Relation Between Dietary Calcium and Vitamin D and Risk of Diabetes and Cancer: A Review and Perspective

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ABSTRACT

The number of people with type 2 diabetes mellitus has been increasing worldwide. In experimental animal studies, calcium and vitamin D have been shown to improve pancreatic β-cell function and peripheral insulin sensitivity and several epidemiologic findings, including our own, have shown that calcium and vitamin D intake may have a preventive effect against type 2 diabetes. Evidence has also accumulated in support of a protective role of calcium and vitamin D against carcinogenesis of several types of cancers. Intriguingly, diabetes has been revealed to be a cancer risk factor in recent years, and we have reported crucial data in regard to this issue based on a longitudinal survey of a middle-aged and older Japanese population. In this brief review article, we attempt to elucidate the fundamental relationship between dietary calcium and vitamin D intake and the risk of diabetes and cancer, and we propose a model to provide new insight into mechanisms of pathogenesis of these lifestyle-related diseases.

Keywords: Calcium, vitamin D, type 2 diabetes, cancer, colorectal cancer

INTRODUCTION

The number of people with type 2 diabetes mellitus has been increasing worldwide, and the estimated worldwide prevalence was 2.8% in 2000 and is predicted to be 4.4% in 2030 [1]. According to a national survey, the prevalence of diabetes in Japan has rapidly increased during the past two decades [2], and thus the prevention of diabetes is of much greater importance than in the 20th century. Insight into the role of dietary factors in the development of diabetes may provide clues as to ways of preventing it. In experimental studies, calcium and vitamin D have been shown to improve pancreatic β-cell function and peripheral insulin sensitivity [3–5]. Several epidemiologic findings, including ours [6], have also shown epidemiologic relevance to this issue (ie, intake of calcium and vitamin D may hold preventive effects to type 2 diabetes).

Similarly, evidence has accumulated in recent years in support of a protective role of calcium against carcinogenesis of several types of cancers, including colorectal cancer [7–9] and pancreatic cancer [10]. Vitamin D may decrease cancer risk by various mechanisms, including by regulating cell proliferation and differentiation, inducing apoptosis, and inhibiting angiogenesis [11, 12]. Intriguingly, diabetes has been shown to be a risk factor for cancer in recent years [13] (with the sole exception of prostatic cancer [14]), and we also have reported crucial data in regard to this issue based on a longitudinal survey of a middle-aged and older Japanese population [15].

In this brief review article of the literature, we attempt to elucidate a fundamental relationship between calcium intake, vitamin D intake, and risk of diabetes and cancer, and we propose a model providing new insight into mechanisms of pathogenesis of these lifestyle-related diseases.

DIETARY CALCIUM, VITAMIN D, AND RISK OF DIABETES

The number of people with type 2 diabetes has been increasing both worldwide [1] and in Japan [2]. In experimental animal studies, calcium and vitamin D have been shown to improve pancreatic β-cell function and peripheral insulin sensitivity [3–5]. However, evidence in regard to this issue in humans has been mainly derived from cross-sectional studies [16], and little evidence has been obtained from prospective studies. Two cohort studies found a moderate, but not statistically significant association between dietary calcium intake and risk of diabetes [17, 18]; however, there was a statistically significant association between supplemental calcium intake and reduced risk of diabetes. A high intake of dairy foods, a major food source of calcium, has been shown to be associated with a lower risk of type 2 diabetes [17–20]. Similarly, vitamin D intake in the form of a supplement [17] or a supplement plus diet [21], but not diet alone, has been found to be associated with a lower incidence of diabetes. A prospective study in Finland showed an inverse association between serum 25-hydroxyvitamin D (25-OHD) concentrations and risk of type 2 diabetes [22]; however, a large-scale, randomized controlled trial of calcium plus vitamin D3 supplementation in women conducted in the United States [23] showed no
reduction in the risk of developing diabetes over a 7-year follow-up period.

Since the average daily calcium consumption by the Japanese population is relatively low [8, 24], we conducted a population-based prospective analysis to elucidate the relation between calcium, vitamin D, and dairy food intake and the risk of type 2 diabetes in a Japanese large-scale cohort [6]. We also assessed their combined effect on the risk of type 2 diabetes. The subjects were 59,796 middle-aged and older men and women who participated in the Japan Public Health Center-based Prospective Study [25] and had no history of type 2 diabetes.

