frontiers | Frontiers in Food Science and Technology

TYPE Mini Review
PUBLISHED 29 January 2024
DOI 10.3389/frfst.2023.1270392

OPEN ACCESS

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RECEIVED 31 July 2023
ACCEPTED 15 December 2023
PUBLISHED 29 January 2024

CITATION
Wong RPM, Zhou ZK and Strappe PM (2024), The anti-obesogenic and anti-diabetic properties of marine collagen peptides.
Front. Food. Sci. Technol. 3:1270392.
doi: 10.3389/frfst.2023.1270392

The anti-obesogenic and anti-diabetic properties of marine collagen peptides

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Marine collagen hydrolysates and purified peptides can be sourced from a variety of species. Application of collagen peptides to animal models of diabetes and obesity is contributing to the goal of elucidating a mode of action and their broad spectrum application includes wound healing and bone fracture, both of which are significant co-morbidities of diabetes and obesity related illnesses.

KEYWORDS

marine collagen, obesity, diabetes, wound healing, microbiome, bone

Introduction

Obesity has reached epidemic proportions in the world and is increasing rapidly as traditional diets are replaced by more readily available processed and high fat content foods. Obesity is a complex condition with several drivers which can influence a person's weight, this results in a number of co-morbidities including cardiovascular disease and type 2 diabetes. In Australia, it is estimated that over 66.9% of adults are overweight or obese and this is increased further in regional and remote communities (Obesity Evidence Hub). According to the World Health Organization 2016 report, 1.9 billion adults were overweight with an estimated 650 million being obese (WHO). In Australia, it is estimated that 1.3 million people have type 2 diabetes, and WHO estimates that around 422 million people have diabetes (WHO).

Metabolic syndrome is attributed to a collection of disorders and behaviors including obesity, lack of physical exercise which contributes to insulin resistance and development of diabetes and increased risk of cardiac and renal dysfunction.

Increasing studies have focused on nutritional and nutraceutical approaches to alleviate dysregulation associated with obesity and diabetes and this focused review will highlight advances in the effects of marine collagen *in vitro* and *in vivo* studies.

Collagen peptides are generated from a variety of sources, from marine creatures to land-based mammals including cows, pigs, and sheep (Table 1). A readily available source of collagen is waste products from the fish industry including fish skins and skeletons. Structurally, collagen as a triple helical molecule is conserved across species, however variation in amino acid composition may confer subtle differences particularly in relation to denaturation temperatures and bioactivity properties. Studies have shown differences in denaturation temperature between different sources of marine collagen from warm and cold waters. Figure 1 illustrates the recent exploration of therapeutic applications of marine collagen peptides in obesity related illnesses.

TABLE 1 Summary of Extraction methods for selected studies.

References	Extraction method
Astre et al. (2018)	Naticol® (commercially available) peptides
Rahabi et al. (2022)	
Baek et al. (2023)	Pretreatment with NaOH, Na_2SO_4, and $NaHCO_3$ and extraction HCl and H_2SO_4 digestion with a mixture of endopeptidases and exopeptidases
Kalmukova et al. (2023)	0.5 M acetic acid extraction and salting out
Vijayan et al. (2022)	
Miao et al. (2022)	Pepsin Soluble Fraction
Zheng et al. (2020)	Treatment with a variety of enzymes, Neutrase, Alcalase, Pepsin, Papain
Zhu et al. (2017)	Mixed peptides (Not specified)
Ren et al. (2022)	Treatment with a variety of enzymes, Trypsin. Neutrase, Alcalase, Pepsin, Papain
Tian et al. (2020)	
Ye et al. (2022)	Neutral protease digestion and ultrafiltration
Lee et al. (2017)	Subcritical water hydrolysis

