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Blood Glucose Levels

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Meet the editor

Leszek Szablewski is a professor of medical sciences. He received his M.S. in the Faculty of Biology from the University of Warsaw and his PhD degree from the Institute of Experimental Biology Polish Academy of Sciences. He habilitated in the Medical University of Warsaw, and he obtained his degree of Professor from the President of Poland. Professor Szablewski is the Head of Chair and Department of General Biology and Parasitology, Medical University of Warsaw. Professor Szablewski has published over 80 peer-reviewed papers in journals such as *Journal of Alzheimer's Disease*, *Biochim. Biophys. Acta Reviews of Cancer*, *Biol. Chem.*, *J. Biomed. Sci.*, and *Diabetes/Metabol. Res. Rev, Endocrine*. He is the author of two books and four book chapters. He has edited four books, written 15 scripts for students, is the ad hoc reviewer of over 30 peer-reviewed journals, and editorial member of peer-reviewed journals. Prof. Szablewski's research focuses on cell physiology, genetics, and pathophysiology. He works on the damage caused by lack of glucose homeostasis and changes in the expression and/or function of glucose transporters due to various diseases. He has given lectures, seminars, and exercises for students at the Medical University.

Contents

Preface

The main and preferred source of energy for the body is glucose. Therefore, most tissues and organs need a constant supply of glucose. The low blood concentrations of glucose can cause several pathologies and diseases such as seizures and loss of consciousness. Hypoglycemia may also cause death. On the other hand, long-term high glucose levels, hyperglycemia, can cause blindness, renal failure, cardiac and peripheral vascular disease, and neuropathy. Therefore, blood glucose concentrations need to be maintained within narrow limits and are carefully regulated to around 90 mg/mL (5 mM). The process of maintaining blood glucose at a steady state is called glucose homeostasis. This is achieved through a balance of the rate of consumption of dietary carbohydrates, utilization of glucose by peripheral tissues, and the loss of glucose through the kidney tubule. The liver and kidney also play a role in glucose homeostasis. A major role in glucose homeostasis is played by the liver by maintaining a balance between the uptake and storage of glucose via glycogenesis, and the release of glucose via glycogenolysis and gluconeogenesis. The body can adjust blood glucose levels by a variety of cellular mechanisms. In this process, a very important role is played by external signals conveyed by hormones, cytokines, and so on. In the past several years, the knowledge of regulation of blood glucose levels, glucose homeostasis, and diseases due to disturbances in glucose homeostasis, has been growing. This book aims to provide an overview on the topic of blood glucose levels in health and diseases. The authors discuss this process from different aspects to enhance the understanding of glucose homeostasis in the human body.

This book contains four sections. Section 1 contains only one chapter and describes the general characteristics of glucose transporters. Section 2 contains chapters in which authors describe mechanisms of regulation of blood glucose levels. These chapters include information on the molecular basis of blood glucose regulation, and role of PI3K/AKT in insulin-mediated glucose uptake. Section 3 focuses on low blood glucose levels (hypoglycemia). The authors describe pathologies due to hypoglycemia, as well as the symptoms and signals of this pathological state. Section 4 presents the influence of lifestyle on metabolic syndromes. This dependence is described on the basis of Ramadan fasting.

I would like to thank Mr. Gordan Tot for his great efforts in the book planning and editing during the process of book publication.

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Section 1

Introduction

Chapter 1

Introductory Chapter: Glucose Transporters

Leszek Szablewski

1. Introduction

The major source of energy for mammalian cells is glucose. Glucose derived from the diet and synthesized within the body is transported from the circulation into target cells. The transfer of glucose across the plasma membrane is necessary. Cell membrane is composed by lipid bilayer, which is hydrophobic. Glucose has hydrophilic nature. Therefore, cell membranes act as barriers to most molecules. For water molecules and a few other small molecules, such as oxygen and carbon dioxide, the lipid bilayer is permeable. These molecules move spontaneously down their concentration gradient by diffusion. For cations such as K^+, Na^+, and Ca^{2+}; anions such as Cl^- and HCO_3^-; and hydrophilic molecules and macromolecules such as proteins and RNA, lipid bilayer is impermeable. Therefore, these molecules and ions need specific transport system. There are two general classes of membrane transporters: channels and carriers.

Glucose transporters belong to the major facilitator superfamily (MFS). MFS contains 74 families of membrane transporters including more than 10,000 members. These transporters transport variety of molecules.

Glucose as well as other monosaccharides cannot penetrate the lipid bilayer because they are hydrophilic in nature; therefore, they require specific carrier proteins to undergo diffusion through the bilayer. In humans, there are three families of genes that encode for glucose transporters: *SLC2A*, *SLC5A*, and *SLC50A* [1].

Glucose is transported across the cell membranes and tissue barriers by a sodium-independent glucose transporter (facilitated transport, GLUT proteins, and *SLC2* genes), sodium-dependent glucose symporters (secondary active transport, SGLT proteins, and *SLC5* genes), and glucose uniporter—SWEET protein (*SLC50* genes). Most cells express more than one kind of glucose transporters. However, these membrane carrier proteins are called glucose transporters; they are involved in the transport of several different molecules, not just glucose.

2. Characteristics of glucose transporters

2.1 Characteristics of GLUT proteins

In humans, 14 members of GLUT proteins have been identified. They are encoded by the solute-linked carrier family 2, subfamily A gene family, and *SLC2A* [2, 3]. All GLUT proteins are predicted to contain 12 hydrophobic membrane spanning, α-helical transmembrane (TM) domains. These domains are connected by hydrophilic loop between TM6 and TM7 of the protein [4–6]. GLUTs contain a site for single glycosylation on the exofacial end, either in the large loop between TM1 and TM2 (first extracellular loop) or between TM9 and TM10 (fifth extracellular

loop) [7]. As was proposed for GLUT1, helices 1, 2, 4, 5, 7, 8, 10, and 11 form an inner bundle that is stabilized by the outer helices 3, 6, 9, and 12 [8].

Based on the phylogenetic analysis of sequence similarity and characteristic elements, the GLUT family of sugar transporters is divided into three classes [4, 5, 9, 10]: an N-linked glycosylation site for GLUTs of class I and II is positioned in the first exofacial loop between TM1 and TM2, and family members of class III contain the glycosylation site between TM9 and TM10 [5].

Class I GLUTs include GLUT1–GLUT4 and GLUT14, which are 48–63% identical in humans. Class II GLUTs comprise of GLUT5, GLUT7, GLUT9, and GLUT11. These transporters are 36–40% identical. Class III GLUTs include GLUT6, GLUT8, GLUT10, GLUT12, and GLUT13 (HMIT). GLUTs in this class are only 19–41% identical.

The human GLUTs are involved in the transport of the several hexoses in addition to myoinositol, urate, glucosamine, and ascorbate [7]. All the members of the GLUT family are facilitative transporters except for GLUT13 (HMIT), which is an H^+/myoinositol symporter [11].

2.2 Pseudogenes

To date, four pseudogenes of *SLC2A* family were described [5, 7]:

1. *SLC2A3P1* (alias GLUT6 or GLUT3 pseudogene) is located on chromosome 5q35.1 and is a retroposon of *SLC2A3*.

2. *SLC2A3P2* (alias GLUT3 pseudogene 2) is located on chromosome 1p31.3 and is a retroposon of *SLC2A3*.

3. *SLC2A3P4* (alias GLUT3 pseudogene 4) is located on chromosome 8q21.3 and is a retroposon of *SLC2A3*.

4. *SLC2AXP1* is located on chromosome 2q11.2 and contains internal stop sequences.

2.3 Characteristics of sodium-dependent glucose symporters

Crane [12] showed that active glucose absorption by hamster's small intestine required sodium ions in the bathing medium. He proposed that these symporters have two binding sites: one for glucose and one for sodium [13].

The sodium-dependent glucose cotransporters belong to the gene family (*SLC5A*), the SGLTs, or sodium/substrate symporters family (SSSF), containing over 450 members [14–16]. In humans, 12 members of sodium-dependent glucose cotransporters have been identified. Amino acid comparison of the human sodium-dependent glucose cotransporters shows the range of identity from 57 to 71% [17]. The members of the SGLT family also share considerable homology among the proteins (21–70% amino acid identity with SGLT1) [10, 16]. These proteins contain of 580–718 amino acid residues, with a predicted mass of 60–80 kDa. There is a diversity in gene structure. In eight genes, the coding sequences are found in 14–15 exons (*SLC5A1, SLC5A2, SLC5A4–SLC5A6,* and *SLC5A9–SLC5A11*), and the coding sequence for *SLC5A7* and *SLC5A3* are present in exons 8 and 1, respectively. In *SLC5A9–SLC5A11* and *SLC5A3*, there is evidence for alternative splicing. These proteins contain 14 TM α-helices (TMHs) in all but not in sodium-iodide symporter (NIS) and SMCT1, which lack TMH^{14} [18]. Both the hydrophilic N- and C-termini are located on the extracellular side of the cell membrane [1]. SGLTs are

highly glycosylated membrane proteins; however, glycosylation is not required in the functioning of the protein. The human *SLC5A* genes are expressed in different tissues, and all of them code for sodium-dependent glucose cotransporter proteins, except for SGLT3 (*SLC5A4*), which acts as a glucose sensor [19]. These carrier proteins transport substrates such as glucose, myoinositol, and iodide; one is a Na^+/Cl^-/choline cotransporter, and another is a glucose-activated ion channel [16].

2.4 Characteristics of SWEET glucose transporters

SWEETs transport mono- and disaccharides across vacuolar and plasma membranes. A new class of glucose transporters, SWEET, was first identified by expressing candidate *Arabidopsis* genes coding for polytopic membrane proteins in HEK293T cells [20]. SWEETs are ubiquitously expressed in plants. In contrast to *Arabidopsis thaliana*, in which up to two dozen SWEETs have been identified, animals usually have only one SWEET, except for *Caenorhabditis elegans*, where seven SWEET-encoding genes have been found. Homologs of the SWEETs are widespread in metazoan genomes, and there is a single homolog in human genome (SWEET1) encoded by the gene *SLC50A1* [1].

Human SWEET1 (RAG1AP1), encoded by *SLC50A1*, comprises 221 amino acids with a molecular weight of 25 kDa. Human SWEET1 did not promote glucose uptake but instead mediated a weak efflux. Human SWEET1 when expressed in HEK293T cells was predominantly found to be localized in the Golgi with minimum expression also found in the plasma membrane. Chen et al. [20] discovered the highest level of expression in the oviduct, epididymis, and intestine, and its expression was induced in mouse mammary gland during lactation. The authors suggest that the human SWEET1 serves to supply glucose for lactose synthesis in the mammary gland. Human SWEET1 glucose transporter is the missing glucose transporter in the basolateral membrane of enterocytes where it may account for the exit of glucose from the cell into the blood in patients with Fanconi-Bickel syndrome and in mice missing the GLUT2 transporter [21, 22].

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Section 2

Regulation of Glucose Levels

Chapter 2

Molecular Basis of Blood Glucose Regulation

Asma Ahmed and Noman Khalique

Abstract

Blood glucose level is regulated by multiple pancreatic hormones, which regulate it by different pathways in normal and abnormal conditions by expressing or suppressing multiple genes or molecular or cellular targets. Multiple synthetic drugs and therapies are used to cure glucose regulatory problems, while many of them are used to cure other health issues, which arise due to disturbance in blood glucose regulations. Many new approaches are used for the development of phytochemical-based drugs to cure blood glucose regulation problems, and many of the compounds have been isolated and identified to cure insulin resistance or regulate beta cell function or glucose absorption in the guts or GLP-1 homoeostasis or two/more pathways (e.g., either cure hyperglycemia or raise insulin resistance or cure pancreatic beta cell regeneration or augmentation of GLP-1, production of islet cell, production and increased insulin receptor signaling and insulin secretion or decreased insulin tolerance or gluconeogenesis and insulin-mimetic action or production of α-glucosidase and α-amylase inhibitor or conserve islet mass or activate protein kinase A (PKA) and extracellular signal regulated kinases (ERK) or activate AMPK and reduce insulin sensitivity or suppress α-glucosidase activity and activate AMPK and downstream molecules or prevents cell death of pancreatic β-cell and activates SIRT1 or lower blood glucose due to their insulin-like chemical structures or decrease lipid peroxidation.

Keywords: genes, molecular and cellular targets, hormones, pathways

1. Introduction

Blood glucose is regulated by the pancreatic hormones alone or in combination with other endocrine glands and all this is controlled by one or more gene or cellular or molecular targets. If any problem occurs in the normal pathway(s), then multiple drugs or therapies are used to cure it. Moreover with the emerging technologies, multiple plant based formulations has been synthesized or in process to cure all blood glucose regulation problems and their associated diseases.

2. Hormones for the regulation of blood glucose levels

2.1 Pancreas: an exocrine and endocrine organ

2.1.1 Location

It is located at the back of stomach, within left upper abdominal cavity.

2.1.2 Parts

Its parts are head, body and tail. Majority of this secretory organ consists of:

a. **Acinar/exocrine cells**: Which secrete pancreatic juice (containing digestive enzymes i.e. amylase, pancreatic lipase and trypsinogen) into main and accessory pancreatic duct.

b. **Endocrine cells**: Which secrete pancreatic hormones directly in blood stream (in endocrine way). These cells cluster together and form the so-called islets of Langerhans (small, island-like structures within the exocrine pancreatic tissue and accounts for only 1–2% of the entire organ) (**Figure 1**). These are five different types of cells and release various hormones [1]:

   i. **Glucagon-producing α-cells:** They are 15–20% of the total islet cells and releases Glucagon to increase blood glucose levels.

   ii. **Amylin-, C-peptide- and insulin-producing β-cells:** They are 65–80% of the total cells and produces insulin to decrease glucose.

   iii. **Pancreatic polypeptide (PP)-producing γ-cells:** 3–5% of the total islet cells, to regulate the exocrine and endocrine secretion activity of the pancreas, is made of them.

   iv. **Somatostatin-producing δ-cells:** Constitute 3–10% of the total cells and releases Somatostatin which inhibits both, glucagon and insulin release.

   v. **Ghrelin-producing ε-cells:** Comprise <1% of the total islet cells.

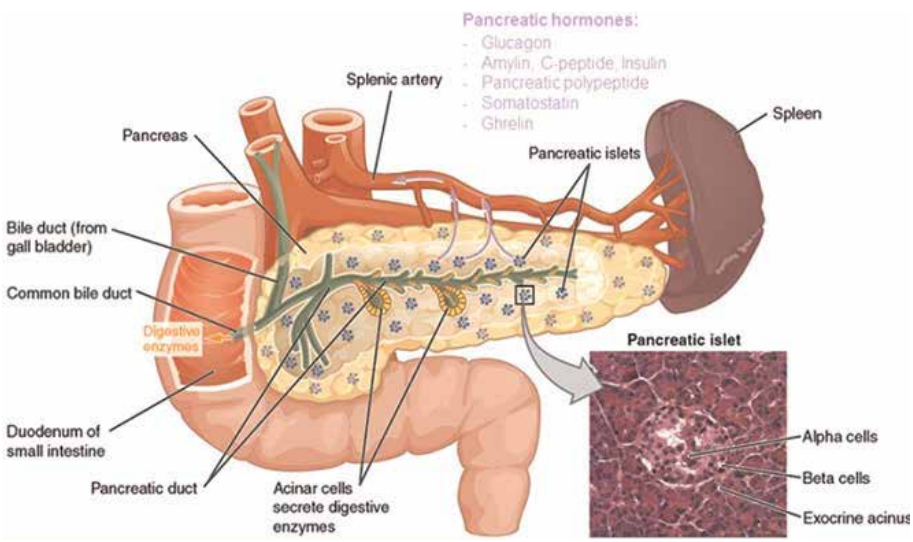


Figure 1.
Anatomical organization of the pancreas.

3. Pathways involved to regulate blood glucose levels in normal and abnormal conditions

Pancreas maintains blood glucose levels within a very narrow range (4–6 MM) through glucagon and insulin by their opposing and balanced actions by the phenomenon of glucose homeostasis. During sleep/between meals/when blood glucose levels are low/during prolonged fasting, α-cells release glucagon and promote hepatic glycogenolysis. Along with this, glucagon do hepatic and renal gluconeogenesis and increase endogenous blood glucose levels. In elevated exogenous glucose levels, after a meal, insulin secretion is stimulated from β-cells and after docking to its receptor on muscle and adipose tissue, insulin enables insulin-dependent uptake of glucose into tissues and lowers blood glucose levels by removing the exogenous glucose from the blood stream (**Figure 2**). Moreover insulin enhances glycogenesis, lipogenesis and incorporation of amino acids into proteins; thus it performs its anabolic action as compared to glucagon which is catabolic. Along with pancreas, other organs also regulate blood glucose levels (**Figure 3**).

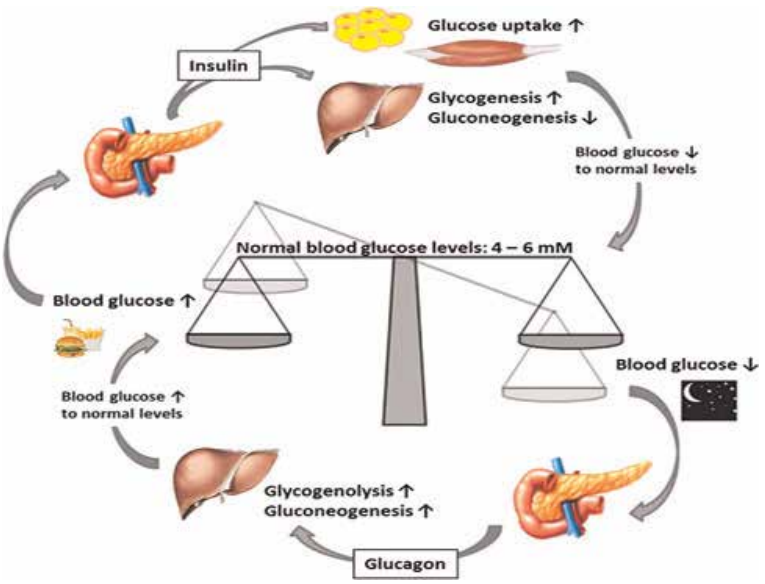


Figure 2.
Maintenance of blood glucose levels by glucagon and insulin.

4. Genes, molecular and cellular targets to regulate blood glucose levels in normal and abnormal conditions

4.1 Genes to regulate blood glucose levels

Genetics is identifying a whole new set of genes, proteins and pathways that are related to diabetes and blood sugar control. Till now, scientist have identified a genetic disorder in MafA (it controls the production of insulin in β-cells). Surprisingly, this genetic defect was present in an unrelated family along with diabetic and insulinoma family members. The link of this gene with a defect was detected for the first time and a stable resultant mutant protein was found with a longer life in the cell, and found to be significantly more abundant in β-cells than its normal version [2].

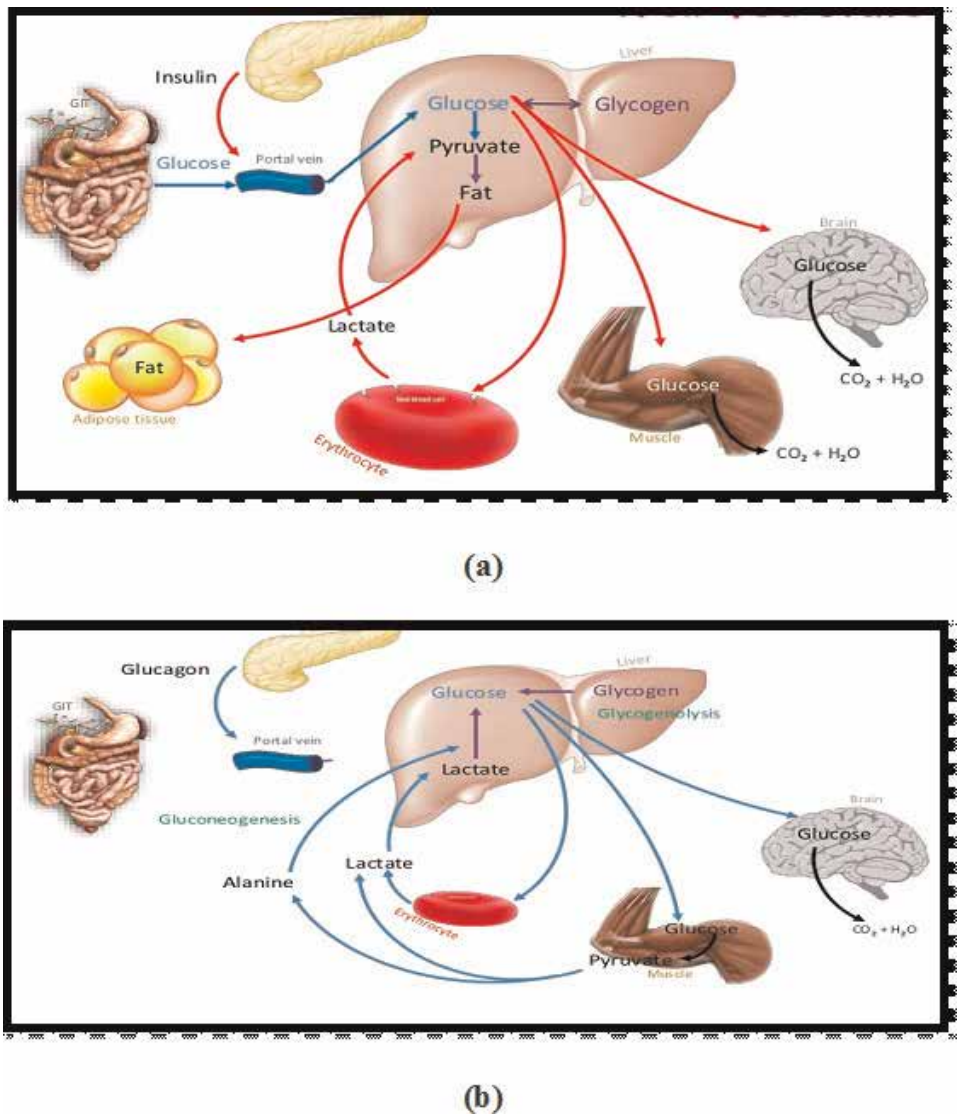


Figure 3.
Maintenance of blood glucose levels by different organs (a) during well fed state (b) during post-prandial state.

Gene on chromosome-2 {encodes glucose-6-phosphatase catalytic 2 (G6PC2)} is linked with fasting glucose levels and is primarily expressed in pancreatic β-cells to convert glucose-6-phosphate back to glucose. Its genetic variation may be responsible for reduction in insulin secretion that increases glucose concentration. Chronically elevated levels of glucose may be a precursor for type 2 diabetes [3].

13 new genetic variants has been discovered by an international research consortium and these variants can manipulate blood glucose regulation, insulin resistance and function of insulin-secreting β-cells in European descent populations, in which 05 of the following newly discovered variants raised the risk of developing type 2 diabetes:

i. SNPs in the region of ADCY5 which influence fasting and postprandial glucose levels.

ii. FADS1 which is linked with fasting glucose as well as lipid traits.

iii. Only one variant, near IGF1 which is associated with insulin resistance

iv. β-cell impairment, which may play a larger role in type 2 diabetes than previously recognized

v. Environment which may contribute to insulin resistance more than it does to insulin secretion.

By using high-density microarray analysis, more than 31,000 genes, linked with pancreas, have been discovered and main aim was to find which gen(s) were most sensitive to glucose and fatty acids particularly from the products of high fat and sugar diets. It was found that TNFR5 gene had maximum compassion to glucose and fatty acids and due to high levels of fat and sugar, beta cells are destroyed due to its over expression. These findings suggested that people with type-II diabetes, primarily with poor blood glucose management/who have not been diagnosed, are more likely to over express this gene that leads to β cell damage. But blocking of TNFR5 in beta-cells, especially when glucose and fatty acids consumption is high, halted their obliteration which shows that reticence of TNFR5 activity could be a promising treatment strategy against type 2 diabetes [4].

To identify genetic variants responsible for blood sugar control, a genome-wide association study was done to find SNPs which could be correlated with Fasting Plasma Glucose levels. It was found that most strongly associated SNP was rs560887 in initial sampling of 650 non-obese French people. Same SNP was correlated with FPG levels in a secondary sample of 3400 same people, approximately 5000 Finns and a group of 860 obese French children. When results of all studied samples were combined, researchers found that each copy of T version of rs560887 leads to a 0.06 mmol/L reduction in FPG while rs560887 did not correlate with insulin levels or BMI of subjects. Moreover even after a 9 year follow-up period in French samples, this SNP also could not correlate with the risk of type 2 diabetes. Moreover two other SNPs; rs1260326 and rs1799884 (previously found to be associated with FPG) were also found to be significantly associated with FPG levels in same study and it was concluded that genes affected by these SNPs affect the threshold level of glucose in the bloodstream and triggered secretion of insulin by pancreas. When threshold will be higher, level of blood glucose increase even before insulin starts to regulate it [5].

4.2 Molecular pathway for blood glucose regulation

4.2.1 Glucagon and GLP-1 receptors

These are class B-GPCRs which are important targets for drugs of type 2 diabetes, obesity and blood glucose regulation problems. Structures of several class A-GPCRs have been solved, but class B receptors have not been well studied because of technical challenges. Their structures were identified and reported by four international research teams; NIDDK, NIGMS, FDA and NIDA. Structure of Glucagon receptor helps to understand how different domains cooperate in modulating the receptor function at molecular level. GLP-1 receptor, identified by cryo-electron microscopy, examined structure of receptor in complex with GLP-1 and its coupled G-protein while detailed structure of GLP-1 receptor, when bound by small molecules (that affect receptor's activity) has also been given and it is difficult to expect the importance of GPCRs which are targeted by about half of all drugs. Structural information about these receptors is crucial for further drug discovery efforts [6].

Control of blood glucose depends heavily on G-protein-coupled receptors (GPCRs) which can span cell membranes to communicate signals from the outside to inside of cell and starts a cascade of reactions in cell when once activated by binding of a substance which had made these receptors an important target for drug development. When blood glucose drops after an overnight fast, pancreas releases glucagon which binds a GPCR, glucagon receptor, on liver and muscle cells and stimulates cells to release glucose in blood. Moreover glucagon-like peptide-1 (GLP-1) hormone works by binding to another GPCR, GLP-1 receptor, on pancreatic cells. After a meal, intestine produces GLP-1, which leads to the production of insulin from pancreas to stimulate cells to pick glucose from blood [7].

4.2.2 Heterocyclic scaffolds

For many years, heterocyclic scaffolds were the basis of anti-diabetic chemotherapies as bioactive scaffolds and have been evaluated for their biological response as inhibitors against their respective anti-diabetic molecular targets over past 5 years (2012–2017). Results revealed a diverse target sets of these scaffolds including protein tyrosine phosphatase 1 B (PTP1B), dipeptidyl peptidase-4 (DPP-4), free fatty acid receptors 1 (FFAR1), G protein-coupled receptors (GPCR), peroxisome proliferator activated receptor-γ (PPARγ), sodium glucose co-transporter-2 (SGLT2), α-glucosidase, aldose reductase, glycogen phosphorylase (GP), fructose-1,6-bisphosphatase (FBPase), glucagon receptor (GCGr) and phosphoenolpyruvate carboxykinase (PEPCK) [8].

4.2.3 Incretin and adipokines

In addition to other several even newer therapies in development, Incretin-based therapies, like dipeptidyl peptidase- 4 (DPP- 4) inhibitor and glucagon like peptide-1 (GLP-1) analogues/mimetic offer a new therapeutic means for the treatment of T2DM. Moreover a great attention has been focused by many researchers on a number of potential molecular targets in adipocytes e.g. adipokines [8].

