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REVIEW

Effects of glycine on metabolic syndrome components: a review

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Abstract

Purpose Glycine is the simplest and major amino acid in humans. It is mainly generated in the liver and kidney and is used to produce collagen, creatine, glucose and purine. It is also involved in immune function, anti-inflammatory processes and anti-oxidation reactions. Here, we reviewed the current evidence supporting the role of glycine in the development and treatment of metabolic syndrome components.

Methods We searched Scopus, PubMed and EMBASE databases for papers concerning glycine and metabolic syndrome.

Results Available evidence shows that the amount of glycine synthesized in vivo is insufficient to meet metabolic demands in these species. Plasma glycine levels are lower in subjects with metabolic syndrome than in healthy individuals. Interventions such as lifestyle modification, exercise, weight loss, or drugs that improve manifestations of metabolic syndrome remarkably increase circulating glycine concentrations.

Conclusion Glycine supplementation improves various components of metabolic syndrome including diabetes, obesity, hyperlipidemia and hypertension. In the future, the use of glycine may have a significant clinical impact on the treatment of patients with metabolic syndrome.

Keywords Glycine · Metabolic syndrome · Diabetes · Hyperlipidemia · Obesity · Blood pressure

Introduction

Glycine is the smallest amino acid and has no D or L enantiomers. Glycine has a sweet taste and its name has been derived from the Greek word "glycinekys" meaning sweet [1]. Diet and endogenous synthesis (in the liver and kidneys) are two sources of glycine intake in humans. Glycine can be generated from choline, glycine oxalate, betaine (trimethylglycine), glucose (via serine), during the endogenous synthesis of L-carnitine and likely from threonine [2].

Glycine has traditionally been classified as a "nutritionally nonessential amino acid" for mammals (including humans, pigs and rodents) due to the presence of its endogenous synthesis in the body [1]. However, available evidence shows that the amount of glycine synthesized in vivo is insufficient to meet metabolic demands in these species [1, 3, 4]. Mild glycine deficiency is not life-threatening, but a chronic shortage can lead to impaired immune responses, insufficient growth and other adverse effects on health and body metabolism [1].

Glycine is utilized in some metabolic pathways including degradation to carbon dioxide and ammonium, producing serine via the reversible reaction catalyzed by serine hydroxymethyltransferase, methylation to generate *N*-methylglycine (sarcosine) and conjugation by acyl groups derived from acyl-CoA esters to generate acyl-glycine derivatives. Glycine is required to synthesize heme group, purines, creatine, collagen and glutathione [2].

In this article, we reviewed the current evidence supporting the role of glycine in the metabolic syndrome components. We searched Scopus, PubMed and EMBASE databases for papers concerning glycine subjects with the following keywords:

– Hypertension or "blood pressure" or hypotensive or antihypertensive

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- Diabetes or insulin or hyperglycemia or hypoglycemic or antidiabetic or antihyperglycemic or “blood glucose”
- Dyslipidemia or "high triglyceride" or hypertriglyceridemia or hyperlipidemia or "high cholesterol" or hypercholesterolemia
- Atherosclerosis or atherogenic
- Overweight or Obesity or anti-obesity
- “metabolic syndrome”

In total, 262 studies were found, of which 93 were included in this review.

Physiological functions of glycine

The small size of the glycine molecule facilitates its role as a link between proteins and the formation of helices as well as an extracellular signaling molecule [5]. 11.5% of total amino acids in body proteins consist of glycine. Collagen and elastin, as the most abundant extracellular proteins in the body, contain glycine as a major component [1]. In addition, glycine residues have a critical role in maintaining collagen structure via stabilizing the triple helix of the collagen molecule.

A collagen molecule consists of three polypeptide chains (named α-chain) and three α chains are arranged in a triple helix, forming the collagen molecule (superhelix). Glycine residues are sited at every third position on α chains to stabilize the collagen superhelix. Glycine moieties are critical to stabilizing the three-chain superhelix. Therefore, the healthy collagen structure in the human body needs glycine [2].

Another physiologic function of glycine is bile acids metabolism and lipid absorption. Glycine is the main amino acid for the conjugation of bile acids and therefore has an important role in the digestion and absorption of fats and lipid-soluble vitamins. Glycine is conjugated with bile acids and other derivatives of acyl-CoA esters to produce acylglycine derivatives. Glycine *N*-acyltransferase catalyzes the transfer of the acyl group to the amino group of glycine [1].

Glycine also is the precursor of various important metabolites, such as purines (RNA and DNA), porphyrins, heme (hemoglobin), glutathione and creatine. Several pathways utilize glycine to produce purines, heme, glutathione, serine and creatine [5]. (See Fig. 1).

In the CNS, glycine acts as an inhibitory neurotransmitter to regulate food intake, behavior and whole-body homeostasis [6]. In addition to the role of glycine in the CNS as an inhibitory neurotransmitter, glycine has a regulatory role in the periphery and adjusts glucose homeostasis via insulin secretion and other pathways. Through ligand-gated chloride channels in macrophages and leukocytes, glycine modulates intracellular calcium concentration and thereby has important roles in regulating immune function, generating superoxide and the production of cytokines [7]. Glycine also acts as a co-ligand for N-methyl-d-aspartate (NMDA) glutamate receptors. Glutamate and glycine bind to the individual glutamate- and glycine-binding domains and activate the channel [8]. By activating NMDA receptors, glycine acts to control insulin secretion and liver glucose output [9] (See below).

Receptors for Glycine

As a central and peripheral neurotransmitter**,** glycine binds to glycine receptors and increases the entry of chloride ions into the cells at postsynaptic sites. The entrance of negatively charged chloride to the neurons inhibits the activity of the CNS. Synaptic transmission via glycinergic neurons contributes to the generation of motor patterns and respiratory rhythm [10].

