Review Article

Diabetes and diabesity in the view of proteomics, drug, and plant-derived remedies

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Diabetes and obesity are highly prevalent in the world. Proteomics is a promising approach to better understanding enzymes, proteins, and signaling molecules involved in diabetes processes which help recognize the basis of the disease better and find suitable new treatments. This study aimed to summarize the molecular mechanisms from the beginning of insulin secretion in response to stimuli to the pathology of the insulin signaling pathway and, finally, the mechanisms of drugs/chemicals remedies that affect this process. The titles and subtitles of this process were determined, and then for each of them, the articles searched in PubMed and ScienceDirect were used. This review article starts the discussion with the molecular basis of insulin biosynthesis, secretion, insulin's mechanism of action, and molecular aspect of diabetes and diabesity (a new term showing the relation between diabetes and obesity) and ends with the drug and plant-derived intervention for hyperglycemia.

Key words: Diabesity, diabetes, metabolomics, signal transduction

How to cite this article: Haeri MR. Diabetes and diabesity in the view of proteomics, drug, and plant-derived remedies. J Res Med Sci 2023;28:77.

METABOLOMICS IN INSULIN SECRETION AND EFFECT

Insulin biosynthesis

In the pancreas, β-cells are the only cells committed to transcribing the insulin gene that may be replaced during β-cells injury by γ-cells.[1] In contrast, the insulin receptors are widely distributed even on cells that are not known as insulin responsive.[2] Human insulin is synthesized as a preproinsulin peptide, which is processed to proinsulin and then to insulin (consisting of A and B chains with a total of 51 amino acids) by the effect of endopeptidases. Insulin gene expression is regulated by some nutrients and insulin itself. Several transcription factors bind to numerous sequences in the promoter region of the insulin gene for regulating the expression of insulin, among them pancreatic and duodenal homeobox-1(PDX-1), MafA, (Mast cell function-associated antigen), and B-2/neurogenic differentiation 1 are the famous ones.[3]

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jrms

DOI: 10.4103/jrms.jrms_487_22

Molecular mechanism of insulin secretion

The blood glucose level is regulated by the opposite action of insulin and glucagon within a narrow range.[4] Elevation of blood glucose after a meal stimulates β-cells to increase insulin secretion. In contrast, α-cells secrete glucagon when the blood glucose is low, thereby increasing gluconeogenesis, glycogenolysis, and blood glucose. Between meals, the reduction of blood glucose triggers the release of norepinephrine and neuropeptide galanin from the sympathetic nerves resulting in increasing glucagon secretion and inhibiting insulin secretion.[5] During a meal, the secretion of acetylcholine and the pituitary adenylate cyclase-activating polypeptide, vasoactive intestinal polypeptide, glucagons like peptide 1 (GLP-1), and gastric insulinotropic polypeptide (GIP) which potentiate glucose-induced insulin secretion.[6]

The effectors that modulate insulin secretion are categorized as initiators, potentiators, and inhibitors.

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Submitted: 08-Jul-2022; **Revised:** 08-Jul-2023; **Accepted:** 31-Jul-2023; **Published:** 26-Oct-2023

Glucose, some amino acids, and fatty acids are the most famous initiators.[7] As an initiator of insulin secretion, arginine increases intracellular calcium [Ca2+]i through a ATP-sensitive K + channel-independent pathway. Only when there is an initiator, do the potentiators enhance insulin secretion.[8]

Glucose transporter 2 (GLUT2) and glucokinase (GK) are two glucose sensors in β-cells. When glucose enters the β-cell via GLUT2, it is phosphorylated by GK and trapped inside the cells. GLUT2 gene expression is increased in diabetes, indicating the importance of β-cell responses. The kinetics properties of GK (like low Km) make it a delicate sensor of glucose.[9,10] Another biochemical property of β-cells is the low levels of lactate dehydrogenase (LDH), which causes levels of NADH to remain high and ultimately increases insulin secretion. That is why pharmacological inhibition of LDH increases NADH levels and stimulates mitochondrial shuttles which ultimately leads to insulin secretion.[11,12]

K + ATP-independent pathways of insulin secretion involve Krebs cycle intermediates (anaplerosis), perhaps via malonyl-CoA. Moreover, insulin release is correlated with citrate and malate.[13] Elevated citrate and a-ketoglutarate trigger the release of calcium-independent insulin secretion, indicating the importance of anaplerosis on the stimulation of β-cells.[13,14] The β-cell resting membrane potential is largely defined by ATP-sensitive K + channels (KATP). As ATP/ADP ratio increases due to glucose metabolism, KATP is closed which leads to depolarization of the cell membrane and the opening of the voltage-dependent L-type Ca2+ channels. This leads to the elevation of [Ca2+]i and the movement of insulin-containing granules toward the plasma membrane [Figure 1].[15,16] Calcium activates calmodulin-dependent protein kinases, which phosphorylate a series of proteins such as myosin light chain and result in insulin secretion.[17]

β-cells express N-, P/Q-, and L-type Ca2+ channels. The earlier one plays a significant role in Ca2+ influx. The L-type channels open if there is a depolarization signal and then inactivate slowly. Inside the cell, calcium ions as a feedback effector can close L-type channels and prevent further calcium entry.[15,18]

The time required for exocytosis of insulin-containing granules is much less than the time required for calcium distribution in the cytoplasm after the opening of calcium channels, indicating that the granules are close to calcium channels and are sensitive to local changes in calcium concentration. Beta cells may contain thousands of secretory granules, but only a tiny number is available for immediate release which is known as the readily releasable pool (RRP). The rest of the granules that are known as reserve pools must be moved to RRP before discharge. The RRP is absent in type 2 diabetes.[19-21] The number of released granules is dependent on the activation of protein kinase C, which phosphorylates the exocytotic proteins such as Mammalian uncoordinated protein (Munc), a protein associated with secretory granules. Any decrease

