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The Role of Milk Products in Metabolic Health and Weight Management

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Abstract

A substantial body of evidence has emerged over the last decade in support of the novel concept that dietary calcium and dairy foods play an important role in regulating energy metabolism and thereby promote healthy weight management and reduce obesity risk. This concept has been demonstrated in experimental animals studies, cross-sectional and prospective population studies and a number of randomized clinical trials. Notably, the effects of dairy foods in weight management are more consistent than the effects of supplemental calcium across clinical trials, and calcium *per se* is responsible for approximately 40-50% of the effects of dairy. The calcium component is only effective in individuals with chronically low calcium intake, as it serves to prevent the endocrine response to low calcium diets which otherwise favors adipocyte energy storage; calcium also serves to promote energy loss via formation of calcium soaps in the gastrointestinal tract and thereby reduce fat absorption. The calcium-independent anti-obesity bioactivity of dairy resides primarily in whey. The key components identified to date are leucine and bioactive peptides resulting from whey protein digestion. The high concentration of leucine in whey stimulates a repartitioning of dietary energy from adipose tissue to skeletal muscle where it provides the energy required for leucine-stimulated protein synthesis, resulting in increased loss of adipose tissue and preservation of skeletal muscle mass during weight loss. Finally, dairy rich diets suppress the oxidative and inflammatory responses to obesity and thereby attenuate the diabetes and cardiovascular disease risk associated with obesity.

Introduction

A substantial body of evidence has emerged over the past decade in support of the novel concept that dietary calcium and other components of dairy foods play a regulatory role in energy partitioning between adipose tissue and lead body mass, resulting in a significant anti-obesity effect. While alterations energy intake and physical activity are clearly the primary components affecting obesity risk, subtle changes in the efficiency of food energy utilization appear to play a significant role in conferring either susceptibility or resistance to diet-induced obesity. The progressive weight gain that characterizes our present obesity epidemic appears to result, in general, from small excesses (0.5-2%, or 12-50 kcal/day) in energy balance experienced over a protracted period of time; consequently, otherwise marginal components of energy balance, including energetic efficiency, have the potential to play a major role in determining whether or not there is a cumulative gain of excess body fat and a corresponding risk of obesity development.

Obesity susceptibility is a complex genetic trait, with multiple genes interacting to confer relative susceptibility (increased energetic efficiency) or resistance (decreased energetic efficiency) to the obesigenic effects of positive energy balance. However, the metabolic pathways operated by these genetic factors may also be modulated by specific nutrients, foods or dietary patterns, providing an opportunity for functional foods and ingredients to significantly reduce susceptibility to obesity. The premise advanced by this paper is that dairy foods are an important example of

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such functional foods, as they uniquely modulate these pathways to reduce energetic efficiency and thereby confer significant resistance to obesity and enhance weight and fat loss during caloric restriction. In addition, we will demonstrate that whey and whey components reduce the risk of obesity-associated co-morbidities and metabolic syndrome by directly suppressing both oxidative and inflammatory stress.

Clinical Studies and Supporting Animal Studies

The original concept of calcium and dairy modulation of body composition and weight management emerged as a surprising set of findings from a clinical trial evaluating the role of dairy in hypertension, with subsequent corroboration via animal studies, cellular studies to provide a mechanistic framework, secondary analysis of clinical studies originally performed to assess skeletal outcomes and finally prospective clinical trials to assess the effects of calcium and dairy foods on adiposity. In the original hypertension study, we noted that isocalorically substituting yogurt (454 g/day) to the daily diet resulted in a significant 4.9 kg reduction in body fat (1). These findings did not appear to have a logical explanation at the time (1988) and were consequently not submitted for publication until we had a metabolic explanation, as described later in this paper.

