BOVINE PROTEIN FOR GOOD HEALTH

Both short- and long-term health require a steady state of protein intake to support growth, development, remodelling and regeneration of the human body; from conception to older age. With an estimated 1 in 3 Australians not achieving the recommended protein intake each day,[1] it's imperative that health practitioners assess protein status and address accordingly.

The enzymatic hydrolysation of bovine protein provides a collagen peptide-rich protein source with a neutral odour and fast dissolution rate. The result is a low reactive, 'paleo' blend of amino acids that's naturally dairy, grain, soy, legume, additive and preservative free. As collagen peptides act like glue, they are fundamental to the integrity, strength and elasticity of the vast array of connective tissues throughout the body. The combination of readily absorbed amino acids also supports the maintenance of the anabolic and catabolic balance fundamental to healthy ageing, including body composition and hormonal, immunological and metabolic factors (Figure 1).

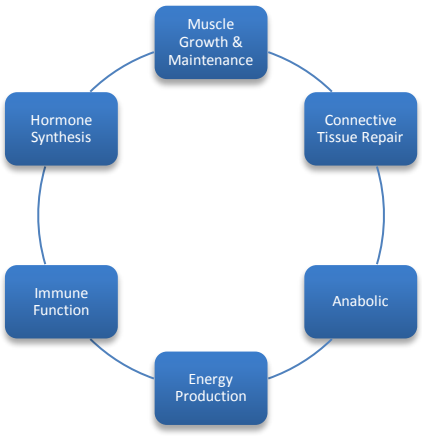

Figure 1: The vast range of actions of collagen peptides.

Ingredient That May Assist

Collagen peptides (from beef)

Actions

- Increase anabolism and decrease catabolism
  - IGF-1 and activation of the mTOR pathway
- Build and repair connective tissues
- Supplies amino acids

Clinical Applications

- Growth and development
- Bone and joint integrity
- Weight management
- Sarcopenia and ageing
- Skin integrity
- Restricted diets

Dosing Considerations*

Co-prescribing considerations:
refer to page 8

Pregnancy ✓

Breastfeeding ✓

* Dosing regimens should be determined by appropriate assessment and monitoring.

BACKGROUND TECHNICAL INFORMATION

The Building Blocks of Life

Every cell of the human body requires protein to function optimally. Therefore, it's not surprising that intracellular protein pools (derived from a combination of dietary protein and the breakdown of body tissues) are an integral part of the cellular makeup. Amino acids within these pools are used to synthesise new proteins, and to repair and maintain the body as a whole. They also provide an important energy source via the process of oxidation and support the production of glucose, ketones and fatty acids. They're also required for the creation of a range of non-protein containing compounds, such as ammonia and urea,[2] as well as immune cells, hormones and other signalling molecules.[3]

The 2011-12 Australian Healthy Survey highlighted surprisingly alarming figures regarding dietary protein consumption, with only 14% of Australians attaining the recommended daily intake (RDI) of dietary protein from lean meats, poultry, eggs, legumes, nuts and/or seeds. Additionally, it showed females were less inclined than males to achieve the RDI.[4] These statistics take into consideration a wide array of dietary regimes, yet we must consider these concerning statistics in light of those with restricted diets and be vigilant in ensuring protein intake is optimal for both structural and functional health.

The Low Reactive Alternative

The source of protein used in protein supplements is a key factor that holds many back from including a quality protein supplement in their daily or weekly diet. The standard protein sources available to the general public are whey, rice or soy-based. There are minimal options for those who are immunologically sensitive to these food groups, seeking broader protein sources or choose to follow a paleo-diet. Bovine-based protein is a natural protein, obtained by enzymatic hydrolysis of collagen-rich material from beef, which has a neutral odour and flavour making it a user-friendly option for many.

'Bovine-based protein is a natural protein, obtained by enzymatic hydrolysis of collagen-rich material.'