4.3 Insulin secretion signaling pathway

4.3.1 Molecular pathways for the insulin secretion

In β-cells, main stimulus for insulin release increases blood glucose levels after a meal. This blood glucose is taken up by facilitative glucose transporter GLUT2 (SLC2A2) on the surface of β-cells. Once inside the cell, glucose undergoes glycolysis and an amplified ATP/ADP ratio and this distorted ratio leads to close ATP-sensitive K^+-channels (K_{ATP}-channels). While in non-stimulated circumstances, these channels open to ensure the maintenance of resting potential by transporting K^+-ions down their concentration gradient out of the cell. Upon closure, succeeding decrease in potency of externally moved K^+-current elicits depolarization of membrane, followed by opening of voltage-dependent Ca^+-channels (VDCCs). Increase in intracellular Ca^+ concentrations ultimately triggers fusion of insulin-containing granules with membrane and succeeding release of their content. Whole secretory process is biphasic and 1st phase lasts for around 5 minutes after the glucose stimulus with the release of majority of insulin while in 2nd phase, which is somewhat slower, the remaining insulin is released. This insulin is stored in large dense-core vesicles which are recruited near plasma membrane immediately after stimulation so that it should be readily available. Key molecules that mediate the fusion of the insulin-containing large dense-core vesicles belong to the superfamily of the

soluble *N*-ethylmaleimide-sensitive factor attachment protein (SNAP) receptor proteins (SNAREs).which are:

i. Synaptosomal-associated protein of 25kDa (SNAP-25)

ii. Syntaxin-1 and synaptobrevin 2 (or vesicle-associated membrane protein VAMP2)

Sec1/Munc18-like (SM) proteins, glucose vesicles form SNARE complex. To initiate fusion, synaptobrevin 2, a *vesicle (v-)* SNARE fuses with the *target (t-)* SNAREs syntaxin-1 and SNAP-25, which are located in the target cell membrane (**Figure 4**) [9].

Numerous SNARE isoforms [syntaxin-1, −3 and −4, SNAP-25 and -23, synaptobrevins 2 and 3 (VAMP2 and 3)] are involved in glucose-stimulated insulin secretion whereas VAMP 8 (a non-essential SNARE protein for glucose-stimulated insulin secretion) has its role to regulate glucagon-like peptide-1-potentiated insulin secretion. In addition to SNARE and SM proteins, a calcium sensor is required to initiate membrane fusion. Synaptotagmins (highly expressed in neurons and endocrine cells) participated in Ca^{2+}-dependent exocytosis processes. Seventeen synaptotagmins (Syts 1–17) have been identified while only eight (Syt-1, −2, −3, −5, −6, −7, −9 and −10) are able to bind Ca^{2+} and form a complex with the SNAREs to smooth the progress of and activate vesicle-membrane fusion process. Only Syt-3, −5, −7, −8 and −9 are concerned with insulin exocytosis [10].

4.3.2 Mechanism of insulin action

Several proteins are disturbed in the insulin signaling pathways in different conditions of insulin resistance, particularly obesity, type-II diabetes mellitus, metabolic syndrome, cardiovascular diseases, inflammatory disorders, and cancer [11].

4.3.2.1 Insulin receptor

It is tetramer protein, composed of 02 extracellular α- subunits and two trans membrane β-subunits. α-subunits have a binding site to insulin while the β-subunits contain an intrinsic tyrosine kinase activity towards intracellular side. Insulin

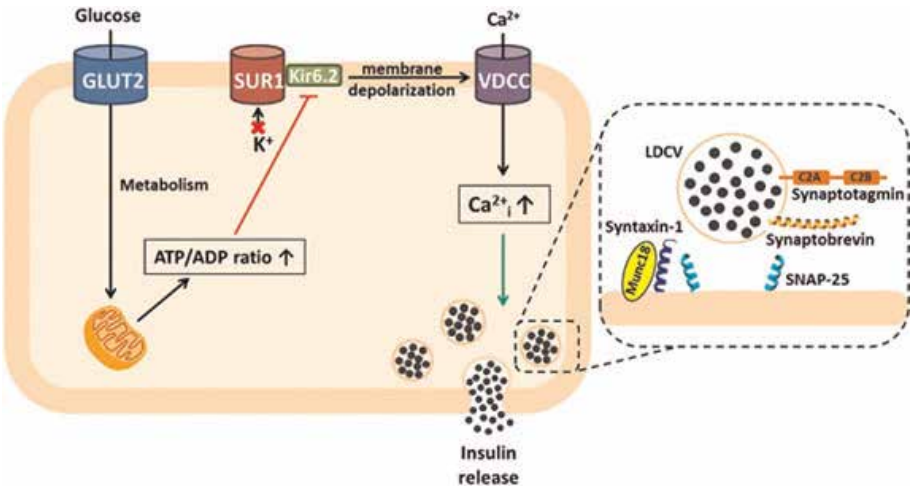


Figure 4.
Glucose-stimulated insulin release from a pancreatic β-cell.

binding to α-subunit leads to conformational change and activation of β-subunit which results in tyrosyl autophosphorylation of the insulin receptor. After being activated and phosphorylated, several major and better characterized insulin signaling intracellular docking proteins {Src homology collagen (SHC), associated protein substrate (APS) and insulin receptor substrates- 1 & 2 (IRS-1 and IRS-2)} binds to insulin receptor for tyrosyl phosphorylation. All these proteins activate glucose uptake and metabolism, protein synthesis, gene expression, cell survival, growth, development, and differentiation. IRS proteins are phosphorylated on various tyrosine residues of the C-terminal region and generate specific sites for binding of proteins containing Src homoly-2 (SH2) domains [phosphatidylinositol-3 kinase (PI-3 K), Nck, and Grb-2.

4.3.2.2 Pi-3 K

It is composed by a catalytic subunit (p110) and a regulatory subunit (p85) and mediate metabolic effects of the insulin. Binding of p85 subunit to phosphorylated tyrosine residues of IRS proteins activate catalytic activity of p110 subunit and subsequent rise in the generation of phosphatidylinositol 3,4-bisphosphate (PIP2) and phosphatidylinositol 3,4,5-trisphosphate (PIP3) content. Downstream proteins from PI3K pathway figure out several serine/threonine kinases e.g. phosphoinositide-dependent protein kinase-1 (PDK-1), protein kinase B (PKB/Akt), protein kinase C (PKC), p70 S6 kinase (p70S6K) and glycogen synthase kinase-3 (GSK-3). All these kinases are involved in translocation of glucose transporter-4 (GLUT-4) from intracellular vesicles to plasma membrane, glycogen and protein synthesis, antiapoptotic effects and gene expression (**Figure 4**).

4.3.2.3 Cbl

Signaling pathways which are involved in glucose uptake due to insulin induction starts with the recruitment of APS to activated insulin receptor and subsequent association and tyrosine phosphorylation of Cbl which interacts with Cbl associated protein (CAP) through an SH_3 domain and with flotillin (a constituent of lipid raft, through a sorbin domain). Complex CrkII/C3G then binds to the phosphorylated tyrosine and residues of Cbl and activate C3G activity that exchanges GDP for GTP of TC10 (a small G-protein that belongs to the Rho family). After being activated, TC10 participates in GLUT-4 translocation (**Figure 5**) [12].

4.3.2.4 Mitogen-activated protein kinase (MAPK)

This cascade starts with

1. The association of Shc to insulin receptor

2. Binding of Grb-2 to Shc or to IRS-1

3. Formation of the Grb-2/SoS (Son of Seven less) in the plasma membrane.

This complex leads to the activation of c-Ras and raf, starting the MAPK cascade. MAPK pathway is involved in insulin induced differentiation, cell growth, and development, along with some metabolic effects e.g. glycogen synthesis and GLUT-4 translocation to plasma membrane (**Figure 4**). However, this cascade is not enough or even required to this later effect [13].

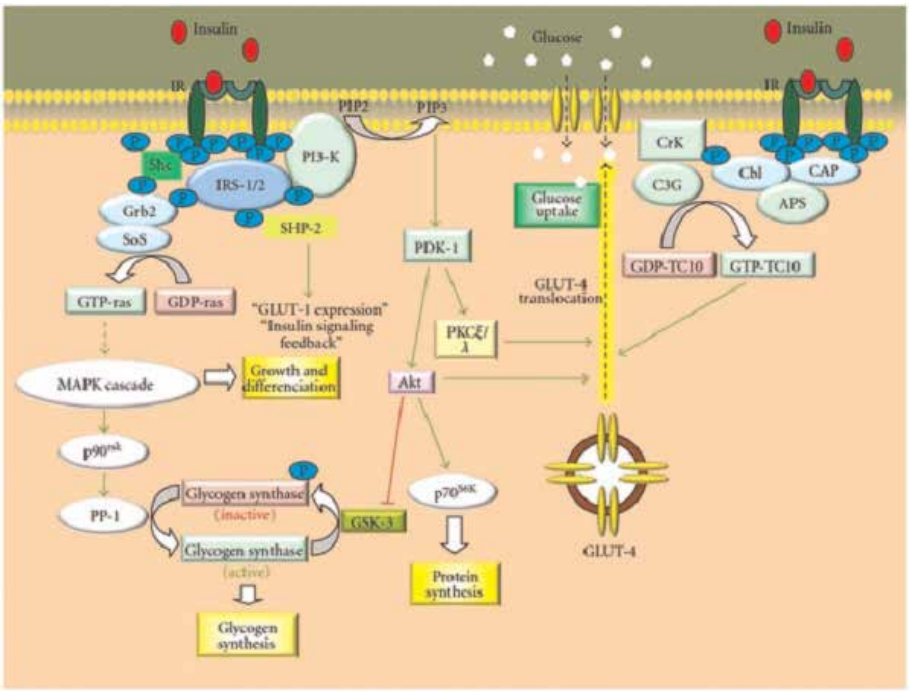


Figure 5.
Summary of the main insulin signaling pathways. GLUT-1 and -4: Glucose transporter-1 and -4; Grb-2: Growth receptor binding-2; GSK-3: Glycogen synthase kinase-3; IR: Insulin receptor; IRS-1 and -2: Insulin receptor substrate-1 and -2; MAPK: Mitogen-activated protein kinase; PDK-1: Phosphoinositide-dependent kinase-1; PIP2: Phosphatidyl-inositol diphosphate; PI3: Phosphatidyl-inositol triphosphate; P: Phosphate; PKC: Protein kinase C; PP-1: Phosphoprotein phosphatase-1; $p70^{S6K}$: Protein 70 S6 kinase; $p90^{rsk}$: Protein 90 ribosomal S6 kinase; Shc: Src homology collagen; SHP-2: Phosphatase with Src homology 2 domain; SoS: Son of Sevenless.

4.3.3 Molecular basis of insulin resistance

It occurs when insulin-sensitive tissues (skeletal muscle, adipose tissue and liver) cannot respond properly to hormones which cause several chronic diseases, particularly those which are linked to obesity (type-II diabetes mellitus, metabolic syndrome, dyslipidemias, cardiovascular diseases, cancer and neurodegenerative diseases). However precise mechanisms of insulin resistance are not fully understood. Following factor have been proposed to participate in its development;

4.3.3.1 Increased plasma-free fatty acid level

As free fatty acids are elevated in obesity and related illness, they are supposed to be responsible for insulin action impairment but still complete mechanisms are not known. More availability of long chain saturated fatty acids results leads to insulin resistance in liver, skeletal muscle and adipose tissue. Various hypotheses proposed to explain insulin resistance induced by saturated fatty acids [14] are;

i. Randle cycle

ii. Oxidative stress

iii. Modulation of gene transcription

iv. Accumulation of intracellular lipid derivatives (diacylglycerol and ceramides)

v. Mitochondrial dysfunction

vi. Inflammation

4.3.3.2 Subclinical chronic inflammation

Chronic state of inflammation in insulin responsive tissues is major contributor to insulin resistance in obesity and related diseases. However, precise mechanisms as well as mediators involved in this interaction are not completely defined yet. Intracellular redox balance is delicately synchronized process that includes multiple generating pathways and degrading systems. Physiologically, ROS contribute in essential biological responses but their accumulation causes oxidative stress condition because of their highly oxidant nature to oxidize multiple intracellular components particularly membrane phospholipids, proteins, and DNA. In insulin resistance, increased ROS production and/or decreased ROS degradation is observed that leads to an oxidative stress condition and activation of signaling pathways related to stress. Oxidative stress is also responsible for muscle disorders and contributes to insulin resistance process. Transgenic mice expressing human ubiquitin protein E3 ligase (a protein that binds and promotes degradation of superoxide dismutase-1) leads to reduced superoxide degradation and as a result increased oxidative stress in the form of atrophy and sclerosis [15].

4.3.3.3 Oxidative and nutritive stress

Activation of signaling pathways to stress is another reason of insulin resistance. Several serine/threonine kinases activated by oxidative stress pathways (JNK, PKC, GSK-3, NF-kB, and p38 MAPK) have been suggested to impair insulin signaling pathways [16].

4.3.3.4 Altered expression of several genes and mitochondrial dysfunctioning

Expression of genes involved in lipid and glucose metabolism, insulin signaling, inflammation, redox balance and mitochondrial function is modified in insulin signaling, which shows that these processes participate in the pathophysiology of insulin resistance. Disturbed mitochondrial function has been suggested to have a central role in these alterations, since this organelle participates in all these processes [17].

5. Current scenario of drugs and therapies to cure blood glucose regulation problems

5.1 Drugs

5.1.1 Drugs to manage type I and type II diabetes or its complications

Many of the drugs have a combination of effects. If a person needs two or more treatments to manage glucose levels, insulin treatment may be necessary. Possible treatments for type 1 diabetes include [18]:

1. **Metformin (Glucophage, Glumetza, others):** It is generally 1st medication for type-II diabetes and works by reducing gluconeogenesis in liver and improves body's sensitivity to insulin so that body utilizes insulin in more effective way.

2. **Sulfonylureas:** They help patients body to secrete more insulin. Its examples are glyburide (DiaBeta, Glynase), glipizide (Glucotrol) and glimepiride (Amaryl) and its possible side effects are low blood sugar and weight gain.

3. **Meglitinides**: Repaglinide (Prandin) and nateglinide (Starlix) works like sulfonylureas by stimulation of pancreas to secrete more insulin but they are faster acting with short duration of their effect in the body and have risk of causing hypoglycemia and weight gain.

4. **Thiazolidinediones:** Along with Metformin, it include rosiglitazone (Avandia) and pioglitazone (Actos). They make the body's tissues more sensitive to insulin but these drugs causes weight gain and increased risk of heart failure and anemia that's why, these medications generally aren't 1st choice treatments.

5. **DPP-4 inhibitors:** Sitagliptin (Januvia), saxagliptin (Onglyza) and linagliptin (Tradjenta) are its different forms and help to lessen blood sugar levels but tend to have very unassuming effect as they do not cause weight gain but may cause joint pain and increase pancreatitis risk.

6. **GLP-1 receptor agonists:** These are injections to sluggish digestion and lower blood sugar levels. They often cause weight loss and its possible side effects are nausea and increased risk of pancreatitis. It includes Exenatide (Byetta, Bydureon), liraglutide (Victoza) and semaglutide (Ozempic). Current research has shown that liraglutide and semaglutide may reduce risk of heart attack and stroke (in people at high risk).

7. **SGLT2 inhibitors:** They prevent kidneys from reabsorbing sugar into blood and leads to its excretion via urine. It includes canagliflozin (Invokana), dapagliflozin (Farxiga) and empagliflozin (Jardiance). They may reduce the risk of heart attack and stroke in people with a high risk of these conditions while its side effects may include vaginal yeast infections, urinary tract infections, low blood pressure and a higher risk of diabetic ketoacidosis. Only Canagliflozin in this drug class has been associated with increased risk of lower limb amputation.

8. **Insulin:** People with type-II diabetes need insulin therapy. In past, insulin therapy was used as a last option but today it's often prescribed due to its instant benefits. It's possible side effects are low blood sugar (hypoglycemia) and its different forms are:

    a. **Rapid-acting injections**: They take their effect within 5–15 minutes but last for a shorter time of 2–4 hours and include:

        i. Insulin lispro (Humalog)

        ii. Insulin aspart (NovoLog)

        iii. Insulin glulisine (Apidra)

b. **Short-acting injections**: Its effect starts between 30 minutes to 1 hour but it last for 3–8 hours e.g.

   i. Regular insulin (Humulin R and Novolin R)

c. **Intermediate-acting injections**: It is effective after 1–4 hours and last for 12–18 hours. e.g.

   i. Insulin isophane, also called NPH insulin (Humulin N and Novolin N)

d. **Long-acting injections**: They are effective after 1/2 hours and last for between 14 and 24 hours. Its different forms are:

   i. Insulin glargine (Toujeo)

   ii. Insulin detemir (Levemir)

   iii. Insulin degludec (Tresiba)

e. **Premixed injections**: These are combinations of the above types of insulin and all takes effect from 5 minutes to 1 hour and last for 10–24 hours and its different forms are:

   i. Insulin lispro protamine and insulin lispro (Humalog Mix 50/50 and Humalog Mix 75/25)

   ii. Insulin aspart protamine and insulin aspart (NovoLog Mix 50/50 and NovoLog Mix 70/30)
   iii. NPH insulin and regular insulin (Humulin 70/30 and Novolin 70/30)

f. People can breathe in **rapid-acting inhalable insulin** which produces its effects within 12–15 minutes and lasts for 2–3 hours e.g.

   i. Insulin human powder (Afrezza)

9. **Non-Inulin Injectables:**

a. **For Patients with Type-1 Diabetes:** These drugs are common for type 1 diabetic patients and its different forms are:

   i. Amylin analogs: Pramlintide (Symlin) which mimics another hormone, amylin, that plays a role in glucose regulation.

   ii. Glucagon which can reverse blood sugar levels when they fall too low as a result of insulin treatment.

b. For patients with Type-II Diabetes:

   i. **Insulin:** It can also manage high blood glucose levels in type-II diabetes but doctors typically prescribe it only when other treatments have not had the desired effect. Type-II diabetic pregnant women may also use it for the reduction of disease effects on fetus while for people with high blood glucose levels, in-spite of applying

lifestyle measures to bring them down, doctors can prescribe non-insulin drugs to lower blood glucose. These drugs are:

1. **Sulfonylureas:** They improve insulin secretion by the pancreas into blood and people use following newer medicines most often because of their less adverse effects. These are:

    a. Glimepiride (Amaryl)

    b. Glipizide (Glucotrol)

    c. Glyburide (DiaBeta, Micronase, Glynase)

    d. The older, less common sulfonylureas are:

        1. Chlorpropamide (Diabinese)

        2. Tolazamide (Tolinase)

        3. Tolbutamide (Orinase)

Today these drugs are less prescribed than in the past as they can cause hypoglycemia, leading to other health issues:

i. **Meglitinides:** They improves insulin secretion and might also improve the effectiveness of body to release insulin during meals. Its different forms are:

    1. Nateglinide (Starlix)

    2. Repaglinide (Prandin)

ii. **Biguanides:** They boost the effect of insulin, reduce the amount of glucose from liver and increase uptake of blood glucose into cells.

iii. **Metformin**: It is the only licensed biguanide in the US and is available in the form of Glucophage, Glucophage XR, Glumetza, Riomet, and Fortamet.

iv. **Thiazolidinediones**: They reduce the resistance of tissues to the effects of insulin and are associated with serious side effects so they need monitoring for potential safety issues. People with heart failure should not use these medications. They include:

    1. pioglitazone (Actos)

    2. rosiglitazone (Avandia)

    3. Alpha-glucosidase inhibitors

    4. acarbose (Precose)

    5. miglitol (Glyset)

    6. Dipeptidyl peptidase inhibitors

7. alogliptin (Nesina)
8. linagliptin (Tradjenta)
9. sitagliptin (Januvia)
10. saxagliptin (Onglyza)

v. **Sodium-glucose co-transporter 2 (SGLT2) inhibitors**: They cause body to release more glucose into the urine from the bloodstream and might also lead to a modest amount of weight loss, which can be a benefit for type-II diabetic patients. These include:

1. canagliflozin (Invokana)
2. dapagliflozin (Farxiga)
3. empagliflozin (Jardiance)
4. ertugliflozin (Steglatro)

vi. **Incretin mimetics:** The drugs that imitate incretin hormone and stimulate insulin release after meals are:

1. exenatide (Byetta, Bydureon)
2. liraglutide (Victoza)
3. dulaglutide (Trulicity)
4. lixisenatide (Adlyxin)
5. semaglutide (Ozempic)

vii. **Oral combination drugs:** Drugs that are obtained after combination of some of previous drugs include:

1. alogliptin and metformin (Kazano)
2. alogliptin and pioglitazone (Oseni)
3. glipizide and metformin (Metaglip)
4. glyburide and metformin (Glucovance)
5. linagliptin and metformin (Jentadueto)
6. pioglitazone and glimepiride (Duetact)
7. pioglitazone and metformin (Actoplus MET, Actoplus MET XR)
8. repaglinide and metformin (PrandiMet)
9. rosiglitazone and glimepiride (Avandaryl)
10. rosiglitazone and metformin (Avandamet)

11. saxagliptin and metformin (Kombiglyze XR)

12. sitagliptin and metformin (Janumet and Janumet XR)

viii. **Alternatives**: U.S. Food and Drug Administration has permitted ergot alkaloid, bromocriptine (Cycloset) to treat type-II diabetes. Doctors do not often propose/set down this medication. Moreover people use bile acid sequestrants to manage cholesterol levels which can also help to maintain steady blood sugar levels. Along with these, only colesevelam (Welchol) is approved for type-II diabetes.

5.1.2 Drugs that may help to prevent the complications of diabetes.

5.1.2.1 ACE inhibitors or angiotensin-II receptor blockers

They are used to treat high blood pressure to prevent or manage kidney complications of diabetes.

5.1.2.2 Statins and aspirin

People can manage cardiovascular risks of diabetes (like heart disease and stroke) by taking them to lower cholesterol levels at a dozen of once per day on doctors recommendation.

5.1.2.3 Drug for weight loss

It is key part of diabetes management and prevention and doctors might suggest medicines to cure it without effective lifestyle measures [19]. These drugs are

i. **Lorcaserin (Belviq)**: It enhances the feeling of being packed after food and help to treat diabetic obesity.

ii. **Orlistat (Alli and Xenical):** This drug decreases absorption of fat from diet and also support weight loss.

iii. **Phentermine and topiramate (Qsymia):** It is a grouped drug and reduce appetite to treat obesity.

5.1.3 Current guidelines at each person's situation and best approach for the individual

There are many guide lines for each person's health situation and each can choose best one according to their health conditions [20] e.g.

i. For people with type 2 diabetes and atherosclerotic cardiovascular disease (CVD), 2018 guidelines recommend following drugs as part of the antihyperglycemic treatment:

   a. Sodium-glucose cotransporter 2 inhibitors (SGLT2)

   b. Glucagon-like peptide 1 receptor agonists (GLP1-RA)

ii. Type-II diabetic people with atherosclerotic CVD and heart failure or a high risk of heart failure should be prescribed with:

   a. Sodium-glucose cotransporter 2 inhibitors

iii. To treat people with type-II diabetes and chronic kidney disease, doctors urged to consider following guidelines to stop chronic kidney disease, CVD or both, from getting worse.:

a. Sodium-glucose co transporter 2 inhibitor

b. Glucagon-like peptide 1 receptor agonist

5.2 Therapies

When medicines and lifestyle changes are not enough to manage diabetes, a less common treatment can become an option. Other treatments include different surgical procedures for treating type-I or type-II diabetes [21–25] which are as follows:

5.2.1. Bariatric surgery

It is also called weight-loss surgery or metabolic surgery and it help obese and type-II diabetic patients to lose a large amount of weight and regain normal blood glucose levels. Even some people with diabetes may no longer need their diabetes medicine after it. Efficacy of this surgery can be checked by the variations in blood glucose level, type of weight-loss surgery and the amount of lost weight by the patients. Moreover it can also be monitored by the time occurrence of diabetes and on duration of usage of insulin. Current research suggested that weight-loss surgery also may help to improve blood glucose control in obese type-I diabetic people but still scientists are finding long-term results of this in type-I and II diabetic patients [21].

5.2.2 Artificial pancreas

NIDDK has leading role to develop artificial pancreas technology. Artificial pancreas replaces manual blood glucose levels by the shots or pumping of insulin. Single system monitors blood glucose levels throughout the patient's life and provide insulin or a combination of insulin and glucagon routinely. The system can also be monitored remotely by parents or by medical staff. In 2016, FDA approved a type of artificial pancreas system, called a hybrid closed-loop system which tested blood glucose level after every 5 minutes throughout the day and night and automatically provided right amount of insulin to body. But when person still needed manual adjustment of insulin amount, pump delivered it at meal times. But artificial pancreas make patient free from some of daily tasks which are needed to keep blood glucose level steady or help to sleep through the night without need of wake and test blood glucose or to take medicine. Hybrid closed loop system was available in the U. S. in 2017. NIDDK has funded several important projects on different types of artificial pancreas devices for the better help of Type- I diabetic people for proper management of disease. These devices may also help type-II diabetic and gestational diabetic people to cure their disease [22, 23].

5.2.3 Pancreatic islet transplantation

This is an experimental treatment for poorly controlled type-I diabetes as in this condition immune system attacks islet cells. Pancreatic islet transplant replace shattered islets with new ones to make and release insulin. In this process, islets are donated from the pancreas of donor of pancreas and are transferred to a type 1 diabetic patient. As researchers are still doing work on pancreatic islet transplantation, so procedure is only accessible to volunteers of research studies [24, 25].