We then confirmed the anti-obesity effect of dietary calcium, with comparisons to dairy products, in a series of studies conducted in a mouse model of diet-induced obesity (aP-2-*agouti* transgenic mice (1-6). These mice respond to low calcium diets with accelerated weight and fat gain, while high calcium diets markedly inhibit lipogenesis, accelerate lipolysis and fat oxidation, increase thermogenesis and suppress fat gain with no change in energy intake (1). Further, when the mice were subjected to modest caloric restriction, low calcium diets inhibited body fat loss while high calcium diets markedly accelerated fat loss (2-6); notably, utilizing dairy as the calcium source without altering macronutrient composition resulted in substantially greater effects compared to calcium carbonate. Studies in other animal models confirm these observations (7-9), although one report has indicated a lack of effect in obese animals (10).

Dietary calcium and dairy also alter the partitioning dietary energy during re-feeding following weight loss by obese mice (11). Although post-obese mice fed low calcium diets exhibited rapid weight and fat re-gain, increasing dietary calcium prevented the suppression of lipolysis and fat oxidation that otherwise accompanies energy repletion and instead up-regulated skeletal muscle fat oxidation (11), reflecting a re-partitioning of energy from storage in adipose tissue to oxidation in skeletal muscle. As a result, high calcium diets prevented 50-85% of the weight and fat re-gain found in the animals fed the low calcium diet, with significantly greater effects found in the dairy versus the high calcium group (11).

A number of randomized clinical trials were subsequently conducted to evaluate the magnitude and significance of this effect in humans. In the initial trial (12), 32 obese adults were maintained on balanced caloric-deficit diets (500 kcal/day deficit) and randomized to control (0-1 serving/day and 400 to 500 mg Ca/day supplemented with placebo), high calcium (control diet supplemented with 800 mg Ca/day), or high dairy (3-4 servings of dairy foods, primarily milk, total Ca intake of 1,200-1,300 mg/day). Control subjects lost 5.4% of their body weight over a 24-week study, and this loss was increased to 8.6% on the high calcium diet and to 10.9% on the high dairy food diet ($p<0.01$). Fat loss followed a similar trend, with the high calcium and high dairy food diets augmenting the fat loss found on the low calcium diet by 38 and 64%, respectively ($p<0.01$). This was accompanied by a marked change in the distribution of body fat loss; central (trunk) fat loss represented 19% of the total fat lost on the low calcium diet, and this was increased to 50% of the fat lost on the high calcium diet and 66% on the high dairy food diet; this effect has now been explained via calcium/calcitriol modulation of adipose tissue cortisol production, as discussed later in this paper.

These findings demonstrate that increasing dietary calcium from suboptimal to adequate levels can enhance the efficacy of an energy-restricted diet in weight and fat loss, while a markedly greater enhancement is found when dairy foods are used compared to calcium supplements (12). A follow-up clinical trial of the effects of a diet supplemented with three servings of yogurt (total calcium intake of ~1,100 mg/day) compared to a placebo control group (calcium intake of 400-500 mg/day) in obese subjects on a balanced calorie-deficit (−500 kcal/day) for 12 weeks supports these findings (13). Both groups lost weight, but the yogurt group lost 61% more fat (4.43 vs. 2.75 kg) and 81% more trunk fat (3.16 vs. 1.74 kg) than the control group ($p<0.001$). Similar to the first clinical trial, the fraction of fat lost from the trunk was markedly higher on the yogurt diet vs. control (60.0 vs. 26.4%). Moreover, there was a significant 31% reduction in the loss of lean tissue mass during energy

restriction in the yogurt group compared to the control group, supporting a role for dairy foods in the preservation of muscle mass.

These findings have been extended in a multi-center trial of 105 overweight and obese adults (14). The design was similar to the first clinical trial, with subjects randomized to low calcium, high calcium and high dairy groups on balanced deficit (−500 kcal/day) diets for 12-weeks. The high dairy food diet resulted in significant, marked (~2-fold) increases in fat loss and trunk fat loss, similar to that seen in the first trial (12), but the calcium supplement was without significant effect. These findings were also replicated in a six-month clinical trial in obese African Americans (15), with essentially similar findings.