Although glycine is classically known for its function in the nervous system, glycine receptors are expressed in other parts of the body including immune cells, the pancreas and the retina [11]. Glycine receptors belong to the pentameric ligand-gated ion channel family and are composed of two α- and three β-subunits [12]. Glycine is a direct agonist of glycine receptors. However, glycine receptors are also activated by taurine and β-alanine and inhibited by picrotoxin and strychnine [12]. Picrotoxin blocks the receptors by blocking the channel pore while strychnine inhibits glycine receptors by binding to the glycine-binding site [10].

Glycine transporters that belong to the sodium-dependent solute carrier family of transporters, regulate extracellular glycine concentrations. There are also two transporters for glycine: glycine transporter 1 (GlyT1) which cotransports two sodium ions, one chloride ion and one glycine; Glycine transporter 2 (GlyT2) cotransports three sodium ions, one chloride ion, and one glycine [11].

Glycine and metabolic syndrome

Metabolic syndrome is a collection of risk factors including hypertension, abdominal obesity, dyslipidemia and insulin resistance. Other comorbidities including the proinflammatory state, prothrombotic state and nonalcoholic fatty liver disease, also are presented in metabolic syndrome [13, 14]. Metabolic syndrome is clinically diagnosed as the co-occurrence of three or more of these disorders [15]. The pathophysiology of this syndrome has not been fully understood; however, it has been strongly suggested that unbalanced diets and immobility play a basic role. [16] Unbalanced diets and immobility predispose the overweight and obesity conditions. Obesity is one of the principal causes of metabolic syndrome and can lead to the development of

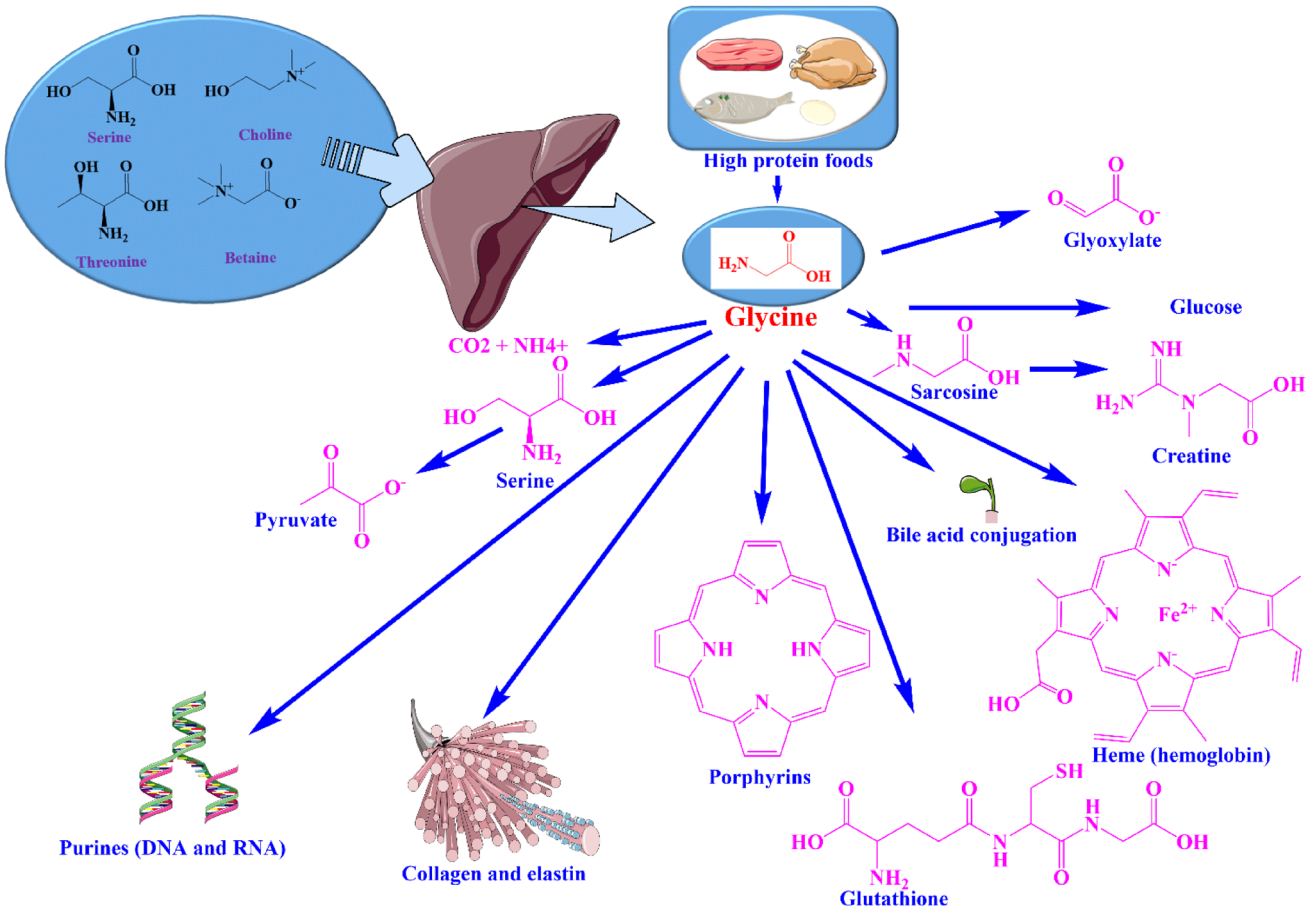

Fig. 1 Pathways of supply and consumption of glycine in the body (Images from: smart.servier.com). Diet and endogenous synthesis (in the liver and kidneys) are two sources of glycine intake in humans. Glycine is utilized in some metabolic pathways and is required to synthesize heme group, purines, creatine, collagen and glutathione

type 2 diabetes mellitus, cardiovascular disease, hypertension and stroke. [15]

The prevalence of obesity and metabolic syndrome is increasing especially among young adults and children [17]. Global obesity rates are expected to exceed 50% of the adult population by 2050 [15]. In almost all nations, the rate of obesity in children and adolescents (aged 5–19) have shown a rise in recent years and the prevalence of obesity almost doubled [18]. In the WHO European Region one child out of 3, is overweight or obese [19]. Metabolic syndrome has serious implications on an individual's health and healthcare costs. Prevention strategies, including lifestyle modification and the use of medications and supplements, are important in lowering the risk of metabolic syndrome and related disorders [17].