6. New approaches to drug development and therapies, with a particular focus on drug development by green synthesis to cure blood glucose regulation problems

Bioactive molecules from Natural products have been proved to improve insulin resistance and its associated complications by suppressing inflammatory signaling pathways [26]. Medicinal plants cannot be obsolete and still play a prominent role in human health care. Among natural sources, over 1200 plants have been claimed as antidiabetic remedies. While over 400 plants along with its 700 recipes and compounds have been scientifically evaluated for type-II diabetes. Metformin was developed on the basis of

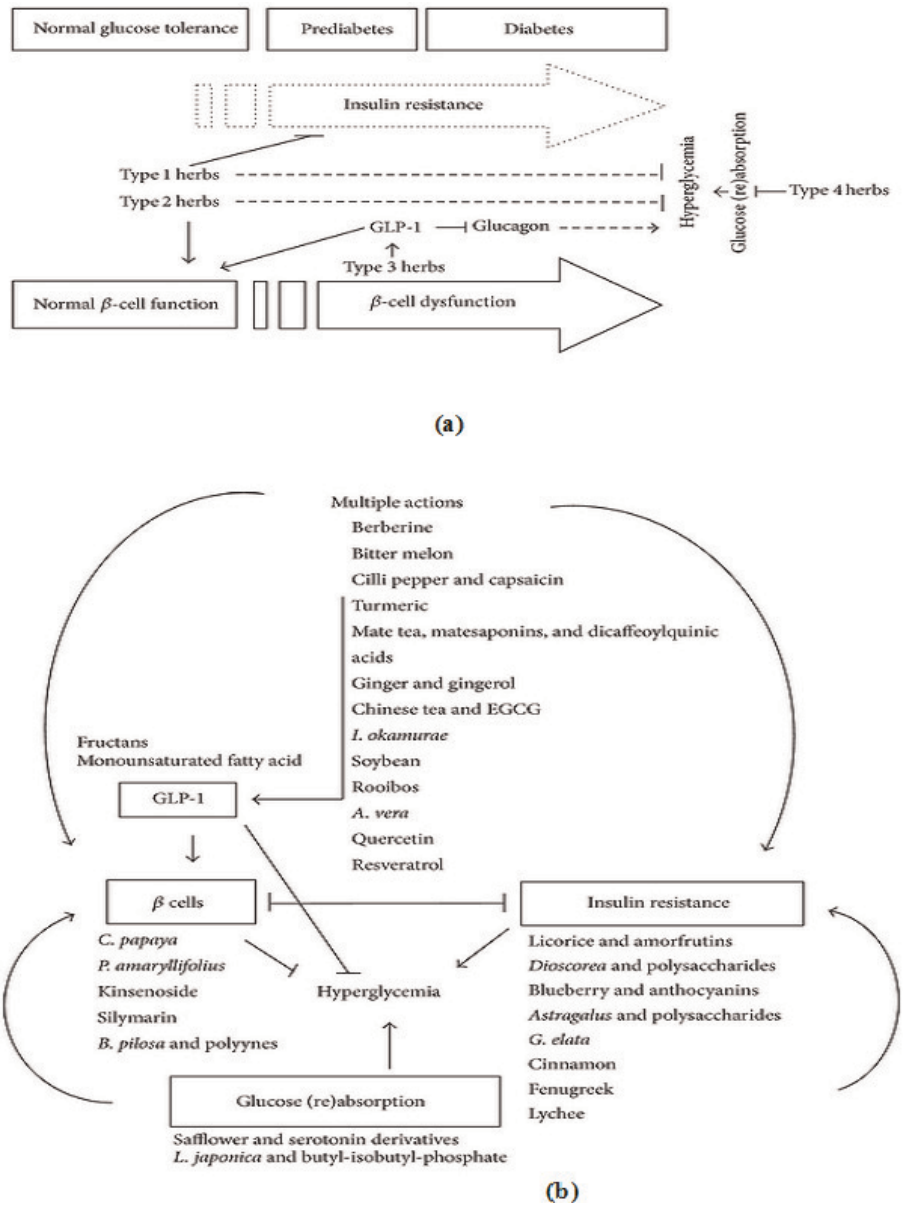
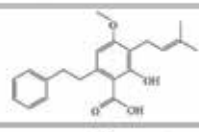
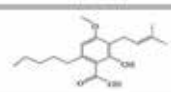
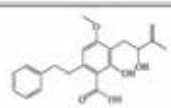
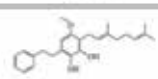
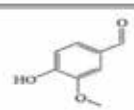
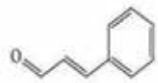
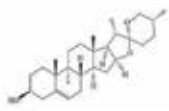
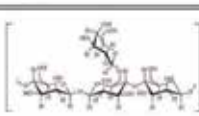
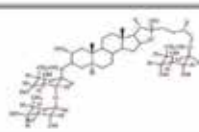
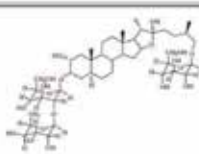
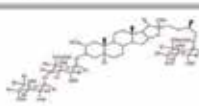
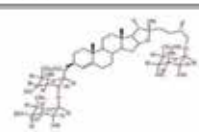
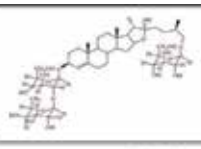
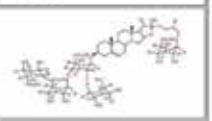
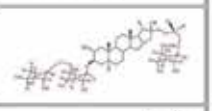
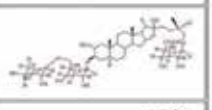
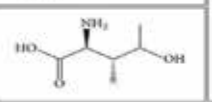
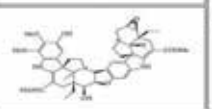
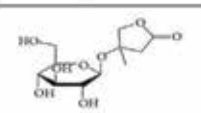
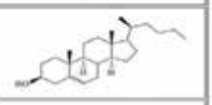
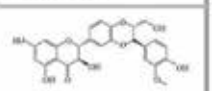
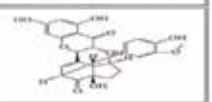
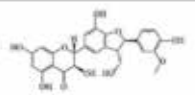
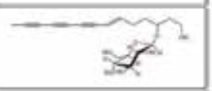
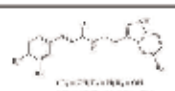
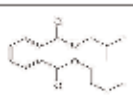
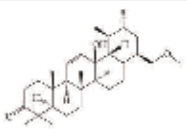
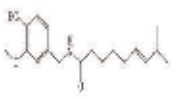
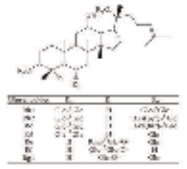
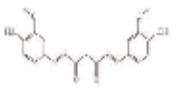
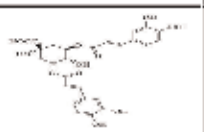
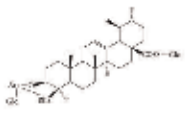
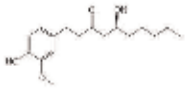
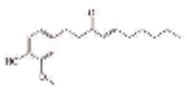
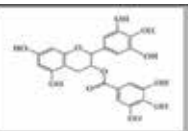
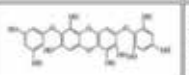
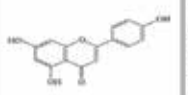
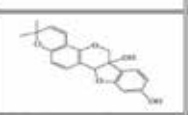
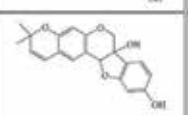
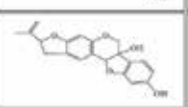
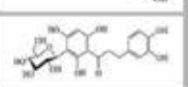
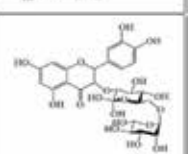
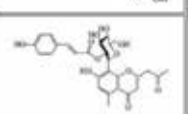
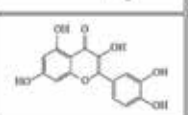
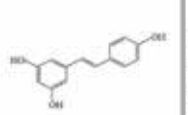
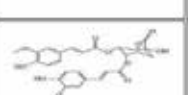


Figure 6.
Mechanisms underlying herbal therapies using antidiabetic plants and phytocompounds. (a) Different types of medicinal herbs can be classified based on their modes of action such as insulin resistance (type 1 herbs), -cell function (type 2 herbs), and GLP-1 (type 3 herbs) and glucose (re) absorption (type 4 herbs), (b) The selected.

Herb	Compound name	Chemical structure	Antidiabetic mechanism (s)
G. sraolensis	Amorfrutin 1		Regulate insulin resistance
	Amorfrutin 2		
	Amorfrutin 3		
	Amorfrutin 4		
D. rhizome	Dioscorea polysaccharides	N.A.	
V. spp.	Phenolics and Anthocyanins	N.A.	
A. membranaceus	Astragalus polysaccharides	N.A.	
G. elata	Vanillin		Reduces insulin resistance
	4-hydroxybenzaldehyde		
C. verum *C. zeylanicum* *C. aromaticum*	Cinnamaldehyde		Regulate insulin resistance
T. foenum-graecum	Diosgenin		Reduces insulin resistance.
	Galactomannan		
	Trigoneoside Xa		
	Trigoneoside Xb		
	Trigoneoside XIb		
	Trigoneoside XIIa		

	Trigoneoside XIIb		
	Trigoneoside XIIIa		
	Trigoneoside Ia		
	Trigoneoside Ib		
	Trigoneoside Va		
	4-hydroxyisoleucine		
L. chinensis	Oligonol (mixture of compounds)	N.A.	Regulate insulin resistance
C. papaya P. amaryllifolius	Flavonoids, alkaloids, saponin, and tannins	N.A.	Regulate β-cell function
T. divaricata E. microphylla	Conophylline		
A. radix	Kinsenoside		
N. stellata	Nymphayol		
S. marianum	Silybin		
	Silydianin		
	Silychristin		
B. pilosa	3-β-D-glucopyranosyl-1-hydroxy-6(E)-tetradecene-8,10,12-triyne		
	2-β-D-glucopyranosyloxy-1-hydroxy-5(E)-tridecene-7,9,11-triyne		
	2-β-D-glucopyranosyloxy-1-hydroxytrideca-5,7,9,11-tetrayne (cytopiloyne)		
G. sylvestre	No reported active compounds	N.A.	

Satureja thymbra L.	Inulin/Stahlose		Regulates GLP-1 homeostasis
Olive oil	Monounsaturated fatty acids	N.A.	
C. inermis	Saponin derivatives		Regulate glucose clearance in the gut
L. japonica	Butyl-isohexyl-phthalate		
B. vulgaris	Betacyanins		Regulate two or more pathways including hyperglycaemia, moderate insulin resistance, pancreatic β-cell regeneration, and favourable lipid profile alteration
M. charantia	Momordicin		Regulate two or more pathways including lower blood glucose due to their insulin-like chemical structure
Cinnamomum zeylanicum	Capsaicin		Regulate two or more pathways including regulation of insulin resistance and pancreatic β-cells
P. ginseng	Ginsenoside Rb1 Ginsenoside Rb2 Ginsenoside Rc Ginsenoside Rd Ginsenoside Re Ginsenoside Rf Ginsenoside Rg1		Regulate two or more pathways including β-cell function, improvement of insulin resistance
C. longa	Curcumin		Regulate two or more pathways including regulation of insulin resistance and β-cell function
	Turmerin		
I. paraguariensis	3,5-O-dicaffeoylquinic acid		Regulate two or more pathways including regulation of GLP-1 production
	Mate saponin 1		
Z. officinale	Gingerol		Regulate two or more pathways including β-cell protection and increased insulin receptor signaling
	Shogaol		Unclear how can elevate glucose uptake in response to insulin in muscle and adipose cells

C. sinensis	Epigallocatechin 3-gallate (EGCG)		Regulate two or more pathways (islet protection, increase in insulin secretion, decrease in insulin tolerance, decrease in gluconeogenesis and insulin-mimetic action)
I. olusanmo	Diphlorethohydroxycarmalol		Regulate two or more pathways (α-glucosidase and α-amylase inhibitor)
G. max	Genistein		Regulate two or more pathways (preserves islet mass, activates protein kinase A (PKA) and extracellular-signal-regulated kinases (ERK) 1/2, activates AMPK, and reduces insulin sensitivity)
	Glycatilin I		
	Glycosilin II		Regulate two or more pathways (enhance GLP-1 secretion, improve insulin secretion, regulate β-cell function)
	Glycosilin III		
A. linearis	Aspalathin		Regulate two or more pathways (insulin tolerance, β-cell function, and inhibition of α-glucosidase)
	Rutin (quercetin-3-O-rutinoside)		
A. vera	Aloesin A		Regulate two or more pathways (suppression of α-glucosidase activity (gut glucose absorption) and insulin resistance)
Commonly found in plants, vegetables, and fruits	Quercetin		Regulate glucose absorption in guts.
Commonly found in plants and fruits	Resveratrol		Regulate two or more pathways (activates AMPK and downstream molecules, prevents cell death of pancreatic β cells, and activates SIRT1)
Coffee	Quinides (e.g. (1R,3R,4S,5R)-3,4-dicitruloyl-1,5-quinide)*		Regulate two or more pathways

N.A.: not applicable

*Quinides are derived from chlorogenic acid during roasting

Table 1.
Active compounds and biological actions of antidiabetic herbs.

biguanide compound from an antidiabetic herb, *French lilac* and is now its a first-line drug against type-II diabetes. Medicinal plants also contains a diverse bioactive compounds and can have multiple actions on insulin action, insulin production, or both. With a focus on scientific studies of selected glucose-lowering herbs, phyto compounds

and their ability to target insulin resistance, cell function, incretin related pathways and glucose (re)absorption (**Figure 6a** and **b**), multiple studies have been done.

While more than 400 plants and compounds have shown *In-vitro* and/or *In-vivo* antidiabetic activities. Instead of listing each extract/compound, here, selected chemicals from plants and/or their extracts with the ability to control blood glucose levels as well as to modulate mechanisms involved in insulin resistance or cell function or incretin-related pathways or glucose (re)absorption can be tabulated (**Table 1**) along with chemical structure, antidiabetic activity and action in cells/ animal models and the results of administration of the plant extracts and compounds to diabetic patients [27].

7. Conclusions

All hormones for the regulation of blood glucose levels along with their source organ up to the level of cell have been discussed in first section of chapter. Then different Pathways involved in regulating blood glucose levels in normal and abnormal conditions has been explained. Genes, Molecular and cellular targets to regulate blood glucose levels in normal and abnormal conditions has been discussed with particular focus on molecular basis of insulin signaling pathways and this pathway has been linked with Mechanism of Insulin Action and Molecular Basis of Insulin Resistance which is may be due to fatty acids, inflammation, stress and altered expression of several genes. Current scenario of Drugs and therapies to cure blood glucose regulation problems for the management of type 1 and type 2 diabetes has been explained. At the end New approaches to drug development and therapies by green synthesis to have been mentioned.

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Conflict of interest

All authors declare that they do not have any conflict of interest with any company or organization or person.

Vote of thanks

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Abbreviations

MafA	musculoaponeurotic Fibrosarcoma Oncogene Family, A
MafB	musculoaponeurotic Fibrosarcoma Oncogene Family, B
SNPs	single Nucleotide Polymorphism
ADCY5	adenylate cyclase 5
FADS1	fatty acid desaturase 1

IGF1	insulin-Like Growth Factor 1
B-GPCRs	class B G protein-coupled receptors
class A-GPCRs	class A G protein-coupled receptors
Cbl	cannabinoid 1
GDP	guanosine diphosphate,
GTP	guanosine diphosphate,
Shc	Src homology and collagen protein
c-Ras	rat sarcoma
raf	rapidly Accelerated Fibrosarcoma
JNK	c-Jun N-terminal kinase
PKC	protein kinase C
GSK-3	glycogen synthase kinase-3
NF-kB	nuclear factor kappa-light-chain-enhancer of activated B cells
p38 MAPK	p38 mitogen-activated protein kinases
ACE inhibitors	acetylcholine Esterase Inhibitors
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
FDA	Food and Drug Administration
NIGMS	National Institute of General Medical Sciences
NIDA	National Institute on Drug Abuse

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Chapter 3

Role of PI3K/AKT Pathway in Insulin-Mediated Glucose Uptake

Ewa Świderska, Justyna Strycharz, Adam Wróblewski, Janusz Szemraj, Józef Drzewoski and Agnieszka Śliwińska

Abstract

Glucose uptake is regulated by several mechanisms, where insulin plays the most prominent role. This powerful anabolic hormone regulates the transport of glucose into the cell through translocation of glucose transporter from an intracellular pool to the plasma membrane mainly in metabolically active tissues like skeletal muscles, adipose tissue, or liver (GLUT4). This translocation occurs through multiple steps of PI3K/AKT signaling pathway. In this chapter, we will focus on molecular events leading to GLUT4 translocation, starting with activation of insulin receptors through signaling cascade involving phosphatidylinositol 3-kinase (PI3K) and protein kinase B (PKB) and finally, the action of their effectors. We will present regulatory mechanisms and modulators of insulin-mediated glucose uptake.

Keywords: insulin, PI3K, AKT, glucose uptake, GLUT4, insulin resistance

1. Introduction

Nowadays, when society is leading an increasingly sedentary lifestyle with constant access to food without the need for effort, we observe the raising occurrence of diseases with metabolic dysregulation. This financial and social burden has caused the great need for understanding mechanistic details of metabolic response pathways, causes of their impairment, and following consequences. Carbohydrate metabolism is mainly related to glucose. Its level should remain in a narrow range (4–7 mM) by balancing glucose release into the circulation, its absorption from the intestine, the breakdown of stored glycogen in liver, and the uptake of blood glucose by peripheral tissues. These processes are regulated by a few metabolic hormones with insulin being the most important one.

2. Mechanism of insulin action

2.1 Insulin

Insulin is an anabolic peptide hormone secreted by pancreatic β cells, whose mature form arises in two stages [1]. First, preproinsulin is processed via cutting of the signal fragment and forming proinsulin [2]. This is followed by the excision of the middle fragment (C chain—35 aa), which gives dipeptide made up of two chains (A—21 aa, B—30 aa) connected by two disulfide bonds [3]. Insulin is a multitask

	Upregulation	Downregulation
Carbohydrate metabolism	Glucose uptake via GLUT4 Glycogen synthesis Glycolysis Conversion of pyruvate to acetyl CoA	Glycogenolysis Gluconeogenesis
Lipid metabolism	Fatty acids synthesis Triglycerides synthesis Cholesterol synthesis	Lipids oxidation Triglycerides breakdown
Protein metabolism	Transcription of proteins involved in energy stores generation	Transcription of proteins involved in energy stores release

Table 1.
Metabolic functions of insulin.

protein involved, among others, in the regulation of carbohydrate and lipid metabolism (**Table 1**). The most important stimulus for insulin production is a postprandial increase of blood glucose level. By increasing insulin production and its impact on effector cells (myocytes, adipocytes, and hepatocytes), glucose transport to the inside of the cells gets increased while reducing blood glucose level. This is achieved by an increased translocation of the insulin-dependent glucose carriers (GLUT), with GLUT-4 being found in skeletal muscle, hepatocytes, and adipocytes [4].

When glucose concentration exceeds 30 mM in the small intestine, glucose transport to the inside of the pancreatic β cells is initiated in an insulin-independent way *via* GLUT2 (**Figure 1**). GLUT2 facilitates transport with a concentration gradient. Inside the cell, glucose is converted into glucose-6-phosphate, which prevents the equalization of glucose levels and sustained transport to the cell. Glucose-6-phosphate enters the glycolysis, which results in the production of ATP molecules. As a result of a continuous glucose supply, the level of ATP is constantly increasing. This causes an inhibition of the potassium channel with the outflow of K^+ ions from the cell being blocked. K^+ ions concentration increases inside the cell, which becomes electropositive until the charges on the membrane are aligned and membrane becomes depolarized. Depolarization activates the voltage-dependent calcium channel, promoting the influx of Ca^{2+} ions to the cell. Ca^{2+} ions activate the ryanodine channel located in the membrane of insulin-accumulating vesicles, inducing their migration into the cell membrane and releasing their content [5].

2.2 Insulin signaling pathway

Released insulin participates in many metabolic actions, such as glycogen deposition in liver and skeletal muscles, a stimulation of lipogenesis and inhibition of lipolysis, and repression of gluconeogenesis in liver, but mainly in increased glucose uptake through insulin receptor signaling pathway [6]. Signal transmission from the blood to the inside of the cell is a complicated and strongly integrated process. It begins with binding of the hormone to the insulin receptor (IR), eliciting the large protein signal complex formation just below the surface of the cell membrane around IR's cytoplasmic domains (**Figure 2**) [7]. IRs are heterotetrameric glycoproteins containing two extracellular (α) and two intracellular (β) subunits. They occur mainly on the cell surface of metabolically active tissues like muscles, liver, and fat. The binding of insulin by extracellular subunits leads to IR dimerization, which allows ATP binding to β-subunits [8]. This causes the activation of the catalytic domains of tyrosine kinases in the cytoplasm [9]. In the first stage, there is an autophosphorylation of the receptor followed by phosphorylation of several substrate proteins, where IRS (insulin receptor substrate) proteins seem

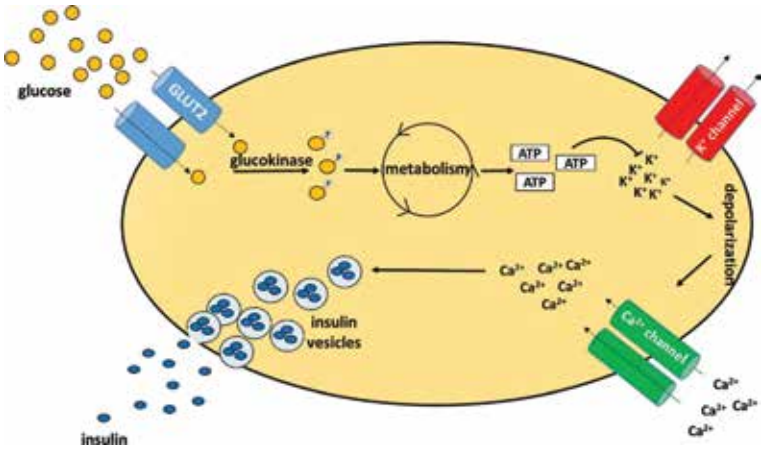

Figure 1.
Insulin release. Glucose is transported into β-cells via GLUT2 in an insulin-independent way with concentration gradient. Then, glucose is phosphorylated by glucokinase to glucose-6-phosphate, which allows for its inclusion to metabolic processes and ATP production. Raised ATP level triggers accumulation of K^+ ions along with membrane depolarization. The latter activates Ca^{2+} channels, leading to increased concentration of Ca^{2+} ions inside the cell and consequent release of insulin from vesicles. For details see text.

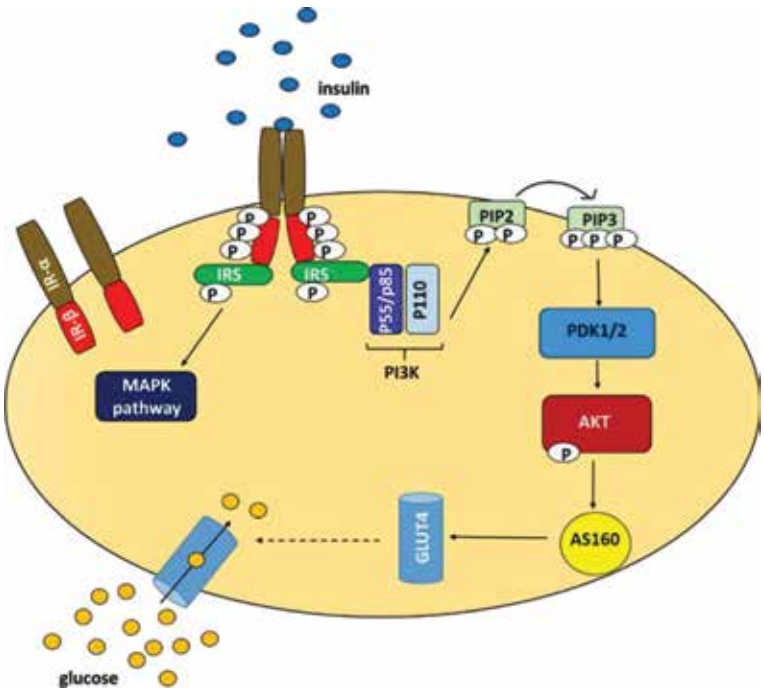

Figure 2.
Insulin signaling pathway. Insulin attaches to insulin receptors triggering its dimerization and intracellular autophosphorylation of their tyrosine residues, which constitute an attachment for IRS proteins. These molecules also undergo phosphorylation and form a complex with PI3K utilizing SH2 domains. PI3K phosphorylates PIP2, which results in PIP3 formation and activation of PDK1/2. AKT gets phosphorylated and activated by PDK1/2, subsequently eliciting phosphorylation of AS160. The latter is responsible for GLUT4 translocation to cellular membrane and glucose inflow.

to be most significant ones. The phosphorylation occurs on tyrosine residues, and then, phosphorylated IRS proteins can trigger two major signaling pathways. First pathway leads from Ras to mitogen-activated kinases (MAPK), being involved in the expression regulation of genes playing a role in cell growth and differentiation.

The second one, phosphatidylinositol 3 kinase (PI3K) pathway, elicits AKT/PKB kinase phosphorylation, and it is responsible for the metabolic action of insulin.

3. PI3K/AKT pathway

As shown in **Figure 2**, activation of PI3K/AKT pathway starts with binding of IRS proteins via SH2 domains to PI3 kinase regulatory subunits. This results in the activation of PI3K that phosphorylates phosphatidylinositol 4,5-biphosphate (PIP2) to phosphatidylinositol(3,4,5)-triphosphate (PIP3). This, in turn, leads to the activation of PIP3-dependent kinases: PDK-1 and PDK-2 and eventually to the activation of AKT/PKB kinase and atypical PKCs [10]. Subsequently, AKT catalyzes the phosphorylation of AS160 substrate protein that stimulates the translocation of GLUT glucose transporters from the cytoplasmic vesicles onto the cell membrane surface and thereby increases the insulin-dependent transport of glucose into the cell. GLUT4 occurs mainly in the interior of the nonstimulated cell, due to the proper proportion of two actions: slow exocytosis and rapid endocytosis. AS160 increases GLUT4 exocytosis and inhibition of its endocytosis via its downstream target, Rab10, in adipocytes. This results in GLUT4 accumulation in the plasma membrane [11]. Besides the activation of insulin-dependent glucose uptake via GLUT4, AKT has many intracellular targets and mediates numerous metabolic effects. For instance, AKT triggers phosphorylation of glycogen synthase kinase 3 (GSK3), which leads to stimulation of glycogen synthesis in liver and skeletal muscle [12].

4. PI3K/AKT regulation

The PI3K/AKT pathway is under strict control, and its disturbances are the cause of many diseases, including primarily insulin resistance. Further knowledge of the mechanisms regulating this signaling is one of the most important challenges of modern science. Currently, three specific signaling nodes have been distinguished: (a) IRS proteins, (b) regulatory-PI3K kinase subunits, and (c) kinase isoform Akt/PKB [13]. Disturbances of any of these nodes are mainly responsible for the reduction of the signal transmission efficiency and related diseases.

4.1 IRS protein node

IRS family consists of six proteins (IRS1–6), where two representatives, IRS1 and IRS2, are crucial in insulin signaling transduction. IRS proteins show tissue-specific expression and functionality [14]. They have three characteristic domains: (a) pleckstrin homology domain at N-terminus, (b) a phosphotyrosine-binding domain enabling binding to IR in the center, and (c) several sites of phosphorylation on tyrosine and serine residues at C-terminus. After tyrosine residues become phosphorylated, IRS binds by C-terminus domain to molecules containing an Src-homology-2 domain (SH2) [15]. IRS-1 and IRS-2 are widely expressed in all tissues, playing major roles in the maintenance of energy balance: muscle, liver, fat, and pancreatic islets. However, it seems that IRS1 plays the main role in myocytes and adipose tissue, while IRS2 is a key player in hepatocytes and islet cells [16, 17].

Generally, there are three ways allowing the regulation of IRS (**Figure 3**). Crucial control occurs mainly by multiple serine and threonine residues, which may be phosphorylated by different kinases. The phosphorylation of serine residues may inhibit insulin signaling by blocking tyrosine phosphorylation, which is necessary for

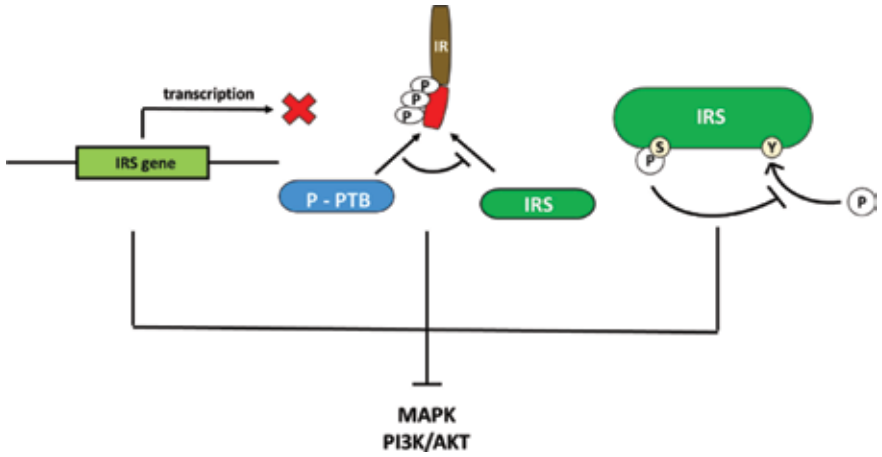

Figure 3.
Overview of three major mechanisms affecting IRS-dependent signal transduction. Signaling via IR may be modulated simply by the decreased rate of IRS gene transcription. Second, proteins with PTB domains may compete with IRS for binding to phosphotyrosines of IR. Finally, IRS phosphorylation of serine residue is known to suppress phosphorylation of its tyrosine, which is indispensable for signal transduction.

signal transduction. However, the details of this inhibitory mechanism are still not well understood. Indeed, there is a strong correlation among serine phosphorylation, decreased tyrosine phosphorylation, and insulin resistance, which is closely related to abnormalities within PI3K pathway. Most critical enzymes being able to phosphorylate IRS in serine residue are stress-induced kinases like ERK, JNK, and AMPK along with inflammatory kinase IKK and other downstream kinases, such as AKT, atypical PKC isoforms, mTOR, or S6K [18, 19]. Blockage of IRS causes the reduced cell response for stimulation with insulin and formation of insulin resistance, the first step toward diabetes. This inhibitory phosphorylation mostly occurs because of low-grade inflammation state, which is caused by lipid accumulation [20]. Studies on palmitate showed that it significantly decreased the insulin-stimulated Ser phosphorylation of Akt and Tyr phosphorylation of IRS-1 [21]. Some drugs exert similar effect. The prominent example is simvastatin, which is commonly used in the prevention and treatment of cardiovascular diseases. Simvastatin reduces the phosphorylation of insulin-induced IR at Tyr, IRS-1 at Tyr, and AKT at Thr [22, 23]. Therefore, therapy with simvastatin or other statins might be a risk factor for the development of insulin resistance or diabetes. This effect can be decreased by many natural substances like silibinin (principal flavonoid contained in silymarin, a mixture of flavonolignans extracted from *Silybum marianum* seeds). Silibinin prevents PI3K/AKT pathway inhibition by decreasing IRS1 phosphorylation on Tyr [24]. Similar mechanism is typical of PTP1B (protein-tyrosine phosphatase 1B), whose overexpression can inactivate the whole PI3K pathway [25]. Since this protein was found to be overexpressed in insulin-sensitive peripheral tissues (fat, muscle) and in hepatic cells during insulin-resistant state, searching for PTP1B inhibitors has become an important area of research in the treatment of impairment of insulin transmission pathway. FYGL (Fudan-Yueyang *G. lucidum* extract) appears to be a promising substance showing PTP1B inhibitory activity with weak cell permeability and bioavailability [26, 27].