Bovine Derived Collagen Peptides

The primary structural proteins, collagen, actin and myosin, constitute approximately 33% of the body's protein matrix. They are required for the growth, repair and maintenance of muscle, connective tissue and bone.[5] Collagen is the primary insoluble fibrous protein within the extracellular matrix. There are over 16 recognised forms, with collagen types I, II and III being primary.[6] Collagens ultimately give anatomical structures the resilience to withstand stretching[7] and other mechanical forces.[8]

Collagen peptides are especially rich in glycine, proline and hydroxyproline (Figure 2).[9] This triad of amino acids is cornerstone to the triple helix, a tripeptide that is vital for strength and resilience of connective tissues. Notably, hydroxyproline is only available from collagen peptides; whey and vegetable proteins are not a source.

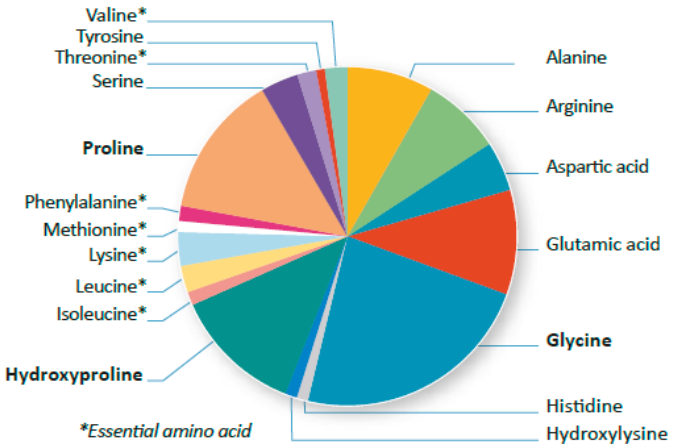

Figure 2: The amino acid profile of collagen peptides.[10]

ACTIONS

Increase Anabolism and Decrease Catabolism

Maintaining the balance between anabolic and catabolic factors is the essence of longevity and quality of life. Nowhere is this more apparent than in those living with degenerative diseases, where this balance swings in favour of the catabolic breakdown of tissues and an increased need for anabolic repair. Substrates are vital for connective tissue remodelling, and are also required to stimulate the hormonal and metabolic factors that drive the rebuild and regulate the cross-talk between the pro- and anti-catabolic and anabolic drivers.[11]

Insulin-like growth factor 1 (IGF-1) is a key anabolic hormone that plays a role in tissue proliferation, differentiation, survival, growth, apoptosis and regeneration.[12] It is also required for the transport and synthesis of proteins throughout the body, especially to skeletal muscle and bones.[13] Produced by the liver, IGF-1 is reliant on growth hormone (GH) stimulation, which in turn, is reliant on an adequate supply of amino acids. Low dietary protein results in reduced IGF-1 production coupled with increased IGF-1 clearance. An interesting consequence to the change in IGF-1 levels is a heightened resistance to this anabolic modulator, resulting in a further reduction in IGF-1's anabolic capacity (Figure 3).[14]

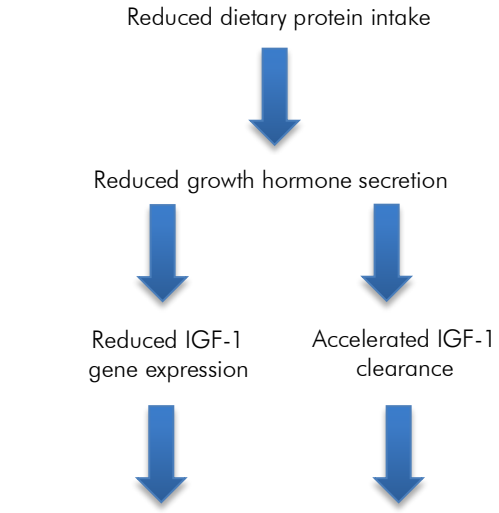

Figure 3: Negative effects of protein deficiency on IGF-1 production and clearance.[15]

A range of prospective and cross-sectional studies highlight the positive relationship between IGF-1 levels, protein intake and bone density. During pubertal growth, for example, increased levels of IGF-1 and protein intake resulted in a significantly positive influence on bone mineral content and accrual.[16] Interestingly, levels of bone marrow IGF-1 have been shown to be 40% lower in individuals with osteoporosis than in individuals without.[17]

Supplemental protein intake, and resulting increased amino acid availability, is shown to stimulate IGF-1 production, especially when coupled with resistance exercise.[18] Providing a quality protein source is a simple method to overcome dietary protein deficiency and support this important anabolic mediator.