In the absence of energy restriction, dairy exerts little effect on body weight but still exerts significant effects on body composition. Isocaloric substitution of three daily servings of dairy products into the diets of obese adults maintained on eucaloric diets for six months results in a 5.4% reduction in total body fat and a 4.6% decrease in trunk fat ($p<0.01$ for both) in the absence of any change in body weight while the control group maintained on a low calcium/low dairy diet with identical macronutrient composition exhibited no significant changes in total body fat or trunk fat (15) Data from the Women's Health Initiative (16) also support a significant role for calcium in improving adiposity in the absence of energy restriction, although the effects of dairy foods were not assessed. Data from this large randomized double-blinded placebo-controlled trial comparing the effects of 1,000 mg calcium plus 400 IU vitamin D/day in 36,282 post-menopausal women (18,176 active treatment and 18,106 placebo) demonstrated a modest but consistent significant attenuation of post-menopausal weight gain after three and seven years of follow-up in the calcium/vitamin D-supplemented group compared to the placebo group.

Two published studies utilizing a similar design to the studies noted above (12-15) found no effect of dairy (17,18), subjects in the higher dairy group in both studies consumed significantly more energy (150-200 kcal/day) than was consumed by subjects in the low dairy control groups. However, data from these studies have been incorporated into a recent meta-analysis of all known clinical trials of the effects of dairy on body weight and body composition during energy restriction (19). Results of this analysis, which consolidated source data from seven clinical trials, demonstrate a highly significant effect of dairy in augmenting weight, fat and trunk fat loss while tending to protect lean mass during energy restriction (19).

The effects of dietary calcium and dairy foods on weight management appear to result from correction of suboptimal intakes, as discussed in the mechanisms section of this paper. Major et al (20) recently reported data in support of a threshold effect in the control of adiposity by dietary calcium. They conducted a 15-week weight reduction program in 63 obese women supplemented with either calcium (1,200 mg/day) and vitamin D (10 μg/day) or placebo. Although there was no significant effect of the supplement on weight loss in the entire group, when the group was subdivided according to calcium consumption, a highly significant effect was noted, as calcium + vitamin D supplementation resulted in a 6 kg weight loss in those with low calcium intakes (<600 mg/day) vs. 1 kg in the placebo group (20).

Other clinical trials also support a role for dairy or dairy components in weight management. Whey supplementation in previously sedentary individuals subjected to an exercise regimen for 10 weeks resulted in a marked increase in fat loss (−9.3% vs. −4.6%) and a corresponding 2.3% increase in muscle mass (21). Similarly, Frestedt et al (22) evaluated the effects of a commercial dietary supplement (Prolibra^{TM}) containing high levels of both calcium and leucine in a 12 week randomized controlled trial of obese patients on a 500 kcal/day deficit diet with either Prolibra or an isocaloric beverage. Although both groups lost similar amounts of weight, the Prolibra group showed a significantly greater loss in body fat mass and a significant attenuation of the loss of fat free mass which otherwise accompanies weight reduction (22).

Although most clinical trials to date have been conducted in adults, a recent six-month trial of 120 obese primary school-aged (5.6 ± 0.5 years) children with a three-year follow-up (23) demonstrates that dairy-rich diets contribute significantly to successful weight management. The children were randomized to dairy-rich, control or energy restricted diets for six months and then followed twice a year for three years. All groups exhibited decreases in BMI and waist circumference during the six-month trial, followed by progressive increases during the follow-up period; however, the dairy-rich group maintained lower than baseline BMI ($p<0.01$ compared to the other two groups) and waist circumference ($p<0.04$ vs. the other two groups) for the first 12 months of follow-up and remained significantly lower than the other two groups throughout the

remainder of the follow-up period (23).

Maintaining weight loss following a successful period of energy restriction is a key challenge, as most dieters rapidly regain weight following successful weight loss. However, Ochner and Lowe (24) reported that when holding energy constant, higher dairy-derived calcium intake was associated with reduced weight gain in an 18-month follow-up following successful weight loss in obese women. Overall, each 100 mg increase in dietary calcium intake was associated with 1,6 kg less weight gained over the 18-month period. Our recent clinical trial data support these observational findings; we recently reported that adequate levels of dairy intake increased fat oxidation during weight maintenance following weight loss and permitted significantly higher energy intake without corresponding increases in body weight compared to a low dairy intake group (25).

