Effect of Ramadan Fasting on Microvascular Complications in Type 1 Diabetic Patients

Thesis

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List of Abbreviations

Abb.	Full term

ACEIs ..... : *Angiotensin converting enzyme inhibitors.*
ACR ..... : *Albumin-Creatinine Ratio.*
ADA ..... : *American Diabetic Association.*
AEDs ..... : *Activated End Degradation Products.*
AGEs ..... : *Advanced Glycation Endproducts.*
BMI ..... : *Body Mass Index.*
BP ..... : *Blood Pressure.*
BUN ..... : *Blood Urea Nitogen.*
CKD ..... : *Chronic Kidney Disease.*
CML ..... : *Carboxy Methyl Lysine.*
COPD ..... : *Chronic Obstructive Pulmonary Disease.*
Cr. ..... : *Creatinine.*
CVD ..... : *Cardio Vascular Disease.*
DBP ..... : *Diastolic Blood Pressure.*
DKA ..... : *Diabetic Ketoacidosis.*
DM ..... : *Diabetes Mellitus.*
DN ..... : *Diabetic nephropathy.*
DN4Q ..... : *Diabetic Neuropathy Questionnaire.*
DPN ..... : *Diabetic Peripheral Neuropathy.*
DSP ..... : *Diabetic Symmetrical Polyneuropathy.*
EDIC ..... : *Epidemiology of Diabetes Interventions and Complications.*
eGFR ..... : *Estimated Glomerular Filtration Rate.*
EPIDIAR ..... : *Epidemiology of Diabetes and Ramadan*
ESRD ..... : *End Stage Renal Disease.*
FBG ..... : *Fasting Blood Glucose.*
GDM ..... : *Gestational Diabetes Mellitus.*
GFB ..... : *Glomerular Filtration Barrier.*

List of Abbreviations (Cont...)

Abb.	Full term
GI	*Glycemic Index.*
HbA1C	*Glycated Haemoglobin A1C.*
HCPs	*Health Care Professionals.*
HDL	*High Density Lipoprotein.*
IDDM	*Insulin Dependent Diabetes Mellitus.*
LDL	*Low Density Lipoprotein.*
MDRD	*Modification of Diet and Renal Disease equation.*
MNT	*Medical Nutrition Therapy.*
NADP	*Nicotinamide Adenine Dinucleotide Phosphate.*
PPBG	*Post-prandial Blood Glucose.*
RNP	*Ramadan Nutrition Plan.*
SGLT2	*Sodium Glucose Transporter*
SMBG	*Self Monitoring Blood Glucose.*
SNRIs	*serotonin-norepinephrine reuptake inhibitors.*
SU	*Sulfonylurea..*
T1DM	*Type 1 Diabetes Mellitus.*
T2DM	*Type 2 Diabetes Mellitus.*
TG	*Triglycerides.*
UACR	*Urinary Albumin Creatinine Ratio.*

INTRODUCTION

Fasting during the sacred month of Ramadan is one of the five pillars of Islam. It consists of stopping eating and drinking from sunrise to sunset. Duration of the fasting ranges from 12 to 18 h per day, and varies according to the geographic location and the season. During this holy month, lifestyle and eating habits change and cause biological variations ***(Houda Mbraky et al., 2015).***

Most healthy adult Muslims should strictly adhere to fasting during the month of Ramadan. However, exemption is given to the sick, travelers, and pregnant and lactating and menstruating women ***(Bernieh et al., 2010).***

Individuals with Type 1 diabetes have often been medically advised against fasting due to risks of hyper- or hypoglycaemia resulting from an imbalance between insulin administration and carbohydrate intake. However, many patients, especially adolescents, have continued to observe fast days due to strong religious and social motivations ***(Salti et al, 2004).***

During fasting, circulating glucose levels tend to fall, leading to decreased secretion of insulin. At the same time, levels of glucagon and catecholamines rise, stimulating the breakdown of glycogen, while gluconeogenesis is augmented. As fasting becomes protracted for more than several hours,

glycogen stores become depleted, and the low levels of circulating insulin allow increased fatty acid release from adipocytes. Patients with severe insulin deficiency, a prolonged fast in the absence of adequate insulin can lead to excessive glycogen breakdown and increased gluconeogenesis and ketogenesis, leading to hyperglycemia and ketoacidosis ***(Al-Arouj et al., 2010).***

