Potential Role of Milk Constituents in Controlling, Improving and Mitigating Metabolic Syndrome

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Introduction

Metabolic Syndrome (MetS) is a collection of risk factors that increase the chance of developing heart disease, stroke, and diabetes. Lifestyle changes like losing weight, exercise, and dietary changes can help to prevent or reverse metabolic syndrome. The incidence of MetS is increasing world-wide and is characterized by increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels. According to the National Cholesterol Education Adult Panel III, an individual has MetS if there are 3 of the following characteristics: waist circumference (WC) > 88 cm for females and > 102 cm for males, TG > 150 mg/dL, HDL < 40 mg/dL for men and < 50 mg/dL for women, fasting blood glucose > 100 mg/dL, and blood pressure > 130/85 mm Hg.

MetS is viewed as a precursor condition, which increases the risk for more serious diseases. However, MetS also affects health prior to the development of chronic disease and increases the risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). According to a recent meta-analysis of 16 cohort studies, the relative risk for developing diabetes in the presence of MetS ranged from 3.53 to 5.17. Thus, early identification and treatment of MetS could potentially lessen both CVD and T2DM disease incidence and improve health outcomes. It has, therefore, become a necessity to control MetS by lifestyle changes before it progresses to T2D or CVD.

Dietary interventions that promote lifestyle changes, weight loss improvements in dyslipidaemia and blood pressure can be used as an appropriate alternative to reduce MetS. These dietary changes include carbohydrate-restricted diets (CRD), the Mediterranean diet and low-fat diets, and dairy based diets. CRD decrease plasma TG, increase HDL-C, lower blood pressure, reduce plasma glucose, and are very effective in reducing visceral obesity. The Mediterranean diet promotes incorporation of healthy fatty acids and phytonutrient rich foods that are beneficial both under weight loss and weight stable conditions. The dairy based diet has shown to increase HDL cholesterol and reduce inflammation and insulin resistance in individuals with MetS. Dietary fibres, probiotics, dairy and fermented products have been identified to reduce MetS.

Individual constituents of dairy such as proteins

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(casein and whey protein), fats (saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids and phospholipids), lactose and minerals such as calcium also have a potential mechanism on controlling MetS and thus further mitigating the chances of Chronic health diseases like CVDs and T2D.

Milk Proteins

Milk contains two protein fractions, namely casein and Whey proteins representing 2.7% and 0.7% of the total weight of milk, respectively. Fractions are primarily separated by acid precipitation or by rennet action in the paneer or cheese making process respectively.

Over the past 20 years of research on dairy protein, we came to know that dairy protein has a direct positive effect on hypertension, dyslipidemia, and hyperglycemia. It also improves metabolic health indirectly by increasing lean body mass and reducing obesity. The beneficial effects are primarily linked to WP. There is no apparent difference between the effects of casein and whey proteins on satiety and hunger, stimulating hormones and body weight.

Bioactive peptides are claimed to provide various benefits to human health and have various bioactivities including antimicrobial, antioxidant, antihypertensive, antagonist and agonist opioid, immunomodulatory, mineral binding, and antithrombotic properties. Several peptides exhibit multifunctional activities including lactoferricin, which has antitumor, immunomodulatory, anti-inflammatory, antimicrobial, and opioid properties. Peptides fractions of β-lactoglobulin produces no bitter taste as compared to peptides of casein fraction. α-lactalbumin have the great ability to bind minerals such as calcium, iron and zinc, thus prevent the metabolic disorders occurs due to the deficiency of such minerals.

