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The Western-Style Diet, Calcium Deficiency and Chronic Disease

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Abstract

The term "Western-style diet" refers to an eating pattern that includes a high content of saturated fat, a large amount of processed carbohydrate and excess total calories. The Western-style diet contributes to the growing epidemic of obesity and several age-related, chronic illnesses seen in the United States and throughout the world. In addition to its high content of fat and sugar, the Western diet is also characterized by a deficiency in calcium (and, undoubtedly) other trace minerals that are nutritionally associated with calcium. While epidemiological evidence suggests that the lack of adequate dietary calcium contributes to several chronic ailments associated with the Western-style diet, studies in experimental animals provides direct evidence. Rodents on a high-fat, low-calcium diet suffer many of the same chronic illnesses that are seen in humans. When the calcium concentration is increased to the level found in rodent chow diets, the ill-effects are mitigated. While calcium alone is protective, a combination of calcium and additional trace elements has been shown, in some studies, to induce even better protection. The implication is that providing an adequate supply of essential minerals (including calcium, of course, but also other trace elements that support calcium's beneficial activities), either through dietary modification or as a supplement if dietary modification fails should be considered as part of an overall strategy for counteracting the negative effects of the Western-style diet.

Keywords: Calcium; Cancer; Cationic trace elements; Chronic disease; Western-style diet

Introduction

The term "Western-style diet" refers to an eating pattern that includes a high content of saturated fat, a large amount of processed carbohydrate and too many calories. Red meat, processed meat products, refined grains and starch (potatoes) are mainstays of the Western-style diet. High-fat dairy products are another component of the typical diet consumed in many Western countries. Fruits, vegetables, legumes, fish, other seafood and whole grains are, generally, under-consumed. While the Western-style diet is commonly assumed to be "unhealthful," there are numerous variations in what is actually consumed by any given individual (as is true of any diet). Not all eating patterns are equally bad. In, perhaps, its worst form, added fat from seed oil extractions and added highly-refined carbohydrate, i.e., sugar- (empty calories) make up a significant percentage of the overall calorie intake. At one time largely associated with individuals in North America, Europe and countries of European descent, the Western-style diet is now a world-wide phenomenon. The Western-style diet underlies the growing epidemic of obesity in the United States and throughout the world [1,2]. It is thought to contribute to the increasing incidence of several chronic illnesses including cancer (especially colon and liver), cardiovascular disease and metabolic disease (e.g. type II diabetes) [1,3,4]. The Western-style diet has been linked to chronic kidney disease [5], non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) [6,7] and osteoporosis [8]. A recent study has shown an association between the Western diet and early-onset dementia [9]. A role in inflammatory skin diseases (acne, psoriasis, atopic dermatitis) has also been suggested [10].

There is little doubt of the relationship between the Western-style diet and the chronic diseases indicated here. What is not clear, however, is how the food components that make up the Western-style diet (either individually or together) bring about their detrimental effect on health. Is it entirely related to the high content of saturated fat and processed carbohydrates? The hypothesis we put forward here is that the Western-style diet, with its high content of processed fat and carbohydrate and, most concomitantly, its relative lack of unprocessed fruits, vegetables and whole grains, leads to a deficiency in essential minerals along with the vitamin co-factors necessary for proper mineral metabolism. The Western-style diet, we hypothesize, is detrimental to health as much by its lack of essential minerals as by what it contains.

The western-style diet, calcium-deficiency and chronic illness

While the Western-style diet includes a large amount of saturated fat and processed carbohydrates, there are additional nutritional features associated with this diet. Fiber, folic acid and choline are under-represented. With a deficiency in methyl group donors, the diet has characteristics of the "choline-deficient, amino acid-defined (CDAA) diet [11]. Additionally, and perhaps most importantly, the Western-style diet is deficient in calcium and vitamin D. With regard to calcium, per se, the recommended intake for adolescents and adults is in the range of 1000-1300 mg per day [12-14]. However, the average intact for many individuals in Western society is lower. Kudlacek et al. [15] reported in 2003 that the average calcium intake among a sample of over one thousand individuals in Austria was 560 mg per day. Many individuals, of course, had much lower intake. A similar pattern in the United States was reported a few years later [16]. The authors of both studies concluded that low calcium intake was more wide-spread than previously thought. In the ensuing decade, the situation has not changed for the better. In its most recent summary of critical nutrients,

the USDA concluded that a high percentage of individuals in multiple age groups failed to reach minimal recommended calcium intake [17].

A calcium deficiency is independently associated with numerous chronic diseases-i.e., with many of the same diseases noted here [18-22]. While bone loss and osteoporosis is the obvious example, the relationship between calcium intake and colon cancer may be particularly instructive. Interventional trials have demonstrated that calcium supplementation can lower the incidence of recurrent colon polyp formation, although the reduction is modest [23-25], and not all studies have confirmed reduced incidence [26,27]. Numerous epidemiological studies have shown a correlation between higher calcium intake and reduction in colon cancer risk [28-32]. While not every study has established a statistically-significant protective relationship, meta-analysis of past findings supports a positive correlation (i.e., reduced polyp incidence with increased calcium intake) [33] and a recent analysis suggest that protection extends to colon cancer itself [34].

