Milk intake and the risk of type 2 *diabetes mellitus*, hypertension and prostate cancer

Ingestão de leite e risco de diabetes melito tipo 2, hipertensão e câncer de próstata

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ABSTRACT

Milk intake is widely recommended for a healthy diet. Recent evidences suggest that milk/dairy products are associated with a lower risk of type 2 diabetes and hypertension. On the other hand, high calcium intake has been associated with a higher risk of prostate cancer. The calcium and vitamin D content in dairy foods could have beneficial effects on glucose metabolism and renin/angiotensin system as well regulates body weight. The association between high dairy/calcium consumption and prostate cancer risk are related to the presence of estrogens and insulin like growth factor (IGF-I) in milk. Based on the current evidence, it is possible that milk/dairy products, when consumed in adequate amounts and mainly with reduced fat content, has a beneficial effect on the prevention of hypertension and diabetes. Its potential role in the pathogenesis of prostate cancer is not well supported and requires additional study. Arq Bras Endocrinol Metab. 2009;53(5):688-94.

Keywords

Milk; dairy products; calcium intake; chronic diseases

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RESUMO

A ingestão de leite é amplamente recomendada para uma dieta saudável. Evidências recentes sugerem que leite e produtos lácteos estão associados a menor risco de diabetes melito tipo 2 e hipertensão. Por outro lado, a ingestão elevada de cálcio foi associada a maior risco de câncer de próstata. A quantidade de cálcio e de vitamina D presentes em produtos lácteos tem efeito benéfico no metabolismo da glicose e no sistema renina-angiotensina, além de regular o peso corporal. A associação entre o consumo elevado de laticínios/cálcio e o risco de câncer de próstata está relacionada à presença de estrogênios e de fator de crescimento semelhante à insulina (IGF-I) no leite. Com base nas evidências atuais, é possível que o leite e os produtos lácteos, se consumidos em quantidades adequadas e, principalmente, com reduzido teor de gordura, tenham um efeito benéfico na prevenção da hipertensão e do diabetes. Sua função potencial na patogênese do câncer de próstata não é bem sustentada e requer estudos adicionais. Arq Bras Endocrinol Metab. 2009;53(5):688-94.

Descritores

Leite; laticínios; ingestão de cálcio; doenças crônicas

OVERVIEW

Milk intake is widely recommended for healthy diet, not only for bone growth and maintenance, but also as a protein, calcium and magnesium sources as part of an adequate diet. Several lines of evidence suggest that milk and dairy products are associated with a lower risk of type 2 *diabetes mellitus* (T2DM) and hypertension. On the other hand, high calcium intake has been associated with a higher risk of certain types of cancer, mainly prostate cancer (1-6).

The present paper reviewed the evidence and potential mechanisms involved in the association of milk or dairy product consumption and the risk of these chronic diseases.

TYPE 2 *DIABETES MELLITUS*

Prospective studies

The prevalence of T2DM is increasing around the world and it is closely connected to the rising rates of obesity. In addition, some epidemiologic studies have found an association between milk and diary product consumption and the risk of T2DM. For example, the association between dairy consumption and T2DM in men was investigated prospectively in the Health Professionals Follow-up Study (7). In 42,125 males followed for 12 years, the relative risk (RR) for T2DM for those in the top quintile of dairy intake (≥ 2.9 daily servings) was 0.77 (95%CI = 0.62-0.95) compared with those in the lowest quintile (< 0.9 daily servings) adjusting for total energy intake, family history of diabetes, smoking status, body mass index (BMI) and various dietary components. When the association was analyzed taking into account fat content, the inverse association was primarily limited to low fat dairy. However, only skim milk reached statistical significance (multivariate RR per serving 0.90; 95%CI = 0.83-0.97). In women, similar results were observed. During a ten-year follow-up among 37,183 women, the adjusted RR for T2DM in the highest quintile of dairy intake (≥ 2.9 daily servings) was 0.79 (95%CI = 0.67-0.94) compared to those in the lowest quintile (< 0.9 daily servings). Again, the inverse association appeared to be mainly attributed to low-fat dairy intake (8). These two large epidemiological studies estimated that each daily serving of dairy foods was associated with an annual reduction in diabetes incidence of 9 and 4% in men and women, respectively.

