Study of Apo A-1 level in type 1 Diabetic children with Dyslipidemia

Thesis

For Partial Fulfillment of MSc Degree in Pediatrics

By

Motaz Mohammed Barham Abu Daqqa

Supervisors

Prof. Fatma Alzahraah Mostafa Gomaa

Professor of Pediatrics

Faculty of Medicine – Cairo University

Prof. Ghada Mohammad Anwar

Professor of Pediatrics

Faculty of Medicine – Cairo University

Prof. Sahar Abd El-Atty Sharaf

Professor of Clinical and Chemical Pathology

Faculty of Medicine – Cairo University

Department of Pediatrics

Faculty of Medicine

Cairo University

2013

Abstract

Background: Cardiovascular disease (CVD) is the leading cause of death in people with type 1 diabetes mellitus (T1DM). Dyslipidemia is a significant CVD risk factor in persons with diabetes. Measurement of apoA-1 in diabetic patients may be helpful to diabetic patients at risk of cardiovascular diseases.

Objective: To assess the level of Apo A-1 in dyslipidemic type 1 diabetic children in Diabetic Endocrine Metabolic Pediatric Unit (DEMPU).

Methods: This case control study was conducted on 40 patients with T1DM and 28 healthy controls. Patients were evaluated clinically by full history taking and thorough clinical examination. Full history includes; chronological age of the patient, age at the onset of diabetes, duration of diabetes, insulin therapy and family history of diabetes mellitus, hypertension and dyslipidemia. Thorough clinical examination laying stress on the anthropometric measurements, early signs of puberty and signs of associated disorders &/or diabetic chronic complications. The records of the patients reviewed especially for the mean of HbA1c done in the last year, presence of diabetic retinopathy or microalbuminuria. We measured Apo A1 for all subjects included in the study.

Results: plasma levels of apoA-1 in diabetic patients (2.774±0.559 g/L) are significantly higher than healthy children (2.506± 0.459 g/L), and that, serum total cholesterol in the diabetic group is significantly higher than in control group (182.50±39.868 mg/dl Vs 149.07±24.375 mg/dl) & serum LDL in the diabetic group is significantly higher than in control group (116.12 ± 32.589 mg/dl Vs 84.04 ± 19.234 mg/dl). Furthermore, there was no significant correlation between serum Apo A-1 and (anthropometric measures, duration of diabetes, serum HDL, serum TG, HbA_{1C} % and insulin dose).

Conclusion: Plasma levels of apoA-1 are higher in the dyslipidemic type 1 diabetic children than healthy childrens. Therefore, assessment of Apo A-1 may be useful especially when patients have a personal or family history of dyslipidemia.

Key words: Type1 diabetes mellitus, Dyslipidemia, Apolipoprotein A-1

Acknowledgment

I am deeply thankful to **Allah**, by grace of whom, the progress and success of this work was possible.

I should express my deep appreciation and great thanks to **Dr Fatma Alzahraah Mostafa Gomaa,** Professor of Pediatrics and Pediatric Cardiology, Faculty of Medicine, Cairo University for her meticulous supervision, loyal encouragement & valuable advice throughout the work.

I would like to express my deepest appreciation to **Dr Ghada Mohammad Anwar**, Professor of Pediatrics and Pediatric Endocrinology**,** Faculty of Medicine, Cairo University for her meticulous supervision, great efforts, helpful suggestions, standing beside me and helping me at any time.

My deepest thanks to **Dr Sahar Abd El- Atty Sharaf**, Professor of clinical and Chemical Pathology, Faculty of Medicine, Cairo University for her outstanding advices and keen interest throughout the work.

Also, I would like to thank children with diabetes and their parents for being cooperative.

Last but not the least, I am deeply thankful and always indebted to my parents and my brothers & sisters who were always supporting and encouraging me.

