ADIPONECTIN SERUM LEVELS IN ADOLESCENT BOYS WITH TYPE 1 DIABETES: RELATIONSHIPS TO PUBERTAL DEVELOPMENT, SEX HORMONE BINDING GLOBULIN AND TESTOSTERONE CONCENTRATIONS

Thesis

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بسم الله الرحمن الرحيم

"يُؤْتِي الْحِكْمَةَ مَنْ يَشَاءُ وَمَنْ يُؤْتَ
الْحِكْمَةَ فَقَدْ أُوتِيَ خَيْراً كَثِيراً وَمَا يَذَّكَّرُ
إِلاَّ أُولُو الْأَلْبَابِ"

صدق الله العظيم

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Abstract

Background: Adiponectin is a protein hormone secreted exclusively by adipocytes that regulate the metabolism of lipids and glucose**.** Adiponectin has antidiabetic, antiatherogenic and anti-inflammatory properties. In addition it has an important protective role in carcinogenesis

OBJECTIVE: To asses adiponectin serum levels in adolescent boys with type 1 diabetes mellitus and to study the relationships between serum adiponectin levels with pubertal development body mass index, testosterone, sex hormone binding globulin and glycemic control.

Research design and methods: The study was a case- control study carried out on 45 adolescent boys with T1DM aged 12-18 years and 37 healthy control boys of similar age .The cases and controls were divided into four subgroups according to their pubertal stage (Tanner stage 2-5).They were subjected to full history, reviewing their medical records, and clinical examinations (Auxology, Blood pressure and Pubertal assessment). Serum total adiponectin level, total testosterone, sex hormone- binding globulin level and free testosterone level were determined by ELISA technique in addition to glycated haemoglobin and fasting blood glucose.

Results: Adiponectin serum level (±SD) was significantly higher in T1DM boys compared to healthy control group (12.93 ± 5.24µg/ml versus 8.91± 3.21µg/ml) (P<0.001).Such higher serum levels of adiponectin were detected mainly at Tanner stage 2 (16.57 ± 4.60µg/ml vs 11.88±3.39µg/ml) (P=0.025) and Tanner stage 3 (12.77±3.71µg/ml vs.6.59±1.54µg/ml) (P=0.002). Adiponectin levels decreased

significantly during pubertal development in control group and T1DM group. The rate of decline in adiponectin serum level in T1DM boys was more smooth and regular in diabetic than control group. In T1DM boys adiponectin levels were negatively associated with pubertal stage, age, total testosterone, free testosterone, intermediate / long acting insulin dose and positively to HbA1c. No correlation was detected with SHBG or BMI. In control group adiponectin levels were negatively associated with pubertal stage, total testosterone and BMI.

Conclusion: Adiponectin serum levels in adolescent boys with type 1 diabetes were significantly higher than control mainly at early puberty. It decreases significantly during pubertal development and correlated negatively to pubertal stage, total and free testosterone levels, intermediate / long acting insulin dosage and positively to HbA1c .

Contents

List of Abbreviations

2-h PG	Two hours post prandial glucose
A1c - HbA1C	Glycated haemoglobin
ACEIs	Angiotensin-converting enzyme inhibitors
ACR	Albumin- creatinine ratio
ADA	American Diabetes Association
AdipoR	Adiponectin receptor
AMPK	Adensine monophosphate kinase
ADPN	Adiponectin
APPL1	Adaptor protein containing a pleckstrin homology domain and a leucine zipper motif
ARBs	Angiotensin II receptor blockers
BGL	Blood glucose level
BM-HSC	Bone marrow-derived hematopoietic stem cell
BMI	Body mass index
CAD	Coronary artery disease
CB1	Cannabinoid -1 receptor
CGM	Continuous glucose monitoring
cIMT	Carotid intimal medial thickness
CRP	C- Reactive Protein
DAFNE	Dose Adjustment for Normal Eating study
DAISY	Diabetes Autoimmunity Study in the Young
DCCT	Diabetes control and complication trial
DD	Double diabetes
DHEA	Dehydroepiandrosterone
DHT	Dihydrotestosterone
DIA-PREV-IT	Diabetes Prevention-Immune Tolerance
DIPP	Diabetes Prediction and Prevention
DKA	Diabetic ketoacidosis
DN	Diabetic nephropathy
DPN	Diabetic polyneuropathy
DPT-1	Diabetes Prevention Trial–Type 1
DR	Diabetic retinopathy
DSCs	Adipose tissue-derived MSCs
EDIC	Epidemiology of Diabetes Interventions and Complications
ELISA	Enzyme-linked immunosorbent assay
ENDIT	The European Nicotinamide Diabetes Intervention Trial
ESCs	Embryonic stem cells
FAI	Free androgen index
FINDIA	Finnish Dietary Intervention Trial for the Prevention of T1DM