These effects are also supported by a number of observational studies reporting an inverse relationship between dairy foods and/or dairy components and either body weight or body fat in multiple population groups, including children, young adults and older adults of multiple ethnicities (26-35). Similar inverse relationships have also been reported in multiple epidemiological studies, including NHANES I (36), NHANES III (1), the HERITAGE study (37), the Quebec Family Study (38), the Coronary Artery Risk Development in Young Adults (CARDIA) study (39), the Strong Heart Study (35) and the Tehran Lipid and Glucose study (40). In contrast, a retrospective analysis of three calcium supplementation trials originally conducted to assess skeletal outcomes reported no significant effect on body weight or fat (41); however, the authors noted that the magnitude and direction of the observed changes were consistent with a hypothesized effect but could not be detected due to sample size limitations. Indeed, Davies et al (42) also conducted a re-analysis of a series of calcium interventions originally conducted to assess skeletal endpoints. In their analysis of data from 780 women from five clinical trials they noted significant negative associations between calcium intake and body weight, and an odds ratio for being overweight of 2.25 for young women in the lower half versus the upper half of calcium intake. Moreover, consistent with data from the Womens Health Initiative (16), they demonstrated a calcium treatment effect of a 0.325 kg weight loss/year over a four-year period with no intentional change in energy intake. Overall, their data indicate that a calcium intake increase of 1,000 mg/day was associated with an 8 kg reduction in body weight (42).

Mechanisms

The anti-obesity effects of dairy foods include both calcium-dependent and calcium-independent mechanisms. The calcium component appears to be mediated by calcium suppression of calcitrophic hormones and by calcium binding to fatty acids in the gastrointestinal tract, forming soaps and thereby reducing fat absorption.

In order to maintain constant circulating calcium levels despite widely varying calcium intakes, a complex calcium regulatory endocrine system is engaged to modulate calcium absorption, renal calcium reabsorption and bone calcium resorption and accretion. Two hormones, parathyroid hormone (PTH) and calcitriol (1,25-dihydroxyvitamin D) are increased in response to suboptimal calcium intakes, and both of these stimulate calcium signaling in other target tissues, including adipose tissue. This provided the initial framework for understanding the role of dietary calcium in regulating energy metabolism and adiposity.

A calcium response sequence has been mapped to the promoter region of the fatty acid synthase (FAS) gene (43), a key regulatory gene responsible for lipogenesis, and increasing intracellular Ca^{2+} in adipocytes stimulates FAS gene expression and enzyme activity (44-46), resulting in increased lipid synthesis. In addition, elevated intracellular Ca^{2+} also inhibits lipolysis, and the combination of increased lipid synthesis and decreased degradation results in an expansion of adipocyte triglyceride storage (45, 47, 48). Calcitriol stimulates rapid increases in human adipocyte intracellular Ca^{2+}. These rapid effects are mediated by a non-genomic membrane receptor (44) distinct from the classical nuclear receptor (50). Dietary calcium, by virtue of suppressing calcitriol levels, has been demonstrated to decrease the intracellular Ca^{2+} concentration in various cell types, including human adipocytes (50-52).

A potential role for calcitriol in regulating energy metabolism and contributing to obesity risk is also suggested by other data. Calcitriol signals via the nuclear vitamin D receptor (nVDR), and polymorphisms in this receptor are associated with the susceptibility to obesity in humans (53, 54), and several lines of evidence demonstrate alterations in the vitamin D-endocrine system in obese humans, with an increase in circulating calcitriol level (55, 56). These observations, coupled with the direct effects of calcitriol on adipocyte metabolism, strongly indicated an increase in calcitriol found on low calcium diets as a

contributory factor to excess adiposity.