Collectively referred to as mTOR, the two subunits of mammalian target of rapamycin (mTORC1 and mTORC2) play a key role in the regulation of growth and proliferation[19] and further promote anabolic metabolism.[20] Taking signals from the intra- and extracellular environment, mTOR reduces autophagy, a process by which cells are broken down, thereby slowing cell turnover.[21] This positively impacts overall longevity and health span,[22] as well as muscle homeostasis.[23] The ageing process has been shown to result in reduced protein-induced mTOR stimulation, referred to as 'anabolic resistance'.[24] Like IGF-1, mTOR is heavily reliant on an adequate amino acid supply for optimal function (Figure 4),[25] hence amino acid supplementation is an important way to support mTOR function.[26]

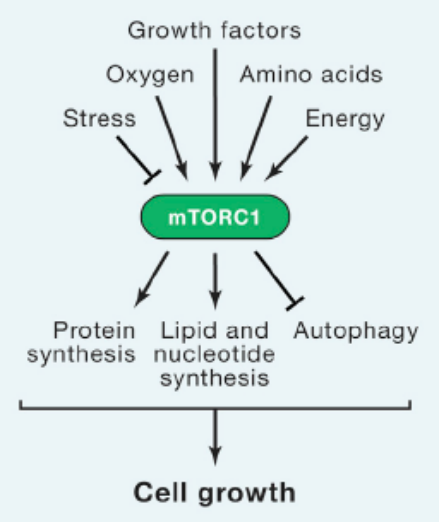

Figure 4: mTOR's actions dependent on amino acid levels.[27]

Build and Repair Connective Tissues

The functions of protein are many and varied with one key role being the provision of structural support to body cells and tissues, primarily the extracellular matrix (ECM). The ECM is considered as a scaffold, required for the integrity of the wide range of connective tissues in the body.[28] Collagens form the basis of the ECM, providing the capacity for the structure to transmit force, prevent mechanical failure and signal adjacent regulatory cells,[29] allowing for optimal maintenance and repair. This applies to a range of tissues including bone, joints, cartilage, tendons, fascia, skin, and blood vessels.[30]

At the heart of collagen is a tripeptide sequence of glycine, hydroxyproline and proline required to create the strength-giving triple helix. The individual helices are arranged to form fibrils (Figure 5), and further crosslinked and assembled to create various collagen classes, which differ only due to the length of the helix and additional α-chains.[31] Hydroxyproline provides both thermal[32] and stabilising[33] support to the helix, with proline and glycine providing structural support. Tissues may incorporate one or many different classes of collagens giving them their varied functions and diverse resilience.[34] Supplementation with collagen peptides, rich in hydroxyproline, proline and glycine, provides the key amino acids required to synthesise quality connective tissue.

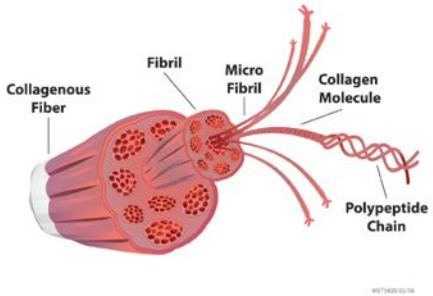

Figure 5: Individual triple helices of glycine, proline and hydroxyproline form the basis of connective tissue fibrils.[35]

Supplies Amino Acids

Of the 300 amino acids present in nature, 20 are considered the 'building blocks of life'. Structurally similar at their core (a primary amino group, carboxyl group and an α-carbon atom), the function of individual proteins are driven ultimately by their side chain's configuration.[36]

Amino acids not only provide structural support required for continued anatomical remodelling and regeneration, but also possess a range of metabolic and regulatory functions required for optimal physiological function. These include:

- Gene expression;
- Synthesis and secretion of hormones;
- Nutrient absorption and metabolism;
- Oxidative defence;
- Intracellular protein degradation;
- Immune function;
- Reproduction and lactation;
- Acid/base balance; and
- Neurotransmission.[37]

