بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / مني مغربي أحمد

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات: لا يوجد

Impact of low carbohydrate diet on Type 1 Diabetic patients

Thesis

Submitted for partial fulfillment of MD degree in Internal Medicine

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Cairo- Egypt

2022

ACKNOWLEDGEMENT

First, I would like to thank God for blessing this work until it has reached its end, as a part of his generous guidance and help throughout my life.

I would like to express my sincere gratitude to ***Prof. Dr. Mohamed Reda Halawa*** *for his support,encouragement and the tremendous effort he has done in the thorough revision of the whole work.*

I would like also to extend my thanks to ***Prof****.* ***Dr. Manal Abou Shady*** *for her sincere guidance throughout this work.*

My sincere appreciation for ***Prof. Dr. Yara Eid*** *who has taken the time effort and patience to read and modify this work.*

My profound indebtedness goes to ***Prof. Dr. Maram Maher*** *for her detailed review of the work and her gentle correction.*

My wholehearted thankfulness goes to ***Ass. Prof. Dr. Nagwa Roshdy*** *for her prompt thorough revision and guidance throughout this work.*

Last but not least I would like to acknowledge my gratefulness to ***Dr. Sahar Ismail,*** *our dedicated professional and certified Diabetes Educator for helping me and my cases.*

I would like to thank all participants for their cooperation, generosity and their patience.

My gratitude cannot be fulfilled without expressing my profound gratitude to my husband, my parents and siblings and even my friends who have been a rich source of concern and encouragement.

Contents

List of Abbreviations

ACR	Albumin/ creatinine ratio
ADA	American Diabetes Association
ALT	Alanine transaminase
ANOVA	Analysis of Variance
AST	Aspartate transaminase
BMI	Body mass index
CBC	Complete blood count
COVID-19	Corona Virus Disease of 2019
CVD	Cardiovascular Disease
DAFNE	Dose adjustment for normal eating
DCCT	Diabetes control and complications trial
DKA	Diabetic ketoacidosis
dL	Decilitre
FBG	Fasting blood glucose
GAD65	Glutamic acid decarboxylase
HbA1c	Glycated haemoglobin
HDL	High density lipoprotein
IA2	insulinoma-associated protein 2 (IA2)
IQR	Interquartile range
IU	International units
KD	Ketogenic diet
kg	Kilogram
km	Kilometres
LCMD	Low carbohydrate Mediterranean diet
LDL	Low density lipoprotein
mg	Milligram
MNT	Medical Nutrition therapy
NGSP	National haemoglobin standardization program
NS	Non-significant
P	Probability
PBF	Percent body fat
PC	Personal computer
RMANOVA	Repeated measure Analysis of Variance
S	Significant

SD	Standard deviation
SPSS	Statistical package for social sciences
T1DM	Type 1 diabetes mellitus
TDD	Total daily dose of insulin
TG	Trigylcerides
TLC diet	True low carbohydrate diet
UKPDS	United Kingdom Prospective Diabetes Study
USDA	United States Department of Agriculture
VLCKD	Very low carbohydrate ketogenic diet
ZNT8	zinc transporter 8

List of Tables

List of figures

رسالة توطئة
للحصول على درجة الدكتوراه في امراض الباطنة العامة

تحت عنوان: **تأثير اتباع نظام غذائي قليل النشويات على مرضى السكري من النوع الاول**

مقدمه: **إيفيت عزت عيد إسكندر**
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أستاذ امراض الباطنة و الغدد الصماء و السكر
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2022

Introduction

Diabetes mellitus is a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion or insulin action or both. The chronic hyperglycemia of diabetes is associated with impairment and failure of different organs. **[Zheng et al, 2018]**

Type 1 diabetes is a failure of the pancreatic beta cells to produce insulin. **[Katsarou et al, 2017]**

The discovery of insulin a century ago is a revolution in the management of this chronic autoimmune disorder. Currently, type 1 diabetes is the most common type of diabetes in children. Estimates suggest that around 100,000 children develop the disease every year **[Patterson et al, 2019]**.

Despite the availability of advanced insulins, affected individuals remain at high risk of serious complications, including cardiovascular mortality **[Petrie et al, 2019]**.

New interventions are, therefore required to improve the prognosis of this growing population of diabetics.

New interventions include changing the ratios of food intake in an attempt to decrease carbohydrate intake. This modification is thought to decrease attacks of hyperglycaemia by limiting the carbohydrate intake. Insulin doses will also decrease following the reduced carbohydrate intake, reducing the risk of hypoglycaemia and glucose excursions altogether. **[Corbin et al, 2018]**

Aim of the work

To assess the impact of low carbohydrate diet on type 1 diabetic patients.