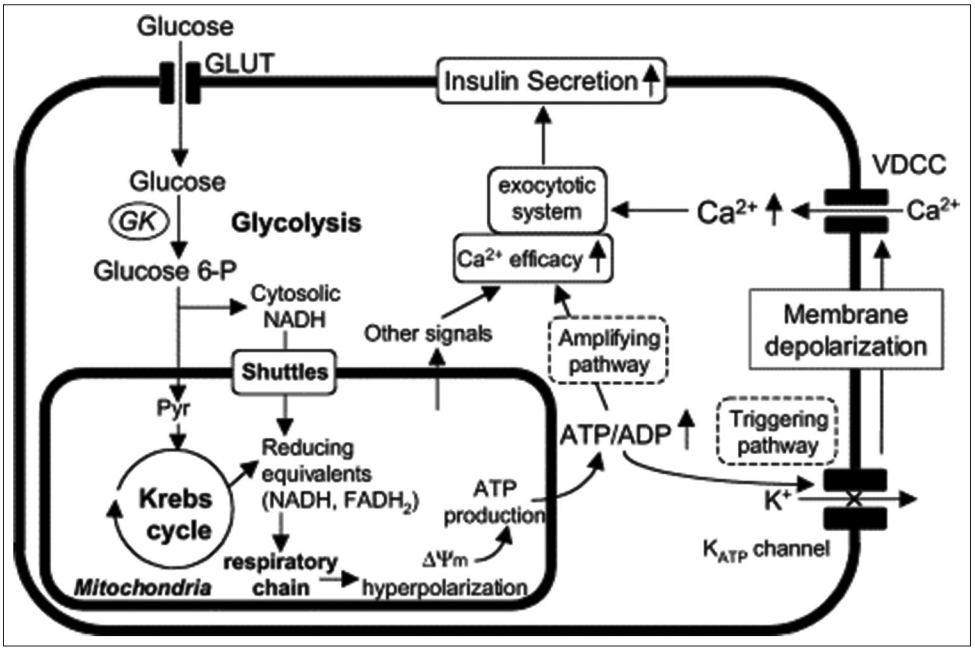

Figure 1: Mechanism of insulin secretion by the cytosolic ATP/ADP ratio (adapted from reference 16). Insulin secretin processes start from entering glucose into β-cells which results in increasing ATP production. As ATP/ADP ratio increases due to glucose metabolism, ATP-sensitive K+ channels are closed which leads to the depolarization of the cell membrane and the opening of the voltage-dependent Ca2+ channels, leading to the elevation of intracellular calcium and movement of insulin-containing granules toward the plasma membrane. GLUT: Glucose transporter 2, VDCC: voltage-gated calcium channel

in Munc production in the cells results in decreased insulin secretion.[17,21,22]

Therefore, glucose-stimulated insulin secretion is biphasic. In the first phase, previously synthesized insulin-containing membrane-docked granules are released from the RRP store triggered by Ca2+ influx, and reach a maximum level after 5-10 min, and is followed by a developing second phase consisting of the release of granules from the reserved pool. Type 2 diabetes patients have problems mainly with first-phase insulin secretion, but second-phase insulin secretion is also affected.[23,24] Although the exact mechanism by which vesicles are transported to the membrane is unclear, kinesin appears to be involved as a protein motor.[25] While inhibition of class IA PI3K (Class IA phosphatidylinositol-3-kinase) decreases insulin secretion,[26] others reported acute inhibition of class IA PI3K enhances glucose-induced insulin secretion.[27]

Insulin's mechanism of action

The main function of insulin is to regulate blood sugar. Insulin is transported through the portal vein to the liver where it reduces glucose release, increases glucose storage and lipogenesis,[28,29] intensifies the transport of amino acids into the cell, and inhibits lipolysis. Insulin affects the expression of several genes and stimulates DNA replication, causing cell proliferation and growth. Glucose enters the cell through glucose transporters (GLUTs) in the cell membrane. GLUT1 is found in most cells. GLUT2 is located in the liver and beta cells, GLUT3 in the brain, and GLUT4 in skeletal muscle, heart, and adipose tissue.[30] In hepatocytes, glucose uptake is greatly increased by activation of glycolytic enzymes (GK, phosphofructokinase 1, and pyruvate kinase) through activation of protein phosphatase and inhibition of protein kinase A. Glucose 6-phosphatase activity is also reduced. The final result of these processes is a decrease in blood sugar and an increase in the glucose content of the liver.[31] In addition, activation of phosphatase and reduction of cAMP levels leads to increased glycogen synthase activity and decreased glycogen phosphorylase activity, with a net consequence of increased glycogen synthesis.[32] Insulin emerges all of the effects through binding to its receptor and consequent activation of several signal molecules. Activation of insulin receptor substrates (IRSs) results in the activation of PI3K which in turn, phosphorylates membrane phospholipids (phosphatidylinositol 4,5 phosphate, PIP2), and produce phosphatidylinositol 3,4,5 triphosphate (PIP3) which activates protein kinase B (PKB, also called Akt), PIP3-dependent kinase (PDK), PKC (principally PKC-λ), and small ribosomal subunit protein 6 kinase (S6K).[32,33]

Second, activation of PKB and PKC-λ leads to displacement of GLUT4 to the cell membrane.[34] Furthermore, activated PKB results in the phosphorylation of glycogen synthase kinase-3 (GSK3), which is a pivotal regulatory molecule of glycogen metabolism.[35] Insulin also exerts its effects by regulating gene expression, mainly through sterol-regulated element-binding protein (SREBP).[36] SREBP increases GK, pyruvate kinase, lipoprotein lipase (LPL), fatty acid synthase, and acetyl-CoA carboxylase and decreases G6Pase, F1,6Pase, and PEPCK activity.[31,37,38]

METABOLOMICS IN DIABETES

Diabetes classification

Diabetes mellitus is a syndrome with numerous symptoms and causes. Based on recently provided guidelines by the American Diabetes Association, four main forms of diabetes mellitus exist, type 1 diabetes (autoimmune diabetes), formerly known as insulin-dependent or juvenile-onset diabetes, type 2 diabetes (due to insulin resistance), formerly known as noninsulin-dependent diabetes, gestational diabetes mellitus, other types of diabetes due to various causes (i.e., monogenic and drug or chemical induced diabetes). Despite previous perceptions, type 1 and type 2 diabetes are seen in both children and adults. Nowadays, the traditional classification of diabetes is no longer valid because diabetes type 1 and 2 are found in both adults and children.[39] Another rarely found diabetes is Brittle diabetes. It is defined by unexplained fluctuation between hyperglycemia and hypoglycemia and recurrent diabetic ketoacidosis.[40]