In vitro and *in vivo* anti-obesogenic properties

An original paper by Lee et al (2017) described the effects of tuna skin collagen hydrolysates on the differentiation of the preadipocyte 3T3 cell line and also in high fat diet (HFD) fed mice. Treatment of 3T3 cells with 0.5–1.0 mg/mL of hydrolysate resulted in a reduced intracellular accumulation of oil droplets, and reduced gene expression of adipogenic markers such as PPAR-gamma. In a parallel *in vivo* study, mice which were previously fed a high fat diet and received 300 mg/kg/day of hydrolysate and gavaged three time per week showed a reduction in body weight compared to control animals. Treatment of animals with marine collagen peptide also showed a reduction in the mRNA expression of key transcription factors involved in regulation of adipogenesis, namely, C/EBR-alpha and PPAR-γ. Histological assessment of HFD mice fed with peptide also showed a reduction in adipocyte size correlating with a reduction in body weight.

Commercially available sea fish collagen peptides, "Naticol" were also administered to mice fed a HFD, at a much higher dose of 4 g/kg/day in drinking water over a 20 week period resulted in a reduction in total body weight of the treated animals by week 12 (Astre et al., 2018). An amino acid analysis of Naticol showed a typical collagen profile of Glycine (approximately 20%) and proline, glutamic acid and Hydroxyproline). Other parameters affected by peptide treatment included some reduction in inflammatory cytokines (IL-6 and IL-1β) concentration in isolated adipocytes whilst no obvious changes in glucose tolerance and insulin sensitivity were observed.

Human clinical trials

A limited number of studies describe the effects of marine collagen peptides in human clinical trials. In one study by Zhu et al. (2010), a cohort of type 2 diabetic patients who received 13 g of peptide daily for upto 3 months showed changes in glucose and lipid metabolism markers with increased levels of insulin sensitivity reported together with reduced levels of fasting glucose, triglyceride, and free fatty acids. Improvements in kidney function were also seen. A similar study was performed in a group of type 2 diabetic patients with hypertension compared with to a non-hypertensive group who received 13.5 g of peptide per day. A therapeutic effect was more apparent in the non-hypertensive group (Zhu et al., 2010).

The effects of collagen peptide administration in animal models of obesity was recently described by Kalmikova et al (2023) using low molecular weight Antarctic fish collagen fragments generated by pepsin digestion followed by ultrafiltration. In rats fed a HFD together with collagen peptides (1 g/kg over a 6 weeks in period), a reduction in body mass and inflammation were observed, which may promote a decrease in adipose tissue content. This study follows on from an earlier investigation by (Raksha et al., 2018) where collagen peptides were associated with lower blood glucose, glycated hemoglobin and serum insulin levels.

Effect of marine collagen peptides on intestinal microbial flora

Obesity and related illnesses, particularly diabetes, can have profound effects on the microbial community that inhabit the gut. This can have a variety of effects including; decreased production of short chain fatty acids (SCFAs), increased localized inflammation, disruption of the gut barrier and a higher abundance in pathogenic bacteria. A number of studies have investigated the effects of collagen peptides on gut microbiome. A recent study by Baek et al (2023) highlighted a change in the ratio of *Firmicutes*/*Bacteriodetes* in an obese mouse model using a fish (Tilapia) collagen peptide co-administered with a HFD compared with soybean and yeast. Whilst there was no change in the alpha index (microbial community richness) of treated animals a number of bacterial taxa were increased which have previously

