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Review Article

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Histidine-Containing Dipeptide and Diabetic Complications

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Abstract

Diabetes is a series of metabolic conditions which threaten public health, caused by a defect in insulin secretion by the pancreatic β-cells or insulin-sensitive tissues that fail to respond to insulin leads to hyperglycemia, which causes a series of metabolic signaling pathways leading to inflammation, cytokine production, cell death, and diabetic complications. Recent research has pointed to Histidine-containing dipeptides (HDPs) to be one of the routes to enhancing diabetic complications. HDPs are synthesized in muscle and are abundantly found in mammals and other vertebrates. L-carnosine (CAR), Anserine, and homocarnosine are dipeptides produced by vertebrate muscles. Carnosine and anserine have both antiglycation and antioxidant activity that help to enhance metabolic dysregulation caused by diabetes. In addition, homocarnosine has anti-inflammatory activity, as well as the ability to reduce DNA damage and advanced glycation end products (AGEs). This review will focus on the protective effects of HDPs against diabetic complications, especially carnosine.

KEYWORDS
Diabetes, Diabetic complications, Histidine-containing dipeptides, L-carnosine.

INTRODUCTION

Diabetes mellitus (DM) is a serious condition, that represents a spectrum of metabolic conditions and inflammatory diseases which affect more than 170 million people worldwide, characterized by hyperglycemia and caused by partial or total insulin deficiency (Volpe *et al*., 2018, Mezil and Abed, 2021). Diabetes is divided into two types: Diabetes mellitus type 1 (T1DM) is a chronic autoimmune disorder characterized by hyperglycemia defined as increasing levels of blood glucose above the normal level, which occurs because of insulin deficiency caused by the loss of pancreatic islet β-cells (Katsarou *et al*., 2017). Diabetes Mellitus type 2 (T2DM) is one of the most common metabolic disorders worldwide and its development is mainly due to a combination of two main factors: 1- defect in insulin secretion by pancreatic islet β-cells. 2- failure of insulin-sensitive tissues to respond to insulin (Galicia-Garcia *et al*., 2020). Another type of diabetes is called Gestational diabetes, detected during the latter stages of pregnancy (Dowarah and Singh, 2020). Hyperglycemia caused by diabetes results in several metabolic signaling pathways that ended with the accumulation of endogenously formed reactive carbonyl stress (RCS) and advanced glycation end products/ advanced lipoxidation end-products (AGEs/ALEs), in addition to inflammation, cytokine secretion, and cell death which subsequently lead to diabetic complications (Volpe *et al*., 2018, Iacobini *et al*., 2022), as shown in Fig.1. Diabetic complications are defined as acute or chronic. Acute complications are hyperglycemia, and diabetic ketoacidosis, while chronic ones are Small blood vessel injuries (Microvascular complications) and large blood vessel injuries (Macrovascular complications) (Yamazaki *et al*., 2018). Microvascular complications could result in diabetic nephropathy, retinopathy, and neuropathy. On the other side, macrovascular complications including coronary, cerebrovascular, and peripheral arterial diseases influence the pathogenesis of the cardiovascular disease (CVD). The existence of micro- or macrovascular complications reduces the quality of life because they could lead to lower leg amputation, renal failure, blindness, and heart failure consequences (Koopmanschap, 2002). HDPs are considered a class of soluble peptides composed of histidine and atypical amino acids. In addition, they comprise a group of bioactive peptides, including carnosine, homocarnosine, anserine, and balenine (known as ophidine) (Chmielewska *et al*., 2020). Carnosine consists of ß--alanine and L-histidine. The methylated analogs anserine and balenine are better referred to as alanyl-N-methyl-histidine (Fig. 2) and alanyl-N-methyl-histidine, respectively (Menon *et al*., 2020, Boldyrev *et al*., 2013). HDPs are generated in muscle and abundant in mammals and other vertebrates, although their dissemination varies greatly between species and tissues(Barbaresi *et al*., 2019). Carnosine exhibit high levels in the mammalian brain, heart, and skeletal muscle(Artioli *et al*., 2019), anserin present in both birds and fish. Homocarnosine is a brain-specific dipeptide that does not exist in skeletal

