Relation between Lipids, Apolipoproteins, Vitamin D levels and Carotid Artery Intima-Media Thickness in Adolescents with Type 1 Diabetes

Thesis submitted for partial fulfillment of the Ph.D.
In Medical Childhood Studies
(Child Health and Nutrition)
By

Ayman Fekrey Saleeb
M.B.B.Ch., M.Sc. Pediatrics

Supervised by

Prof. Medhat Hassan Shehata
Professor of Pediatrics
Institute of Postgraduate Childhood Studies
Ain Shams University

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

Prof. Adel Naguib Hanna
Research Professor of Child Health
National Research Centre

Prof. Zakaria A. Al-Khayat
Research Professor Medical Biochemstry
National Research Centre

Dr. Iman Hussin Kamel
Researcher of Child Health
National Research Centre

Institute of Postgraduate Childhood Studies
Department of Medical Studies for children
Ain Shams University

2014

Table of Content

Abstract:

Background: Carotid intima media thickness (cIMT) is now used commonly as a non-invasive test for assessment of degree of atherosclerosis, it is important to determine which factors, contribute to the cIMT in adolescents with T1DM. The risk factors predicting cIMT are not well established in paediatric diabetic patients.

The aim of this Cross sectional, case-control study was to detect the difference between adolescents with and without type 1diabetes in the levels of cIMT, lipid, apolipoproteins and vitamin D levels. Also to study the relations between lipids, apolipoproteins, vitamin D levels and cIMT in adolescents with type 1diabetes.

Subjects and methods: A total of 80 subjects were included in the study, those subjects were classified into two groups. Forty adolescents with T1DM aged 12-18 years (14.56±1.65 years), and forty healthy age and sex matched adolescents as a control group. All candidates were subjected to full clinical evaluation and anthropometric measurements. All the candidates had the following laboratory investigation been done (FBG, average HbA1c, C-peptide, lipid profile, 25 (OH) vitamin D, Apolipoprotein B, Apolipoprotein A-I and Apolipoprotein B/ Apolipoprotein A-I ratio. cIMT was done for all the subjects included in the study.

Results: cIMT levels were significantly higher in cases (0.051±0.005 cm) than in healthy controls (0.045±0.006 cm), P value <0.001. Vitamin D and Apolipoprotein A-I levels were significantly lower in cases (29.500±6.37 ng/dl), (123.05±19.26 mg/dl) than in controls (40.25±6.49 ng/dl), (139.62±12.77 mg/dl) P value <0.001. While Apolipoprotein B level was significantly higher in cases (108.87±41.19 mg/dl) than healthy controls (83.33±31.03 mg/dl), P value 0.002. Apolipoprotein B / Apolipoprotein A-I ratio was significantly higher in cases (0.898±0.33) than healthy controls (0.5910±0.22), P value <0.001. significant negative linear correlation between cIMT and vitamin D (r value -0.265 and P value 0.018), statistically significant negative correlation with apolipopro-tein A, positive correlations with apolipoprotein B and apolipoprotein B\ apolipoprotein A-I ratio, also statistically significant negative correlation with HDL level, while it shows statistically significant positive correlations with LDL/HDL ratio and TG/HDL ratio.

Conclusion: The results of the present study shows that patients with type 1 diabetes have significantly increased mean (cIMT) compared to the control subjects. Increased (cIMT) was directly correlated with apolipoprotein B, apolipoprotein B/ apolipopro-tein A-I ratio, LDL/HDL ratio and with glycemic control according to HbA1c level, while it was inversely correlated with vitamin D, apolipoprotein A-I and HDL.

Key Word: T1DM, cIMT, apolipoprotein B, apolipoprotein A-I, lipid profile

First and foremost thank **ALLAH** for allowing me to begin, to go through and to complete this work. Without His help, this work would have not been fulfilled.

Acknowledgment

I have been honored to work under the supervision of such distinguished and great professors.

I would like to express my sincere gratitude to **Prof. Medhat Hassan Shehata,** Professor of Paediatrics**,** Institute of Postgraduate Childhood Studies Ain Shams University**,** not only for his valuable supervision and great help, but also for his constant support, encouragement and patience, as well as an endless help, support and sympathy during this work.

I would like to express my deepest gratitude to **Prof. Mona Hussein El Samahy** Professor of Pediatrics**,** Faculty of Medicine, Ain Shams University, for her valuable experience and for her generous guidance, supervision, kindness, and support.

I am greatly indebted and grateful to **Prof. Adel Naguib Hanna,** Research Professor of child health, national research centre, for his outstanding effort and unlimited co-operation in supervising this work, and for his valuable advice and encouragement as well as an endless help, support and sympathy during this work.

I am greatly indebted and grateful to **Prof. Zakaria A. Al-Khiyat,** Research Professor Biochemstry, national research centre, for his outstanding effort and unlimited co-operation in supervising the practical laboratory part of this work, and for his valuable advice as well as an endless help, support and sympathy during this work.

I would like to express my deepest gratitude to **Dr. Iman Hussin Kamel**, Researcher of Child Health, National Research Centre, for her generous guidance, supervision, kindness, special advises and support.