Diabetic kidney disease, or kidney disease attributed to diabetes, occurs in 20–40% of patients with diabetes and is the leading cause of end-stage renal disease (ESRD). Screening for kidney damage (albuminuria) can be most easily performed by urinary albumin–to–creatinine ratio (UACR) in a random spot urine collection. The physicians have to face with issues like the management of diabetic kidney diseases in Muslim patients that want to fast during Ramadan. However, information is sparse and no guidelines or standardized protocols exist ***(ADA 2016; Bragazzi, 2014).***

AIM OF THE WORK

The aim of the study is to evaluate the effect of Ramadan fasting primarily on eGFR & microalbuminuria in people with type 1 diabetes and secondarily on neuropathy & retinopathy.

Chapter 1

COMPLICATIONS OF DIABETES MELLITUS

The physical, social, and economic costs of type 1 diabetes are difficult to calculate, and attempts to quantify these variables typically do not distinguish between type 1 and type 2 disease. However, two studies have provided cost estimates specifically for type 1 diabetes, proposing an annual figure of $14·4–14·9 billion in the USA.‑Regardless of the financial costs, achieving normoglycaemia is an important therapeutic goal for patients with type 1 diabetes, especially for avoiding complications ***(Tao et al., 2010).***

Complications in type 1 (and type 2) diabetes are classified as macrovascular or microvascular. Cardiovascular disease is becoming a more common macrovasular complication as individuals with type 1 diabetes live longer. Individuals with type 1 diabetes have a ten-times higher risk for cardiovascular events (eg, myocardial infarction, stroke, angina, and the need for coronary-artery revascularisation) than age-matched non-diabetic populations. The Pittsburgh Epidemiology of Diabetes Complications study of type 1 diabetes reported cardiovascular events in adult patients younger than 40 years of age to be 1% per year, and three times higher in individuals older than 55 years. The Epidemiology of Diabetes Interventions and Complications (EDIC) study, which

followed participants with type 1 diabetes for long-term complications, found intensive diabetes treatment reduced the risk of cardiovascular events by 42% compared with conventional treatment. The risk for microvascular complications, including retinopathy, nephropathy, and neuropathy, decreases with intensive insulin therapy. Over the past 5 years, several large clinical trials have advanced the prediction and prevention of microvascular complications ***(Eckel et al., 2012).***

Complications of diabetes mellitus are acute and chronic. Risk factors for them can be modifiable or not modifiable. Overall, complications are far less common and less severe in people with well-controlled blood sugar levels ***(Nathan, 2005).***

Microvascular complications:

Pathophysiology of microvascular complications:

Microvascular disease

The first pathological change in the small blood vessels is narrowing of the blood vessels. As the disease progresses, neuronal dysfunction correlates closely with the development of blood vessel abnormalities, such as capillary basement membrane thickening and endothelial hyperplasia, which contribute to diminished oxygen tension and hypoxia. Neuronal ischemia is a well-established characteristic of diabetic neuropathy. Blood vessel opening agents (e.g., ACE inhibitors) can lead to substantial improvements in neuronal blood flow,

with corresponding improvements in nerve conduction velocities ***(Behl et al., 2015).***

Advanced glycated end products

Elevated levels of glucose within cells cause a non-enzymatic covalent bonding with proteins, which alters their structure and inhibits their function. Some of these glycosylated proteins have been implicated in the pathology of diabetic neuropathy and other long-term complications of diabetes ***(Behl et al., 2015).***

Polyol pathway

Hyperglycemia, induced through decreased of insulin secretion or insulin resistance, is responsible for the enhanced of the polyol pathway activity. The rate-limiting first enzyme of this pathway aldose reductase catalyzes the formation of sorbitol from glucose, with the oxidation of nicotinamide adenine dinucleotide phosphate (NADPH) to $NADP^+$. Sorbitol is further oxidized to fructose by sorbitol dehydrogenase, which is coupled with the reduction of nicotinamide adenine dinucleotide (NAD^+) to NADH. It is described that during hyperglycemic states, the affinity of aldose reductase for glucose is higher, generating intracellular osmotic stress due to accumulation of sorbitol, since sorbitol does not cross cell membranes ***(Sheetz, 2002).***