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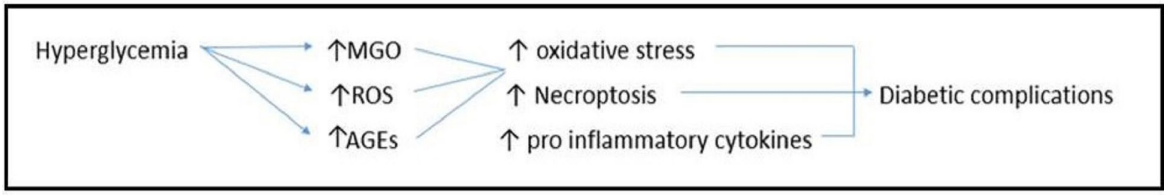

Fig. 1. Cell death and Oxidative stress: can be made in diabetes by (AGEs, ROS, and MG), leading to diabetes complications.

muscles (Boldyrev *et al*., 2013).

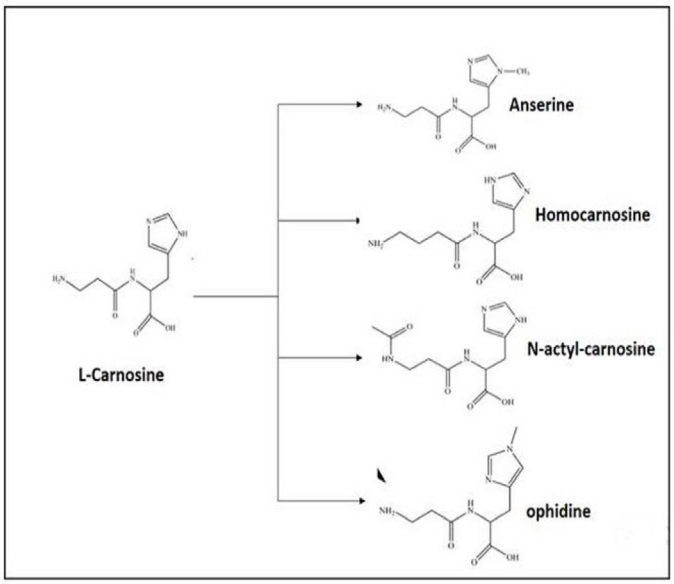

Fig. 2. Chemical names and Structure of carnosine and related dipeptides.

Carnosine (ß-alanyl-L-histidine)

Carnosine is a dipeptide formed by carnosine synthase enzyme from beta-alanine (BA) and L-histidine that exhibit high levels in the mammalian brain, heart, and skeletal muscle that is predominantly derived from the consumption of meat and fish in varying amounts depending on cooking methods, (20-30 mmol. kg/dry muscle) in human skeletal muscle, kidney where it is mainly present in the glomeruli and the apical membrane of the proximal tubules (Rezende *et al*., 2020; Rezende *et al*., 2019; Gallwitz, 2019). In 1900 it was discovered as a plentiful non-protein-nitrogen-containing-meat-component (Boldyrev *et al*., 2013). The activity of L-biological histidine is given by the dipeptide's imidazole ring, whereas β -alanine regulates its rate of synthesis. According to its chemical formula ($C_9H_{14}N_4O_3$), it has a molar mass of 226.236 g.mol-1 and a melting point of 253°C (Hussein and Gaafar, 2022).

Metabolism of carnosine

Carnosine synthsis

Carnosine homeostasis depends on its synthesis from, and breakdown of its constituent amino acids. Carnosine is produced from BA and L-histidine in a process mediated by the skeletal muscle non-specific carnosine synthase enzyme (CARNS) encoded on ATPGD1 gene which is one of metabolic enzymes gene. In rats, a second enzyme, the dipeptidase PM20D2, helps the CARNS in synthsis of carnosine (Perim *et al*., 2019; Gallwitz, 2019).

Carnosine absorption

CAR is carried by proton-coupled oligopeptide transports (POTs) known as peptide transporter1 (PEPT1), peptide transporter2 (PEPT2), phosphate transporter1 (PHT1), and phosphate transporter2 (PHT2) (Jappar *et al*., 2009). Therefore, CAR can be absorbed by tissues that express these transporters particularly, PEPT1 is highly represented in proximal tubules of the kidney cortex and apical membranes of the small intestine. PEPT2 has primarily located in the proximal tubule brush border as well as the brain, choroid plexus, eyes, lung, and mammary gland. PHT1 is prominent in rat brains and eyes, while PHT2 is prominent in the spleen, thymus, lung, and immunocytes (Yeum *et al*., 2010).