The pathogenesis of the metabolic syndrome is complex and not well understood but central obesity and insulin resistance seem to be the main causative factors. Insulin action in skeletal muscle and adipocytes plays a central role in maintaining glucose balance. The abnormal action of these key insulin-response tissues develops metabolic syndrome. Lifestyle, demographics, genetic factors and environmental fetal programming are other factors that play a role in the development of metabolic syndrome [20]. Many drugs (for example metformin and statins), endogenous ligands (including melatonin) and plant-derived natural compounds (such as berberine, thymoquinone and silymarin) have been shown to provide positive effects on different components of metabolic syndrome [14, 21–24].

In patients with diabetes mellitus and obesity, the plasma level of glycine is consistently lower in comparison to healthy individuals [25]. On the other hand, weight loss, exercise or drugs that improve insulin resistance are associated with the increase of plasma glycine concentration in subjects with diabetes or obesity [26].

Recent studies using metabolomics technologies have shown the correlation between plasma levels of glycine and metabolic syndrome [2]. Another study in elderly patients has shown that in the elderly also plasma levels of glycine are associated with metabolic syndrome and this correlation

is more prominent in elderly patients than in younger people [27]. Figure 2 summarizes the effects of glycine on different components of metabolic syndrome.

It is expected that nutritional interventions can correct hypoglycinemia. Glycine content in the protein fraction of different dietary sources is relatively uniform, except for rice, which is about twice as rich in glycine as compared to other proteins from animal or vegetable origins. The average daily intake of glycine is estimated to be from 2.28 to 3.12 g/day in adult males. However, it should be noted that food consumption, in terms of dietary patterns, rather than dietary glycine intake, is a key determinant of glycine availability, potentially through modulation of glycine endogenous metabolic pathways [28].

Diabetes

Most individual amino acids induce insulin secretion and when ingested with foods diminish the plasma glucose levels [29, 30]. But in the case of glycine, there is an inverse and negative association between this amino acid and diabetes [31]. In patients with type 2 diabetes, the concentration of glycine is reduced in plasma before the clinical appearance of diabetes and, therefore, plasma level of glycine may be considered as a biomarker for the prediction of prediabetes and disease onset. In prospective studies, higher levels of glycine are associated with a reduced risk of diabetes [2]. Consistently, in the lean offspring of parents with type 2 diabetes, serum glycine concentration is lower in comparison to normal subjects [32].

Diabetic patients have lower serum glycine levels in comparison to healthy individuals [31, 33]. Moreover, improving insulin resistance with exercise, weight loss or drugs ameliorates hypoglycinemia in diabetic patients [2].

It is not yet known whether a drop in glycine levels is directly involved in the development of diabetes, but as mentioned, the interventions such as lifestyle modification, exercise, weight loss or drugs that delay or counteract against diabetes onset, remarkably increase circulating glycine concentrations [2, 26].

On the other hand, beyond its role as a biomarker, it is not clear whether glycine is directly involved in blood glucose control or not. So far it has been determined that dietary glycine supplementation improves glucose tolerance, increases insulin and reduces systemic inflammation. There are some clinical studies regarding the antidiabetic effects of dietary glycine supplementation (Table 1).