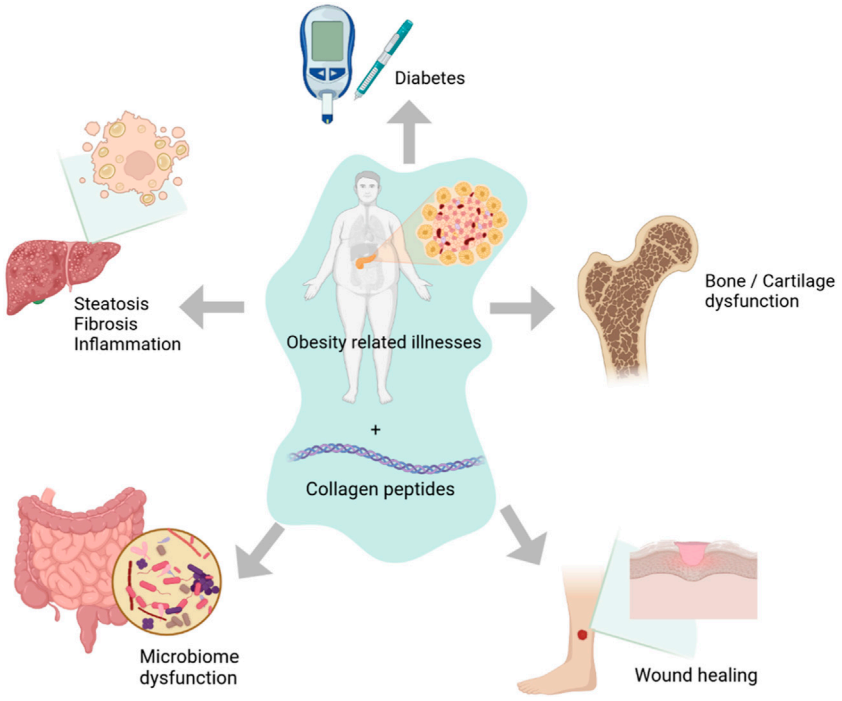

FIGURE 1
Target sites for applications of marine collagen peptides in obesity and diabetes related illnesses.

been associated with anti-obesogenic effects such as *Faecalibaculum*, however there were no changes in *Akkermansia muciniphilia*.

In a novel modification of collagen peptides through ferrous chelation, Jiang et al (2022) showed changes in the microbial community in a rat model of iron deficiency which reversed gut dysbiosis. The collagen peptide-iron complex increased the relative abundance of short chain fatty acid-producing bacteria, such as *Blautia*, *Ruminococcus* and *Roseburia* that can restore the pH of intestinal lumen, promote repair of intestinal tissue and inhibit inflammation. The collagen peptide-iron complex also enhanced the abundance of bacterial flora such as *Subdoligranulum* and *Christensenellaceae_R-7_ group* which have been linked to beneficial effects related to obesity and type II diabetes (Chen et al., 2021). In this study by Chen et al. (2021), the microbiota profile of patients with diabetic nephropathy was compared to patients with diabetes alone and a healthy control group. A number of distinguishing characteristics were found, including a lower diversity of gut microbiota in the group with an advanced stage of diabetic nephropathy. The presence of urinary protein following a 24 h collection correlated with certain species, including *Alistipes* and *Subdoligranulum*. A reduced estimated glomerular filtration rate (eGFR) was associated with the *Ruminococcus* (torques group).

Applications of collagen peptides in models of liver steatosis and diabetic nephropathy

Diabetic nephropathy is a major microvascular complication of chronic diabetes compromising the structural integrity of the nephron with increased extracellular matrix deposition, basement membrane thickening and tubular fibrosis. The effect of marine collagen peptides in the streptozotocin induced diabetes rat model was explored by Lin et al (2021) where tilapia skin peptides used at 3 g/kg/day over an 8 week period showed a reduction in the kidney hypertrophy index, and other biochemical parameters such as blood urea nitrogen (BUN), creatine and cholesterol. Histological examination also showed a reduction in kidney injury and the protective mechanism of the peptides was proposed to involve increased Bnip/nix signaling and mitophagy. Table 2 presents a summary of recent studies on the modulatory effects of marine derived collagen peptides in metabolic diseases.

Obesity is also linked to chronic kidney disease collagen peptides derived from monkfish meat which had the highest 2,2-diphenyl-1-picrylhydrazyl (DPPH) clearance rate, were administered to mice on HFD at 100 or 200 mg/kg for 8 weeks. Treatment showed a reduction in biochemical parameters (creatinine, uric acid, and BUN) in conjunction with a reduction in thickness around renal tubules (Ren et al., 2022). The peptide treated group also showed changes in gut microbial communities with an improvement in the Firmicutes/Bacteroidetes ratio. In a similar murine study of HFD induced kidney damage by Miao et al., 2022, the effect of monkfish peptides (at 100 or 200 mg/kg which showed the highest DPPH clearance rate), were associated with a reduction in biochemical parameters (creatinine, BUN, uric acid). Histopathological staining also showed reduced glomerular surface area and mesangial area compared to HFD controls. HFD fed mice exhibited a characteristic liver steatosis and monkfish collagen peptide fed

mice showed a more regular hepatocyte morphology (Miao et al., 2022) Table 3.