Molecular aspects of type 2 diabetes

Recent research revealed some genetics and epigenetics factors involved in the pathogenesis of type 2 diabetes. Some monogenic loci are known to be associated with type 2 diabetes, but none of them are the main cause of the disease (i.e., >50% in all cases). The most important genes that are involved in the progression of diabetes type 2 are GLUT-2, HNF4α,[41] pancreatic GK (MODY 2), preproinsulin gene (INS), and peroxisome proliferator-activated receptor γ (PPARγ).[42-44] Recent evidence has proposed a role for a ligand-gated transcription factor named PPARγ in the etiology of type 2 diabetes.[45] When activated, PPARγ binds to another transcription factor, retinoid X receptor. After dimerization, a specific set of insulin-sensitive genes in adipose tissue such as LPL, fatty acid transporter protein (FATP), fatty acyl CoA synthase, and glucose transporter 4 (GLUT4), become activated [Figure 2]. Thiazolidinediones (TZDs) as hypoglycemic agents and PPARγ ligand increase the sensitivity of the body to insulin. Thus, TZDs provide a new way of treating insulin resistance.[46,47] Mutations in the PPARγ gene seem to be related to insulin resistance,[43] adipocyte hypertrophy, and hepatic steatosis.[48]

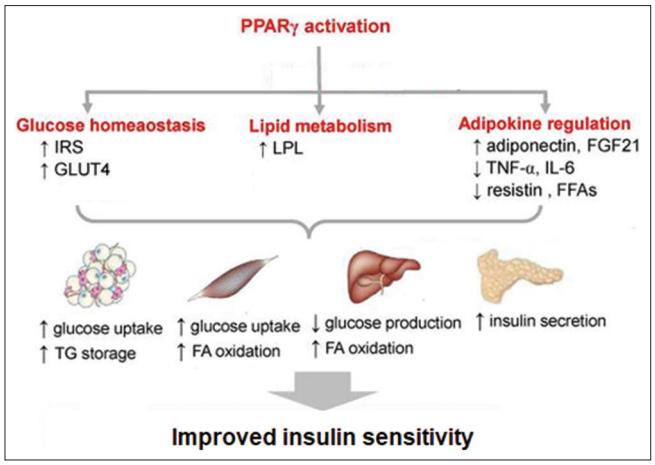

Figure 2: Mechanisms of actions of peroxisome proliferator-activated receptor (PPAR) γ ligands in glucose and lipid metabolism resulting in improved insulin sensitivity, adapted from reference 49. The activation of PPAR affects the gene expression of three different pathways. It increases IRS and glucose transporter 4 in glucose metabolism, increases lipoprotein lipase in fat metabolism and increases adiponectin, and decreases tumor necrosis factor-alpha. The set of these effects in important metabolic tissues such as fat, muscle, and liver leads to an increase in glucose uptake and consumption and glucose tolerance. PPAR: Proliferator-activated receptor, IRS: insulin receptor substrate, GLUT4: Glucose transporter 4, LPL: Lipoprotein lipase, FGF21: Fibroblast growth factor 21, TNF: Tumor necrosis factor, IL-6: Interleukin-6

Another important molecule involved in the regulation of lipid metabolism in the liver is PPARα, which regulates the expressions of enzymes of fatty acid metabolism such as fatty acid transport proteins (FATPs), carnitine palmitoyl transferases, acyl-CoA oxidase, and apolipoprotein A-I.[49] Therefore, PPARα agonists (pemafibrate) improve hyperlipidemia (hypertriglyceridemia) in high fructose-fed rats.[50] Furthermore, it has been postulated that activation of PPARα can improve insulin resistance.[51]

In pancreatic β-cells, the glucose-sensing system consists of GLUT2 and GK.[52] The GK gene contains two different promoters for the expression of tissue-specific GKs in the liver and β-cells. Both GLUT2 and GK sense the oscillation of blood glucose levels. When glucose enters the cells via GLUT2 is phosphorylated by GK and trapped in the cells. GK is a key enzyme in glycolysis, and GLUT2 plays an important role in the equilibration of glucose inside and outside the cells.[53]

Epigenetics as a new molecular approach helps scientists to link genetics, environmental factors, and diseases. Epigenetics processes such as DNA methylations, histone modifications, and microRNAs make changes in gene functions, not necessarily changes in the nucleotide sequence, that may be inherited by the next generation. For example, infants born from mothers with gestational diabetes represent hypermethylation and epigenetic downregulation of IGF2 gene, which affects insulin sensitivity. Epigenetic mechanisms were found to affect genes involved in insulin resistance such as GLP-1 receptor. However, much more studies are necessary to fully understand epigenetic mechanisms in the pathogenesis of type 2 diabetes.[41]

Diabesity (diabetes + obesity)