I would like to express my deep gratitude to **Dr. waleed rizk and Dr. yasmine A. mahmoud** who helped me greatly in conducting the clinical part of the study, the cIMT and the laboratory part of this research.

I would like to express my thanks to my family, my mother, my wife and my children who continued supporting me in all the stages of this work.

Furthermore, I would like to convey my special thanks to all the patients, their parents and staff members in the Pediatric diabetology clinic of the pediatric hospital of Ain Shams University for their generous co-operation.

Last but not least, I would like to present this work to **the soul of my father,** I miss his love, support and kindness greatly, I felt getting elder after his death.

LIST OF ABBREVIATIONS

1,25 OH 2D	1,25-dihydroxy vitamin D
25OH D	25-hydroxyvitamin D
ABC	ATP-binding cassette protein
ABCA1	ATP-binding cassette protein A 1
ACE-I	Angiotensin-converting enzyme- inhibitor
ADA	American Diabetes Association
AGEs	Advanced glycation end products
AHA	American Heart Association
Apo A-I	Apolipoprotein A-I
Apo B	Apolipoprotein B
ARIC	The Atherosclerosis Risk in Communities study
BFP	Body fat percentage
CAC	Coronary artery calcification
CAD	Coronary artery disease
CARE	The Cholesterol And Recurrent Events trial
CCA	Common carotid artery
CETP	Cholesteryl ester transfer protein
CHD	Coronary heart disease
cIMT	Carotid intima-media thickness
CSII	Continuous Subcutaneous Insulin Infusion
DAFNE	Dose Adjustment For Normal Eating study
DBP	Diastolic blood pressure
DCCT	Diabetes Complications and Control Trial
DiaMond	Diabetes Mondiale trial
DKA	Diabetic ketoacidosis
ECAT	European Concerted Action on Thrombosis and Disabilities
EDIC	Epidemiology of Diabetes Interventions and Complications Study
ELISA	Enzyme-Linked Imunosorbent Assay
ESRD	End stage renal disease
FACS	Fluorescence-Activated Cell Sorting
FAs	Fatty acids
FGF-23	Fibroblast growth factor 23
FPG	Fasting plasma glucose
GH	Growth hormone
GI	Glycemic index
GL	Glycemic load
GM-CSF	Granulocyte macrophage-colony-stimulating factor

HbA1C	Glycosylated hemoglobin (Hemoglobin A1c)
HC	Hip circumference
HDL	High Density Lipoprotein
HNF	Hepatocyte nuclear factor
hsCRP	High sensitive C- Reactive Protein
HTN	Hypertension
ICA	Internal carotid artery
IDF	International Diabetes Federation
IDL	Intermediate density lipoprotein
IFG	Impaired fasting glucose
IGF-1	Insulin-like growth factor 1
IGT	Impaired glucose tolerance
IHD	Ischaemic heart disease
IL-1ra	Interleukin-1 receptor antagonist
IL-1α	Interleukin-1 alpha
IL-1β	Interleukin-1beta
IMT	Intima-media thickness
INF-γ	Interferon gamma
INS-1E	Rat insulinoma cell line 1-E
IOM	Institute Of Medicine
IPF-1	Insulin promoter factor-1
IRAS	Insulin Resistance Atherosclerosis Study
IRS	Insulin resistance syndromes
ISPAD	International Society for Pediatric and Adolescent Diabetes
LCAT	Lecithin-cholesterol acyltransferase
LCFA	Long-chain fatty acids
LDL	Low-density lipoprotein
LL	Lipoprotein lipase
Lp(a)	Lipoprotein(a)
Lp-PLA2	Lipoprotein-associated phospholipase A2
LysoPC	Lysophosphatidylcholine
MAP	Mean arterial pressure
MIS	Meal-induced insulin sensitization
MODY	Maturity Onset Diabetes of the Young
MTP	Microsomal triacylglycerol transfer protein
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
NGT	Normal glucose tolerance
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NO	Nitric oxide

NOD	Non obese diabetic
NPH	Neutral Protamine Hagedom Insulin
PAD	Peripheral arterial disease
pdx1	Pancreatic and duodenal homeobox 1
PHYLLIS	Plaque Hypertension Lipid Lowering Italian Study
PRIME	Prospective Epidemiological Study of Myocardial Infarction study
PTH	Parathyroid hormone
PWV	Pulse wave velocity
QTc	Corrected QT interval
RAGEs	Receptors for Advanced glycation end Products
SBP	Systolic blood pressure
SPSS	Statistical package for social science
STZ	Streptozocin
T1DM	Type 1 diabetes mellitus
TCh	Total cholesterol
TDEI	Total daily energy intake
TG	Triacylglycerol
TGF-β1	Transforming growth factor beta1
TNF-α	Tumor necrosis factor alpha
TRPV6	Transport protein V 6
UVB	Ultra violet B radiation
VDBP	Vitamin D-binding protein
VDR	Vitamin D receptor
VDRE	Vitamin D Responsive Element
VLDL	Very low density lipoprotein
WC	Waist circumference
W\H ratio	Waist /Hip ratio