An increasing number of studies have highlighted the protective effects of Monkfish peptides in non-alcoholic fatty liver disease (NAFLD) induced by HFD. Ye et al. (2022) applied monkfish peptides to a mouse model of NAFLD, specifically low molecular weight peptides of < 1 KDa and sequencing revealed a range of peptide sizes with octa and nona peptides being predominant. Monkfish peptides were administered at a dose range of 50–200 mg/kg/day for 8 weeks and NAFLD mice treated with peptides showed a decrease in body weight of up to 28%, lower triglyceride levels and elevated antioxidant enzymes. In this study, liver function (ALT and AST) was improved at the high dose together with a reduction in cholesterol and triglycerides. Liver pathology was also improved, including a reduction in the number of lipid droplets. The mechanism was proposed to be via enhancement of pathways that increased lipid beta oxidation and therefore reduced fatty acid synthesis.

Other non-fillet parts from the monkfish, including the swim bladder has been shown as a rich source of bioactive peptides. An extensive analysis of papain digests of the swim bladder (Shenkoohi et al., 2023) revealed a number of peptides with increased DPPH scavenging activity and protection of HepG2 cells for H_2O_2 induced oxidative stress. A comparison of enzyme treatments by Tian et al (2020) found that neutrase, alcalase and papain digestion of monkfish meat yielded peptides with greater DPPH clearance and ultrafiltration to acquire peptides of <1 kDa also contributed to greater antioxidant activity and upregulation of antioxidant enzymes in RAW 264.7 cells. An interesting approach in generating hydrolysates from monkfish muscle by Hu et al (2017), involved a gastrointestinal digestion mix of pepsin and trypsin and appropriate conditions with peptides showing increased DPPH and hydroxyl ion scavenging activity and protection of HepG2 cells from H_2O_2 oxidative stress.

Underutilized fish may also provide an alternative to generation of bioactive products for value adding. One example is sprat, a small oily fish that is widely used as a food source in Eastern Europe but otherwise underutilized. In a recent study sprat protein hydrolysate (Shekoohi et al., 2023) was characterized for its antioxidant activity and for its ability to stimulate muscle protein synthesis in the C2C12 myotube cell line. Ageing is associated with both a growing risk of diabetes and increased muscle loss and the features of type 2 diabetes, insulin resistance and inflammation have a negative impact on muscle mass. Sprat protein hydrolysate showed active antioxidant and free radical scavenging ability, promoting muscle protein synthesis and increased myotube thickness compared to controls. A similar study, although not involving purified collagen peptides, evaluated muscle hypertrophy in rats fed Alaska pollock protein (Uchida et al., 2022). This study demonstrated increased gastrocnemius muscle mass attributed to larger muscle fiber size in rats fed fish protein which was incorporated into a normal and HFD. The authors noted that the hypertrophy maybe associated with a suppression of pathways involved in protein degradation. In a related study, Ayabe et al. (2015) applied a novel peptide purified from tryptic digestion of Alaska pollock protein and when applied to a mouse model of type 2 diabetes, resulted in glucose lowering. A specific C-terminal peptide was used at a lower concentration of 1 mg/kg also lowered blood glucose and enhanced glucose uptake in a mouse skeletal muscle cell line.

The interplay between collagen peptides and muscle paracrine factors involved in wound healing was highlighted in a study by Li et al (2021) where squid cartilage type II collagen was shown to enhance tibial fracture healing in mice via upregulation of IGF-1 and Irisin.

