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Review Article

Peptides and Proteins in Whey and Their Benefits for Human Health

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Abstract

Whey protein is derived from milk or the watery by-product of cheese production and is rapidly digested and absorbed. In addition to vitamin-binding proteins and several enzymes, whey protein contains a number of bioactive components including beta-lactoglobulin, alpha-lactalbumin, serum albumin, immunoglobulin, and lactoferrin. These components demonstrate a range of immune enhancing and antioxidant properties that result in effects on hypertension, cancer, hyperlipidemia, and virus infections. The conversion of the amino acid cysteine to glutathione can partially explain these effects. Further, whey protein is a great source of branched chain amino acids, which are particularly useful for athletes and sarcopenic conditions. In this review, we summarize the characteristics of whey protein and the recent findings regarding the effects of whey protein on specific conditions/disorders.

Introduction and Background

Epidemiological studies indicate that the consumption of milk and dairy products contributes to a reduction in the incidence of metabolic diseases [1,2]. Dairy proteins in milk are composed of approximately 80% casein and 20% whey protein. Whey protein is found in the liquid material created as a by-product of cheese production during which the watery portion of milk is separated from the curds. Advances in processing technology have resulted in a number of different finished whey products with varying nutritional profiles.

Whey protein seems to be more effective in physiological systems than casein, as a result of faster digestion and absorption kinetics, in addition to the presence of bioactive components [3]. The molecular structure of casein is easily hydrolyzed by enzymes in the gut and metabolized to simple structures that can be easily utilized by the body. Whey protein is hydrolyzed at a slower rate and maintains its function in the gut; therefore, it is retained in the intestines for a longer period of time. Boirie et al. hypothesized that the absorption rate of dietary amino acids in the gut varies according to the type of ingested dietary protein; as a result, postprandial protein synthesis, breakdown, and deposition are also affected [3]. To determine this, the authors provided a single meal containing 2 intrinsically ^{13}C-leucine-labeled milk proteins, casein and whey proteins, to healthy adults. Whey proteins are considered to be "fast proteins" in that they reach the jejunum quickly after entering the gastrointestinal tract. Once in the small intestine, whey undergoes hydrolysis slowly, enabling greater absorption over the length of the small intestine. The rate of protein digestion and amino acid absorption from the intestines has a major effect on whole body protein anabolism following a single meal, and slow and fast proteins modulate the postprandial metabolic response, a concept that can be applied to wasting situations.

Whey protein is used in a variety of foods, including ice cream, bread, and infant formula. It has also been used to replace fat in a number of products. With its high protein quality score and branched chain amino acid (BCAA) content, whey protein has also long been popular in the exercise industry as a muscle-building supplement [4,5]. In comparison to all other structural animal proteins, whey proteins provide the greatest amount of BCAAs [6], which are hydrolyzed more easily than others, and increase the postprandial plasma BCAA levels within minutes [7,8].

Further, whey protein may act as an appetite suppressant and aid in the control of blood sugar [9,10]. However, research suggests it may have far wider applications as a functional food in the management of conditions such as cancer, hepatitis B, human immunodeficiency virus (HIV) infection, cardiovascular disease, osteoporosis, and even chronic stress [1]. Whey protein might also help prevent some hereditary conditions, such as a predisposition to allergies [11].

More recently, Melnik et al. reported that milk is not just a food but appears to represent a more sophisticated endocrine signaling system that activates mTORC1 via special maternal milk-derived dietary messengers controlled by the mammalian lactation genome. The BCAAs in the milk proteins and exosomal miRs produced by the mammary gland appear to augment mTORC1 signaling for postnatal growth [12].

Whey peptides are powerful isolates of amino acids derived from much longer whole whey protein molecules. These isolated whey peptides provide the following benefits: increased release of insulin-like growth factor, improved overall endocrine hormone response [9,13], increased nitrogen utilization and retention [14,15], increased intracellular glutathione and anti-aging antioxidants [16,17], improved immune function [18,19], improved gastrointestinal health [20,21], and increased rate of muscle growth [22,23]. Here, we summarize the characteristics and clinical indications of whey protein/peptide from recently published trials and studies.

