Mesenteric blood flow in diabetics with and without autonomic neuropathy

THESIS

Submitted for partial fulfillment of MSc Degree in Internal Medicine

By

Mai Galal Abdel Monium Elshenofey
(M.B.Bch)

Supervised by

Dr. Reda Mohamed Amer
Professor of internal medicine
Faculty of medicine
Cairo University

Dr. Sahar Abdel Rahman Nassef
Professor of internal medicine
Faculty of medicine
Cairo University

Dr. Mary Wadie Fawzy
Lecturer of internal medicine
Faculty of medicine
Cairo University

2014


بسم الله الرحمن الرحيم

Table of Contents

Acknowledgement

Above all and first of all; all thanks to **ALLAH,** the source of all knowledge, by whose abundant aid this work has come to fruition.

It has been a great honor to proceed into this work under the supervision of **Dr.Reda Mohamed Amer**, Professor of Internal medicine, Faculty of Medicine, Cairo University. I am greatly indebted to his suggesting and planning the subject, supervising the whole work, reading and criticizing the manuscript. I will never forget his unlimited help, continuous support, kind encouragement, constructive criticism and wise guidance.

I would like also to express my sincere gratitude and appreciation to **Dr. Sahar Abdel Rahman Nassef,** Professor of Internal Medicine, Faculty of Medicine, Cairo University, for her helpful guidance, valuable advice, meticulous care, great effort and generous help and support. She offered me much of her time and advice to accomplish this work.

I'm particularly very grateful to **Dr.Mary Wadie Fawzy**, Lecturer of internal medicine, Faculty of Medicine, Cairo University, who offered much of her time and advice for suggesting, reading and supervising throughout this work. To her words of praise are not sufficient.

✍ *Mai Galal Elshenofey.*

List of Tables

List of Figures

List of Abbreviations

- **2HPP:** 2 hours post prandial.
- **A/C ratio:** Albumin creatinine ratio.
- **ABCA1:** ATP-binding cassette, sub-family A , member 1
- **ACE**: Angiotensin converting enzyme
- **ADA:** American Diabetes Association
- **AGEs:** Advanced glycosylation end products
- **ALT:** Alanine aminotransferase
- **ANOVA:** Analysis of variance
- **APCs:** Antigen-presenting cells
- **AST:** Aspartate aminotransferase.
- **ATP:** Adenosine triphosphate
- **BMI:** Body mass index
- **CA:** Celiac artery
- **CGM:** Continuous glucose monitoring
- **CHD:**Coronary heart disease
- **CHF:** Congestive heart failure
- **CIDP:**Chronic Inflammatory Demyelinating Polyneuropathy
- **CIDP:**Chronic Inflammatory Demyelinating Polyneuropathy
- **CNS:** Central nervous system
- **CRP:** C-reactive protein
- **CSII:** Continuous subcutaneous insulin infusion

- **CT:** Celiac trunk
- **CTLA-4:**Cytotoxic T-lymphocyte-associated protein 4
- **CVD:** Cardiovascular disease
- **DAN:**Diabetic Autonomic Neuropathy
- **DCCT:**Diabetes Control and Complications Trial
- **DKA:**Diabetic ketoacidosis
- **DM:**Diabetes Mellitus
- **DN:** Diabetic Neuropathies
- **DPN:** Diabetic Peripheral Neuropathy
- **DPP-4 inhibitors:** Dipeptidyl peptidase-4 inhibitor
- **EDIC:** Epidemiology of Diabetes Interventions and Complications
- **EDV:** End Diastolic Velocity
- **EPO:** Erythropoietin
- **ESRD:**End-stage renal disease
- **FBS**: Fasting blood glucose.
- **FDA:** Food and Drug Administration
- **FFA:** Free fatty acid
- **GAD**: Glutamic acid decarboxylase
- **GFR:** Glomerular filtration rate
- **GLP-1:** Glucagon like peptide 1
- **GLUT-2:** glucose transporter 2
- **HbA_{1C}:**HemoglobinA_{1c}

- **HDL_c:** high density lipoprotein cholesterol
- **HF:** Heart failure
- **HHS:**Hyperosmolar hyperglycemic state
- **HIV:**human immunodeficiency virus
- **HLA**: Human leukocyte antigen
- **HNF**: Hepatic nuclear factor
- **IBM:** International Business Machines
- **ICAs:** Islet cell autoantibodies
- **IFG:** Impaired fasting glucose
- **IGT:** Impaired glucose tolerance
- **IL2:** Interleukin–2
- **IL-6:** Interleukin-6
- **IMA:**inferior mesenteric artery
- **IR:** Insulin resistance
- **JNK:**c-Jun N-terminal kinases
- **LDDP:**length dependent diabetic polyneuropathy
- **LDL_c:** low density lipoprotein cholesterol
- **MDI:** Multiple daily injections
- **MHC:** Major histocompatibility complex
- **MODY**: Maturity onset diabetes of the young.
- **MRI:**Magnetic resonance imaging
- **NaCl:** Sodium Chloride