FPG	Fasting blood glucose
FSH	Follicle-stimulating hormone
GADA	Glutamic acid decarboxylase autoantibodies
GC	Genetic Consortium
GDM	Gestational diabetes mellitus
GFR	Glomerular filtration rate
GH	Growth hormone
GnRH	Gonadotropin releasing hormone
GPR54	KiSS-1 receptor
HDL	High- density lipoprotein
HIV/AIDS	Human Immunodeficiency Virus.
HLA	Human leucocyte antigen
HMW	High molecular weight
HNF	Hepatocyte nuclear factor
HOMA-IR	Homeostatic model of insulin resistance
HPA	Hypothalamic-pituitary-adrenal axis
HPG	Hypothalamic-pituitary-gonadal axis and
hs CRP	Highly sensitive CRP
IAA	Insulin autoantibodies
IA-2A	Insulinoma-2-associated autoantibodies
ICA	Islet cell cytoplasmic autoantibodies
IFG	Impaired fasting glucose
IGF-I	Insulin growth factor 1
IGT	Impaired glucose tolerance
IL-6	Interleukin 6
iPSCs	Induced pluripotent stem cells
IR	Insulin resistance
ISPAD	International Society for Pediatric and Adolescent Diabetes
JDRF	Juvenile Diabetes Research Foundation
KISS1	Kisspeptins gene
LADA	Latent autoimmune diabetes of adults
LDL	Low- density lipoprotein
LH	Luteinizing hormone
LMW	Low molecular weight
MAP	Mycobacterium avium subsp Paratuberculosis
MAP	Mean arterial pressure
MDI	Multiple daily injections
MHC	Major Histocompatibility Complex
MIH	Mullerian inhibiting hormone
MMW	Middle molecular weight
MODY	Maturity-Onset Diabetes of the Young

MS	Metabolic Syndrome
MSC	Mesenchymal stromal cell
NAFLD	Non -alcoholic fatty liver disease
NASH	Non- alcoholic steatohepatitis
NEFA	Non -Esterified fatty acid
NIH	National Institutes of Health
NO	Nitric oxide
NPH	Neutral Protamine Hagedorn Insulin
OGTT	Oral glucose tolerance test
ORPS	Oxford Regional Prospective Study
Ox LDL	Oxidized low density lipoprotein
PA	Physical activity
PCOS	polycystic ovarian syndrome
PHV	Peak height velocity
PPARα	Peroxisome-proliferator activated
RA	Rheumatoid arthritis
RAS	Renin-angiotensin system
ROS	Reactive-oxygen species
SEARCH	Search for Diabetes in Youth
SHBG	Sex hormone binding globulin
SIRT1	Sirtuin 1
SLE	Systemic lupus erythematosis
SMBG	Self-Monitoring of Blood Glucose
SMR	Sexual maturity rating
SNPs	Two single nucleotide polymorphisms
SREBP1c	Sterol regulatory element binding protein 1c
T2DM	Type 2 Diabetes Mellitus
T2-T3-T4- T5	Tanner stage 2-3-4-5
TDD	Total daily Dose
TG	Triglycerides
TIDM	Type 1 Diabetes Mellitus
TNFα	Tumor necrosis factor alpha
TZD	Thiazolidinedione
UCB-MSCs	Umbilical cord blood-derived MSCs
VAT	Visceral adipose tissues
WHR	Waist to hip ratio
ZnT8A	Zinc transporter

List of Tables

List of Figures

INTRODUCTION

Diabetes mellitus is a serious chronic disorder of childhood and represents a major public health problem. Type 1 diabetes is the predominant form of diabetes during childhood and adolescence, accounting for about 90% of cases **(Craig et al., 2009; Patterson et al., 2009).**The global incidence of type 1 diabetes is increasing worldwide, at an annual rate of 3-5%, particularly in children under the age of 5 years, and this trend leads to a significant health burden **(Patterson et al., 2009).**

Pubertal development is characterized by many physiological changes, involving both hormonal and metabolic processes, and these factors together with psychological issues are frequently responsible for poor glycaemic control. Treatment may be complicated by poor compliance, difficulties in targeting insulin therapy and concerns about weight gain **(Dunger, 1992).**

Adiponectin is a protein hormone secreted exclusively by adipocytes that regulate the metabolism of lipids and glucose **(Savino et al., 2008).** Among adipokines, adiponectin has gained considerable attention because of its antidiabetic, antiatherogenic and anti-inflammatory properties. Interest in adiponectin has increased significantly with demonstration that it has an important protective role in carcinogenesis **(Barb et al., 2007).**

Studies in adolescents have documented that pubertal development has an effect on adiponectin serum levels and that gender difference in adiponectin develop during pubertal development and sex steroids may be