Obesity, diabetes and wound healing: application of marine collagen peptides

Obesity and type 2 diabetes can both be associated with dysfunctional wound healing, in particular chronic ulcer development, caused by poor capillary flow. Peripheral artery disease is also prevalent in diabetic patients which can also contribute to delayed wound healing. There is growing interest in the application of marine collagen to improving wound healing and this has recently been reviewed by Cruz et al (2021) and Geachan et al (2022). Application of Tilapia skin collagen hydrolysates prepared by protease and papain digestion promoted *in vitro* wound healing at 50 µg/mL in the commonly used HaCat cell scratch assay (Hu et al., 2017). The same study also applied peptides to a rabbit model of scalding and wound healing was promoted by day 11 post scald. In an interesting combination of marine based bioactives, Ouyang et al (2018) developed a hydrogel composed of chitosan and tilapia peptides, which enhanced cell migration and proliferation of L929 cells *in vitro*. It also promoted wound healing as observed in a rabbit burn assay with increased epithelialization. Collagen peptides derived from marine sponges are attractive due to their relative ease of extraction from raw material. Pozzolini et al (2018) showed HPLC purified marine sponge collagen peptides exhibited antioxidant and oxygen free radical scavenging ability which also promoted cell proliferation in a variety of cells (L929, Raw 264.7 and HaCat). The sponge collagen also enhanced *in vitro* wound healing in the scratch assay.

Jellyfish species have also been investigated as a source of collagen peptides which may have wound healing capabilities. Felician et al (2019) isolated collagen peptides from *Rhopilema esculentum* using pepsin digestion and demonstrated *in vitro* proliferation in an endothelial cell line (HUVECs). The jellyfish derived collagen peptides when administered orally up to 0.9 g/kg for 6 days, improved wound closure in a mouse model.

Vascular endothelial growth factor (VEGF) is a major contributor to effective wound healing. An approach to elucidate the mode of action of marine collagen peptides, Yang et al (2019) tested peptides isolated from the skin of the giant croaker *Nibea japonica*. The study demonstrated that marine collagen peptides modulated the expression of VEGF together with other growth factors including fibroblast growth factor (FGF) and epidermal growth factor (EGF) via the NF-κ B signaling pathway.

Protein hydrolysates derived from salmon and mackerel skeletons were formulated as a nutritional supplement and fed to mice which had received a punch biopsy wound. The mode of action of collagen peptides in wound healing was highlighted by increased expression of Ccl3 and Cx3cl-1 chemokines which are

TABLE 2 Reported anti-obesity effects exerted by marine collagen.