Carnosine Breakdown

Carnosinase is the enzyme that catalyzes the enzymatic hydrolysis of carnosine, which has two forms; Serum carnosinase (CN1), and Tissue carnosinase (CN2) (Teufel *et al*., 2003). CN1 s extremely active in humen, resulting in the complete absence of carnosine from human blood, in contrast to other vertebrates such as rats, who lack serum carnosinase and have high quantities of carnosine in their blood. CN2, also known as cytosolic nonspecific dipeptidase, has a limited role in the breakdown of carnosine in humans (Derave *et al*., 2010). As already mentioned, very little or no carnosine is carried into the muscles after intake. Histidine and certain amino acids are transported throughout the skeletal muscle by amino acid transporters (Fig. 3), but β-alanine is transported by taurine transporters (Perim *et al*., 2019).

The biological function of carnosine

Carnosine has a variety of biological functions which may include an antioxidant activity that is mediated by different mechanisms concerning reactive oxygen species (ROS) scavenger and reactive nitrogen species (RNS), a zinc and copper ion chelator, antiglycation, anticross-linking activities, decreasing reactive carbonyl stress(RCS) and improving lipid and glucose metabolism and carnosine capacity to respond to hazardous aldehydes, such as methylglyoxal (MG), malondialdehyde (MDA), hydroxynonenal, and acetaldehyde may also contribute to its defensive properties (Hipkiss, 2009; Iacobini *et al*., 2022) as carnosine direct interface with these particles suppresses the synthesis of lipid peroxidation end substances that are dangerous to the body (Guiotto *et al*., 2005). Carnosine act as pH-buffering, in addition to its ability to inhibit the production of AGEs and lipoxidation end-products. Also, has role in the treatment of diabetes and its complications, aging, ophthalmic illnesses, and neurodegenerative disorders, affect nitric oxide (NO) release, metabolism, and activity, as well as intramyocellular homeostasis during muscle contractions (Boldyrev *et al*., 2013).

Carnosine was postulated to play a role in sensory neurotransmission, either as a neurotransmitter or a neuromodulator on glutamatergic neurons by control of the glutamate transporter 1 and lowering of glutamate concentrations in the central nervous system (Araminia *et al*., 2020; Sassoè-Pognetto *et al*., 1993). Carnosine is essential for skeletal and cardiac muscle contraction. Severin, one of Gulewitch's students, hypothesized that carnosine contributes to the contractile activity of skeletal

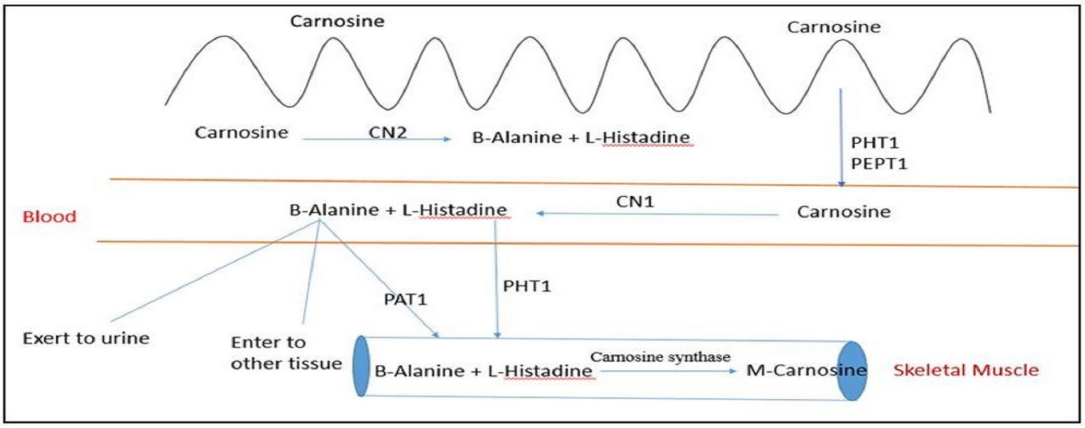

Fig. 3. Carnosine metabolism.