The simultaneous increase in the prevalence of obesity and insulin resistance as a major component of metabolic syndrome and diabetes type 2 encouraged the scientists to coin a new term expressing the relationship between diabetes and obesity, diabesity. Obesity and type 2 diabetes are spreading epidemically, and the number of people diagnosed with diabetes has increased by about six times in the last 40 years. Type 2 diabetes is complex because it is a multifactorial disease related to several pathological factors such as high blood levels of triglycerides, obesity, impaired glucose tolerance, and insulin resistance, all of which are referred to as metabolic syndrome (insulin resistance syndrome).[54-56] However, although most individuals with type 2 diabetes are obese, obesity alone does not always provide a route to insulin resistance because some obese persons do not have insulin resistance and vice versa, suggesting the role of other factors in insulin resistance.[55] The hallmarks of almost all metabolic syndromes include obesity, insulin resistance, low high-density lipoprotein cholesterol (HDL-C), dyslipidemia, and high blood pressure. Evidence suggests that metabolic syndrome starts in the early years of life and spreads from childhood to adulthood, leading to type 2 diabetes. Inflammatory processes are believed to link obesity and insulin resistance, known as the inflammation hypothesis. For example, chemokines and interleukin 6 (IL-6) production released from adipose tissues trigger insulin resistance.[55] Furthermore, elevated plasma fatty acids reduce activation of IRS-1-linked PI-3K activity by insulin in skeletal muscle. Lipid-induced insulin resistance is linked to defects in the transport of GLUT4. Saturated fatty acids initiate metabolic inflammation through toll-like receptors and inflammasomes that lead eventually to increased production of pro-inflammatory cytokines. It is now believed that pro-inflammatory cytokines interfere with insulin signaling and insulin action in adipocytes and hepatocytes by activating numerous kinases.[56] The main factor increasing the prevalence of insulin resistance is diet and the resulting obesity. Nutrition, along with other factors such as physical activity, sleep, and mental health, should be considered in diabesity prevention.[57] It has previously been shown that saturated fats cause weight gain, hyperlipidemia, and insulin resistance. However, a low carbohydrate-high fat diet is more effective in comparison to a low-fat diet in reducing central fat,[58] indicating that focusing on fat alone is not enough. Recent studies suggest that consumption of refined carbohydrates especially fructose may increase the risk of insulin resistance.[59-61]

Fructose in diabetes and metabolic syndrome

Fructose consumption (in many food products), the prevalence of obesity, and related metabolic syndrome have simultaneously increased in the past four decades, indicating the causal effect of fructose on insulin resistance.[62] Fructose leads to several metabolic derangements, most importantly insulin resistance.[63] Fructose reduces the expression of GLUT4 gene, significantly increases hepatic triglyceride synthesis, impairs insulin signaling, and subsequently reduces insulin sensitivity.[59,64] Fructose reduces hepatic expression of IRS-2, increases plasma insulin levels, and causes an abnormal glucose tolerance test indicating disturbed hepatic insulin signaling.[65] Furthermore, phosphorylation of some members of the insulin signaling pathway (IRS1 and Akt) is reduced after feeding a fructose-rich diet presumably through increased activation of protein-tyrosine phosphatase 1B which leads to insulin resistance.[59,66] Moreover, increased free fatty acids in fructose-fed animals contribute to insulin resistance. If free fatty acids are not removed effectively, it can lead to increased triglyceride production.[65,66] Therefore, high fructose intake leads to visceral adiposity and weight gain. Fructose as a palatable food additive encourages overeating. Further, it is essential to know that fructose cannot efficiently suppress appetite, but instead increases ghrelin, known as the hunger hormone.[67]

The effect of chronic fructose consumption in adipogenesis performed by activating sterol regulatory element-binding protein 1c (SREBP1c), a potentiator of lipid synthesis. Fructose activates SREBP1c indirectly by induction of hyperinsulinemia.[68] Fructose also reduces PPARα expression in the liver cells.[69] Hence, decreased PPARα expression can result in reduced β-oxidation which was seen in insulin resistance.[70] There is also a close relationship between a high fructose diet and impaired vascular relaxation through induction of oxidative stress that may be the underlying mechanism for blood pressure.[71,72]

Liver in diabetes and insulin resistance status

Among several diabetic-related organ complications, the liver plays a major role in insulin resistance. Several epidemiological studies have reported an association between elevated aspartate transaminase (AST) and alanine aminotransferase (ALT) levels and diabetes type 2 and insulin resistance status.[73-75] AST and especially ALT may be valuable tools for diagnosis and prediction of diabetes type 2 and insulin resistance,[76-78] especially when considered along with gamma-glutamyltransferase (GGT) to improve the prediction of impaired fasting glucose.[79] It has been reported that changes in the ALT/AST ratio are parallel with changes in β-cell function and insulin sensitivity, providing a pathologic basis for the association of the aminotransferases with a higher risk of developing type 2 diabetes.[80] On the other hand, Liu *et al*. reported elevated ALT, AST, and GGT levels in nondiabetic but insulin-resistant adults, especially those who were obese, indicating the impact of obesity in this relationship.[81] Increased risk of diabetes incidence is correlated to nonalcoholic fatty liver disease (NAFLD) and circulating liver enzymes (AST, ALT, GGT, and alkaline phosphatase).[82] The relation between NAFLD and its advanced form of nonalcoholic steatohepatitis (NASH) can be explained by the lipotoxic state, which results in the necroinflammation of hepatocytes.[83]

Increased ALT activity even within the reference intervals correlates with increasing hepatic fat. Elevated hepatic aminotransferases indicate fat accumulation in the liver, as seen in NAFLD, a characteristic feature of insulin resistance syndrome.[84] NAFLD is defined as high lipid deposition in the liver parenchymal cells in patients without a history of high alcohol consumption.[85] There is a vicious circle between insulin resistance and inflammation, so that each condition accelerates the other to develop NAFLD. Regarding inflammatory processes, nuclear factor-kappa B (NF-κB) plays a transcriptional regulator in the expression of IL-6 and tumor necrosis factor-alpha (TNF-α), known as pro-inflammatory cytokines.[86] Inhibition of TNF-α receptor improves insulin resistance and ameliorates NAFLD.[87] Furthermore, as previously described, high fructose diet could lead to metabolic syndrome and insulin resistance. One possible mechanism may be triggering an inflammatory response by fructose feeding through stimulation of TNF-α production.[61] Mazzoli *et al*. showed that inflammation reversed after removing fructose from the diet,[88] indicating fructose-induced inflammatory processes that lead to liver injury and increasing circulating liver markers.

THERAPEUTIC INTERVENTION FOR HYPERGLYCEMIA

Persistent hyperglycemia is the major concern in insulin resistance and diabetes. For this reason, all treatment strategies aim to lower blood glucose. Many pharmacologic agents act through different mechanisms to normalize blood sugar. In this section, conventional drugs along with new hypoglycemic drug candidates, some of which with no risk of hypoglycemic shock, and plant-derived drugs will be discussed. Therapeutic agents and their proved/proposed mechanisms of action are summarized in Table 1.