Analysis and Interpretation

Biological components

From the standpoint of nutrition and food science, whey proteins, which are rich in essential amino acids, are of a higher biological value

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than the majority of proteins in the diet. Further, whey protein is the richest natural source of BCAAs and has a high bioactive value. In addition, Aydin recently found that adropin, nesfatin-1, apelin-12, des-acyl ghrelin, and salusins in cheese whey were higher than in the corresponding milk peptides and plasma of dairy cows, with the exception that salusin alpha and acylated ghrelin in milk were the same as that of the corresponding cheese whey concentration and plasma of dairy cows [24].

The nutritional value of proteins is determined by their ability to supply nitrogen through the appropriate balance of essential and non-essential amino acids. The biological value is the ratio of the amount of nitrogen that is consumed to the amount of nitrogen that is absorbed, and this value is 74 for soy protein, 71 for casein, and 104 for whey protein. The protein efficiency ratio indicates the increase in body weight associated with an intake of 1 g protein, and the protein efficiency ratio is 2.0 for soy protein, 2.5 for casein protein, and 3.0 for whey protein. Protein-related nutritional status is assessed using growth in infants and children, while the maintenance of nitrogen balance plays a critical role in adults. The proteins in whey have a variety of roles and immune-related functions, which are discussed further in the following paragraphs (Table 1).

Table 1: Immuno-function of whey proteinv.

Protein	Function
b-lactoglobulin	Binds retinol (vitamine A) and promotes uptake of retinol via gut. High binding capacity to long-chain fatty acids.
a-lactoalbumin	Kills tumour cells. Has bactericidal effects in the upper respiratory systems and protective effects on gastric mucosa.
lactoferrin	Regulates absorption of Fe via gut. Inhibits grrowth of various bacteria. Binds free irons released from bacteria cells (fungus bodies) phagocytized and destroyed by neutrophils and block the oxidization process. Regulates immunological response of immunocomponent cell.
serum albumin	Binds and carries fatty acids and bile pigment.
immuno-globulin G	Involves with bactericidal effects with complements and prevents bacteria from adhering to tissues. Neutralizeds toxin and virus.
immuno-globulin A	Inhibits growth of various bacteria by condensing them. Prevents bacteria from adhering to the surface of mucosa. Neutralizes toxin produced by virus and bacteria.
immuno-globulin M	Has the same effects as IgG, but its bioactivity is stronger.
lactoperoxidase	Catalyzzes the reaction of producing cyanogen ion with strong bactericidal power from cyanic ion and hydrogen peroxide in the body.
Lysozyme	Bacteriolysis by destroying cell walls

Amino acid content

Whey is made up of a number of proteins including beta-lactoglobulin, alpha-lactalbumin, bovine serum albumin, and glycomacropeptide. These proteins contain a full spectrum of amino acids including the BCAAs leucine, isoleucine, and valine. BCAAs are required for tissue growth and repair, and leucine, in particular, plays a key role in the translation-initiation of protein synthesis [1]. Whey protein is also rich in cysteine, which is essential for glutathione (GSH) production in our cells. GSH is a small molecule found in almost every cell, but it cannot enter most cells directly and, therefore, must be made inside the cell from its 3 constituent amino acids: glycine, glutamate, and cysteine. The rate at which GSH can be made depends on the availability of cysteine, which is relatively scarce in foodstuffs. GSH is the major antioxidant produced by the cell, protecting it from "free radicals," and it is also known as a very important detoxifying agent, enabling the body to get rid of undesirable toxins and pollutants. GSH is required in many of the intricate steps needed to carry out an immune response. In addition, beta-lactoglobulin, and probably also other whey proteins, has been hypothesized to be a potential carrier of glutathione [25]. The protein content of bovine milk is 3-fold that of human breast milk. However, they have a similar whey protein content. Of course, the whey protein-to-casein ratio is very different between human and bovine milk**.** The complete list of amino acids that are found in whey is provided in (Table 2).