Calcitriol also acts via the nuclear vitamin D receptor in adipocytes to inhibit the expression of uncoupling protein2 (UCP2) (57), potentially resulting in reduced coupling of mitochondrial energy metabolism to ATP production and thereby reducing the efficiency of adipocyte energy storage. Dietary calcium-induced suppression of calcitriol in mice results in increased adipose tissue UCP2 expression and attenuation of the decline in thermogenesis which otherwise occurs with energy restriction (46), suggesting that high calcium diets may also affect energy partitioning by suppressing calcitriol-mediated inhibition of adipocyte UCP2 expression. However, the role of UCP2 in thermogenesis is not clear, and the observed thermogenic effect may be mediated by other, as of yet unidentified mechanisms. Moreover, thermogenic effects of dietary calcium and/or dairy products have not yet been demonstrated in humans. Nonetheless, in addition to inducing a mitochondrial proton leak, UCP2 serves to mediate mitochondrial fatty acid transport and oxidation; this suggests that calcitriol suppression of UCP2 expression may contribute to decreased fat oxidation and increased lipid accumulation on low calcium diets and that increasing dietary calcium result in increased fat oxidation and reduced lipid accumulation (57, 58).

Human data support these mechanisms, as increasing the intake of dairy foods results in increased indices of lipolysis (14, 15, 59), and high dairy diets suppressed circulating calcitriol and caused a 30 g/day (370 kcal/day) increase in fat oxidation in a randomized, controlled crossover study under highly controlled conditions using a whole-room calorimeter (59). Similarly, long-term (one year) consumption of a dairy-rich high calcium diet resulted in increased fat oxidation responses to meal challenges (60).

Increasing dietary calcium may also result in increased fecal fatty acid excretion and, accordingly, it is possible that the resultant increase in fecal energy loss also contributes to the anti-obesity effects of dietary calcium, and this concept is supported by both rodent and human studies (61, 62). However, these effects are of modest magnitude (8.3 g additional fat in the human trial, representing a 75 kcal/day loss), which is insufficient to explain the magnitude of the effects observed in clinical trials. Nonetheless, the modest reduction in net energy balance resulting from this mechanism may have a pronounced effect in maintaining healthy weights and promoting weight loss over an extended period of time, and the contributory role of increased fecal fat loss should not be overlooked. In support of this concept, we have found high calcium and high dairy food diets to exert a substantial greater anti-obesity effect in obese mice on a high fat diet compared to those on a low fat diet, and attributed the additional effect to increased fecal energy loss in the mice on the high fat diets (5).

Dietary calcium and calcitriol may also participate in the energy metabolism by regulating adipose tissue fat depot location and expansion. Both rodent and human studies demonstrate a shift in the distribution of body fat loss on high versus low calcium diets during energy restriction. In rodents, high calcium and milk-based diets produce a preferential loss of visceral adipose tissue, while the clinical trials discussed earlier in this paper demonstrate a preferential loss of fat from the trunk region. Excessive central fat deposition in obesity may result from the greater capacity for regeneration of active glucocorticoids in the visceral fat depot. Local adipose tissue glucocorticoid levels and intracellular glucocorticoid availability are controlled by the activity of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD 1) to generate active cortisol from inactive cortisone. We recently demonstrated that calcitriol also directly up-regulates adipocyte 11β-HSD 1 expression and cortisol release and, consequently, correspondingly affects local cortisol levels, indicating a potential role for calcitriol in visceral adiposity (63). These findings are further supported by our recent microarray study in human adipocytes (64), as well as by data demonstrating that dietary calcium-induced suppression of calcitriol resulted in suppression of adipose tissue 11β-HSD 1 expression in diet-induced obese mice (63). These effects are dependent upon the nuclear vitamin D (calcitriol) receptor in adipocytes. Although this receptor is expressed at low levels in mature adipocytes, we have recently demonstrated a direct role for cortisol in increasing the expression of this receptor (65). This results in a positive feedback loop in which calcitriol stimulates cortisol production, and the cortisol then increases the calcitriol receptor, thereby further increasing cortisol production and release (69). Consequently, reducing calcitriol levels with high calcium diets results in a corresponding decrease in adipose tissue cortisol production, and thereby contributes to reduced visceral adipose tissue mass.