IRS function can be also regulated by competitively inhibiting the binding of IR to IRS, primarily by proteins containing phosphotyrosine-binding (PTB) domain. One of them, NYGGF4, is highly expressed in obese individuals. Studies on skeletal myotubes showed the reduced insulin-induced phosphorylation of IRS1 at Tyr and Akt phosphorylation at Ser residue without changes in the insulin-stimulated tyrosine phosphorylation of IR [28, 29].

Among other IRS modulatory mechanisms, it is worth mentioning about expression regulation of IRS mediated by hyperinsulinemia and other hormones [30]. Anjali et al. showed that FSH (follicle stimulating hormone) induces expression of IRS2 in granulosa cells [31]. Also, some natural medicines like Tangzhiqing formula, a mix of five herbs, modulate IRS expression level in HEPG2 cells (IR1 and IRS2) and L-6 myotubes (IRS1) [32].

4.2 PI3K kinase subunits

PI3 kinases constitute protein family, which exhibits activity of phosphorylation of lipids and proteins. They are divided into three groups according to their structural features and substrate preferences (**Table 2**). Members of I class are the most crucial in insulin signaling pathway. PI3K-1 are heterodimers made up of regulatory and catalytic subunits. The regulatory subunit is generally referred to as p85. They all have a similar domain structure: SH3 domain, breakpoint cluster region homology (BH), and two SH2 domains with iSH2 (interSH2) domain in between [33]. Signaling is initiated by p85 interacting through the SH2 domain with IRS phosphotyrosine motif. Subsequently, p85 is joined through its iSH2 domain to the adapter binding domain (ABD) of catalytic subunit called p110. Besides ABD, p110 also contains Ras-binding domain (RBD), which is involved in interaction with Ras protein superfamily, C2 and the helical scaffolding domains, along with kinase domain participating in PIP3 formation [34].

p85 protects p110 from degradation by forming a heterodimer. Furthermore, this binding allows p110 translocation to the cell membrane, where catalytic subunit is able to send a signal via phosphorylation of PIP2 to PIP3, a lipid second messenger. Interestingly, p110α is the most prominent one from all PI3K catalytic subunits in insulin-dependent pathway [35]. Cells with its deletion exhibit hyperglycemia and glucose intolerance [36]. While p110β seems to play a secondary role, its presence is necessary for p110α activity and thus maintenance of basal threshold of PIP3 [37, 38]. PIP3 is bound by proteins with PH domain such as AKT and PDK1. This critical event allows further signal transduction to downstream proteins.

In this control node, a few aspects are taken into account. Firstly, signaling via PI3K is critically dependent upon PI3K regulatory subunit with p85 mediating either its restriction or promotion. In cells deprived of upstream stimuli, p85 reduces p110 activity. It is executed through C2 and helical scaffolding domains, which form inhibitory contacts with p85. Furthermore, monomeric p85 binds to phosphorylated sites of IRS, thus blocking p85-p110 heterodimer attached to IRS [39]. p110, another

Class	Members	Catalytic subunit	Regulatory subunit	Main reaction	Reference
Ia	PI3Kα PI3Kβ PI3Kδ	p110 (α/β/δ)	p85α, p55α, p50α, p85β, p55γ	PtdIns(4,5)P2 → PtdIns (3,4,5)P3	[33]
Ib	PI3Kγ	p110γ	p101 p84/87	PtdIns(4,5)P2 → PtdIns (3,4,5)P3	[33]
II	PI3K-C2α PI3K-C2β PI3K-C2γ	Monomeric		PtdIns(4)P → PtdIns (3,4)P2	[76]
III	PI3K-C3	Vps34	Vps15	PtdIns → PtdIns (3)P3	[77]

Table 2.
Classification of PI3K family members.

essential regulatory molecule, undergoes spatial regulation in some types of human cancer. Studies on HepG2 cells demonstrated that PAQR3 (progestin and adipoQ receptor family member 3) associates with p110α by attracting it to Golgi apparatus, a place of PAQR3 exclusive localization. This event inhibits the interaction between p85a and p110α [40, 41].

There are two other possible PI3K activation pathways, both being dependent on ligand-membrane receptor binding. The first mechanism is based on binding the adaptor protein GRB2 to RTK (receptor tyrosine kinase). When GRB2 is already attached to GAB protein, it is allowed to bind p85. By contrast, the second way of PI3K activation is not dependent on p85 subunit. In this scenario, GRB2 binds to SOS, which activates RAS, leading to activation of p110α subunit. In addition, the p110β catalytic subunit may be stimulated in a similar, p85-independent way via G protein-coupled receptors [42].

Another critical regulatory mechanism is associated with the control of PIP3 level. There are several well-known inhibitors which dephosphorylate PIP3 with phosphatase and tensin homolog (PTEN) being the most well-known one. Undoubtedly, PTEN is an intriguing protein for research in the context of diseases with PI3K signaling impairment. For instance, in adipose tissue, it can be blocked by H2S or its precursor, L-cysteine. Diet supplementation of L-cysteine increases PIP3 level and mediates the activation of PI3K, resulting in improvement of glucose metabolism [43, 44]. Expression level of PTEN is also regulated epigenetically in adipocytes via several miRNAs such as miR-21, miR-23a-3p, miR-26a, miR-26b, and miR-181a-5p [45–49]. Another widely known PIP3 inhibitor is SHIP (SH2-containing inositol 5′-phosphatase). SHIP dephosphorylates PIP3 at 5′-inositol position (in contrast to PTEN targeting 3′-inositol position) and inhibits AKT primarily through regulation of its cellular localization [50].

Last but not least, PI3K dysregulation can be also underlain by gene mutations of p110α and p85 subunits or PI3K negative regulators. For instance, loss of function or deletion of PTEN is known to occur in numerous types of cancer. Therefore, enormous attempts are put into research focused on searching compounds targeting PI3K. The most common PI3K regulators are Wortmannin (steroid fungal metabolite) and LY294002 (morpholine-containing chemical compound) [51]. Moreover, there are multiple members of a new generation of more stable molecules such as SF-1126, CAL101, GSK615, XL147, and PF-4989216, which evoke the suppression of overactive PI3K signaling particularly in cancer [52].

4.3 Kinase isoform AKT/PKB

AKT (also named PKB) occurs in mammals in three isoforms (AKT1, AKT2, and AKT3). Although they share a similar domain structure (N-terminal PH domain, a central kinase domain, and C-terminal domain), AKT isoforms exhibit target specificity and play divergent roles. AKT2 is the most essential in glucose uptake [53].

The PH domain enables AKT to be attracted by PIP3 just as PDK1. After binding to PIP3, AKT undergoes conformational changes that allow revealing the phosphorylation site. While they are in nearby, PDK is able to phosphorylate AKT on Thr308. Nevertheless, for full activation of AKT (besides AKT3), second phosphorylation on Ser residue is necessary (AKT1-Ser473 and Ser-474 AKT2). Ser473 is modified by PDK-2/mTORC2 (mammalian target of rapamycin complex 2) [54]. AKT activation is terminated through the action of PP2 (protein phosphatase 2) and PHLPP (PH domain leucine rich repeat phosphatase), which perform dephosphorylation of Thr308 and Ser473, respectively [55].

While phosphorylation status of both of these sites is fundamental for AKT activity, there is plethora of other posttranslational modifications affecting its

performance [56]. For instance, oxidation of Cys124 triggered by PDGF-induced (platelet-derived growth factor) ROS leads to the blockage of AKT2 activity [57]. Besides PI3K-dependent activation, AKT may be switched on by alternative modulators. Namely, two groups of uncommon AKT activators are distinguished: tyrosine kinases (e.g., ACK1, SRC, PTK6) and serine/threonine kinases (e.g., TBK1, IKBKE). ACK1, a non-receptor tyrosine kinase, is capable of regulating AKT recruitment to the plasma membrane due to AKT phosphorylation on Tyr176, making it preferentially binding to phosphatidic acid—a membrane phospholipid. This elicits AKT attachment to plasma membrane even in the presence of some specific PI3K inhibitors. The increase of AKT2 activity occurs in many cancers, which may be underlain by auto-activating mutations of ACK1. Another nonreceptor kinase involved in AKT regulation is Src. Its action takes place on Tyr315 and 326. By contrast, PTK6 responds to epidermal growth factor (EGF), whose overexpression is typical of many cancers, via phosphorylating Tyr215 and 326. Modifications triggered by Src and PTK6 are resistant to some popular PI3K inhibitors. The second group of AKT activators, Ser/Thr kinases, modifies Thr195, Ser378, and Ser473 (TBK1), as well as Ser137, Thr308, and Ser473 (IKBKE). These alternative activation modes may suggest that under some particular conditions, cells can turn on AKT signaling in quick response [58].

Due to the fact that AKT, just like PI3K, is one of the most commonly deregulated molecules in human cancers, AKT inhibitors development constitutes an important field of research. Currently tested molecules utilize two major mechanisms. First group acts as competitors for ATP-binding site of AKT (e.g., GSK690693, GDC-0068, GSK2110183, and GSK2141795). They share features of major pharmacophore with minor differences. The second group is composed of allosteric AKT inhibitors (e.g., 2,3-diphenylquinoxaline and analogs, alkylphospholipids). Many of these molecules are in clinical trial phase and have a potential in the treatment of AKT dysregulations [59].

5. Environmental insulin signaling modulating factors

The relationship between environmental factors like diet, drugs, lifestyle in general, and PI3K pathway remains undeniable. Herein, we will discuss major agents responsible for PI3K modulation. In terms of mediated effect, they can be divided into two types: insulin sensitizing factors and insulin-resistance inducing factors. They do not usually affect a specific protein, but through their action, they dysregulate the entire pathway and the overall metabolism.

5.1 Factors inducing insulin resistance

Due to the fact that insulin is one of the key regulators of metabolism, it is not surprising that the most important factor modulating its action is diet. Impairment of PI3K signaling is well known to be connected with obesity. Depending on the tissue, the mechanism of obesity-induced insulin resistance seems to differ, but it is in general connected with lipid overload. In liver and muscles, the most crucial is elevation of FFA level, which is characteristic for the obese. In consequence, toxic lipids, mainly ceramides and diacylglycerol (DAG), do accumulate. The increased amount of ceramides causes PP2A stimulation, which terminates insulin pathway via AKT dephosphorylation. On the other hand, DAG activates PKC isoforms (ε and θ) [60]. The latter ones are able to obstruct signaling either by IRS (muscles) or IR (liver). PKC isoforms activation leads to increased expression of NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells), which takes part

in inflammatory cell response. Subsequently, NFκB activates pro-inflammatory cytokines and stress-induced serine-threonine kinases like JNK, which are able to block insulin signaling pathway via improper IRS phosphorylation. Furthermore, the increasing concentration of lipids in the cells leads to the aggregation of toxic metabolites derived from the incomplete oxidation, and, as a result, the elevated synthesis of free radicals. This is also correlated with increased activation of stress-induced kinases. In overall, these events lead to PI3K pathway impairment and the emergence of insulin resistance [60–62].

The mechanism of obesity-induced insulin resistance formation in adipose tissue is also related to lipid overload but has a different course. It is connected to the constant enlargement of adipocytes, which along with dysregulation of adipogenesis leads to the introduction of hypoxia. Reduced oxygen supply introduces cellular stress response, which includes activation of stress-induced kinases, pro-inflammatory cytokines, and tissue infiltration by pro-inflammatory macrophages. These events result in low-grade inflammation state characteristic of PI3K impairment. Adipose tissue is not only an energy reservoir but also an active endocrine organ, which produces hormones called adipocytokines. They are sensors of nutritional and metabolic homeostasis. Accumulation of visceral fat and inflammation development alters the secretary profile of adipocytokines. Adipocytes start to send pro-inflammatory signals like TNF-α and interleukin1 (IL1). Other typical insulin resistance-inducing cytokines are resistin and IL-6, which activate pro-inflammatory pathways of NFκB and JNK kinase, leading to defective response to insulin [63].

5.2 Insulin-sensitizing factors

While prolonged high-calorie diet undeniably leads to insulin resistance, proper dietary style can be a sensitizing factor as well. There are many diet supplements improving insulin signaling. Herein, we will point out only a few members of this enormous group. For instance, glutamine (Gln) supplementation Gln increases the expression of key PI3K signaling molecules (PI3K, PDK1, and GLUT4) and promotes AKT phosphorylation, GLUT4 translocation, and glucose uptake in the presence of insulin during exposure to hyperglycemia [64]. An epidemic of obesity and numerous side effects of drugs that increase insulin sensitivity has caused the great interest among scientists to search for natural sensitizers. They include dieckol (an extract from a brown seaweed), which enhances translocation of GLUT4 in peripheral tissues [65]. Another seaweed improving glucose uptake is *Gelidium amansii*. It exhibits antihyperglycemic, antioxidant, and antiobesity effects potentially *via* PI3K/AKT/GLUT4 signaling [66]. Also, carnosol, a compound found in spices such as sage or rosemary, increases glucose uptake *via* GLUT4 [67]. Interestingly, it has been proven that 1,25-dihydroxyvitamin D3 (active form of vitamin D3), which is mainly provided with food, can improve glucose uptake and has a potential in acting as an anti-inflammatory factor [68]. It seems that an alternative for typical drugs like metformin or pioglitazone, which cause side effects, may be products containing natural substances like Jiangtang Xiaoke granule. The latter is composed of 10 herbs, and it can significantly increase the expression of vast PI3K proteins in mice even upon hyperglycemia [69].

Components of the diet are not the only ones able to improve the signaling via discussed pathway. Studies on rat model demonstrated that long-term caloric restriction may enhance AKT2-dependent mechanism for improving insulin-stimulated glucose uptake. Moreover, a lot of research has been carried out to indicate that physical exertion has a positive effect on insulin [70–73].

6. PI3K/AKT pathway impairment

PI3K pathway impairment is related to many diseases, among which the most common and worth attention are insulin resistance and numerous types of cancers.

Insulin resistance may be defined as a subnormal glucose response to endogenous and/or exogenous insulin. Peripheral tissues are not able to respond to the hormone by increasing glucose uptake from the bloodstream. Initially, pancreatic β-cells are not harmed yet, and in response to high glucose level, they synthesize more and more insulin. However, if this state lasts for a long time, islet cells start to overgrow, and deterioration of their function and/or decline of β-cell mass do occur. As normalization of glucose level does not occur, cells are becoming more and more resistant to insulin simultaneously forming a vicious circle of insulin resistance. The most affected tissues are the most metabolically active ones like liver, muscles, and fat. Although the pathogenesis of insulin resistance is getting better understood, the exact mechanism is still not clear. The causes may be connected to abnormal insulin production, but in most cases, the changes in insulin receptors and their substrates along with defects in post-receptor signaling play the role.

PI3K pathway is one of the most frequently deregulated signaling pathways in human cancers. As it plays an essential role in many biological processes like cell survival, proliferation, migration and differentiation, its dysregulation may result in tumorigenesis. The most common changes are mutations (*PIK3CA*, *AKT1*, and *PTEN*), genes amplification (*PIK3CA*, *AKT1*, and *AKT2*), and loss of expression or deletion of the tumor suppressor PTEN [74]. The highest prevalence of mutations within PI3K pathway is typical of lung cancer, breast cancer, endometrial cancer, and head and neck cancer along with glioblastoma [75].

7. Conclusions

Insulin is the most crucial agent in glucose metabolism. It stimulates glucose uptake from the bloodstream to peripheral tissues. Furthermore, it is responsible for energy storage through accelerating glycogen synthesis and lipogenesis. In general, it promotes cellular events leading to energy storage and represses processes of energy release (**Figure 4**). Insulin action takes place mainly through PI3K pathway and results not only in metabolic effects but also in mitotic response. Insulin is also

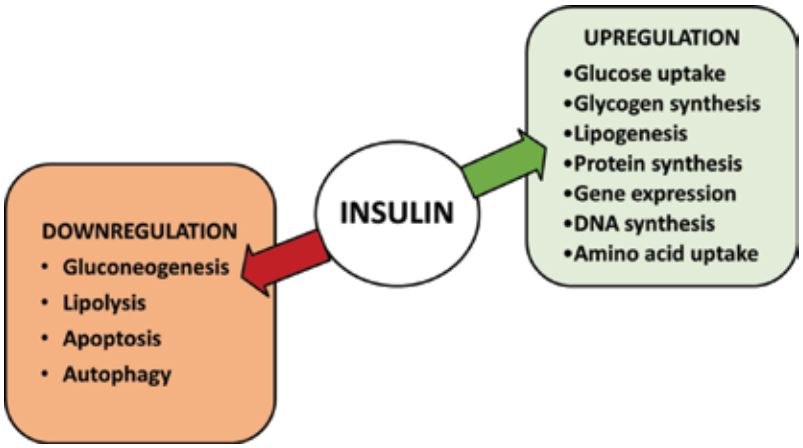

Figure 4.
Critical actions and pathways controlled by insulin.

involved in phenomena connected with cell survival. Multitasking nature of this hormone causes that any abnormality in its signal transmission can result in serious consequences, such as diabetes and cancer. These two diseases are the scourge of the modern world. The steadily increasing percentage of people suffering from insulin resistance or full-blown diabetes and the high incidence of cancer have caused scientists to focus on seeking therapeutic goals that may contribute to the prevention or treatment of these disorders. In insulin-resistance, the main target constitutes the improvement of insulin sensitivity. Among common approaches, it is worth to highlight two of them: increasing fatty acids oxidation and elongation of IR activation state by blocking PTP1B activity. Promising therapeutic targets seem to be also pro-inflammatory cytokines and other proteins involved in inflammation response. On the other hand, cancer cells show mainly hyperactivity of PI3K pathway and the increased glucose uptake. Therefore, it seems that blockage of impaired signal transduction may contribute to suppression of the growth of the tumor. For this reason, intensive search for selective inhibitors or silencers of the insulin pathway are underway. Conducting further research may become the basis for the development of new methods of prevention and more effective treatment strategies for these diseases.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

List of abbreviation

ABD	adapter binding domain
ACK-1	activated CDC42 kinase 1
AKT (PKB)	protein kinase B
AMPK	5'AMP-activated protein kinase
AS160	Akt substrate of 160 kDa
BH domain	breakpoint cluster region homology domain
EGF	epidermal growth factor
ERK	extracellular signal-regulated kinase
FSH	follicle stimulating hormone
FYGL	Fudan-Yueyang *G. lucidum* extract
GAB	GRB2-associated binding protein
GLUT1–4	glucose transporter type 1–4
GSK3	glycogen synthase kinase 3
GRB2	growth factor receptor-bound protein 2
HEPG2	human liver cancer cell line
IKBKE	inhibitor of nuclear factor kappa-B kinase subunit epsilon
IKK	IκB kinase
IR	insulin receptor
IRS	insulin receptor substrate
JNK	c-Jun N-terminal kinase

MAPK	mitogen-activated protein kinase
mTOR	mammalian target of rapamycin kinase
mTORC2	mammalian target of rapamycin complex 2
NYGGF4 (PID1)	phosphotyrosine interaction domain-containing protein 1
PAQR3	progestin and adipoQ receptor family member 3
PDGF	platelet-derived growth factor
PDK1	pyruvate dehydrogenase lipoamide kinase isozyme 1
PH domain	pleckstrin homology domain
PHLPP	PH domain leucine rich repeat phosphatase
PI3K	phosphatidylinositol-4,5-bisphosphate 3-kinase
PIP2	phosphatidylinositol 4,5-bisphosphate
PIP3	phosphatidylinositol (3,4,5)-trisphosphate
PKC	protein kinase C
PP2	protein phosphatase 2
PTB domain	phosphotyrosine-binding domain
PTB1	polypyrimidine tract binding protein-1
PTEN	phosphatase and tensin homolog
PTK6	tyrosine-protein kinase 6
PTP1B	protein-tyrosine phosphatase 1B
RBD	Ras-binding domain
ROS	reactive oxygen species
S6K	ribosomal S6 kinase
SH2 domain	Src-homology-2 domain
SHIP	SH2-containing inositol 5′-phosphatase
SOS	son of sevenless, guanine nucleotide exchange factor
SRC	proto-oncogene tyrosine-protein kinase Src
TBK1	TANK binding kinase 1

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Chapter 4

Cardiovascular and Biochemical Responses in Exercise Recuperation in Diabetic Rats

Luiz Augusto da Silva, Jéssica Wouk and Vinicius Muller Reis Weber

Abstract

The objective of this study was to assess the cardiovascular and biochemical responses during aerobic exercise recuperation in diabetic rats. There were utilized 12 animals, of 60 days, divided in two groups: control and diabetic. On the test day, the animals performed a 60 minutes' session of predominantly aerobic exercise, using an overload of 6% of their body's weight. After and before the exercise, the animals had their systolic blood pressure (SBP) and heart rate (HR), lactate, glycerol and glucose measured. The animals were trained during 30 days by swimming tank, with an extra weight equivalent to 4% extra weight a 40-min session. A decrease in glucose value occurred in the diabetic animals after exercising, as well as an increase of lactate in the same group. 1', 3', 5' and 7' after the exercise, a significant reduction of HR in the diabetic group was noticed when compared with the control group, such behavior was also observed with double product (DP) together with SBP values 1', 3' and 5' after the exercise. The diabetic animals' recovery has been possibly affected by a reduction of blood flow and a reduction of energetic substrates contribution, as well as lactate clearance.

Keywords: exercise, glycemia, recuperation

1. Introduction

Diabetes mellitus (DM) is a complication that triggers problems to public health all around the world [1]. It most frequently type, diabetes mellitus type 2 (T2DM), face to hyperglycemia impact, may evolve to cardiovascular, neuromuscular and degenerative complications [2], being able to rise considerably the morbidity and mortality [3].

During DM complications' evolution, cardiac dysfunctions or diabetic cardiomyopathies occur, independent of the presence of vascular diseases, arteriosclerosis or heart attack [4, 5]. The development of diabetic condition alters the hemodynamic balance and, as a consequence, triggers a reduction of physical capacities of the organism [6, 7].

With regard to the muscular system, a good functioning of it causes the action of insulin which connects itself to its receptor leading to the phosphorylation of its tyrosine receptor to the substrate of the insulin's receptor (IRS-1 and 2). IRS-1 and 2 mediate the effects over glucose metabolism, through the activation of

phosphatidylinositol (PI)-3 kinase, PKA/AKt and the increase of glucose transporter type 4 (GLUT4), from intracellular compartments into plasma membrane. However, the non-functioning of the insulin's receptor with its respective hormone cause its resistance over the cell, in that way, glucose metabolism does not occur [8, 9], what entails blood's hyperglycemia and fatigue of the skeletal muscle involved.

It is well accepted that physical exercise may be related to the enhancement of insulin sensibility, GLUT4 expression and to the glycogen synthase enzyme activity in muscular cells of patients with DMT2, and that this stimulus may remain for up to 48 h [10, 11]. The physical exercise causes important changes in glucose homeostasis, actuating in specific proteins such as adenosine monophosphate-activated protein kinase (AMPK) that assists in the stimulus of liberation of glucose transporter 4 (GLUT4) of its cellular vesicles, in order to actuate in the glucose's input in the cell [12]. In this way, the exercise might rapidly decrease the glucose level in hyperglycemia condition.

There is the necessity of comprehending the way in which physical exercise may act in the physiological behavior of the organism, and the cardiovascular and biochemical responses bring along directions to understand how the organism reacts to physical exercise, in detriment of training variables as volume and intensity. In this way, the objective of this study was to evaluate the cardiovascular and biochemical responses during the recovering of aerobic exercise in diabetic rats.

2. Material and methods

2.1 Animals

Twelve male Wistar rats at 60 days of age were used in the study. The animals were kept in cages with controlled temperature (23 ± 2°C) and humidity (55 ± 10% humidity), and a light/dark cycle of 12 h. This study was approved by the Ethics Committee of research studies using animals (015/2015 Protocol).

2.2 Diabetes induction and experimental design

The animals were divided into two groups: [1] control (weights of 393 ± 44 g), [2] diabetic (weights of 308 ± 40 g). Alloxan (ALX) (Sigma, St. Louis, USA) dissolved in sodium chloride solution (0.9%) was administered intraperitoneally (ip) (120 mg/kg), after 12 h of fasting. Rats with fasting BG values between 150 and 250 mg/dL were considered diabetic. With 90 days old, the animals were submitted to an oral glucose tolerance test (OGTT) to verify their glycemic curve. Thus, a maximal exercise test (MET) was performed to evaluate the biochemical (glucose, lactate and glycerol) and cardiovascular (HR and SBP) responses before and after the exercise.

2.3 Effort exercise test and training

All animals were adapted to an aquatic environment to be able to swim during the test, through one daily session of 10 min, for 7 days prior to the experiment. On testing days, the animals performed a 60-min session of predominantly aerobic exercise by carrying an extra weight equivalent to 6% of their body weight in a swimming tank with 40 cm in depth, 70 cm in diameter, and water heated to 30 ± 1°C, according to the protocol proposed by Gobatto et al. [13]

Post testing, the animals were trained during 30 days by swimming tank, with an extra weight equivalent to 4% extra weight a 40-min session, according to the

protocol modified proposed by Scariot et al. [14]. Exercise sessions and laboratory procedures were always conducted at the same time of the day (08:00 am).

2.4 Oral glucose tolerance test

Blood was collected from the tail vein in animals that fasted for 12 h to a posterior glucose analysis. These animals subsequently received one single dose of glucose (1 mg/kg of body weight) by gavage, and new blood samples were collected at times 30, 60, and 120 min. Blood glucose levels were determined in a glucometer (Accu-chek Advantage®).

2.5 Biochemical analyses

Blood glucose, lactate, and glycerol doses were performed in a glucometer (ACCU-CHEK® Active®) using approximately 25 μl of blood collected through caudal puncture, before and after the effort test.