Review of the Literature

Type 1 Diabetes

Type 1 diabetes is a chronic illness characterised by autoimmune destruction of the beta cell mass in the pancreatic islets of Langerhans **[Katsarou et al, 2017]**. Hypotheses suggest that the loss of functional beta cell mass occurs in a chain of events synonymous to an 'assisted suicide', where the loss of the beta cell is likely due to a combination of a dysfunctional beta cell that becomes more visible to the immune system. The immune system in turn, overreacts and destroys the beta cell. **[Roep et al, 2020]**

In its early stage (Stage 1), type 1 diabetes is usually asymptomatic; however, the development of autoimmunity is often detectable in early life, with circulating autoantibodies targeting insulin or other proteins, such as GAD65, insulinoma-associated protein 2 (IA2) or zinc transporter 8 (ZNT8) . When a large portion of the beta cell mass has become dysfunctional or lost, asymptomatic dysglycaemia (Stage 2) and, later, symptoms of hyperglycaemia (Stage 3) ensue due to insufficient or absent insulin secretion. **[Pociot et al, 2016]**

Also Type 1 diabetes is considered as a polygenic disorder, in which susceptibility loci or genetic variation contributes to risk of the disease. The HLA region on chromosome 6 is the main susceptibility locus. In recent years, many other loci across the genome have been associated with the disease risk. It has become evident that non-genetic factors play a major role in triggering or perpetuating overt type 1 diabetes by studying monozygotic twins **[Redondo et al, 2008]**.

A multitude of efforts have failed at robustly identifying such factors hence no single pathogen is responsible. Infection by some enteroviruses and herpes viruses have also been suggested **[Sabouri et al, 2020]**.

People living with type 1 diabetes remain dependent on exogenous insulins as the cornerstone medical option **[ADA, 2022]**

Since the isolation of insulin in 1921, novel and versatile formulations, analogues and delivery methods have been discovered **[Beck et al, 2019]**

With much improved glucose monitoring, these advances have contributed to the increases in the survival and life expectancy of type 1 diabetics **[Miller et al, 2012].**

Still, only a minority of type 1 diabetics achieve recommended glycaemic and time-in-range targets **[Weinstock, 2016]**, and hyperglycaemia continues to be a threat causing short-term metabolic and long-term macro- and microvascular complications **[Petrie et al, 2019].**

The use of exogenous insulins requires dedicated glycaemic monitoring and dose titration to minimize the risk of hypoglycaemia. The all-cause mortality risk is around threefold higher for the type 1 diabetics than for the general population, and type 1 diabetes has been shown to be linked to cardiovascular outcomes more than any other disease **[Schofield et al, 2019].**

Diagnostic criteria by the American Diabetes Association (ADA) in 2022 include the following :

- A fasting plasma glucose (FPG) level ≥126 mg/dL (7.0 mmol/L), or
- A 2-hour plasma glucose level ≥200 mg/dL (11.1 mmol/L) during a 75-g oral glucose tolerance test (OGTT), or
- A random plasma glucose ≥200 mg/dL (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis

- A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.

Table1: Stages of type 1 diabetes are according to ADA 2022:

	Stage 1	**Stage 2**	**Stage 3**
Characteristics	• Autoimmunity • Normoglycemia •Presymptomatic	1. • Autoimmunity 2. • Dysglycemia 3. • Presymptomatic	New-onset hyperglycemia Symptomatic
Diagnostic criteria	Multiple autoantibodies No IGT or IFG	1. • Multiple autoantibodies 2. • Dysglycemia: IFG and/or IGT 3. • FPG 100–125 mg/dL (5.6–6.9 mmol/L) 4. • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) 5. • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	Clinical symptoms Diabetes by standard criteria

Characteristics and diagnostic criteria of the stages of type 1 diabetes [ADA, 2022]

It is important to recognise the stages of diabetes as this is crucial for appropriate prompt treatment. A misdiagnosis of the type of diabetes may delay the introduction of insulin to the patient.

As mentioned earlier, novel interventions are needed for the management of type 1 diabetes. Whilst progress has been limited, the evolving profile of a person with type 1 diabetes suggests that beyond ensuring accurate titration of exogenous insulin, efficient management of the disease should rely on other additional principles.

Diet modification has always been a very important line of management when handling a case of diabetes especially type 1 diabetes.

Current status of individuals with type 1 diabetes

Around 10% of all people with diabetes have **type 1 diabetes**. More than 1.2 million children and adolescents (0-19 years) are living with type 1 diabetes **[IDF, 2021]**

The incidence in Egypt is about 8/100 000 per year. Currently, diabetes is a leading cause of vision loss in Egypt. It is estimated that 42% of patients with diabetes in Egypt have diabetic retinopathy, 5% are legally blind, and 22% had peripheral neuropathy. Diabetes is also the major cause of end-stage renal disease and leg amputation in Egypt**. [El-Ziny et al, 2014]**

In the long-term due to lifetime exposure to imperfect glucose control, people with type 1 diabetes are at increased risk of micro- and macrovascular complications **[Livingstone et al, 2019]**

The American Diabetes Association guidelines suggest a target HbA1c of <7.0% as primary management target to reduce the risk of long-term diabetes-related complications **[ADA, 2022].**

Only 21% of adults with type 1 diabetes have achieved the ADA HbA1c goal of <7.0% **[Foster et al, 2019]**

Currently, intense insulin regimens, monitoring of blood glucose and carbohydrate counting are standard ways of treating type 1 diabetes. The fact that HbA1c levels are deteriorating, rather than