CLINICAL APPLICATIONS

Growth and Development

Given the role of protein, both structurally and functionally, it's not surprising that polypeptides, peptides and amino acids are considered vital to *in utero*, infant and childhood growth and development. For example, it's suggested that bone development is most responsive to protein, exercise and calcium levels before the onset of puberty.[38]

Furthermore, suboptimal protein intake during pregnancy and/or lactation has been shown to have negative consequences on the growth and development of the infant in the short- and long-term. Studies suggest an increased risk of a range of chronic conditions, including increased fat storage, altered glucose metabolism, and dyslipidaemia, especially in relation to triglyceride levels. This suggests that maternal protein intake, especially in relation to carbohydrate consumption, may play a role in 'developmental programming' that sets up a persistent response well into adulthood.[39,40]

Bone and Joint Integrity

Like all tissues of the body, the 213 bones of the skeletal system are in a constant state of remodelling. Evidence suggests that peak bone mass, and later fracture risk, are influenced by the pattern of bone growth in childhood and by nutritional exposure to bone nutrients, especially protein, in the period between *in utero* and adolescence.[41] Bone nutrition is, therefore, an important consideration throughout the lifetime, not simply middle age and onwards. The majority of prospective and cross-sectional studies support a positive relationship between protein intake and bone integrity.[42]

Large portions of osteocytes (osteoblasts surrounded by the materials they secrete) reside in the bone's collagen-dense ECM (Figure 6), and contribute greatly to bone mineral homoeostasis.[43] Eighty to ninety percent of bone is made of collagen, primarily collagen types I and III, and it's the collagen that is the key determinant of bone strength.[44]

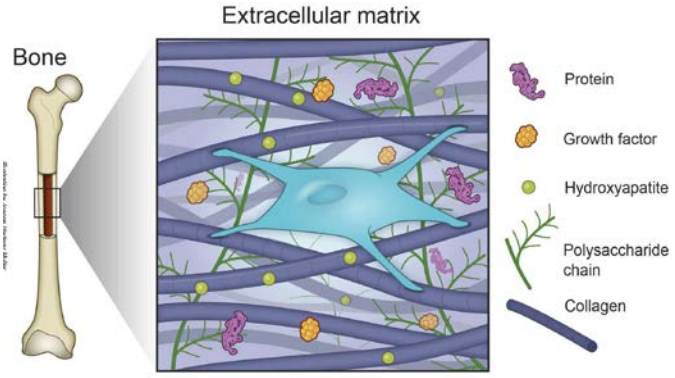

Figure 6: An osteocyte within the collagen-rich extracellular matrix of bone.[45]

The quality and quantity of protein intake also has an important impact on calcium regulation in bone. Optimising quality protein intake not only provides the scaffolding for bone growth, but also supports calcium absorption and in turn, bone mineral content (BMC) and other long-term endocrine markers of bone health.[46] Interestingly, historical concerns regarding calcium levels being impacted as a result of increased protein intake and potential renal acid load (PRAL) have been refuted. Evidence indicates that protein intakes which are twice that of the recommended daily allowance increases calcium absorption and retention, with no negative impact on bone resorption or formation.[47]

A nutritional intervention study looked at the impact of collagen peptides on bone remodelling in 60 children aged 11 to 16. In this randomised, double-blind study, bone metabolism markers, such as IGF-1, along with bone formation and bone resorption markers, were analysed. Results suggest that collagen peptides not only increase the rates of bone formation but also slow bone resorption. Notably, the authors advised that collagen peptides are an important consideration for use both during key periods of growth and development, such as pre-puberty, and for the prevention of bone loss in later life.[48]

In addition, the positive impact of peptides on bone and joint integrity has been demonstrated in a recent systematic review. Nine *in vivo* and *in vitro* studies assessing the impact of collagen peptides on bone composition and strength, as well as cartilage growth and proliferation were included. The review highlights the positive impact that peptides have on a range of parameters relating to the structure and function of bones and joints, including:

- An overall osteoprotective action via the modulation of osteoblast and osteoclast differentiation;
- Greater conservation of bone strength;
- Increased bone mineral density;
- Protection of cartilage;
- Reduction in pain, swelling and pro-inflammatory cytokines; and
- A high safety and efficacy profile.[49]