2.6 Cardiovascular analyses

Heart rate values (HR) and systolic blood pressure (SBP) were obtained using a tail plethysmograph that transmitted data to a software that codified the results (Insight®, Ribeirão Preto, Brazil). In order to adapt animals to this device, it was attached to animals' tails three times a day for 5 days before the test. On test day, HR and SBP were obtained in triplicate for all animals, by the same evaluator, before and after treatments and prior to exercise. The Double Product index was used as an indirect indicator of the cardiac work, calculated through the formula:

$$DP = \text{Systolic pressure} \times \text{Heart rate} \quad (1)$$

2.7 Statistical analyses

All results are presented as mean ± E.P.M. Statistical analysis was performed using a Student's t-test for unpaired sample or one-way ANOVA. Values were considered statistically significant based on $P < 0.05$. The post hoc Student-Newman-Keuls test was used, when appropriate, to identify differences between groups.

3. Results

3.1 Oral glucose tolerance test

Figure 1 represents the blood glucose values during OGTT of the rats from different groups. The glycemic curve was significantly higher to the diabetic group, when comparing with the values related to the controls and diabetes post trained groups at times 0, 30, 60 and 120 min.

3.2 Biochemical responses

Figure 2 represents the blood glucose values before and after exercise. The glucose values were significantly different between control and diabetes groups, and intragroup a significant reduction occurred to the diabetic group after exercising ($P < 0.05$). Furthermore, the glucose post training, pre and post exercise was smaller than the same diabetes group pre-training ($P < 0.05$).

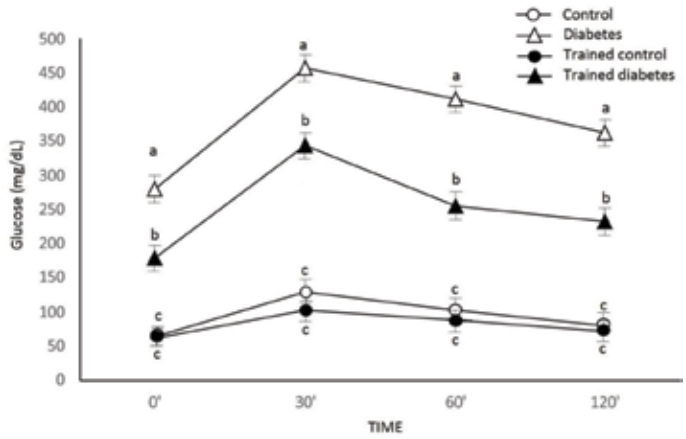

Figure 1.
Oral glucose tolerance test results of control and diabetes groups rats pre and post 30 days of training. The data represent the average ± E.P.M, n = 6, (a,b,c) difference letters = P < 0.05 (Student-Newman-Keuls after one-way ANOVA).

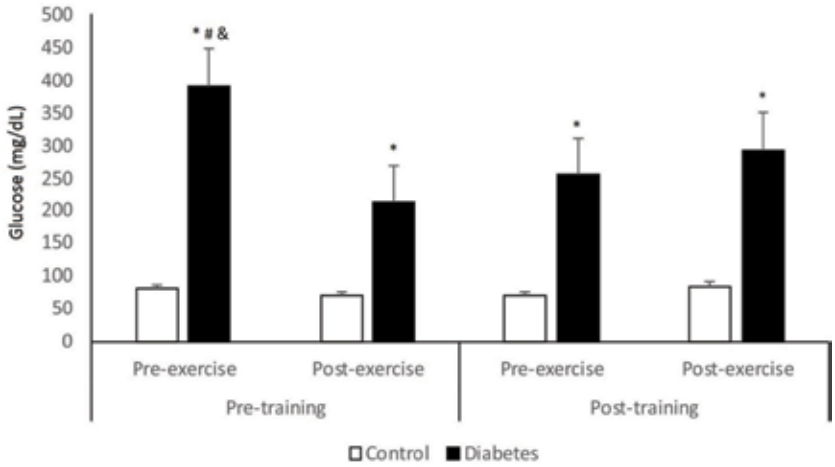

Figure 2.
*Plasma concentration of glucose levels before and after the exercise protocol and 30 days of training. The data represent the average ± E.P.M, n = 6, * = P < 0.05 when compared with the control group, # = P < 0.05 when compared with the same group, & = P < 0.05 when compared with the same group post-training (Student-Newman-Keuls after one-way ANOVA).*

Figure 3 represents the glycerol and lactate values before and after exercise. No difference was observed in glycerol values between groups. Concerning the lactate values, a significant difference occurred between groups, both for pre and post-training and diabetes pre-training groups.

3.3 Cardiovascular responses

Figure 4 represents the HR, SBP and double product in rats of different groups. No statistical difference was noticed concerning the hemodynamic measures during resting. 1, 3, 5 and 7 min after the exercise, a significant reduction of HR in the diabetic group was noticed when compared with the control group, such behavior was also observed with DP together with SBP values 1, 3 and 5 min after the exercise. After 30 days of training, the diabetes and control groups maintained their HR similar between the time of 1, 4, 5 and 7 min, being that they were different

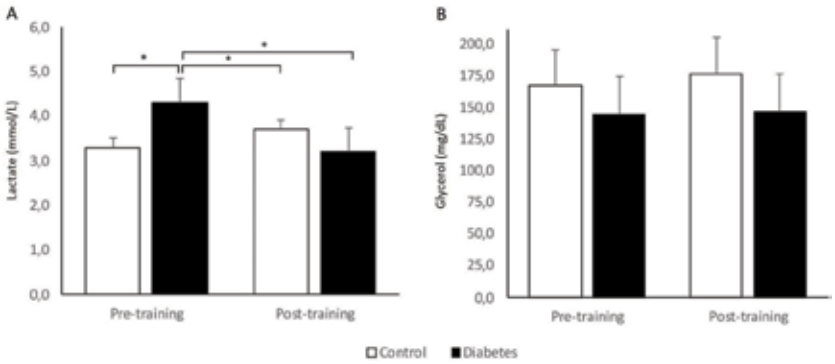

Figure 3.
*Plasma concentration of (A) lactate and (B) glycerol levels after the exercise protocol pre and post 30 days of training. The data represent the average ± E.P.M, n = 6, * = P < 0.05 when compared with the control group, # = P < 0.05 when compared with the same group (Student-Newman-Keuls after one-way ANOVA).*

from their respective groups before the training. Significant reduction of SBP and DP values was observed for the control group after training compared to the same group ($P < 0.05$). The diabetic groups did not show significant differences.

4. Discussion

This study demonstrates that the HR analysis post-exercise presents intensity and performance information as well as the physical condition of the organism. The relation between the recuperation time and HR must be characterized, investigated and explained in order to obtain a better understanding of the whole picture, in other words, the clinical condition or hemodynamic/metabolic balance to the exercise with the intensity in question.

The HR revealed a better recuperation in the diabetic animals, what may be related to the quantity of muscle present in these animals. According to Polito and Farinatti [15], this happens because in dynamic exercises, a greater volumetric load occurs in the left ventricle and the cardiac and hemodynamic responses are proportional to the intensity and to the muscular mass involved in this activity. In this case, this event would trigger a reduction of muscular mass in these animals due to the metabolic deregulation and consequent atrophy displayed in this clinical condition related to the diseases [16].

The lactate increased after exercise in diabetic animals compared to the healthy ones, what would have related to the muscular metabolic capacity, because with a smaller consumption of glucose due to its reduced input in the muscle, the utilization of existent substrates or reutilization of resulting metabolites that derive lactate is necessary [17], in this situation, a better recuperation and a greater lactate removal from bloodstreams occurs, that demonstrates a better capacity of the animal to face physical stress.

The heart of a patient with a diabetic condition has lower metabolic capacity because the main glucose capturer in cardiac muscle is also GLUT-4 [17], tending to have a lower response to recuperation after exercising due to the minor consumption of glucose. Some conditions associated with this response, such as the metabolic acidosis, general fatigue and reduction of neuronal function are due to hyperglycemia [18], causing a reduction of prompt reply to exercise in the body's systems.

Although this phase of exercise may be starting to be investigated, the results still diverge about the necessary time to a total restoration to the rest levels after exercise, and the autonomic nervous system (ANS) might be involved in this event

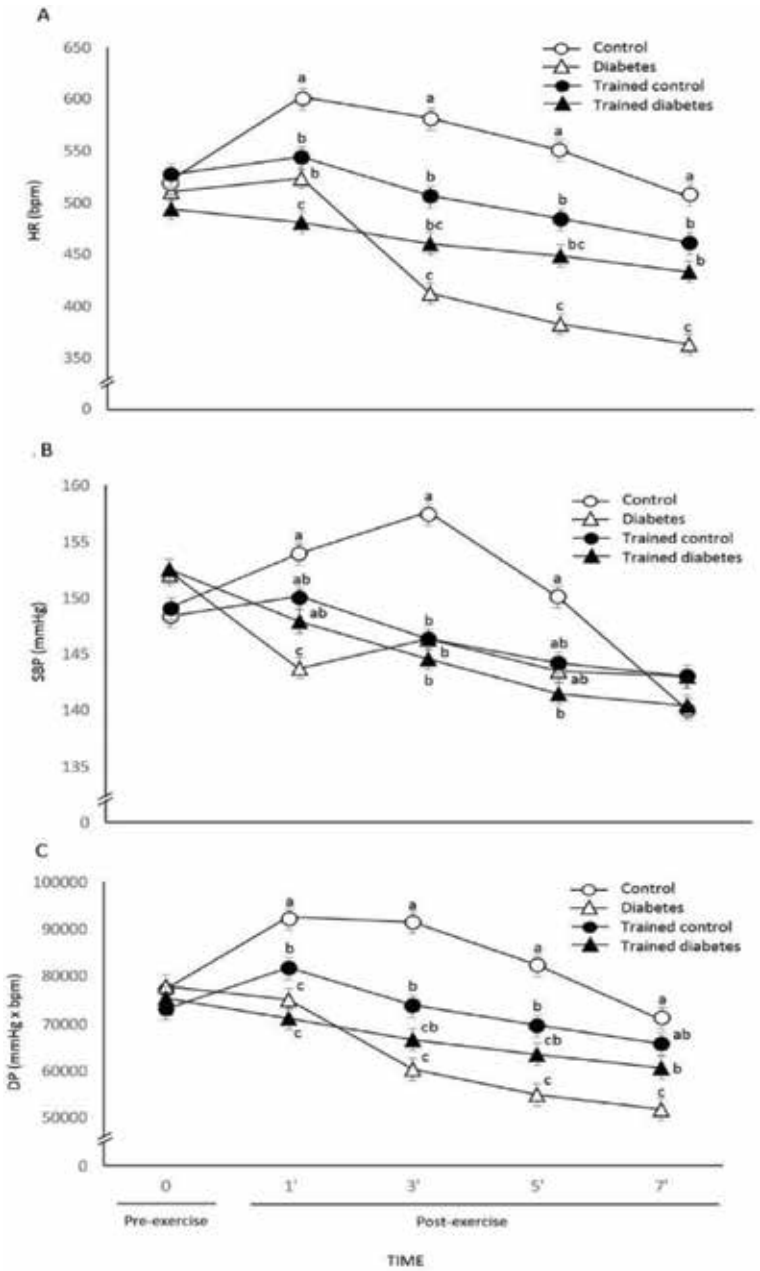

Figure 4.
Heart rate (A), systolic blood pressure (B), and double product (C) pre and post exercise in control and diabetes group rats pre and post 30 days of training. The data represent the average ± E.P.M, n = 6, (a,b,c) difference letters = P < 0.05 (Student-Newman-Keuls after one-way ANOVA).

[19–21]. The time spent to the HR to return to resting levels depends on the interaction between the autonomic functions, the level of physical conditioning and the exercise intensity as well [22]. Evaluation post-effort show a hypotension after exercise in a gradual way, as it can be observed in the healthy animals [23]; however, the ANS reduced the resting values of the diabetic animals, demonstrating a failure in the hemodynamic involvement to a muscular recuperation and a desirable lactate removal, what could be hindered with the reduction of the bloodstream [24] due to the diabetic condition, demonstrating that after exercise complication are visible.

What must be observed is the recuperation of the diabetic animals that was harmed by a possible reduction of bloodstream, a reduction in the contribution of energetic substrates, as well as a lactate removal, that demonstrate the effects of the diseases upon the organism. This information demonstrates how homeostasis is unregulated due to a clinical condition that triggers complications in many tissues of the body. Yet, if the progression of the disease is slow, the complication of diabetes would also be reduced and the beginning of its limitations in tissues could be prevented or eliminated.

In this way, exercise is an important tool to glucose control for the animals because it may enhance systems that are essential to metabolic balance, such as the skeletal muscle, which has an important function in the movement, increasing the physical capability of the organism to resist to situations that aim to adapt the tissues to a better function.

5. Conclusion

This chapter showed which diabetic animals' recovery has been possibly affected by a reduction of blood flow and a reduction of energetic substrates contribution as well as lactate clearance. This information demonstrates how homeostasis is dysregulated due to a clinical condition that triggers complications in several body tissues.

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Declaration of interest

There are no issues to disclose. There is no potential conflict of interest with the mentioned trademarks.

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Section 3

Hypoglycemia

Chapter 5

Carbohydrate Metabolism in Hypoglycemia

María L. Kennedy and Miguel A. Campuzano-Bublitz

Abstract

Hypoglycemia is generated by mechanisms directly related to an increase in insulin secretion, by metabolic disorders that require increased glucose consumption or by a deficient metabolic production of glucose by the body. Mechanisms include high glucose intake, increased dose of oral hypoglycemic, exogenous administration of insulin, metabolic hepatic conditions that lead to an increase in the production of amino acids, growing tumors, and in diabetic pregnant woman with abnormal increase in glucose and amino acids that end up producing insulin hypersecretion in the newborn. Work that requires high glucose expenditure or reduction of insulin antagonist, such as cortisol and glucagon, ends up in hypoglycemia. Finally, hypoglycemia is generated by metabolic deficit in pathophysiological situations such as defects in enzymatic systems, alcoholic hepatitis, and insufficient nutrition. The most characteristic symptoms include bulimia, fits of sweating, and tremors due to a strong activation of the sympathetic system. Obviously, the CNS is strongly affected by the lack of glucose, which is even more complicated because also hypoglycemia leads to a situation of decreased lipolysis and ketone bodies that finally seriously compromise the supply of energy to the nervous system, producing losses of consciousness, spasms, and even irreversible brain damage.

Keywords: hypoglycemia, increased glucose consumption, hyperinsulinemia, exogenous insulin control, uncontrolled diabetes, high glucose expenditure

1. Introduction

The human body is dependent on a tight control of its blood glucose levels to ensure normal body function. Survival of individuals, the conscious state, the integration of different types of internal and external stimuli, and appropriate responses to these stimuli depend on the proper functioning of the central nervous system, which puts intense activity in their cells. This requires the consumption of oxygen and glucose to obtain the energy that enables the activity of the central nervous system (CNS) and keeps the neurons in constant activity [1].

The lack of oxygen causes, in minutes, serious and irreparable damage to the central nervous system. However, the lack of glucose is tolerated for a longer time because in a deficit situation, the CNS itself makes autonomous adjustments leading to inactivity to other non-vital systems of the body and preserves for more time the availability of glucose for neurons, and ultimately, in multiday starvation states, it substitutes glucose for ketone bodies as a nutrient, which allows life expectancy to be extended during fasting. The availability of glucose in people is vital for a good quality of life, since it allows the lucid and full functioning of the CNS [2, 3].

The rest of the body's cells also obtain energy through oxygen and glucose, thus enabling metabolism and cellular response. The main source of glucose is through

food and specifically depends on the consumption of carbohydrates [4]. The use of this carbohydrate in the body is finely regulated by a hormonal system capable of always maintaining blood glucose (glycemia) in a concentration ranging from 4.0 to 5.4 mmol/L (72 to 99 mg/dL) [5]. The human body is prepared to store excess of glucose (glycogenesis) and use it in the future (glycogenolysis) when this is required and is also able to synthesize glucose from noncarbohydrate precursors (substrates) such as amino acids, lactate, and/or glycerol (gluconeogenesis).

The pancreas is the body in charge, among other functions, of maintaining glycemia at tolerable levels for the organism, through a system of hormones, where insulin is responsible for reducing glycemia in situations of postprandial hyperglycemia, while glucagon is responsible for reversing situations of hypoglycemia [6, 7].

2. Carbohydrate metabolism

The carbohydrates present in foods are primarily as polysaccharides that are digested by various digestive enzymes. Starch is the most common polysaccharide in foods and is metabolized to maltose by the enzyme alpha amylase present in saliva and secreted by the pancreas and this to glucose by the maltases in the microvilli of the duodenum. The lactose present in dairy products is metabolized by lactases in the intestinal villi to glucose and galactose. Sucrose is also metabolized in the intestinal microvilli in glucose and fructose.

The absorption of glucose and galactose is carried out by a secondary active cotransport of Na^+ to the interior of the enterocyte and from there to the portal flow by facilitated diffusion through the GLUT2 glucose transporter (**Figure 1**). Fructose, on the other hand, is only entered into the enterocyte by facilitated diffusion through GLUT5 type transporters located on the apical side, and then they are poured into the portal circulation by the same carrier proteins that are also found on the basal side of the enterocyte.

The duodenum has a very extensive contact surface, in order to take advantage of and absorb as much of these nutrients as possible. The excess, which passes to the jejunum, stimulates the release of the glucose-dependent insulinotropic peptide (GIP) from the K cells and the glucagon-like peptide type 1 (GLP-1) from the L cells. Both stimulate the postprandial release of insulin from the pancreas (**Figure 1**).

Absorbed glucose increases suddenly in the blood, reaching values above 90 mg/dL, and is transported by the GLUT2 carrier protein inside the pancreas where it undergoes glycolysis to generate pyruvate. This is used by the mitochondria for the production of ATP, which is released into the cytoplasm of the beta cells of the pancreas. This excess of ATP desensitizes the ATP-dependent K^+ channels that close and prevent the migration of K^+ ions to the extracellular fluid. With the intracellular increase of K^+, a depolarization begins; this stimulates the opening of voltage-gated calcium channels, which finally ends with the exocytosis of insulin (**Figure 1**), peptide C, and amylin stored in the vesicles into the bloodstream.

The average life of this circulating insulin is 3–5 minutes; its main action is to stimulate the uptake of glucose from the bloodstream, mainly by the liver and muscle cells. The receptor for insulin in these cells is a tyrosine kinase that, when insulin binds, dimerizes and initiates a signaling cascade that rapidly activates the phosphatidylinositol-3-kinase (PI3K) pathway that translocates GLUT4 carrier to the cell membrane, which allows the massive entry of glucose into the cell. Then the same pathway activates the enzyme glycogen synthetase that converts excess of glucose into glycogen, activates Acetyl CoA carboxylase that stimulates lipogenesis, and finally, in the longer term, activates the pathway of the mitogen-activated kinases (MAP kinases) responsible for the expression of the protein synthesis (**Figure 1**).

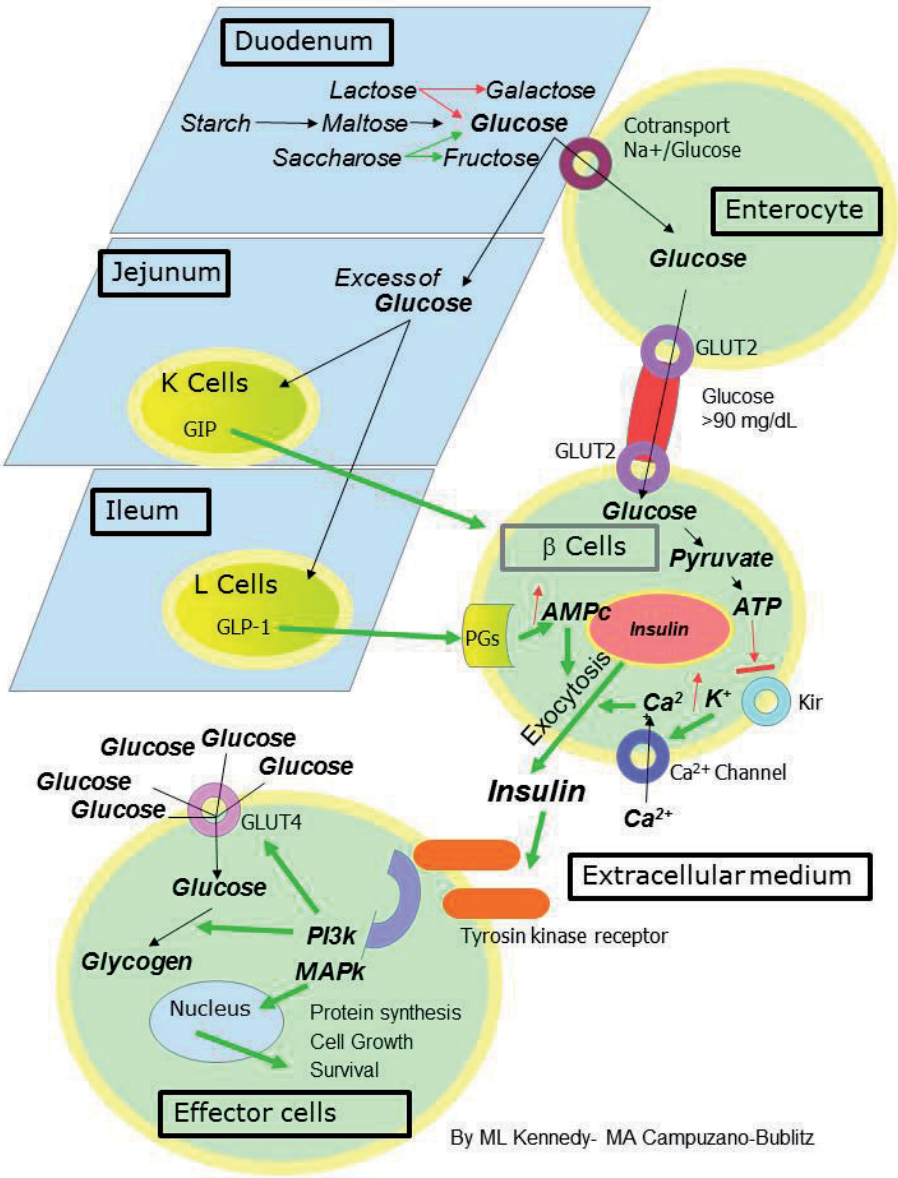
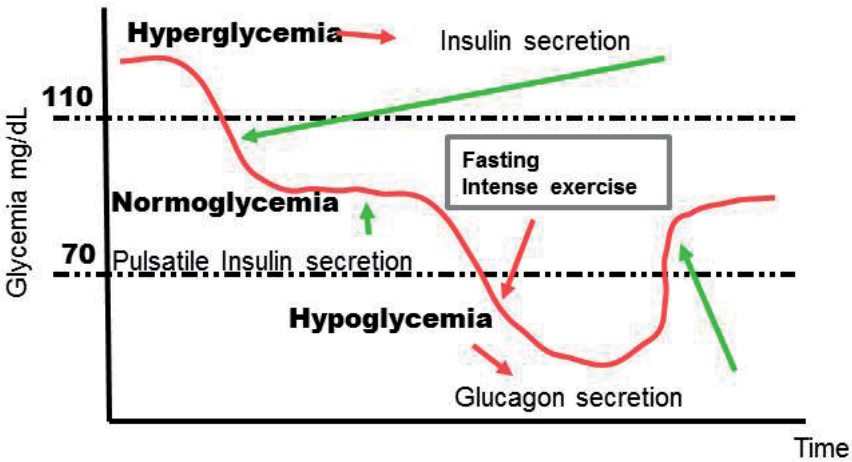


Figure 1.
Carbohydrate metabolism. Polysaccharides in food are digested, by several enzymes. The absorption is mainly in the duodenum. Glucose in the jejunum and ileum stimulates the release of GIP and GLP-1, and postprandial release of insulin is stimulated. Glucose in blood reaches the pancreas and undergoes glycolysis to generate pyruvate and then ATP; ATP closes K^+ channels, and a depolarization begins. Next, voltage-gated calcium channels are open and exocytosis of insulin occurs. Insulin binds to its tyrosine kinase receptor and initiates a signaling cascade that rapidly produces the massive entry of glucose into the cell.

C peptide is a small molecule that is released when proinsulin is metabolized to insulin; in spite of not knowing the specific physiological role of this molecule, in the clinical environment, it serves to correlate it with the quantity of insulin synthesized by beta cells, because for each molecule of insulin, there is a C peptide, and this remains in the bloodstream for a longer time. Amylin, a peptide hormone produced in the pancreas, and co-secreted with insulin, and in the brain, improves postprandial blood glucose levels by suppressing gastric emptying and glucagon secretion. Amylin also acts centrally as a satiation signal, reducing food intake and body weight.

In this way the glycemia values are usually maintained between 70 and 110 mg/dL; values below this range produce hypoglycemia that stimulates the release of the hormone glucagon from the alpha cells of the pancreas, which promotes anti-insulin effects in such a way to re-raise the glycemia values (**Figure 2**). To this is added a third pancreatic hormone, somatostatin, of paracrine regulation which collaborates to modulate the release of insulin and glucagon.



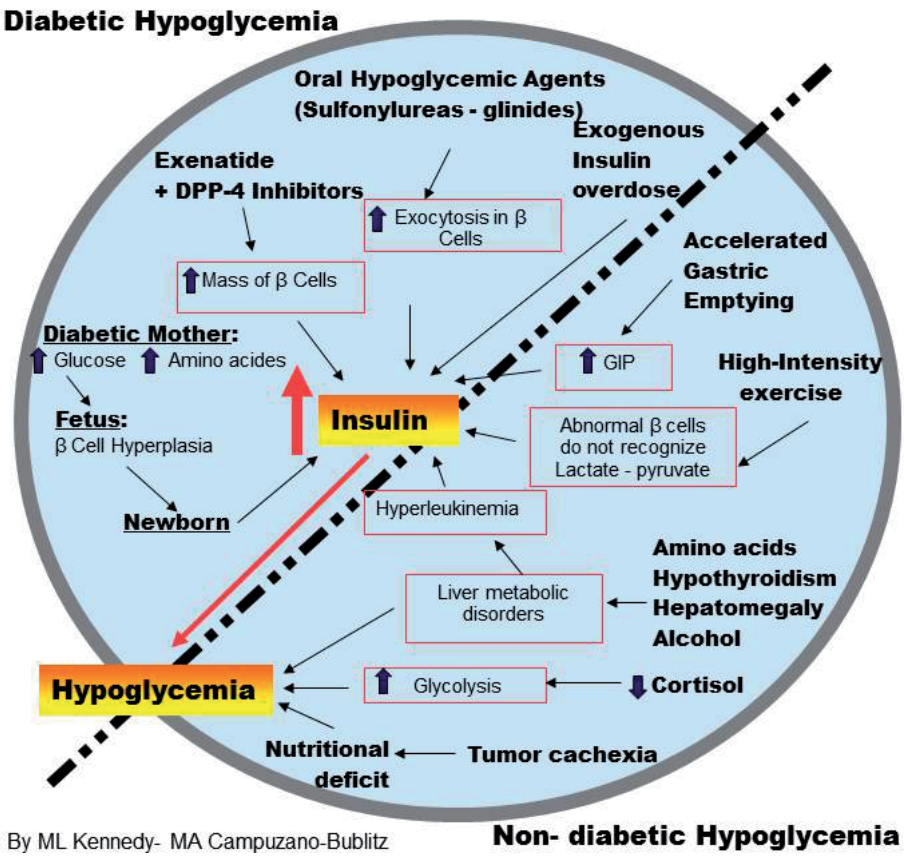


Figure 2.
Regulation of plasma glucose level by insulin and glucagon. Hypoglycemia situations related to diabetes and not related to diabetes.

After intense physical activity, the adrenaline released by the stimulus of exercise and the increase of lactate and pyruvate in blood blocks insulin secretion and stimulates glucagon to always make glucose available to the body and avoid reactive hypoglycemia [6, 8, 9].