muscle through their studies on frog nerve muscle (Severin *et al*., 1953). In cardiac muscle, carnosine can improve heart contractions through myosin which is a type of protein concerned with heart contraction and has been found to promote cardiac pumping, a direct relationship exists between carnosine and myosin as carnosine increase the heart pumping, so When there is an abundant of carnosine in the body, it increases myosin (Kim). Carnosine has a beneficial effect on diabetes Because of its ability to impact glycemic management and enhance diabetic complications such as nephropathy and ocular impairment. Lee *et al*., employing Balb/cA mice were the first to report a general safeguarding effect of carnosine in diabetic animal models. (Lee *et al*., 2005). Carnosine treatment lowered hyperglycemia, regulated dyslipidemia, improved liver damage, and controlled blood glucose levels. Carnosine decreases sympathetic nerve neuronal activity while promoting parasympathetic nerve activity which induces an increase in insulin release and a decrease in pancreatic glucagon release, producing a hypoglycemic effect (Boldyrev *et al*., 2013). Diabetes-induced nephropathy was reported to be reduced by carnosine therapy particularly by inhibiting glomerular apoptosis, preventing loss of podocyte, and reducing expression of cytochrome c and Bcl-2-associated X protein (Bax) (Riedl *et al*., 2011). Carnosine was also proven to improve diabetic neuropathy, mainly abnormal sensory perception (Kamei *et al*., 2008). Carnosine plays a role in neurological disorders as it has a protective effect on Alzheimer's disease (AD) in vitro research conducted in the late 1990s showed the dipeptide's capacity to prevent both the development of β-amyloid polymerization and cell toxicity which is the main etiology of AD (Preston *et al*., 1998)

Effect of carnosine on diabetic complications

The consequence of carnosine supplementation on diabetic-related complications has been studied in rodent models of type 1 or type 2 diabetes as following:

In diabetic nephropathy

Diabetic nephropathy (DN) is one of the most common complcation of DM which lead to end stage renal disease ; charactrized by albuminuria , reduced kidney function (Sanchez-Rangel and Inzucchi, 2017) , hypertension, hyperglycemia due to renal inflammation which lead to glomerulosclerosis, interstitial fibrosis, tubular atrophy, thickening of basement membranes , and finally end stage renal faliure (Macauley, 2016). DN is classified into five stages: stage 1 charactrized by renal hypertrophy; stage 2 charactrized by normal albuminuria; stage 3 called early DN, charactrized by microalbuminuria ; stage 4 called clinical DN, charactrized by macroalbuminuria; and stage 5 charactrized by end-stage renal disease (Kawanami *et al*., 2020) .

In 2005, the first study on the effect of L-carnosine on glucose-induced damage in renal cells (Zarkogianni *et al*., 2015). Morover, In diabetic rats, renal carnosine concentrations were 100 times higher after Carnosine therapy (1g/kg body weight for 12 weeks), achieving protein concentrations up to 300 μg/g in renal tissue (Magkos *et al*., 2020). Because of DM, there is a gradual glomerular podocyte loss. In vitro, it significantly reduced podocyte pyroptosis and podocyte inflammatory response and lowered renal IL-6 and TNF-α in rats exposed to nickel-induced nephrotoxicity (Zhu *et al*., 2021; Busa *et al*., 2022). According to trials on rats with STZ-induced diabetes it was revealed that administration of carnosine (1 g/kg body weight per day) enhances carnosine levels in the kidney, prevents podocyte loss, glomerular apoptosis, and lower Bax and cytochrome C expression (Prokopieva *et al*., 2016).

In Reproduction

DM has many effect on reproduction either for male or female. in female there is relationship between Insulin, insulin resistance, hyperglycaemia, and ovarian dysfunction (Hu *et al*., 2009) Fig. 4. Adminstration of carnosine may be very beneficial in the treatment of ovarian torsion because it protects the ovaries from ischemia-reperfusion damage (Sarac *et al*., 2018). In male there is a relationship between diabetis and the sexual life and fertility capability due to degenerative changes as a result of testicular damage and increase oxidative stress level (Trevisan, 2017) , reduce semen volume, sperm counts, motility , abnormal sperm morphology, and reduce testosterone levels (Croxtall and Keam, 2008). Administration of carnosine improves reproductive dysfunction by comparison to the protein-deficient diet (PDD) treated group (CAR-PDD), the co-treatment restored body and testicular weights, sperm motility, count and viability, and testosterone levels to normal (Kamel *et al*., 2020).

