Kurdistan Journal of Applied Research (KJAR)
Print-ISSN: 2411-7684 | Electronic-ISSN: 2411-7706

Website: Kjar.spu.edu.iq | Email: kjar@spu.edu.iq

Glycolysis Regulation to Maintain Blood Glucose Homeostasis

Karzan Jalal Salih
Pharmaceutical Chemistry Department
Medical and Applied Science College
Charmo University
Sulaimani, Iraq
Karza.salih@charmouniversity.org

Dana Khdr Sabir
Department of Medical Laboratory Sciences
College of Medical and Applied Sciences
Charmo University
Sulaimani, Iraq
dana.sabir@charmouniversity.org

Hayman Jalal Abdoul
Pharmaceutical Chemistry Department
Medical and Applied Science College
Charmo University
Sulaimani, Iraq
hayman.abdoul@charmouniversity.org

Article Info

Volume 7 - Issue 1- June 2022

DOI: 10.24017/Scince.2022.1.10

Article history:

Received: 20/4/2022
Accepted: 04/7/2022

Keywords:

Carbohydrates, glycolysis, glucose transporters (GLUTs), insulin, glucagon

ABSTRACT

Carbohydrates are the major energy source for the living cells that synthesized from carbon dioxide and water during photosynthesis process by green plants through absorption of sun light. In human, carbohydrates provide more than 55% of body energy which are mostly come from exogenous source. Carbohydrates can also provide energy from endogenous source such as glycogenolysis process. To be used as source of energy, carbohydrates compounds should undergo series of enzymatic metabolic reactions in the cell. Beside the energy productions, catabolism of carbohydrates provides different metabolites for synthesis of several biomolecules such as fatty acids, amino acids, DNA, and RNA. Among the three main examples of monosaccharide (glucose, galactose, and mannose). Glucose is considered as the central molecule in carbohydrate metabolism that all the major pathways of carbohydrate metabolism relate to glucose molecule such as glycolysis and glycogenesis process. Glucose is also considered as an important component of cellular metabolism in preserving carbon homeostasis. Liver plays a significant role in controlling and stabilizing blood glucose levels; therefore, it can be considered as glucostate monitor. In this article, we will review the major metabolic pathways of carbohydrate metabolism, their biochemical role in cellular energy production, and latest development in the understanding in these fields. Also, we discussed about the factors that participate in regulation of blood glucose concentration. We believe understanding this process is essential for control carbohydrate-related human disorders.

1. INTRODUCTION

The monosaccharide is the central molecule in the metabolism of carbohydrate since it is related to all the major pathways of carbohydrate metabolism. Glucose, as a major carbohydrate molecule, undergoes three major pathways to be metabolized, glycolysis [1], glycogenesis [2], and hexose monophosphate (HMP) shunt [3].These pathways are regulated inside the living organisms either enzymatically or through the actions of different hormones [4, 5].

The glycolytic pathway is carried out by most tissues by breaking down of glucose to provide energy in the form of ATP, and also it offer several metabolites, which can later be used for other metabolic pathways [6]. Glycolysis, also called Embden-Meyerhof pathway, is an extramitochondrial pathway in a cell in which one molecule of glucose is oxidized into two pyruvate molecules through several enzymatic reactions in the cytosol of the cell [7, 8]. In the present of oxygen, the pyruvate molecule enters mitochondrial matrix from the cytoplasm to form tricarboxylic acid (TCA) cycle to be fully oxidized to CO_2 and water [9]. However, in the absence of oxygen (anaerobic condition), pyruvate is converted into lactate [10]. Examples of anaerobic glycolysis such as exercise, overproduction of pyruvate, or under hypoxic conditions during disfunction or damaging of mitochondria.

In terms of structure, carbohydrates are classified into three major classes, (1) simple carbohydrates, they include monosaccharides such as glucose, galactose, and mannose; and disaccharides such as lactose, and sucrose, (2) complex carbohydrates that consist of multiple sugar units linked to each other through glycosidic bonds. The well-known examples of the complex carbohydrates are glycogens in animal, starch in plants and cellulose, (3) carbohydrates that bound to other groups such as protein (glycoprotein) or lipids (glycolipids) [11]. Carbohydrate digestions begin in the mouth through hydrolysis of poly and complex carbohydrate and into shorter molecules by the action of salivary and pancreatic α-amylase to di-, tri- and oligosaccharides. The next step of carbohydrate digestion takes place in the small intestine for further hydrolysis catalyzed by several digestive enzymes that located in the small intestinal brush-border membrane such as sucrase, maltase and lactase; to produce glucose, galactose, and fructose [12]. After the digestion process, these monosaccharides are absorbed into the blood stream to control blood sugar through several transporter proteins [13].

The pancreatic hormones including insulin and glucagon monitor the flow of glucose to and from the cells. Insulin keeps the concentration of glucose in the blood at a normal level; once the blood sugar level is too high, insulin triggers the liver to uptake blood sugar and store glucose as glycogen molecule. However, the lack of insulin or the body's inability to produce enough insulin to regulate the amount of glucose in the blood (diabetes mellitus) increase the glucose level of the blood. On the other hand, incase of low blood sugar levels, glucagon has an important role in maintaining blood glucose homeostasis by stimulating hepatic glucose production through breakdown of glycogen to glucose via glycogenolysis process which is then released into the blood. Furthermore, glucagon stimulates gluconeogenesis process by promoting liver cells to make glucose from amino acids [14].

In this article we provide an updated review on the process of glucose metabolism including glycolysis, and glycogenolysis, and types of transporter proteins that participate in these processes. Also, we describe those regulators that stimulates and inhibits these processes.