Source of marine collagen	Key findings	Models & parameters	Authors' interpretation	References
Warm sea fish skin, Type I and III collagen peptides (Naticol®)	-Lower gain of weight and fat mass in HFD group at 9 and 18 weeks	Mice (C57BL/6J)	-Delay of obesity	Astre et al (2018)
	-Lower basal glycemia, (but no effect in glucose tolerance)	*in vivo*	-L-arginin content in collagen may have enhanced glycemic control	
	-Decrease of inflammatory cytokines (IL-6, IL-1β)	4 g/kg bw/d	-Potential enhancement of insulin sensitivity	
	-Decreased plasma cholesterol in HFD	Duration: 20 weeks	-Target inflammatory processes to improve metabolism of adipose tissues in non-obese or obese mice	
Fish skin (Tilapia), collagen peptides	-Reduced gut microbiota Firmicutes/ Bacteroidetes ratio	Mice (C57BL/6)	-Anti-obesity effects and associated metabolic pathways due to altered gut microbiota	Baek et al (2023)
	-Increased *Clostridium_sensu stricto_1, Faecalibaculum, Bacteroides, Streptococcus*	*in vivo*	-Potential application as auxiliary therapy to slow the onset of obesity	
	-Lower gain of weight, fat mass, blood glucose in HFD	100 µL peptide (gavage)	-May alleviate HFD-induced intestinal inflammatory responses via reduced faecal endotoxin levels	
	-Decreased HFD-induced faecal endotoxin	Duration: 3 weeks days		
	-Normalisation of pro-inflammatory cytokines (IL-6)	*In vitro*		
	-Enhanced polysaccharide degradation and essential amino acid synthesis in HFD	Murine macrophage cell line (Raw264.7)		
		Gut Microbiome taxonomic & 27 obesity metabolic pathways prediction analysis		
Antarctic marine fish scales (mackerel icefish), low-molecular mass collagen fragments	-Lower rate of mass gain and relative subcutaneous fat in HFD	Rat (Wistar)	-Anti-obesity effects	Kalmukova et al (2023)
	-Reduced infiltration of immune cells, mast cells and fibrosis	*in vivo*	-Promising application to modulate comorbidities linked to obesity	
	-Improved morphological parameters (decrease in hypertrophy of adipocytes and markers of chronic inflammation seen in obesity)	1 g/kg intragastric		
		Duration: 6 weeks		
		Histology		
Warm sea fish skin, Type I and III collagen peptides (Naticol®Gut)	-Immunomodulation (colonic macrophage, CD4 T cells towards a Th2 response and decreased CD8 activation during colitis	Mice (C57BL/6)	-Protective agent against colitis	Rahabi et al., 2022
	-Promotion of anti-inflammatory and anti-oxidant phenotype in human monocytes	*in vivo*	-Fish collagen peptides enhances gut microbiota via immune modulation	
	-Alters gut microbiota, supports probiotic species in colitis group	0.1 g/kg bw/d	-Application as new functional food in gut health	
		Duration: 8 days		
		Ex vivo		
		human monocytes		
		(IBD patients)		
Great hammer-head shark skin (Sphyrna mokarran)	-Prevented formation of ulcerative lesions on gastric tissues	Rat (Wistar)	-Protective action of fish collagen peptides towards the HCl-ethanol induced gastric ulceration	Vijayan et al., 2021
	-Normalised the pH and volume of gastric juice	*In vivo*		
	-Downregulated pro-inflammatory marker (IFN-γ), upregulated IL-4	600 mg/kg/day (gavage)		

(Continued on following page)

TABLE 2 (*Continued*) Reported anti-obesity effects exerted by marine collagen.

Source of marine collagen	Key findings	Models & parameters	Authors' interpretation	References
	-Enhance antioxidant defence enzymes (SOD) and catalase, lowering membrane lipid peroxidation	Duration: 10 days		
		Ulcer induction: day 10		
		Histopathology		
Great hammer-head shark skin (Sphyrna mokarran)	-Lower weight gain	Rat (Wistar)	-Dietary supplement of fish collagen peptides attenuated HFD induced hyperlipidemic abberations in the liver	Vijayan et al., 2022
	-Enhanced cholesterol metabolism and lipid lowering ability	*In vivo*	-Promising nutraceutical to ameliorate liver dysfunctions and oxidative stress	
	-Decreased fatty acid synthase, 3HMG-CoA reductase	600 mg/kg/day		
	-Upregulation of LCAT in the liver	HFD, Alcohol		
	-Enhanced SOD, catalase and reduced lipid peroxidation in liver tissues	Duration: 60 days		

HFD, high fat diet; IBD, inflammatory bowel disease; IFN, interferon; IL, interleukin; LCAT, lecithin-cholesterol acryltransferase; SOD, superoxide dismutase; ROS, reactive oxygen species, 3HMG-CoA, 3-Hydroxy-3-methylglutaryl-CoA.

associated with enhanced migration of inflammatory cells that can release pro-angiogenic growth factors such as VEGF (Lapi et al., 2021).

A further insight into the mechanism of collagen peptides in a wound healing setting is provided by Mei et al (2020), who applied marine collagen peptides (*Salmo salar* and *Tilapia nilotica*) via intragastric delivery (2 g/kg) to rats which received an incision wound for up to 12 days. Both peptides improved wound healing compared to controls and this was associated with decreased expression of pro-inflammatory cytokines (TNF-α, IL-6) and upregulated expression of VEGF. Interestingly, molecules associated with pathogen pattern recognition were upregulated and a wound healing bacterial community was promoted (*Enterococcus* and *Bacillus*).