In diabetic retinopathy (DR)

It is one of the most common diapeticcomplication charactrized with pericyte loss, microaneurysm development, capillary basement membrane thickening, vascular leakage, and subsequent retinal oedema, followed by microvascular blockage, and neurodegeneration which lead to loss of vision (Farmer and Fox, 2011). It begins with microvascular complications in the retina, which can progress to severe complications such as vision loss due to malnutrition and retinal cell degeneration (He, 2012). Oral carnosine treatment reduces vascular damage in experimental

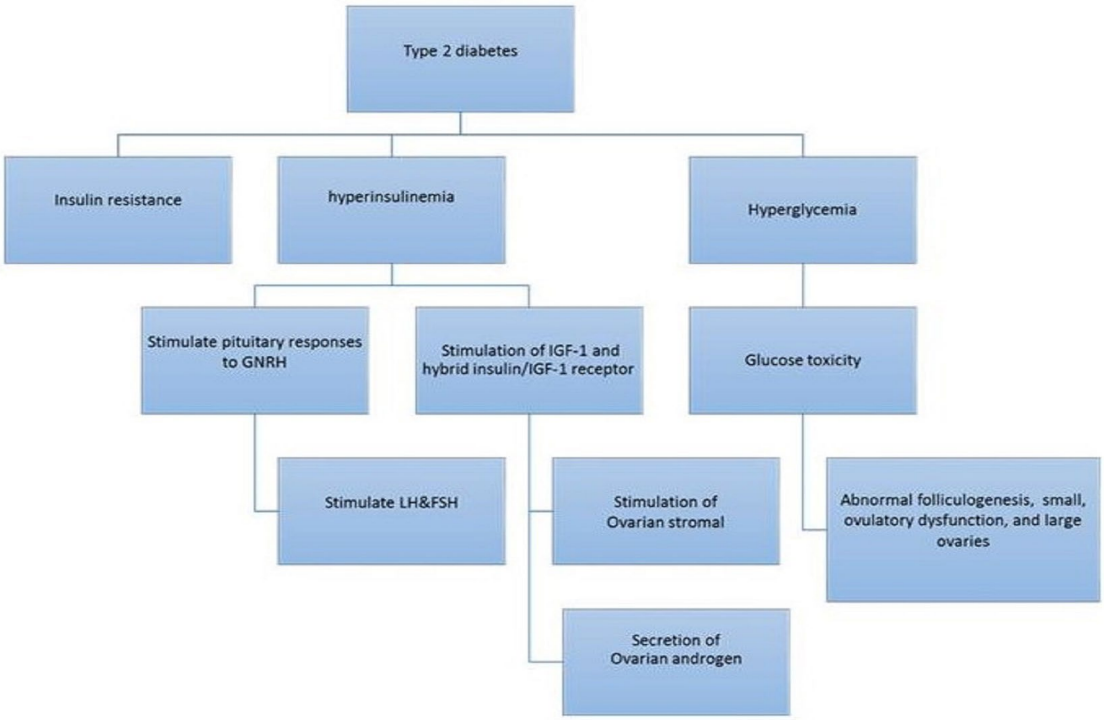

Fig. 4. Mechanisms of interactions between diabetes mellitus and reproductive function.

DR rats, contrary to its biochemical activity, as ROS or AGE inhibition (Li *et al*., 2021).