2. GLUCOSE TRANSPORTERS (GLUTS) AND GLYCOLYSIS PROCESS

Glycolysis is the process that six carbon atoms of one glucose molecule are oxidized to two molecule of pyruvate (three carbon atom each) via several enzymatic pathways. The process of glucose oxidation in the cells starts from its absorption from the blood into the cells through glucose transporters that are located in the plasma membrane of different tissues such as liver, kidney muscle and adipose tissues. However, due to solubility of glucose and present of lipids in the cellular membrane, making it difficult for glucose and other hexoses to diffuse from

blood into the plasma membrane. From the middle of the last century, several researches proposed several mechanisms of the passing of glucose molecule into the cellular membrane [15, 16].

Several glucose transport proteins were found located on the cellular membrane, which are essential for glucose metabolism in diverse organisms [17]. In human, approximately 14 glucose transports GLUTs are found; among these GLUT 1-4 which have the fundamental roles in many physiological processes [18, 19]. Furthermore, these different types of GLUTs are specialized based on the tissue that glucose is adsorbed into. GLUT1 is located in blood cells and blood brain barrier to uptake glucose from blood to these cells. However, mutations of GLUT1 may result in a syndrome known as De Vivo disease which is consequently impaired transport of glucose into brain cells which leads to cerebral energy failure. [20-22]. GLUT2 is another type of glucose transporter proteins which is mostly found in liver, kidney, and pancreas β-cells, while its deficiency resulted in Fanconi–Bickel syndrome which is characterized by buildup of glycogen in the liver and kidney [23, 24]. GLUT3 is a glucose transporter of placenta, kidney and neurons [25]. GLUT4 on the other hand is the major glucose transporter protein in muscle and adipose tissue. GLUT4 is an insulin dependent glucose transporter, that depends on the present of insulin to regulate blood glucose , whereas the other types of GLUTs are not dependent on the present of insulin and they regulate glucose concentration based on high and low blood glucose concentration that contributes to obesity and [26].

Blood glucose concentration level is maintained by both glycolysis and gluconeogenesis to around 5.5 mM [11]. Once glucose is diffused into the cells, it is phosphorylated to glucose 6-phosphate in an irreversible process with the action of the enzyme of hexokinase (HK) and glucokinase (GK). Glucokinase is a type of glycosidase enzyme with high K_m value that is characterized by a low affinity for glucose that functions as the glucose sensor which is expressed at the highest levels hepatocytes and pancreatic β cells that regulate the glycolysis pathway [27]. The enzyme of hexokinase (HK) which has high affinity for glucose is present in most tissues such as muscle that catalyze various hexoses, for example, HK converts glucose molecule to glucose 6-phosphate [6, 28]. Next, Glucose 6-phosphate undergoes isomerization reaction in the presence of the enzyme phosphohexose isomerase and Mg^{2+} to give fructose 6-phosphate [29]. The synthesized fructose 6-phosphate is phosphorylated in the present of ATP and the action of phosphofructokinase1 (PFK-1) to fructose 1,6-bisphosphate and an irreversible and a regulatory step in glycolysis (Figure 1).

The role of PFK-1 in the regulation of glycolysis has been reported for several types of cells in different animals [30, 31]. Mutation in the gene encoded for PFK-1 causes a disease known as glycogen storage disease type VII that is an inherited disorder resulted in inability to break down glycogen in muscle cells, and consequently inability of the muscle to use glucose as an energy resource [32]. The six-carbon fructose 1,6-bisphosphate breakups into two molecules by the enzyme aldolase to generate glyceraldehyde 3-phosphate (GA3-P) and dihydroxyacetone phosphate (DHAP). The enzyme phospho triose isomerase reversibly catalyzes the interconversion of glyceraldehyde 3-phosphate and dihydroxyacetone phosphate, depending on body demand. Later, 1,3-bisphosphoglycerate, a product of the glyceraldehyde 3-phosphate dehydrogenase enzyme, and NAD^+ molecule is reduced to NADH. Deficiency of this enzyme contributes to NADPH supply and lipid accumulation [33]. The formation of cofactor NADH is reduced to NAD^+ during the formation of lactate from pyruvate in the anaerobic condition [34]. The 1,3-bisphosphoglycerate converts to 3-phosphoglycerate with the synthesis of ATP through the action of phosphoglycerate kinase. The phosphate group on the 3-phosphoglycerate through an isomerization reaction is switched to carbon number two of glycerate molecule and generating 2-phosphoglycerate by the enzyme phosphoglycerate mutase. Additionally, 2-phosphoglycerate is converted to a high energy compound called phosphoenol pyruvate by the enzyme enolase. Finally, the high energy phosphate from phosphoenol pyruvate is transferred to ADP through an irreversible process by the enzyme pyruvate kinase, leading to the formation of ATP and three carbon pyruvate molecules. There are many researches have shown the significant role of pyruvate metabolism in human

diseases such as cancer, heart failure, and neurodegeneration [35].