Collagen supplementation was therefore considered beneficial in both the treatment and prevention of osteoporosis (OP) and osteoarthritis (OA), with a daily dose of 12 g resulting in significant improvements in these common and debilitating conditions.[50]

The key to a healthy joint rests firmly on the volume and quality of the semi-rigid cartilage (both hyaline and articular), which is the connective tissue that covers and protects the ends of articulating bones. Approximately two thirds of the dry weight of cartilage is made up of collagen; crosslinking of the collagen is responsible for much of the joint's resilience.[51]

Notably, a prospective, randomised, placebo-controlled, double-blind study aimed to assess the impact of collagen peptides on joint pain, mobility and inflammation.[52] One hundred and forty-seven athletes, all undergoing strenuous activity and reporting current joint issues, were provided with 10 g/day of collagen peptides, or placebo, for 24 weeks. Using a visual analogue scale, results showed a statistically significantly improvement in joint pain at rest ($p<0.039$) and when walking ($p<0.007$), standing ($p<0.011$), lifting ($p<0.018$) and carrying heavy objects ($p<0.014$). The frequency of use of additional therapies to alleviate the join pain was assessed in the last month of the study period. The treatment group reported a requirement only 12 times, as compared to 39 times in the placebo group ($p<0.001$).[53]

Moreover, studies in the use of collagen peptides for the management of osteoarthritis (OA) suggest 7 to 10 g/day has far-reaching benefits, including reduction in pain levels and the use of pain medications, and an improvement in leg strength.[54]

Combined, these findings suggest that collagen peptides not only support joint function in young, healthy, active individuals but also those living with more degenerative joint conditions, such as OA.

Weight Management

'High protein' intake is generally considered to be greater than 0.8 g/kg of body weight, or greater than 35% of total energy intake.[55] Meta-analysis and large well-controlled clinical trials have shown that high protein, low carbohydrate dietary strategies are associated with positive impacts on weight reduction and maintenance, energy expenditure and a range of cardio-metabolic parameters.[56]

The mechanisms by which protein supports hormonal and metabolic weight loss and management are many, including, but not limited to:

- Increased satiety due to increased levels of circulating cholecystokinin (CCK),[57] ghrelin,[58,59] glucagon-like peptide 1 (GLP-1),[60,61] and leptin;[62]
    - Studies suggest satiating effects of protein are achieved with protein levels between 25% to 81% of total energy intake.[63]
- Modulation of hepatic gluconeogenesis to maintain a steady state of blood glucose levels;[64]
- Diminished food-associated brain reward systems, thereby reduced risk of reward-based overeating;[65] and
- Increased diet-induced thermogenesis (percent increase of energy expenditure over the basal metabolic rate).[66,67]

The positive effect of collagen peptides on appetite and satiety has been clinically demonstrated and found to be superior to some other forms of protein. To assess the appetite-suppressing effects of various protein sources, a randomised, single-blind, within-subject experimental study in 24 women and men assessed satiety and resulting energy intake after a breakfast of various protein based supplements. Supplements were provided at either a normal protein ratio (protein/carbohydrate/fat 10/55/35) or a high protein (protein/carbohydrate/fat 25/55/20) formulation. Using a visual analogue scale, appetite was assessed 30, 60, 90, 120 and 180 minutes after eating. After 180 minutes the participants were asked to eat an *ad lib* lunch until they were satiated, with further appetite assessment at 210, 240, 300, and 360 minutes after the initial time of breakfast.

Both collagen peptide formulations (along with the alpha-lactalbumin formulation) resulted in an approximate 20% reduced lunch intake and 40% reduction in appetite compared to the other protein sources. This was regardless of the protein/carbohydrate/fat distribution. It's postulated that increased insulin and GLP1 levels after intake of the collagen peptides and alpha-lactalbumin, are the primary mechanisms leading to the positive impact on satiety and appetite.[68]