Role of Other Components of Dairy

Data from clinical trials, population studies and animal studies

discussed earlier in this paper indicate that calcium is responsible for approximately 40% of the anti-obesity activity of dairy and that other dairy components are responsible for the remainder of this effect. We have found that the majority (but not all) of this non-calcium bioactivity resides in whey, and that much of it may be explained by the high concentration of branched chain amino acids in whey. Whey proteins have a high protein quality score and contain a high proportion (~26%) of branched chain amino acids (BCAA) (66). In addition to supporting protein synthesis, the BCAA (leucine, isoleucine and valine) play specific metabolic roles as energy substrates and leucine plays a unique role in the regulation of muscle protein synthesis; however, their potential to participate in these additional metabolic processes are limited by their availability, with first priority provided to new protein synthesis (66, 67). Accordingly, only diets which provide leucine at levels which exceed requirements for protein synthesis can fully support the intracellular leucine levels required to support additional signaling pathways. Consequently, the abundance of leucine in dairy protein is of particular interest, as it plays a distinct role in protein metabolism, as it plays a pivotal role in translation initiation of protein synthesis (67-70) and appears to be an important factor in the re-partitioning of dietary energy from adipose tissue to skeletal muscle (69-71). Thus, This suggests an interaction between the high levels of BCAA in dairy protein, in combination with the calcium in dairy appear to synergize to minimize adiposity and maximize lean mass.

Depletion of calcium from milk reduces it's anti-obesity efficacy in rodents, but calcium-depleted milk still retains over ½ of the anti-obesity bioactivity of intact milk, most of which can be recapitulated by increasing the BCAA content of a low calcium/non-dairy diet to the level found in whey (72). Moreover, we recently found leucine to coordinately regulate lipid metabolism and energy partitioning between adipocytes and skeletal muscle cells (73). Leucine inhibited energy storage in adipocytes, as evidenced by marked suppression of FAS expression and activity, and instead stimulated skeletal muscle fatty acid oxidation. Accordingly, the effects of leucine on adiposity are likely to represent the additional energetic cost of leucine-stimulated protein synthesis, and that leucine stimulated fatty acid oxidation in skeletal muscle represents the source of the additional metabolic energy necessary to support this additional protein synthesis (73, 74). Notably, leucine also stimulates mitochondrial biogenesis in both skeletal muscle cells and adipocytes, thereby providing increased capacity for fatty acid oxidation (74).

Dairy Modulation of Metabolic Risk

An inverse association between dairy intake and each of the major components of the metabolic syndrome (Insulin resistance syndrome; IRS) was reported in the CARDIA study (39). This prospective 10-year population based prospective study of 3,157 black and white adults demonstrated that overweight individuals who consumed the most dairy products had a 72% lower incidence of IRS compared to those with the lowest dairy food intakes. Moreover, the cumulative incidence of obesity in those who started the study in the overweight category was significantly reduced from 64.8% in those consuming the least amount of dairy foods to 45.1% in the highest dairy food-consuming group. Notably, the inverse relationship between dietary calcium and either IRS or obesity incidence in the CARDIA study was explained solely by dairy food intake and was not altered by adjustment for dietary calcium, indicating the presence of an additional effect of dairy beyond the mechanisms already cited for dietary calcium in modulating adiposity and obesity risk; this is consistent with both the experimental animal and clinical trial data discussed elsewhere in this paper which also suggest that other dairy components, in addition to calcium, contribute to an anti-obesity effect. Consistent with the CARDIA data, recent data from the Caerphilly Cohort Study (75) demonstrate that milk and dairy food consumption is associated with a markedly reduced prevalence of the metabolic syndrome; men who regularly drank milk exhibited an adjusted odds ratio of 0.38 (i.e. a 62% reduction in risk), while those in the highest quartile for consuming all dairy foods (defined as milk, yogurt, cheese, butter and cream) exhibited an adjusted odds ratio of 0.44 (i.e. a 56% reduction in risk). Thus, both prospective and cross-sectional epidemiological data support the mechanistic and clinical observations of an anti-obesity effect of dairy and further indicate significant protection against the metabolic syndrome.