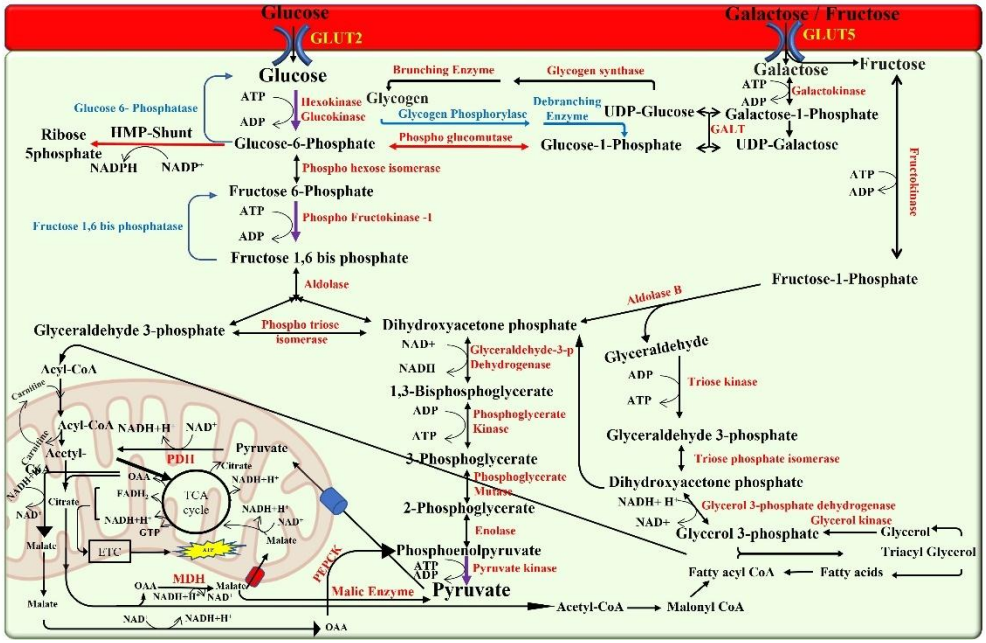

Figure 1: Glycolysis and glycogenolysis pathways. Monosaccharide molecules uptake from blood into the cells via glucose transporter protein (GLUT), then in several enzymatic processes glucose in the cells convert to two pyruvate molecules. In the glycolysis pathway, among ten steps there are three irreversible steps (blue bold arrow) and the rest of the steps are reversable pathways. Enzymes that catalyze the glycolysis are shown in red color except for Fructose 1,6 bis phosphatase and Glucose 6-Phosphatase that are written with blue color which participate in glucose synthesis (gluconeogenesis). Beside the glucose, metabolism of other monosaccharides (galactose and fructose) is described in the figure.
PDH: Pyruvate Dehydrogenase, ETC: Electron Transport Chain, TCA cycle: Tri Carboxylic Acid Cycle. HMP shunt: Hexose Mono Phosphate shunt, GALT: Galactose 1- phosphate uridyl transferase. OAA: Oxaloacetate, MDH: Malate dehydrogenase, PEPCK: Phosphoenol pyruvate carboxy kinase.

In case of aerobic condition pyruvate molecule moves from cytosol into mitochondria through a specialized transporter and converts in to two carbon molecule acetyl CoA with the action of the enzyme pyruvate dehydrogenase (PDH), and in this oxidized reaction NAD^+ is reduced to NADH. In case of absent or very little amount of oxygen such as those tissues that do not have mitochondria such as red blood cells or in cells that deprived from sufficient oxygen, the pyruvate molecule is reduced to lactic acid by the enzyme lactate dehydrogenase (LDH) [36], and the NADH molecule that is generated from the synthesized 1,3-bisphosphoglycerate is oxidized to NAD^+ molecule (Figure 2)[10].

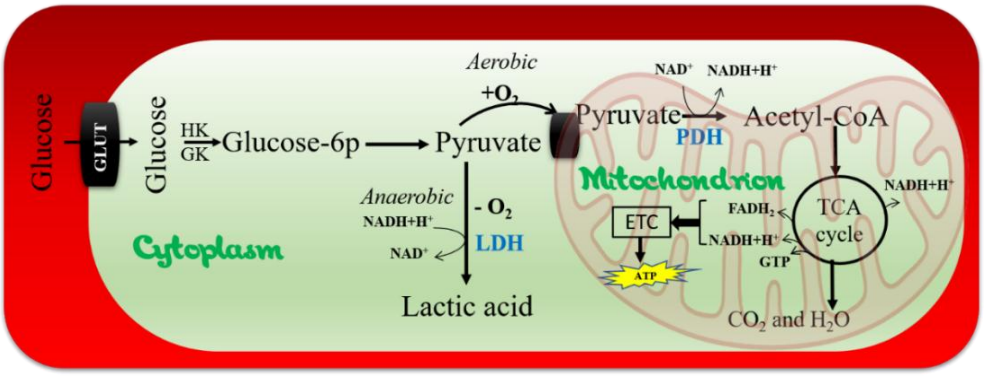

Figure 2: Aerobic and anaerobic condition.
In the present of oxygen, pyruvate transfer from cytoplasm to mitochondrial through transporter protein, from there it oxidizes to acetyl CoA and the reaction is catalyzed by pyruvate dehydrogenase, however, in the absence of oxygen (aerobic) pyruvate molecule reduces to lactate (lactic acid) molecule in the present of the enzyme lactate dehydrogenase.
GLUT: Glucose Transporter, GK: Gluco Kinase, HK: Hexo Kinase, LDH: Lactate Dehydrogenase, PDH: Pyruvate Dehydrogenase, ATP: Adenosine Tri Phosphate.

3. REGULATION OF GLYCOLYSIS PROCESS

There are four known enzymes that have shown to play a crucial role in the regulation of glycolysis process which are: glucokinase (GK), hexokinase (HK) [37, 38], phosphofructokinase-1 (PFK-1)[39, 40], and pyruvate kinase (PK) [41, 42]. All of these enzymes catalyze the glycolysis process irreversibly either allosterically or hormonally [43].
The enzyme hexokinase (HK), which is present in the cytoplasm of most tissues, is stimulated by a glucose molecule during glycolysis and is inhibited by glucose-6-phosphate if glycolysis is not required. It has shown that HK is the key for the first step in erythrocyte glycolysis, and its deficiency has been observed in patients with Fanconi's syndrome [6, 28]. Glucokinase (GK) is specific in liver cells located in the nucleus and is also simulated by glucose during high glucose level in the blood and consequently catalyze the glycolysis process. Regulation of this enzyme is controlled by fructose-6 phosphate which stimulates binding of glucokinase (GK) to glucokinase regulatory protein (GCKR) as a competitive inhibitor which causes the removal of the enzyme back into the nucleus [44]. Both of these types of glycolysis regulation are known as allosteric regulation (Figure 3A).
Hormonal regulation of glycolysis includes two hormones, glucagon, and insulin. Insulin stimulates both GK and HK during high blood glucose level and they catalyze the glycolysis process, while glucagon inhibits these two enzymes during low blood glucose level and, consequently, decrease glycolysis process and promotes gluconeogenesis. Moreover, insulin and glucagon regulate glycolysis process by phosphorylation and dephosphorylation of phospho fructokinase II (PFK-II) respectively, and it has been shown that PFK-II is a central regulator of cardiac glycolysis [45]. PFK-II can catalyze fructose 6-phosphate and convert it to fructose 2,6 bis phosphate, a reaction that is stimulated by insulin which dephosphorylates PFK-II [38]. The synthesized fructose 2,6 bis phosphate is a highly regulator compound which stimulates the enzyme of phospho fructokinase I (PFK-I) and consequently glycolysis occurs. Glucagon on the other hand, during low blood glucose level, starts to phosphorylate phospho fructokinase II (PFK-II) and inhibits the synthesis of fructose 2,6-phosphate as a result of inducing the gluconeogenesis process (Figure 3B).