The positive adaptive impact of protein supplementation on muscle mass and strength has been highlighted in a meta-analysis of 22 randomised controlled trials, totalling 680 participants. The analysis focused on the impact of protein intake on both younger and older individuals after a single bout of exercise (Figure 7), and also compared results based on whether the participants exercised regularly or not (Figure 8). The combined results suggested that not only was muscle mass significantly improved ($p<0.00001$) but muscle strength, as assessed by leg press strength, also benefited ($p<0.005$). The benefits were apparent across each of the populations evaluated.[69]

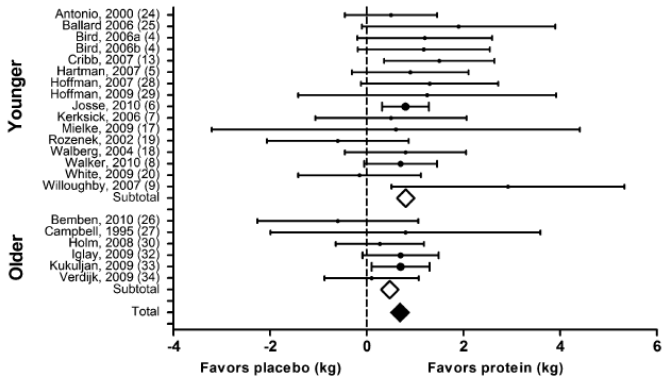

Figure 7: Forest plot showed favourable results of protein intake in muscle mass in younger and older populations.[70]

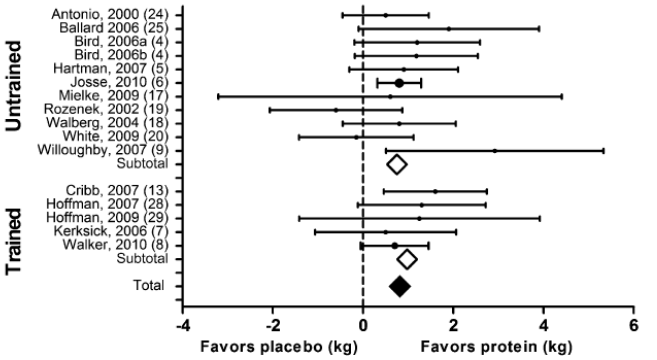

Figure 8: Forest plot showed favourable results of protein intake in muscle mass in younger trained and untrained populations.[71]

Sarcopenia and Ageing

Physical strength and muscle mass is central to quality of life as people age. The balance between protein degradation and synthesis is a critical factor in the degree of muscle mass and strength. Although considered a natural part of ageing, reduction in either muscle quality or quantity will result in an increased risk of mortality and morbidity, along with a decrease in quality of life and independence.[72] This is due to factors all heavily reliant on muscle capacity, from reduced mobility and chewing capacity, to a decreased ability to perform tasks such as those required for personal hygiene.[73] Those at risk of protein malnutrition are at increased risk of sarcopenia, 'the age-related loss of skeletal muscle mass and function', with the decline in muscle mass estimated to be 30 to 50% between the age of 40 to 80.[74]

Based on a review of evidence, the European Society for Clinical Nutrition and Metabolism (ESPEN) made the following recommendations to support optimal muscle function, and in turn the prevention of sarcopenia, highlighting the importance of protein in muscle function:

- For healthy older people: a minimum of 1.0 to 1.2 g/kg of body weight per day;
- For malnourished or acute or chronically ill: 1.2 to 1.5 g/kg of body weight per day; alongside
- Daily physical activity or exercise.[75]

Notably, a study suggested that 30% of people older than 60 years of age had less protein than 0.8 g/kg of body weight per day and 15% less than 0.6 g/kg/day,[76] far less than the ESPEN recommendations.

Importantly, protein supplementation has produced significant benefits in the elderly. In a randomised, double-blind, placebo-controlled study 65 frail, elderly individuals, received 15 g of protein supplement, or placebo, at both lunch and dinner for 24 weeks. Significant improvement in physical performance was reported; 8.9 ± 0.6 to 10.0 ± 0.6 points in the protein group and 7.8 ± 0.6 to 7.9 ± 0.6 points in the placebo group,[77] an important outcome regarding quality of life.

