Serum Trypsinogen and Serum Lipase as Biomarkers of Exocrine Pancreatic Function in Newly Diagnosed Type1 Diabetic Children and Adolescents and Correlation with Pancreatic β Cells Function

Thesis

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Samar Abdullah

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List of Abbreviations

Abb.	Full term
AAB-	*Negative autoantibodies*
AAB+	*Positive autoantibodies*
AD	*Autosomal dominant*
ADA	*American Diabetes Association*
AI	*(Tyrosine phosphatase-like insulinoma antigen)*
AIDS	*Acute immunodeficiency syndrome*
APCs	*Antigen presenting cells*
AR	*Autosomal recessive*
ATP	*Adenosine triphosphate*
AUC	*Area under curve*
BG	*Blood glucose*
BMI	*Body mass index*
BSDL	*Bile salt-dependent lipase*
CCK	*Cholecystokinin*
CD	*Cluster of differentiation*
CFRD	*Cystic fibrosis related diabetes*
CSII	*Continuous subcutaneous insulin infusion therapy*
CT	*Computer Tomography*
CTLA	*Cytotoxic T lymphocyte associated*
CVB	*Coxasacki virus B*
CVD	*Cardio vascular disease*
DAISY	*Diabetes Autoimmunity Study In The Young*
DC	*Dendritic cells*
DCCT	*Diabetes Control and Complications Trials*
DHC	*Diabetes Healthcare*
DIPP	*Diabetes Perdiction and prevention*
DKA	*Diabetic ketoacidosis*
DM	*Diabetes mellitus*

List of Abbreviations (Cont...)

Abb.	Full term
DNA	*Deoxyribonucleic acid*
EDTA	*Ethylene diamine tetra-acetic acid*
ELISA	*Enzyme-linked immunosorbent assay*
FBG	*Fasting blood glucose*
FBS	*Fasting blood sugar*
FDA	*Food and Drug Administration*
GAD	*Glutamic acid decarboxylase*
GDM	*Gestational diabetes mellitus*
GLUT	*Glucose transporters*
HbA1c	*Hemoglobin A1c*
HDL	*High density lipoprotein*
HHS	*Hyperglycemic hyperosmolar state*
HIV	*Human Immunodeficiency virus*
HLA	*Human leukocyte antigen*
HNF	*Hepatocytes Nuclear Factor*
HPLC	*High performance liquid chromatography*
IA	*Insulin antibodies*
IDO	*Indoleamine-2,3 dioxygenase*
IFG	*Impaired fasting glucose*
IGT	*Impaired glucose tolerance*
IM	*Intramuscular*
INF	*Interferone*
iNOS	*Inducible NO-synthase*
IQR	*Interquartile range*
IUGR	*Intrauterine growth restriction*
LCA	*Leucocyte Common Antigen*
LDL	*Low density lipoprotein*
LPL	*Lipoprotein lipase*
MDI	*Multiple daily injections*

List of Abbreviations (Cont...)

Abb.	Full term
MHC	*Major Histocompability Complex*
MODY	*Maturity-Onset Diabetes of the Young*
MRI	*Magnetic resonance imaging*
NAFLD	*Non-alcoholic fatty liver disease*
NICE	*National Institute for Health and Care Excellence*
nPOD	*Network for Pancreatic Organ Donors*
NPV	*Negative predictive value*
OGTT	*Oral glucose tolerance test*
PG	*Plasma glucose*
PPV	*Positive predictive value*
PTDM	*Posttransplantion diabetes mellitus*
RCAD	*Renal cysts and diabetes*
RCT	*Randomized controlled trials*
RNA	*Ribo Ncleic Acid*
ROC	*Receiving operation Curve*
SC	*Subcutaneous*
SDS	*Standard déviation scores*
SGLT2	*Sodium-glucose cotransporter 2*
SH	*Severe hypoglycemia*
SMBG	*Self-monitoring blood glucose*
SME	*Self-management education*
SPSS	*Statistical Package for the Social Sciences*
US	*United States*
USA	*United States of America*
USD	*United states dollar*
VLDL	*Very low density lipoprotein*
WHO	*World health organization*
ZnT8	*Zn transporter 8*

Abstract

Introduction: Type1diabetes mellitus is chronic metabolic disease in children and adolescents, in which pancreatic insulin-producing beta cells are destroyed. Islets are distributed through the acinar tissue facilitating the interaction between endocrine and exocrine tissues. Serum trypsinogen and lipase are good biomarkers to evaluate the exocrine function of pancreas. Several studies showed patients with recent onset type1DM have abnormalities in the exocrine pancreatic function.

Aim of the study: To validate the utility of serum trypsinogen and lipase as biomarkers of exocrine pancreatic function in newly diagnosed type 1 diabetic children and adolescents and correlation with pancreatic B cells function assessed by fasting C-peptide.