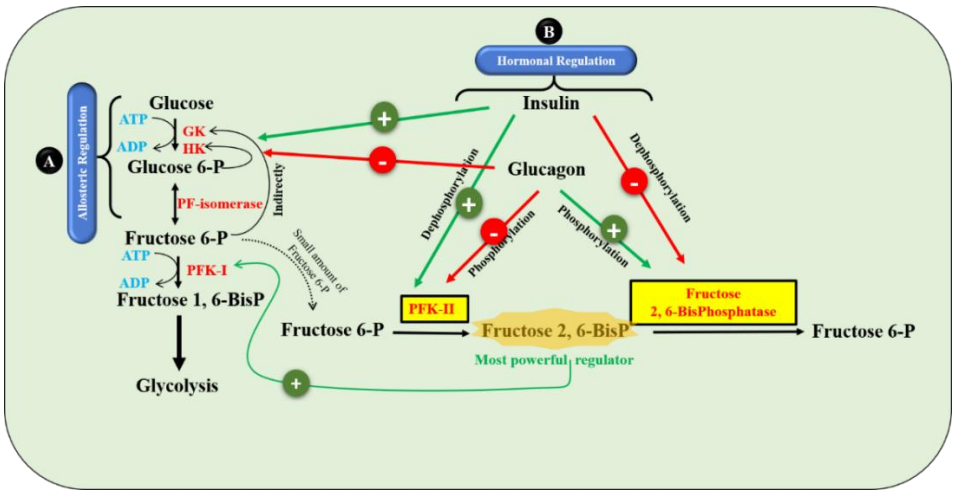

Figure 3: Regulation of glycolysis process.

A) Alosteric regulation: The glycolysis process is allosterically regulated by each of GK, HK and PFK-1.

B) Hormonal regulation: The glycolysis process is hormonally regulated by insulin and glucagon.

GK: Gluco kinase, HK: Hexo Kinase, PFK: Phosphophructo Kinase. Red arrow: inhibition, Green arrow: stimulation.

4. BLOOD GLUCOSE HOMEOSTASIS

Glucose homeostasis is a process of keeping blood glucose concentration at a steady-state level. Carbohydrate compounds, plant polysaccharides such as starch and animal polysaccharides such as glycogen are the main source of glucose for the body. Glucose can also be synthesized endogenously in the liver via several processes such as gluconeogenesis and glycogenolysis that have a significant role in providing energy for most of the tissues particularly the brain [46, 47]. The deficiency of blood sugar can lead to several problems in body function including loss of consciousness sweating, palpitations to cognitive dysfunction and seizures [48]. However, elevation of blood glucose concentrations can also result in several diseases such as blindness and renal failure. Therefore, maintain the blood glucose concentrations within narrow range is important for the healthy status of the human being [49, 50]. In the feed state; glucose is taken up from the blood into the cell and phosphorylated mainly by glucokinase (GK) to glucose-6 phosphate via glycolysis process which initiates either several metabolic processes or can be used as a source of glycogenesis and gluconeogenesis [51].

The main aim of digestion of carbohydrates is to breakdown complex and all disaccharides into monosaccharides for absorption, and then energy production. The process of carbohydrate digestion starts in the mouth with the action of salivary enzyme α-amylase that acts briefly on breaking down α (1→4) glycosidic bonds in dietary components starch and glycogen. However, the enzyme cannot hydrolyze those sugars that contain α (1→6) bonds such as amylopectin. Therefore, a mixture of small, branched, and unbranched oligosaccharides are produced in the mouth known as dextrin [52]. The carbohydrate digestion does not occur in the stomach due to present of gastric juice with a pH between 1 and 3 which deactivates α-amylase activity. Then, further digestion of dextrin by pancreatic enzyme (α-amylase) after it has been neutralized by pancreas secreted bicarbonate [53]. Final step of digestion occurs at the intestinal mucosal cells; several enzymes known as brush border enzymes in the microvillus membrane like isomaltose that cleaves the α (1→6) bond of isomaltose, maltase which cleaves glycosidic bonds in maltose and maltotriose, sucrase which cleaves sucrose and lactase that cleaves lactose to produce glucose, galactose and fructose [54].

After all the forms of carbohydrates are digested and converted into the monosaccharides, they must be absorbed by the duodenum and upper jejunum.

Absorption of both glucose and galactose molecules occur through their diffusion via sodium-dependent glucose cotransporter 1 (SGLT-1) molecule into enterocytes of the intestine, whereas the uptake of fructose requires a sodium-independent monosaccharide transporter (GLUT-5) for its absorption. Later, all produced monosaccharides are transported from the intestinal mucosal cell into the blood circulation by another glucose transporter-2 (GLUT-2) (Figure 4). Once monosaccharides are transported into the blood, they pass through tissues like liver and muscle through transporter proteins. In the liver, the transported monosaccharide such as glucose can either undergoes glycolysis process to produce energy or it could be stored as glycogen to be used later through glycogenolysis process to control the concentration of blood sugar. In the muscle, the glucose is mostly used to get energy as ATP, particularly during exercise [55].