Lactalbumin

Alpha-lactalbumin is a major whey protein found in milk with potential antiproliferative effects in human adenocarcinoma cell lines such as Caco-2 and HT-29 [26]. Moreover, human alpha-lactalbumin and oleic acid (HAMLET), which is the first member in a new family of protein-lipid complexes, was originally isolated from human milk and acts as a potent anticancer agent, killing tumor cells with high selectivity. As the protein component of HAMLET, alpha-lactalbumin, in its native state, is a substrate specifier in the lactose synthase complex; therefore, it has an essential role in the survival of lactating mammals. HAMLET confers tumoricidal properties on a broad basis; in this way, the complex may assist with targeting novel treatments by identifying death pathways [27]. BAMLET is a complex of bovine alpha-lactalbumin and oleic acid; therefore, it is the bovine counterpart of HAMLET. BAMLET also kills tumor cells; however, its action involves lysosomal membrane permeabilization [28]. Rammer et al. demonstrated that, in cancer cells, BAMLET triggers a pathway for lysosomal cell death; therefore, alpha-lactalbumin:oleate complexes have the ability to kill tumor cells that are highly resistant to apoptosis [28].

Lactoglobulin

Beta-lactoglobulin is the major whey protein; it affects milk composition and product functionality in addition to binding hydrophobic ligands such as fatty acids. Recently, le Maux et al. demonstrated that beta-lactoglobulin acts as a molecular carrier and alters the bioaccessibility of linoleate/linoleic acid [29]. On the other hand, Bovine milk β-lactoglobulin has been demonstrated significant resistance against both gastric- and simulated duodenal digestions. It

Table 2: Amino acid profile Grams/100g of protein.

Essential Amino Acid	whey	Casein	Breast milk
Isoleucine	5.75	4.7	0.056
Leucine	12.32	9.0	0.095
Lysine	10.32	7.4	0.068
Methionine	2.11	2.6	0.021
Penylalanine	3.85	4.9	0.046
Threonine	5.83	4.1	0.046
Tryptophan	2.58	2.1	0.017
Valine	6.13	6.4	0.063
Non-Essential AminoAcids			
Histidine	2.15	2.7	0.023
Alanine	5.15	2.9	0.036
Arginine	3.25	3.4	0.043
Aspartic acid	11.68	6.6	0.082
Cysteine/cystine	2.36	0.4	0.019
Glutamic acid	17.28	21.2	0.168
Glycine	1.8	1.7	0.026
Proline	4.79	10.1	0.082
Serine	5.15	5.5	0.043
Tyrosine	3.23	5.3	0.053

Source; McDonough et al. 1974

has been proposed as a potential carrier for delivering gastric labile hydrophobic drugs; therefore, it may be a realistic protein candidate for safe delivery and protection of particularly pH sensitive drugs in the stomach [30].

Lactoferrin

Lactoferrin is a non-heme iron-binding glycoprotein with antimicrobial and antioxidant effects [31,32]. Comprising a single polypeptide chain with 2 binding sites for ferric ions, whey lactoferrin appears to exert its effects by regulating iron absorption [33]. The review by McGregor also discusses the suppression of interferon secretion from mitogen activated lymphocytes by lactoferrin [34].

Immunoglobulins

Immunoglobulins (Ig) form a significant 10–15% of total whey proteins derived from bovine milk and, of these, IgG has been found at concentrations of 0.6–0.9 mg/mL [1,35]. According to the results of an *in vitro* study, bovine IgG at concentrations as low as 0.3 mg/mL suppressed the synthesis of human IgG, IgA, and IgM by up to 98%. On the basis of these findings, the study concluded that bovine milk has the potential to modulate the immune response in humans. Other studies have demonstrated that raw milk from non-immunized cows contains specific antibodies to *Escherichia coli, Salmonella enteritidis, Salmonella typhimurium, Shigella flexneri*, and human rotavirus [36].

Lactoperoxidase

Lactoperoxidase is the most abundant enzyme in whey and has demonstrated antibacterial effects across a range of species. Its effects are linked to its ability to reduce hydrogen peroxide by catalyzing the peroxidation of thiocyanate and certain halides (including iodine and bromium) [37]. Lactoperoxidase appears to have the qualities of a stable preservative, resisting inactivation during the pasteurization process.

Mechanisms of action

The mechanisms relating to the whey functions are varied. The antioxidant and detoxifying activity of whey is most likely linked to its contribution to GSH synthesis. Cysteine, which contains an antioxidant thiol group, combines with glycine and glutamate to form GSH. GSH is the major endogenous antioxidant produced by cells, providing production for RNA, DNA, and proteins via its redox cycling from the reduced form, GSH, to the oxidized form, GSSH. Though direct conjugation, GSH detoxifies a host of endogenous and exogenous toxins including toxic metals, petroleum distillates, lipid peroxides, bilirubin, and prostaglandins [38].