Subjects and methods: comprised fifty (50) children and adolescents with newly diagnosed type 1diabetes attending Pediatric and Adolescents Diabetes Clinic, Children's Hospitals, Ain Shams University compared with fifty (50) age- and sex-matched healthy controls. Patients were subjected to detailed medical history, thorough clinical examination with assessment of HbA1c, Fasting C-peptide and Lipid profile. Serum trypsinogen was performed by ELISA and Serum lipase was assessed using lipase quantitative kinetic assay.

Results: Serum trypsinogen and lipase were significantly decreased in all type 1 diabetic patients compared to the control group ($p<0.01$).There was no correlation between serum trypsinogen and serum lipase and sex, age, disease duration, weight, height, body mass index(BMI),fasting C-peptide,HbA1c,lipid profile and insulin dose (p value> 0.05). ROC curve analysis revealed that serum trypsinogen and lipase cut off value $\leq$ 40 ng/dl and $\leq$ 14.9u/l, respectively could differentiate people with and without type 1 diabetes with a sensitivity of 96.00% and 69.39% and specificity of 100.00%, respectively. Logistic regression analysis revealed that serum trypsinogen and lipase were independently related to newly diagnosed diabetic patients.

Conclusion: The impairment in exocrine function of pancreas in type 1 diabetes mellitus occurs without overt manifestations of pancreatitis. Lack of correlation between exocrine pancreatic dysfunction in type 1 diabetes mellitus and Beta cell dysfunction assessed by fasting c- peptide. More studies are needed to follow up both pancreatic enzymes and exocrine pancreatic autoantibodies searching for correlations with disease development and progress.

INTRODUCTION

Type 1 Diabetes Mellitus

Type 1 diabetes remains one of the most complex chronic diseases in childhood. It is a chronic autoimmune disease in which pancreatic insulin-producing beta cells are destroyed, leading to chronic hyperglycemia ***(ADA, 2018)***. Unfortunately, annual incidence rates are increasing ~3–4% worldwide. Abnormalities of the pancreatic exocrine compartment have been described in the past decades in both anatomy and function. It is unclear whether the exocrine changes in type 1 diabetes are related to the same genetic, immunological, and environmental events resulting in beta cell destruction or are secondary to the loss of functional β cells ***(Gale, 2014)***.

Insulin acts as a trophic factor for the exocrine compartment. However, in contrast to the well-studied autoimmunity against pancreatic β cells, autoimmune responses towards the exocrine pancreas partitions might result in Type 1 Diabetes ***(Gale, 2014)***.

The exocrine pancreas unit is composed of acinar, centroacinar and ductal cells forming the acinus. The exocrine region is divided by connective tissue into lobules containing hundreds of acinar units. Acinar cells secrete more than 20 different enzymes including trypsinogen, proteases, lipases, amylases, ribonucleases and hydrolases into the intralobular

ducts, which drain via the main pancreatic duct into the duodenum ***(Whitcom, 2007)***.

In contrast to the exocrine portion of the pancreas, only a small proportion of the entire pancreas (1–2%) is comprised of neuroendocrine cells located in the highly vascularized and innervated 25 islets of Langerhans. Islet neuroendocrine cells are critical for multiple metabolic and physiologic functions of the body. Several hormones, neurotransmitters, and peptides are derived from the islets and these agents could also play important roles in the homeostasis of the exocrine pancreas. Insulin-producing beta cells are the most abundant islet cell type followed by alpha cells (producing glucagon), delta cells (producing somatostatin), gamma cells (producing pancreatic polypeptide), and epsilon cells (producing ghrelin) ***(Campbell et al., 2017)***.

With respect to diagnostic tests for exocrine pancreatic function, serum levels of trypsinogen, also known as immunoreactive trypsinogen, provide one well-accepted clinical biomarker. Testing of serum trypsinogen levels is used in a variety of pediatric settings, including newborn screens for cystic fibrosis and meconium ileus and in infants and older children with symptoms that suggest cystic fibrosis ***(Zybert et al., 2015)***.

In terms of its biology and function, trypsinogen represents the inactive precursor of the digestive enzyme

trypsin that becomes active once cleaved by enteropeptidases produced in the intestinal mucosa. Pancreatitis has been attributed to aberrant activation of trypsinogen within the acinar cell or pancreatic ducts ***(Basnayake et al., 2015)***.

Pancreatic lipase (triacylglycerol acyl hydrolase) fulfills a key function in dietary fat absorption by hydrolyzing triglycerides into diglycerides and subsequently into monoglycerides and free fatty acids. It is secreted into the duodenum through the duct system of the pancreas. Its concentration in serum is normally very low ***(Brandon et al., 2012).***

Under extreme disruption of pancreatic function, such as pancreatitis or pancreatic adenocarcinoma, the pancreas may begin to autolyze and release pancreatic enzymes including pancreatic lipase into serum. Thus, through measurement of serum concentration of pancreatic lipase, acute pancreatitis can be diagnosed ***(Lunder et al., 2005).***

Aim of the Work

The aim of the study is to validate the utility of serum trypsinogen and serum lipase as biomarkers of type 1 diabetes in newly diagnosed type 1 diabetic children and adolescents and correlation with pancreatic B cells function assessed by fasting C-peptide.