Additionally, collagen peptide supplementation specifically has been shown to be beneficial in improving body composition, including fat mass and free fat mass (muscle mass) in 53 men over 65 years of age, in combination with resistance exercise. In this randomised, double-blind, placebo-controlled study, participants received 15 g/day of collagen peptides, or placebo, along with three 60 minute exercise sessions/week for 12 weeks. There was a statistically significant reduction in fat mass ($p<0.001$) and a statistically significant increase in muscle mass ($p<0.001$) compared to placebo (Figure 9) without any significant change in weight. Muscle strength, sensory motor control (Figure 10), a measurement of core stability, and bone mass also improved ($p<0.001$) with muscle strength improving significantly more in the collagen peptide group than that of the placebo group.[78]

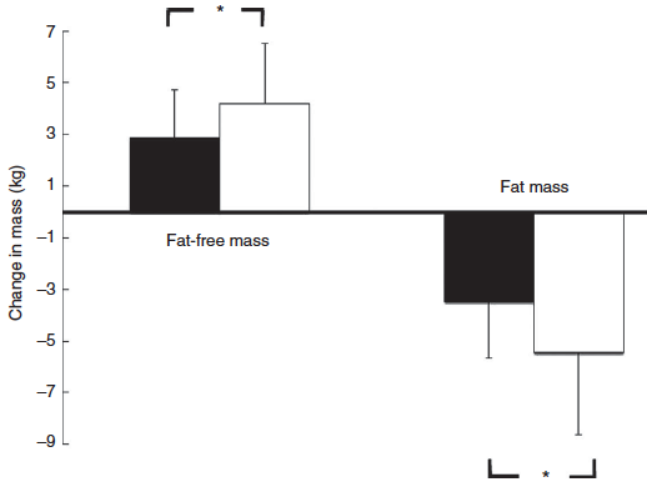

Figure 9: Change in muscle mass over 12 weeks with a combination of 15g/day of collagen peptides or placebo, and resistance exercise.[79]
[Black = placebo; white = collagen peptide]

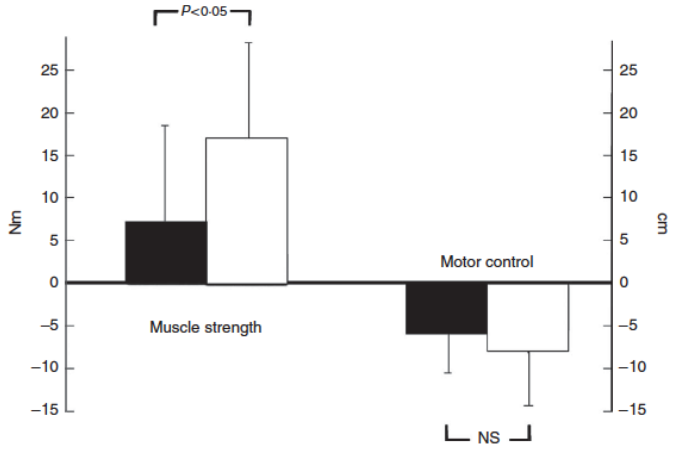

Figure 10: Change in muscle strength and motor control over 12 weeks with a combination of 15g/day of collagen peptides or placebo, and resistance exercise.[80]
[Black = placebo; white = collagen peptide]

Skin Integrity

Change in the integrity of skin provides a visual representation of the degeneration of connective tissues over the course of a lifetime. Collagen fibre degeneration, particularly at the layer of the dermis, is a key component of the structural changes in skin.[81] Optimising collagen structure and function can therefore be beneficial in minimising these changes. Animal models have demonstrated the high bioavailability of collagen peptides, with evidence suggesting peptides, not just the free amino acids, are absorbed. In one animal study bioavailability was reported to be 95%.[82]

A randomised, double-blind, placebo-controlled study of 69 women, aged between 35 and 55 years of age, received 2.5 or 5.0 g/day of collagen peptide supplementation, or placebo, for eight weeks. The elasticity, moisture and roughness of the skin, along with transepidermal water loss, were measured at baseline and weeks four and eight. A statistically significant improvement in skin elasticity was noted in both groups receiving collagen peptides after four weeks of treatment. Five g/day showed a greater and more lasting improvement, with some participants showing a 30% increase in skin elasticity over the course of the study. Interestingly, the greatest improvements were noted in women over 50 compared to the younger participants ($p<0.05$).[83]

