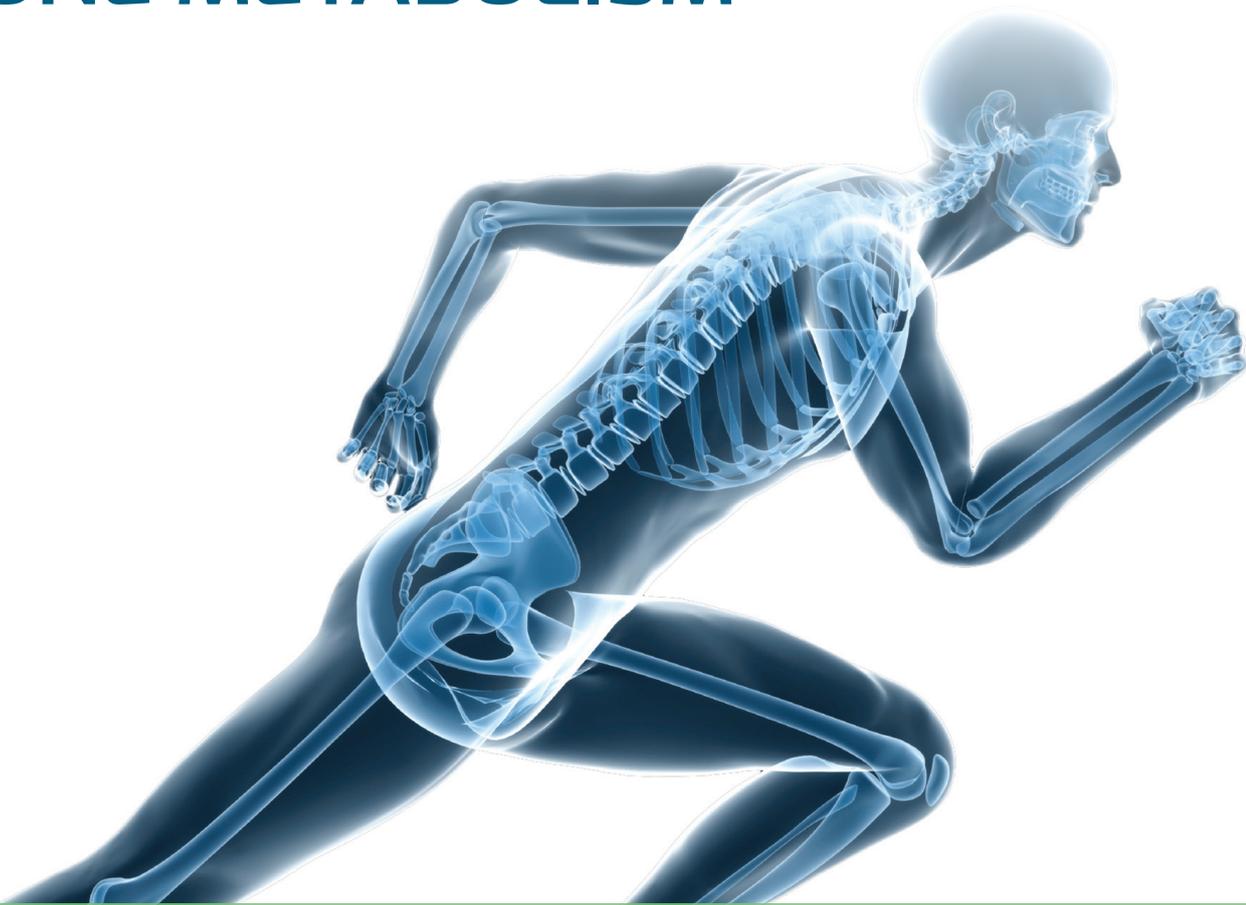


WHITE PAPER

THE BENEFICIAL EFFECTS OF COLLAGEN PEPTIDES ON BONE METABOLISM



A 2017 published review of current science regarding the effect of hydrolyzed collagen on bone health has highlighted the benefits of Peptan for supporting bone health. The review, published in the critical reviews in food science and nutrition journal, includes many references to in-vivo and mechanistic studies performed with Peptan collagen peptides.