3. Glucagon

Insulin secretion from the beta cells of the pancreas is a standard response that is directly related to glucose absorbed from food. Thus, if the glycemia increases significantly after an intake, this results in a large insulin secretion, while if the glycemia remains within the normal range, the stimulus decreases and produces a pulsatile insulin secretion that favors the glycemia to remain within the physiological range.

In the case that the glycemia falls below 60 mg/dL, the signal to secrete insulin weakens and eventually becomes blocked. In contrast, this allows the alpha cells of the pancreas to release considerable amounts of glucagon (**Figure 2**). This hormone travels through the portal vein to the liver, where it activates signaling pathways to initiate glycogenolysis, which will cause the formation of glucose in the liver so that it is released into the bloodstream to immediately increase glycemia. Additionally, glucagon increases the recruitment of amino acids to the liver for gluconeogenesis that reinforces the effect of glycogenolysis [10].

4. Nondiabetic hypoglycemia

Hypoglycemia is almost always related to a normal or increased amount of insulin as a direct response to glucose intake in food or other pathophysiological factors that induce an excessive increase in insulin secretion. A balanced intake of carbohydrates, fats, and proteins provides all the nutrients that the body needs for survival, but an inadequate diet, deficient in carbohydrates, leads to a reactive hypoglycemia.

The chronic and excessive intake of alcohol produces metabolic alterations in the liver that lead to decrease the synthesis and release of glucose from the liver to the blood and therefore a decrease in blood sugar (**Figure 2**).

In the case that the gastric emptying is accelerated (dumping syndrome), due for example, to a gastric resection, the digestion and absorption of carbohydrates are much faster than normal and also produce the early release of intestinal hormones, including the GIP, which leads to hyperinsulinemia and then the consequent hypoglycemia (**Figure 2**).

The alteration of various functions of the organism has as one of its consequences the reduction of glycemia to critical values, as occurs in the reduction of glucocorticoid secretion, such as cortisol, which causes an increase in glycolysis and reduced gluconeogenesis from amino acids. This in turn leads to a greater secretion of adrenaline that is contrasted in its effects to insulin. On the other hand, thyroid hormones regulate many cellular metabolic processes, including hepatic metabolism; therefore, in a situation of hypothyroidism, glycogenolysis and gluconeogenesis are drastically reduced (**Figure 2**).

An alteration in the hepatic metabolism of amino acids, either due to liver failure or due to specific enzymatic defects, such as that inducing high leucine level, has an effect on insulin secretion, which is increased producing hypoglycemia (**Figure 2**).

Hepatomegaly is usually caused by an increased hepatic storage of glycogen, known as glycogenosis, due to metabolic alterations produced by defective enzymes such as glucose-6-phosphatase, in Gierke's disease, or a debranching enzyme in Cori

Forbes disease, a phosphorylase in Hers disease, or a phosphoryl kinase in Huijing's disease. This increase in hepatic glycogen deposition produces a marked hypoglycemia throughout the system (**Figure 2**).

Aberrations in the expression of certain genes in beta cells make them unable to relate the increase in lactate and pyruvate with the state of physical activity and therefore induce an increase in insulin secretion that causes significant hypoglycemia in the organism (**Figure 2**).

The development of tumors, of any type, entails an increase in the need for energetic molecules so that cell proliferation is possible. This added to the fact that the formation of tumors produces long-term hormonal disorders that keep oncological patients with hypoglycemia for a long time. This effect is compensated by lipolysis of the adipocytes in order to make more energetic molecules available, and finally the patient develops tumor cachexia [11, 12] (**Figure 2**).

5. Hypoglycemia related to diabetes

One of the most common causes of hypoglycemia in diabetics occurs as a result of the excess administration of insulin or oral hypoglycemic drugs [13, 14]. Patients suffering from diabetes mellitus type 1 and whose treatment is based on the exogenous administration of insulin must previously corroborate the level of glycemia and then adjust the amount of hormone to be administered, considering that 100% of the dose, approximately half, is used to immediately regulate the metabolism of carbohydrates and the other half is to cover the metabolism at night or fasting hours. Therefore, the amount of insulin administered is higher than required, and if the necessary precautions are not taken, there is a high probability that the dose administered will produce a strong hypoglycemia, especially during sleep hours, known as the Somogyi effect. The amount of insulin units to administer considers the actual value of the glycemia, which forces the patient to measure it, compare and extract the difference with the theoretical optimum value of 120 mg/dL of fasting blood glucose, and divide it by the factor 50, since one unit of insulin reduces blood glucose by approximately 50 mg/dL (**Figure 2**).

Even so, the correct amount of insulin to be administered must also be defined by other factors, such as the total amount of carbohydrates ingested with food, the type of insulin to be administered, and the recommendations of the treating medical professional.

Oral hypoglycemic agents, used in the treatment of type 2 diabetes mellitus, can also lead to a strong insulin secretion. The large family of sulfonylureas (chlorpropamide, glibenclamide, gliclazide, glisentide, glipizide, gliquidone, and glimepiride) and the secretagogue glinides (repaglinide and nateglinide) are characterized by the ability to induce hypoglycemia and cause weight gain, due to the decrease in the lipolysis in the patients who use it for their treatment (**Figure 2**).

Another interaction with a high probability of producing hypoglycemia is the concomitant treatment with incretin analogues (exenatide) and inhibitors of dipeptidyl peptidases (vildagliptin) because it significantly increases the pancreatic β cell mass, which leads to greater insulin secretion and even with high risks of producing pancreatitis (**Figure 2**).

Diabetic women during pregnancy have poor control of carbohydrate metabolism and thus coexist with high blood levels of glucose and amino acids; this long-term hyperglycemia is transferred to the fetus and forces hyperplasia in fetal pancreatic beta-cell tissue, which finally predisposes the newborn to a greater secretion of insulin and the consequent hypoglycemia [15–17] (**Figure 2**).

6. Clinical manifestations

The decrease in blood sugar below 60 mg/dL is known as hypoglycemia. In a first phase, this leads to a stimulation of the parasympathetic autonomic nervous system that causes a sensation of hunger and leads the patient to bulimia. In the second phase, the sympathetic autonomic nervous system is stimulated, producing the secretion of important quantities of catecholamines that activate their receptors in important target organs such as the heart, which produces an acceleration of the heartbeat, in sweat glands increases the production of sweat, and in the somatic nervous system causes tremors. It is frequent double vision, difficulty concentrating, loss of ease of speech, and confusion states. A hypoglycemia below 20 mg/dL induces a coma (**Figure 3**).

The most serious effect is a marked cognitive dysfunction, since the supplies of nutrients, glucose, and ketones to the nervous system are markedly diminished; produce loss of consciousness, brain spasms, and epileptic seizures in children; and can potentially lead to irreversible neuronal damage [18, 19].

Glycemia mg/dL	Clinical consequences		Treatment	Precautions
	Mechanism	Patient		
↓ 70	1. Parasympathetic Activation. Activation of the appetite center	Conscious and with bulimia	Ingestion of carbohydrate-rich foods	Follow up of the patient to avoid recidivism
	2. Sympathetic activation. Catecholamines produce tachycardia, sweating, tremor	Conscious, concentration problems, double vision, difficulty in speech, confusion	Administer pharmaceutical preparations containing glucose through a rapid absorption route	Avoid hyperglycemia crisis due to excess glucose, especially in diabetic patients
↓ 20	Energy supply to the S.N.C. is severely compromised, triggering severe cognitive dysfunction	Unconscious with cerebral spasms, epilepsy in children and potential irreversible neuronal damage.	Administration of intravenous glucagon or glucose preparations for rapid recovery of the patient	Verify the recovery of the patient, especially if there is no neuronal damage.

By ML Kennedy- MA Campuzano-Bublitz

Figure 3.
A summary of glycemia levels and clinical consequences.

7. Treatment of hypoglycemia

The treatment will depend on the degree of hypoglycemia that the patient develops. That, which does not pass the first phase of the clinical manifestation, requires rapid replacement of glucose from food. The CNS itself is the one that predisposes to this action by triggering bulimia in the patient. Most of the foods available to patients contain abundant amounts of carbohydrates that help to remedy hypoglycemia (**Figure 3**).

In cases where hypoglycemia is more pronounced, it is necessary to administer pharmaceutical preparations containing glucose, but this treatment should be monitored to avoid the opposite effect, i.e., hyperglycemia, especially in diabetic patients who triggered hypoglycemia due to excess insulin.

In patients with severe hypoglycemia crisis, which affects the conscience, it is necessary to act urgently administering parenteral glucagon preparations, or glucose will be administered directly, and the rapid recovery of the patient will be monitored [14, 15, 19–21] (**Figure 3**).

8. Conclusion

Hypoglycemia is generated by mechanisms directly related to an increase in insulin secretion or by metabolic disorders that require increased glucose consumption or by a deficient metabolic production of glucose by the body.

Hyperinsulinemia can be produced by various mechanisms, including high glucose intake in foods, an increased dose of oral hypoglycemic agents, as well as exogenous insulin administration without control, liver metabolic conditions that lead to an increase in the production of amino acids by this organ, tumors in permanent growth, and an abnormal increase in glucose and amino acids in the case of uncontrolled diabetic pregnant women that end up producing insulin hypersecretion in the newborn.

Work that requires high glucose consumption, more than what the body can supply, ends up in situations of hypoglycemia, as well as when there is a decrease in hormone antagonists to insulin, such as cortisol or glucagon. The state of hypoglycemia is generated by metabolic deficit in pathophysiological situations such as defects in enzymatic systems, alcoholic hepatitis, and insufficient diet.

The most characteristic symptoms include bulimia, fits of sweating, and tremors due to a strong activation of the sympathetic system. Primarily, the CNS is strongly affected by the lack of glucose, which is even more complicated because also hypoglycemia leads to a situation of decreased lipolysis and ketone bodies that finally seriously compromise the supply of energy to the central nervous system, producing loss of consciousness, spasms, and even irreversible brain damage.

The treatment of less severe hypoglycemic patients is preferably carried out with the rapid administration of carbohydrate-rich foods. For more serious cases, the use of pharmaceutical products that supply carbohydrates is resorted to, but the glycemia must be monitored to avoid hyperglycemia. Those patients who are much compromised, with loss of consciousness, should receive parenteral glucagon or glucose in an urgent way to recover them.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this chapter.

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Chapter 6

Symptoms of Hypoglycaemia

Panagiota Loumpardia and Mohammed S.B. Huda

Abstract

Hypoglycaemia is common in clinical practice for people with diabetes. However, the symptoms can vary between individuals and at different stages of their condition. Moreover, several factors influence symptoms experienced by people with diabetes, and many are amenable to intervention. Symptoms are commonly neuroglycopenic or neurogenic in aetiology, and these lead to different clusters of symptoms. Certain patient groups such as the elderly and pregnant women are particularly susceptible to hypoglycaemia. In this chapter, we describe the physiology and pathophysiology behind the symptoms of hypoglycaemia, with reference to current knowledge from neuroimaging studies, and outline potential interventions to modify or restore hypoglycaemia symptoms.

Keywords: hypoglycaemia, symptoms, treatment, hypoglycaemic unawareness

1. Introduction

Hypoglycaemia is common in clinical practice with up to 45% of people with type 1 diabetes mellitus (T1DM) experiencing mild to moderate hypoglycaemia and 6% experiencing severe hypoglycaemia [1]. The average individual with type 1 diabetes experiences two symptomatic hypoglycaemic episodes a week, and the prevalence of severe hypoglycaemia can be up to 30–40% [2].

The signs and symptoms of hypoglycaemia however can be variable and can change over time. In this chapter, we discuss the presentations of hypoglycaemia and the underlying pathophysiology.

2. Definition of hypoglycaemia

This has been a controversial area for many years, and only recently, a consensus has been developed. Normal blood glucose levels can range between 3.5 mmol/l (63 mg/dl) and 7.0 mmol/l (126 mg/dl), but individuals can develop lower values physiologically during fasting or starvation. Blood glucose levels less than 3.0 mmol/l (54 mg/dl) are associated with poorer clinical outcomes.

The International Study Group suggests that a level of <3.0 mmol/l (54 mg/dl) be defined as denoting serious clinically important hypoglycaemia, whether that level is associated with symptoms or not, and that incidences of hypoglycaemia within that range be reported during clinical trials and in clinical practice [3].

The statement outlines proposed glucose levels to define severe hypoglycaemia as:

- Level 1: a glucose alert value of 3.9 mmol/l (70 mg/dl) or less. This need not be reported routinely in clinical studies, although this would depend upon the purpose of the study.

- Level 2: a glucose level of <3.0 mmol/l (<54 mg/dl) is sufficiently low to indicate serious, clinically important hypoglycaemia.

- Level 3: severe hypoglycaemia, as defined by the American Diabetes Association, denotes severe cognitive impairment requiring external assistance for recovery.

2.1 Symptoms

The most frequently reported symptoms during hypoglycaemia in diabetes are sweating, trembling, inability to concentrate, weakness, hunger and blurred vision [4].

Generally, symptoms are divided into two groups:

a. Neuroglycopenic symptoms caused by brain glucose deprivation:

   - Cognitive impairment (altered perception, poor concentration, slow/hesitant speech, slow decision-making).

   - Behavioural changes (irritation, frustration, refusal to help).

   - Psychomotor abnormalities (incoordination, unsteadiness, weakness).

   - Seizure/coma.

   - Permanent neurological damage if prolonged severe hypoglycaemia.

b. Neurogenic symptoms caused by the sympathoadrenal response:

   - Adrenergic (palpitations, tremulousness, anxiety, arousal, skin pallor/flushing or blotchy rashes, tingling around the mouth/lips).

   - Cholinergic (sweating, hunger, paresthesia) [5].

To try and understand why the above symptoms are present, or not present, we describe physiological and pathophysiological response to hypoglycaemia in people with diabetes.

Glucose is the fuel for the most of the body functions including cerebral function. The brain is not able to synthesize glucose and therefore is critically dependent on a continuous glucose supply from the circulation (20% of circulated glucose).

Glucose is transported into the brain across the blood–brain barrier by the glucose transporter protein GLUT-1, and antecedent hypoglycaemia causes upregulation of this transporter [6]. If however the glucose level falls quickly to critically low levels, then despite the upregulation of the transporter, the supply is not adequate, and it may lead to impairment of brain function.

2.2 Physiological response to hypoglycaemia

Normal body physiology (without diabetes) has a sequence of responses to handle hypoglycaemia.

The first response is to decrease insulin production from the β-cells and increase the glucose counter-regulatory (plasma glucose raising) hormones: glucagon and adrenaline. Glucagon and adrenaline are the principle hormones

to protect against acute hypoglycaemia by stimulating gluconeogenesis. Other hormones, cortisol and growth hormone play a less important role during hypoglycaemia. However deficiencies of these hormones can lead directly or exacerbate hypoglycaemia (i.e. Addison's disease, hypopituitarism). As plasma glucose concentration progressively falls, the increasing sympathoadrenal (sympathetic and adrenomedullary) response leads to neurogenic symptoms. These symptoms cause awareness of hypoglycaemia that prompts behavioural defense of ingestion of carbohydrates (hunger) [7, 8].

2.3 Pathophysiological response to hypoglycaemia

However, in people with type 1 or type 2 diabetes mellitus (T2DM), the above defense mechanisms may be compromised due to:

Relative or absolute therapeutic hyperinsulinemia may lead to hypoglycaemia without intervention. The physiological defense mechanism of downregulation of insulin secretion may be impaired due to β-cell failure.

β-cell failure is also associated with the loss of an appropriate increase in circulating glucagon [7–9]. In addition, the increase in circulating adrenalin is attenuated [7, 10]. Absent insulin/glucagon responses and attenuated epinephrine responses contribute to the clinical syndrome of defective glucose counter-regulation [7, 8, 10]. As a consequence of losing the physiological control of glucose homeostasis, the body will develop neuroglycopenic and neurogenic symptoms as already listed above. The glucose level at which cognitive function declines is subject to substantial variation (from levels between 3 and 4 mmol/l (54–72 mg/dl), whereas others continue to seemingly function with levels below 2.5 mmol/l (45 mg/dl). Almost all domains of cognitive function are potentially at risk during acute hypoglycaemia, with complex tasks being affected earlier than simple tasks [11].

2.4 Hypoglycaemic unawareness

The attenuated sympathoadrenal response is responsible for the reduced neurogenic symptom responses, well known contributing to the syndrome of hypoglycaemic unawareness [7, 8]. The patient has less time or no time between the onset of symptoms and the development of severe neuroglycopenia (impaired awareness/unawareness). Hypoglycaemic unawareness prevents patients from taking corrective action by eating which can potentially lead to seizure/coma and permanent neurological damage, if prolonged and severe. Thus, for many T1DM patients, the immediate fear of hypoglycaemia exceeds the fear of long-term diabetes complications [12, 13]. **Figure 1** is a diagrammatic summary of the physiological response to hypoglycaemia as well as the alterations in diabetes and hypoglycaemic unawareness.

In addition, certain drugs and alcohol may impair a patient's perception of these symptoms. Beta-blockers may diminish the effect of adrenaline, potentially leading to reduced adrenergic warning symptoms (i.e. tremor, palpitations). Beta-blockers are not contraindicated in diabetes, but they should be considered when dealing with recurrent hypoglycaemia or hypoglycaemic unawareness. Other factors that can modify physical symptoms of hypoglycaemia are listed in **Table 1**. Nocturnal hypoglycaemia that can affect a significant percentage of patients and can be unrecognized is a contributing factor to hypoglycaemic unawareness.

The syndrome of defective glucose counter-regulation and hypoglycaemic unawareness usually develops early in T1DM and later in T2DM, due to differing rates of progressive beta-cell failure and also due to insulin or sulphonylurea medications often being started later.

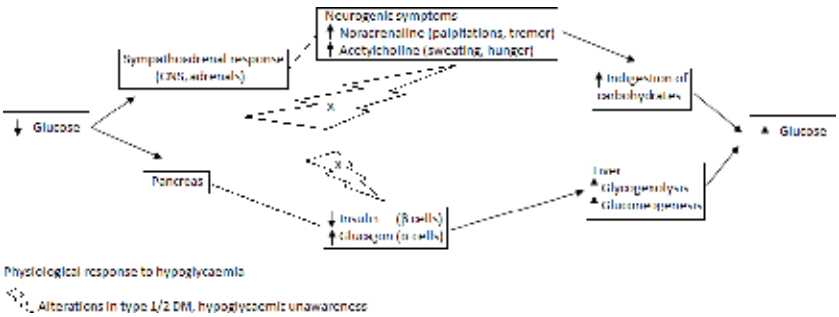

Figure 1.
A schematic diagram describing the physiological response to hypoglycaemia.

1. Posture (the intensity of autonomic symptoms is greater in erect position compared to supine position)
2. Medications—toxins
   - Impairing ability to perceive and interpret symptoms (i.e. hypnotic medications, alcohol, beta-blockers)
   - Magnitude of symptomatic response (i.e. caffeine)

Table 1.
Factors that alter hypoglycaemic symptoms.

2.5 Hypoglycaemia-associated autonomic failure (HAAF)

HAAF is a dynamic functional disorder that includes several episodes of recent antecedent hypoglycaemia, combined with previous exercise or sleep, and causes defective glucose counter-regulation and hypoglycaemic unawareness. Late post-exercise hypoglycaemia occurs 6–15 h after strenuous exercise and is often nocturnal [14, 15]. Sleep-related HAAF is the result of further attenuation of the sympathoadrenal response to hypoglycaemia during sleep [16–18]. Subsequently, a vicious cycle of recurrent iatrogenic hypoglycaemia may occur. HAAF is distinct from the autonomic neuropathy. However, HAAF is more prominent in people with diabetic autonomic neuropathy [19, 20].

2.6 Symptoms in different groups

2.6.1 Children

Symptoms in children differ from those in adults. Children have a more vigorous catecholamine response to hypoglycaemia than adults. Behavioural changes such as irritability, stubbornness, quietness and tantrums may be the primary features of low blood glucose in children [21].

2.6.2 Elderly

This age group may have a more limited perception of autonomic symptoms of hypoglycaemia, which they report as lower intensity than young people. Therefore, older people are at greater risk of developing neuroglycopenia, as the warning symptoms do not always precede the development of cognitive dysfunction [22]. This may reduce the opportunity to take appropriate treatment before developing disabling confusion and neuroglycopenia. It is worth mentioning that the frequency of hypoglycaemia in this group is probably underestimated. This is partly because of inadequate

education in elderly or their relatives, and also frequently hypoglycaemic events are misinterpreted as TIAs, vertebrobasilar insufficiency and vasovagal attacks [23].

2.6.3 Pregnancy

It has been suggested that the intensity of the warning symptoms may be blunted during pregnancy [24, 25]. Of course this is very difficult to be study due to the ethical constraints surrounding the deliberate induction of experimental hypoglycaemia in early pregnancy. Considering that during pregnancy, women aim for stricter glycemic control, it is very difficult to distinguish whether the symptomatology is a true alteration in the symptomatic response or the result of tight glycemic control and increased antecedent hypoglycaemia.

2.7 Functional and metabolic studies during hypoglycaemia

Recurrent hypoglycaemia which impairs awareness and the subsequent brain adaption is of scientific interest but incompletely understood. Several studies have been performed in order to understand brain network function during declining glucose levels.

Studies have shown significant EEG changes in euglycemia and hypoglycaemia during day and night in children with T1DM (20). Various neuroimaging techniques have been employed to study brain glucose metabolism including positron emission tomography (PET), magnetic resonance spectroscopy (MRS), functional magnetic resonance imaging (fMRI) and arterial spin labelling (ASL) [26].

Studies that have employed the above techniques have shown that cerebral glucose metabolism appears to be largely maintained during moderate hypoglycaemia. However, recurrent hypoglycaemia may initiate cerebral adaptions at many different levels. There is interference with the accurate detection of hypoglycaemia, probably occurring at the level of the ventromedial hypothalamus. Brain areas that control appetite and induce fear and anxiety may not become activated during hypoglycaemia. The underlying mechanisms, as to whether altered glucose uptake or neuronal activation or both in the hypothalamic area is responsible, remain unclear. Interestingly, patients with T1DM (particularly with impaired awareness) seem to be better able in maintaining brain glucose metabolism during hypoglycaemia than healthy controls [26].

2.8 Reversing hypoglycaemic unawareness

Avoidance of hypoglycaemic events enables people with unawareness to regain their symptoms when the glucose level is low. Often, preventing hypoglycaemia for 2 weeks results in increased symptoms of a low blood glucose and a return to nearly normal symptoms after 3 months. There are different strategies that can be used in clinical practice to enable avoidance of hypoglycaemia. Some are listed below:

- *Set blood sugar targets higher*: this can lead to decreased frequency of hypoglycaemia.

- *Education*: educating patients in insulin adjustment is important. For example, a UK-based structured education program, Dose Adjustment for Normal eating (DAFNE), restores awareness in 43% of people with impaired awareness of hypoglycaemia [27]. Similarly, the HypoCOMPaSS trial showed that education around the prompt treatment of hypoglycaemia was as important as technologies such as insulin pump therapy and glucose sensors [28].

- *Insulin pumps and continuous glucose sensors*: insulin pump therapy, particularly sensor-augmented insulin pumps, has a role in reducing severe hypoglycaemia and restoring unawareness [29].

- *Islet cell transplantation/pancreatic transplant*: studies suggest immediate improvement of hypoglycaemic awareness in cases of functioning islet transplantation [30]. Reversal of hypoglycaemia-associated autonomic failure is responsible for the long-term maintenance of hypoglycaemic awareness that returns after islet cell/pancreas transplantation [31].

3. Conclusions

Hypoglycaemia symptoms are variable and usually arise from impairment in counter-regulatory hormone or sympathoadrenal responses. Certain patient groups such as children, the elderly and pregnant women may be particularly vulnerable. A degree of hypoglycaemic unawareness is often a consequence of recurrent hypoglycaemia and can be challenging to manage. Various strategies including education, technology and islet/pancreas transplants may all be useful.

Conflicts of interest

None declared.

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Chapter 7

Hypoglycemia: Essential Clinical Guidelines

Thenmozhi Paluchamy

Abstract

Hypoglycemia is the acute complication of diabetes mellitus and the commonest diabetic emergency and is associated with considerable morbidity and mortality. It can be caused by too much insulin intake or oral hypoglycemic agents, too little food, or excessive physical activity. The level of glucose that produces symptoms of hypoglycemia varies from person to person and varies for the same person under different circumstances. It characterized by sweating, tremor, tachycardia, palpitation, nervousness, hunger, confusion, slurred speech, emotional changes, double vision, drowsiness, sleeplessness, and often self-diagnosed which may leads to serious symptoms of seizure, cognitive impairment, coma and death. The immediate treatment of hypoglycemia should be known by all the diabetic patients, so that need for hospitalization could be avoided. Hypoglycemia and its severity can be prevented by early recognition of hypoglycemia risk factors, self-monitoring of blood glucose, selection of appropriate treatment regimens, appropriate educational programs for healthcare professionals. The major challenges of the treatment of hypoglycemia are good glycemic control, minimize the risk of hypoglycemia and thereby minimize long-term complications. Hence there is an urgent need to understand the clinical spectrum and burden of hypoglycemia so that adequate control measures can be implemented against this life-threatening complication.

Keywords: blood glucose, diabetes mellitus, glucagon, glycemic index, hypoglycemia, insulin

1. Introduction

The blood sugar level, blood sugar concentration, or blood glucose level is the amount of blood sugar level in the blood. Glucose is required for cellular respiration and is the preferred fuel for all body cells. Plasma glucose concentration is the balance between the rate of glucose entering the circulation and the rate of removal of glucose from the circulation. Circulating glucose comes from intestinal absorption from the ingestion of carbohydrate during the fed state and by the process of glycogenolysis, and gluconeogenesis in the fasting state. Glycogenolysis is the biochemical breakdown of glycogen into glucose which takes place in the cells of the muscle and liver in response to hormonal and neural signals. Gluconeogenesis is the metabolic process of generation of glucose from non-carbohydrate substances such as protein and fat which takes place in the liver and kidney in response to diabetogenic hormones. There are hormones involved in glucose regulation are called glucoregulatory hormones which include insulin, glucagon, amylin, glucogan-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), epinephrine,

cortisol, and growth hormone. Among, insulin and amylin are secreted from the β-cells of islets of Langerhans, glucagon from the α-cells of islets of Langerhans of the pancreas, GLP-1 from the small intestine and colon, and GIP from upper small intestine. If these glucoregulatory or counter-regulatory hormones fail to balance the blood sugar level causes hypoglycemia or hyperglycemia.

Hypoglycemia, also called low blood glucose or low blood sugar, occurs when the level of glucose in blood drops below normal. The term literally means "under-sweet blood". It may also be referred to as an insulin reaction, or insulin shock. This condition typically arises from abnormalities in the mechanisms involved in glucose homeostasis. Hypoglycemia is the commonest diabetic emergency and is associated with considerable morbidity and mortality. The American Diabetes Association defines the hypoglycemia as any abnormally low plasma glucose concentration that exposes the subject to potential harm [1]. Hypoglycemia is common in insulin dependent diabetic patients and may also occur in patients with non-insulin-dependent diabetes mellitus. It can be caused by too much insulin intake or oral hypoglycemic agents or too little food or excessive physical activity [2]. The other causes or risk factors of hypoglycemia are dosage, combination of anti-diabetic drugs, timing of consuming the drug and anti-diabetic drug with simultaneous use of other interacting drugs. The symptoms of hypoglycemia depend on the level of blood glucose and vary from one person to another person and also vary within the same person under different circumstances [3]. It may range from a very mild with minimal or no symptoms (60–70 mg/dl), to severe hypoglycemia, and neurological impairment (<40 mg/dl) [4].