Full-thickness wounds can be associated with an increased risk of bacterial infection, necrosis, and life-threatening complications. To overcome these challenges, a novel biomaterial which incorporate marine collagen may also accelerate wound healing. Feng et al (2020) described a hybrid hydrogel composed of aminated fish collagen, oxidized sodium alginate, and antimicrobials (polymyxin and bacitracin) applied to a full-thickness wound in a rat model. The hydrogel with marine peptides appeared to improve wound healing compared to controls, in terms of epithelialization and collagen deposition. *In vitro* cell proliferation and angiogenesis assays suggested that the addition of the antimicrobials also had an enhancing effect.

Wound healing complications can be associated with cesarean section and further compounded by co-morbidities such as obesity and diabetes. In a study by Peng et al (2020), marine collagen peptides (4.4 mg/kg) were delivered intragastrically to rats which has received a cesarean section. Higher dosages of peptides appeared to improve skin wound tensile strength and uterine bursting pressure. The use of marine peptides (Tilapia) in a composite biomaterial containing hydroxyapatite also showed wound healing potential via inhibition of inflammatory cytokine expression in a rabbit scald burn model (Ouyang et al., 2021). Incorporation of marine collagen peptide (*Sipunculus nudus*) into an ointment has been applied to a full-thickness excision wound in mice (Lin et al., 2021), with improved wound closure at day 10 compared to controls. Peptide treatment was again associated with a reduction in inflammatory markers and improved collagen deposition.

Obesity and diabetes: bone health

Obesity can affect overall bone health and function through a variety of mechanisms including increased weight and fat volume, dysregulation of bone formation, resorption and expression of pro-inflammatory cytokine. Adipokines, such as leptin can exert direct anabolic effects on osteoblasts. In diabetes, a complex interplay of hyperglycemia, insulin resistance and dysregulation of insulin-like growth factors maybe associated with increased risk of fracture.

Whilst collagen-based biomaterials have been extensively applied to models of fracture repair, recent studies have highlighted a potential role for marine collagen peptides to improve bone health directly or indirectly. An early study by Xu et al (2010) demonstrated that marine collagen based salmon hydrolysates administered to rats could increase serum osteocalcin levels which may enhance osteoblast activity and reduce bone resorption. The application of collagen scaffolds derived from jellyfish has shown promise in promoting bone formation via inflammatory macrophage recruitment. Flaig et al., 2020), implanted jelly fish 3D scaffolds into a rat model and demonstrated increased *de novo* bone formation after 60 days.

Squid derived collagen II has been shown to improve tibia fracture repair in a mouse model, where new bone formation was accelerated via upregulation of muscle paracrine factors, IGF-1 and Irisin (Li et al., 2021). Furthermore, Cruz et al (2020) generated a collagen scaffold for application in a rat cranial critical bone defect

TABLE 3 Modulatory effects of marine peptides in metabolic dysfunction.

