Assessment of Association of Trace Elements (Magnesium & Zinc) and Insulin Resistance

Thesis

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ABBREVIATIONS

AKt	AK,a mouse strain, transforming protein (protein kinase)
AMPK	Adenosine monophosphate-activated protein kinase
ATM	Adipose tissue macrophage
AUC	Area under curve
BMI	Body mass index
BP	Blood pressure
CD	Cluster of differentiation
CO	Carbon monoxide
Creb	Clean renewable energy bond (a transcription factor)
DM	Diabetes mellitus
FFA	Free fatty acids
F4/80	a transmembrane protein macrophage
G0	fasting glucose
GH	Growth hormone
Glut	glucose transporter
GLP-1	Glucagon –like peptide 1
GR	Glucocorticoid receptors

GTP	Guanosine triphophate
HBV	Hepatitis B virus
HCV	Hepatitis c virus
HDL	High density lipoprotein
I0	fasting insulin
IFG	Impaired fasting glucose
IGF-1	Insulin like growth factor 1
IGT	Impaired glucose tolerance
INS gene	Insulin gene
IL	Interleukines
IRS 1	Insulin receptor substrate 1
IP3	Inositol triphosphate
JCI	Journal of clinical investigation
JNK	cJun N-terminal kinases
LH	Luteinizing hormone
MafA	Musculo aponeurotic fibrosarcoma type A (a transcription factor)
MCP-1	Monocyte chemotactic factor 1
MR	Mineralocorticoid receptors

NO	Nitric oxide
NF	Nuclear factor
PaI1	Plasminogen inhibitor 1
Pdx1	Pancreatic and duodenal home box 1(a transcription factor)
PI3K	Phosphatidyl inositol 3 kinase
PPAR	Peroxisome proliferator- activated receptor (a nuclear receptor protein)
PPRE	peroxisome proliferator hormone response element
RBP4	Retinol binding protein 4
SOC	Supprssor of cytokines
TG	Triglyceride
TGFb1	Transforming growth factor beta 1
Th	T lymphocyte helper cell
TRPM	Transient receptor potential ion channel (M stands for melastanin
VDR	Vitamin D receptor

Introduction

The metabolic syndrome is highly prevalent in populations around the world **(Cameron et al., 2004).**

Insulin resistance, which is a corner stone in metabolic syndrome, appears to be a common feature and a possible contributing factor to several frequent health problems, including type 2 diabetes mellitus, polycystic ovary disease, dyslipidemia, hypertension, cardiovascular disease, sleep apnea, certain hormone-sensitive cancers, and obesity **(Eckel et al., 2005).**

There are many factors affect insulin sensitivity; the alteration of these factors may affect insulin action and emerging of insulin resistance.

Trace elements are one of the factors which affect insulin sensitivity in our body; one of them is (zinc) which is an essential trace element involved in the structure of crystalline insulin, its antigenic properties and action **(Winterberg et al., 1989).**

Another trace element is magnesium, which is a cofactor of many enzymes involved in glucose metabolism and insulin action **(Barbagallo et al., 2003).**

Aim of the work

This study aims to assess the association of the levels of plasma trace elements (zinc and magnesium) and insulin resistance.

Review of Insulin Hormone

Insulin is a peptide hormone composed of 51 amino acids and has a molecular weight of 5808 Da. It is produced in the islets of Langerhans in the pancreas. The name comes from the Latin *insula* for "island". Insulin's structure varies slightly between species of animal. Insulin from animal sources differs somewhat in "strength" (in carbohydrate metabolism control effects) than in humans because of those variations. Porcine (pig) insulin is especially close to the human version **(Saladin et al., 2007).**

Gene:

The proinsulin precursor of insulin is encoded by the *INS* gene **(Bell et al., 1980).**

Regulation of Gene Expression:

There are several regulatory sequences in the promoter region of the human insulin gene, to which transcription factors bind. Where A-boxes , E-boxes and C-boxes are main segments of the DNA of insulin gene that regulate its expression when binding to other proteins called transcription factors like Pdx1, NeuroD, MafA and CREB. In general, the A-boxes bind to Pdx1 factors, E-boxes bind to NeuroD, C-boxes bind to MafA and cAMP response elements to CREB **(Fig. 1)**. There are also silencers that inhibit transcription **(Melloul et al., 2002).**