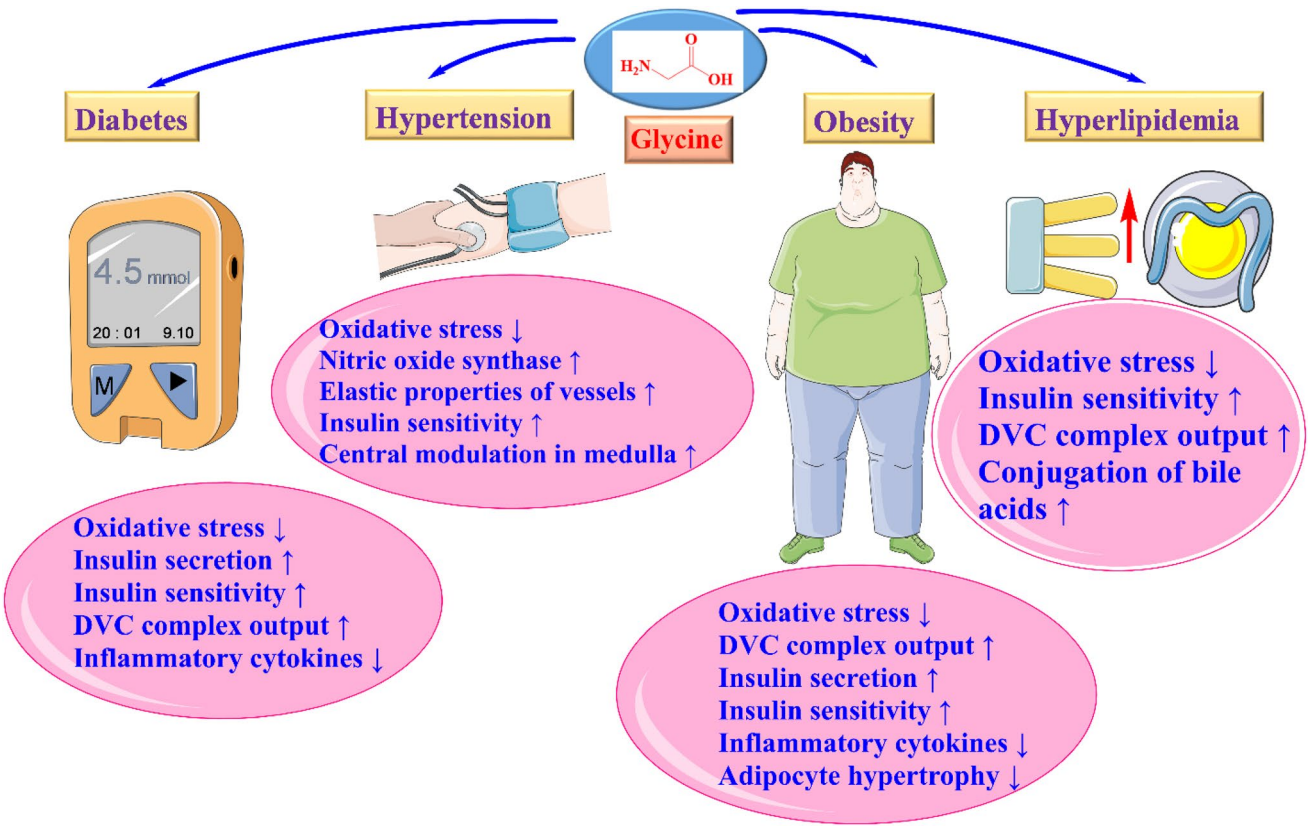

Fig. 2 Effects of glycine on different components of metabolic syndrome (Images from smart.servier.com)

Table 1 Summary of clinical studies regarding the antidiabetic effects of dietary glycine supplementation

Study design	No. of patients	Dosage–duration	Outcomes	References
Double-blind, RCT	74	5 g/day–3 months	Decrease of A1 C levels; reduction in TNF-receptor I levels; Increase of interferon (IFN)-γ level	[37]
Double-blind, RCT	12	A morning dose of glycine 5 g orally	Increase of early, late and total insulin responses	[38]
Double-blind, RCT	24	A constant intravenous infusion of glycine (20 µmol/kg) for 8 h	Increase of GSH synthesis and concentrations and decrease of plasma oxidative stress and lipid peroxides	[48]
Double-blind, RCT	60	15 g/day–3 months	Decrease of TBARS and SOD-specific activity	[84]
Pilot RCT	9	1 mmol glycine/kg lean body mass	Increase of serum insulin concentration and decrease of serum glucose concentration	[92]

In diabetic patients treated with glycine (5 g/d), there was a remarkable decrease in A1C and proinflammatory cytokines (38%) after 3 months of treatment and also a significant increase of IFN-gamma (up to 43%) [31]. In healthy first-degree relatives of diabetic patients, administration of glycine 5 g/day increased insulin responses [36].

There is also an animal study in rats to evaluate the possible side effect of glycine supplementation. This study shows that 6 months of supplementation with glycine (1%) did not have any effects on plasma insulin levels, glucose plasma concentration, plasma triglyceride, urine tests and the histological analysis of liver and kidneys [35]. In human, however, there is not any study to evaluate the probable side effect of glycine supplementation and need to be evaluated.

Mechanisms of antidiabetic activity

Glycine has several roles in controlling plasma glucose levels via both central and peripheral pathways. Here we review the different antidiabetic mechanisms of glycine using current evidence suggesting a role for glycine in glucose homeostasis (Fig. 3).

1- Oxidative stress: oxidative stress and the balance between oxidants and antioxidants play a significant role in the pathogenesis of diabetes and metabolic syndrome [33]. Persistent hyperglycemia leads to depletion of the cellular glutathione and thus causes tissue damage. In patients with uncontrolled diabetes, glutathione synthesis is reduced. Dietary supplementation with glycine can restore glutathione resources [34]. In sucrose-fed rats, glycine treatment decreases the levels of markers of oxidative stress and augments the γ-glutamylcysteine synthetase, a key enzyme of glutathione biosynthesis and also increases the concentrations of glutathione in the liver of these diabetic rats [33].

   Glycine supplementation improves glutathione deficiency and reduces oxidative stress [33]. Glycine also protects against diabetic oxidative stress via suppressing the renal Nox4 (a NAD(P)H oxidase subunit) expression in streptozotocin-induced diabetic rats [35, 42] NAD(P)H oxidase is a major source of ROS production in the kidney that is overexpressed in the kidney of diabetic rats [36].

2- Insulin secretion and sensitivity: several neurotransmitters modulate the membrane potential of islet β-cells via ion channels or their receptors and thereby change insulin secretion [9]. Glycine receptors (mainly the GlyRα1 subunit) and the glycine transporter isoforms (GlyT1 and GlyT2) are highly expressed on human β-cells. Glycine receptors cause significant glycine-related Cl^- currents in β-Cells that raise membrane potential, induce Ca^{2+} entry, and eventually release insulin from β-cells [43]. Considering that glycine is an inhibitory neurotransmitter, and activates a Cl^- current to suppress membrane potential, how does it promote membrane depolarization? The answer is that in β-cells, unlike the nervous system, glycine receptors do not act as an inhibitory modulator (Fig. 3). As in β-cells, the Cl^- gradient is different from neurons. In neurons, the intracellular concentration of chloride is very low (7 mM), whereas the concentration of chloride in β-cells is markedly higher (32 mM) [9]. It means that the opening of glycine receptors in β-cells, instead of causing chlorine ions to enter the cell, causes chlorine ions to leave the beta cells. Therefore, the opening of the glycine receptors will depolarize β-cells (an excitatory action), unlike neurons, which hyperpolarize the cells (an inhibitory function).