The metabolic syndrome is independently associated with increased oxidative and inflammatory burden (76-78), and this observation may explain the disproportionate increase in CHD risk (79) that results when metabolic syndrome accompanies obesity compared to uncomplicated obesity. Accordingly, the next section addresses emerging data on the role of calcium

and dairy foods in attenuating oxidative and inflammatory stress.

Dairy Modulation of Oxidative and Inflammatory Stress

Overnutrition and obesity result in increased oxidative stress and a subclinical chronic inflammatory state (80, 81), both of which plays an important role in initiation and progression of cardiovascular disease. Adipose serves as an active secretory organ, releasing many peptides and cytokines into circulation (82, 83). In the presence of obesity, the balance between these numerous molecules is altered such that enlarged adipocytes produce more pro-inflammatory cytokines such as tumor necrosis alpha (TNF α) and interleukin 6 (IL-6), and less anti-inflammatory factors such as adiponectin (80, 81). This dysregulation of adipocytokines (adipokines) production contributes to the development of metabolic disorders associated with obesity. However, adipose tissue is not only composed of adipocytes but also contains a stromal-vascular fraction that consists of endothelial cells, cells with characteristics of progenitor cells and leukocytes (84). Moreover, adipose tissue are infiltrated by more macrophages as the degree of obesity increases (85-87), and these macrophages are a major source of cytokines that initiate an inflammatory state that precedes the development of insulin resistance and arthrosclerosis (84). Oxidative stress also plays a major role in regulating inflammatory status in adipose tissue as well as in modulating the adipocyte-macrophage interaction. Reactive oxygen species (ROS) production is augmented in obesity, resulting in increased expression of inflammatory cytokines and suppression of anti-inflammatory cytokines, such as adiponectin (88).

Adipocyte ROS production is regulated, in part, by mitochondrial uncoupling status and cytosol Ca^{2+} signaling; since calcitriol increases mitochondrial coupling by suppressing UCP2 and stimulates Ca^{2+} signaling, it also stimulates ROS production in both murine and human adipocytes (89) and thereby contributes

