioxidant Capacity (TAC) is capable of serving as a parameter to monitor diabetes of patients with type 1 DM ***(Akkaya and Celik, 2009).***

A depletion of the total antioxidant capacity is associated with a higher incidence of diabetic complications ***(Opara et al., 1999).***

Nitric oxide is also a natural antioxidant which mediates endothelial-dependent vasodilatation and possesses additional anti-atherogenic properties associated with the coagulation cascade, platelet activation and angiogenesis. Reduced bioavailability of nitric oxide has been reported in diabetes ***(Browne et al., 2007).***

Giannini et al. (2009) concluded that serum nitrite/ nitrate can be used as positive determinants of atherosclerosis assessed by carotid intima media thickness in diabetic patients.

Aim of the Work

Assessment of carotid intima media thickness in type1 diabetes mellitus in relation to plasma nitric oxide and plasma total antioxidant capacity levels and with diabetes duration, glycemic control and microvascular complications.

Diabetes Mellitus

Definition:

"A group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both" ***(Fenn, 2011).***

Classification of diabetes mellitus:

Table (1): Etiologic classification of diabetes mellitus

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 of diabetes		
A. Genetic defects of B-cell function:		
1. Chromosome 12, HNF-1α (MODY3) 2. Chromosome 7, glucokinase (MODY2) 3. Chromosome 20, HNF-4α (MODY1) 4. Chromosome 13,insulin promoter factor 1(IPF-1; MODY4)		5. Chromosome 17, HNF-1β (MODY5) 6. Chromosome 2, neuro D1(MODY6) 7. Mitochondrial DNA 8. Others
B. Genetic defects in insulin action:		
1. Type A insulin resistance 2. Leprechaunism 3. Rabson-Menednhall syndrome		4. Lipotrophic diabetes 5. Others
C. Diseases of the exocrine pancreas:		
1. Pancreatitis 2. Neoplasia 3. Trauma / pancreatectomy 4. Cystic fibrosis		5. Hemochromatosis. 6. Fibrocalculous pancreatopathy 7. Others
D. Endocrinopathies:		
1. Acromegaly 2. Cushing's syndrome 3. Glucagonoma 4. Pheochromocytoma		5. Hyperthyroidism 6. Somatostatinoma 7. Aldosteronoma 8. Others