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Assessment of the serum protease inhibitors: alpha 1 antitrypsin and antithrombin III in adolescents with type 1 diabetes

Thesis

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LIST OF ABBREVIATIONS

A1AT	**:**	Alpha 1 antitrypsin
ACE	**:**	Angiotensin Converting Enzyme
ACR	**:**	Albumin Creatinine Ratio
ADA	**:**	American Diabetes Association
AER	**:**	Albumin Excretion Rate
AGEs	**:**	Advanced Glycation End products
ANOVA	**:**	Analysis of variance
AP	**:**	Antiphospholipid
APCs	**:**	Antigen-presenting cells
A1PI	**:**	Alpha 1 proteinase inhibitor
AT	**:**	Antithrombin
BG	**:**	Blood Glucose
BMI	**:**	Body Mass Index
COPD	**:**	Chronic obstructive pulmonary Disease
CV	**:**	Coxsackie virus
CVAN	**:**	Cardiovascular autonomic neuropathy
CVD	**:**	Cardiovascular disease
CVS	**:**	Cardiovascular system
DCCT	**:**	Diabetes Control and Complications Trial
Dias	**:**	Diastolic
DIC	**:**	Disseminated intravascular coagulation
DKA	**:**	Diabetic Ketoacidosis
DM	**:**	Diabetes Mellitus
EDIC	**:**	Epidemiology of Diabetes Interventions and Complications
e.g.	**:**	Example
ESRD	**:**	End stage Renal Disease
FBG	**:**	Fasting blood glucose
FDA	**:**	Food and drug administration
FPG	**:**	Fasting plasma glucose
GAD	**:**	Glutamic Acid Decarboxylase
GDM	**:**	Gestational Diabetes Mellitus
Hb	**:**	Hemoglobin
HbA1c	**:**	Glycated Hemoglobin

HCT	**:**	Hematopoeitic cell transplantation
HHS	**:**	Hyperglycemia Hyperosmolar State
HNF	**:**	Hepatocyte nuclear factor
HPLC	**:**	High-performance liquid chromatography
Ht	**:**	Height
IAA	**:**	Insulin auto antibodies
IA-2A	**:**	Insulinoma associated antigen 2 antibodies
ICAs	**:**	Islet cell antibodies
IDF	**:**	International Diabetes Federation
IFCC	**:**	International Federation Calibrator Chemistry
IFG	**:**	Impaired fasting glucose
IGT	**:**	Impaired glucose tolerance
INS	**:**	Insulin (gene)
IRMA	**:**	Intra Retinal Microvascular Abnormalities
ISPAD	**:**	International Society of Pediatric and Adolescent Diabetes
IVGTT	**:**	Intra Venous Glucose Tolerance Test
IZS	**:**	Insulin zinc suspension
MA	**:**	Microalbuminuria
MIN	**:**	Murine insulinoma cells
MODY	**:**	Maturity Onset Diabetes of Young
NOD	**:**	Nonobese diabetic
NPH	**:**	Neutral protamine hagedorn insulin
OGTT	**:**	Oral glucose Tolerance Test
PAD	**:**	Peripheral arterial disease
PAI-1	**:**	Plasminogen activator inhibitor-1
PBMCs	**:**	Peripheral blood mononuclear cells
Perc	**:**	Percentile
Pi	**:**	Protease inhibitor
ROC	**:**	Receiver operating characteristic
SD	**:**	Standard deviation
SMBG	**:**	Self Monitoring Blood Glucose
SPSS	**:**	Statistical package for Social Sciences
STZ	**:**	Streptozotocin
Sys	**:**	Systolic
TAT	**:**	Thrombin antithrombin complex

TBI	**:**	Total body irradiation
T1DM	**:**	Type 1 diabetes mellitus
T2DM	**:**	Type 2 diabetes mellitus
TF	**:**	Tissue factor
TIC	**:**	Trypsin inhibitory capacity
TNFα	**:**	Tumor necrosis factor α
U.S.	**:**	United States
VEGF	**:**	Vascular endothelial growth factor
VOD	**:**	Venoocclusive disease
WHO	**:**	World Health Organization
Wt	**:**	Weight
YAP	**:**	Yeast aspartic protease

INTRODUCTION

Type I diabetes results from an autoimmune destruction of the insulin-producing pancreatic beta cells. Although the exact immunologic processes underlying this disease are unclear, increasing evidence suggests that immunosuppressive, immunoregulatory and anti-inflammatory agents can interrupt the progression of the disease (***Song et al., 2004).*** In fact, an imbalance of the immune-regulatory pathways plays an important role in the development of type 1 diabetes and its' vascular complications ***(Lu et al., 2006).*** Moreover, studies in patients with peripheral arterial disease (PAD) have reported an association between inflammatory markers and severity of disease or worsening of symptoms ***(Engstrom et al., 2004).***

The shifting balance between proteinases and proteinase inhibitors in blood, a function of their relative affinities and concentrations, has long been hypothesized to influence immune competency. The identification of proteinase-activated receptor responses in cells of the mononuclear phagocyte system suggests a potential

explanation ***(Bristow et al., 1998).*** Alpha 1 antitrypsin (AAT) is a multifunctional serine proteinase inhibitor that also displays a wide range of anti-inflammatory properties ***(Song et al., 2004).*** Several studies suggest a potential therapeutic role for AAT gene therapy-based approaches to prevent type 1 diabetes and ameliorate the disease effectively ***(Lu et al., 2006)***.

Vascular complications are the main cause of morbidity in diabetes mellitus ***(Reverter et al., 1997).*** The risk of vascular complications is increased during adolescence ***(Lioswska-Myjak et al., 2006).*** Several studies have demonstrated that alpha1-antitrypsin protects elastic tissue and may play a role in atherogenesis prevention ***(Talmud et al., 2003).***

Another proteinase inhibitor is Antithrombin III. Diabetes mellitus is associated with a hypercoagulable state. Blood hypercoagulability may accelerate atherosclerosis and the diabetic microvascular complications. Thrombin-antithrombin complex (TAT) and fibrinogen levels are parameters of coagulation and fibrinolysis ***(Asakawa et al., 2000).*** It has been suggested that TAT and fibrinogen may act as risk factors for the development of diabetic

microangiopathy ***(Asakawa et al., 2000).*** Antithrombin III is one of the naturally occurring anticoagulants in the body and currently molecular genetic approaches are underway to utilize the structure of antithrombin III to cause downregulation of thrombin ***(Chu, 2004).***

Taking into account the fact that diabetic vascular complications are more likely during adolescence, the unfavorable consequences of vascular complications resulting from protease- antiprotease imbalance would be more detrimental then ***(Lioswska-Myjak et al., 2006).***

AIM OF THE WORK

Assessment of the concentration of two serum protease inhibitors: alpha 1 antitrypsin and antithrombin III in adolescents with type 1 diabetes mellitus as predictors for the development of diabetic microangiopathy and possible correlation with diabetes duration and glycemic control.