The antioxidant and antimicrobial effects of lactoferrin have already been described above. In addition, lactoferrin demonstrates an ability to stimulate immune responses involving natural killer cells, neutrophils, and macrophage cytotoxicity [1,18]. Furthermore, a mouse study concluded that lactoferrin acts as an anti-inflammatory by regulating the levels of tumor necrosis factor and interleukin-6 [39]. Owing to its ability to chelate iron, organisms requiring iron for replication appear to be particularly vulnerable to the effects of lactoferrin.

The protein beta-lactoglobulin contains anti-hypertensive peptides, which lower blood pressure as significantly as angiotensin converting enzyme (ACE) inhibitors. Cholesterol-lowering effects have also been noted as a result of changes in micellar cholesterol solubility in the intestine.

Another mechanism for delivering beneficial effects could be the formation of peptides through the hydrolysis of whey proteins. Whey peptide is one of the major peptides that inhibit ACE [40], which induces blood-pressure regulating effects.

Effects on lipid and glucose metabolism

Pal et al. demonstrated a decrease in fasting plasma concentrations of triacylglycerols after long-term whey protein intake (12 weeks) in overweight and obese individuals [41-43]. Although the mechanisms for the effects of whey protein on triacylglycerols are not understood, Mortensen et al. proposed that a meal containing whey might have resulted in reduced production of chylomicrons and accelerated chylomicron clearance resulting from the stimulation of lipoprotein lipase by whey [44]. Pal et al. further supported this by reporting that circulating triacylglycerol-rich chylomicrons were reduced in those consuming whey protein owing to its effects on digestion and absorption rates [42]. In addition, McGregor et al. discusses the effects of whey protein ingestion on lipid levels, including a decrease in postprandial triglycerides, free fatty acids, and the rate of appearance of chylomicron-rich lipoproteins after a high-fat meal in type 2 diabetes patients [34].

A number of studies have demonstrated the effects of whey protein on glucose and insulin metabolism [9,42,45-47]. The majority of these studies reported that whey protein intake decreases blood glucose and insulin levels, including an 11% decrease in fasting

plasma insulin levels after 12 weeks of whey protein intake (54 g/day) in adults [42]. On the other hand, the review by McGregor indicates that whey protein increases insulin levels in individuals with type 2 diabetes [34]. They also discusses that the acute effects of whey protein on postprandial blood glucose are comparable to sulfonylureas and other insulin secretagogues used for the pharmaceutical management of hyperglycemia in type 2 diabetes. Whey ingestion has also been associated with increases in both glucagon-like peptide-1 and glucose-dependent insulinotropic levels in healthy patients and those with type 2 diabetes, suggesting an inhibition of insulin secretion and glucagon synthesis [48,49]. In contrast, Hoppe et al. reported that an intake of 10.5 g/day of whey protein for 7 days increased fasting insulin by 7% in young boys, suggesting an increase in insulin resistance [50].

Recently, Morato et al. demonstrated that whey protein and whey protein hydrolysate increased Glut-4 translocation to the plasma membrane and glycogen concentrations; however, they did not trigger alterations in insulin levels in rats [51]. The effect was significantly higher in the whey protein hydrolysate group, and even greater increases were observed when the animals performed aerobic exercise. In addition, Jakubowicz et al. reviewed the biochemical and metabolic mechanisms of dietary whey protein in obesity and type 2 diabetes [52]. Whey protein, via bioactive peptides and amino acids generated during gastrointestinal digestion, enhances the release of several hormones that lead to reduced food intake and increased satiety, including cholecystokinin, peptide YY, glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), and insulin. Insulin secretion is associated with glucose lowering and the control of food intake. One possible mechanism is the production of bioactive peptides that serve as endogenous inhibitors of dipeptidyl peptidase 4 in the proximal gut, preventing the degradation of the insulinotropic incretins GLP-1 and GIP. Another mechanism may involve BCAAs, specifically leucine, which activate the mTOR signaling pathway and protein synthesis leading to elevated hormone expression and secretion and increased thermogenesis. The resulting increases in satiety, thermogenesis, and reduction of blood glucose, which is comparable to pharmaceutical treatment, support the use of whey protein in the management of type 2 diabetes and obesity.

