THE EFFECTS OF VITAMIN D ON INSULIN RESISTANCE AND NERVE CONDUCTION VELOCITY IN MALE RATS WITH TYPE 2 DIABETES

Thesis

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&

My children Salma, Talia & Marwan

For their support & patience

Abstract

Background: There is an emerging evidence of the neuroprotective roles for vitamin D. However its role in the pathogenesis of type 2 diabetes (T2 DM) and its exact mechanism of action in neuroprotection are still uncertain. The present work was designed to examine the effect of vitamin D supplementation on insulin sensitivity and nerve conduction velocity with and without insulin treatment in diabetic model.

Methods: The study was conducted on 50 male adult rats. They were divided into five groups :***Group 1****:Control group*, ***Group 2:****Diabetic group*, in which T2DM was induced; ***Group 3:****Diabetic-insulin treated group* in which diabetic rats were treated with insulin alone; ***Group 4:****Diabetic - vitamin D treated group* in which diabetic rats were treated with vitamin D alone and finally,***Group 5:****Diabetic with combined insulin and vitamin D treatment group.*At the end of the experimental period, blood samples were taken from all animals of all groups for measurement of serum glucose & insulin, insulin resistance index (HOMA-IR),together with the oxidative stress marker : Malondialdehyde (MDA) and inflammatory markers: Interleukins 1β &10 (IL1β and IL10) . VDR gene expression in pancreatic (VDR-P) and sciatic nerve (VDR-N) tissues were estimated. In addition Nerve conduction velocity was performed on dissected sciatic nerve .

Results: Data showed a significant reduction of nerve conduction velocity of sciatic nerve together with increased insulin resistance in diabetic rats that paralleled increased MDA and IL1β and the decreased IL10. Administration of insulin, vitamin D alone or combined after induction of diabetes improved the previous changes. This improvement was accompanied with significant enhancement of VDR –P and VDR-N gene expression.

Conclusion: The improvement of insulin sensitivity and the neuroprotection induced by vitamin D supplementation in T2DM is related to restoration of VDR-P and VDR-N expression. Thus vitamin D could be a novel approach to lower neuropathic risk in diabetes.

Keywords:

Vitamin D receptor; 1,25-dihydroxyvitamin D3; Type2 diabetes mellitus, Insulin resistance, Nerve conduction velocity.

Contents

List Of Abbreviations

1α,25(OH)2D3	**1α,25(OH)2Di hydroxyvitamin D3**
2HPP	Two hours post prandial
AGEs	Advanced glycemic end products
AIR	Acute insulin response
ANOVA	Analysis of variance
ARE	Antioxidant response element
BGP	Bone gamma carboxyglutamic acid protein
BMD	Bone mineral density
BMI	Body mass index
BNC	Bayonet Neill-concelman
CAPs	Compound action potentials
CGRP	Calcitonin gene related peptide
CIDP	Chronic inflammatory demyelinating polyneuropathy
COX	Cyclo-oxygenase
CVD	Cardiovascular disease
CY	Cytochrome
dATP	Deoxyadenosine triphosphate
DBP	Vitamin D binding protein
DCCT	Diabetic control and complication trial
dCTP	Deoxycytidine triphosphate
dGTP	Deoxyguanosine triphosphate
DI	Disposition index
DIN	Deutsches institute fur normung
DKA	Diabetic ketoacidosis
DM	Diabetes Mellitus
DN	Diabetic neuropathy
DNA	Deoxyribonucleic acid
dNTPS	Deoxynucleotide triphosphate

DPP	Diabetes prevention program
DRIs	Dietary reference intake
Drp1	Dynamin related protein
Drp1	Dyanamin related protein
DSPN	Distal symmetrical peripheral neuropathy
dTTP	Deoxythymidine triphosphate
EAE	Experimental autoimmune encephalomyelitis
EAR	Estimated average requirement
ELISA	Enzyme linked immunosorbent assay
EMG	Electromyography
FBG	Fasting blood glucose
FGF-23	Fibroblast growth factor twenty three
FOXO3	Forkhead protein
FPG	Fasting plasma glucose
GDNF	Glial cell derived neurotrophic factor
GENNID	Genetics of non-insulin dependent diabetes mellitus
GIP	Gastric inhibitory polypeptide
GLP-1	Glucagon like peptide one
GTC	Guanidine thiocyanate
HAART	High active antiretroviral treatment
HbA1C	Glycated haemoglobin
HFD	High-fat diet
HO-1	Hemoxygenase one
HOMA-IR	Homeostasis model assessment of insulin resistance
HXXO	Hypxanthine/xanthine oxidase system
IBD	Inflammatory bowel disease
IENF	Intra-epidermal nerve fiber
IFG	Impaired fasting glucose
IGI	Insulinogenic index
IGT	Impaired glucose tolerance

IL	Interleukin
iNOS	Inducible nitric oxide synthase
INS	Insulin
IOM	Institute of medicine
IRR	Insulin real risk
ISSI	Insulin secretion sensitivity index
LPO	Lipid peroxidation
MAPK	Mitogen activated protein kinase
MDA	Melondialdehyde
MMLV	Molony murine leukemia virus
NAD	Nicotinamide adenine dinucleotide
NADPH	Nicotinamide adenine dinucleotide phosphate
NCS	Nerve conduction studies
NCS	Nerve conduction studies
NCV	Nerve conduction velocity
NGF	Nerve growth factor
NPH	Neutral protamine Hagedorn
NQO1	Quinoneoxide reductase 1
Nr	Nuclear factor
Nrf	Nuclear factor
NT3	Neutrotrophin three
OGTT	Oral glucose tolerance test
P	Probability
PAD	Peripheral arterial disease
PAD	Peripheral arterial disease
PARP	Poly(ADP-ribose)polymerase pathway
PARP	Poly(ADP-ribose) polymerase activity
PCR	Polymerase chain reaction
PKC	Protein kinase c
PL	Parometer logistic

PPAR	Peroxisome proliferation activated receptor
PTH	Parathyroid hormone
QST	Quantitative sensory testing
RCT	Randomized controlled trials
RDA	Recommended dietary allowance
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
rpm	Round per minute
RR	Rapid response
RXR	Retinoid X receptors
SC	Subcutaneous
SHR	Spontaneous hypertensive rats
SPF	Sun protection factor
SPPL	Osteoponin
STZ	Streptozotocin
SWMT	Semmes-Weinstein monofilament test
T1DM	Type one diabetes mellitus
T2DM	Type two diabetes mellitus
Taq	Thermos aquaticus
TBA	Thiobarbituric acid
TCA	Trichloracetic acid
TGF	Transforming growth factor
TNF	Tumour necrosis factor
TrKA	Tropomysin related kinase receptor
TZD	Thiazolidinedions
UPS	Ubiquitin- proteasome system
UVB	Ultraviolet B
VDDS	Vitamin D deficiency syndrome
VDR	vitamin D receptor
VDRE	Vitamin D response element

VDR-N	Vitamin D receptor gene in nerve tissue
VDR-P	Vitamin D receptor gene in pancreatic tissue
VPT	Vibration perception threshold
WC	Waist circumference
WHO	World Health Organisation

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