Potential mechanisms

The mechanisms underlying the effects of dairy on T2DM development includes the calcium and vitamin D content in dairy foods (9) and the possible positive effect of high milk and calcium intake on weight control (10). The salutary effects of calcium and vitamin D on glucose homeostasis have been demonstrated in a series of experimental studies. The fact that pancreatic β-cells express vitamin D receptor (VDR), 1α-hydroxylase enzyme and calcium binding protein is consistent with an ability of this cell type to respond to the active *in vitro* form of the vitamin D [$1,25(OH)_2D_3$] with increased insulin secretion (11). In addition, the observation that mice without functioning VDR have lower circulating insulin concentration and higher plasma glucose than VDR competent wild-type mice is consistent with a role of vitamin D in pancreatic function (12). The administration of a single dose of $1,25(OH)_2D_3$ (calcitriol) of vitamin D to deficient rats increased insulin secretion and decreased blood glucose levels (13). The mechanism by which $1,25(OH)_2D_3$ might act on insulin secretion may involve calcium and parathyroid hormone (PTH), because a significant rise in cytosolic calcium levels was observed in β-cells after incubation with $1,25(OH)_2D_3$, resulting in insulin secretion (14); continuous elevated endogenous plasma PTH also seemed to negatively influence insulin sensitivity (15).

A cross-sectional study of Chiu and cols. (16) found in glucose tolerant subjects a positive association between serum vitamin D concentration and insulin sensitivity, and a negative effect of hypovitaminosis D on β-cell function. However, in a large clinical trial, no benefit was observed on glucose homeostasis from the daily administration of 1,000 mg of calcium and 400 IU of vitamin D for seven years (17). A systematic review and a meta-analysis (9), that combined data from studies evaluating the association of serum 25-OHD levels and dietary calcium with prevalent and/or incident DM, suggests that both nutrients may have a role in the prevention of T2DM – but only in populations at high risk of T2DM, such as those with glucose intolerance (impaired glucose tolerance or impaired fasting glycemia).

Some studies have shown that calcium and dairy product intake may have an anti-obesity effect (10,18), which would be desirable for the prevention of T2DM. There is evidence that synthesis of the hormonally active $1,25(OH)_2D_3$ metabolite can be suppressed by high dietary calcium intake. Based on experimental observations in the *agouti* mouse obesity model and cultured human adipocytes, Zemel and Sun (18) proposed a potential mechanism whereby dietary calcium, which would affect plasma $1,25(OH)_2D_3$ concentration, influences the development of obesity. They proposed that, during a low calcium diet, plasma $1,25(OH)_2D_3$ and PTH increase and exert coordinated effects on human adipocyte lipogenic and lipolytic systems, resulting in increased lipid storage, whereas the suppression of these hormones, during consumption of high calcium diets, inhibits lipid storage. Calcitriol via the VDR has also been shown in cell culture studies to suppress the expression of uncoupling protein 2 (UCP2), which would decrease thermogenesis and energy expenditure.

In addition, $1,25(OH)_2D_3$ exerts a dose-dependent effect on adipocyte apoptosis and regulates adipose tissue fat depot location and expansion by promoting glucocorticoid production and release via up-regulation of the 11β-hydroxysteroid dehydrogenase (11β-HSD), which generates active cortisol from inactive cortisone (10,18). However, a randomized double-blind clinical trial with cholecalciferol supplementation during one year (19) did not support the hypotheses that vitamin D could contribute to weight loss.

It has also been suggested that other components in dairy products, such as lactose and dairy protein, may enhance satiety and reduce the risk of overweight and obesity (risk factors for T2DM) relative to other high-carbohydrate foods and beverages (20). However, a recent evaluation of clinical trials that assessed the effect of dairy product or calcium intake on adiposity, with or without concomitant energy restriction (21), did not support this hypothesis.

Thus, while there is support from prospective cohort studies that high dairy intake is associated with lower risk of T2DM, there is as yet no convincing evidence from clinical trials that increased dairy or milk intake would help to reduce the incidence of this disease. Possible biological mechanisms underlying any inverse association of milk/dairy consumption and glucose metabolism are unclear.

HYPERTENSION

Low fat dairy foods are one of the main components of the Dietary Approaches to Stop Hypertension (DASH) diet, which has been presented with the aim of reducing blood pressure (22). In the DASH Study, patients (n = 459) were randomly assigned to receive, during eight weeks, a control diet (low in fruits, vegetables and dairy products); a diet rich in fruits and vegetables; or a "combination" diet rich in fruits, vegetables, and low-fat dairy products and with reduced saturated and total fat. Sodium intake and body weight were maintained at constant levels. At baseline, the mean systolic and diastolic blood pressures were 131.3 ± 10.8 mmHg and 84.7 ± 4.7 mmHg, respectively. The combination diet, that included low fat dairy products, significantly reduced systolic and diastolic blood pressure by 5.5 and 3.0 mmHg more, respectively, compared to the control diet, while the fruits-and-vegetables-diet reduced, alone, systolic blood pressure by 2.8 mmHg ($p < 0.001$) and diastolic blood pressure by 1.1 mmHg ($p = 0.07$) more than the control diet. Similar patterns of response were also observed among 133 subjects with hypertension, the combination diet significantly reduced systolic and diastolic blood pressure by 11.4 and 5.5 mmHg more, respectively, than the control diet.