Effects on muscle metabolism

Focus has been placed on the supply of amino acids via whey protein for athletes and individuals who resistance train from the point of the effect of whey protein on muscle synthesis [53,54]. Reviews indicate that pre- or post-exercise intake of protein or indispensable amino acids could increase muscle protein synthesis and result in a positive net protein balance, which might be beneficial for muscle hypertrophy [55]. Resistance exercise followed by whey protein supplementation stimulates muscle protein synthesis [56] [54] [57], and post-training whey supplementation could abate exercise-induced damage [53].

Lollo et al. compared the effects produced by 3 types of protein supplements (whey protein, whey protein hydrolysate, and casein) on body composition, biochemical parameters, and performance in a top Brazilian professional soccer team during an actual tournament [4]. Supplementation with protein immediately after training sessions during the competitive period was beneficial and safe, as well as capable of sustaining or even increasing muscle mass. Whey protein and whey protein hydrolysate, in particular, favored the maintenance of initial muscle mass.

The review by McGregor have suggested that milk protein ingestion in combination with resistance exercise training may result in greater skeletal muscle hypertrophy, and in turn increased insulin sensitivity, metabolic control and basal metabolic rate [34]. Tipton et al. demonstrated that acute ingestion of whey protein resulted in an increase in net muscle protein after resistance exercise [58]. Direct assessment of myofibrillar protein synthesis rate 1-6 h post exercise revealed similar increases after 20 g dose of whey protein [57]. Acute, early phase, post exercise muscle protein synthesis was also higher following whey protein hydrolysate compared to casein [59].

Clinical indications

Owing to the high content of bioactive compounds in whey, including lactoferrin, immunoglobulins, glutamine, and lactalbumin, whey protein has been associated with a lower risk of metabolic disorders and other diseases.

Cancer

A number of animal studies have examined the anti-cancer potential of whey, believed to be primarily associated with the antioxidizing, detoxifying, and immune-enhancing effects of GSH and lactoferrin [1]. In the presence of lactoferrin, colon cancer in rats demonstrated reduced tumor expression while the metastasis of primary tumors in mice was inhibited [60,61]. Results of an *in vitro* study have also been encouraging, demonstrating the inhibition of some of the important steps in breast cancer development when treated with the protein bovine serum albumin, although the mechanisms were not fully understood [62]. A few clinical trials have been undertaken, proposing that high levels of GSH in tumor cells confer resistance to chemotherapeutic agents. One of these studies showed that 20 patients with stage IV malignancies were treated daily with 40 g whey in combination with supplements such as ascorbic acid and a multi-vitamin/mineral formulation [63]. The 16 survivors demonstrated increased levels of natural killer cell function, GSH, hemoglobin, and hematocrit 6 months later. An aggressive combination of immunoactive nutraceuticals was effective in significantly increasing natural killer function, other immune parameters, and plasma hemoglobin in patients with late stage cancers.

Hepatitis B

The results of trials for the hepatitis B virus have been positive, particularly those from an open study that included 8 patients administered 12 g whey/day [64]. The patients demonstrated improved liver function markers, decreased serum lipid peroxidase levels, and increased interleukin-2 and natural killer cell activity. Regarding hepatitis C, several trials have proved inconclusive, although an initial *in vitro* study found that bovine lactoferrin prevented the hepatitis C virus in a human hepatocyte line [65].

HIV

Since patients with HIV commonly have low levels of GSH, several studies have sought to address this by testing if whey protein could induce beneficial effects on the GSH levels in HIV-positive patients. In one instance, 18 participants were randomized to receive

daily doses of 45 g whey protein from 2 different products over a 6-month period. Only 1 of the products significantly elevated GSH levels, a result that may be related to production at differing isolation temperatures and non-comparable amino acid profiles.

Cardiovascular disease

According to the results of a number of studies, intake of milk and milk products can lower blood pressure and reduce the risk of hypertension [1]. Kawase et al. performed an 8-week trial in which 20 healthy men were given a combination of fermented milk and whey protein concentrate and examined the effect on serum lipids and blood pressure [66]. After the 8 weeks, the fermented milk group demonstrated comparatively higher high-density lipoproteins, lower triglycerides, and lower systolic blood pressure. Pal et al. published a systematic review on the effects of whey protein on cardiometabolic risk factors in which many of the reviewed studies demonstrated a beneficial effect of whey on cardiovascular disease [67]. The improvement of obesity by whey intake might contribute mostly to lower blood pressure.