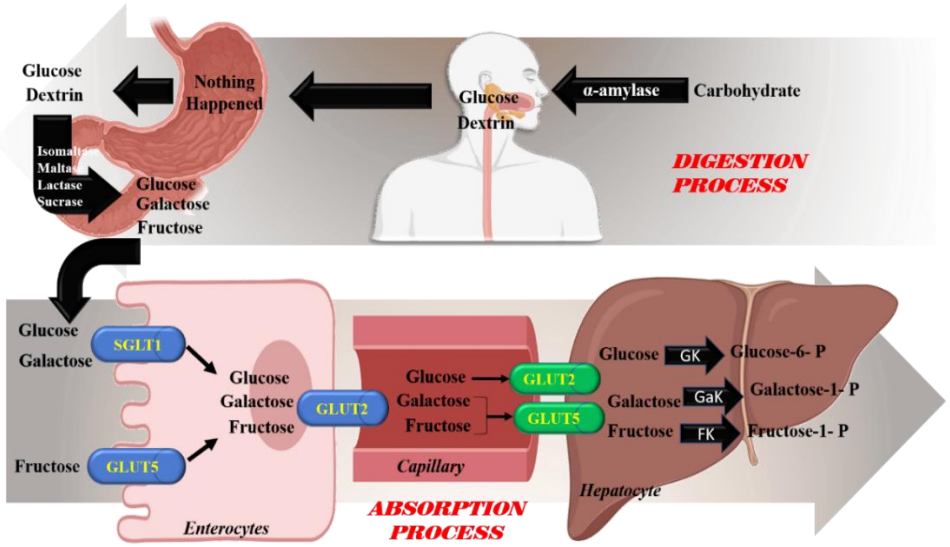

Figure 4: Carbohydrate digestion and absorption.
To begin the digestion process, the complex carbohydrates must break down into monosaccharides, which this small amount of carbohydrate digestion occurs in the mouth and most of the catalyzing process occurs in the small intestine with the action of the brush border enzymes. Next, there is the absorption of the digested carbohydrate into the blood stream and, finally, into the tissues.

Increase of blood glucose level can lead to a condition which is known as diabetes mellitus. Two types of diabetic mellitus are known insulin dependent diabetes mellitus or (type 1 diabetic mellitus) [56] and insulin independent diabetic mellitus or (type 2 diabetic mellitus) [57, 58].
Insulin is a hormone that is secreted by the pancreatic islet beta cells. In high blood glucose level, insulin increases uptake of blood glucose by stimulating the translocation of the glucose transporter isoforms (GLUTs), particularly GLUT2 in the liver and GLUT4 in the muscles, from intracellular pools to the surface cellular membrane. The concentration of insulin secretion has a significant role in increasing the number of glucose transport (GLUTs) to be translocated into the cell membrane [59]. Once GLUTs move into the cell membrane , the glucose in blood translocate into the tissues, consequently control the blood glucose level [60]. Insulin in the liver and muscle promotes glycogenesis process to regulate blood glucose concentration through uptake of glucose via insulin sensitive glucose transporter (GLUT2), which can be later used via glycogenolysis during low blood glucose level [61]. In skeletal muscle, the process of glycogenolysis does not occur due to the absence of the enzyme of glucose 6-phosphatase, the enzyme that is responsible for converting glucose 6-phosphate to glucose. Therefore, the glucose molecule which is adsorbed by insulin into the skeletal muscle is used as an energy source through glycolysis process.

Type 2 diabetes, is a polygenic disease that is related to insulin resistance condition and, consequently, raise blood glucose concentration. There are several risk factors that result in insulin resistance, such as dyslipidemia by increasing the concentration of lipids such as cholesterol and triglyceride in the blood, obesity, and visceral adiposity (accumulation of fat that wraps around the abdominal cavity) [62, 63]. Furthermore, sedentary lifestyle is considered as a factor that resulted in the development of insulin resistance and type 2 diabetes, which is low physical activity that increases the complication of cardiovascular diseases and mortality [55, 64].

Glucagon, on the other hand, is a polypeptide hormone that is secreted by the α cells of the pancreatic islets of Langerhans. This hormone is secreted during hypoglycemia particularly during overnight or prolonged fasting that stimulate hepatic glucose production by promoting both glycogenolysis and gluconeogenesis process [65, 66]. It has been found that the majority of glycogen is stored in the skeletal muscles and hepatic tissue [2], and at the process of glycogenolysis the stored glycogen molecule in the liver not in muscle is degraded into glucose molecule and moved into blood through GLUT2 membrane protein. Glucagon also has a great role by regulating glycolysis process and consequently offers energy requirements for the muscles [67].

Glucagon is one of the regulator biomolecules that promote indirectly glycogen break down into glucose 1-phosphate and glucose molecule [68, 69]. In the first step of glycogenolysis, the glycogen molecule is degraded by breaking α (1→4) glycosidic bonds by the action of glycogen phosphorylase to produce one molecule of glucose 1-phosphate and the remaining part of glucose units in the glycogen molecule. The process is continuing till on each chain four glucosyl units remain before a branch point [70].

Beside the glycogen phosphorylase enzyme, debranching enzymes also participate in glycogenolysis process by breakdown of α (1→6) glycosidic bonds that is located in the branched part of the sugar units remain one glucose molecule which is then cleaved by hydrolysis to yield free glucose. The produced glucose 1-phosphate is converted to glucose 6-phosphate in the cytosol by phosphoglucomutase [71]. In the liver, glucose 6-phosphate is transported into the endoplasmic reticulum (ER) and converted there to glucose by glucose 6-phosphatase, and finally transported into the blood to maintain blood glucose level (Figure 1). Research has shown that the deficient activity of the enzyme glucose 6-phosphatase leads to a one of a type of glycogen storage disease (GSD) which is known as Von Gierke disease resulting in excessive growth of glycogen and fat in the liver, kidney, and intestinal mucosa [67]. Recently, in human adipocytes, it has been shown that glucagon has a direct effect on glucose uptake and lipolysis process [72].