Dietary intake of dairy products, calcium and vitamin D and the risk of incident hypertension in middle-aged and older women have been investigated by Wang and cols. (23) in the Women's Health Initiative Study. Incident cases of hypertension (n = 8,710) were identified from annual questionnaires, during a ten-year follow-up. After adjusting for major hypertension risk factors, the RR of incident hypertension across increasing quintiles of low-fat dairy product intake were 1.00 (23), 0.98, 0.97, 0.95, and 0.89 (p for trend = 0.001). Furthermore, the risk of hypertension decreased in the higher quintiles of dietary calcium and vitamin D (multivariate RR in the highest calcium quintile: 0.87, and vitamin D quintile: 0.95).

Recently, an inverse association between dairy intake and hypertension was observed in the Rotterdam Study (24). The incidence of hypertension was examined in 2,245 individuals for two and six years. The hazard ratio for hypertension was 0.76 (95%CI = 0.61-0.96) in the highest quartile of energy-adjusted dairy products intake (median intake = 691 g/d) compared to the lowest (median intake = 164 g/d) quartile (p for trend = 0.008). For low-fat dairy, the hazard ratio was 0.69 (95%CI = 0.56-0.86) in the highest quartile (p for trend = 0.003). After six years, the hazard ratio was 0.84 (95%CI = 0.70-1.01; p for trend = 0.09) and 0.84 (95%CI = 0.70-1.01; p for trend = 0.07) total dairy and low-fat dairy, respectively.

Interestingly, The Coronary Artery Risk Development in Young Adults (CARDIA) Study also reported a lower ten-year cumulative incidence of hypertension in young adult overweight subjects with dairy consumption in the highest quartile (≥ 35 servings/week) (20).

Proposed mechanism

The proposed mechanism, by which dairy products reduce blood pressure, remains uncertain, but again, calcium and vitamin D content in dairy products, as well as milk peptides, are hypothesized to exert a beneficial effect on blood pressure by inhibiting the angiotensin I converting enzyme (ACE), modulating endothelium function or affecting body weight (25-27).

Zemel (28) proposed a mechanism by which the regulation of intracellular calcium plays a key role in

hypertension and obesity. According to his model, dysregulation of calcium homeostasis induced by a low dairy/calcium diet would increase plasma $1,25(OH)_2D_3$ concentration, which would increase vascular smooth muscle intracellular calcium, thereby increasing peripheral vascular resistance and blood pressure. Calcium influx in human adipocytes is also stimulated by $1,25(OH)_2D_3$, resulting in stimulation of lipogenesis, inhibition of lipolysis and expansion of triglyceride stores. Accordingly, suppression of plasma $1,25(OH)_2D_3$ by high dietary calcium may contribute to the prevention and management of obesity and hypertension.

Hatton and McCarron (29) have reviewed possible mechanisms by which low dietary calcium might affect blood pressure. One possible mechanism is related to an increase in urinary calcium excretion due to a defect in calcium reabsorption. As a consequence, there is an increase in PTH secretion, in an attempt to restore plasma calcium. The elevated plasma PTH concentration is responsible for an increase blood pressure via activation of renin-angiotensin system (30). Other potential mechanisms were also discussed, including direct effects on vascular smooth muscle, calcium-regulating and calcium-sensitive hormones, interactions between calcium and sodium-potassium, and increased appetite for sodium, when calcium intake is low.

The relationship between vitamin D and blood pressure control was demonstrated in experimental studies, which presented that the $1,25(OH)_2D_3$ administration could inhibit renin expression at the juxtaglomerular apparatus (31) and also block vascular smooth muscle cells proliferation (32). In fact, several human studies demonstrated an inverse association between serum $1,25(OH)_2D_3$ concentration and blood pressure, as well as with renin activity (33-36).

Another potential mechanism is related to milk-derived peptides that can reduce blood pressure by inhibition of ACE. Anti-hypertensive peptides that inhibit ACE have been isolated from milk products (27) and it has been suggested that peptides with hydrophobic amino acids at the C-terminal position would be the most likely ACE inhibitors (37).