- **NADPH:** Nicotinamide adenine dinucleotide phosphate-oxidase
- **NGSP:** National Glycohemoglobin Standardization Program
- **NKT:** natural killer T cell
- **NMDA:**N-methyl-D-aspartate
- **NPH:** Neutral protamine hagedorn
- **NPL:** Neutral protamine lispro
- **OGTT:** Oral glucose tolerance test
- **PAI-1:** plasminogen activator inhibitor 1
- **PDE5 inhibitor:** Phosphodiesterase type 5 inhibitor
- **PDFV:** Peak Diastolic Forward Velocity
- **PGE1:** Prostaglandin E1
- **PI:** Pulsatility index
- **PSV:** Peak Systolic Velocity
- **PTP:** Protein tyrosine phosphatase
- **PTPN22:** Protein tyrosine phosphatase, non-receptor type 22
- **PVR:** Post void residual volume
- **QDIRT:** Quantitative Direct and Indirect Reflex Test
- **QSART:** Quantitative Sudomotor Axon Reflex Test
- **RCT:** Rational choice theory
- **RI:** Resistive Index
- **ROS:** Reactive oxygen species
- **SD:** Standard deviation

- **SMA:** Superior Mesenteric Artery
- **SNRIs:** Serotonin-norepinephrine reuptake inhibitors
- **SPSS:** Statistical program for social science
- **SSRIs:** Selective serotonin reuptake inhibitors
- **TCA:**Tricyclic Antidepressants
- **TCR:** T-cell receptors
- **TG:** Triglycerides.
- **TLR4:** Toll like receptors 4
- **TNF-α:** Tumor necrosis factor alpha
- **TST:** Thermoregulatory sweat testing
- **ZnT8:** Zinc transporter

Abstract

Background: The splanchnic circulation is essential for oxygenation of the small and large intestine, transport of absorbed nutrients, maintenance of systemic blood pressure and is regulated by neuronal, myogenic and humoral factors. Blood supply of the gastrointestinal tract is potentially affected in patients with diabetes mellitus, since diabetes may be associated with abnormalities in one or more of these regulatory factors. Recent advances in duplex ultrasound technology have permitted the noninvasive examination of the mesenteric circulation at rest and after a variety of physiologic and pharmacologic situations in healthy individuals. This method, because of its noninvasive nature, allows for studies in humans that could lead to better understanding of the physiology of the mesenteric circulation and could be the ideal tool for the diagnosis of chronic mesenteric ischemia

Aim of work: To compare the pattern of blood flow velocity in the superior mesenteric artery (SMA) and celiac artery in diabetic patients with and without autonomic neuropathy.

Subjects and methods: Cross sectional study included 15 diabetics with no clinically detected autonomic neuropathy and 15 diabetic patients with autonomic neuropathy was compared to 15 of healthy control. All patients were subjected to: Full history taking and thorough clinical examination stressing on the peripheral and autonomic neuropathy and BMI, Biochemical tests including; FBS, PPBS, HBA1c, Lipid profile, urine analysis and detection of microalbuminuria.Colored Doppler study was done for all patients and the control group in both the fasting state and 45 min after a standardized meal(1000 calories).

Results: Results of our study showed that Diabetic patients with autonomic neuropathy don't exhibit the same response to meal as that in diabetics without autonomic neuropathy.

Conclusion: Thus we concluded that diabetic autonomic neuropathy can influence the mesenteric circulation and results in gastrointestinal manifestations unrelated to occlusive vascular disease.

Keywords: Diabetes, mesenteric blood flow, autonomic neuropathy.

Introduction

The splanchnic circulation is essential for oxygenation of the small and large intestine, transport of absorbed nutrients, maintenance of systemic blood pressure and is regulated by neuronal,myogenic and humoral factors ***(Texter;1963)***

Blood supply of the gastrointestinal tract is potentially affected in patients with diabetes mellitus, since diabetes may be associated with abnormalities in one or more of these regulatory factors ***(Horowitz et al;2004)***

Recent advances in duplex ultrasound technology have permitted the noninvasive examination of the mesenteric circulation at rest and after a variety of physiologic and pharmacologic situations in healthy individuals ***(Lilly et al;1989)***

This method, because of its noninvasive nature, allows for studies in humans that could lead to better understanding of the physiology of the mesenteric circulation and could be the ideal tool for the diagnosis of chronic mesenteric ischemia ***(Nicholls et al;1986)***

However, although the normal flow characteristics of the normal individuals, in whom the superior mesenteric artery (SMA) is well visualized, has been well described, the range of normal flow velocities in a more varied population is still unknown ***(Jager; 1986).***

In addition, to be able to define a typical ultrasonographic waveform of chronic intestinal ischemia, it would appear advantageous to describe as well the pattern of blood flow velocity encountered in patients with gastrointestinal manifestations unrelated to occlusive vascular diseases.