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MILK PROTEIN FOR IMPROVED METABOLIC HEALTH: A REVIEW OF THE EVIDENCE

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Abstract: Epidemiological evidence shows that consumption of dairy products is associated with decreased prevalence of metabolic related disorders, whilst evidence from experimental studies points towards dairy protein as a dietary component which may aid prevention of type 2 diabetes (T2DM). Poor metabolic health is a common characteristic of overweight, obesity and aging, and is the forerunner of T2DM and cardiovascular disease (CVD), and an ever increasing global health issue. Progressive loss of metabolic control is evident from a blunting of carbohydrate, fat and protein metabolism, which is commonly manifested through decreased insulin sensitivity, inadequate glucose and lipid control, accompanied by a pro-inflammatory environment and hypertension. Adverse physiological changes such as excess visceral adipose tissue deposition and expansion, lipid overspill and infiltration into liver, muscle and other organs, and sarcopaenia or degenerative loss of skeletal muscle mass and function all underpin this adverse profile. 'Sarcobesity' and sarcopaenic diabetes are rapidly growing health issues. As well as through direct mechanisms, dairy protein may indirectly improve metabolic health by aiding loss of body weight and fat mass through enhanced satiety, whilst promoting skeletal muscle growth and function through anabolic effects of dairy protein-derived branch chain amino acids (BCAAs). BCAAs enhance muscle protein synthesis, lean body mass and skeletal muscle metabolic function. The composition and processing of dairy protein has an impact on digestion, absorption, BCAA kinetics and function, hence the optimisation of dairy protein composition through selection and combination of specific protein components in milk may provide a way to maximize benefits for metabolic health.

Keywords: rational nutrition, balanced composition, functional ingredients, vegetable paste, quality, nutritional value.

Introduction. Poor metabolic health represents an ever increasing global epidemic based on estimates from countries as far ranging as the US and China [1, 2]. Encompassed within metabolic health are the cluster of interrelated adverse metabolic markers of hyperglycaemia, dyslipidaemia and hypertension which alongside central or abdominal obesity have been termed the metabolic syndrome [3, 4]. Individuals with metabolic syndrome are at

twice the risk of developing cardiovascular disease (CVD) within 5-10 years, in addition to a 5-fold increase in risk of developing T2DM [3], and therefore maintenance of good metabolic health is critically important.

A continuum of metabolic health exists from young, lean, healthy individuals with good physiological control to those with impaired metabolic regulation who are commonly overweight or obese, as well as older. Progressive loss of metabolic control is characterized by a range of physiological changes which include excess adipose deposition, lipid overspill, infiltration and accumulation in key organs such as liver and skeletal muscle, alongside blunting of carbohydrate (CHO), fat and protein metabolism, decreased insulin sensitivity and hyperglycaemia, dyslipidaemia, increased inflammation, impaired endothelial function [5], and blunted muscle protein synthesis and decreased muscle mass, structure and function [6]. Multiple factors may contribute to the progressive loss of metabolic control, but obesity, ageing and physical inactivity are recognized as major drivers of these changes in metabolic health [3].

Obesity is of particular importance and a prolonged positive energy balance with subsequent lipid deposition and expansion of adipose depots , particularly visceral depots which secrete inflammatory cytokines, play a role in insulin resistance and decreased insulin-mediated glucose uptake. Lipid turnover is decreased and mitochondrial oxidation is suppressed in obese subjects, promoting intracellular accumulation of lipids and the buildup of deleterious lipid metabolites in multiple tissues including skeletal muscle, liver, pancreatic beta cells, kidney and hypothalamus amongst others . Subsequently, infiltration of inflammatory cells to clear toxic metabolic byproducts is accompanied by release of inflammatory cytokines that inhibit metabolic signaling pathways , as well as promote cell death, tissue fibrosis and functional impairment. The recommended treatment to improve metabolic health includes changes in diet and physical activity, which promote adipose tissue loss, enhance metabolically active skeletal muscle mass and hence improve metabolic control. Energy restricted diets are widely recommended for weight-loss in overweight or obese individuals with poor metabolic health, however ~25% of body weight loss can be attributable to decreases in skeletal muscle mass. Loss of skeletal muscle is undesirable because it is essential for mobility and activities of daily living. In addition, skeletal muscle also plays a major role in glycaemic control accounting for up to 75% of tissue glucose uptake. Mitochondrial oxidative capacity is decreased in obese skeletal muscle, as well as in T2DM, possibly due to underlying physical inactivity [4].

Advancing age and a sedentary lifestyle are also risk factors for a gradual loss of skeletal muscle mass, function and in turn muscle strength. The problem is commonly compounded by increased adipose tissue accumulation and myocellular lipid infiltration which provides the basis of

sarcopenic (accelerated muscle loss) obesity, and which in turn may drive insulin resistance and increase metabolic risk [15]. Intramyocellular lipid accumulation in obese individuals appears to be difficult to reverse through weight-loss interventions. Activation of skeletal muscle protein anabolism appears to be blunted in both the obese and the elderly, although again this may be attributable to a common underlying physical inactivity and insulin resistance. If metabolic health does not improve with diet or exercise interventions, pharmacological agents can be resorted to in order to manage dyslipidaemia, hypertension and hyperglycemia and loss of metabolic homeostasis.