   It has been shown that glycine depolarizes β-cells and increases the Ca^{2+} current in these cells. However, in β-cells from diabetic patients, the expression of glycine receptors (GlyRα1 subunit) and glycine-related currents are reduced [11]. The cause of this receptor downregulation can be related to a decrease in protein levels due to mRNA expression, or impaired activity of β-cell because of insulin resistance. Also, there is a significant positive interaction between insulin and glycine receptors, so that via a phosphoinositide 3-kinase-dependent manner, insulin enhances the glycine-activated current in normal

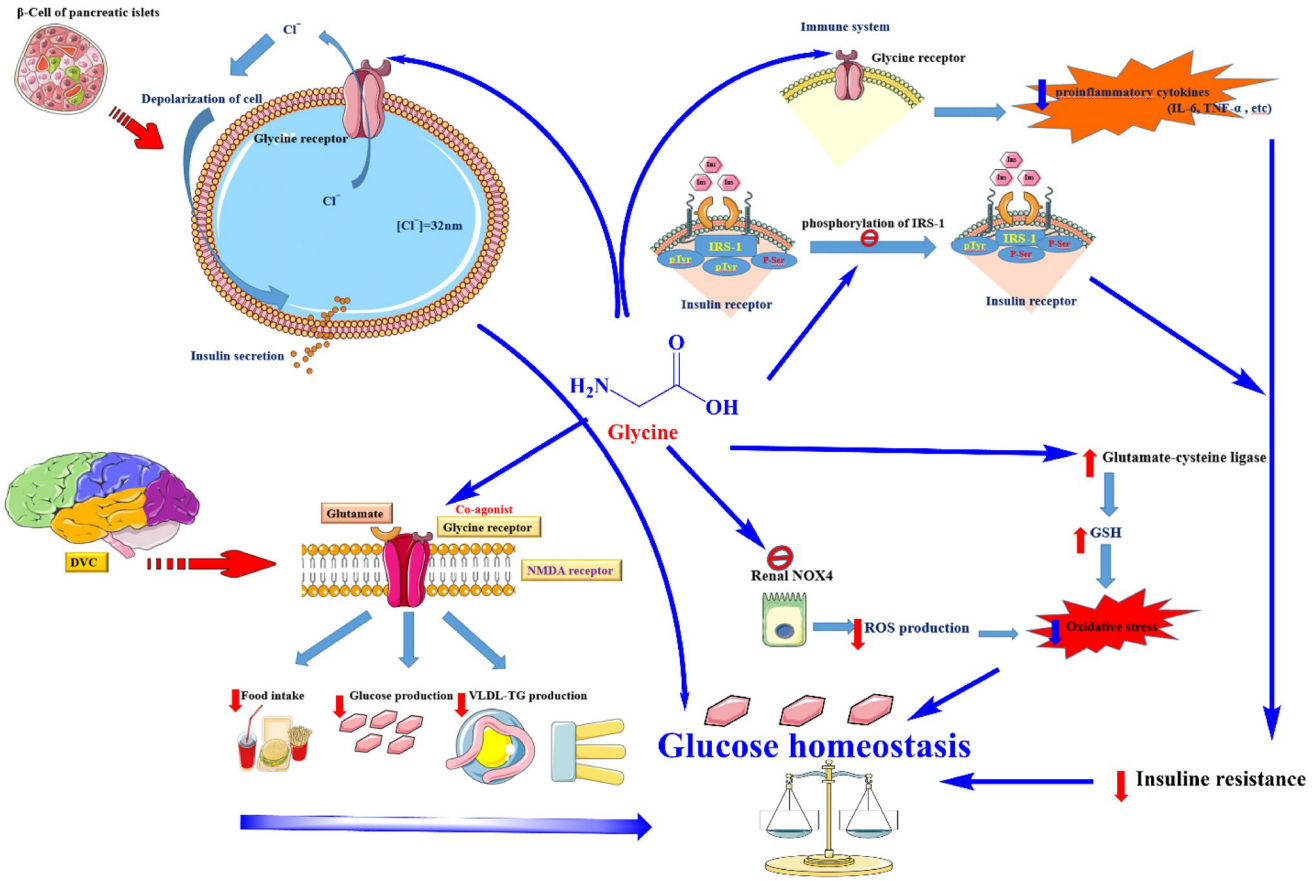

Fig. 3 Antidiabetic mechanisms of glycine. The figure shows different central and peripheral mechanisms of antidiabetic activity of glycine using current evidence suggesting a role for glycine in glucose homeostasis. Glycine increases the secretion of insulin from β-cells of pancreatic islets (via Glycine receptor-mediated depolarization of β-cells), reduces desensitization of insulin receptors, controls oxidative stress (through increasing glutathione synthesis and reducing ROS production) and improves glucose hemostasis by activating DVC (dorsal vagal complex) in the CNS that suppresses food intake, glucose production and VLDL-TG secretion from the liver. (Images from: smart.servier.com)

β-cells. In β-cells of diabetic patients, however, this positive interaction has been destroyed [11]. Glycine also decreases the insulin-induced phosphorylation of insulin receptor substrate-1 in serine residue and increases the phosphorylation of insulin receptor β-subunit in tyrosine residue that augments insulin sensitivity [39].

3- Anti-inflammatory effects: although there is controversy regarding the effects of inflammation on diabetes and glucose tolerance and some researchers suggest positive effects of inflammatory mediators on glucose control in the short term, it seems that inflammation causes insulin resistance and impaired central metabolic sensing [44, 45]. Anti-inflammatory drugs can be considered as a new potential in the treatment of diabetes [46].