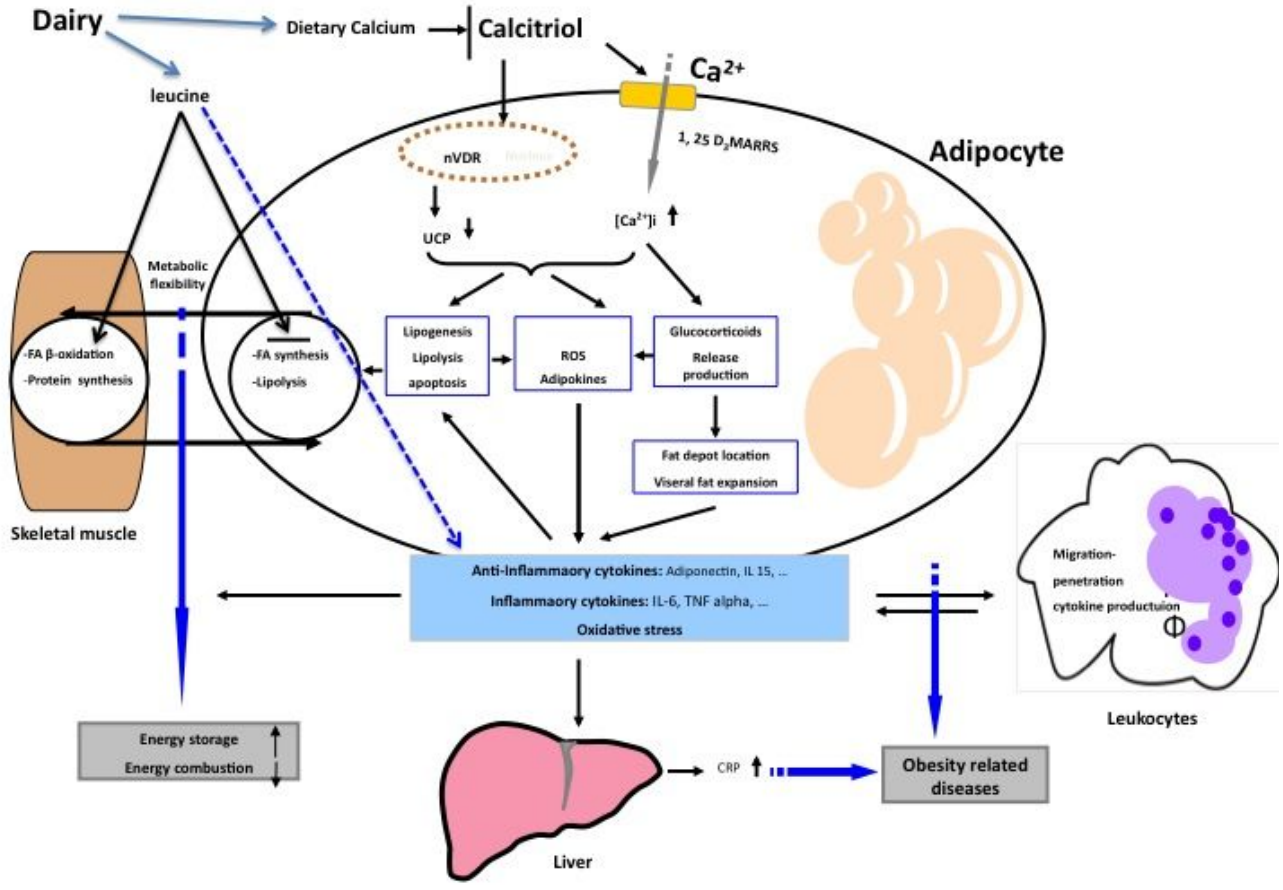

Fig. 1. Effects of dairy components on adipocyte-skeletal muscle cross-talk, energy metabolism and oxidative and inflammatory stress.

to systemic oxidative stress. Accordingly, since dietary calcium suppresses calcitriol, high calcium diets would be anticipated to correspondingly decrease adipose tissue ROS production and systemic oxidative stress. In support of this concept, we have demonstrated that high calcium diets inhibited adipose tissue NADPH oxidase expression (a key source of intracellular ROS) and resulted in a striking 64% reduction visceral adipose tissue ROS production in mice (90). Moreover, using an increase in dietary calcium to suppress calcitriol resulted in significant decreases in inflammatory cytokine production and corresponding increases in anti-inflammatory cytokines in mice (91). 〈Fig. 1〉 summarizes the metabolic effects of calcium and other dairy food components in attenuating oxidative and inflammatory stress as well as obesity.

Notably, similar to the effects of dairy versus calcium on adiposity and obesity risk, our recent data demonstrate that dairy foods elicit a significantly greater suppression of systemic oxidative and inflammatory stress compared to supplementary calcium in mice (92). Further, our recent human data demonstrate that increasing dairy food intake results in suppression of a key clinical marker of oxidative stress (C-reactive protein) and an augmentation of an anti-inflammatory cytokine (adiponectin) during both weight loss and weight maintenance in obese subjects (92). In a more stringently controlled randomized crossover study in overweight and obese subjects, we recently found that dairy food supplementation suppressed both oxidative stress and oxidative stress within seven days of initiation of supplementation, and that these effects increased in magnitude with increased duration of supplementation (93). We have also extended these findings to metabolic syndrome patients with elevated oxidative and inflammatory stress. Feeding a dairy-rich diet to metabolic syndrome patients resulted in 25-35% decreases in biomarkers of oxidative stress and 35-55% decreases in biomarkers of inflammatory stress, including C-reactive protein (94). These effects were manifested within 7 days, demonstrating that they are independent of dairy-induced adiposity changes, and increased in magnitude over the 12-weeks of study (94). Collectively, these data demonstrate an important role of both calcium and dairy foods in attenuating obesity-induced oxidative and inflammatory stress and suggest that, in addition to exerting an anti-obesity effect, dairy can function as a functional food to attenuate the key metabolic risk factors associated with obesity and the metabolic syndrome.

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