The authors conducted an additional randomised, double-blind, placebo-controlled study of 114 women, aged between 45 and 65 years of age, with the primary outcome being the impact of collagen peptides on the impact on skin wrinkles, a primary sign of ageing skin. Participants received 2.5 g/day of collagen peptides, or placebo, for eight weeks. The results demonstrated a significant decrease in eye wrinkles in the treatment group (Figure 11), along with increased levels of procollagen type 1 (65%) and elastin (18%), two key components of the skin's ECM and biomarkers of skin health (Figure 12). Assessment at four weeks after the completion of the study continued to show an improvement in the volume of wrinkles ($p<0.01$), highlighting a positive long-lasting effect.[84]

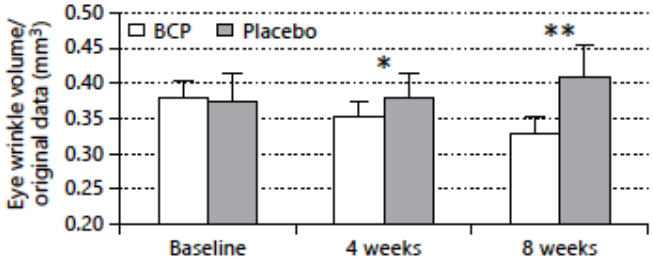

Figure 11: Improvement in eye wrinkle volume with the use of bovine collagen peptides (BCP).[85]
* $p<0.05$ ** $p<0.01$

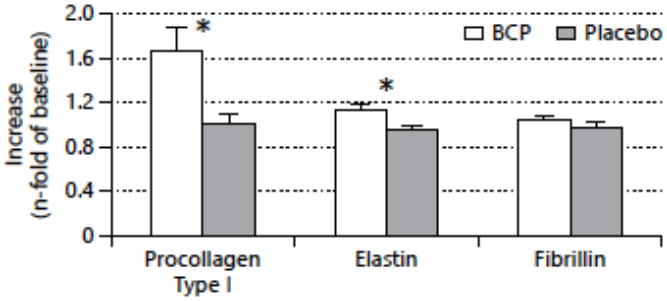

Figure 12: Increase in procollagen type 1 and elastin levels after eight weeks of treatment with bovine collagen peptides.[86]

Restricted Diets

Many members of our community are required to, or choose to restrict or avoid components in their diet which may result in suboptimal levels of a range of macro- or micronutrients. It's important to remain cognisant to the risk of protein deficiency and provide high quality, protein supplementation when required.

Examples of restricted diets that may result in protein deficiency include calorie restriction protocols. There are a range of purported health benefits in calorie restriction, including increased longevity,[87] and reduced risk of a range of chronic diseases.[88] The combination of increased protein and calorie restriction has shown metabolic benefits in animal models where insulin sensitivity increased alongside reduced serum triglyceride levels and biomarkers of hepatic lipogenesis.[89]

Those convalescing post illnesses, living with an acute or chronic infection,[90] and the elderly can live with a range of factors that lead to suboptimal protein intake. These include reductions in appetite, digestive and absorptive capacity and ability and/or desire to prepare protein-rich meals.[91]

Collagen peptides are an easy to use protein supplement that may correct a dietary deficiency in these at risk populations.

Cautions and Contraindications

Contraindications	• **Amino Acid Intolerances**: Protein restriction is usual for patients with amino acid intolerances, therefore protein supplements are best avoided. Examples of conditions that require protein restriction include genetic disorders such as phenylketonuria,[92,93] homocystinuria,[94] lysinuric protein intolerance,[95,96] and others. • **Vegetarians:** As this collagen is sourced from beef, it is not suitable for vegetarians.
Moderate Level Cautions	• **Levodopa:** Protein naturally contains peptides and amino acids which may theoretically decrease the absorption of levodopa, decreasing its effectiveness.[97,98] Advise to consume protein supplement at a different time to levodopa.
Low Level Cautions	• None of note.

Pregnancy and Breastfeeding

- Appropriate for use in pregnancy and breastfeeding.

Prescribing Tips and Notes

- None of note.

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