Thus, there is consistent evidence from some large prospective studies that high diary intake is associated with a lower risk of incident hypertension. The biological mechanisms are still unclear, but may involve calcium-mediated effects on circulating calcemic hormones, such as PTH and $1,25(OH)2D_3$, that influence vascular resistance, or milk-derived peptides, that influence mediators of blood pressure control.

PROSTATE CANCER

The relationship between calcium and dairy food intake in fatal prostate cancer was evaluated in the Health Professionals Follow-up Study (38), in which 47,750 healthy males over 16 years were followed. The investigators identified 3,544 cases of prostate cancer, being 523 advanced and 312 fatal. Higher calcium intake was not associated with total or non-advanced cases of prostate cancer. However, they observed a significantly higher risk of advanced or fatal cases in prostate cancer patients with reported calcium intakes of 1,500 to 1,999 mg/d, with RR of 1.87 (95%CI = 1.17-2.01), while those with calcium intakes ≥ 2,000 mg/d had a RR of 2.43 (95%CI = 1.32-4.48; p for trend = 0.003). However, when total dairy products and calcium intake were modeled simultaneously, no significant increase in RR was observed for total or advanced prostate cancer: RR of 1.05 (95%CI = 0.91-1.21) for the highest dairy intake quintile (3.72 servings/day) compared to the lowest dairy intake quintile (0.5 servings a day) for total prostate cancer; and RR of 1.08 (95%CI = 0.75-1.55) for the highest dairy intake compared to the lowest dairy intake for advanced prostate cancer. The researchers concluded that high calcium intakes (≥ 1.500 mg/d) were associated with an increased risk of poorly differentiated, clinically advanced and fatal prostate cancer, but not with generally moderate to well-differentiated cancer. Additionally, no association was observed with dairy foods.

In the Multiethnic Cohort Study (39), 82,483 men were followed for up to eight years. During this time, 4,004 cases of prostate cancer were identified. In comparison with the findings of the Health Professionals Follow-up Study (38), no association was observed between calcium (or vitamin D intake) with prostate cancer risk, even in those with calcium intakes ≥ 1,300 mg/d. Also, no association was observed between dairy products and total milk consumption and prostate cancer risk. However, the Multiethnic Cohort Study find that low/nonfat milk consumption was related to an increased risk (RR = 1.16; 95%CI = 1.04-1.29) of prostate cancer for the highest (≥ 243 g/day) compared to the lowest (0 servings/day; p for trend = 0.02). On the other hand, a marginally reduced risk of incident prostate cancer was observed for whole milk consumption (RR =

0.88; 95%CI = 0.77-1.00) for the highest (≥ 163 g/day) compared to the lowest (0 servings/day; p for trend = 0.03). These findings on low/nonfat and whole milk were related to localized or low-grade prostate cancer, but not to high advanced or high grade prostate cancer.

Additionally, a meta-analysis of 26,769 cases of prostate cancer accrued from 45 observational studies did not support an association between dairy product consumption and an increased risk of prostate cancer (40).

Possible mechanisms

The hypothesized mechanisms concerning the association between dairy product/calcium consumption and prostate cancer risk are focused on the presence of estrogens and insulin like growth factor (IGF-I) in milk and also that a high calcium consumption lowers the level of circulating $1,25(OH)_2D_3$, an inhibitor of prostate carcinogenesis (3,41).

The effects of estrogens on prostate cancer cells are mediated by specific estrogen receptors (ER). It has been demonstrated that ER-β activation limits cell proliferation directly or through ER-α inhibition, and loss of ER-β has been associated with tumor progression (42). Regarding the presence of estrogens in milk, it was been demonstrated that such content is very low (43); the mean 17β-estradiol concentration in samples of whole cow milk was only 1.4 ± 0.2 pg/mL. Therefore, one cup of whole milk would provide only 330 pg – a very small amount compared to a typical mean estradiol concentration in older men, of 21 pg/mL. Thus, although serum estrogen concentration is positively related to prostate cancer (42), the effect of even five cups of milk/day, which would supply about 1.300 mg calcium/day, would have a minimal impact on plasma estrogen concentration. Another important consideration is that 17β-estradiol is fat-soluble and its concentration is skim milk may be very low (3). Thus, the role of estrogen content in milk and its association with prostate cancer need further investigations.