5. CONCLUSION

Carbohydrates are one of the major energy sources in the body. Carbohydrates can be stored in the body as a glycogen molecule or it can be used to provide energy via several metabolic pathways such as glycolysis, glycogenolysis and hexomino phosphate shunt. Digestion of carbohydrates occurs via several enzymatic processes into monosaccharides, followed by absorption of the monosaccharides into the blood via several glucose transporter proteins (GLUTs). Glycolysis is one of the main metabolic pathways in the body that converts glucose molecules into two molecules of pyruvate in the cytoplasm. Glycolysis is important to control blood glucose level and provide cellular energy. It consists of ten reversable enzymatic reaction processes except three of them are in the form of an irreversible process. The regulation of glucose metabolism is controlled by both allosterically and hormonally. Both insulin and glucagon hormones are important to maintain glucose concentration in the blood. Increased glucose level in the blood results in hyperglycemia and consequently diabetes mellites, while low blood concentration resulted in hypoglycemia, this can be controlled by the action glucagon hormone which participates in the regulation of glycogenolysis process by hydrolyzing glycogen molecule into glucose molecule to control blood glucose level.

REFERENCE

[1] J. S. Park *et al.*, "Mechanical regulation of glycolysis via cytoskeleton architecture," *Nature*, vol. 578, no. 7796, pp. 621-626, Feb 2020.

[2] C. Q. Anderson, E. Wechter, and L. A. Siegmund, "Glycogen Storage Disease Type l: Don't Miss the Signs," *The Journal for Nurse Practitioners*, vol. 16, no. 6, pp. 442-446, 2020.

[3] M. Akram *et al.*, "Hexose monophosphate shunt, the role of its metabolites and associated disorders: A review," vol. 234, no. 9, pp. 14473-14482, 2019.

[4] R. Laurian *et al.*, "Hexokinase and Glucokinases Are Essential for Fitness and Virulence in the Pathogenic Yeast Candida albicans," *Front Microbiol*, vol. 10, p. 327, 2019.

[5] G. M. Kowalski and C. R. Bruce, "The regulation of glucose metabolism: implications and considerations for the assessment of glucose homeostasis in rodents," *Am J Physiol Endocrinol Metab*, vol. 307, no. 10, pp. E859-71, Nov 15 2014.

[6] J. W. Pelley, "6 - Glycolysis and Pyruvate Oxidation," in *Elsevier's Integrated Review Biochemistry (Second Edition)*, J. W. Pelley, Ed. Philadelphia: W.B. Saunders, 2012, pp. 49-55.

[7] M. Akram *et al.*, "Hexose monophosphate shunt, the role of its metabolites and associated disorders: A review," *J Cell Physiol*, Jan 29 2019.

[8] L. Copeland and J. F. TURNER, "The regulation of glycolysis and the pentose phosphate pathway," in *Biochemistry of Metabolism*: Elsevier, 1987, pp. 107-128.

[9] B. Jiang, "Aerobic glycolysis and high level of lactate in cancer metabolism and microenvironment," *Genes Dis*, vol. 4, no. 1, pp. 25-27, Mar 2017.

[10] M. G. Vander Heiden, L. C. Cantley, and C. B. Thompson, "Understanding the Warburg effect: the metabolic requirements of cell proliferation," *Science*, vol. 324, no. 5930, pp. 1029-33, May 22 2009.

[11] N. S. Chandel, "Carbohydrate Metabolism," *Cold Spring Harb Perspect Biol*, vol. 13, no. 1, Jan 4 2021.

[12] H. Kozáková *et al.*, "Brush border enzyme activities in the small intestine after long-term gliadin feeding in animal models of human coeliac disease," (in eng), *Folia Microbiol (Praha)*, vol. 43, no. 5, pp. 497-500, 1998.

[13] N. G. MacFarlane, "Digestion and absorption," *Anaesthesia & Intensive Care Medicine*, vol. 19, no. 3, pp. 125-127, 2018.

[14] K. M. Habegger, K. M. Heppner, N. Geary, T. J. Bartness, R. DiMarchi, and M. H. Tschöp, "The metabolic actions of glucagon revisited," (in eng), *Nat Rev Endocrinol*, vol. 6, no. 12, pp. 689-97, Dec 2010.

[15] P. G. J. T. J. o. g. p. LeFevre, "Evidence of active transfer of certain non-electrolytes across the human red cell membrane," vol. 31, no. 6, pp. 505-527, 1948.

[16] W. J. T. J. o. p. Widdas, "Inability of diffusion to account for placental glucose transfer in the sheep and consideration of the kinetics of a possible carrier transfer," vol. 118, no. 1, pp. 23-39, 1952.

[17] L. Sun *et al.*, "Crystal structure of a bacterial homologue of glucose transporters GLUT1-4," *Nature*, vol. 490, no. 7420, pp. 361-6, Oct 18 2012.

[18] J. M. Pascual *et al.*, "GLUT1 deficiency and other glucose transporter diseases," vol. 150, no. 5, pp. 627-634, 2004.

[19] M. J. E. j. o. b. Mueckler, "Facilitative glucose transporters," vol. 219, no. 3, pp. 713-725, 1994.

[20] J. J. E. Klepper, "Glucose transporter deficiency syndrome (GLUT1DS) and the ketogenic diet," vol. 49, pp. 46-49, 2008.