List of contents

Title **Page No.**

List of Abbreviations

AACE	American Association of Clinical Endocrinologists
ACE	Angiotensin-converting enzyme
ACR	Albumin-to-creatinine ratio
ACTH	Adrenocorticotropic hormone
ADA	American Diabetes Association
Apo A-1	Apolipoprotein A-I
Apo B	Apolipoprotein B
APS	Autoimmune Polyglandular Syndromes
ARB	Angiotensin receptor blocker
BG	Blood glucose
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CCB	Calcium channel blocker
CD	Celiac Disease
CETP	Cholesteryl ester transfer protein
CI	Confidence interval
CKD	Chronic kidney disease
CSII	Continuous subcutaneous insulin infusion
CSF	Cerebrospinal fluid
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DCCT	Diabetes Control and Complications Trial
DEMPU	Diabetic Endocrine Metabolic Pediatric Unit
DHC	Diabetes healthcare

DKA	Diabetic ketoacidosis
EASD	European Association for the Study of Diabetes
ECFV	Extracellular fluid volume
FFA	Free fatty acids
FPG	Fasting plasma glucose
GAD	Glutamic acid decarboxylase
GADAs	Glutamic acid decarboxylase antibodies
GDM	Gestational Diabetes Mellitus
HbA_{1c}	Glycosylated hemoglobin
HDL	High-density lipoproteins
HHS	Hyperosmolar hyperglycemic state
HNF	Hepatocyte nuclear factor
HBOT	Hyperbaric oxygen therapy
IA-2As	Islet antigen-2 antibodies
IDF	International Diabetes Federation
IDL	Intermediate density lipoprotein
IPF	Insulin promoter factor
LCAT	lecithin-cholesterol acyltransferase
LDL	Low-density lipoprotein
LJM	Limited joint mobility
Lp(a)	Lipoprotein A
LPL	Lipoprotein lipase
MDI	Multiple daily injections
MI	Myocardial infarction
MODY	Maturity Onset Diabetes of the Young
NASH	Non-alcoholic steatosis hepatis
NGSP	National Glycohemoglobin Standardization Program

NPH	Neutral Protamine Hagedorn
OGTT	Oral glucose tolerance test
PAD	Peripheral arterial disease
PG	Plasma glucose
RAAS	Renin-angiotensin-aldosterone system
SBP	Systolic Blood Pressure
SMBG	Self-monitoring of blood glucose
T1DM	Type 1 Diabetes Mellitus
TC	Total cholesterol
TG	Triglycerides
VLDL	Very low density lipoprotein
WHO	World Health Organization

List of Tables

List of figures

Introduction

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both. The chronic hyperglycemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidneys and nerves, as well as an increased risk for cardiovascular disease (CVD). The diagnostic criteria for diabetes are based on thresholds of glycemia that are associated with microvascular disease, especially retinopathy **(Goldenberg and Punthakee , 2013)**.

CVD is the leading cause of death in people with type 1 diabetes mellitus (T1DM). Several studies demonstrate tracking of childhood CVD risk factors into adulthood. Furthermore, CVD risk factors in childhood correlate with abnormalities in surrogate markers of atherosclerosis and atherosclerotic lesions in pathology evaluations. Although data indicate that progress has been made reducing microvascular complications in T1DM and that intensive management with lower glycosylated hemoglobin (HbA1c) can reduce CVD events, evidence from the Pittsburgh Epidemiology of Diabetes Complications Study suggests a lack of similar progress in reduction of macrovascular as compared with microvascular complications. Furthermore, people with T1DM suffer macrovascular complications and death at earlier ages than non-diabetics. Importantly, dyslipidemia is a significant CVD risk factor in persons with diabetes **(Maahs et al., 2008)**.

Dyslipidaemia was defined by the American Diabetes Association (ADA) as having Low density lipoproteincholesterol (LDL-C) ≥ 100 mg/dl, high density lipoprotein-cholesterol (HDL-C) < 40 mg/dl (males) & < 50 mg/dl (females), total cholesterol (TC) ≥ 200mg/dl and triglycerides (TG) ≥ 150 mg/dl **(Wysham et al., 2012)**.

The increased cardiovascular mortality seen in subjects with T1DM is only partly explained by abnormal lipid and lipoprotein profiles. Dyslipidemia is very strongly linked to glycemic status with poorly controlled subjects showing a worse lipid profile. Children with T1DM have been shown to exhibit abnormal lipid profiles **(Krishnan and Short, 2009)**.

Despite guidelines for the management of dyslipidemia in children and longitudinal studies of serum lipids in the general pediatric population, there are fewer data on lipids in pediatric subjects with T1DM. The antecedents of adult CVD, the primary cause of death in T1DM, are present in children **(Maahs et al., 2007)**.