Elevated oxidative stress increased proinflammatory factors and a deficiency in ROS scavengers and antioxidants are common in diabetic patients [47]. As mentioned, glycine has antioxidant activity and glutathione, as an endogenous antioxidant, is consumed during ROS scavenging. Glutathione synthesis requires glycine, along with glutamate and cysteine. In A clinical study, the supplementation of diabetic participants with two substrates of glutathione synthesis (cysteine and glycine) increased glutathione synthesis [48]. Glycine may also show a direct anti-inflammatory effect. Glycine receptors are expressed on T lymphocytes, macrophages and neutrophils. Glycine, via these receptors, inhibits pro-inflammatory cytokines secretion probably through hyperpolarization of immune cells. More details about the anti-inflammatory effect of glycine have been explained in some review articles [49, 50]. Table 2 summarizes the anti-inflammatory effect of glycin.

4- Central mechanisms (NMDA receptors): an animal study in rats and a clinical study in human patients show that glycine supplementation increases glycine concentration in CSF and the brain [51, 52]. Evidence for the role of brain glycine receptors in glucose homeostasis is very limited; [9] however, it has been shown that glycine

Table 2 Summary of anti-inflammatory effects of glycine

Effects	Mechanism	Reference
Oxidative stress	Increase of glutathione synthesis and suppressing of the renal Nox4	[41, 48]
Pro-inflammatory cytokines secretion	Hyperpolarization of immune cells via Glycine receptors	[49]
Cytoprotection in non-neuronal cell	Preventing plasma membrane leakage	[50]

acts as a co-ligand for N-methyl-d-aspartate glutamate (NMDA) receptors and activation of NMDA receptors proposed as a mechanism of antidiabetic activity of glycine [53]. The dorsal vagal complex (DVC) is an important region for the regulation of glucose and VLDL-TG production in the liver [54]. NMDA receptors are expressed in DVC and glycine, via activation of these receptors, suppresses food intake, glucose production and VLDL-TG secretion from the liver [9]. N-methyl-D-aspartate (NMDA) receptor-mediated neurotransmission in the dorsal vagal complex has an important role in the regulation of glucose homeostasis and energy balance [47]. Direct activation of NMDA receptors in the dorsal vagal complex cause hypothalamic neural transmission to regulate hepatic glucose production [66]. The inhibition of NMDA receptors by pharmacological antagonists or the use of nucleic acid-based drugs (RNA interference (RNAi) technology) has been shown that centrally administered glycine inhibits VLDL-TG production and glucose production via NMDA receptor. Interestingly, co-infusion of strychnine (as an antagonist of inhibitory glycine receptors) was not different from glycine infusion alone that means this antidiabetic effect is not dependent on the activation of inhibitory glycine receptors [53].

In addition to the direct infusion of glycine into the DVC, increasing the concentration of glycine in the brain via administration of a glycine transporter 1 inhibitor improves plasma glucose levels energy homeostasis. In an animal study, administration of a GlyT inhibitor to a high-fat-fed rat model prevented weight gain and this effect appeared 4 days after the start of the study [55]. GlyT1 inhibitors have been used in clinical trials for schizophrenia and have been shown to be safe and efficient in raising glycine levels. Therefore, it has been suggested to test the efficacy of GlyT1 inhibitors in the treatment of diabetes [56].

5- Generation of acyl-glycine derivatives: in diabetic patients, the formation of fatty acyl groups has been increased. In this situation, glycine acts as an acceptor of acyl groups and inhibits excess acyl groups via generating acyl-glycine derivatives. This enhanced glycine consumption in diabetic patients depletes the glycine pool and causes hypoglycinemia [2].

Diabetic retinopathy and cataract

Diabetic retinopathy and its related blindness are the most common complications of diabetes. Although diabetic retinopathy usually refers to vascular disorders, increasing evidence indicates that before vascular abnormalities, neuronal impairments of the retina begin in diabetic retinopathy [57].

In the pathogenesis of diabetic retinopathy, the inflammation of neurons and vessels of the retina plays a key role via the involvement of both innate and adaptive immunity [58]. As mentioned above, glycine modulates the immune system and prevents tissue injury via inhibition of proinflammatory cytokines. Glycine and GABA modulate retinal neurotransmission and about 50% of the amacrine cells in the inner retina are glycinergic. It has been shown that in the retina from diabetic animals, the mRNA and protein expression of α subunit of glycine receptors has decreased 80 percent. It means that retina glycinergic neurotransmission has been ameliorated in diabetes and this loss can be one of the causes of visual impairment in diabetic patients [59].

Glycine also regulates hyperglycemia, hypercholesterolemia and glycated hemoglobin (A1C) levels. All of these factors are effective in reducing retinal damage caused by diabetes.

Glycine supplementation (1% w/v drinking water for up to 16 weeks) considerably reduced retinal damage in diabetic rats and can be considered as a potential candidate for protection of retina against diabetic retinopathy [57].

Further studies in different time durations from the onset of diabetes and also the investigation of changes in the expression and distribution of typical proteins of gliosis (including GFAP) are needed to confirm the neuroprotective effects of glycine [57].

It is thought that glycine via anti-inflammatory and neuroprotective effects, and also by the regulation of hyperglycemia and glycated hemoglobin levels, attenuates retinal neuronal damage.

Moreover, glycine can prevent cataract progression in diabetic patients. In the homogenate lens of humans, glycine considerably reduces the extent of glycation of lens proteins. The mechanism of this protective action of glycine on cataracts seems to be via scavenging of intracellular glucose and protecting the lens proteins from excessive glycation [60]. In an animal study, oral administration of glycine (1% of

glycine in drinking water for 3 months) significantly inhibited the progression of diabetic cataracts in rats via reduction of lens glycation and also due to the inhibition of polyol pathway and oxidative stress [61].

