Study of relation between long term Metformin treatment and Vitamin B_{12} Deficiency In type 2 diabetic Patients

Thesis

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Mai Mohamed Abass Tolba

List of Contents

List of Tables

List of Figures

List of Abbreviations

Abb.	Full term
µg	Microgram
AACE	The American Association of Clinical Endocrinologists
AAs	Amino acids
ABCC8	ATP-binding cassette, subfamily C
ACE	The American College of Endocrinology
ACR	Albumin to creatinine ratio
ADA	American Diabetes Association 1
ALT	Alanine Amino Transferase
AMA	Antimitochondrial antibodies
AMPK	Adenosine monophosphate activated protein kinase
AST	Aspartate Amino Transferase
B cells	
BCAAs	Branched-chain amino acids
BLK	B-lymphocyte kinase
BMI	Body Mass Index
CBC	Complete Blood Count
CEL	Carboxyl ester lipase
CMN	contrast media-induced nephrotoxicity
CT	Computed tomography
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DN	Diabetic nephropathy
DPP-4	Dipeptidyl peptidase IV inhibitors
DR	Diabetic retinopathy
EASD	European Association for the Study of Diabetes
eGFR	Estimated glomerular filtration rate
EIA	Enzyme immunoassay
ELISA	Enzyme Linked Immuno Sorbant Assay

List of Abbreviations cont…

Abb.	Full term
ETDRS	Early Treatment of Diabetes Retinopathy Study
FBG	Fasting blood glucose
Fig	Figure
GCK	Glucokinase
GGT	Gamma-glutamyltranspeptidase
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-Like Peptide -1
Glut4	Glucose transporter 4
HbA1c	Hemoglobin A1c
HHS	Hyperglycaemic hyperosmolar state
HNF4A	Hepatocyte nuclear factor 4 α
HT	Height
IF	Intrinsic factor
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IL-1	Interleukin -1
IL-6	Interleukin -6
INS	Insulin
IPF1	Insulin promoter factor 1
IR	Insulin Resistance
IRS	Insulin receptor substrate proteins
KCNJ 11	Potassium channel, inwardly rectifying subfamily J, member 11
Kg	Kilo gram
KLF11	Kruppel-like factor 11
LDL	Low-density lipoprotein
LPL	Lipoprotein lipase
m2	Squared meter
MALA	Metformin-associated lactic acidosis
MATE	Multidrug and toxin extrusion transporter
MATE1	Multidrug and toxin extrusion protein 1
MATE2	Multidrug and toxin extrusion protein 2

List of Abbreviations cont…

Abb.	Full term
MetS	Metabolic syndrome
Ml	Milliliter
MMCoAM	Methylmalonic coenzyme A mutase
MODY	Maturity-onset diabetes of the young
mRNA	Messenger Ribonucleic acid
MS	Methyl synthase
mtDNA	Mitochondrial DNA
Mtor	Mammalian target of rapamycin
NEUROD1	Neurogenic differentiation 1
NFkB	Nuclear factor kappa light chain enhancer of activated
Ng	Nanogram
NHANES	National Health and Nutrition Examination Survey
NIDDM	Non insulin dependent diabetes mellitus
NPDR	Nonproliferative DR
NPV	Negative predictive value
OAD	Oral antidiabetic agents
OCT1	Organic Cation Transporter 1
OCT2	Organic Cation Transporter 2
OCT3	Organic Cation Transporter 3
p value	A probability value
PAX4	Paired-box-containing gene
PDR	Proliferative DR
PDX1	Pancreatic and duodenal homeobox 1
PKB	Protein kinase B
PMAT	Plasma membrane monoamine transporter
PNDM	Permanent neonatal diabetes
PP	2 hours post prandial blood glucose
PPAR-γ	Peroxisome Proliferator Activated Peptide
PPV	Positive predictive value
Q	Long arm of chromosome
R	Correlation coefficient

List of Abbreviations cont…

Abb.	Full term
SCr	Serum creatinine
SD	Standard deviation
SGLT-2	Selective sodium-glucose transporter-2
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TC	Transcobalamin
TCF2	Transcription factor 2
TNF-α	tumor necrosis factor alpha
TZDs	Thiazolidinediones
UKPDS	United Kingdom Prospective Diabetes Study
WHO	World Health Organization
WT	weight

INTRODUCTION

Metformin is one of the most widely used oral hypoglycemic agents ***(Mazokopakis and Starakis, 2012)***.