During a 5-year follow-up period, 1,114 participants were newly diagnosed with diabetes (634 men [2.4%], 480 women [1.4%]). Overall, calcium intake was not associated with a significantly lower risk of type 2 diabetes; the multivariable odds ratio for the highest quartile vs. the lowest quartile was 0.93 (95% CI 0.71–1.22) in the men and 0.76 (95% CI 0.56–1.03) in the women. However, calcium intake was inversely associated with diabetes risk among the participants with a higher vitamin D intake; the odds ratio for the highest intake category vs. the lowest intake category was 0.62 (95% CI 0.41–0.94) in the men and 0.59 (95% CI 0.38–0.91) in the women [6]. Dairy food intake was significantly inversely associated with a risk of type 2 diabetes. In models in which adjustments were made only for age and participating public health center area, the odds ratio for the highest intake category vs. the lowest intake category was 0.65 (95% CI 0.49–0.88; P = .007 for trend) for dairy products as a whole, 0.79 (95% CI 0.64–0.97; P = .02 for trend) for milk, 0.94 (95% CI 0.68–1.30; P = .71 for trend) for cheese, and 0.72 (95% CI 0.55–0.93; P = .04 for trend) for yogurt [6]. No significant association was found between daily protein intake and risk of diabetes in the men [6].

A stratified analysis according to vitamin D intake (Figure 1) showed that the inverse association between calcium intake and the risk of diabetes was more pronounced among subjects who consumed the median or a greater amount of vitamin D; the odds ratio (95% CI) for the highest quartile vs. the lowest quartile of calcium intake was 0.62 (0.41–0.94; P = .050 for trend) in the men and 0.59 (0.38–0.91; P = .043 for trend) in the women. By contrast, calcium intake was not associated with a risk of diabetes in the lower vitamin D intake group of either sex; the P-value for the interaction between calcium (continuous) and vitamin D (dichotomous) was 0.02 and 0.06 in the men and the women, respectively. Our findings [6] suggest that calcium intake and vitamin D intake may not be independently associated with the risk of type 2 diabetes, but that the effect of those two nutrients against type 2 diabetes may be interactive.

A noteworthy finding in our study is that a clear inverse association between calcium intake and risk of diabetes was observed in the higher, but not in the lower vitamin D intake subgroup [6]. This finding is consistent with the hypothesis that calcium and vitamin D act jointly to protect against type 2 diabetes. In a prospective study of nurses conducted in the United States [17], a combined daily intake of >1200 mg of calcium and >800 IU of vitamin D was found to be associated with a 33% lower risk of type 2 diabetes than a daily intake of ≤600 mg and ≤400 IU, respectively. The benefit of the two nutrients, however, appeared to be additive in this U.S. population.

In our study we found a marginally significant reduction in the risk of type 2 diabetes associated with the highest intake of calcium and dairy products in women, but not in men [6]. This sex-related difference in association may be attributable to the difference in baseline characteristics in this cohort, in which the women had a higher median daily calcium intake (546 mg) than the men (404 mg). If a clear risk reduction is observed only above a certain intake level, a lower intake of calcium and dairy products by the men than by the women could explain the observed difference in association. Several intervention studies, including the one mentioned above, have examined the effects of a combined intake of calcium and vitamin D on the risk of type 2 diabetes, and their results have been inconsistent. More specifically, daily

![Figure 1](image-url)
supplementation with 400 IU of vitamin D and 1000 mg of calcium did not reduce the risk of type 2 diabetes over a 7-year follow-up among subjects with normal or impaired fasting glucose levels [23].

We found statistically significant inverse associations between the intake of dairy foods and the risk of type 2 diabetes in age- and area-adjusted analyses in women, but the associations were attenuated after multivariate adjustments. An inverse association with type 2 diabetes has been reported for the intake of dairy foods in both men [19] and women [17], for intake of low-fat dairy foods in women [18, 20], and for yogurt intake in both men [19] and women [20].

Vitamin D intake was found to not be independently associated with the risk of type 2 diabetes in our study. Two prospective studies have shown an inverse association with supplemental [17] and total [21] vitamin D intake, but not with dietary vitamin D intake [17, 21]. A possible explanation for the lack of association with dietary vitamin D in our own and other studies is that because sunlight-induced cutaneous synthesis of vitamin D also contributes to systemic vitamin D levels [4], dietary vitamin D intake alone may not account for overall vitamin D status. The data obtained in our study population [6] do not enable an examination of the contribution of dietary vitamin D intake to the circulating 25-OHD concentration, an indicator of systemic vitamin D status. However, a study of Japanese women conducted in winter [26] showed that women who frequently consumed fish, a rich source of vitamin D, had a higher mean blood 25-OHD concentration than those who consumed fish infrequently. Thus, dietary vitamin D intake can be used to rank members of a population according to a systemic vitamin D status, at least when the amount of sunlight-induced cutaneous synthesis of vitamin D is low.