By Dr. Janne Prawitt, Principal Scientist – Nutrition, Aug 2017

Collagen Peptides for a Healthy Lifestyle

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DARLING
INGREDIENTS

INTRODUCTION

A growing body of scientific evidence demonstrates the effectiveness of collagen peptides in supporting bone strength and metabolism. Collagen peptides' bioactive properties have been shown to contribute to bone formation, through the stimulation of osteoblast and inhibition of osteoclast activity. At the same time, positive effects on bone mineral density (BMD) and calcium absorption have been recorded, with a direct impact on bone strength.^{i,ii}

A new review of the literatureⁱⁱⁱ critically examines the results of scientific reports that investigated the effects of collagen peptides on bone tissue. Results from growth, bone loss and bone healing models are collected and critically revised to validate the results suggesting increased bone size and BMD as well as reduced bone loss following collagen peptide supplementation.



DR. JANNE PRAWITT

Dr Janne Prawitt is the Principal Scientist – Nutrition at Rousselot where she is responsible for the Nutrition and Health Science portfolio supporting Peptan[®], Rousselot's collagen peptides brand. A nutritional scientist by education she has spent 10 years in academic research in Germany and France, investigating mechanisms that contribute to the development of metabolic diseases such as obesity and diabetes. Janne joined Rousselot in 2013, where her main interest is to understand the benefit of collagen peptides for musculoskeletal health and skin physiology, and to develop related products for the global market.

ⁱ Wu, J. et al., 2004. Assessment of effectiveness of oral administration of collagen peptide on bone metabolism in growing and mature rats. *Journal Bone Miner. Metab.* 22 (6):547-553. doi:10.1007/s00774-004-0522-2

ⁱⁱ Kim, G. H. et al., 1998. Effect of calcium compounds from oyster shell bound fish skin gelatin peptide in calcium deficient rats. *J. Korean Fish. Soc.* 31(2):149-159.

ⁱⁱⁱ Daneault, A. et al., 2017. Biological effect of hydrolysed collagen on bone metabolism. *Critical Reviews in Food Science and Nutrition*, 57:9, 1922-1937

COLLAGEN PEPTIDES BENEFITS FOR BONE HEALTH

Bone resistance to mechanical forces and external impacts depends upon two factors: the quantity and quality of bone tissue. These are attributable to the mineral content and collagen framework, respectively. Collagen represents about 80% of the total protein in bones and forms the flexible scaffold to anchor key macromolecules, including calcium phosphate. Directly related to the amount of mineral deposition, collagen is an essential component of skeletal toughness and flexibility.

In healthy bones, the bone matrix density and composition is regulated by a process called bone turnover, the replacement of aged bone tissue by fresh substance, balanced through the activity of bone forming cells, osteoblasts, and cells responsible for bone resorption, osteoclasts. During this process, hormones and growth factors regulate the activation of osteoclasts, to remove old matrix and release the minerals required for the formation of new bone. In the next phase, osteoblastic stem cells proliferate to form a population of osteoblasts that differentiate into mature and active cells, responsible for the synthesis of collagen and the deposition and mineralization of the matrix that forms the new bone.

When this finely-tuned equilibrium is disrupted, the synthesis of new bone is outpaced by the matrix breakdown, leading to lower bone mineral density, less flexible and more fragile bones. By providing the necessary building blocks to support bone formation and by acting as messengers that actively promote the function of bone-forming osteoblasts over bone-resorbing osteoclasts, collagen peptides have an important role to play in future nutrition strategies to maintain healthy bones.

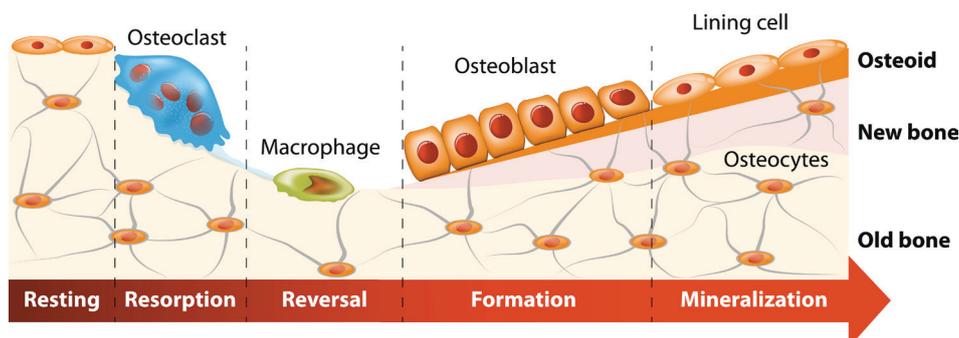
The role of nutritional supplementation is well recognised as a preventative measure to support bone health. Since bone mass peaks and starts to decline from the age of 30, with collagen synthesis and bone turnover slowing down with age as well, early prevention to avoid or delay limitations of skeletal functions is key. Dietary supplements can provide the key constituents of the bone matrix, including collagen and calcium, actively contributing to maintain bone health.