Besides the idea of negative effects of IGF-I content in milk on prostate cancer, a recent review suggest that IGF-I from milk is a promoter of chronic Western diseases (2). IGF-1 is a peptide hormone expressed in most tissues, which shares significant structural and functional similarities with insulin. There is accumulating evidence of a role for IGF-1 in multiple vascular pathologies, including atherosclerosis, hypertension, angiogenesis, and diabetic vascular disease (44). Giovannucci and cols. (6) observed, in healthy middle-aged men, that the consumption of animal protein, including milk, fish and poultry, but not red meat, was associated with an increase in serum IGF-I concentration. In a previous study, the same group of investigators observed a modest increase in circulating IGF-I in men with higher dairy consumption, although intake of low-fat milk in that study was associated with lower risk of colorectal cancer (5). Cows treated with recombinant growth hormone had increased levels of IGF-I in their milk, even after milk pasteurization and homogenization (45). However, oral IGF-I is not absorbed in humans (46). Considering such observations, the potential role of milk/dairy in the pathogenesis of cancer and its association with milk IGF-I content is not well supported and requires additional study.

Additional complications in evaluating the potential health benefits or risks of high dairy/calcium consumption are that opposite effects may exist for cancers of different origins, such as colon cancer.

MILK AND CALCIUM CONSUMPTION

The estimation of adequate and optimal milk/dairy intake by populations is not settled. One measure of evaluation that can be used is to estimate if intake of these foods is in adequate quantities by evaluating the nutritional needs of a major component of milk/dairy products/calcium. It is well established that calcium intake is below recommended nutritional levels in almost all countries. Table 1 represents mean calcium intake in several countries. The studies used different dietary methods to evaluate calcium intakes, as well different sample sizes and age groups. In general, however, mean calcium intake is higher during adolescence and lower in the elderly (47). Moreover, there is considerable intergroup variability and a five-fold spread in mean calcium intake between some groups. The lowest reported calcium intake calculated was 255 mg/day (men older than 40 years, in Brazil) (48) and the highest reported calcium intake was 1,395 mg/day (men, 18 to 24 years, in German). Considering that one serving size of milk/dairy products contains approximately 250 to 300 mg/calcium, roughly the mean milk/dairy products intake is ≅ 3 servings/day. In the epidemiological studies above, a higher risk of prostate cancer was observed when calcium intake was greater than 1,500 mg/day and dairy intake was ≥ 3.72 servings/day (38). Such observations demonstrated that, in most countries, the mean intake of calcium and milk/dairy products is below

Table 1. Mean calcium intake around the world

Country	Survey name and/or areas covered	Calcium intake (mg/day)		
		Both sexes min - max	Male min - max	Female min - max
Australia	National Nutrition Survey		866-1,054	691-794
Austria	Vienna and lower Austria	796-1,095		
Brazil*	Brazos Study		255-545	276-591
Britain	National Diet and Nutrition Survey		625-1,035	595-903
Denmark	Danskerns Kostvaner		822-1,362	864-1,100
Finland	National FINNDIET		1,075-1,391	946-1,001
France	L'énquête INCA	790-884		
Germany	German Nutrition Survey		949-1,395	973-1,129
Ireland	North/South Ireland Food Consumption Survey		840-996	722-742
Italy	Nationwide Nutritional Survey of Food Behaviour	797-893	826-936	742-850
The Netherlands	Dutch National Food Consumption Survey		846-1,095	790-995
New Zealand	National Nutrition Survey		799-998	670-783
Singapure	National Nutrition Survey	480-506	445-523	446-503
Sweden	Riksmaten		1,035-1,201	901-973
United States	NHANES	721-938	797-1,081	660-860

Adapted from Looker (47).
*Data of Brazil from Pinheiro and cols. (48).

the cut-offs related to altered risk of prostate cancer. Furthermore, it has been demonstrated that milk intake decreases as carbonated beverages intake increases. An evaluation of the trends in milk and carbonated soft drinks consumption, from 1945 to 2001, by the US Department of Agriculture/Economic Research Center, clearly demonstrated that Americans drank nearly 2.5 more soda than milk (49). However, soda consumption has also been related to chronic diseases risk (50-52).

CONCLUSIONS

Based on the current evidence, it is possible that milk/dairy products, when consumed in adequate amounts and, mainly, with reduced fat content, have a beneficial effect on the prevention of important chronic diseases, as hypertension and diabetes. The role of milk/dairy products, as well as calcium intake, in the development of prostate cancer, is relatively unclear at this point. However, it may be prudent for men to avoid very high intakes of milk/dairy products, which would not be a problem for most individuals. Considering that milk is an important source of several nutrients, such as protein, calcium, magnesium and potassium, health professionals and researchers can safely advise that the consumption of adequate amounts of low-fat milk/dairy products should be part of a healthy diet.

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