Potential Antidiabetic and Antihyperlipidemic effects of Myoinositol Versus Metformin in High Fat Diet, Streptozotocin - Induced Diabetes in Rats

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List of abbreviations

HBA_{1C}	Hemoglobin A_{1C}
AGEs	Advanced glycosylation end products
AMPK	Adenosine monophosphate- activated protein kinase
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body mass index
BW	Body weight
CD	Chow diet
CVD	Cardiovascular disease
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DDT	Dichloro Diphenyl Trichloro ethane
DPP-4	Dipeptidyl peptidase 4
eGFR	estimated Glomerular Filtration Rate
FBG	Fasting blood glucose
FPG	Fasting plasma glucose
g	Gram
GDM	Gestational diabetes mellitus
GLP-1	Glucagon-like peptide-1
GLUT4	Glucose transporter type 4
G6P	Glucose 6 phosphate
GPI	Glycosyle – phosphatidylinositol
Gs	Glycogen synthase
HDL	High density lipoprotein
HFD	High fat diet

HMIT	Hydrogen ion myoinositol transporter
HOMA	Homeostatic model assessment
HRP	Horseradish peroxidase
IDF	International diabetes federation
IFG	Impaired fasting glycemia
IGT	Impaired glucose tolerance
IMPA-1	Inositol monophosphatase-1
InsP6	Inositol hexakiphosphate
IP7	Inositol 7 phosphate
IPGs	Inositol phosphoglycans
IR	Insulin receptor
IRS	Insulin receptor substrate
ITT	Insulin tolerance test
i.v.	Intravenous
K+	Potassium ion
KITT%/minute	Glucose disappearance rate
LDL	Low density lipoprotein
MATE1	Multi-antimicrobial extrusion protein 1
MATE2	Multi-antimicrobial extrusion protein 2
Mg/dl	Milligram per deciliter
MIOX	Myoinositol oxygenase
MIPS	Myoinositol-phosphate synthase
MODY	Maturity onset diabetes of the young
MPV	Mean percentage value
MSG	Monosodium glutamate
MYO+MET	Myoinositol + metformin
NO	Nitric oxide

OGTT	Oral glucose tolerance test
OCT1	Organic cation transporter 1
OCT3	Organic cation transporter 3
O.D.	Optical density
PAD	Peripheral arterial disease
PCOs	Polycystic ovarian disease
PI	Phosphatidyl inositides
PI(3,5)P2	Phosphatidylinositol 3,5 biphosphate
PI(3,4,5)P3	Phosphatidylinositol 3,4,5 trisphosphate
PI3K	Phosphoinositide 3 Kinase
PKC	Protein kinase c
PMAT	Plasma monoamine transporter
PPAR	Peroxisome proliferator-activated receptor
ROS	Reactive oxygen species
SEM	Standard error of mean
SGLT2	Sodium glucose transporter 2
SMIT2	Sodium myoinositol transporter2
STZ	Streptozotocin
T2DM	Type 2 diabetes mellitus
TGF-B1	transforming growth factor B1
TMB	3,3’,5,5’-tetramethylbenzidine

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Abstract

Background: Many experimental and clinical studies showed that myoinositol has insulin-sensitizing effect in insulin resistance conditions as typically seen in type 2 diabetes mellitus (T2DM). Since there is a lack of evidence about the use of myoinositol in T2DM.

Aim: Our study was conducted to assess the possible antidiabetic and antihyperlipidemic effects of myoinositol, compare its effect to those of metformin and evaluate if there are more beneficial effects when using both drugs together in an animal model of diabetes induced by high fat diet (HFD) / streptozotocin (STZ).

Methods and drugs: 50 male Wister rats were randomly divided into 5 groups (10 per group), named as normal control group, diabetic control group, myoinositol treated group, metformin treated group and myoinositol+metformin treated group. After induction of type 2 diabetes, all drugs were taken for 4 weeks by gastric gavage.