Amino acid derivatives

Some amino acid derivatives have been studied in recent years with promising outcomes as new treatments for type 2 diabetes. Nateglinide, an o-phenylalanine derivative, is the most famous hypoglycemic agent with an amino acid backbone. Nateglinide increases blood insulin levels after a few minutes of oral administration.

Table 1: Therapeutic agents and their proved/proposed mechanisms of action

	Drug/chemical	Proposed mechanism (s)	Reference
Amino acid derivatives	Nateglinide	↑ glucose-dependent insulin secretion	[89]
	Agmatine	↑insulin secretion through secretion of endorphins	[91]
	4-hydroxyisoleucine	Insulinotropic↑GLUT4, expression of IRS-1, activates PI3-kinase, ↓ TNFα expression	[93-96]
PPARγ activators	TZDs	↑ expression of GLUT4, LPL, GK, fatty acyl-CoA synthase, and adiponectin	[97]
GLP-1 receptor agonists	TZDs	↑ insulin secretion, through upregulation of AMP-activated protein kinase	[102]
	Pioglitazone	↓ PEPCK, and G6Pase	[103,104]
	Lobeglitazone	↑ β-cell viability	[108]
SGLT2 inhibitors	Ertugliflozin, dapagliflozin, canagliflozin, and Empagliflozin	↓ glucose reabsorption, GLP-1	[99,110]
Dipeptidyl peptidase-IV inhibitors	Vildagliptin, sitagliptin, linagliptin, saxagliptin, alogliptin	↓ GLP-1 and GIP degradation	[114,115]
α-glucosidase inhibitors	Miglitol, acarbose, nicotinic acid, hydroxyproline	Pancreatic α-glucosidase competitive inhibition	[117-119]
Biguanides	Metformin	↓ gluconeogenesis through inhibition of glycerol-3-phosphate dehydrogenase, ↓ cyclic AMP downregulation of gluconeogenic genes, ↓ glucose uptake, ↑ expression and translocation of GLUT4	[123-125]
GLP-1 receptor agonists	Albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, dayexenatide	Improve glycemic control through activation of GLP-1	[128]
Drug candidates	Bromocriptine	through CNS, reduces insulin resistance and hepatic gluconeogenesis, ↓ IL-6 and leptin, ↑ PPAR-γ/adiponectin, and GLP-1	[130,131]
	Vanadium compounds	↑ GK activity, inhibition of PEPCK, in part, by nonselective inhibition of phosphotyrosine phosphatase	[99,133]
	Colesevelam (bile acid sequestrants)	↑ secretion of incretin	[134]

PPARγ=Peroxisome proliferator-activated receptor gamma; GULT 4=Glucose transporter 4; IRS-1=Insulin receptor substrate-1; PI3=Phosphatidylinositol-3; TNFα=Tumor necrosis factor-alpha; LPL=Lipoprotein lipase; GK=Glucokinase; AMP=Activated protein kinase; PEPCK=Phosphoenolpyruvate carboxykinase; GLP-1=Glucagons like peptide 1; IL-6=Interleukin 6; TZDs=Thiazolidinediones ;↑=Means increase; ↓=Mean decrease

Nateglinide binds to the sulfonylurea receptor in β-cells and increases insulin secretion by closing the K-ATP channels. Unlike sulfonylureas, nateglinide does not inhibit the opposite activity of glucagon, so its effect is without risk of hypoglycemia. It is essential to know that action of nateglinide is glucose-dependent. KATP channels' response to nateglinide is lower in euglycemia in comparison to hyperglycemia. Therefore nateglinide does not cause prolonged insulin release. This impedes the continuous secretion of insulin and protects β-cells from exhaustion. Recent research has shown that nateglinide affects the exocytosis of insulin-containing granules. This function is independent of its effect on the K-ATP channels. Therefore, nateglinide is effective not only in the first but also in the second phase of insulin secretion showing its great benefits in treating type 2 diabetic patients.[89]

Agmatine, a decarboxylated form of arginine, is another amino acid derivative that is under investigation for its hypoglycemic effect. It reduces blood sugar by increasing insulin secretion and glucose uptake through increased secretion of endorphins from the adrenal glands. This effect may be performed via activation of the imidazoline I2 receptor.[90] It also impedes the reduction of insulin signaling members in a high-fat diet, streptozotocin (STZ)-induced diabetic mice.[91]

Another amino acid derivative with hypoglycemic effects comes from the fenugreek seeds. In 1973 for the first time, Fowden *et al*. isolated and reported an unusual amino acid in the defatted seeds and identified it as 4-hydroxyisoleucine (4-OH-Ile).[92] Glucose-dependent insulinotropic effect of 4-OH-Ile was approved using isolated β-cells.[93] More importantly, it has been reported that the hypoglycemic effect of 4-OH-Ile is not limited to its insulinotropic effect. Haeri *et al*. showed that in multiple injected diabetic type 1 rats, 4-OH-Ile still is having a hypoglycemic impact without any increase in insulin recreation, indicating that 4-OH-Ile potentiates insulin signaling.[94] This possibility was reinforced by the provision of molecular evidence. It has been shown that 4-OH-Ile increases the number of GLUT4, downregulates the expression of TNF-α, stimulates the expression of IRS-1,[95] and activates PI3-kinase in the muscles of diabetic rats.[96] These pieces of evidence show that 4-OH-Ile has multiple mechanisms from insulinotropic to insulinomimetic actions.