Marine peptides	Type of dysfunction	Reported effects	Models	References
Fish *(Tilapia)* Skin collagen peptides	Diabetic nephropathy	-Activated Bnip3/Nix signaling	Rat, Diabetic Streptozotocin-induced T2DM	Jin et al (2020)
	Mitochondrial dysfunction	-Reversed the over-production of mitochondrial superoxide and cellular ROS, improving mitochondrial dysfunction	8 weeks	
		-Improved renal morphology	(8 g/kg/day)	
		-↓ glomerular injury	Histopathology	
		-Protective against renal fibrosis	Cell culture	
			(rat GMCs)	
Monkfish *(Lophius litulon)* Skin collagen peptides	Chronic kidney disease in HFD	-Pepsin-solubilized collagen peptide (200 mg/kg) ↓ serum uric acid, creatinine and blood urea nitrogen	Mice, HFD	Miao et al (2022)
	Liver steatosis in HFD	-Improved renal tubule and glomerular integrity, alleviated renal fibrosis in HFD	6 weeks	
		-↑ SOD, glutathione peroxidase, catalase	(100 or 200 mg/kg)	
		-↓ MDA	Histopathology	
		-↓ inflammatory cytokines (IL-1β, IL-6, TNF-α) via modulation of Nrf2 & NLRP3 pathways		
Giant Croaker *(Nibea japonica)* Swim bladder collagen peptides	Chronic diseases with excessive reactive oxygen radicals	-Dose-dependent scavenging on free radicals	Cell culture	Zheng et al (2020)
		-Promoted proliferation of human umbilical vein endothelial cells	(human umbilical vein endothelial cells)	
		-↓ oxidative stress damage by H_2O_2	H_2O_2-induced oxidative injury	
		-↓ ROS, MDA		
		-↑ SOD, glutathione peroxidase, catalase		
		(25–100 μg/mL)		
Chum Salmon *(Oncorhychus keta)* Skin collagen peptides	Liver steatosis	-Prevented weight loss	Rat, Diabetic Streptozotocin-induced T2DM, 4 weeks	Zhu et al (2017)
	Type 2 diabetes mellitus	-Improved blood lipid metabolism	Histology	
	Blood lipid metabolism disorder	-↓ oxidative stress markers, inflammatory cytokines and adipocytokines		
		-Improved liver steatosis (2.5–4.5 g/kg/day)		
		-Improved glucose metabolism and insulin sensitivity (≥4.5 g/kg/day) in T2DM via modulation of GLUT4 and PPAR-α		
Monkfish *(Lophius litulon)* Meat peptides	Nephrotoxicity induced by HFD	-↓ oxidative stress and inflammation	Mice, 8 weeks (200 mg/kg)	Ren et al (2022)
		-↑ SOD, glutathione peroxidase	Histopathology	
		-Regulated intestinal dysbiosis, improved *Firmicutes*/*Bacteroidetes* ratio	Intestinal Microbiome	

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TABLE 3 (*Continued*) Modulatory effects of marine peptides in metabolic dysfunction.

Marine peptides	Type of dysfunction	Reported effects	Models	References
		-Reversed renal impairment caused by HFD		
		-Protective via reactivation of the Nrf2/Keap1 signaling pathway		
Monkfish *(Lophius litulon)* Meat peptides	Chronic diseases with excessive reactive oxygen radicals	-Antioxidant activities	Cell culture	Tian et al (2020)
		-Attenuated H_20_2 oxidative injury	macrophages	
		-↓ ROS, MDA	(RAW264.7)	
		-↑ SOD, glutathione peroxidase, catalase	H_2O_2-induced oxidative injury	
		-Protective of macrophages viability post-H_2O_2 induced oxidative damage (200 μg/mL)		
Monkfish *(Lophius litulon)* Meat peptides	Fatty liver disease (non-alcoholic)	-↓ weight of body and liver in HFD	Mice, HFD	Ye et al (2022)
	Liver steatosis	-↓ Liver enzymes (AST & ALT) in HFD	8 weeks	
		-Improve antioxidant capacity of the liver to slow NAFLD via Nrf2 & AMPK	(50, 100, 200 mg/kg/day)	
		-↓ MDA in hepatocytes	Histopathology	
		-Inhibitory effects on HFD-induced inflammation		
		-Improved liver morphology in HFD		
		-Promoted liver function repair		

↑ Increased, ↓ Reduced, AST, aspartate transaminase; ALT, alanine transaminase; GMCs, glomerular mesangial cells; HFD, high fat diet, AMPK, AMP-activated protein kinase, GLUT4, glucose transporter type 4, PPAR-α, peroxisome proliferator-activated receptor- α; NAFLD, non-alcoholic fatty liver disease, T2DM, type 2 diabetes mellitus; SOD, superoxide dismutase; ROS, reactive oxygen species; MDA, malondialdehyde.

which in combination with photobiomodulation resulted in an increased amount of connective tissue and newly formed bone.

Author contributions

RW: Writing–original draft, Writing–review and editing. ZZ: Writing–review and editing. PS: Writing–original draft, Writing–review and editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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