Hypertension

Hypertension is a major global public health issue, and its specific treatment will likely reduce the risk of cardiovascular diseases. Various investigators have hypothesized that certain bioactive peptides formed through the hydrolysis of food proteins have the ability to inhibit ACE, and this subject has been comprehensively reviewed in a number of studies [40, 41, 66, 68-73] [74]. In general, it has been claimed that a diet rich in foods containing antihypertensive peptides is effective for the prevention and treatment of hypertension. ACE-inhibitory peptides may be obtained from precursor food proteins via enzymatic hydrolysis, the use of viable or lysed microorganisms, or specific proteases [75] [76] [40]. However, studies relating to whey peptides with ACE inhibitory activities are more limited; this may be due to the rigid structure of beta-lactoglobulin, which makes it particularly resistant to digestive enzymes. ACE inhibitory peptides can reduce blood pressure in a process regulated, in part, by the renin-angiotensin system; renin is a protease, which is secreted in response to various physiological stimuli that cleaves the protein angiotensinogen to produce the inactive decapeptide angiotensin I. In addition, ACE acts on the kallikrein-kinin system, catalyzing the degradation of the nonapeptide bradykinin, which is a vasodilator [77], and ACE inhibitory peptides exert a hypotensive effect by preventing angiotensin II formation and the degradation of bradykinin.

Osteoporosis

As Caroli et al. reported in a recent review on dairy intake and bone health, there are complex relationships between milk and dairy foods and osteoporosis [78]. Milk basic protein (MBP) is a component of whey that demonstrates the ability to not only suppress bone resorption but also stimulate proliferation and differentiation of osteoblastic cells [1]. Milk protein primarily contains lactoferrin and lactoperoxidase. Animal studies suggest that lactoferrin may be the key active component, mediating its effects through 2 main pathways: LRP1, a low-density lipoprotein receptor–related protein that transfers lactoferrin into the cytoplasm of primary osteoblasts via endocytosis, and p42/44 MAPK, which stimulates osteoblast activity [79]. The role of calcium intake in determining bone mineral mass is well recognized to be the most critical nutritional factor to achieve optimal peak bone mass; milk protein is also important for preventing osteoporosis. A number of clinical trials support milk protein's positive effects in both men and women, the latter ranging in age from young to postmenopausal. Daily doses of 40 mg MBP (equivalent to 400–800 mL milk) appear to be sufficient to significantly increase bone mineral density and reduce bone resorption [80-82].

Stress adaptation

Whey enriched with the protein alpha-lactalbumin has been shown to improve cognitive performance and mood in stress-vulnerable subjects [83,84]. Alpha-lactalbumin is particularly high in tryptophan, and the authors proposed that this acts as a substrate to increase serotonin levels, which may be vulnerable to depletion by chronic stress. At the completion of the studies, all of the participants had higher ratios of plasma Tryp-LNAA (the ratio of plasma tryptophan to the sum of the other large neutral amino acids), believed to be an indirect indication of brain serotonin function.

Recently, de Moura et al. evaluated the effects of whey protein intake on the expression of heat shock protein HSP70 [85]. HSP70 confers cellular tolerance against stressors, and there was a greater increase in the HSP70 expression in the soleus, gastrocnemius, and lungs of the whey protein hydrolysate-fed rats than in the casein-fed rats.

Gastrointestinal Support

Whey is also used for gastrointestinal support by health professionals such as nutritional therapy practitioners. Its mucosa-protective effects have been demonstrated in several animal studies and are likely to be associated with its GSH-stimulating properties [1]. In addition to its role in GSH synthesis, the amino acid glutamate may play a further role when it is converted to glutamine, an amino acid utilized as a fuel by intestinal mucosa [86]. In our experience, whey peptide based formula induces less diarrhea than casein based formula because of better and faster absorption (unpublished data). Since digestion function is reduced in critically ill patients, and diarrhea is one of the more severe problems for them, whey protein plays an important role in protection against diarrhea-induced hydration also.