Peroxisome proliferator-activated receptor γ activators

Activators of PPARγ exert their clinical benefits by activating several genes involved in fat and glucose metabolism. PPARγ responsive genes are present in three major tissues, adipose tissue, liver, and muscle which are involved in glucose regulation and fatty acid storage. PPARγ agonists

increase the expression of several genes including, GLUT4, LPL, GK, fatty acyl-CoA synthase, and adiponectin, thereby increasing glucose uptake and fatty acid oxidation, leading to improve insulin sensitivity.[97] Treating patients with pioglitazone, a PPARγ activator maintains β-cell function, increases HDL-C cholesterol, improves insulin sensitivity, and decreases glucose levels with no enhancement of endogenous insulin secretion.[98,99]

It has been reported that TZDs protect the β-cells from apoptosis through activation of AMP-activated protein kinase (AMPK) independent of PPARγ[100] and improve the glucose-sensing ability of β-cells via upregulation of GLUT2 and GK gene.[101] Furthermore, TZDs potentiate insulin secretion, mediated through upregulation of AMP-activated protein kinase,[102] indicating multiple sites of actions of TZDs. In the liver cell line, pioglitazone decreases PEPCK, and glucose-6-phosphatase and increases GK expressions, thereby reducing gluconeogenesis and increasing glycolysis.[103,104]

Besides the crucial beneficial effect of TZDs, there have been reports of their severe several side effects such as fractures, water retention, and weight gain.[105] Troglitazone, the first generation of TZDs, has been withdrawn from the market because of its potential hepatotoxicity.[106] Recently, some new PPARγ agonists have been introduced or are under investigation. Lobeglitazone as a new member of the TZDs family of antidiabetic drugs activates both PPARα and PPARγ with a lower effective dose and acceptable safety. In fat cells, it works as an insulin sensitizer to improve cell response to insulin.[107] In β-cell line (INS-1), lobeglitazone increases cell viability and improves hyperglycemia.[108] Reglitazar (also known as Reglixane) is the newest non-thiazolidinedione dual PPAR agonist (PPARα/γ) developed by Pfizer. It shows a potent capacity to lower triglycerides and blood glucose besides its ameliorating effect on diabetic complications, such as cataracts, nephropathy, and neuropathy.[109]

Sodium-glucose co-transporter type 2 inhibitors

Sodium-glucose co-transporter type 2 (SGLT2) is the predominant transporter of glucose found in the kidney, responsible for the reabsorption of glucose, whereas SGLT1 is expressed in the kidney and small intestine to pass glucose or galactose across the epithelial cells.[110] Recently discovered SGLT2 inhibitors (ertugliflozin, dapagliflozin, canagliflozin, and empagliflozin) through blocking glucose reabsorption lower the kidney threshold and increase excretion of glucose in the urine with a lower risk of hypoglycemia in comparison to other hypoglycemic agents. Desirable bioavailability and the need to use only one dose per day introduced them as a suitable choice to control hyperglycemia. However, these inhibitors are less effective in people with reduced kidney function (104 and 115). In addition, since SGLT1 is also expressed in the intestine, a dual-action inhibitor that inhibits both types 1 and 2 can be more effective. Comparing sotagliflozin as the first dual SGLT1/SGLT2 inhibitor to SGLT2 inhibitors showed greater glucosuria and glycemic control.[110] Sotagliflozin also increases GLP-1 which can help to reduce hyperglycemia.[99] Metformin has long been used for treating polycystic ovary syndrome.[111] Interestingly, other members of the dual SGLT1/SGLT2 inhibitors, licogliflozin, attenuate hyperinsulinemia, and androgen production in women with polycystic ovary syndrome.[112,113] These two hypoglycemic agents with different mechanisms of action but with similar effect on PCOS initiates some new hypothesis on the pathological basis of the disease.

Dipeptidyl-peptidase-4 inhibitors

Dipeptidyl-peptidase-4 (DPP4), a transmembrane peptidase, inactivates GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). Several DPP-4 inhibitors (vildagliptin, sitagliptin, linagliptin, and saxagliptin) and a new generation, alogliptin, are clinically available to treat diabetes type 2. DPP4 inhibitors reduce hyperglycemia by impeding GLP-1 and GIP degradation. This results in increased insulin secretion, delayed gastric emptying, and decreased glucagon secretion, thereby reducing blood sugar.[114,115] Recent researches show a pathological role for DPP4 in lung diseases, especially COVID-19, which is believed to have a role in disease progression. Therefore, DPP4 inhibitors may have a beneficial effect in treating DPP4-related lung diseases.[116]

Alpha-glucosidase inhibitors

Miglitol and acarbose are the most known α-glucosidase competitive inhibitors that impede hyperglycemia by inhibiting pancreatic α-glucosidase in the intestine. By inhibiting α-glucosidase, glucose production in the intestine is reduced, leading to glycemic control.[117] Nowadays, many studies are performed to find more potent and tolerable α-glucosidase inhibitors. New α-glucosidase inhibitors come from microbial metabolites such as nicotinic acid and hydroxyproline, which inhibit α-glucosidase, equal or stronger than acarbose.[118,119]

Biguanides

Biguanides are a class of antihyperglycemic drugs that are used for treating diabetes, prediabetes, and polycystic ovary syndrome. Phenformin and buformin have been excluded from the market because of their toxic effect (lactic acidosis). However, metformin is still globally used as a safe hypoglycemic agent for treating type 2 diabetes.[120,121] Two different forms of the drug include immediate-release (metformin IR), known under the commercial name, Glucophage, and slow-release (metformin SR). Reports suggest that although

metformin SR is famous for more tolerability, metformin IR lowers HbA1c (but not blood sugar) more effectively than the other.[122] After years of research on the action mechanism of metformin, several modes of action have been proposed, some of which are achieved by a concentration of metformin beyond pharmacological doses that is not achievable in clinical practice. Decreased liver gluconeogenesis through inhibition of glycerol-3-phosphate dehydrogenase remains the main mechanism of the hypoglycemic effect of metformin. Inhibition of glycerol-3-phosphate dehydrogenase leads to an increment of NADH/NAD+ ratio and a subsequent decrease in gluconeogenesis from glycerol and lactate. It is worth knowing that gluconeogenesis from other sources (alanine) is not mainly affected by metformin, explaining why metformin rarely causes hypoglycemia. However, other mechanisms should also be considered. Metformin regulates gluconeogenesis in the liver by decreasing the levels of cyclic AMP. Low levels of cAMP inhibit activation of cAMP-responsive element-binding protein 1 leading to reduced expression of key gluconeogenic enzymes; phosphoenolpyruvate carboxykinase (PEPCK), and glucose-6-phosphatase (G6Pase). In addition, metformin downregulates gluconeogenic gene expression by activating AMPK.[123]