Hyperlipidemia

Hypertriglyceridemia and hypercholesterolemia are important components of metabolic syndrome [62]. Animal studies have demonstrated that glycine supplementation can lower cholesterol levels and improve lipid profile [63, 64].

In an animal study in hypercholesterolemic diet rats, oral supplementation of glycine improved the plasma cholesterol to phospholipids ratio by 40% and lowered the hepatic cholesterol by 29%. Plasma asymmetric dimethylarginine (ADMA) levels, which are increased under hypercholesterolemic conditions, were reduced and on the other hand, plasma symmetric dimethylarginine (SDMA) levels were increased. Oral supplementation of glycine also decreased plasma homocysteine levels and increased total nitric oxide concentration in hypercholesterolemic rats [63]. Another animal study in sucrose-fed rats showed that the addition of 1% glycine to the drinking water containing 30% sucrose, for 4 weeks, significantly decreases the plasma triglyceride levels, adipose cell size and intra-abdominal fat compared with sucrose-fed rats without treatment [64].

In male rats that were fed a cholesterol-free diet, supplementation with 1.5% glycine in a diet for 5 weeks significantly lowered the plasma levels of total cholesterol (27% decrease) and LDL-plus VLDL-cholesterol (39% decrease) compared to the values male rats that were fed a cholesterol-free diet. In this study, glycine also reduced hepatic triglyceride concentrations (53% decreases), and increased hepatic free fatty acid levels (77% increases) [65]. There are no suitable human studies about the effect of glycine on lipid profile and this issue needs further investigation.

Mechanisms of antihyperlipidemic effects

As we mentioned above, N-methyl-D-aspartate (NMDA) receptor-mediated neurotransmission in the dorsal vagal complex has an important role in the regulation of glucose homeostasis and energy balance [47]. Direct activation of NMDA receptors in the dorsal vagal complex causes the hypothalamic neural transmission to regulate hepatic glucose production [66].

The possible role of this neuronal transmission in the dorsal vagal complex in the regulation of hepatic lipid metabolism has not yet been elucidated. Considering that glycine is a co-agonist of the NMDA receptor and potentiates the activation of the NMDA receptors, it seems that glycine adjusts high-fat diet-induced hypersecretion of hepatic VLDL and triglyceride via activating NMDA receptor and related neuronal transmission in the dorsal vagal complex. Therefore, glycine or glycine analogs may have therapeutic benefits in lowering plasma lipid levels in obesity and metabolic syndrome by triggering the CNS [62].

It has been suggested that glycine also directly increases the rate of fatty acid oxidation in liver mitochondria and this mechanism may, therefore, reduce triglyceride production in the liver and can explain the antihyperlipidemic effect of glycine supplementation through the diet [64].

Bile acid formation is a major pathway for the excretion of cholesterol. Bile acids are synthesized from cholesterol in the liver and before secretion into the bile are conjugated to either taurine or glycine. This conjugation plays an important role in the secretion of cholesterol into bile and feces [67]. It has been shown that glycine supplementation enhances acidic sterol excretion into the feces of rats. It has been suggested that glycine might enhance the excretion of cholesterol via increasing the synthesis or conjugation of bile acids [68].

Nonalcoholic fatty liver disease (NAFLD)

NAFLD is the hepatic component of metabolic syndrome [69]. NAFLD encompasses a wide spectrum of liver diseases ranging from non-alcoholic fatty liver to nonalcoholic steatohepatitis and cirrhosis [70]. Epidemiologists estimate that about 20 to 30% of the population in developed countries have some form of NAFLD [64]. The liver has a principal role in lipid metabolism. Disturbance in the uptake, transport, excretion, synthesis and catabolism of lipids leads to the development of NAFLD [71]. In NAFLD, cholesterol metabolism has been dysregulated which leads to an increase in the cholesterol content of the liver [72, 73].

In patients with NAFLD, there is a reduced level of circulating glycine and Rom et al. reported a reduced expression of glycine biosynthetic genes in humans and mice with NAFLD. Also, it seems that glycine has a potential causative role in NAFLD onset because dietary restriction of glycine worsens the symptoms of NAFLD [74]. The cause of reduced levels of glycine remains to be determined. In some animal studies, glycine supplementation has attenuated experimental NAFLD by stimulating fatty acid transport protein (FATP), hepatic fatty acid oxidation and glutathione synthesis [74, 75].

Obesity

Circulating levels of glycine are lower in obese and overweight patients in comparison to control subjects [9, 76, 77]. After weight loss in obese patients, Plasma glycine levels increase compared to baseline values [2]. In an animal

model of intra-abdominal obesity, glycine supplementation has decreased the adiposity and adipocyte size and also reduced the levels of triglycerides and free fatty acids [64]. Therefore, glycine supplementation can be considered as a potential new therapy for obesity.

Several pathways and mechanisms may be involved in the anti-obesity effect of glycine including the regulation of secretion of very-low-density lipoproteins from the liver via NMDA receptor-mediated activation of neuronal transmission in the dorsal vagal complex [62] and improvement of insulin secretion and sensitivity [39, 43]. Anti-inflammatory and antioxidative properties are also involved in the anti-obesity effects of glycine [40, 49].

Obese patients have a pro-inflammatory situation due to the production of inflammatory cytokines (IL-6, TNF-α, etc.) in white adipose tissue. Glycine has anti-inflammatory properties and can be considered for the treatment of inflammation in obesity. It has been shown that glycine decreases IL-6 and TNF-α levels and increases adiponectin in adipocytes and fat tissue of obese mice [78].