Regarding glycemic status itself, an association between 25-OHD levels (in plasma and serum) and current [27] and future [28] insulin resistance has been reported in a cross-sectional study [27] and a prospective study [28], respectively, and one of the studies found that lower levels predict future higher glycemia [28].

The precise mechanisms by which calcium and vitamin D exert their glucose-lowering effects are unclear. Calcium is essential for insulin-mediated intracellular processes, and intracellular calcium levels are tightly controlled within a narrow range to maintain insulin signaling [29]. It is especially noteworthy that calcium ions have been inferred to play a crucial role in insulin secretion through voltage-gated Ca2+ channels [30] and channels of the large transient receptor potential (TRP) superfamily [31, 32]. In addition, calcium deficiency leads to the secretion of parathyroid hormone (PTH) and increases calcium inflow from the extracellular fluid into intracellular regions, resulting in a cellular calcium overload and impaired insulin sensitivity [5, 33]. Epidemiologic studies have shown a positive association between calcium intake and insulin sensitivity [34–36].

Pancreatic islets have vitamin D receptors (VDRs) [37], suggesting a role for vitamin D in insulin secretion. Its effect on β cells is to increase the insulin response to glucose stimulation, and it does not affect basal insulin secretion [38]. A study in a mouse model with nonfunctioning VDRs showed that both the serum insulin concentrations and cellular insulin mRNA levels were reduced in comparison with wild type mice, and that their blood glucose levels were increased [39], and it was suggested that the effect of vitamin D on insulin secretion and synthesis is independent of the effects of calcium levels [39].

Systemic inflammation has been found to be increased in obesity and type 2 diabetes [40]. Vitamin D may reduce the insulin resistance in these conditions by its anti-inflammatory effects [3]. The vitamin D deficiency observed in obese subjects [41, 42] is thought to be accounted for by deposition of vitamin D in fat stores, where it becomes less bioavailable [43]. Vitamin D-deficient obese subjects also have elevated PTH levels [3] and increased PTH can decrease insulin sensitivity, as stated above. In this regard, it is interesting that a recent study revealed that the PTH concentration depended on the concentration of ionized calcium only in subjects with higher 25-OHD levels, whereas in those with lower levels it depended only on the 25-OHD values [44].

Vitamin D is also involved in regulation of the effect of insulin [3, 4]. The 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3), an active form of circulating vitamin D, binds to the VDR and upregulates insulin receptor expression, resulting in improved insulin sensitivity [45, 46].

Moreover, since vitamin D facilitates calcium absorption in the intestines [47], vitamin D and calcium may act synergistically to reduce the risk of type 2 diabetes. Dairy foods rich in calcium may decrease the risk of diabetes through calcium-related mechanisms. In addition, milk protein induces the release of insulinogenic amino acids and the peptide hormone incretin, both of which augment insulin secretion [48].

The inverse association between calcium intake and risk of type 2 diabetes in persons with a higher vitamin D intake suggests that these nutrients may act jointly, rather than independently, in lowering the risk of type 2 diabetes.

**DIETARY CALCIUM, VITAMIN D, AND RISK OF CANCER**

Evidence that supports a protective role of calcium against carcinogenesis of several cancers, including colorectal cancer [7–9] and pancreatic cancer [10], has accumulated in recent years. Vitamin D may decrease cancer risk by various mechanisms, including regulating cell proliferation and differentiation, inducing apoptosis, and inhibiting angiogenesis [11, 12].

Colorectal cancer is a major cause of cancer death worldwide [49] and in Japan [13, 50]. Colorectal cancer mortality has sharply increased in Japan since the end of World War II [50] and is now among the highest in the world [51]. Experimental data [11, 12] have shown that calcium has an anticarcinogenic effect in the colon and rectum. A preventive
role of vitamin D against human colorectal carcinogenesis was first proposed [53] based on an observation of higher incidences of colorectal cancer mortality in regions with low solar radiation levels, a finding that has been replicated in several studies, including studies reported in recent articles from the United States [53] and Japan [54].

Some of the molecular mechanisms involve the following: 1,25-(OH)2D3, when bound to the high-affinity nuclear VDR, regulates cell growth and differentiation in multiple normal and malignant cell types. For example, 1,25-(OH)2D3 exerts antiproliferative effects in breast cancer cells that are thought to result from changes in cell-cycle regulators, such as p21WAF1/CIP1, p27kip1, cyclins, and the retinoblastoma tumor suppressor protein [55]. Studies have shown that 1,25-(OH)2D3 inhibits the growth and promotes the differentiation of colon carcinoma cells [56].