BONE LOSS MODEL

Most of the studies on the effect of collagen peptide supplementation on bone loss have used *in vivo* models, that mimic the hormonal conditions of post-menopausal women affected by osteoporosis, i.e. oestrogen deficiency. A growing body of evidence demonstrates the ability of collagen peptides to prevent bone loss in those models. For instance, Guillerminet et al. (2010) demonstrated that collagen peptide supplementation to 3-month old ovariectomised (OVX) mice increased bone mineral density and bone strength. Circulating blood plasma concentrations of the bone resorption marker CTX (carboxy-terminal collagen crosslinks) were lower than the bone formation marker BALP (bone alkaline phosphatase), suggesting that collagen can positively impact bone remodelling.^{iv}

In a second study by the same group, the administration of collagen peptides for three or six months significantly prevented bone loss in the same *in vivo* model.^v Ingestion of collagen peptide for three months was as effective as raloxifene, an oestrogen modulator clinically used to treat osteoporosis, in protecting three-month old mice from bone loss.

The bone remodelling process



^{iv} Guillerminet, F. et al., 2010, Hydrolyzed collagen improves bone metabolism and biomechanical parameters in ovariectomized mice: An *in vitro* and *in vivo* study, *Bone*, 46: 827-834

^v Guillerminet, F. et al., 2012, Hydrolyzed collagen improves bone status and prevents bone loss in ovariectomized C3H/HeN mice. *Osteoporosis International*, 23(7):1909-1919

CLINICAL TRIALS

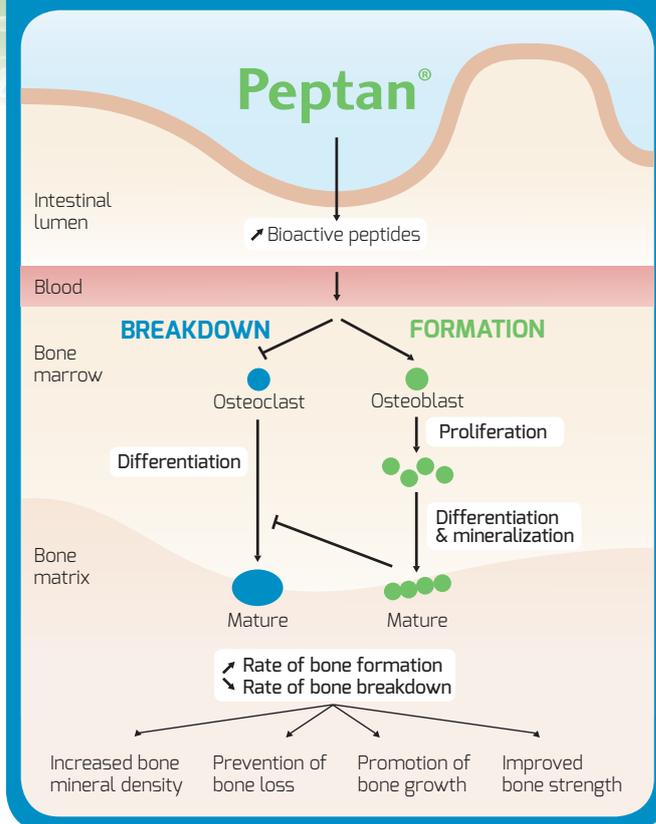
Most of the clinical studies on collagen peptides have been carried out in association with other bone-health stimulating compounds like drugs or calcium. In a clinical investigation, calcitonin, a drug used to treat conditions that lead to loss of calcium from the bones, has been tested alone and in combination with a collagen peptide rich diet to assess the effects on bone metabolism in postmenopausal women. The results revealed that a daily ingestion of 10 g of collagen peptides intramuscular injection of calcitonin enhanced together with an prolonged the effect of the drug.^{vi} Consistently, another study reported that, in osteopenic postmenopausal women, consumption of a 5 g calcium/collagen/vit D mix enhanced bone mass by orienting bone turnover toward formation rather than resorption.^{vii viii}

MECHANISMS INVOLVED IN COLLAGEN PEPTIDES EFFECTS ON BONE

The literature on collagen peptides has provided a useful understanding of the mechanisms underlying their beneficial effects on bone metabolism. After ingestion, collagen peptides are digested in the gastro-intestinal tract, absorbed in form of free amino acids as well as di- and tripeptides and then delivered to the target tissues via the bloodstream. Kim et al^{ix, x} confirmed collagen peptides' capability to dose-dependently support osteoblast proliferation, the first key step in bone formation, while more recent data specifically shows enhanced osteoblast differentiation as well as improved cell survival.^{xi} Liu et al^{xii} carried out studies on collagen peptides of bovine origin reporting improved mineralized bone matrix formation. In parallel, Guillerminet et al (2010) investigated osteoclast biology, reporting a significant inhibition of activity. Consistently, Daneault et al (2014) registered a higher ratio between OPG, the protein involved in the inhibition of osteoclasts, and RANKL, responsible for the activation of osteoclasts, suggesting the ability of collagen peptides to inhibit osteoclast activity.