Effect of milk proteins and their hydrolysate on diabetes/hyperglycaemia

Both WP and casein show insulin tropic properties in healthy subjects with the WP fraction being a more potent insulin tropic than casein. Continued consumption of 35 g casein/day (over 12 weeks) increased the concentration of connecting-peptide (C- peptide) in the plasma of overweight adolescents. The slow absorption of casein can be regulated by hydrolysis of the casein fraction. This ensures faster digestion and thereby quicker availability of BCAA, essential amino acids and total plasma amino acids in the circulation. *Hydrolyzed casein in doses higher than 12 g/day enhance the carbohydrate-induced insulin and regulate the glucose responses compared to lower doses of hydrolysed casein and intact casein in T2D subjects.* Hormones (GIP and GLP-1) are proposed only to play a minor role in the insulin tropic effect of casein in T2D subjects. However, hydrolysed casein stimulates the release of GIP more substantially than intact casein, whereas the GLP-1 response is independent of protein fractionation.

The consumption of WP is known to acutely reduce the postprandial glucose response in both healthy and T2D subjects. WP also improves the insulin response in lean individuals and diabetics. In healthy subjects, the consumption of WPH induces greater insulin stimulation than intact WP. The consumption of WPH 30 minutes prior to a carbohydrate-rich meal stimulates insulin and incretin secretion more as compared to WP. These results indicate that WP acutely improves glycemic control by stimulating insulin secretion, and reduces plasma glucose levels, an effect that may be enhanced by consumption of WP prior to meal. Thus, in healthy adults, WP contributes to an insulin-independent reduction of blood glucose concentration. The absorption rate of WP is dependent on the degree of hydrolysis and thereby the size of the available peptides. Consumption of WPH results in a more rapid increase of plasma amino acids compared with intact WP.

Effect of milk proteins on dyslipidemia

The consumption of casein in combination with carbohydrates and a fat-rich meal acutely suppresses the TG response in the chylomicron-rich fraction in T2D. Casein and WP have similar suppressive effects on postprandial TG levels and TG concentrations in the chylomicron-rich fraction after a fat-rich meal. An enhanced TG response leads to MetS and T2D due to postprandial dyslipidemia which is due to insulin resistance. Therefore, the effect of casein is beneficial for lipid metabolism. Consumption of milk protein causes more pronounced FFA suppression in plasma TG. This indicates that both WP and casein are able to reduce lipotoxicity. WP is more efficient than casein in reducing the postprandial TG response in overweight post-menopausal women.

Branched chain amino acids essential amino acids in WP influence the lipid metabolism. Lysine is involved in the metabolism of long-chain fatty acids, which are essential for the endogenous synthesis of carnitine. Lysine deficiency reduces carnitine concentrations in the body and increases lipid accumulations. However, a 12-week intervention with lysine did not change the lipid profile in men with hypertriglyceridemia. Leucine and alanine have also been linked to beneficial metabolic effects such as reduced body fat accumulation.

WP has an outstanding acute postprandial effect on the TG response compared to other dietary protein sources. Postprandial TG concentration is affected by many factors, e.g., intestinal chylomicron secretion, hepatic very low-density lipoprotein (VLDL) secretion, conversion of TG-rich lipoproteins to TG-depleted lipoproteins and tissue uptake of TG-depleted lipoproteins. Thus, WP consumption may result in a lower production of chylomicrons, which is consistent with the more pronounced FFA suppression. Lipoprotein lipase (LPL) is a key enzyme in the hydrolysis of TG in chylomicrons and VLDL. The insulin tropic effect of WP may enhance LPL activity and hence accelerate chylomicron clearance. The peptide fraction of β-lactoglobulin like β lactorphins also controls the abnormal blood lipid levels and solves the problem of CVD.