Metformin also decreases the transport of glucose from the intestine into the blood. This is the earliest hypoglycemic effect of oral consumption of metformin.[124] Furthermore, metformin has been considered for decades to reduce insulin resistance. This property has led to its clinical use in the treatment of obesity and polycystic ovary syndrome, in addition to the treatment of diabetes. This effect is achieved by inducing the expression and translocation of GLUT4 to the membrane. Epigenetic modifications are believed to be implicated in this phenomenon. After activation of AMPK by metformin, transcriptional repressor histone deacetylase 5 is decreased which leads to a subsequent increase in GLUT4 expression.[125] Through activation of AMPK, metformin exerts anti-inflammatory properties by reducing NF-κB p65 phosphorylation, leading to the reduction of inflammatory cytokines (TNF-α, IL-6, and C-reactive protein).[126] The multifunctional properties of metformin make it a suitable candidate for treating COVID-19, probably as an addictive drug. It reduces entry of the virus to host cells, virus assembly, and maturation.[127]

Glucagons like peptide 1 receptor agonists

Response to food ingestion that mediates by incretin (like GLP-1) is impaired in diabetes type 2 patients. The application of GLP-1 receptor agonists solves this problem and improves glycemic control. GLP-1 receptor agonists consist of many members, albiglutide, dulaglutide, exenatide extended-release (which are prescribed once weekly), liraglutide, lixisenatide is administered once, and dayexenatide is taken twice a day.[128] GLP-1 receptor agonists increase insulin sensitivity, suppress appetite, decrease glucagon, HbA1C, and free fatty acid levels and decrease body weight. Furthermore, liraglutide reduces hyperglycemia-induced atherosclerosis by suppressing PI3K/AKT signaling pathway that thereby the reduction of abnormal proliferation of vascular smooth muscle cells. Interestingly, GLP-1 receptor agonists increase nerve cell survival and differentiation and therefore have a beneficial effect on the treatment of Alzheimer's disease, Parkinson's disease, and stroke.[129]

Drug candidates need further investigation

Bromocriptine, a dopamine agonist, has long been used to treat hyperprolactinemia and prolactinoma. Bromocriptine shows a moderate antihyperglycemic effect in type 2 diabetes. It may be helpful in the treatment of diabetic individuals that respond poorly to conventional drugs. The exact mechanism of action is poorly understood. Bromocriptine is different from other hypoglycemic agents because by acting through CNS, it reduces insulin resistance and hepatic gluconeogenesis and improves glucose tolerance.[130] In diabetic rat models, bromocriptine reduced IL-6 and leptin, increased PPAR-γ/adiponectin, and GLP-1 altogether ameliorated hyperglycemia.[131]

The biological activity of vanadium compounds, including the hypoglycemic effect, has been studied for years. However, their clinical use is limited due to low bioavailability and difficulty in crossing the biological membrane.[99] The binding of vanadium to organic compounds (such as glycine and EDTA) facilitates its passage through bacterial membranes and increases its effectiveness.[132] Furthermore, an organic vanadium complex (Bis [α-furancarboxylato] oxovanadium [IV]) increases insulin sensitivity, and GK activity, and inhibits PEPCK, a key enzyme in gluconeogenesis. These effects may be exerted, at least in part, by nonselective inhibition of phosphotyrosine phosphatase.[99,133]

Bile acid sequestrants like cholestyramine and colesevelam are resins that bind to cholesterol in the intestine and reduce the enterohepatic circulation of bile acid, and then serum cholesterol levels. Colesevelam, the new generation, enhances glycemic control by increasing the secretion of incretin and improving the function of beta cells.[134] The clinical benefits of bile acid sequestrants and their exact mechanism of action are under investigation.

Plant-derived remedies

Before the invention of oral hypoglycemic drugs, the major remedies came from medicinal plants. Plants are a massive source of phytochemicals with several biological activities. The isolation, purification, and identification

of their active ingredients with antidiabetic activity have drawn the attention of many researchers for decades. One of the most famous medicinal plants is fenugreek. Fenugreek (*Trigonella foenum graecum* L.) is cultivated in the Middle East and Mediterranean region. Fenugreek is used for its hypolipidemic, antihypercholesterolemic, and antidiabetic properties.[99,135] Feeding STZ-injected diabetic rats with powdered fenugreek seeds significantly reduced blood sugar. Moreover, creatinine, AST, ALT, and triglycerides levels reduced while HDL-C levels increased after oral administration of fenugreek seeds, showing that it may protect liver and kidney tissues.[136] The antidiabetic, and insulin-sensitizing effect of fenugreek was also confirmed by human studies.[137,138]

Chemical analysis of fenugreek indicates that the seeds consist of high dietary fiber, mucilaginous fiber, steroidal saponins (diosgenin, gitogenin, and tigogenin), fenugreekine (a sapogenin peptide ester), and trigonelline (a major important alkaloidal found in the seeds). The seeds also contain coumarins, galactomannan (a specific type of soluble fiber consisting of mannose and galactose), and 4-OH-Ile a hydroxyl derivative of isoleucine.[138] Trigonelline, the major alkaloid of fenugreek, has been reported as a hypoglycemic agent.[139] Li *et al*. reported that trigonelline ameliorates diabetic nephropathy and insulin resistance by increasing protein levels of PPARγ. Moreover, it simultaneously decreased the protein levels of TNF-α and leptin in type 2 diabetes mellitus rats.[140] Trigonelline also suppresses inflammation, regulates the secretion of adipocytokines, and increases β-cell mass.[141] Another molecular study suggested that trigonelline increases insulin sensitivity by promoting insulin receptor autophosphorylation and GLUT4.[142] 4-OH-Ile is another constituent found in the seeds responsible for the antidiabetic activity of fenugreek (review in section 3-1). Other ingredients found in fenugreek are coumarin (and its derivatives like scopoletin) and fenugreekine. It has been reported that coumarins and relative derivatives are involved in the suppression of gluconeogenesis, α-glucosidase, protein tyrosine phosphatase, and increasing cellular uptake of glucose, insulin levels, insulin sensitivity, and the half-life of GLP-1, which all contribute to help glycemic control.[143] Coumarins upregulate or stimulate PPARγ, GLUT4, adiponectin, GK, and glucose 6-phosphate dehydrogenase.[144] There is no valuable report about the hypoglycemic effect of fenugreekine. Fenugreek seeds have a high content of soluble fiber that regulates blood sugar by delaying gastric emptying and interfering with the intestinal absorption of glucose.[145] This evidence suggests that fibers might be responsible for the antihyperglycemic of fenugreek instead of a hypoglycemic activity. Fenugreek may affect intestinal glucose uptake by directly acting on α-amylase activity.[146] Because fenugreek increases insulin receptors in red blood cell membranes, a possibility was strengthened that in addition to its antihyperglycemic effect in the digestive system, it also has a hypoglycemic effect by increasing glucose uptake into peripheral tissues.[147]