Parameters measured: Body weight (BW), fasting blood glucose level (FBG), fasting plasma insulin, homeostasis model assessment of insulin resistance (HOMA-IR), glucose disappearance rate (KITT%/minute) of insulin tolerance test, lipid profile and glucose transporter 4 (GLUT4) expression.

Results: All treated groups showed non-significant change in BW, significant reduction in FBG, significant reduction in plasma insulin level, significant decrease in HOMA-IR and increase in KITT %/minute, significant improvement of lipid profile and significant increase in GLUT4 expression. The improvement of insulin resistance, hyperglycemic state and hyperlipidemia were better in combination therapy than in using either drug alone.

Conclusion: These findings suggest that myoinositol plays an effective role in glucose disposal into skeletal muscles by increasing GLUT4 expression that represents one of the most common causes of insulin resistance; hence, it may be used in the treatment of T2DM. In addition, combining myoinositol to metformin is more effective than using either drug alone.

Key words: myoinositol, metformin, high fat diet, streptozotocin, type 2 diabetes mellitus.

INTRODUCTION AND AIM OF THE WORK

Introduction

T2DM is "a chronic metabolic disease characterized by a progressive loss of ß-cells insulin secretion frequently on the background of insulin resistance". It is the most prevalent type as it represents 90-95% of all diabetes mellitus (DM) cases ***(American Diabetes Association, 2018)***. The chronic hyperglycemia of DM caused long-term damage, dysfunction, and failure of several organs, particularly the eyes, kidneys, nerves, heart, and blood vessels. ***(American diabetes association, 2014)***

DM is a major health issue that has reached alarming levels. In 2019, nearly half a billion people (9.3% of adults 20 - 79 years) are living with diabetes worldwide. Egypt ranks ninth among the world top 10 countries as regard the number of people with DM in 2019. ***(Saeedi, et al., 2019)***

Insulin resistance is the first step in the development of T2DM, in which the pancreatic ß-cells compensates by increasing insulin secretion in an attempt to overcome defects in peripheral insulin action. This compensation causes stress damage to pancreatic ß cells and become unable to secrete more insulin to compensate insulin resistance, so chronic hyperglycemia occured and type 2 diabetes established***. (Kahn, et al., 2014)***

To date, no drugs are fully able to treat T2DM and stop its progression and complications, so searching for new drugs, combinations, or strategies to treat diabetes is still opened. Thus, recent studies have focused on the pathogenesis of T2DM and its complications and on searching for new drugs or combination that may help in treating diabetes and stopping its progression and complications. ***(Antony, et al., 2017)***

One of the most common causes of insulin resistance is decrease GLUT-4 expression and translocation, which leads to

decrease glucose uptake in muscular and adipose tissues causing alterations at the metabolic level. ***(Gutiérrez-Rodelo, et al., 2017)***

Inositol consists of six carbon arranged in a cyclitol and existing under nine stereoisomeric forms. Myoinositol is the predominant form of inositol present in nature and in our food ***(croze & Soulage, 2013)***. It is a precursor in the phosphatidylinositol cycle and a source of many second messengers including diacylgycerol, which controls some members of the protein kinase C family, inositol-3,4,5-triphosphate, that alters intracellular calcium levels, and phosphatidylinositol-4,5-biphosphate, which play a vital role in signal transduction. It is also a constituent in the cell membranes and is essential for growth and survival of human cells ***(Carlomagno & Unfer, 2011)***. Other studies reported that it has also antidiabetic and antihyperlipidemic effects ***(Kim, et al., 2014; Foster, et al., 2016)***, as myoinositol can increased GLUT4 translocation in skeletal muscle ***(croze & Soulage, 2013)*** and can also increase the expression of PPAR-γ, GLUT4 and IR in adipose tissues ***(Antony, et al., 2017).***

Aim of the work

The present study aimed to

- Evaluate the possible antidiabetic and antihyperlipidemic effects of myoinositol.
- Compare between the antidiabetic and antihyperlipidemic effects of myoinositol to those of metformin.
- Investigate if there are more beneficial effects from using them together.

In an animal model of diabetes induced by high fat diet and streptozotocin.