Effect of milk proteins on Blood Pressure

Epidemiological studies suggest that the dietary intake of milk and dairy foods is related to decreased risk of hypertension. In addition to their high mineral content (e.g., calcium, potassium, and magnesium) that can lower blood pressure, other milk components such as proteins and their hydrolyzed products have been also linked to the antihypertensive effects. Controlled hydrolysis of protein may produce many low molecular (<10 Kda) peptides which have bio functional activities. Angiotensin converting enzyme (ACE) is a multifunctional enzyme that acts as one of the main regulators of blood pressure. Thus, ACE inhibition is currently considered as one of the best strategies for hypertension treatment. Most biologically active peptides generated from milk proteins have demonstrated ACE inhibitory activity. The hydrolyzate obtained by the action of pepsin on casein, containing the αs1-casein-derived peptides RYLGY and AYFYPEL, has been patented and commercialized under the name of Lowpept. Pepsin has been also used to hydrolyze whey protein lactoferrin, with the release of peptides containing ACE activity and ACE-dependent vasoconstriction inhibitory properties. Trypsin and Flavourzyme are other gastrointestinal enzymes used to release the antihypertensive peptide αs1-casein peptide f (23-34) from casein during the manufacture of the commercial ingredient peptide C12. Peptides like lactotripeptide Val-Pro- Pro and Ile-Pro-Pro (100 mg) in combination with alginic acid (1754 mg) reduce both SBP (9.2 mmHg) and DBP (6.0 mmHg) 6 hours after oral administration. Protein hydrolysate showed better suppressive effects than intact protein in both the cases.

Milk Fat

The composition of the lipid fraction in milk is dominated by TG (95-96%). The remaining percentage is composed of phospholipids (PL), cholesterol, 1,2-diacylglycerol, FFA, monoacylglycerol, cholesteryl ester, and hydrocarbons. The fatty acid composition is dominated by Saturated Fatty Acid (SFA - 70%) followed by Mono unsaturated fatty acid (MUFA - 25%) and Poly unsaturated fatty acid (PUFA - 2.3%). Milk is characterized by a relatively high content of low molecular weight fatty acids, with approximately 400 different fatty acids, where butyric acid (C4:0) is the primary constituent.

Medium-chain fatty acids (C6:0-C12:0) have beneficial effects on metabolic health and improve insulin sensitivity. Under certain *in vivo* conditions, they may reduce intestinal injury and protect from hepatotoxicity. α-linolenic acid is another major PUFA in milk; it comprises 0.5-2% of the total fatty acid composition in milk. Palmitoleic acid (*cis* and *trans*C16:1) and oleic acid (C18:1) are the MUFAs with quantitative significance in the dairy lipid fraction. They represent 1-2% and 20-30% of the total fatty acid composition in milk fat, respectively. C18:1 is suggested as a dietary element reducing the incidence of metabolic diseases. Milk supplemented with C18:1 and in combination with folic acid and vitamins A, B6, D, and E reduce total, LDL, and HDL cholesterol in subjects with MetS and moderate CVD risk.

Conjugated linoleic acid (CLA) is one of the most studied PUFA (C18:2) in a dietary context. It represents 1-3% of the total fatty acid composition in milk. The primary CLA isomers in dairy fat is *cis*-9, *trans*11 CLA (70-90%); the second most frequent CLA is *trans*10, *cis*-12. Several studies observing the metabolic effects of CLA on mice have Shown that CLA reduces body fat in animals fed both a low and a high-fat diet. Both the *cis*-9, *trans*-11 and *trans*-10, *cis*-12 CLA isomers have been recognized as having antitumor capabilities in the inhibition of angiogenesis in mammary tissues.

Studies have shown that CLA can delay or reduce the onset of chemically induced tumors in various sites of rats and mice and its anticarcinogenic activities include a reduction in cell proliferation and prostaglandin metabolism.