In diabetic neuropathy

diabetic neuropathy is one of the most common diabetic complications affects more than 60 % of diabetic patients, due to oxidative stress causesd by Hyperglycemia which lead to activation of the transcription factor NF-B in peripheral neurons which mediate the production of proinflammatory cytokines such as TNF-, IL-6, and COX-2 causes neuroinflammatory-mediated nerve injury in peripheral neuropathy, and this appeare as severe pain, loss of sensation, tingling, and burning feeling (Kleppinger and Helms, 2007). High-dose carnosine treatment in rats reduced nuclear factor kappa-B activity (NF-kB) which is a key pathway for the development of brain oxidative stress, inflammation, and hippocampal acetylcholinesterase (Schön *et al*., 2019). It also protected neurons against MDA-induced protein cross-linking, mitochondrial degeneration, reduced TNF- α levels, and the activation of the ROS-dependent MAPK signaling pathway (Yehia *et al*., 2019). Also, Carnosine promotes lactic acid production from cells and provides metabolic support for neurons and axons (Gallwitz, 2019).

In cardiomyopathy

cardiovascular disease is the most common reason for mortality in diabetic patients, the damage caused by diabetic oxidative stress revealed that free radical was increasing and antioxygen was decreasing. Because of myocardial ischemia, there is an increase in lactate production which gives rise to changes in intracellular PH. L-carnosine is involved in the maintenance of cardiac muscle intracellular physiological PH through decreasing lactate content and increasing oxygen consumption, and the exciting contraction force of cardiac muscle cells (Liu *et al*., 2016; Creighton *et al*., 2022). As it is known the perfect antioxidant pathophysiological mechanism of carnosine in cardiac myocytes; is the detoxification process mediated by carnosine which connects with catecholaldehydes, which are pathologically reactive catecholamine metabolites produced in the myocardium (Derave *et al*., 2019). In addition, it has regulated myocardial calcium levels and increased the contractile system's sensitivity to calcium release channels which has beneficial effects on cardiac contractility and function (Muniyappa *et al*., 2021). So L-carnosine could be an effective treatment for the reduction of diabetic complications (Table 1).

Carnosine and Insulin Resistance

Insulin resistance is a metabolic syndrome in which target tissues are unable to mount a typical coordinated glucose-lowering response that would normally involve suppressing endogenous glucose production, lipolysis, cellular consumption of available plasma glucose, and net glycogen synthesis even after a normal level of plasma insulin (Petersen and Shulman, 2018). The islet cell of the pancreas is a primary target of disease in diabetes due to its distinct role in insulin production and insulin secretion stimulated by glucose (Hussein and Gaafar, 2022). Carnosine may increase pancreatic β -cells' capability to secrete insulin, that could offset peripheral insulin resistance, and enhance glycemic control. Additionally, as supplementation began before the development of the disease, it is conceivable that carnosine can contribute to preventing or delaying disease progression (Matthews *et al*., 2021). The TGF-/Smad3 signaling pathway is the mechanism of action, it has potential therapeutic benefits on a variety of systems, including glucose, lipid metabolism, and insulin resistance, and it reduces ROS formation (Saadat *et al*., 2021). In vivo study in diabetes-induced mice receiving carnosine supplement revealed decreased fasting plasma glucose (FPG) levels, reduced insulin resistance and increased β-cell mass (Siriwattanasit *et al*., 2021). In diabetic patients, higher levels of pro-inflammatory cytokines (IL-6 and TNF-α) are associated with insulin resistance and alterations in insulin sensitivity. So Carnosine controls the previously discussed effects by limiting pro-inflammatory cytokine production and decreasing inflammation (Busa *et al*., 2022).

Other histidin containing dipeptide

Anserine(ß-alanyl-Np-Methyl-L-histidine)

L-anserine is a member of the histidine-containing dipeptides family, chemical formula is (C10H16N4O3), it is sensitized by carnosine methylation through carnosine N-methyltransferase enzyme (EC 2.1.1.22) (Kwiatkowski *et al*., 2018). It is present in both birds and fish (Boldyrev *et al*., 2013).

Metabolism and Absorption of anserine

Anserine synthsysis

There are two different pathways for the synthesis of anserine, the first one is catalyzed by carnosine N-methyltransferase (CMT), which catalyzes the transfer of a methyl group of S-adenosylmethionine (SAM) to carnosine to produce anserine (Winnick and Winnick, 1959). The second one is by enzymatic alanine-Npi-methylhistine (or Ntau-methylhistidine) condensation (Boldyrev *et al*., 2013).