Currently, there is considerable interest in the use of dairy proteins as supplements or in conjunction with lifestyle changes to improve metabolic health. Evidence from some epidemiological studies suggest that greater consumption of dairy products is associated with lower risk of metabolic related disorders and CVD [5]. Multiple dairy components in milk such as whey protein, casein and minerals have been posited as drivers of these beneficial effects, and there is a growing body of intervention studies assessing the effects of cow's milk-derived proteins or peptides on metabolic health . The focus of many of these interventions has been the whey component of milk, which may act to improve cardiometabolic risk factors. Whey protein has been shown to be an insulin secretagogue, as well as to improve body weight and adiposity through increased satiety . In addition to a dietary strategy to promote adipose loss, dairy proteins have also been shown to increase skeletal muscle mass through stimulation of muscle protein synthesis. Peptides derived from dairy protein have also been widely investigated as potential inhibitors of angiotensin-converting enzyme (ACE), thereby regulating blood pressure, and may influence activation of the innate immune system and inflammation [6].

Milk processing, protein composition and kinetics

Dairy protein consumed by humans is predominantly from cow's milk, which consists of around 80% (w/w) casein, 20% (w/w) whey proteins and is also a rich source of minerals such as calcium. The casein in cow's milk comprises alpha-s1, alpha-s2, beta and kappa-casein, whilst whey comprises multiple globular proteins including beta-lactoglobulin, alpha-lactalbumin, lactoferrin, immunoglobulins, serum albumin, glycomacropeptide, enzymes and growth factors. All of these components have potential to contribute to the observed association between increased consumption of dairy products and decreased risk of metabolic disease observed in several epidemiological studies [7].

Cow's milk processing

Cow's milk processing is an important factor determining the composition, concentration and physiological effects of whey protein or

casein. Milk is commonly separated into different protein fractions for different food applications. Milk protein concentrate (MPC), produced by ultrafiltration of skimmed milk, contains both casein and whey proteins in similar proportions to whole milk, but the total amount of protein, lactose and mineral content may vary between different MPC formulations. Micellar casein can be extracted from milk protein concentrate by further ultrafiltration. Casein is produced from skim milk by acid precipitation or enzymatic coagulation, washing and drying. Caseinates are produced by treatment of acidified or coagulated casein curd with alkali such as sodium hydroxide or calcium hydroxide, which forms sodium or calcium caseinates respectively; caseinates contain ~90% protein. Whey protein concentrate is produced by coagulation of milk with the enzyme rennet or acid, resulting in separation of curds and whey, further ultrafiltration and drying produces whey protein concentrates containing ~25-80% protein. Additional processing can produce whey protein isolates containing >90% protein with very low amounts of lactose and lipids. Hydrolysis with enzymes or acids provides a way to breakdown the structure of whey or casein. In metabolic-related studies a range of processed milk proteins have been used including milk protein concentrate, micellar casein, casein, sodium caseinate, calcium caseinate, casein hydrolysate, whey protein concentrate, whey protein isolate and whey protein hydrolysate, as well as a range of whey and casein peptides.

Amino acid profile of milk proteins

Whey protein and casein are both classified as high quality proteins based on human amino acid (AA) requirements, digestibility and their bioavailability. They contain a relatively high proportion of indispensible AAs, score higher than most other protein sources across a wide range of assessment methods including the protein digestibility corrected AA score (PDCAAS) and recently developed digestible indispensable amino acid score (DIAAS) method. Nevertheless, differences in the physiological effects of whey protein and casein have been attributed to differences in their AA composition . Whey protein contains a higher proportion of the branched chain amino acids (BCAA) leucine, isoleucine and valine compared to casein [8]. The BCAAs alone and in particular leucine have been shown to trigger a potent increase in protein synthesis in T2DM . Among the other indispensible or essential amino acids (EAAs), casein contains a higher proportion of histidine, methionine, phenylalanine and valine than whey protein. In addition, casein also contains a higher proportion of several non-EAAs including arginine, glutamic acid, proline, serine and tyrosine [8].

Gastric emptying, absorption and serum kinetics of milk proteins

Whey protein is reported to be absorbed faster than casein. The lower absorption rate of casein in its native micellar form is because the low pH conditions in the stomach cause casein to clot and delays gastric emptying . Therefore, plasma AAs are more rapidly elevated following whey protein

consumption, whereas changes in plasma AAs are lower and more sustained following micellar casein consumption . Processing of whey protein or casein fractions via hydrolysis can markedly influence absorption and subsequent plasma AA profiles. A casein hydrolysate is reported to be absorbed more rapidly than intact micellar casein, resulting in a greater increase in plasma AAs. Conversely, whey protein hydrolysate intake is reported to result in similar plasma AA levels compared to whey protein concentrate, because of similar rapid rates of gastric emptying and absorption. The processing of micellar casein by acidification and then neutralization with alkali such as sodium hydroxide or calcium hydroxide to form caseinates also markedly alters plasma AA profiles compared to micellar casein [9].

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