Glycine also modulates the enzymatic activity of adipocytes and prevents adipocyte hypertrophy probably via the β subunit of glycine receptor in adipocytes. Glycine supplementation (1% glycine in drinking water) in a rat model of intra-abdominal obesity (30% sucrose administered in the drinking water for 16 weeks) decreased bodyweight, adipocyte hypertrophy and intra-abdominal adipose tissue. These results suggest that glycine regulates the metabolism of lipids in the adipocytes via the glycine receptor [79].

Blood pressure

Hypertension and high normal blood pressure are one (and the most frequent) of the five main components of metabolic syndrome [20]. The cause of hypertension in patients with metabolic syndrome is complex. Several factors in metabolic syndrome including insulin resistance, obesity, and hyperlipidemia may be involved in inducing hypertension and high normal blood pressure in these patients [80].

Several studies in animal models of metabolic syndrome demonstrate that supplementation with glycine decreases blood pressure and prevents hypertension [64, 81, 82]. The mechanism of this antihypertensive effect of glycine can be related to its activity against the generation of free radicals and increasing the nitric oxide levels in vessels [83]. As we mentioned earlier, abdominal fat and uncontrolled glucose metabolism produce reactive oxygen species that lead to oxidative stress in patients with metabolic syndrome [84]. In isolated aorta of sucrose-fed rats, glycine supplementation also increases glutathione (GSH) content via regulation of glutathione synthesis and thereby reduces oxidative stress and prevents alteration of endothelium-dependent relaxation [81].

Moreover, glycine increased the amount of copper/zinc superoxide dismutase and endothelial NO synthase in the aorta of animals with metabolic syndrome which indicates two other pathways for the antihypertensive effect of glycine in the sucrose-fed rats [81]. Another mechanism is related to the role of glycine in some critical metabolic pathways, such as the synthesis of collagen and elastin as structural proteins. Glycine deficiency can interfere with these synthesis pathways and lead to impaired elastin formation in the aorta. It causes changes in the aorta's elastic properties and thereby would contribute to the development of hypertension [83].

In addition, central mechanisms may have some roles in the control of blood pressure by glycine. In the ventral surface of the medulla, the cells in the small circumscribed glycine-sensitive areas, contribute to the maintenance of blood pressure. In an animal study in cats, topical glycine application through paired Perspex rings produced a fall in arterial blood pressure [85].

In a clinical study in metabolic syndrome patients, glycine supplementation (15 g/day) for 3 months reduced SOD-specific activity and SOD2 expression and decreased thiobarbituric acid reactive substances. In the glycine-treated patients, the systolic blood pressure also decreased significantly compared with the placebo-treated group [84].

On the other hand, a cross-sectional epidemiologic study on 4680 persons from 17 random population samples has shown that if glycine is obtained through animal protein and meat, it has a different effect and slightly increases the blood pressure which is probably related to the direct effect of meat and animal protein on blood pressure [86].

The more interesting finding is that in both spontaneously hypertensive rats and NG nitro L-arginine methyl ester-pretreated hypertensive WKY rats, administration of glycine has increased the blood pressure. Pretreatment with MK-801, the N-methyl D-aspartate receptor antagonist, repressed this pressor effect of glycine [87]. In another study, microinjections of glycine into the nucleus tractus solitarii (NTS) of the rat also led to an increase in blood pressure and heart rate and these responses were blocked by strychnine (a GLYR antagonist). Therefore, it seems that NTS is also involved in the regulatory effects of glycine on blood pressure [88].

An animal study has shown that adequate glycine intake during pregnancy and the embryonic period also contributes to the normal development of the cardiovascular system. The offspring of rat dams that consumed a diet low in protein during pregnancy developed high blood pressure. As stated in the introduction, in vivo synthesis of glycine is insufficient to meet the metabolic demands of the body and during pregnancy, on a low-protein diet, the endogenous formation

of glycine is insufficient to meet metabolic needs of the fetus [89].

Atherosclerosis

As mentioned in the introduction, quantitatively, glycine is a major component of collagen. In addition, glycine is required to stabilize the triple helix of the collagen molecule and thus glycine has a critical role in maintaining the collagen structure [2]. Without glycine, the collagen is unstable and unable to maintain the three chains that compose the collagen helix. That is why the glycine-lacking collagen in the arterial wall is degraded and prepares the arteries for calcification and explains why there is an elevated cardiovascular risk associated with metabolic syndrome [90].

In human carotid atherosclerotic plaques, there is an inverse relationship between normal collagen content and microcalcification area. Normal collagen inhibits the calcification of human arteries. Inversely, collagen degradation promotes the calcification of arteries. Hypoglycinemia observed in metabolic syndrome can lead to the formation of malformed collagen in vasculatures [2]. A cross-sectional study has shown that plasma glycine level is inversely related to the risk of acute myocardial infarction in 4109 participants undergoing coronary angiography for suspected stable angina pectoris. Further studies are needed to evaluate the relationship between glycine and atherosclerosis [91].

Summery

Plasma glycine level is lower in subjects with metabolic syndrome compared with healthy individuals. The interventions such as lifestyle modification, exercise, weight loss or drugs that improve manifestations of metabolic syndrome remarkably increase circulating glycine concentrations. Moreover, glycine supplementation improves various components of metabolic syndrome including diabetes, obesity, hyperlipidemia and hypertension. The pathophysiological mechanisms underlying glycine depletion and the clinical consequences of hypoglycinemia associated with metabolic syndrome have not been fully identified and need further investigation. In the future, the use of glycine may have a significant clinical impact on the treatment of patients with metabolic syndrome. On the other hand, more studies are needed to evaluate the possible side effects of glycine supplementation.

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