Major Health Benefits of Milk Proteins

Type of protein	Biological function	Outcome
Whey proteins		
Whey protein concentrate	Anticarcinogenic activity	Inhibition of incidence and growth of chemically induced tumors
	Immuno-modulation	• Higher mucosal antibody responses to antigens • Impact on T-cell populations, increase in the T-helper cells concentration and T-helper cells/T-suppressor cells ratio
β-Lactoglobulin	Anticarcinogenic activity	Stimulation of the glutathione synthesis
	Antiviral activity	Inhibition of *HIV-1* protease and integrase activities
α-Lactalbumin	Anticarcinogenic activity	Antiproliferative action on colon adenocarcinoma cell lines
	Antibacterial and antiviral activity	Reduction in cell numbers of the infant fecal *E. coli*
Lactoferrin	Anticarcinogenic activity	Antiproliferative, anti-inflammatory and antioxidant activities
	Immuno-modulating	improving delayed-type hypersensitivity responses to a range of antigens
	Antibacterial activity and antiviral activity	• Inhibitory effect against *H. pylori* • Inhibition of *HIV-1* reverse transcriptase, protease and integrase activities
Immunoglobulin	Antibacterial activity	• Prevention of shigellosis • Protection against oral challenge with enterotoxigenic *E.coli*
	Anticariogenic activity	• Slight inhibitory activity against *S. mutans* adherence to S-HA
Casein		
Whole casein	Anticarcinogenic activity	• Protect against colon cancer • Decreasing the incidence of chemically induced intestinal tumors
	Hypocholesterolemic effects	Reduction in the total cholesterol, LDL-C, HDL-C and lipoprotein (a) concentrations
k-Casein	Ant cariogenic activity	• Reduction in the activity of the plaque-promoting enzyme • Inhibiting the adherence of *S. mutans* to the S-HA surfaces of teeth
β-Casein	Hypocholesterolemic effects	• Reduction in blood cholesterol levels
Bioactive peptides		
Lactoferricin	Anticarcinogenic Activity	Cytotoxic, antitumor, and apoptotic activity against cancer cell lines
	Immuno-modulation	Increase in Igs (IgM, IgG, and IgA) production
	Antibacterial activity	Growth inhibition of diverse range of Gram-positive and Gram-negative bacteria
	Antihypertensive activity	Inhibition of ACE activity and ACE-dependent vasoconstriction
Lactorphin	Antihypertensive activity	Decrease in blood pressure in hypertensive rats
Casein-phosphopeptides	Anticariogenic activity	Stabilization of calcium phosphate and decreasing the mineral loss
Kappacin	Antibacterial activity	Inhibition of *S. mutans, Porphyromonas gingivalis* and *E. coli*
Glycomacropeptide	Antiviral activity	Inhibition against human *influenza* virus and *Epstein Barr* virus
	Immuno-modulation	Indirect anti-inflammatory effect of intestinal by Promotion host defence against microorganisms
Casomorphin peptides	Anticarcinogenic activity	• Decrease in proliferation of prostatic cancer cell lines • Promotion of apoptosis in human leukemia cells (HL-60)

Milk Sugar

Lactose (β-D-galactosyl-D-glucose) is a disaccharide occurs exclusively in the milk of mammals which is composed of galactose and glucose linked by a β 1-4 glyosidic bond. Human milk has the highest content (approx 7%) and in cows' milk the concentration is lower (appx 4.6 %). Sweetness of lactose is relatively less to sucrose (20-30%) of that of sucrose and increases the sensitivity of insulin, thus reduces the risk of cardiovascular diseases and T2D. *Low Glycemic index of lactose is attributed to two factors.* First, incomplete digestion of lactose in the small intestine. Second, Galactose component must be converted into glucose in the liver before it can contribute to the blood glucose level.

The derivates from lactose-lactulose, lactosucrose, lactitol, and galactose-oligosaccharides have potential prebiotic properties including enhancing mineral uptake, reducing serum lipids, reducing the risk of intestinal infections and colon cancer. Lactulose is formed from heating lactose, in which the glucose moiety is epimerized to fructose. It is recognized as a bifidogenic factor. It is present in heated milk (up to 0.2%) but not digestible, and acts as a soluble fiber that has been shown to alleviate constipation and chronic encephalopathy, stimulate the immune response, enhance calcium absorption in infants, and stimulate the growth of *Bifidobacterium bifidum* in the lower colon area of the human gastrointestinal tract.