[21] I. E. Scheffer, "GLUT1 deficiency: a glut of epilepsy phenotypes," ed: AAN Enterprises, 2012.

[22] K. J. B. Brockmann and Development, "The expanding phenotype of GLUT1-deficiency syndrome," vol. 31, no. 7, pp. 545-552, 2009.

[23] R. Santer, R. Schneppenheim, A. Dombrowski, H. Götze, B. Steinmann, and J. J. N. g. Schaub, "Mutations in GLUT2, the gene for the liver-type glucose transporter, in patients with Fanconi-Bickel syndrome," vol. 17, no. 3, pp. 324-326, 1997.

[24] A. Leturque, E. Brot-Laroche, M. J. A. J. o. P.-E. Le Gall, and Metabolism, "GLUT2 mutations, translocation, and receptor function in diet sugar managing," vol. 296, no. 5, pp. E985-E992, 2009.

[25] I. A. Simpson *et al.*, "The facilitative glucose transporter GLUT3: 20 years of distinction," vol. 295, no. 2, pp. E242-E253, 2008.

[26] S. E. Leney and J. M. J. T. J. o. e. Tavare, "The molecular basis of insulin-stimulated glucose uptake: signalling, trafficking and potential drug targets," vol. 203, no. 1, pp. 1-18, 2009.

[27] K. S. Polonsky and C. F. Burant, "Chapter 31 - Type 2 Diabetes Mellitus," in *Williams Textbook of Endocrinology (Thirteenth Edition)*, S. Melmed, K. S. Polonsky, P. R. Larsen, and H. M. Kronenberg, Eds. Philadelphia: Elsevier, 2016, pp. 1385-1450.

[28] G. W. Löhr and H. D. Waller, "Glucose-6-phosphate Dehydrogenase: (Zwischenferment)," in *Methods of Enzymatic Analysis*, H.-U. Bergmeyer, Ed.: Academic Press, 1965, pp. 744-751.

[29] T. Komoda and T. Matsunaga, "Metabolic Pathways in the Human Body," in *Biochemistry for Medical Professionals*, 2015, pp. 25-63.

[30] T. Kagimoto and K. J. J. o. B. C. Uyeda, "Hormone-stimulated phosphorylation of liver phosphofructokinase in vivo," vol. 254, no. 13, pp. 5584-5587, 1979.

[31] I. Mor, E. C. Cheung, and K. H. Vousden, "Control of glycolysis through regulation of PFK1: old friends and recent additions," *Cold Spring Harb Symp Quant Biol*, vol. 76, pp. 211-6, 2011.

[32] N. Raben and J. B. J. H. m. Sherman, "Mutations in muscle phosphofructokinase gene," vol. 6, no. 1, pp. 1-6, 1995.