Metformin treatment usually begins at the time of diagnosis of diabetes with lifestyle modification in the absence of contraindications ***(Kos et al., 2012).***

Long-term metformin treatment is a known pharmacological cause of vitamin B12 deficiency, as was evident within the first 10–12 years after it started to be used ***(De Jager et al., 2010).***

In addition, metformin treatment may be an iatrogenic cause for the exacerbation of peripheral neuropathy in patients with type 2diabetes who exhibit depressed vitamin B12 levels ***(Wile and Toth, 2010).***

We previously reported a high prevalence of vitamin B12deficiency in patients with type 2 diabetes treated with metformin, particularly in subjects with a longer duration and higher daily dose of metformin use ***(Ko et al., 2014).***

Although the clinical significance of vitamin B12 deficiency related to metformin treatment is debatable, monitoring for vitamin B12 has been recommended for patients with type 2 diabetes, especially those on long-term metformin treatment ***(De Jager et al., 2010).***

Clinically, vitamin B12 deficiency could lead to altered mental status, megaloblastic anemia, and neurological damage ***(Bell, 2010).***

Unfortunately, diabetic neuropathy symptoms can overlap with paresthesias, impaired vibration sensation and propriocaption ***(Pflipsen et al., 2009).***Therefore, peripheral neuropathy due to vitamin B12 deficiency may be confused with diabetic peripheral neuropathy or may contribute to the aggravation of diabetic peripheral neuropathy ***(Pierce et al., 2012).***

The progression of neurologic damage due to vitamin B12 deficiency can be stopped by early detection and treatment with cobolamin supplementation ***(Lindenbaum et al., 1988).*** However, if this occurrence is misdiagnosed as diabetic neuropathy, permanent neurological damage may occur ***(Pierce et al., 2012).***

AIM OF THE WORK

The aim of this work is to Study the relation betweenlong term Metformin treatment andVitamin B12 Deficiency in type 2 diabetic patients.

TYPE 2 DIABETES MELLITUS

Introduction

Type 2 diabetes mellitus consists of dysfunctions characterized by hyperglycemia and resulting from the combination of resistance to insulin action, inadequate insulin secretion, and excessive or inappropriate glucagon secretion. Poorly controlled type 2 diabetes is associated with an array of microvascular and macrovascular complications ***(ADA, 2012).***

Microvascular complications of diabetes include retinal, renal, and possibly neuropathic disease. Macrovascular complications include coronary artery and peripheral vascular disease. Diabetic neuropathy affects autonomic and peripheral nerves ***(ADA,2012).***

Although type 2 diabetes mellitus typically affects individuals older than 40 years, it has been diagnosed in children as young as 2 years of age who have a family history of diabetes ***(ADA, 2015).***

Etiology

The etiology of type 2 diabetes mellitus appears to involve complex interactions between environmental and genetic factors. Presumably, the disease develops when a diabetogenic lifestyle (ie, excessive caloric intake, inadequate caloric expenditure, obesity) is superimposed on a susceptible genotype **.**

The body mass index (BMI) at which excess weight increases risk for diabetes varies with different racial groups. For example, compared with persons of European ancestary, persons of Asian ancestary are at increased risk for diabetes at lower levels of overweight ***(ADA, 2014).***

In addition, an in utero environment resulting in low birth weight may predispose some individuals to develop type 2 diabetes mellitus ***(Li et al., 2012).*** Infant weight velocity has a small, indirect effect on adult insulin resistance, and this is primarily mediated through its effect on BMI and waist circumference ***(Slining et al., 2011).***

About 90% of patients who develop type 2 diabetes mellitus are obese. However, a large, population-based, prospective study has shown that an energy-dense diet may

be a risk factor for the development of diabetes that is independent of baseline obesity ***(Wang et al., 2008).***

Some studies suggest that environmental pollutants may play a role in the development and progression of type 2 diabetes mellitus.A structured and planned platform is needed to fully explore the diabetes-inducing potential of environmental pollutants ***(Hectros et al., 2011).***

Secondary diabetes may occur in patients taking glucocorticoids or when patients have conditions that antagonize the actions of insulin (e.g., Cushing syndrome, acromegaly, pheochromocytoma)**.**

Major risk factors *(ADA, 2016).*

The major risk factors for type 2 diabetes mellitus are the following:

- Age greater than 45 years (though, as noted above, type 2 diabetes mellitus is occurring with increasing frequency in young individuals).
- Weight greater than 120% of desirable body weight
- Family history of type 2 diabetes in a first-degree relative (e.g., parent or sibling).
- Hispanic, Native American, African American, Asian American, or Pacific Islander descent.