In line with these observations, one of the authors of this review investigated whether these nutrient intakes are associated with the risk of colorectal cancer [7] based on data from a case-control study in Japanese men and women, a population that consumes a diet high in vitamin D but low in calcium [24]. Special consideration was given to occupational and leisure-time physical activities as a surrogate for sunlight exposure and the potential effect modification of calcium intake by vitamin D status. The subjects were participants in a large-scale, case-controlled study in Fukuoka, Japan [7, 57]. The results of a multivariate analysis with adjustment for potential confounding variables showed that calcium intake was significantly inversely associated with risk of colorectal cancer (P for trend = .01); the odds ratio for the highest quintile vs. the lowest quintile of calcium intake was 0.64 (95% CI 0.45-0.93) [7]. Higher levels of dietary vitamin D were significantly associated with a decreased risk of colorectal cancer among those who had fewer opportunities for sunlight exposure at work or in leisure activities (P for trend = .02) [7]. A decreased risk of colorectal cancer associated with high calcium intake was observed among those who had higher levels of vitamin D intake and among those who had greater opportunities for daily sunlight exposure, but not among those with a medium or lower level of vitamin D intake or among those with potentially less sunlight exposure [7]. These results add support to the possibility of joint action between calcium and vitamin D in the prevention of colorectal carcinogenesis.

DIABETES AND RISK OF CANCER: A BRIEF REVIEW

Although an association between diabetes and cancer has long been speculated, no conclusive evidence had been obtained until recent years. We prospectively examined the data in the Japan Public Health Center-based Prospective Study [25] and showed an association between a history of diabetes and subsequent risk of cancer [15]. Similar results have been obtained in other Asian [58] and Western [59] nations.

These associations are likely to be the result of the metabolic and hormonal abnormalities in diabetes, which should include biological mechanisms common to carcinogenesis and at least in part related to insulin and insulin-like growth factors (IGFs) [60–62]. The most salient changes in diabetes are reduced insulin sensitivity with compensatory hyperinsulinemia and elevated IGF-1 levels, which may in turn stimulate cell proliferation.

The mechanisms of the association between insulin resistance and cancer risk were first proposed in regard to the pathogenesis of colon cancer [62, 63], and subsequently expanded to include the pathogenesis of cancer of the breast, pancreas, and endometrium, which have been reviewed in detail [13, 64].

In addition, hyperglycemia per se may have promoting effects on carcinogenesis [58, 59], as inferred in our previous report regarding hepatocellular carcinoma [65], in which the effects of a high glucose state and overweight appeared to be the main contributors to the association between the metabolic factors in aggregate and an increased risk of hepatocellular carcinoma in the study population. Diabetes is characterized by an increased oxidative stress, and hyperglycemia is thought to generate oxidative stress in a variety of cells via various metabolic pathways, thus causing DNA damage, the initial step in carcinogenesis [66].

SUMMARY AND PERSPECTIVE

Much evidence has accumulated of a complex but definite relationship between calcium regulation, diabetes, and carcinogenesis, as we have discussed. After sorting out the current epidemiologic information, we devised a model that illustrates the underlying cause-effect relationship between calcium regulation and diseases (Figure 2). It is interesting that insulin secretory capacity [67], as well as the risk of prostate cancer [68], the risk of which is decreased in diabetic men possibly because of their lower testosterone levels [69, 70], has been reported to be regulated by VDR polymorphism. In this regard it should be mentioned that a recent paper has reported a possible direct interaction between the vitamin D concentration and diabetes [71]. Moreover, it is noteworthy that diabetes susceptibility genes are also associated with several types of cancers (eg, colorectal cancer [72] and prostate cancer [73]). Coffee consumption as well as physical activity may have an effect to carcinogenesis and diabetes in common, because incidence of many cancers is inversely associated with both factors [13] and so is the incidence of diabetes. We have previously reported that coffee consumption is inversely associated with prevalence or incidence of abnormal glucose regulation or diabetes [74–76].

In summary, it is particularly important that calcium intake and vitamin D intake are inferred to modulate glucose metabolism and preexisting metabolic processes that lead to diabetes, and that these inferred effects are likely to be mediated by their combined effects on both insulin secretion and insulin sensitivity, since diabetes itself is a risk factor not only for micro- and macrovascular complications of diabetes but also for malignant neoplasms as stated above. Further epidemiologic and basic research is necessary for us to
command an overview of this vast and yet to be fully explored field of calcium regulation and pathogenesis of lifestyle-related diseases.

Abbreviations: CI, confidence interval; HR, hazard ratio.

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