Capparis spinosa (Caper), is another edible medicinal plant widely used as a food additive. It has long been used as diuretics, analgesic, antihemorrhoid, and antirheumatic. Furthermore, roots and bark are effective against fever, rheumatism, paralysis, coughs, asthma, and inflammation. Antidiabetic properties of caper have been attributed to the bioactive components found in different parts of the plant.[148] Several bioactive components are present in caper, including alkaloids, glucosinolate (glucocapperin), and sitosterol derivatives.[149]

Different parts of Capparis spinose show valuable antihyperglycemic activity. In our previous study, oral administration of caper root extract to diabetic rats significantly reduced plasma glucose without increasing insulin levels, indicating its insulinomimetic property.[150] Moreover, other studies have shown that fruit extract could potentiate insulin sensitivity and reduce gluconeogenesis in STZ-induced diabetic mice, confirming previous results.[151] These results were confirmed by a human study in Iran showing a hypoglycemic and hypolipidemic effect of the fruit extract.[152] Several mechanisms have been proposed for the hypoglycemic effect of caper. Caper can reduce the absorption of carbohydrates in the intestine, inhibit gluconeogenesis, and increase cellular uptake of glucose. It also shows antihypercholesterolemic and hypolipidemic properties that make it suitable for treating metabolic syndrome and fatty liver.[149] It has been proposed that it may alleviate steatohepatitis through up-regulation of fibroblast growth factor 21.[153] At the molecular level, Capparis spinose decreases PEPCK, a key enzyme in gluconeogenesis, presumably through reduction of hepatic nuclear factor-4α (HNF-4α) and subsequent decrease in PEPCK gene expression.[154]

Many other herbs with various bioactive compounds have been used to treat diabetes. Bitter melon is one of the most frequently used medicinal herbs that contains an insulin-like polypeptide (polypeptide-p or p-insulin). Subcutaneous injection of the plant extract reduces blood sugar in type 1 diabetic patients. Recombinant p-insulin has been produced with a similar hypoglycemic property.[155] Gymnemic acids extracted from Gymnema sylvestre have a similar atomic structure to that of glucose, so they inhibit the absorption of glucose in the gastrointestinal tract and thus prevent glucose increase after a meal. It activates insulin-dependent enzymes such as glycogen synthetase, glucose 6-phosphate dehydrogenase, and hexokinase. In addition, Gymnema sylvestre extract regenerates beta cells and therefore increases the level of insulin in the

blood of diabetic patients.[156] Ginkgo biloba (Ginkgo) has high levels of flavoglucoside, and its administration of the leaf extract prevents diabetic nephropathy by suppressing tissue transglutaminase.[157] It protects β-cell cells and improves insulin expression in diabetic type 2 rat models.[158] Additionally, flavonoid compounds in Silybum marianum (milk thistle) such as silybin may reduce insulin resistance and improve glucose metabolism in high-fat-fed mice. It may show its effects at least in part through activating the Farnesoid X receptor.[159] Silymarin can recover pancreatic function, regulate IRS-1/PI3K/Akt signaling pathway, and increase GLUT4 expression, and glucose uptake.[160] Ameliorating effect of milk thistle on the fatty liver has been noted in a diabetic model.[161] At the molecular level, the expression of transcription factors involved in lipid metabolism, such as PPARγ, and PPARα in the liver, has been postulated by Silymarin, suggesting its beneficial effects in the treatment of fatty liver.[162]

Securigera securidaca is used in traditional Iranian medicine for various purposes. The seed extract of the plant significantly reduces blood sugar and lipids levels in diabetic rats.[163] Green tea (Camellia sinensis) contains catechins (mainly epicatechin, epicatechin gallate, and epigallocatechin), flavanols, and flavandiols.[164] Administration of green tea extract to laboratory animals increases glucose tolerance, and insulin secretion and decreases DPP-IV activity, and starch digestion.[165] Moreover, flavonoids found in Camellia sinensis seeds ameliorate insulin resistance induced by TNF-α.[166]

Diallyl disulfide is an organosulfur distilled oil from garlic composed of two allyl groups connected by two sulfur atoms, which is hydrophobic and has a strong garlic odor. There are several reports regarding the antitumoral activity of allyl disulfide in different types of cancer.[167] Allyl disulfide inhibits glucose metabolism in breast cancer stem cells through inhibition of CD44/pyruvate kinase M2/AMPK pathway. Inhibition of glucose metabolism which is more active in cancer cells than normal cells may be the underling mechanism of its antitumor activity. However, the antidiabetic activity of allyl disulfide should be further studied *in vitro* and *in vivo* due to conflicting reports.[168]

CONCLUSIONS

Diabetes and insulin resistance are becoming a problem for health systems worldwide. Therefore, from the human point of view and the budget that it imposes on health systems, diabetes, and its related disorders should be considered a special worldwide issue. It is clear that to find a way to reduce the incidence of the disease or to effective treatment of existing patients, the physiological pathways and underlying pathological mechanisms of the disease must be identified. Therefore, it is necessary to know the signaling pathways, proteins and enzymes, and effective metabolic substances involved in this pathway. This study tried to review from the beginning of this pathway, i.e., the mechanisms of insulin secretion to the factors affecting its impact on the target tissues in the view of proteomics. Ultimately, the mechanism of medications and drug candidates on different parts of this long signaling pathway was discussed. An exciting field of study in the future is the investigation of chemicals that reduce the incidence or severity of diseases such as Covid-19 by lowering insulin resistance.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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