2. Prevalence of hypoglycemia in diabetes

Hypoglycemia is one of the most feared complications of diabetes treatment [5]. Individuals who take insulin, which includes all people with T1DM and some people with type 2 diabetes, are prone to hypoglycemia [6]. Hypoglycemia commonly occurs in clinical practice as approximately 90% of all patients who receive insulin have experienced hypoglycemic episodes [7]. Furthermore, surveys investigating the prevalence of hypoglycemia have provided some alarming results. The Diabetes Control and Complication Trial (DCCT) reported a threefold increase in severe hypoglycemia and coma in intensively treated T1DM patients versus conventionally treated patients [8]. A meta-analysis study reported that the prevalence of hypoglycemia was 45% for mild/moderate and 6% for severe. Incidence of hypoglycemic episodes per person-year for mild/moderate and for severe was 19 and 0.80, respectively. Hypoglycemia was prevalent among patients on insulin; among, the prevalence of mild-moderate and severe hypoglycemia episodes was 50 and 21%, respectively. Similarly, among patients on the treatment of sulfonylurea, the prevalence of mild-moderate and severe hypoglycemia was 30 and 5%. It was also found 5% of prevalence among those who did not include sulfonylureas in the treatment regime [9].

A population-based study conducted in the UK to determine the frequency and predictors of hypoglycemia in type one diabetic patients. The study findings concluded that type 1 diabetes mellitus patients who are on intensive treatment may experience up to 10 episodes of symptomatic hypoglycemia per week and severe temporarily disabling hypoglycemia at least once a year [10]. It is estimated that 2–4% of deaths occur in people with type 1 diabetes due to hypoglycemia [11]. Hypoglycemia is also equally common in type 2 diabetes, with prevalence rates of 70–80% [12]. Donnelly et al. who conducted a survey with 267 individuals with

type 1 diabetes and insulin-treated type 2 diabetes to record hypoglycemic events over a 4-week period and 155 individuals reported 572 incidents of hypoglycemia. Of these, the rate of hypoglycemia events in type 1 diabetic was 43 per patient per year whereas in type 2 diabetes was 16 events per patient per year. The predictor of hypoglycemia for individuals with type 1 diabetes and insulin-treated type 2 diabetes was a history of previous hypoglycemia and duration of insulin treatment [10]. Similarly other study findings also concluded that hypoglycemia occurs more often than previously reported [12] in insulin-treated type 2 diabetes and with sufficient frequency to cause significant morbidity.

3. Risk factors for hypoglycemia

Several factors influence an individual at risk (**Table 1**) for a hypoglycemic episode. These include a mismatch in the timing, amount, or type of insulin, skipping meals, eating small meal, irregular dietary pattern and lack of physical activity. Additional factors such as alcohol consumption, obesity, elderly people, liver disorders, renal disease, adrenal insufficiency (glucocorticoid or catecholamine deficiencies) and pituitary insufficiency and leukemia which increase the risk for hypoglycemia. Other factors at risk are those who have ingested medication salicylates and those who have surgery with general anesthesia, which places them in an altered state of consciousness and hyper-metabolic state [13].

Another potential risk for hypoglycemia is the use of β-blocker and ACE inhibitor medication in cardiac and hypertensive patients which mask the symptoms of hypoglycemia. β-Blockers inhibit the secretion of insulin and glycogenolysis due to diminishing of adrenergic counter regulation and also conceal the symptoms of catecholamine-mediated neurogenic hypoglycemia such as tremor, palpitation, hunger, irritability and confusion. However sweating remains unmasked and may be the only sign of patients treated with β-blockers [14].

Medical-related factors	**Lifestyle-related factors**
• Strict glycemic control	• Increased exercise (relative to usual)
• Previous history of severe hypoglycemia	• Irregular lifestyle
• Long duration of type 1 diabetes	• Alcohol
• Duration of insulin therapy in type 2 diabetes	• Increasing age
• Lipohypertrophy at injection sites	• Early pregnancy
• Impaired awareness of hypoglycemia	• Breast feeding
• Severe hepatic dysfunction	• No or inadequate blood glucose monitoring
• Impaired renal function (including those patients requiring renal replacement therapy)	**Reduced carbohydrate intake/absorption**
• Sepsis	• Food malabsorption, e.g., gastroenteritis, coeliac disease
• Inadequate treatment of previous hypoglycemia	• Bariatric surgery involving bowel resection
• Terminal illness	**Other factors:**
• Cognitive dysfunction/dementia	• Hypoglycemia unawareness
	• Number of years since diabetes diagnosis
	• Time since insulin initiated

Table 1.
Risk factors of hypoglycemia.

4. Causes of hypoglycemia

Hypoglycemia is commonly occur in people with both type 1 and type 2 diabetes taking insulin or certain oral hypoglycemic agents. The common causes of hypoglycemia are:

4.1 Insulin and oral hypoglycemic agents

Diabetes medications such as insulin and Sulfonylureas are the most common causes of hypoglycemia in diabetic subjects [15]. Of these, Insulin is a definite cause of low blood glucose. One reason why newer insulin are preferred over NPH and regular insulin is that they are less likely to cause blood glucose lows, particularly overnight. Insulin pumps may also reduce the risk for low blood glucose. Accidentally injecting the wrong insulin type, too much insulin, or injecting directly into the muscle instead of subcutaneous can cause low blood glucose. The long-acting sulfonylureas such as glibenclamide and chlorpropamide are associated with more severe hypoglycemia than the shorter-acting drugs [16]. Metformin was the most frequent used oral hypoglycemic agents (66.4%) followed by sulfonylurea and the most prevalent combination therapy was metformin/glibenclamide regimen (28.5%). The majority of patients treated with metformin at the time when they were diagnosed with diabetes (45.3%). Hypoglycemic episodes were most commonly reported adverse events with insulin and gastric upset with oral hypoglycemic agents. 60.3% of the patients did not follow regular blood glucose checkup [17]. Several reports reveal that various pharmacological agents like metformin, rosiglitazone, etc., which have wide ranging side effects, including weight gain, hypoglycemia and risk of coronary heart disease [18]. Occasionally episodes of hypoglycemia may occur with metformin, as the most commonly used anti-diabetic drug, due to an imbalance between food intake and dose of metformin [19].

4.2 Food pattern

Eating foods with less carbohydrate than usual without reducing the amount of insulin taken. Timing of insulin based on whether consumption of carbohydrates is from liquids or solids which can affect blood glucose levels. Liquids are absorbed much faster than solids, so timing the insulin dose to the absorption of glucose from foods. The composition of the meal contains the amount of fat, protein, and fiber which can also affect the absorption of carbohydrates.

4.3 Dietary habit

If meal is skip or delay, blood glucose could drop too low. Hypoglycemia also can occur when asleep and have not eaten for several hours.

4.4 Drinking alcohol

Alcohol consumption increase the insulin secretion and makes the liver not to release the glucose effectively into the blood circulation especially if have not eaten enough food within around 6 h and also makes more difficulty to generate new glucose by liver. Hypoglycemia occur overnight if fall asleep after consuming alcohol without eating food among people with diabetes.

4.5 Physical activity

Exercise has plays a vital role and has many potential health benefits. However the exercise can lower blood glucose by utilizing glucose for energy. Nearly half of the individual with diabetes mellitus who exercised an hour during the day may experience a low blood glucose reaction overnight. The factors influencing exercise induce hypoglycemia are the intensity, timing of exercise and duration. Hypoglycemia can occur during, 1–2 h after, or up to 17 h after exercise. Endogenous insulin secretion is reduced up to 40–60% while doing moderate-intensity exercise among non-diabetic individuals. Hence it is mandate that decrease insulin dose or increase glucose intake is recommended before, during or after exercise depending on the intensity of exercise to prevent exercise associated hypoglycemia.

Additionally, recent studies have observed the cruel cycle of counter-regulatory failure between exercise and hypoglycemia. Thus, subsequent two episodes of prolonged, moderate-intensity exercise can inhibit autonomic nervous system and neuroendocrine responses by 50%. Similarly, 40–50% of counter-regulatory responses reduced during two episodes of antecedent hypoglycemia due to subsequent exercise [20]. Hence, there is a greater risk of hypoglycemia during exercise among individuals who have had a previous episode of hypoglycemia. This may be prevented by adjusting pre-exercise insulin dose, and consuming appropriate amounts of glucose.

4.6 Potential causes of in-patient hypoglycemia

Common causes of inpatient hypoglycemia are listed in **Table 2**. One of the most serious and common causes of inpatient hypoglycemia are insulin prescription errors including:

- Misreading poorly written prescriptions
- Confusing the insulin name with the dose

Treatment-related causes	Glucose intake-related causes
• Inappropriate use of short acting insulin • Incorrect prescription and administration insulin or oral hypoglycemic agent • Mismatch between insulin/oral hypoglycemic therapy and meal or enteral feed • Acute withdrawal of long term steroid therapy • Recovery from stress of critical illness • Polypharmacy • Mobilization after illness • Amputation of limb • Intravenous insulin infusion with or without glucose infusion • Failure to monitor blood glucose adequately especially on Intravenous insulin infusion	• Reduced carbohydrate intake than normal • Anorexia • Nausea and/or vomiting • Nothing by mouth orders • Delay in serving food tray • Poor coordination in meal and medication timing • Skipping of meal

Table 2.
Etiological factors of hypoglycemia.

- Confusing the insulin strength with the dose
- Transcription errors
- Inappropriately withdrawing insulin using a standard insulin syringe
- Confusion between the prescription of a glucose and insulin infusion for hyperkalemia and glucose and
- insulin infusion to blood glucose control

5. Physiology of glucose counter-regulation

The most metabolically active organ is brain and it is the first organ affected by lower blood glucose level. The brain requires continuous supply of oxygen and glucose to meet the needs of energy requirement as it does not store excess energy and derives almost all of its energy from aerobic oxidation of glucose. Hence brain cells are vulnerable to glucose deprivation and also cannot survive more than 5–6 min without glucose. The sequence of counter-regulatory response will play significant role when the blood glucose levels fall below 70 mg/dl to protect the brain from further deterioration of effects of hypoglycemia.

Decline in Blood glucose levels below the physiological range may trigger hierarchically organized sequence of responses in the non-diabetic individual [21, 22]. It includes release of neuroendocrine hormones or counter-regulatory or anti-insulin hormones, stimulation of the autonomic nervous system (ANS), and manifestation of neurogenic and neuroglycopenic symptoms. Pancreatic beta cells suppressed the insulin secretion when blood glucose levels declines within the physiological range results in reduction of peripheral glucose uptake and increase in hepatic glucose production to prevent true hypoglycemia. In further, declining intra-islet insulin plays an important role for the glucagon response to hypoglycemia by increase the release of glucagon by pancreatic alpha cells [23–25] and pancreatic polypeptide from the pancreas. Similarly catecholamines such as epinephrine secreted from the adrenal medullae and norepinephrine from sympathetic postganglionic nerve terminals and adrenal medulla. Cortisol from the adrenal cortex and growth hormone from the anterior pituitary gland also triggered when blood glucose level falls. The primary physiological fast acting hormones in response to hypoglycemia are glucagon and epinephrine.

Glucagon hormones enhance endogenous glucose production by the process of glycogenolysis and gluconeogenesis and generating glucose substrates such as lactate, pyruvate, alanine, and glycerol. In addition, epinephrine also has similar effects like glucagon in increase of endogenous glucose production and inhibition of utilization of glucose in the peripheral tissue and converts the gluconeogenic pathway. It can also stimulate net renal glucose production. However inhibition of insulin secretion is the primary physiological defense against decrease blood glucose and occurs at a plasma glucose concentration of less than 80 mg/dl. The response of sympathetic nervous system against hypoglycemia is activated by both circulating catecholamines and direct innervation results in increased fat metabolism of lipolysis in adipocytes which release free fatty acid. It is estimated that 25% of the total defense against hypoglycemia by the contribution of free fatty acid. Cortisol and growth hormone are metabolic defense which are released in response to prolonged hypoglycemia; but they have modest significant effect on glucose counter-regulation during acute stage. The actions of these hormones are increasing glucose

production and restraining glucose disposal after 4 h onset of hypoglycemia. It has only 20% of counter-regulatory response compared to the action of epinephrine.

If counter-regulatory mechanism fails to maintain the glucose homeostasis and blood glucose value of 3.0–3.5 mmol/l, may trigger the autonomic nervous system mediated warning symptoms such as sweating, palpitation and hunger to warn subjective awareness of hypoglycemia and provoke feeling of eating to improve blood glucose level. If not consume adequate glucose during this stage, central nervous deprives for glucose, neuroglycopenia develops and cognitive function declines. Counter-regulatory responses to hypoglycemia also referred to as glycemic thresholds and may be altered to higher plasma glucose levels following chronic hyperglycemia [26] or to lower plasma glucose levels following repeated hypoglycemia [27–29]. On the whole, the magnitude of counter-regulatory function is decrease with age 18 and is more obvious in male than in female [30].

6. Hypoglycemia and glycemic threshold

The glycemic threshold has a dynamic and significant role in the activation of counter-regulatory physiological response against the low plasma glucose level [20]. Though the individuals have increased level of glycated hemoglobin (HbA1C) may perceive the symptoms of hypoglycemia at higher blood individuals who undergo intensive glucose level with diabetes [31]. It means sudden and rapid declines of blood glucose from higher level to a lower but not too low and at this level brain started reacting to change and release of counter-regulatory hormones. This phenomenon is called "**relative hypoglycemia**" and it is self-limiting. Brain will usually takes 2–4 weeks to readjust and to improve that relatively reduced circulating glucose levels [27, 31–34].

In contrast, among diabetic patients who are on the intensive treatment of control of plasma glucose level may not perceive hypoglycemia until their plasma glucose is considerably lower than the normal physiological glycemic thresholds [33, 35]. The changes in this glycemic control are highly influenced chronically by persistent hyperglycemia and acutely by antecedent hypoglycemia [12, 35–38]. **Antecedent hypoglycemia** is a condition caused by hypoglycemia itself which impairs and reduces the reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia. An experimental study found that there is a significant reduction in glucagon, epinephrine, cortisol, pancreatic polypeptide responses to next-day of hypoglycemia among antecedent hypoglycemic patients who experienced two episodes with the blood glucose level of 50 mg/dl. It was also demonstrated that antecedent hypoglycemia reduced the neurogenic and neuroglycopenic symptom responses [28]. In later another study investigated the responses of metabolic and neuroendocrine on the effect of morning hypoglycemia to subsequent afternoon hypoglycemia. The findings revealed that only one prolonged, moderate hypoglycemic episode can also blunt the substantial changes of physiological counter-regulatory defense and the neurogenic and neuroglycopenic symptom response to subsequent hypoglycemia [39].

This impaired counter-regulatory responses otherwise called as "**hypoglycemia-associated autonomic failure**" causes reduced neuroendocrine counter-regulatory responses to hypoglycemia and lowered glycemic thresholds for activation of physiological defenses against hypoglycemia, which together lead to a condition called **hypoglycemic unawareness**. During this stage, because of failure to trigger the epinephrine secretion against severe drop in blood sugar, the individuals unaware of hypoglycemic symptoms of sweating, palpitation, anxiety generated by epinephrine. These symptoms are very significantly important to warn the individuals of the

lowering blood glucose level. Same scenario happened in intensively treated type 1 and type 2 diabetic individuals due to shifting of glycemic threshold to lower plasma glucose level [33, 39–42] which further limits the efforts to attain euglycemia [37, 38].

7. Clinical manifestations of hypoglycemia

Hypoglycemic signs and symptoms (**Table 3**) may occur unexpectedly and suddenly depends on the blood glucose level and may also vary from one person to another. The hyperglycemic individuals who have blood glucose level with 200 mg/dl or greater may feel adrenergic hypoglycemic symptoms when blood glucose suddenly falls to 120 mg/dl or less. Whereas a person with usual blood glucose levels in the low range may not experience symptoms when blood glucose slowly drops under 50 mg/dl and also patients who have had diabetes for many years have decreased hormonal (adrenergic) response to hypoglycemia.

Hypoglycemic symptoms may manifest as neurogenic (autonomic) symptoms and cholinergic-mediated symptoms. Low blood glucose level triggered the neurogenic symptoms by activating the autonomic nervous system which releases the catecholamines (norepinephrine and epinephrine) from the adrenal medullae and acetylcholine from postsynaptic sympathetic nerve endings. Elevated epinephrine levels leads the symptoms and signs of shakiness, palpitations, sweating, nervousness, anxiety, pupil dilation, dry mouth, pallor. The cholinergic-mediated symptoms are hunger, diaphoresis and paresthesia. However, only 20% of the total neurogenic symptom was found during hypoglycemia among epinephrine infusion in intensively and conventionally treated euglycemic type 1 diabetic individuals which indicates that the symptoms of hypoglycemic is multifocal and is mainly araised from efferent pathways of central nervous system [43].

Neuroglycopenic symptoms occur as a result of deprivation of glucose in the brain cells during hypoglycemia. Neuroglycopenic symptoms are very difficult to perceive by an individual rather it is most often recognized by family members, friends and bystanders. These symptoms include irritability, confusion, aphasia, paresthesias, ataxia, headache and the most severe symptoms are seizures stupor, coma, and even death. It can also include transient focal neurological deficits such as diplopia, hemiparesis.

Autonomic symptoms	**Neuroglycopenic symptoms**
Sweating	Blurred vision
Tingling	Difficulty speaking
Trembling	Feeling faint
Feeling shaky	Difficulty thinking
Feeling hungry	Confusion
Palpitations	Dizziness
Anxiety	Feeling drowsy
	Irritability
Autonomic signs	**Neuroglycopenic signs**
Tachycardia	Transient Focal Neurological Deficit occasionally
Increased systolic blood pressure	
Pallor	
Diaphoresis	
Mydriasis	

Table 3.
Signs and symptoms of hypoglycemia.

Autonomic	Neuroglycopenic	General malaise
Sweating	Confusion	Headache
Palpitations	Drowsiness	Nausea
Shaking	Odd behavior	
Hunger	Speech difficulty	
	Incoordination	

Table 4.
Edinburgh hypoglycemia scale.

Neurogenic and neuroglycopenic symptoms are manifested by the activation of the sympatho-adrenal system and brain's glucose deprivation. The brain is continuously depends on a circulating glucose for energy and for cognitive function. If blood glucose levels fall causes cognitive dysfunction [44]. The 11 most commonly reported symptoms were used to form the Edinburgh Hypoglycemia Scale [45] and are reproduced in **Table 4**.

8. Levels of hypoglycemia

According to the blood glucose level and manifestation of signs and symptoms in response to low blood glucose level, hypoglycemia can be categorized into Level I, Level II and Level III or mild, moderate and severe hypoglycemia.

8.1 Level I (mild) hypoglycemia

The range of blood glucose level is 54–70 mg/dl. Symptoms include tremor, palpitations, tachycardia, nervousness, sweating and hunger due to sympathetic nervous system is stimulation.

8.2 Level II (moderate) hypoglycemia

The range of blood glucose level is 40–54 mg/dl. It may produce confusion, irritation, inability to concentrate, headache, lightheadedness, memory loss, numbness of the lips and tongue, slurred speech, lack of coordination, emotional changes, drowsiness, and double vision, or any combination of these symptoms due to impaired function of central nervous system.

8.3 Level III (severe hypoglycemia)

In severe hypoglycemia, the blood glucose level is less than 40 mg/dl. Central nervous system function is impaired further. Symptoms may include disoriented behavior, seizures, stupor, or loss of consciousness. During this stage they need help from another as they unable to function because of physical and mental changes.

9. Mechanisms of counter-regulatory responses to hypoglycemia in type 1 diabetes

Type 1 diabetes mellitus is otherwise called insulin dependent diabetes mellitus which occur due to little production of insulin or no insulin from pancreatic beta-cells characterized by hyperglycemia and its associated symptoms. The treatment include for the management of diabetes mellitus is insulin, diet and exercise and

lifestyle modification. Insulin helps to convert the glucose into glycogen and store in the liver and muscles. If there is an imbalance between the insulin administration and food intake leads to hypoglycemia. Physiologically glucagon will be secreted by the pancreatic alpha-cells to convert the stored glycogen into glucose or from non-carbohydrate substances. However in patients with type 1 diabetes for more than years epinephrine is main physiological defense in response to hypoglycemia because glucagon secretory response to hypoglycemia is irreversibly lost. In later, epinephrine response to hypoglycemia also impaired unfortunately among patients with type 1 diabetes undergoing intensive treatment of insulin and at greater risk for recurrent hypoglycemia [46, 47]. There is more than 50% reduction in counter-regulatory responses toward the future hypoglycemia due to repeated attack of hypoglycemia which results in vicious cycle of iatrogenic hypoglycemia-associated autonomic failure and also subsequent hypoglycemia may also leads to antecedent hypoglycemia. Even short durations 20 minutes of antecedent hypoglycemia can produce significant impairment in counter-regulatory responses and also two episodes of hypoglycemia of 70 mg/dl can also blunt subsequent counter-regulatory responses by ~30% in men [48]. Patient may experience severe and significant clinical consequences due to reduced adrenergic sensitivity of poor tissue responsive to circulating epinephrine and deficient responses of glucagon with reduction in ANS counter-regulatory responses. These patients also had reduced β-adrenergic sensitivity compared to patients with normal counter-regulatory responses to hypoglycemia and healthy control subjects [49] and had reduced whole-body tissue sensitivity to epinephrine, which was exacerbated by intensive glycemic control. This reduced tissue responsiveness to epinephrine is an additional contributor to the syndrome of hypoglycemia-associated autonomic failure and reduced tissue sensitivity to epinephrine resulted in decrease endogenous glucose production and less inhibition of insulin-stimulated glucose uptake. Despite with persistent blunted epinephrine response to hypoglycemia, hypoglycemic symptom and β-adrenergic sensitivity responses increase [50] to restore the endocrine and autonomic function. Although controversial, other studies have also stated that with strict avoidance of antecedent hypoglycemia some or all of the features of hypoglycemia-associated autonomic failure can be reversed [51–53].

9.1 Mechanisms of counter-regulatory responses to hypoglycemia in type 2 diabetes

Type 2 diabetes mellitus is a heterogeneous group of disease caused by inadequate secretion of insulin or improper utilization of secreted insulin or both. It may the affect all groups of people from children to older adults. Children are more commonly affected nowadays due to rise in childhood obesity. Treatment regime includes diet, exercise, oral hypoglycemic agents, glucagon like peptide-1 analogs, insulin, or combination of these and varies depending on the response to treatment and progressive β-cell failure [54]. The symptoms of hypoglycemia associated autonomic failure among type 2 diabetes depends on age, treatment modality (diet versus oral hypoglycemic agents versus insulin), comorbidity, body fat composition, metabolic control, and the presence of diabetic neuropathies [54, 55]. However, neuroendocrine contributes in glycemic responses to hypoglycemia in advanced type 2 diabetes. The glucagon response to low blood glucose level was also absent in advanced insulin-treated type 2 diabetes. Autonomic and symptomatic responses by glycemic threshold to hypoglycemia were also altered to lower plasma glucose concentrations by recent antecedent hypoglycemia. Hence, the risk for hypoglycemia-associated autonomic failure was high in advanced type 2 diabetes as like those with type 1 diabetes and leads to harmful cycle of recurrent iatrogenic hypoglycemia [46, 55].

10. Inborn errors of metabolism causing hypoglycemia

Non-diabetic hypoglycemia also results from inborn errors of metabolism. Such hypoglycemia most commonly occurs in infancy but can also occur in adulthood. Cases in adults can be classified into those resulting in fasting hypoglycemia, postprandial hypoglycemia, and exercise-induced hypoglycemia.

10.1 Fasting (postabsorptive) hypoglycemia

It is rare; disorders of glycogenolysis can result in fasting hypoglycemia. These disorders include glycogen storage disease (GSD) of types 0, 1, 3, and 4 and Fanconi-Bickel syndrome.

10.2 Patients with GSD

Type 1 and 3 characteristically have high blood lactate levels before and after meals, respectively. Both groups have hypertriglyceridemia, but ketones are high in GSD type 3. Defects in fatty acid oxidation also result in fasting hypoglycemia. These defects can include (1) defects in the carnitine cycle; (2) fatty-acid β-oxidation disorders; (3) electron transfer disturbances; and (4) ketogenesis disorders. Finally, defects in gluconeogenesis (fructose-1, 6-biphosphatase) have been reported to result in recurrent hypoglycemia and lactic acidosis.

10.3 Postprandial (reactive) hypoglycemia

Inborn errors of metabolism resulting in postprandial hypoglycemia are also rare. These errors include (1) glucokinase, SUR1, and Kir6.2 potassium channel mutations; (2) congenital disorders of glycosylation; and (3) inherited fructose intolerance.

10.4 Exercise-induced hypoglycemia

Exercise-induced hypoglycemia, by definition, follows exercise. It results in hyperinsulinemia caused by increased activity of monocarboxylate transporter 1 in β cells.

11. Accidental, surreptitious, or malicious hypoglycemia

Hypoglycemia caused by endogenous hyperinsulinism due to functional β-cell disorders, insulinoma, or the insulin autoimmune syndrome is called as accidental, surreptitious, or malicious hypoglycemia. It may also occur by accidental administration of insulin, or accidental ingestion of an insulin secretagogue such as sulfonylurea because ingestion of an insulin secretagogue causes hypoglycemia with increased C-peptide levels and hypoglycemia caused by exogenous insulin with decrease C-peptide levels reflecting suppression of insulin secretion.

12. Assessment and diagnostic methods

- History collection
- Physical examination

- Diagnostic investigation: It includes
- Glucose—fasting and postprandial blood glucose
- Complete blood count
- Insulin
- C-peptide
- Beta-hydroxybutyrate
- Proinsulin
- Antibodies for insulin and its receptors
- Sulfonylurea and meglitinide screen
- Electrolytes, BUN/Cr, UA
- liver function tests,
- cortisol and thyroid levels, growth hormone level
- Other tests: CT and MRI

Whipple triad is the clinical presentation of pancreatic insulinoma and consists of: fasting hypoglycemia (<50 mg/dl), symptoms of hypoglycemia, immediate relief of symptoms after the administration of IV glucose.

13. Management of hypoglycemia

The aim of the treatment includes correction of glucose deficiency, prevent the complication associated with hypoglycemia and treat the underlying the cause. Treat the patient in the emergency department as shown in the **Figure 1**.

- History collection and physical examination
- Check the blood glucose—capillary blood glucose
- Assess the mental status of the client
- Access intravenous line if needed
- Monitor blood glucose level
- Administer 15 g of fast acting glucose in the form of glucose tablets or glucose containing fluids, candy or food. For, e.g., three or four commercially prepared glucose tablets; 4–6 oz. of fruit juice or regular soda, 6–10 hard candies, 2–3 tsp. of sugar or honey is appropriate if the patient is able to take orally
- Check for blood glucose 15 min later.

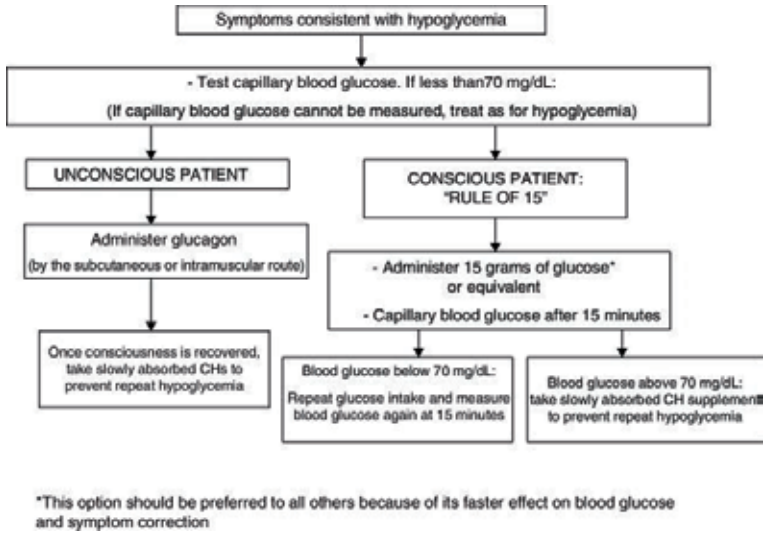

Figure 1.
Schematic representation of emergency management of hypoglycemia.