[33] S. Wang *et al.*, "The Role of Glyceraldehyde-3-Phosphate Dehydrogenases in NADPH Supply in the Oleaginous Filamentous Fungus Mortierella alpina," *Front Microbiol*, vol. 11, p. 818, 2020.
[34] P. F. Kantor, G. D. Lopaschuk, and L. H. Opie, "CHAPTER 32 - Myocardial Energy Metabolism," in *Heart Physiology and Pathophysiology (Fourth Edition)*, N. Sperelakis, Y. Kurachi, A. Terzic, and M. V. Cohen, Eds. San Diego: Academic Press, 2001, pp. 543-569.
[35] L. R. Gray, S. C. Tompkins, and E. B. Taylor, "Regulation of pyruvate metabolism and human disease," *Cell Mol Life Sci*, vol. 71, no. 14, pp. 2577-604, Jul 2014.
[36] B. Quistorff and N. J. A. Grunnet, "The isoenzyme pattern of LDH does not play a physiological role; except perhaps during fast transitions in energy metabolism," vol. 3, no. 5, p. 457, 2011.
[37] F. M. Matschinsky *et al.*, "The network of glucokinase-expressing cells in glucose homeostasis and the potential of glucokinase activators for diabetes therapy," vol. 55, no. 1, pp. 1-12, 2006.
[38] F. M. Matschinsky and D. F. Wilson, "The Central Role of Glucokinase in Glucose Homeostasis: A Perspective 50 Years After Demonstrating the Presence of the Enzyme in Islets of Langerhans," *Front Physiol*, vol. 10, p. 148, 2019.
[39] N. Al Hasawi, M. F. Alkandari, and Y. A. Luqmani, "Phosphofructokinase: a mediator of glycolytic flux in cancer progression," *Crit Rev Oncol Hematol*, vol. 92, no. 3, pp. 312-21, Dec 2014.
[40] T. E. J. C. t. i. c. r. Mansour, "Phosphofructokinase," vol. 5, pp. 1-46, 1972.
[41] W. Yang and Z. Lu, "Regulation and function of pyruvate kinase M2 in cancer," *Cancer Lett*, vol. 339, no. 2, pp. 153-8, Oct 10 2013.
[42] V. Gupta and R. N. Bamezai, "Human pyruvate kinase M2: a multifunctional protein," *Protein Sci*, vol. 19, no. 11, pp. 2031-44, Nov 2010.
[43] J. F. Turner and D. H. Turner, "7 - The Regulation of Glycolysis and the Pentose Phosphate Pathway," in *Metabolism and Respiration*, D. D. Davies, Ed.: Academic Press, 1980, pp. 279-316.
[44] L. J. P. o. t. N. S. Agius, "Dietary carbohydrate and control of hepatic gene expression: mechanistic links from ATP and phosphate ester homeostasis to the carbohydrate-response element-binding protein," vol. 75, no. 1, pp. 10-18, 2016.
[45] L. B. Bockus *et al.*, "Cardiac Insulin Signaling Regulates Glycolysis Through Phosphofructokinase 2 Content and Activity," *J Am Heart Assoc*, vol. 6, no. 12, Dec 4 2017.
[46] P. V. Roder, B. Wu, Y. Liu, and W. Han, "Pancreatic regulation of glucose homeostasis," *Exp Mol Med*, vol. 48, p. e219, Mar 11 2016.
[47] M. H. Lundqvist, K. Almby, N. Abrahamsson, and J. W. Eriksson, "Is the Brain a Key Player in Glucose Regulation and Development of Type 2 Diabetes?," *Front Physiol*, vol. 10, p. 457, 2019.
[48] S. Kalra *et al.*, "Hypoglycemia: The neglected complication," (in eng), *Indian journal of endocrinology and metabolism*, vol. 17, no. 5, pp. 819-834, 2013.
[49] A. C. Hauge-Evans *et al.*, "Somatostatin secreted by islet δ-cells fulfills multiple roles as a paracrine regulator of islet function," vol. 58, no. 2, pp. 403-411, 2009.
[50] N. Wierup, H. Svensson, H. Mulder, and F. J. R. p. Sundler, "The ghrelin cell: a novel developmentally regulated islet cell in the human pancreas," vol. 107, no. 1-3, pp. 63-69, 2002.
[51] C. Bouche, S. Serdy, C. R. Kahn, and A. B. Goldfine, "The cellular fate of glucose and its relevance in type 2 diabetes," *Endocr Rev*, vol. 25, no. 5, pp. 807-30, Oct 2004.
[52] Y. Kong *et al.*, "Types of carbohydrate in feed affect the growth performance, antioxidant capacity, immunity, and activity of digestive and carbohydrate metabolism enzymes in juvenile Macrobrachium nipponense," *Aquaculture*, vol. 512, 2019.
[53] S. Brooks *et al.*, "Report of the ad hoc Glycemic (Net) Carbohydrate Definition Committee to AACC International Board of Directors," ed, 2006.
[54] C. Hurtado and C. Waasdorp, "Carbohydrate Digestion and Absorption NASPGHAN Physiology Series," ed, 2018.
[55] S. C. Moore *et al.*, "Leisure time physical activity of moderate to vigorous intensity and mortality: a large pooled cohort analysis," *PLoS Med*, vol. 9, no. 11, p. e1001335, 2012.
[56] P. Zimmet, K. Alberti, and J. J. N. Shaw, "Global and societal implications of the diabetes epidemic," vol. 414, no. 6865, pp. 782-787, 2001.
[57] M. A. Atkinson and N. K. J. N. E. j. o. m. Maclaren, "The pathogenesis of insulin-dependent diabetes mellitus," vol. 331, no. 21, pp. 1428-1436, 1994.
[58] A. R. J. C. Saltiel, "New perspectives into the molecular pathogenesis and treatment of type 2 diabetes," vol. 104, no. 4, pp. 517-529, 2001.
[59] G. Wilcox, "Insulin and insulin resistance," (in eng), *The Clinical biochemist. Reviews*, vol. 26, no. 2, pp. 19-39, 2005.
[60] M. Mishra and J. J. C. P. D. Fomusi Ndisang, "A critical and comprehensive insight on heme oxygenase and related products including carbon monoxide, bilirubin, biliverdin and ferritin in type-1 and type-2 diabetes," vol. 20, no. 9, pp. 1370-1391, 2014.
[61] M. C. Petersen, D. F. Vatner, and G. I. J. N. r. e. Shulman, "Regulation of hepatic glucose metabolism in health and disease," vol. 13, no. 10, pp. 572-587, 2017.
[62] J. F. Ndisang and M. J. A. j. o. h. Mishra, "The heme oxygenase system selectively suppresses the proinflammatory macrophage m1 phenotype and potentiates insulin signaling in spontaneously hypertensive rats," vol. 26, no. 9, pp. 1123-1131, 2013.
[63] L. Duvnjak and M. J. J. P. P. Duvnjak, "The metabolic syndrome-an ongoing story," vol. 60, no. Suppl 7, pp. 19-24, 2009.

[64] B. K. Pedersen, "Anti-inflammatory effects of exercise: role in diabetes and cardiovascular disease," *Eur J Clin Invest*, vol. 47, no. 8, pp. 600-611, Aug 2017.
[65] J. E. Gerich, M. Langlois, C. Noacco, J. H. Karam, and P. H. J. S. Forsham, "Lack of glucagon response to hypoglycemia in diabetes: evidence for an intrinsic pancreatic alpha cell defect," vol. 182, no. 4108, pp. 171-173, 1973.
[66] A. Cherrington, J. Chiasson, J. Liljenquist, W. Lacy, and C. Park, "Control of hepatic glucose output by glucagon and insulin in the intact dog," in *Biochemical Society symposium*, 1978, no. 43, pp. 31-45.
[67] P. S. Kishnani *et al.*, "Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics," *Genet Med*, vol. 16, no. 11, p. e1, Nov 2014.
[68] G. Jiang, B. B. J. A. J. o. P.-E. Zhang, and Metabolism, "Glucagon and regulation of glucose metabolism," vol. 284, no. 4, pp. E671-E678, 2003.
[69] N. Kedia, "Treatment of severe diabetic hypoglycemia with glucagon: an underutilized therapeutic approach," *Diabetes Metab Syndr Obes*, vol. 4, pp. 337-46, 2011.
[70] N. J. M. B. Bhagavan, "Carbohydrate Metabolism II: Gluconeogenesis, Glycogen Synthesis and Breakdown, and Alernative Pathways," vol. 4, 2001.
[71] B. Y. Pan *et al.*, "Role of phosphoglucomutase in regulating trehalose metabolism in Nilaparvata lugens," *3 Biotech*, vol. 10, no. 2, p. 61, Feb 2020.
[72] M. J. Pereira *et al.*, "Direct effects of glucagon on glucose uptake and lipolysis in human adipocytes," *Mol Cell Endocrinol*, vol. 503, p. 110696, Mar 1 2020.