Anserine degredation and absorption

At high pH, anserine can be degraded by carnosinase 1 (EC 3.4.13.20) and carnosinase 2 (EC 3.4.13.18). Anserine is completely absorbed in human blood and hydrolyzed to π-methyl histidine and β-alanine by tissue and serum carnosinases (Kubomura *et al*., 2009).

Function of anserine

Anserine works as a strong antioxidant and prevents methylglyoxal (MG)-induced AGEs, N epsilon-(Carboxyethyl)lysine (CEL) formation (Teufel *et al*., 2003). It was revealed that oral administration of anserine reduces blood glucose levels in individuals by oral glucose tolerance tests and modulates the autonomic nervous system through central histamine receptors (Kubomura *et al*., 2010). Anserine activates the intracellular Hsp70-defense system under oxidative and glycation stress and also improves proteinuria, blood glucose, and vascular permeability (Peters *et al*., 2018). In addition to animal studies, clinical trials on humans showed that anserine significantly affects metabolic, neurological, immunological, cardiovascular, and renal functions. Anserine dietary supplementation is beneficial in numerous types of oxidative stress. Anserine administered intraperitoneally to hyperglycemic rats inhibited the activity of sympathetic nerves and reduced hyperglycemia and plasma glucagon levels (Hussein and Gaafar, 2022).

Table 1. Overview on Role of carnosine in different diabetic complications

Diabetic complication	Dose of carnosine	Finding	Reference
Diabetic nephropathy	Dose of Carnosine: 45 mg/kg body weight dissolved in drinking water	• Enhanced glucose metabolism by stimulating insulin secretion, albuminuria. • Restores glomerular ultrastructure.	Moharir and Naikwadi (2020)
	Dose of Carnosine: 250 mg/kg body weight; i.p; 5 times /week) for 4 weeks	• Increase creatinine levels and decrease albumin levels. • Increase glucose, triglyceride, and cholesterol levels. • Decrease the accumulation of oxidation and AGEs in renal tissue.	Shakeel and Tabassum (2022)
	Dose of Carnosine: 70 mg/kg carnosine for 7 days.	• Enhance the histological structure of the renal tissue from injury and glomerular damage due to oxidative stress. • Decrease the accumulation of oxidation and AGEs in renal tissue.	Yay *et al*. (2014)
	Dose of Carnosine: Oral administration of 1 g /kg per day for 8, 12, and 16 weeks.	• Improve clinical symptoms and kidney injury in STZ-induced mice by improving albuminuria, inhibiting renal apoptosis. • Reduce the level of TNF-α and IL-1β.	Matthews *et al*. (1985)
	Dose of carnosine: oral administration of 1 g /kg body weight for 12 weeks.	• Reduce albuminuria level. • Prevent podocytes cell damage.	Zhu *et al*. (2021)
Cardiovascular diseases	Dose of carnosine: 250 mg/kg/day I/p. or with vit E (200 mg/kg) once every 3 days; I/m) for 12 days.	• Decreases in levels of serum ALT and AST. • Prevent doxorubicin-induced toxicity in heart and liver. • Regulate myocardial calcium levels.	Muniyappa *et al*. (2021)
Diabetic retinopathy	1% carnosine in diabetic Rat retinal vascular endothelial cell for 24 h.	• Inhibition of retinal over vascularization. • Control the activation of the MAPK/ERK signaling pathway so reduce DR.	Li *et al*. (2021)
	(1000 mg/kg body weight I/p) before induction of Retinal ischemia.	• Improve Retinal ischemia by reducing RGC loss via reduced expression of HIF-1a, GFAP, Drp-1, and Bax and increased expression of Bcl-2.	Abdelkader *et al*. (2015)
	Dose of carnosine: (1g/kg body weight/day for 1 week).	• Prevent retinal vascular damage through protecting capillary cells of the retina. • Reduce pericytes loss and AGEs.	Maynard *et al*. (2001)
Wound healing	(100 mg/kg body weigh I/P) and topically (25 mg/ml in 60 % polyethylene glycol) on the wound.	• Improve wound healing through increase growth factors and proteins as s insulin-like growth factor 1 (IGF1), transforming growth factor beta (TGFb), and stromal derived factor 1 (SDF1) • Increase carnosine level in serum.	Ansurudeen *et al*. (2012)