Similarly, lactosucrose is recognized as a bifidogenic factor due to its ability to enhance the amount of faecal bifidobacteria and possible effectiveness in modifying the faecal flora in patients with inflammatory bowel disease. Lactitol is a synthetic sugar alcohol produced by the reduction of lactose. It has been shown to significantly reduce the activity of procarcinogenic enzymes and aromatic compounds in the colon, when 20 g/day is administered.

Hydrolysis of lactose by exogenous lactase solves the problem of lactose digestion in lactose intolerant patients whereas Galacto-oligosaccharides [GOS; gal-(gal)n-glu] are also produced by the hydrolysis of lactose by galactosyl transferase helps in suppressing the activity of enzymes that convert procarcinogens to carcinogens and leads to proliferation of *Bifidobacterium* that activate cell wall and extracellular immune system components. Thus, GOS has proven to show anti cancerous effect in colon. Fermentation of GOS (degradation of GOS by intestinal microflora) results in the production of butyrate, which serves as a fuel for colonic epithelial cells and stimulates apoptosis. GOS fermentation in large intestine also produces propionate, which has been shown to be anti-inflammatory with respect to colon cancer cells. GOS feeding in combination with mixture of probiotic bacteria significantly reduce IgE-associated diseases, eczema and atopic eczema.

Minerals

The high intake of calcium, a mineral prevalent in dairy products, may promote weight reduction through modulation of serum 1, 25-hydroxyvitamin D concentrations. Serum calcium concentration is tightly regulated by dietary calcium intake which modulates adiposity. The calcium supplementation enhances the ratio of HDL: LDL cholesterol which is even a stronger reason to support the fact that dietary calcium helps in controlling MetS. The calcium obtained from milk and milk products are essentially in the form of calcium phosphates which is believed to be a reason behind better absorption of it in the intestine as compared to calcium carbonates obtained from other dietary sources, Moreover the amount of calcium furnished by dairy products are high enough to impart significant reduction of SFAs thus LDL cholesterol. Studies have indicated a definite impact of calcium intake on body weight control and fat deposition in body.

Effect of Dairy Calcium on blood pressure

Intake of calcium also affects the blood pressure favourably and the possible mechanism explains an inverse relation of calcium concentration and blood pressure. One mechanism explains that the increase in dietary calcium causes reduction in 1, 25-dihydroxy vitamin D, responsible for lipogenesis. Binding of calcium with 1, 25-dihydroxy vitamin D causes reduced intracellular calcium inflow which leads to reduction in synthesis of fatty acids and decrease in triglycerides reserves of cells. This helps to smoothen vascular muscle and altered vascular tone resulting in reduction of blood pressure.

Apart from calcium, other mineral like magnesium and potassium are present in dairy products which help in reducing blood pressure. An approx. estimate of calcium from milk is 1,2 g/L as well as fairly good sources of potassium and magnesium. Other components like lactose, citrates and protein derived peptides help in increasing the bioavailability of calcium and other minerals like magnesium, zinc and selenium, etc. from milk source thus enhancing the benefits in relation to metabolic health.

Conclusions

The present evidences confirm the definite role of milk constituents to improve the metabolic health. Milk proteins have an insulinotropic effect and amino acids like BCAA appear to have lot of health importance. Hydrolysis of protein shows increased effects on insulinotropic activity, reduction in blood pressure and mineral binding ability.

Recent study reveals that consumption dairy fat is not typically associated with an increased risk of weight gain, CVD and T2D. Lactose enhances absorption of calcium and other minerals. It also controls chronic constipation. Hydrolysis of lactose serves as substrate for the intestinal flora and favour the growth of *bifidobacteria* and *lactobacillus*. Dietary calcium through milk products has inverse relation with blood pressure. It reduces the risk of colorectal cancer, prevents osteoporosis, supports weight loss and improves immune system. Therefore, there are huge opportunities of utilization of milk constituents and their further processing in dealing with MetS and related health issues at various levels.