Peptan: the mechanism of action

Schematic summary of the effect of Peptan on bone metabolism, adapted from Daneault, 2015ⁱⁱⁱ



COLLAGEN AND CALCIUM

In addition to a direct modulation of bone cells, collagen peptides have been shown to improve calcium absorption.^{xiii} Several studies suggest that dietary protein such as collagen peptides work synergistically with calcium to would be nice to add to the figure to complete the current knowledge improve calcium retention and bone metabolism.

^{vi} Adam, M. et al., 1996. Postmenopausal osteoporosis. Treatment with calcitonin and a diet rich in collagen proteins. *Cas Lek Cesk.* 135(3):74-78.

^{vii} Hooshmand, S. 2013. Evidence for bone reversal properties of a calcium-collagen chelate, a novel dietary supplement. *J. Food Nutr. Disord.* 2: 1. doi:10.4172/2324-9323.1000102

^{viii} Elam, M. L., et al., 2014. A calcium-collagen chelate dietary supplement attenuates bone loss in postmenopausal women with Osteopenia: A randomized controlled trial. *J. Med. Food.* doi:10.1089/jmf.2014.0100

^{ix} Kim, H. K. et al., 2013. Osteogenic activity of collagen peptide via ERK/MAPK pathway mediated boosting of collagen synthesis and its therapeutic efficacy in osteoporotic bone by back-scattered electron imaging and microarchitecture analysis. *Molecules.* 18(12):15474-15489. doi:10.3390/molecules181215474.

^x Kim, H. K. et al., 2014a. Collagen hydrolysates increased osteogenic gene expressions via a MAPK signaling pathway in MG-63 human osteoblasts. *Food Funct.* 5(3):573-578. doi:10.1039/c3fo60509d

^{xi} Daneault, A. et al., 2014. Hydrolyzed collagen contributes to osteoblast differentiation in vitro and subsequent bone health in vivo. *Osteoarthritis and Cartilage* 22: S131

^{xii} Liu, J.L. et al., 2014. Bovine collagen peptide compounds promote the proliferation and differentiation of MC3T3-E1 pre-osteoblasts. *PLoS ONE* 9 (6): e99920.

^{xiii} Liu, J.L. et al., 2015. Combined oral administration of bovine collagen peptides with Calcium citrate inhibits bone loss in ovariectomized rats. *PLoS ONE* 10 (8): e0135019.

CONCLUSION

As seen in the studies outlined in this review, collagen peptides represent a promising ingredient for the formulation of future nutritional strategies addressing bone health. A growing body of evidence demonstrates that collagen peptides own bioactive properties beneficial for bone tissue, including stimulation of bone forming cells and improvement of calcium absorption.

Those properties render collagen peptides a new and innovative candidate for putative dietary intervention in promoting bone health. Further research to provide

large scale clinical evidence is required to confirm these conclusions but altogether, collagen peptides offer additional value to calcium and vitamin D in bone health formulations, thus responding to the growing demand for primary prevention.

The collagen peptides used in Daneault, 2014, Gullerminet, 2012 and Guillerminet, 2010 studies are Peptan, produced and marketed by Rousselot.

Your Rousselot and Peptan sales contact information

About Rousselot. Reaching Further Together.

Rousselot and Peptan are both brands of Darling Ingredients Inc. Rousselot is the global leader* of gelatin and collagen peptides. Rousselot's wide range of collagen peptides are marketed under the Peptan brand. We work in partnership with our customers all over the world, delivering innovative and advanced ingredient solutions manufactured through state of the art operations. We help our customers achieve their goals, enabling them to create world class pharmaceutical, food and nutritional products to inspire and excite today's demanding consumers.

*Source: Global Industry Analysts, Inc., Gelatin a Global Strategic Business report, Nov 2016

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Rousselot Headquarters:

Rousselot B.V. Kanaaldijk Noord 20 5691 NM Son The Netherlands

Phone: +31 499 364 100 peptan@rousselot.com

peptan.com



PeptanbyRousselot



@Peptan_Global



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