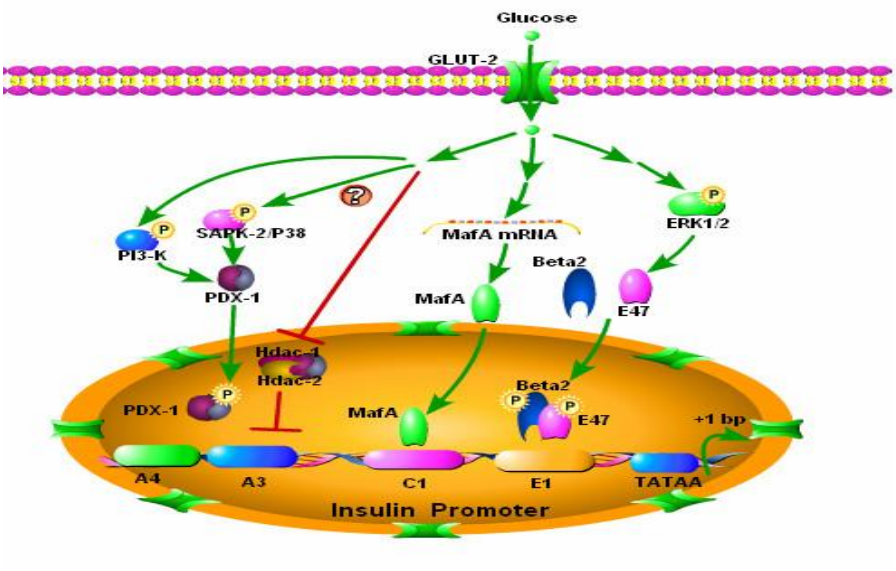

Fig. (1): Insulin Gene Expression

The activated insulin receptor substrate-1(IRS-1) acts as a secondary messenger within the cell to stimulate the transcription of insulin-regulated genes. First, the protein Grb2 (Growth factor receptor bound protein-2) binds the phosphorylated tyrosine residue of IRS-1 in its SH2 domain. Grb2 is then able to bind SOS, which in turn catalyzes the replacement of bound GDP with GTP on Ras, a G protein. This protein then begins a phosphorylation cascade, culminating in the activation of mitogen-activated protein kinase (MAPK), which enters the nucleus and phosphorylates various nuclear transcription factors **(Ward and Lawrence, 2009).**

Alleles:

A variety of mutant alleles with changes in the coding region have been identified. There is a read-through gene, INS-IGF2, which overlaps with this gene at the 5' region and with the IGF2 gene at the 3' region **(O'Dell and Day, 1998).**

Protein Structure:

Within vertebrates, the amino acid sequence of insulin is extremely well preserved. Bovine insulin differs from human in only three amino acid residues, and porcine insulin in one. Even insulin from some species of fish is similar enough to human to be clinically effective in humans. Insulin in some invertebrates is quite similar in sequence to human insulin, and has similar physiological effects. The strong homology seen in the insulin sequence of diverse species suggests that it has been conserved across much of animal evolutionary history. The C-peptide of proinsulin , however, differs much more amongest species **(Hills and Brunskill, 2008).**

Insulin is produced and stored in the body as a hexamer (a unit of six insulin molecules), while the active form is the monomer. The hexamer is an inactive form with long-term stability, which serves as a way to keep the highly reactive insulin protected, yet readily available. The hexamer-monomer conversion is one of the central aspects of insulin formulations for injection. The hexamer is far more stable than the monomer, which is desirable for practical reasons; however the monomer is a much faster reacting drug because diffusion rate is inversely related to particle size. A fast reacting drug means that insulin injections do not have to precede mealtimes by hours, which in turn gives diabetics more flexibility in their daily schedule **(Dunn, 2005).** Insulin can aggregate and form fibrillar interdigitated beta-sheets. This can cause

injection amyloidosis, and prevents the storage of insulin for long periods **(Ivanova et al., 2009).**

Insulin Receptor:

The insulin receptor is a transmembrane receptor that is activated by insulin **(Ward and Lawrence, 2009).** It belongs to the large class of tyrosine kinase receptors **(fig.1).**

Two alpha subunits and two beta subunits make up the insulin receptor. The beta subunits pass through the cellular membrane and are linked by disulfide bonds **(Perz and Torlińska, 2001).** The alpha and beta subunits are encoded by a single gene (*INSR*). The insulin receptor has also been designated CD220 (cluster of differentiation 220**) (Zola et al., 2005).**

Tyrosine kinase receptors, including the insulin receptor, mediate their activity by causing the addition of a phosphate group to particular tyrosines on certain proteins within a cell. The "substrate" proteins which are phosphorylated by the Insulin Receptor include a

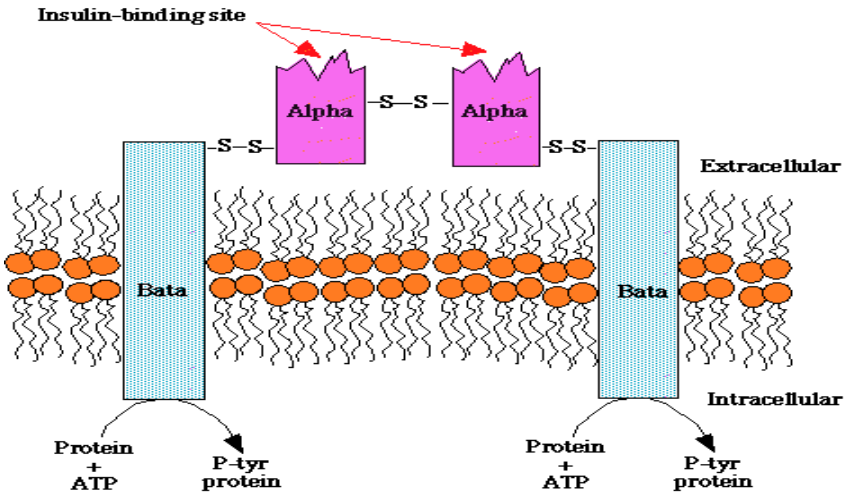

Fig.(2): Insulin Receptors

protein called glucose transporter (Glut4) molecules on the outer membrane of insulin-responsive tissues, including muscle cells and adipose tissue, and therefore to an increase in the uptake of glucose from blood into these tissues. Briefly, the glucose transporter Glut4 is transported from cellular vesicles to the cell surface, where it then can mediate the transport of glucose into the cell **(Watson et al., 2004).**