- Instruct the patient to eat protein and carbohydrate containing snack to maintain their blood glucose after 60 min if the blood glucose is higher than 70 mg/dl

- Treatment is repeated with 15 g of carbohydrates if glucose level is remains less than 70 mg/dl after the initial intake of 15 g of glucose. It may be probably repeated up to 1–3 times

- Instruct the patient to avoid adding more table sugar to juice, even "unsweetened" juice, which may cause a sudden increase in glucose, resulting in hyperglycemia in later hours.

- Administer parenteral therapy with 25% dextrose if unable to take oral foods

- Administer inj. glucagon 1.0 mg subcutaneous/intramuscular can be used especially in type 1 diabetes mellitus.

- The somatostatin analog octreotide can be used to suppress insulin secretion in sulfonylurea-induced hypoglycemia.

- Identify and treat the underlying cause

13.1 Management of hypoglycemia in the unconscious patient

- Assessment of glasgow coma scale

- Monitor airway, breathing, circulation

- Constant monitoring of blood glucose level

- Administer 1 g of glucagon subcutaneously or intravenously

- Administer 50% dextrose in 25–50 mL of water intravenously

- Check the patient for regaining from the state of unconsciousness. If hypoglycemic state extends for more than 5 h results in profound hypoglycemia which may cause permanent brain damage.

- Administer IV Mannitol and dexamethasone, IV glucose with constant glucose monitoring to necessary until regain from the state of unconsciousness to conscious and restore normal brain function

13.2 Management of non-diabetic hypoglycemia

Depend on the underlying etiology

- Discontinue the offending drugs or reduce their doses

- Treat the underlying critical illnesses

- Replace the cortisol and growth hormone if levels are deficient.

- Surgical, radiotherapeutic, or chemotherapeutic reduction of a non–islet cell tumor.

- Surgical resection of an insulinoma is curative

- Medical therapy with diazoxide or octreotide can be used if resection is not possible and in patient with a non-tumor beta cell tumor

13.3 Health education

- Consult with a dietitian to develop or adjust meal plan to maintain consistency in carbohydrates at meals by calculating grams of carbohydrates so that plan for medication and/or insulin.

- Self-monitoring of blood glucose to detect the episodes of hypoglycemia at the earliest. Self-monitoring of blood glucose level should give an idea of what makes the blood glucose level drop.

- Do not skip meal and balance the meal plan with insulin or oral hypoglycemic agent.

- Quit alcohol and smoking.

- Maintain the body weight.

- Follow medication dose regularly.

- Avoidance of exercise while having the symptoms of hypoglycemia.

- Ingestion of carbohydrate especially rapidly absorbed glucose during the symptoms of hypoglycemia.

- Remember and follow rule of 15 which means 15 g of glucose raise 50 mg/dl in 15 min during hypoglycemia state.

- Intravenous glucose is the preferable treatment of severe hypoglycemia, particularly that caused by a sulfonylurea.
- Keeping the hypo box hypoglycemic kit which contains glucose, glucagon, juice, etc.
- Instructing the family members and care givers about usage this kit, check for expiry date and replacing the used content in the kit.
- Always carry the sweetener which contains easily absorbable simple sugar and identity card.
- Regular check-up and follow-up care.

14. Conclusion

Hypoglycemia is a common, potentially avoidable consequence of diabetes treatment. This chapter emphasis on causes and risk factors of hypoglycemia, recognition of symptoms of hypoglycemia, glucose regulatory and counter regulatory mechanism, management and prevention of hypoglycemia thereby prevent the potential complications of hypoglycemia. Health care professionals have a major role in educating clients with diabetes mellitus about hypoglycemia and to follow their hypoglycemia management plan while caring the clients.

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Conflict of interest

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Section 4

Lifestyle and Metabolic Syndrome

Chapter 8

The Effect of Ramadan Fasting on Metabolic Syndrome (MetS)

Khalid S. Aljaloud

Abstract

The effect of Ramadan fasting on most of the metabolic syndrome (MetS) markers is still controversial. However, most of the available evidences showed positive effect on most of the MetS markers. In general, Ramadan fasting may help to reduce the risk of MetS. Nevertheless, most of the positive results seem to be impermanent and reading many variables (MetS markers) return to the previous reading after few weeks (~3–4 weeks). Therefore, intermittent fasting such as Ramadan fasting could be one of the cure alternatives especially in people with MetS, cardiovascular or metabolic diseases with considering their physician supervision. Again, more evidences are recommended to clarify the controversial issues related to the role of Ramadan fasting on MetS markers.

Keywords: Ramadan fasting, cholesterol, glucose, metabolic syndrome (MetS)

1. Introduction

Lifestyle plays significant role in metabolic syndrome. Habitual diet, physical activity status, type of sleep—including quantity and quality—and unhealthy behaviors such as smoking, consuming alcohol, etc. may affect metabolic syndrome markers [1]. This chapter will demonstrate overview of lifestyle during the month of Ramadan including diet, physical activity and sleep. Moreover, the effects of Ramadan fasting on each metabolic syndrome (MetS) markers will be revealed including central obesity, plasma triglyceride, high density lipoprotein-cholesterol, fasting plasma glucose and blood pressure.

2. Lifestyle during the month of Ramadan

The month of Ramadan is a holy month in the Islamic calendar (lunar calendar vary between 29 or 30 days) once a year. About 1.5 billion Muslims worldwide are—religiously—abstained from having any kind of food, oral intake such as medicine (unless in necessary cases) or smoking during the daylight starting from dawn to sunset. The Holy month of Ramadan retreats 11 days each year. As a result, Ramadan month moves in all seasons over time including summer season. Usually fasting time extends between 13 and 18 hours per day depending on season (spring, summer, autumn or winter) and the geographical location of the country. During the month of Ramadan, lifestyle of most Muslim people changes. In most Muslim country, people become less active during the daytime (before the sunset) compared with the nighttime (after the sunset), especially when most

are Muslims population [2]. The reason is mainly due to their nature of life during the night as majority of them engaging in social activities with friends and family. Moreover, most of the markets and media become more vital. However, the lifestyle of some Muslims will not change greatly during Ramadan [3]. Hence, the change in habitual diet, physical activity and sleep may change the body composition and some blood markers such as cholesterol, triglyceride, glucose which may alert MetS markers.

3. Diet during the month of Ramadan

Muslims break their fasting just after sunset by having a main meal and then they may have two or three meals during the night until the dawn time. Current study found that diet did not change significantly during the month of Ramadan while comparing before or after Ramadan [2]. However, Al-barha's study recruited apparently healthy graduate and undergraduate students. Data from different studies reported that diet during the month of Ramadan varies due to the differences between Muslim population in different countries and their habitual lifestyle. Further, seasonal and weather differences may play role in the quality and quantity of the food intake as well as the diet behavior during the month of Ramadan. In a review study, 9 out of 13 publications reported either significant reduction or no significant difference in energy intake between during and pre-or-post the month of Ramadan [4–12]. Only four studies showed a significant increase in energy intake during Ramadan [13–16]. However, all of the studies in these publications use self-report to assess the energy intake, which is known to be less accurate comparing to objective measures [17, 18]. Amount and type of food intake as well as timing are key factors in diet and its effect on body including metabolic syndrome. During the month of Ramadan, carbohydrate and fat are consumed just after sunset. Different Muslim population reported high intake of dietary fat during Ramadan which exceeded the dietary recommendations [6, 11, 19]. In contrast, some studies found no significant change in carbohydrate and protein. However, the type of carbohydrate switched from complex sugar such as bread, cereal and vegetable to more simple sugar such as sweets [20]. These changes could elevate blood parameters such as blood lipids level. Hence, it could affect the metabolic syndrome markers negatively.

4. Physical activity during the month of Ramadan

The recent guidelines of physical activity and exercise encourage people to be physically active. The recommendation has been issued for each age group such as children and adult as well as people with special conditions such as elderly, diabetics and obese individuals [21]. The changes in people lifestyle may affect health and wellbeing [3]. During Ramadan, lifestyle may change including habitual physical activity. Although some studies found that there is no significant change in physical activity levels during Ramadan comparing to pre-Ramadan [2], numerous evidences reported significant changes in physical activity levels during the month of Ramadan. Ramadan fasting has been found to affect physical activity level in different ways. Some studies indicated that habitual physical activity may change during the month of Ramadan [22, 23]. Moreover, number of previous studies has investigated the association between Ramadan fasting and physical activity in Muslim population. These studies reported that physical activity levels were

lowered in Muslim population during the month of Ramadan [24–28]. For instant, about one-third of Saudi families reported a decrease in physical activity levels [29]. Furthermore, recent study found that Ramadan fasting is associated with decrease in physical activity levels [30]; and may causes a decline in the physical work capacity in adolescent soccer players especially cardiorespiratory fitness capability [31]. However, these evidences showed no significant change in resting metabolic rate (RMR) or total energy expenditure (TEE) [30].

The reduction in physical activity and exercise may alert the metabolic syndrome markers. Several studies have shown significant association between low physical activity level and negative changes in some of the metabolic syndrome markers. Individuals with low physical activity are more likely to have negative changes in metabolic syndrome [20, 32]. More about the impact of low physical activity in MetS will be discussed later in this chapter. These results may help to understand the influence of Ramadan fasting on body composition and the characteristics of metabolic syndrome.

5. Body composition

Body mass, BMI and waist circumference (WC) decreased gradually, especially in the end week of Ramadan compared with the reading before Ramadan. However, most of the recent studies concluded that the slightly decrease in some body composition parameters were not significant [4, 20, 33–36]. Although some the studies reported significant reduction in body weight at the end of Ramadan, the reduction was temporary. In a recent review study, the relationship between body composition parameters (i.e. body mass, body mass index, fat percentage and waist circumference) and Ramadan fasting is elucidated. Fernando and colleagues [29] concluded that there was a significant reduction in fat percentage at the end of Ramadan compared with pre-Ramadan in overweight or obese individuals, but not in those of normal weight. Moreover, even the change in body composition during the month of Ramadan was temporary as most of the investigated body composition parameters return to the normal weight [37].

6. Sleep during the month of Ramadan

In terms of sleep pattern, working hours during the month of Ramadan—at least in some countries—are shorter for those who fast. In such countries, workers are given more time to sleep after having the last meal just before the dawn time. For this reason, people start work later in the morning (between 09:00 and 10:00 am) instead of the early morning (i.e. 07:00–08:00 am). This change could affect sleep patterns. Hence, this may affect the times they go to bed and wake up [38]. Moreover, sleep habits may change more during the daytime. In turn, the change in sleep pattern may lead to some changes in some of the physiological parameters including metabolic syndrome as well as body composition [39, 40]. In a recent review study, they found that well-organized studies that controlled sleep/wake time, sleep duration and light exposure do not influence Ramadan fasting.

Furthermore, well-designed studies showed no effect of Ramadan fasting on circadian rhythms. However, in unstable society in which they do not control for lifestyle changes, evidences have demonstrated sudden and significant delays in bedtime and wake time [41]. Controllable and uncontrollable MetS risk factors may lead to cardiovascular and metabolic diseases as illustrated in **Figure 1**.

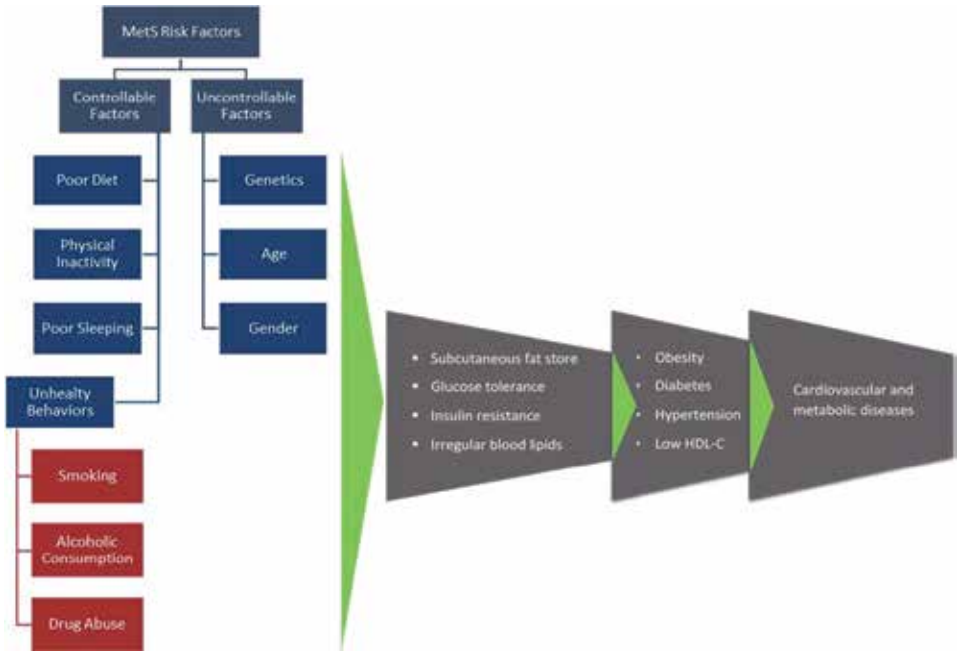

Figure 1.
Risk factors of MetS including controllable and uncontrollable factors that might lead to cardiovascular and metabolic diseases.

7. Metabolic syndrome

Historically, the first time metabolic syndrome (MetS) was defined by Kylin , a Swedish physician, in 1923 [42]. He described MetS as a cluster of cardiovascular risk factors comprising of hypertension, hyperglycemia and gout. Since then, the metabolic syndrome has gradually progressed over time with definition modification. However, the core turbulences, hypertension, consisting of glucose intolerance, obesity and dyslipidemia remain the cornerstone of all diagnostic criteria. In turn, these features may develop and increase the risk of cardiovascular morbidity and mortality [43, 44]. The term "Syndrome X" was commonly used in 1980s to describe the proposed interrelationships between resistance to insulin-stimulated glucose uptake, hypertension, type 2 diabetic and cardiovascular diseases. Now, the term MetS has the International Classification of Disease (ICD-9) code 277.7. In 1990s, visceral adiposity becomes important when obesity is considered as a main factor of the insulin resistance syndrome [45]. World Health Organization (WHO) launched the first formal definition of the MetS in 1998 [46]. In 2001, the National Cholesterol Education Program's Adult Treatment Panel III (NCEP:ATPIII) issued a set of criteria based on common clinical investigations: WC, blood lipids, blood pressure and fasting glucose [47–49].

8. Diagnostic criteria for MetS

Over the years, there have been several societies attempted to issue the diagnostic criteria for metabolic syndrome [50]. In 1998, WHO is the first organization that launched the worldwide definition of MetS, which was modified by other organizations such as the European Group for the Study of Insulin Resistance (EGSIR). In 2003, the American Association of Clinical Endocrinologists (AACE) proposed

WHO, 1998	EGIR, 1999	NCEP:ATPIII, 2001	AACE, 2003	IDF, 2006
High insulin levels, IFG or IGT, and two of the following:	Top 25% of the fasting insulin values among nondiabetic individuals and two of the following:	Three or more of the following:	IGT and two or more of the following:	Central obesity as defined by ethnic/racial, specific WC, and two of the following:
Abdominal obesity: WHR 0.9, BMI 30 kg/m^2, WC 37 inches	WC: 94 cm for men, 80 cm for women	WC: 40 inches for men, 35 inches for women	Triglycerides 150 mg/dl	Triglycerides 150 mg/dl
Lipid panel with triglycerides 150 mg/dl, HDL-C 35 mg/dl	Triglycerides 2.0 mmol/liter and HDLC 1.0 mg/dl	Triglycerides 150 mg/dl	HDL-C: 40 mg/dl for men, 50 mg/dl for women	HDL-C: 40 mg/dl for men, 50 mg/dl for women
BP 140/90 mm Hg	BP 140/90 mm Hg or antihypertensive medication	HDL-C: 40 mg/dl for men, 50 mg/dl for women	BP 130/85 mm Hg	BP 130/85 mm Hg
	Fasting glucose 6.1 mmol/liter	BP 130/85 mm Hg FPG 110 mg/dla		FPG 100 mg/dl

WHR, Waist-to-hip ratio; BP, blood pressure; FPG, fasting plasma glucose. In 2003, the ADA changed the criteria for IFG tolerance from 110 to 100 mg/dl.
Source: Ref. [51].

Table 1.
Criteria for the definitions of the metabolic syndrome.

their definition. However, the definition of the cut-off for obesity was not agreed yet. **Table 1** illustrates the development stages of the MetS diagnostic criteria [52].

9. The effect of Ramadan fasting on metabolic syndrome

In this section, the role of Ramadan fasting positively affect the MetS markers including central obesity, waist circumference (WC), fasting plasma glucose (FPG) level, triglycerides (TG) level, high density lipoprotein (HDL) and blood pressure (BP), will be deliberated with recent evidences. In terms of metabolism and hormonal serum levels, Ramadan fasting may affect the metabolism of lipids, carbohydrates and proteins, as well as related hormones levels. Although there are beneficial changes in HDL and LDL levels, evidences showed that Ramadan fasting could lead to elevate the urea and uric acid which may be attributed to dehydration during the Holy month of Ramadan [23]. In the next sessions, the effect of Ramadan fasting on metabolic syndrome markers will be elucidated with more details.

10. The effect of Ramadan fasting on central obesity

Intermittent fasting during the month of Ramadan may enhance the cure from some of the MetS markers including body weight reduction. Although some evidence showed increase in some of the body composition parameters [53], Ramadan

fasting has been found to reduce waist circumference even in apparently healthy young adults [54]. In some studies, the reported weight reduction occurred without significant changes in energy and macronutrient intake and physical activity level [4]. The reduction was interpreted as loss of body water and body fat percentage.

There is a strong recent evidence that support the effect of Ramadan fasting on reducing body fat percentage and even fat-free mass especially with obese/overweight people. In a recent review and meta-analysis study, data obtain from 70 publications found a significant reduction in fat percentage between pre-Ramadan and post-Ramadan in overweight and obesity individuals. (−1.46 [95% confidence interval: −2.57 to −0.35]%, $P = 0.010$). However, there was no changes reported in those of normal weight (−0.41 [−1.45 to 0.63]%, $P = 0.436$). The reduction also reported in fat-free mass between pre-Ramadan and post-Ramadan. Nevertheless, the changes in body composition measurements seem to be temporary. Evidences showed that body weight body composition parameters were returned toward the pre-Ramadan measurements just after 2–5 weeks from the month of Ramadan [37]. Furthermore, it has been suggested that this decrease in body weight could be attributed to a decrease in fluid intake [34, 55–57]. Sequentially, dehydration during the month of Ramadan may cause increase in urea and uric acid which is attributed to the reduction of the glomerular filtration rate [58]. The physiological aspects that may explain the association between Ramadan fasting and body composition parameters has been investigated. For instance, plasma leptin and insulin have been found to play a key role in body weight regulation homeostasis. Leptin level send signals to the brain about the amount of energy stores which in turn, stimulates the hypothalamic centers to regulate the energy intake and energy expenditure [59]. Although an evidence showed that there is a positive association between plasma leptin and insulin levels and body fat, the elevation in plasma leptin and insulin during the month of Ramadan is probably due to the energy intake and diet behavior [14]. In sum, Ramadan fasting may help to reduce body composition including central obesity such as waist circumference. However, the reduction may not be healthy as the weight loss attribute to loss of body water. One possible reason for this greater weight loss is that people with greater BMI are due to greater glycogen stores than people of normal weight, and hence would be expected to lose more fluid in response to fasting [60], and in some cases loss of lean tissue [34] carry more body. One of the most challenges is that body composition parameters are affected by different factors including calorie intake, physical activity level, age and gender. More investigations are needed to clarify the role of Ramadan fasting on central obesity.

11. The effect of Ramadan fasting on triglycerides

In general, the role of Ramadan fasting on triglyceride concentration tends to be more positive in many case studies. This may enhance health promotion for people who have no clinical conditions that may prevent them from fasting during the month of Ramadan. In a systematic review study, data revealed that 6 out of 15 studies reported reduction in triglyceride level at the end of Ramadan month. Nevertheless, other 9 studies showed no significant changes in triglycerides concentration [61]. Moreover, Ramadan fasting also has been found to be healthy by helping diabetic patients to reduce triglycerides level especially those who can fast the whole month of Ramadan. Recent evidence indicated clear effect of Ramadan fasting on triglycerides level in diabetic patients. Bener et al. [62] tried to investigate the effect of Ramadan fasting on some blood parameters including blood lipids (total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, etc.)

in patients with type 2 diabetes mellitus (T2DM) in Turkey. They concluded that fasting during the month of Ramadan may help to reduce triglycerides level even in people with type 2 diabetes [62]. Interestingly, rare of the available evidences showed negative effect of Ramadan fasting on triglycerides concentration. Thus, Ramadan fasting could enhance health promotion and reduce the risk of cardiovascular and metabolic diseases via the positive control of different lipid profile including triglycerides level.

12. The effect of Ramadan fasting on high-density-lipoprotein (HDL)

Health organizations recommend lifestyle that help to elevate high-density-lipoprotein (HDL) [46]. In general, a desired improvement has been found in plasma HDL at the end of Ramadan month and even after few weeks afterward [63]. Although there are some few studies that found no favorable changes in HDL as a result of Ramadan fasting [2, 64], recent strong evidences approved the health effect of Ramadan fasting on plasma HDL [61, 62]. However, the contradictory may due to the limitations of some studies. Kul et al. [65] did a meta-analysis to investigate the impact of Ramadan fasting on some health-related parameters in healthy population including blood lipids. They analyzed the data obtained from 13 studies to explore the effect of Ramadan fasting on HDL concentration (661 healthy individuals: 462 men and 199 women). They concluded that Ramadan fasting may help to reduce HDL concentration in women but not in men [65]. Moreover, the negative effect of Ramadan fasting has been observed in special population such as older adults with hypertension disease [66]. In sum, most of the recent and soled evidences have proved the beneficial effect of Ramadan fasting on plasma HDL level. Furthermore, more studies are encouraged to clarify the role of Ramadan fasting on HDL in different cases and population.

13. The effect of Ramadan fasting on fasting plasma glucose

Unhealthy elevation in fasting plasma glucose (FPG) has been found to be one of the MetS markers. The holy month of Ramadan has different lifestyle in most Muslim populations including diet and physical activity pattern which may influence the FPG [20]. Nevertheless, Ramadan fasting may help to reduce FPG even in diabetic individuals in both male and female [62]. However, the beneficial reduction in FPG during or end of Ramadan month seems to be temporary [67, 68]. Hence, any change in blood glucose during Ramadan is minor and improbable to affect healthy people especially if there is no major changes in diet or physical inactivity levels [69]. Recently, the effect of Ramadan fasting on FPG has been investigated in health young adults. The study found that Ramadan fasting elevated FPG significantly during the end of Ramadan comparing the levels before Ramadan. Nevertheless, the elevated value of FPG was within the normal level in both occasions [2]. On the other hand, Ramadan fasting may reduce FPG of apparently healthy young adults (19–23 years old) during the end of Ramadan month [70]. Furthermore, intermittent fasting such as Ramadan fasting improve FPG in obese/overweight adults. One of the main outcomes of Ramadan fasting is losing weight and FPG as well as related metabolic parameters such as insulin, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) [71]. Insulin promotes the storage of glucose in liver and muscles as glycogen. However, during Ramadan fasting, circulating glucose levels decrease which lead to decrease the secretion of insulin and increase the level of glucagon hormone and catecholamines to enhance the

breakdown of glycogen to provide body with energy [64]. Hence, one can conclude that Ramadan fasting may improve FPG especially after a couple of weeks. One of the explanation is that alterations in lifestyle during the month of Ramadan may lead to changes in the rhythmic pattern of different related hormonal including thyroid hormones, melatonin, pituitary hormones (prolactin, luteinizing hormone, follicular stimulating hormone, growth hormone and thyroid-stimulating hormone) and steroid hormones (cortisol and testosterone) [72]. These hormones are related to energy metabolism and regulation of energy intake [14, 72]. These hormonal changes could explain decreases in blood glucose levels.

However, FPG may return to previous level afterward. Thus, intermittent fasting is recommended to reduce the risk of having one or more of the MetS markers such as FPG.

14. The effect of Ramadan fasting on blood pressure

Blood pressure (BP) is one of the complicated factors liked to different cardiovascular diseases.

High blood pressure is one of the MetS that may develop cardiovascular and metabolic diseases [52]. Although some studies reported slight, but significant, elevation in blood pressure in apparently healthy young adults during the month of Ramadan [2], different evidences concluded that Ramadan fasting may lead to reduce blood pressure in apparently healthy people as well as patients with hypertension, stable cardiovascular, metabolic syndrome and dyslipidemia [73]. In a systematical review study, Mazidi and colleagues found that data from different studies reported reduction in blood pressure especially systolic blood pressure (SBP) but no significant changes has been observed in diastolic blood pressure (DBP) [61]. Data from several investigations revealed that Ramadan fasting could reduce blood pressure unless there are some conditions that may influence BP such as diet and stress [74–76]. However, Topacoglu et al. [77] observed an increase in the number of admissions for hypertension during the holy month of Ramadan [77]. The reduction in blood pressure parameters during the month of Ramadan can be explained as a result of dehydration due to the long fasting time. On the other hand, it can be attributed to lower daytime activity which may cause a noticeable reduction in sympathetic tone [78]. In some countries the holy month of Ramadan comes in hot season (June–August) which makes people fast longer (~15 hours). Therefore, hypertensive patient should be advised to avoid diuretics during fasting and they can fast with paying attention to type and amount of food that may raise BP [79]. Remarkably, very few available evidences observed unhealthy effects of Ramadan fasting on hypertensive patients. In fact, the role of Ramadan fasting on controlling blood pressure is controversial. Partly, it is due to the lack of the available evidences that investigated the comprehensive effect of Ramadan fasting on blood pressure in people with different health conditions. Thus, more investigations are recommended to clarify the role of Ramadan fasting on blood pressure parameters.

15. Conclusion

The effect of Ramadan fasting on most of the MetS markers is still controversial. However, most of the available evidences showed positive effect on most of the MetS markers. In general, Ramadan fasting may help to reduce the risk of MetS. Nevertheless, most of the positive results seem to be impermanent and

reading of many of the variables (MetS markers) return to the previous reading after few weeks (~3–4 weeks). Therefore, intermittent fasting such as Ramadan fasting could be one of the cure alternatives especially in people with MetS, cardiovascular or metabolic diseases with considering their physician supervision. In general, Ramadan fasting is associated with positive improvements in different related hormones such as insulin, leptin, adiponectin, adipocytokine, Gamma glutamyl transferase and others that may be directly or indirectly affect MetS markers. Hence, Ramadan as an intermittent fasting might be more beneficial for most population and cardiovascular and metabolic patients should consult their physicians when they decide to fast during the month of Ramadan. Again, more evidences are recommended to clarify the controversial issues related to the role of Ramadan fasting on MetS markers.

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The main source of energy for the body is glucose. Its low blood concentrations can cause seizures, loss of consciousness and death. Long lasting high glucose levels can cause blindness, renal failure, cardiac and peripheral vascular disease, and neuropathy. Blood glucose concentrations need to be maintained within narrow limits. The process of maintaining blood glucose at a steady state is called glucose homeostasis. This is achieved through a balance of the rate of consumption of dietary carbohydrates, utilization of glucose by peripheral tissues, and the loss of glucose through the kidney tubule. The liver and kidney also play a role in glucose homeostasis. This book aims to provide an overview of blood glucose levels in health and diseases.

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