Mechanism of action in insulin resistance

Anserine acts as a detoxifying agent for RCS and reduces serum insulin (Yeum *et al*., 2020). It improves pancreatic β-cells capacity to secrete insulin, that may compensate for peripheral insulin resistance, and improve glycemic control (Matthews *et al*., 2021). In vitro studies, anserine can be decreased methylglyoxal (MG) induced AGEs and CEL production. Both type 1 and 2 diabetes have greater blood and tissue AGEs levels. Anserine acts to prevent this by suppressing Receptors for Advanced Glycation End products (RAGE) expression and acting with AGEs, reducing serum glucose levels and trapping MG (Brings *et al*., 2017). In diabetic db/db mice, Anserine intravenous injection (every 2 days for 6 days) reduced vascular permeability, and proteinuria by 50% and reduced blood glucose level by 20% (Peters *et al*., 2018; Hussein and Gaafar, 2022).

Homocarnosine (γ-aminobutyryl-L-histidine)

Homocarnosine (γ-aminobutyryl-L-histidine) is a member of a class of histidine-containing dipeptides (Boldyrev *et al*., 2013). Homocarnosine is a brain-specific dipeptide that does not exist in skeletal muscles. It may contribute as a precursor for the neurotransmitter gamma-aminobutyric acid (GABA), as well as an antioxidant, free radical scavenger, and metal-chelating agent, especially for copper(II) and zinc (II) (Grasso *et al*., 2014; Wang *et al*., 2021, Bauer, 2005).

Metabolism of homocarnosine

Homocarnosine synthsis

As carnosine, homocarnosine synthesis by Carnosine synthase enzyme (CS; EC 6.3.2.11). CS is a member of the ATP-grasp family of ligases and the gene (ATPGD1) is principally present in skeletal and cardiac muscle and additionally in certain areas of the brain, and kidneys (Peters *et al*., 2015).2.2.2.1.2. homocarnosine degredation. Its degradation by Carnosinase (CN1) which is a dipeptidase enzyme encoded by the CNDP1 gene (Kumrungsee *et al*., 2020).

Function of Homocarnosine

Homocarnosine acts an essential role in muscle function and homeostasis, because of its pH buffering capacity, antioxidant capacity, enhanced Ca2+ sensitivity, and protein glycation suppression (Boldyrev *et al*., 2013; Blancquaert *et al*., 2015). HCDs are found in the highest concentrations in vertebrate skeletal muscle, cardiac muscle, brain, olfactory bulb, stomach, and kidneys (Gariballa and Sinclair, 2000). Homocarnosine obtains anti-inflammatory character (Huang *et al*., 2018), DNA damage, and AGEs inhibition. Additionally, it has greater resistance to serum carnosinase hydrolysis than carnosine (Pavlin *et al*., 2016). In immortalized rat brain cells, homocarnosine has been revealed to prevent β-amyloid peptide-induced toxicity, but to a lesser extent than carnosine (Freund *et al*., 2018). At the same concentration, homocarnosine suppressed galactose-induced glycation of bovine serum albumin and inhibited glycation by glucose (Han *et al*., 2014).

Homocarnosine and Insulin resistance

Insulin resistance is indicated by AGEs and free radicals (Artioli *et al*., 2019). The most favorable reactive dicarbonyl molecule in diabetes individuals' plasma is MG (Fleming *et al*., 2012). The therapeutic reducing of MG levels is a potential strategy for treating diabetic neuropathy and other problems related to MG (Brings *et al*., 2017). Considering Homocarnosine should be used with caution as a treatment option for diabetic nephropathy patients. Moreover, therapy with Homocarnosine may be able to decrease blood carnosine degradation. In contrast, high levels of homocarnosine can lead to high levels of its breakdown products such as Gama Aminobutyric Acid (GABA) and histidine which are easily converted into histamine, which improves both renal insufficiency and neuronal activity (Kumrungsee *et al*., 2020).

CONCLUSION

This review summarized the relationship between HCDs and diabetes, it focused on the protective effect of HCDs especially carnosine for lowering diabetic complications and their mechanism. In future, we should focus on nano histidin containing dipeptide and their effect on diabetic complications.

CONFLICT OF INTEREST

The authors declare that they do not have a conflict of interest.

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