Sarcopenia and muscle wasting

Associated with cancer, whey may also play a role in integrated approaches that combine nutrition, exercise, and hormonal support to counteract the muscle wasting. Coker et al. reported that whey protein and essential amino acids promote the reduction of adipose tissue and increased muscle protein synthesis during caloric restriction-induced weight loss in elderly, obese individuals [23]. Sarcopenia has been attributed to a diminished muscle protein synthetic response to food intake. Differences in digestion and absorption kinetics of dietary protein or its amino acid composition, or both, has been suggested to modulate postprandial muscle protein accretion. Pennings et al. compared protein digestion and absorption kinetics and subsequent postprandial muscle protein accretion after ingestion of whey, casein, and casein hydrolysate in healthy older adults and concluded that whey protein stimulates postprandial muscle protein accretion more effectively than do casein and casein hydrolysate in older men [56]. This effect is attributed to a combination of whey's faster digestion

and absorption kinetics and higher leucine content and assists with prevention of sarcopenia and muscle wasting.

In addition to the conditions described thus far, several studies have also reported that whey may be indicated as a therapy in allergies, diabetes, amyotrophic lateral sclerosis, and burns. However, the evidence for the clinical efficacy in these conditions is limited, particularly to establish dose and duration recommendations.

Applications for supplemental formulas

There are currently many products available that include whey as the protein source. Recently, a number of formulas have been targeted for the effects of whey protein, particularly its anti-inflammatory effects. There are some reports on the beneficial effects of the whey based formula MHN-02;MEIN® (Meiji, Japan) in a hepatitis mouse model [87,89]. The tryptic peptides prevent increases in plasma aspartate aminotransferase and alanine aminotransferase via the regulation of tumor necrosis factor-a and interferon-g production in a concanavalin A-induced hepatitis model [88]. Further, in a d-galactosamine-induced hepatitis model, whey proteins and peptides demonstrated a hepatoprotective effect via the prevention of an increase in the plasma levels of hepatic function markers, including aspartate aminotransferase, alanine aminotransferase, lactate, dehydrogenase, and bilirubin [8]. Kaido et al. demonstrated that early enteral nutrition with this immune-modulating formula enriched with whey peptide can prevent post-transplant bacteremia and hyperglycemia without increasing the incidence of acute cellular rejection in patients [90].

More recently, we demonstrated the anti-inflammatory effect of the whey peptide based formula Peptamen AF® (Nestle Healthcare Science, Japan) in a lipopolysaccharide-induced septic model in mice, where chow containing whey peptide as the protein source prevented protein digression and improved insulin resistance. Interestingly, compared to a casein diet, a whey-based diet changed the intestinal flora.

Further, the enhanced absorption of whey protein in the intestines makes whey an ideal optional source of vital protein for those with compromised gastrointestinal function, such as ileostomy patients. It is speculated that cancer patients undergoing chemotherapy may also benefit from this feature of whey, as anti-cancer therapies influence nutrient intake and absorption.

Side effects and safety of whey protein and choosing the right whey product

To date, no severe adverse reactions have been associated with the administration of whey products. Whey protein is likely to be safe for most adults when used appropriately. High doses can cause side effects such as increased bowel movements, nausea, thirst, bloating, cramps, reduced appetite, fatigue, and headache. For pregnant and breast-feeding women, not enough is known about the use of whey to make recommendations. Reports indicate that whey may be beneficial for weight control; however, owing to its rapid absorption, it can also readily be stored as fat.

Given the variety of different whey products available, it is possible to select products for specific indications. For athletes or those looking for a highly absorbable, low allergen protein source, hydrolyzed whey, with its readily available di- and tri-peptides, may be a good option. For the immune-compromised or microbe-challenged, the high levels of lactoferrin and immunoglobulins in undenatured whey may be helpful. In all cases, the presence of fat, lactose, and minerals should also be considered.

Conclusion

Milk is one of the oldest functional foods available to mammals. A number of scientists have been interested in the function of whey protein for various reasons. Although the combined results of randomized clinical trial data do not provide clear evidence regarding its use, whey protein is likely to result in beneficial changes to the metabolic status of healthy and diseased patients. Further studies investigating the mechanisms underlying the effects of whey protein are needed.

Abbreviations

GSH: Glutathione; BCAA: Branched chain amino acid; HIV: Human immunodeficiency virus; MBP: Milk basic protein; IG: Immunoglobulin; HAMLET: Human alpha-lactalbumin and oleic acid; BAMLET: Bovine alpha-lactalbumin and oleic acid; ACE: Angiotensin converting enzyme; GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide 1

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