LDL-C is the ‘cornerstone’ for assessment of lipoprotein-related cardiovascular risk. Elevated LDL-C is an established risk factor for CVD. However, LDL-C does not reflect the classic ‘diabetic

dyslipidemia', which consists of hypertriglyceridemia and low levels of HDL-C. Financial costs, as well as morbidity and mortality associated with the complications of diabetes, threaten to overcome health-care budgets. Better identification of risk factors and development of effective screening strategies are critical in meeting these challenges **(Mingyuan and Timothy, 2011)**.

Apolipoprotein A-I (ApoA-I) is the major apo in HDL particles and initiates the 'reverse cholesterol transport'. ApoA-I can 'pick up' excess cholesterol from peripheral cells and transfer it back to the liver in the HDL particles. ApoA-I also manifests anti-inflammatory and antioxidant effects. The antiatherogenic properties of apoA-I in coronary arteries were recently documented. ApoA-I is not contained in the potentially atherogenic apoBcontaining particles and thus apoA-I in most cases only reflects the athero-protective part of the metabolism **(Walldius and Jungner, 2006)**.

Diabetic children are at higher risk of dyslipidemia and atherosclerosis. Measurement of apoA1 in diabetic patients may be helpful to diabetic patients at risk of cardiovascular diseases **(Hashemi et al., 2012)**.

Aim of the work

The aim of this work is to assess the level of Apo A-1 in dyslipidemic type 1 diabetic children and to study the relation of Apo A-1 level to the duration of diabetes, degree of glycemic control, insulin dose (IU/kg/day), body mass index (BMI), epidemiological risk factors including family history and life-style, blood pressure and other diabetes complications.

Type 1 diabetes

Introduction

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both. The chronic hyperglycemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidneys and nerves, as well as an increased risk for cardiovascular disease (CVD). The diagnostic criteria for diabetes are based on thresholds of glycemia that are associated with microvascular disease, especially retinopathy **(Goldenberg and Punthakee , 2013)**.

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 **(ADA, 2012)**.

Epidemiology: Incidence and prevalence:

First, it does appear that two peaks of Type 1 Diabetes Mellitus (T1DM) presentation occur in childhood and adolescence: one between 5 and 7 years of age, with the other occurring at or near puberty **(Harjutsalo et al. 2008)**.

Incidence rate varies greatly between different countries, within countries, and between different ethnic populations. The incidence of type 1DM increased worldwide in the closing decades of the 20th century. Steep rises in the age group under 5 years has been recorded recently **(Gale, 2002)**.

Diabetes prevalence in some Eastern Mediterranean countries is among the highest in the world. The highest rates are reported in Egypt, Kuwait, Lebanon, Oman and Qatar where the incidence of T1DM is reported to be 8-10 per 100,000 population per year in children aged <15 years **(Khatib and Oussama, 2006)**.

In Egypt, the prevalence rate of T1DM among school children in Heliopolis district in Cairo was 1.09/1000 with male predominance and in El Manyal district, the prevalence was 1.12/1000 school children with female predominance **(Ghali and El-Dayem, 1990)**.

An Egyptian study showed that age, seasonal variations, viral infections, emotional stress, high birth order and consanguinity between the parents and family history of diabetes were risk factors for development of T1DM **(Salem et al, 1990)**.

There is a clear seasonal variation in diagnosis of diabetes, and among children who had a preceding, perhaps precipitating, infection. However, seasonal factors could influence not only precipitating mechanisms just before diagnosis, but also initiating or promoting mechanisms very early in the disease process. Seasonal pattern was evident at diagnosis and at birth which is more common during summer **(Ismail et al, 2008)**.

Classification of Diabetes Mellitus and other categories of glucose regulation:

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

Immune-mediated diabetes (Type 1 A)

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 autoimmune destruction of the β-cells of the pancreas. Markers of the immune destruction of the β-cell include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to GAD (GAD65), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2β. One and usually more of these autoantibodies are present in 85–90% of individuals when fasting hyperglycemia is initially detected. Also, the disease has strong HLA associations, with linkage to the DQA and DQB genes, and it is influenced by the DRB genes. These HLA-DR/DQ alleles can be either predisposing or protective **(ADA, 2012)**.

In this form of diabetes, the rate of β-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Some patients, particularly children and adolescents, may present with ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or ketoacidosis in the presence of infection or other stress.

Autoimmune destruction of β-cells has multiple genetic predispositions and is also related to environmental factors that are still poorly defined. Although patients are rarely obese when they present with this type of diabetes, the presence of obesity is not incompatible with the diagnosis. These patients are also prone to other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo,