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Histidine-Containing Dipeptides in Obesity and Cardiometabolic Health: A Systematic Scoping Review

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Keywords: cardiometabolic health | cardiovascular diseases | carnosine | diabetes | histidine-containing dipeptides | insulin resistance | obesity | type 2 diabetes

ABSTRACT

Background: Histidine-containing dipeptides (HCDs) have been reported to have anti-inflammatory and antidiabetic properties. Yet, no previous reviews have examined the impact of HCDs on Type 2 diabetes (T2D) risk factors (e.g., obesity) and progression (e.g., microvascular and macrovascular complications). In this scoping review, we aimed to thoroughly examine the evidence on the effects of HCDs, particularly carnosine, which is the most studied HCD, on T2D risk factors and complications and the underlying mechanisms of action.

Methods: We systematically searched Ovid-Medline, Embase, CINAHL, Scopus, Web of Science, and Cochrane Library from inception to December 2023. We included experimental studies (animal models and cell studies), observational studies, and randomized controlled trials (RCTs) investigating the mechanism of action of HCDs and the effects of supplementation in individuals with obesity and/or T2D.

Results: The primary literature search yielded 10,973 articles and 121 studies were eligible for inclusion. HCDs have been shown to mitigate inflammation and improve lipid profile and glycemic control in obesity and T2D with or without microvascular and macrovascular complications. However, most studies are experimental, focusing on elucidating the potential mechanisms of action of HCDs, with limited observational data or RCTs of individuals with obesity and/or T2D. No RCTs have investigated the effects of HCDs in individuals with neuropathy, retinopathy, cerebrovascular disease, and cardiovascular disease within a diabetic context.

Conclusions: Although the existing evidence, predominantly from preclinical studies, generally supports the use of HCDs for improving cardiometabolic health, further human studies, especially RCTs with adequately powered sample sizes, are needed.

Aya Mousa and Barbora de Courten equally contributed as shared senior authors.

1 | Introduction

Type 2 diabetes (T2D) is an increasingly important public health concern, with its worldwide prevalence tripling from 151 million in 2000 to 537 million in 2021 [1]. By 2045, the total number of individuals with T2D is expected to rise by 46% if effective prevention and treatment measures are not implemented [1]. Most individuals with T2D have concomitant overweight or obesity, which are critical modifiable risk factors for T2D development and progression [2]. The two main features of T2D are insulin resistance and pancreatic β-cell dysfunction, both of which are exacerbated by obesity [3]. Insulin resistance plays a substantial role in atherosclerotic cardiovascular disease (ASCVD), which is a major cause of morbidity and mortality among patients with T2D [4]. ASCVDs associated with T2D, including coronary artery disease and stroke, are the major causes of mortality for at least 50% of patients with T2D [5, 6]. Given the high incidence of obesity, T2D, and ASCVD, preventive approaches to reduce the burden of these diseases should be prioritized.

Although glycemic control and weight management have long been targeted in T2D management, the treatment of T2D remains challenging due to the side effects of antidiabetic medications and the challenges associated with lifestyle changes [7]. Conventional medications for T2D management including insulin, sulfonylureas, and thiazolidinediones, tend to contribute to additional weight gain [8]. Despite achieving good glycemic control using these glucose-lowering agents, about half of individuals with T2D die of ASCVD [9, 10]. Newer medications such as sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) analogs produce weight loss and reduce ASCVD incidence [11–13] but have important side effects. Bariatric surgeries including sleeve gastrectomy and Roux-en-Y gastric bypass are effective in diabetes remission and losing weight [14]. However, long-term efficacy and safety data are lacking, and surgical risk and cost-effectiveness need to be considered. Lifestyle modification and subsequent weight loss have remained the cornerstone of treatment for obesity, T2D, and its associated complications [15]. Although effective, these treatments face several challenges associated with sustaining lifestyle changes, including adherence difficulties at the population level, socioeconomic factors, lack of motivation, and environmental factors. Therefore, there is an urgent need for novel approaches that are safe, cost-effective, and easy to implement on a broad scale.

Histidine-containing dipeptides (HCDs) have shown some promise in mitigating diabetes-related risk factors and complications [16]. One HCD of interest is carnosine, also known as β-alanyl-L-histidine, which was discovered during a study performed by Gulewitsch and Amiradžibi [17] at Charkow University in Ukraine and was extracted from Liebig's meat extract in 1900. This naturally occurring dipeptide is synthesized from β-alanyl (formed by uracil and thymine degradation in the liver) and L-histidine (derived entirely from diet), with the reaction catalyzed by the enzyme carnosine synthetase 1 (CARNS1) [18, 19]. Carnosine is highly abundant in meat, particularly red meat, and its methylated derivatives (anserine and ophidine/balenine) are present in skeletal and cardiac muscles [18, 20]. Homocarnosine is another HCD that is brain-specific in the mammalian nervous system and is made of γ-aminobutyric acid (GABA) and L-histidine [21]. Carnosine levels in the human body depend on several factors, with aging, female gender, and vegetarianism linked to decreased muscle carnosine levels [22–24]. Considering the diversity of human dietary habits and the aforementioned factors, most humans would likely benefit from dietary supplements as the most effective means to achieve and sustain higher carnosine levels [25].

Mechanisms of action of carnosine include anti-inflammatory, antioxidant, and anti–advanced glycation end product (AGE) properties [26, 27], as well as the ability to modify the energy metabolism of immune cells [28, 29]. Given its promising therapeutic function, carnosine has been studied in numerous experimental models of disease including obesity, T2D, and cardiovascular disease (CVD) [16, 24, 30–37]. However, to our knowledge, there has been no previously published evidence synthesis examining the impact of HCDs on T2D risk factors and complications. As the body of evidence around HCDs continues to expand, there is an increasing need to synthesize the research and identify areas where knowledge gaps exist [38–40]. To this end, we conducted a systematic scoping review to synthesize all available evidence from experimental, animal, and human studies examining the effects of carnosine and other HCDs on T2D risk factors (obesity, poor glycemic control, cardiovascular risk measures [e.g., dyslipidemia and hypertension], inflammation, and oxidative stress), as well as microvascular and macrovascular complications, and to identify relevant knowledge gaps.

2 | Materials and Methods

2.1 | Study Protocol and Registration

This review is reported in accordance with the updated 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [41]. The protocol was registered a priori on open science framework (OSF) (registration number: https://doi.org/10.17605/OSF.IO/8XQPU).

2.2 | Search Strategy

A comprehensive systematic literature search was conducted from inception to April 2023 and then updated in December 2023 across the following electronic databases: Ovid/Medline, Embase, CINAHL, Scopus, Web of Science, and Cochrane Library. The following keywords were used in the primary searches: "carnosine" OR "beta alanyl histidine" OR "anserine" OR "beta alanyl 3 methylhistidine" OR "ophidine" OR "beta-alanine" OR "3 aminopropionic acid" OR "N-Acetyl-Carnosine" OR "N-Acetyl-L-Carnosine" OR "beta alanyl l histidine" OR "beta-ala-his" OR "l histidine beta alanyl" OR "l alpha alanyl l histidine" OR "histidine" OR "balenine." The search terms were also translated into the appropriate subject terms used in the six literature databases. Details of the search strategy are presented in Table S1. Broad search terms were used intentionally to capture the maximum number of relevant articles. The search string did not include limits on time frame, setting, or language; however, non-English papers were

excluded at the subsequent screening stage. In addition, a manual search of the reference lists of relevant studies was performed to identify additional studies.

2.3 | Study Selection

The Population, Intervention, Comparison, Outcomes, and Study (PICOS) design framework was used to determine the eligibility of articles, as outlined in Table 1. Briefly, we included studies of any design as well as meta-analyses, which examined the effects of carnosine on T2D risk factors or complications in any population. Exclusion criteria were as follows: (1) studies investigating the effect of HCDs in combination with other active components (other combined interventions such as diet and/or exercise were included if the intervention was delivered in the same way to both groups); (2) studies not evaluating an outcome of interest for the present systematic scoping review; and (3) non-English papers, non–peer-reviewed literature, narrative reviews, systematic reviews without meta-analyses, letters, commentaries, editorials, book chapters, conference abstracts, and case reports.

TABLE 1 | PICOS criteria for inclusion of studies.

Parameters	Inclusion criteria
Patient or population	All the individuals and experimental models with obesity, T2D with or without microvascular and macrovascular complications
Intervention, prognostic factor, and exposure	Carnosine, beta-alanine, or related HCDs (anserine, NAC, etc), administered alone (pure) and in any form (oral, intravenous, or intramuscular)
Comparator (if appropriate)	Comparison with placebo, usual care, or any pharmacological or nonpharmacological intervention(s)
Outcome	Those which reported outcome interest related to obesity, T2D, and its microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (cardiovascular disease, cerebrovascular disease, and peripheral artery disease) complications. Also, the studies evaluating mechanisms of action in which HCDs exerted anti-inflammatory, antioxidant, and anti-AGE properties
Study design	Experimental design, longitudinal and cross-sectional studies, randomized clinical trials, and meta-analyses

Abbreviations: AGEs, advanced glycation end products; HCDs, histidine-containing dipeptides; NAC, N-acetylcarnosine; T2D, type 2 diabetes.

A systematic review management software (Covidence; Veritas Health Innovation Ltd.) was used to manage all the papers from the searches and subsequent screening. After removing duplicates, title and abstract screening was performed for all the identified studies by two independent reviewers (S.S. and R.K.). Then, a full-text review was performed to identify studies that satisfied all the eligibility criteria. Any discrepancies regarding the eligibility of the studies were resolved by a third reviewer (A.M.) to reach consensus.

2.4 | Data Extraction and Synthesis

Two independent reviewers (S.S. and R.K.) extracted data from eligible articles using a predefined data extraction form. Descriptive information was extracted from all articles including authors and year of publication, country, study design, population and sample size, intervention/exposure regimens or definitions, outcome measures, and key findings, as well as corroborating data where relevant. Additional information also extracted from articles included the mechanisms by which HCDs exerted anti-inflammatory, antioxidant, and anti-AGE properties.

3 | Results

3.1 | Study Selection

The process of study selection is shown in Figure 1. The primary literature search yielded 10,973 studies, and an additional 4458 were identified in the updated search. A total of 6479 duplicates were removed and 8952 were assessed by title and abstract. Of these, 1567 were eligible for full-text review of which 1446 records were excluded. No additional studies were identified via manual checking of reference lists of relevant studies or reviews. Thus, a total of 121 studies were eligible for inclusion in this review. We excluded any mixed interventions provided with HCDs, as we could not isolate the sole effects of HCDs [24, 32, 42–49]. The 121 included studies were published between 1994 and 2023 and consisted of 90 experimental studies (68 animal models and 22 cell studies), 17 observational studies, 10 randomized controlled trials (RCTs) (reported in 19 papers), and four systematic reviews with meta-analyses.

3.2 | Effects of HCDs on Obesity-Related Outcomes

Obesity is an important risk factor for T2D as well as several other chronic conditions, including CVD, chronic kidney disease (CKD), and several cancers [50]. Marked by the dysregulation of adipose tissue, this multifactorial and progressive disorder initiates an inflammatory cascade and promotes systemic insulin resistance [50]. In turn, obesity and its contribution to the dysregulation of glucose and fatty acid metabolism have detrimental effects on several organs including the pancreas, heart, arteries, and liver. The severity of these adverse effects is closely correlated with the degree and distribution of excess body weight [50, 51]. Details of the included studies related to the effect of HCDs on T2D risk factors, including obesity, are summarized in Table S2.

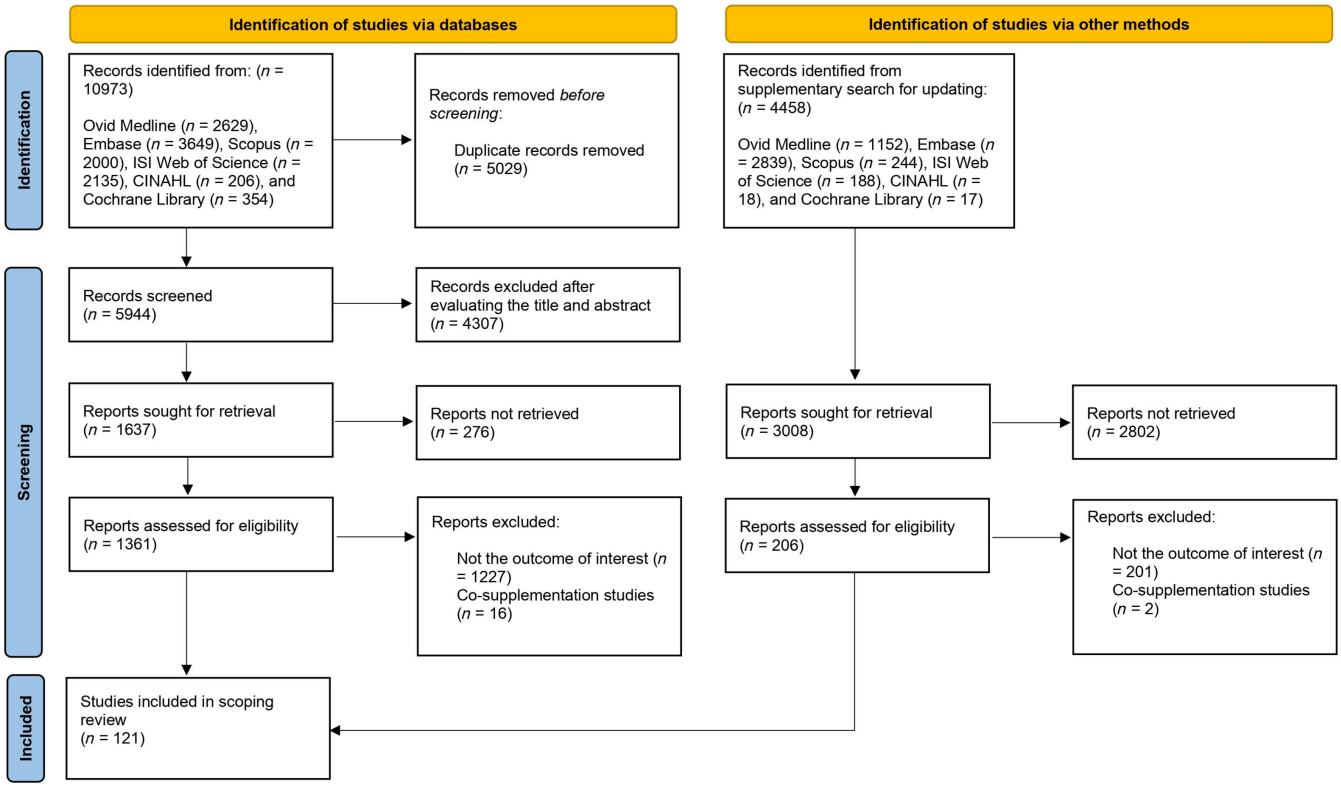

FIGURE 1 | PRISMA flow diagram of the screening and selection process for the scoping review of the effects of carnosine and histidine-containing dipeptides on cardiometabolic health.

3.2.1 | Experimental Studies (*In Vitro* and *In Vivo*)

Experimental data reports some benefits of HCDs for obesity, though results are inconsistent. Body weight and abdominal obesity were significantly reduced with the use of L-carnosine in high-fat diet-fed rats and rats with metabolic syndrome in two studies [52, 53], whereas another study reported no differences in body weight between carnosine-treated and untreated rats with T2D [54]. Histidine supplementation suppressed food intake and fat accumulation in another rat study, suggesting that HCDs may be beneficial in obesity management [55]. Similarly, knockout of carnosine dipeptidase1 (CNDP1), which increases carnosine levels, prevented weight gain in zebrafish [56], whereas cats consuming diets enhanced with L-carnosine gained more lean body mass compared with cats consuming a control diet [57]. L-carnosine supplementation is proposed to decrease body weight via the browning and thermogenesis of adipocytes, as previously demonstrated in obese rats [58]. This is thought to occur via increased irisin concentrations, a myokine that modifies adipogenesis and promotes the browning of adipose tissue [58]. Based on these studies, targeting brown adipose tissue may be an effective strategy for obesity management because of its effect on energy metabolism [58].

3.2.2 | Human Studies

In line with most experimental studies, a cross-sectional study involving 88 participants with overweight or were obese showed that dietary histidine intake was inversely related to body mass index (BMI), waist circumference, energy intake, and prevalence of overweight/obesity in northern Chinese adults [59]. Similarly, there was an inverse relationship between histidine to protein intake ratio and energy intake among young women [60]. A higher dietary intake of histidine contributed to increased production of histamine, which is known to play an important role in energy expenditure [61].

RCTs have produced mixed results, albeit with limited data. Histidine supplementation (4 g/day) for 12 weeks was shown to reduce BMI, fat mass, and nonesterified fatty acids (NEFA) in one trial of 92 women with obesity [62]. In another RCT, carnosine supplementation did not improve body weight or BMI in 54 participants with T2D, but reduced fat mass and increased fat-free mass were reported [63]. In contrast, supplementation with β-alanine for 6 weeks increased the time to exercise exhaustion but did not change anthropometric measurements in sedentary women classified as overweight [64]. We have also shown that 12-week carnosine supplementation (2 g/day) did not change body weight, BMI, and percentage of body fat in 30 individuals without diabetes but with overweight or obesity [36] and in 43 individuals with prediabetes and T2D [65].

3.3 | Effects of HCDs on Glycemic Outcomes

Dysglycemia can result from insulin resistance, defective or insufficient insulin secretion, or both. Insulin resistance results

in hyperinsulinemia, which over time results in a decline in β-cell function, impaired glucose tolerance, and hyperglycemia. Insulin resistance and hyperglycemia are related to other cardiometabolic risk factors including chronic low-grade inflammation, accumulation of AGEs, and subsequent development of T2D-associated complications [66, 67].

3.3.1 | Experimental Studies (*In Vitro* and *In Vivo*)

Experimental data have produced mixed results for HCDs in relation to glycemic outcomes. Several studies have demonstrated that carnosine and other HCDs reduce plasma glucose and HbA1c levels in rodent models of diabetes [53, 54, 68–78]. Similarly, some studies reported that carnosine and histidine increased insulin secretion in experimental models of both type 1 diabetes (T1D) and T2D [68, 69, 77, 79–82]. Some studies report that carnosine is lower in the cardiac muscle of diabetic rats compared with healthy controls [83] and increases glucose uptake in skeletal muscle cells [79, 80]. In an *in vitro* study of kidney tissue of mice, L-carnosine showed considerable antidiabetic activity through inhibition of α-glucosidase and α-amylase [84]. In a cross-species study, muscle carnosine levels were found to increase with progressive glucose intolerance in both rodents and human subjects, with significantly higher levels observed in individuals with prediabetes and diabetes compared to lean controls. This suggests that elevated muscle HCDs may serve as a compensatory mechanism to mitigate cellular damage under conditions of impaired glucose tolerance [85]. However, not all studies report beneficial outcomes; some found no improvement in glucose homeostasis following carnosine or HCD intervention [86, 87], and others observed no effects on insulin concentrations in rats with metabolic syndrome [53] or insulin resistance in diabetic rodents [69, 81, 88].

3.3.2 | Human Studies

Human observational data are largely in agreement with findings from animal models. In a case–control study of 14 patients with T2D and 14 matched controls, those with T2D had less muscle carnosine content, which is thought to facilitate their higher insulin resistance [89]. These results are supported by a cross-sectional study of 88 participants with overweight or obesity, whereby dietary histidine intake, which would increase carnosine synthesis, was inversely related to insulin resistance [59]. Moreover, other cross-sectional studies in individuals with overweight or obesity ($n = 65$) found that muscle carnosine levels were inversely correlated with 2-h glucose levels [90] and insulin resistance [91], whereas serum carnosinase-1 (CN-1) (which degrades carnosine in serum and tissue) was negatively associated with insulin sensitivity [90].

In clinical trials, carnosine supplementation (1 g/day) for 12 weeks improved glycemic control in 85 patients with T1D with nephropathy [92] and patients with T2D [63, 93]. In addition, 2 g/day of carnosine supplementation for 12 weeks reduced insulin resistance in 24 sedentary individuals with overweight or obesity [94, 95] and improved glucose parameters in our pilot trial of 30 individuals without diabetes but with overweight and obesity [36]. When supplemented for 14 weeks in 43 individuals with prediabetes or T2D, it also reduced blood glucose without significant changes in insulin secretion during an oral glucose tolerance test [96]. The benefits of anserine, another HCD, have also been investigated in relation to glycemic control in healthy individuals, demonstrating reduced blood glucose during glucose tolerance testing [73]. Histidine supplementation administered at 4 g/day for 12 weeks improved insulin resistance measured by the homeostatic model assessment for insulin resistance (HOMA-IR) among 92 women with obesity and metabolic syndrome [62]. In contrast, 28 days of supplementation with β-alanine (4 g/day) did not change insulin sensitivity and insulin resistance in a small study of 12 participants with T2D [97].

Findings from a systematic review and meta-analysis involving 16 animal studies and four clinical trials of individuals with obesity and all types of diabetes showed that carnosine or β-alanine supplementation reduced HbA1c, fasting glucose, and HOMA-IR in both humans and rodents and fasting insulin in humans [98]. Another systematic review and meta-analysis involving three studies revealed that carnosine significantly decreased fasting glucose and HbA1c [24]. However, in another meta-analysis with four RCTs, carnosine reduced HbA1c only, with no effects on fasting glucose and HOMA-IR [99].

3.4 | Effects of HCDs on Cardiovascular Risk Measures

Cardiovascular risk factors, including dyslipidemia (hypertriglyceridemia and low levels of high-density lipoprotein cholesterol [HDL-C]) and hypertension, are important precursors of T2D, often presenting as a combination of symptoms termed "metabolic syndrome" [66]. Diabetes-associated dyslipidemia and impaired lipid metabolism are also indicative of potential macrovascular complications arising with the progression of T2D [67].

3.4.1 | Experimental Studies (*In Vitro* and *In Vivo*)

In high-fat and high-cholesterol-fed rats, treatment with L-carnosine resulted in improved serum lipid profiles through reduced levels of low-density lipoprotein cholesterol (LDL-C) [52, 53, 77, 100] and increased levels of HDL-C [100]. Carnosine supplementation also resulted in a significant reduction in obesity-related dyslipidemia in obese rats [31, 58]. In addition, histidine and carnosine were found to reduce the expression of sterol regulatory element-binding proteins (SREBP)-1c and SREBP-2 in high-fat high-carbohydrate-fed rodents [53, 101]. This led to the reduced expression of fatty acid synthase and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase [101], thus reducing levels of triglycerides (TG) [101] and total cholesterol (TC) [53, 101].

3.4.2 | Human Studies

In a cohort study of 602 adults with mild to high CVD risk, urinary levels of nonconjugated carnosine and its acrolein conjugates (carnosine-propanal and carnosine-propanol) were measured [102]. Both conjugated and non-conjugated urinary carnosine were positively associated with CVD risk factors,

including BMI and diabetes diagnosis, and negatively associated with HDL-C levels. However, no associations were found between these markers and other CVD risk factors, including blood pressure, TC, fibrinogen, platelet aggregates, and high-sensitivity C-reactive protein (hsCRP) [102]. Although these findings suggest that urinary carnosine and its conjugates may serve as informative biomarkers for CVD risk assessment, the study did not assess the prospective predictive value of this marker for future CVD events [102]. In a prospective cohort study, the 5L–5L (homozygosity for 5-leucin repeat) genotype in CNDP1 was associated with increased CVD mortality in women with T2D [103].

In addition to the limited observational data, small RCTs have been conducted to date, demonstrating the potential antihyperlipidemic properties of HCDs. Carnosine (1 g or 2 g/day for 12 weeks) was shown to improve the plasma lipidome in 24 sedentary individuals with overweight and obesity [94]; improve TG in 54 patients with T2D [63, 93]; and improve TG, TC, and HDL-C in 85 patients with T1D with nephropathy [92]. However, other RCTs reported no improvements in plasma TG or TC levels among 30 participants with overweight or obesity [36], and no change in any lipid profile parameters in 43 individuals with prediabetes and T2D [104], following similar carnosine supplementation regimens (2 g/day for 12–14 weeks).

3.5 | Effects of HCDs on Inflammatory and Oxidative Stress Biomarkers

Inflammation and oxidative stress are key risk factors for the development of metabolic diseases, including obesity, T2D, and CVD, and are thought to be linked with high rates of mortality among these individuals [105, 106]. An inflammatory state occurs when the production of pro-inflammatory cytokines, including interleukin (IL)-6, IL-1β, and tumor necrosis factor-α (TNF-α) exceeds the circulating levels of anti-inflammatory mediators, such as IL-10 and transforming growth factor-β1 (TGF-β1) [107]. Oxidative stress is a state in which there is an imbalance between the generation of reactive oxygen species and the processes responsible for eliminating them [108]. The primary mechanism for detoxification involves glutathione (GSH) and the superoxide dismutase (SOD) enzyme [109, 110]. The relationship between oxidative stress and inflammation can create positive feedback, whereby oxidative stress triggers the production of inflammatory mediators, in turn promoting inflammation. This inflammatory response further increases the generation of ROS, perpetuating oxidative stress [111, 112].

3.5.1 | Experimental Studies (*In Vitro* and *In Vivo*)

In both cell culture studies and animal models, carnosine and HCDs have been found to mitigate oxidative stress [77–80, 84, 87, 88, 113–119], lipid peroxidation [72, 75, 86, 87, 120], and chronic low-grade inflammation [75, 78, 88, 116, 119]. *In vitro* studies reported that carnosine mitigated oxidative stress, inflammation, and apoptosis [121–126]. However, L-carnosine had no effects on leptin and adiponectin concentrations in rats with metabolic syndrome [53], and its effects on antioxidant capacity remain controversial [58, 72, 75, 86, 87, 127–130].

3.5.2 | Human Studies

Despite compelling evidence from animal studies, human data remain sparse. A case–control study ($n = 452$) found that serum histidine levels were significantly lower in women with obesity compared to non-obese controls, with histidine negatively associated with inflammation and oxidative stress in obesity [131]. A cross-sectional study showed that dietary histidine intake was inversely related to inflammation and oxidative stress in 88 participants with overweight or obese [59]. The findings from this observational study were supported by a clinical trial of 100 women with obesity and metabolic syndrome, whereby 4 g/day of histidine supplementation for 12 weeks ameliorated inflammation and oxidative stress [62]. In addition, supplementation with 1 g/day of carnosine for 12 weeks improved antioxidant defense and reduced oxidative stress biomarkers, serum levels of TNF-α and AGEs as add-on therapy in 54 patients with T2D, but there was no effect on RAGEs, L-1β, and IL-6 [63, 93]. Carnosine supplementation (2 g/day for 12 weeks) in 29 individuals with overweight led to the detection of carnosine–acrolein adducts in urine, indicating that carnosine can trap acrolein in the body, potentially reducing its harmful effects associated with oxidative stress and disease progression [132, 133]. However, 2-g/day carnosine for 14 weeks did not improve inflammation in 43 individuals with prediabetes and T2D [134]. Consistent with the findings from experimental studies, carnosine supplementation did not improve serum adiponectin, leptin, or adipsin but normalized serum resistin, in the small pilot RCT of 24 individuals with overweight/obesity [35, 36].

3.6 | Effects of HCDs on Microvascular T2D Complications

Prolonged elevation of glucose levels, as is seen in poorly controlled diabetes, results in damage to multiple organs [135]. Diabetic nephropathy (DN) is one of the major microvascular complications of diabetes with persistent albuminuria, nodular glomerular lesions, and a progressive decline in the glomerular filtration rate (GFR) [136]. Diabetic retinopathy is another important complication of T2D which stands as the leading cause of visual impairment [137]. The progression of this condition begins with the development of multiple microaneurysms and occasional hemorrhages and can worsen proliferative retinopathy and maculopathy with neovascularization and the presence of hard exudates within the macula [137]. Diabetic neuropathy is also caused by damage to the peripheral and autonomic nervous systems [138]. Details of the included studies related to the effect of HCDs on microvascular complications associated with diabetes are summarized in Table S3.

3.6.1 | Experimental Studies (*In Vitro* and *In Vivo*)

Several studies have assessed the biological association between carnosine metabolism and diabetes complications. Certain variations in the CN-1 gene have been associated with progression of diabetic kidney disease [69, 74, 139–141]. However, knockout of CNDP1 alone was not sufficient to protect from diabetic complications in zebrafish [56]. In experimental rodent models of diabetes, carnosine was effective

in reducing albuminuria [68, 69, 126, 141, 142], glomerular hypertrophy [68, 69], and nodular glomerular lesions [126]. Carnosine has shown potential in protecting the kidneys of diabetic rats from podocyte apoptosis and loss [143]. Carnosine has been shown to increase nephroprotection through enhancing hydrogen sulfide (H2S) synthesis in human proximal tubular cells and endothelial cells [144]. CN-1 knock-out decreased kidney fibrosis in streptozotocin-induced diabetes [84]. Additionally, a novel derivative of carnosine called FL-926-16 has demonstrated beneficial effects in reducing glomerular matrix protein expression, cell apoptosis, and circulating and tissue oxidative and carbonyl stress, and renal inflammatory markers in adult male mice [116]. It is worth noting that the reported effects of anserine on the development of T2D and DN are conflicting, with some showing benefits [71, 145–147] and others reporting no effect [148].

Transforming growth factor β (TGF-β) overexpression is associated with excessive deposition of extracellular matrix (ECM), one of the main contributors to diabetic kidney disease [114, 147]. In human podocyte and mesangial cells, carnosine prevented TGF-β overexpression and ECM accumulation [149, 150], suggesting a renoprotective property of carnosine. In addition, carnosine is beneficial in DN alleviation by targeting glycine N-methyltransferase (GNMT), which is a key enzyme for mediating renal inflammation and fibrosis [145].

In rat models of diabetic retinopathy, carnosine supplementation was shown to mitigate oxidative damage [151], prevent retinal vascular damage [152], and improve retinopathy [153]. Carnosine has not been studied in models of diabetic neuropathy; there is only one study investigating the effect of zinc L-carnosine on the changes of nociceptive threshold, suggesting a beneficial effect for reducing thermal hyperplasia, thus protecting mice from progressive diabetic neuropathy [46]. In addition, carnosine significantly enhanced wound healing in db/db mice, likely through increased expression of growth factors and cytokines, supporting its therapeutic potential in diabetic wound care [154].

3.6.2 | Human Studies

In line with experimental studies, a case–control study showed that an increase in CN1 concentration was correlated with a decline in renal function [155, 156]. Although experimental models did not support a strong role for the CNDP1 gene, a case–control study reported that patients with diabetes with two copies of the CNDP1 Mannheim gene variant, which has the lowest number of leucin, were less susceptible to DN [150]. Certain variations in the CNDP1 gene or (CNDP1 and CNDP2) genes have also been linked to the progression of diabetic kidney disease in the observational literature of individuals with T2D [150, 157–159]. This is supported by a systematic review and meta-analysis involving nine observational studies, where CNDP1 polymorphisms were associated with susceptibility for DN [160]. In contrast, there was no association between DN and polymorphisms in the CNDP2–CNDP1 genomic region in one study of individuals with T1D [161]. In addition, there was no interaction between CNDP1 polymorphism and prediction of mortality in patients with T1D with DN [162]. Interestingly, another observational study showed that the association between the CNDP1 gene and susceptibility to T2D is sex-specific, with a lower frequency among women [163].

The potential nephroprotective properties of carnosine supplementation have also been demonstrated in two RCTs of DN [92, 164]. Here, administration of carnosine (1–2 g/day for 12 weeks) led to reductions in TGF-β expression in patients with T2D with nephropathy [164] and improvements in oxidative stress and renal function in patients with T1D with nephropathy [92]. Conversely, carnosine supplementation (2 g/day for 14 weeks) did not have renoprotective properties in 43 individuals with prediabetes and T2D [104].

3.7 | Effects of HCDs on Macrovascular T2D Complications

Atherosclerosis is the leading cause of CVD in patients with T2D [67]. Peripheral vascular disease (PVD), also known as peripheral artery disease, is a progressive atherosclerotic disease leading to occlusion of arteries mainly supplying the lower extremities. This is an important macrovascular complication of T2D but can occur without diabetes [165, 166]. Patients with diabetes also have a high risk of cerebrovascular diseases, including acute ischemic stroke, transient ischemic attack, and intracerebral hemorrhage compared to their counterparts without diabetes [167]. Atherosclerosis is the main mechanism involved in the progression of these coronary artery, cerebrovascular, and PVDs in patients with T2D [168]. Details of the included studies related to the effect of HCDs on macrovascular complications associated with diabetes are summarized in Table S4.

3.7.1 | Experimental Studies (*In Vitro* and *In Vivo*)

Early treatment with D-carnosine-octylester (DCO) has been shown to protect mice from vascular disease with the development of more stable lesions [169]. In mice fed a Western diet, oral DCO prevented the formation of early atherosclerotic lesions by facilitating aldehyde removal largely mediated by oxidative stress modulation [170, 171]. Although the findings from human trials of the effect of carnosine on serum TG have been inconsistent, benefits were demonstrated in diabetic mice, whereby prolonged carnosine supplementation led to a significant decline in TG and plaque formation as well as increased recruitment of macrophages [172]. In nondiabetic rats with myocardial infarction, oral L-histidine and β-alanine supplementation increased functional capacity and strength gained through aerobic exercise, but did not change echocardiographic parameters [173]. Carnosine also promoted postischemic revascularization through increased pro-angiogenic hypoxia-inducible factor-1α/vascular endothelial growth factor (HIF-1 α/VEGF) signaling, possibly through Fe^{2+} chelation in the ischemic limb of mice [174].

In an *in vitro* study employing rat vascular smooth muscle cells (VSMCs), carnosine attenuated calcification through inhibition of the mammalian target of rapamycin (mTOR) signaling pathway and osteoblastic trans-differentiation [175]. Using a similar cell culture model, carnosine prevented the proliferation of platelet-derived growth factor (PDGF)-stimulated VSMCs

through modulation of c-Jun N-terminal kinase (JNK) signaling, and transcription factor–mediated matrix metalloproteinase-9 (MMP-9) activity [176]. Carnosine also prevented the modification of LDL-C by carbonyl compounds derived from glucose, effectively reducing the accumulation of cholesterol in human macrophages and inhibiting foam cell formation when exposed to glycated LDL-Cs [177].

Rat models of ischemia showed that pretreatment with carnosine [178] and carnosine-entrapped elastic liposomes [179] could be beneficial as a prophylactic treatment for brain tissue, whereas a similar animal model found that carnosine is effective in both prevention and postischemic treatment of stroke [180]. It is noteworthy that both L- and D-carnosine exhibit similar efficacy in mediating acute focal cerebral ischemia in both transient ischemic [181] and permanent models [182].

Recent studies also suggest that histaminergic neurotransmission plays a significant role in ischemic stroke [183], making it a promising therapeutic approach. A study of histidine decarboxylase knock-out mice, which are unable to convert carnosine into histamine, showed that carnosine had a neuroprotective effect, improving neurological function and reducing the size of brain infarcts [184]. Carnosine also reduced glutamate levels and maintained the glutamate transporter-1 expression in ischemic astrocytes. This suggests that the neuroprotective mechanism of carnosine does not rely on the histaminergic pathway but involves a regulation of glutamate excitotoxicity. Similar observations supporting the limited importance of the histamine pathway in carnosine-induced neuroprotection against ischemic injury have been reported by others [185, 186].

The neuroprotective effect of carnosine in ischemic stroke has been examined in various experimental studies, showing that carnosine reduces edema, MMP activation, and infarct volume and improves neurological function in rodent models [187–189]. L-carnosine protected brain tissue from autoblood-induced damage in hypertensive rats by preserving glutamatergic and gamma-aminobutyric acid GABAergic receptor activity, reducing swelling, and maintaining neuronal bioelectric function [190]. Carnosine also had a dual effect on N-methyl-D-aspartate (NMDA), the glutamate receptor, with an increase in their expression following long-term supplementation, alongside a decline in NMDA binding postischemic stroke [191].

In a systematic review and meta-analysis comprising eight animal studies, carnosine was effective when supplemented prior to or after the onset of ischemia in rodents [192]. The same study showed that the efficacy of carnosine was reduced when administered more than 6 h after ischemia [192].

3.7.2 | Human Studies

In human clinical trials, 500 mg/day of carnosine for 24 weeks resulted in enhanced exercise capacity (VO_2 max and 6-min walk test), and a higher quality of life in 50 patients with heart failure with reduced ejection fraction [193]. However, 2 g/day of carnosine supplementation for 14 weeks did not improve endothelial function and arterial stiffness in 43 individuals with prediabetes and T2D [104].

4 | Discussion

To our knowledge, this is the first systematic scoping review to describe the breadth of available literature investigating the preventive and therapeutic effects of carnosine and other HCDs for T2D and its microvascular and microvascular complications, as well as their cellular and molecular mechanisms of action. Carnosine and its derivatives have been extensively studied in the context of T2D and its related complications. However, the evidence is largely of an experimental nature, with conflicting results regarding the potential mechanisms of action of HCDs due to variations in dosing, study durations, and the use of different carnosine derivatives. On the other hand, there are limited observational studies and RCTs involving individuals with obesity and/or T2D, and no RCTs investigating the effect of HCDs in individuals with neuropathy, retinopathy, cerebrovascular disease, and CVD within a diabetic context.

Results from studies on the effects of HCDs on T2D risk factors are conflicting. Although carnosine and histidine have been shown to contribute to obesity management by reducing body weight, BMI, fat mass, increasing lean body mass, and food intake suppression in both preclinical and some clinical settings [52, 55, 62], evidence from some RCTs failed to show improvement of anthropometric measures following carnosine supplementation [63]. The addition of carnosine to standard care might be a cost-effective option for T2D management [30]. However, findings from experimental and human studies on glycemic control are controversial, with some showing improvement [36, 53] and others no effect [97, 115]. A proposed mechanism in which carnosine exerts its antidiabetic property is the suppression of carbohydrate-digesting enzymes such as α-amylase and α-glucosidase, which consequently results in a postprandial antihyperglycemic effect [194]. Carnosine has also shown antihyperlipidemic properties in some animal and human studies [53, 93] but not others [36].

Data from clinical trials showed promising effects of HCDs on oxidative stress and chronic low-grade inflammation [63, 93], conflicting with the findings from experimental studies [58]. The potential for carnosine lies in its antioxidant activity of carnosine both directly as a scavenger of free radicals and in an indirect way, by increasing endogenous antioxidant concentrations [20, 27]. Carnosine directly demonstrates antioxidant activity by acting as a nonenzymatic chelator of metal ions and a scavenger of free radicals [195]. As a result, it reduces the levels of reactive oxygen/nitrogen species (ROS/RNS) [196–198]. Carnosine also neutralizes toxic heavy metals and interacts with by-products of lipid peroxidation [199–201]. Indirectly, carnosine modulates cellular antioxidant response through up-regulation of nuclear factor erythroid 2-related factor (Nrf2) which modulates the expression of various genes, such as catalase, SOD, and thioredoxin-1 [72, 124, 202]. Carnosine can also activate and enhance the expression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α), which is a transcription coactivator involved in various biological pathways, including glucose and fatty acid metabolism and lowering inflammation and oxidative stress [203]. Coactivation of PGC1α and Nrf2 works synergistically to mitigate the harmful consequences of oxidative stress [27, 204–206].

Carnosine has also been shown to have promising effects in the management of DN in some preclinical and clinical studies [68, 164]. This is thought to occur through a reduction in pro-inflammatory cytokine secretion and trapping reactive carbonyl species (RCS) while simultaneously increasing the synthesis and release of TGF-β1 [26]. This decreases matrix accumulation in the kidney and mitigates related pathologies, including DN [149]. Carnosine can also decrease the phosphorylation of p38 mitogen-activated protein kinase (MAPK) and extracellular regulated kinases 1 and 2 (ERK1/2) in mesangial cells which may improve DN [207]. In contrast, some studies failed to show any improvement in renal outcomes, most likely due to the normal values of outcomes at baseline [104].

Although human studies are scarce, experimental evidence suggests that carnosine may be an effective therapeutic option in atherosclerosis and related conditions including PVD, through the prevention of plaque formation and inhibition of foam cells [208]. Carnosine may also have significant impacts on cardiac health through enhanced regulation of calcium and improvement of muscle contraction [209, 210] and may potentially reduce oxidative stress in myocardial disease models [209]. Given the ability of carnosine to cross the blood–brain barrier, carnosine has also been suggested to provide neuroprotective effects in cerebrovascular diseases [211, 212]. Several studies have shown that carnosine and its analogs exert their neuroprotective effects by inhibiting neuronal cell apoptosis via signal transducer and activator of transcription 3 (STAT3) signaling pathway [213], downregulating nod-like receptor protein 3 inflammasome (NLRP3) expression [214], 4-hydroxynonenal (4-HNE) scavenging [215], reduced levels of malondialdehyde (MDA) [128], and attenuation of oxidative stress and apoptosis [216] in rat models of cerebral ischemia and intracerebral brain hemorrhage [216].

One key challenge in the therapeutic application of carnosine is its reduced bioavailability due to degradation by the serum-circulating CNDP1 and the cytosolic CNDP2 [19, 20]. As a result, over the last 20 years, different research groups have focused on the development of new formulations of carnosine, as well as novel approaches such as drug delivery systems to protect carnosine from degradation and consequently enhance its bioavailability [19, 217]. For instance, carnosinol was developed as a next-generation carnosine derivative, which cannot be degraded by circulating carnosinase [218]. FL-926-16 is another bioavailable carnosine derivative, which is carnosinase-resistant [116]. It is also proposed that erythrocytes take up carnosine and protect it from degradation by serum carnosine [219].

4.1 | Strengths, Limitations, and Future Directions

This is the first study to provide a broad and comprehensive, up-to-date synthesis of the literature investigating the effects of HCDs on T2D risk factors and complications. Through systematic exploration of the available literature, our review identifies key gaps in knowledge to direct future research. Specifically, we highlight the scarcity of RCTs examining the impact of HCDs on obesity and/or T2D complications and we provide an overview of the vast experimental and observational data on this topic. However, there are several limitations in both the included studies and the present review which need to be acknowledged and addressed in future research. First, it is important to note that the majority of studies included in the present scoping review were experimental animal models, which are not directly applicable to the human context. Further validation of these data is needed through the use of prospective human studies and clinical trials, both of which are currently lacking. Second, there were limited studies investigating the effect of HCDs in animal models of retinopathy and neuropathy related to diabetes, highlighting a gap in evidence in this area. Third, there was considerable heterogeneity across the included studies in terms of methodologies, sample sizes, study designs, and the types, forms, and doses of supplementation, leading to challenges in comparing findings and uncertainty in the overall effect(s). Fourth, it is essential to note that the present study focused specifically on obesity, T2D, and diabetes complications, and these findings cannot be generalized to other diseases or populations. Finally, as this was a scoping review, quality appraisal, and meta-analyses were not included but are important to confirm the purported effects of HCDs and determine the reliability of the evidence.

5 | Conclusion

Carnosine and other HCDs may be beneficial in individuals with obesity and T2D with or without microvascular or macrovascular complications. Benefits may occur through amelioration of inflammation, oxidative stress, and AGE formation, leading to potential improvements in lipid profile and glycemic control. It is important to note, however, that existing evidence is predominantly derived from experimental studies, many of which are heterogeneous and have yielded conflicting results. To date, the number of observational studies and RCTs involving individuals with obesity and/or T2D have been limited, and no RCT has investigated the effect of HCDs in individuals with neuropathy, retinopathy, cerebrovascular disease, and CVD within a diabetic context. Further studies, in particular clinical trials with adequately powered sample sizes, are needed to establish a more definitive understanding of the effect of carnosine and HCDs in the context of diabetes and cardiometabolic health.

Author Contributions

S.S. and R.K. assisted in the title and abstract screening. S.S., R.K., and A.M. assisted in full-text screening and data extraction. S.S., J.F., A.M., and B.d.C. provided intellectual input. S.S. and A.M. reviewed and synthesized the extracted data, and S.S. wrote the first draft of the manuscript. S.S., G.A., T.R.T., J.E.S., K.N., Ar.M., S.M.B., J.F., A.M., and B.d.C. reviewed and revised the manuscript. A.M. and B.d.C. conceptualized and determined the scope of the manuscript and supervised the review process. All authors meet ICMJE criteria for authorship and all authors reviewed and approved the final version for publication.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.