Work with epithelial cells in culture provides mechanistic insight [35-38]. Epithelial cells from various sources (including the colon) proliferate optimally over a broad range of low-calcium concentrations (0.05-0.5 mM). Under these conditions, cells do not express features of the differentiated state. As the calcium concentration is increased above 0.5 mM, differentiation is induced. Key features include induction of E-cadherin synthesis; its translocation from the cytoplasm to the cell surface; and formation of the cell surface adhesion complex. This process is readily reversible. When calcium is removed, cells revert to an undifferentiated state. This is depicted in Figure 1.

Two consequences of calcium-induced differentiation include: i) reduced proliferation and ii) formation of the epithelial barrier. In regard to proliferation, β-catenin is sequestered in the adhesion complex along with E-cadherin. This leads to decreased β-catenin movement into the nucleus where it otherwise functions as a Wnt-pathway (growth-promoting) enhancer [36-38]. The end-result is decreased proliferation. Equally important, E-cadherin - mediated cell-cell cohesion allows the differentiated epithelial cells to form a cohesive cell sheet (Figure 1). This is essential for barrier protein synthesis and formation of barrier structures (tight junctures and desmosomes) [39]. Defective barrier function in the gastrointestinal tract and chronic inflammation go "hand in hand". Commonly, it is thought that chronic inflammation is responsible for barrier breakdown, but it is more likely that poor barrier function contributes to the tendency toward inflammation [40]. In the absence of an effective barrier, bacteria, bacterial products, toxins and food allergens can all gain access to the interstitium. Inflammation in the gastro-intestinal tract and carcinogenesis in the colon are linked [41] and decreased inflammation can contribute to reduced tumor incidence with calcium. While calcium-induced tumor suppression could reflect a direct action on intracellular (growth-regulating) signaling pathways or result from inhibition of chronic inflammation in the gastrointestinal tract, these are not the only ways in which calcium might act. Calcium may be anti-carcinogenic by altering luminal pH with an effect on the microbial community [42] or by precipitating carcinogenic bile acids in the gastrointestinal tract [43]. These mechanisms are not mutually exclusive.

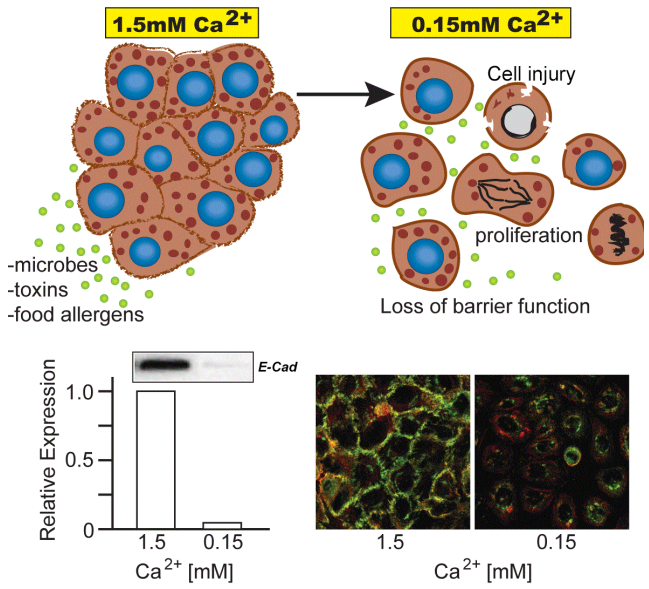

Figure 1: The cartoon depicts a cohesive sheet of epithelial cells in the presence of 1.5 mM calcium. When the extracellular calcium level is reduced to 0.15 mM, there is a rapid change in cell shape and a loss of cell-cell cohesion. This change can be seen within minutes. Subsequently, some of the cells undergo proliferation. Other cells undergo injury. In addition, there is a loss of barrier function. Microbes, toxins, allergens etc. penetrate the interstitium. The lower panels of the figure demonstrate changes in E- cadherin production/expression by epithelial cells in response to alterations in extracellular calcium. A rapid loss of total E-cadherin can be seen by Western blotting (left panel) and loss of E-cadherin from the cell surface (right panel) occurs, resulting in dis-cohesion.

There is little doubt of the importance of calcium to effective growth regulation (by whatever mechanism) in the colon. Ultimately, however, the question is not whether calcium has beneficial properties, but whether the level of calcium in the Western-style diet is sufficiently low as to obviate any of these potential mechanisms by which calcium could affect tumor formation in the colon. Studies in experimental animals have begun to address this issue. Newmark et al. [44-46] maintained C57BL/6 mice on a rodent version of the Western-style diet for 18-24 months. A higher incidence of precancerous colon polyps was observed in these animals than in littermates maintained on a rodent chow diet for the same period (29% incidence versus 12%). When calcium (reduced from 5.25 mg/kg in the rodent chow diet to 0.41 mg/kg in the Western diet) was replenished to the level of the rodent chow diet, the adenoma incidence was reduced to near-background levels. When other modifications of the Western diet (low fiber, folate and choline; and replacement of methionine with cysteine) were adjusted to conditions in the control diet, there was no mitigation of polyp formation. In a subsequent study using mice containing a mutated adenomatous polyposis coli (APC) gene, a similar trend was observed; that is, there was a higher incidence of colon polyps (as well as tumors in other sites) in Western diet-fed mice than in controls. As seen with C57BL/6 mice, the combination of calcium and vitamin D provided significant protection [47]. The same combination has also

been shown to suppress formation of pre-neoplastic colon lesions induced by the strong carcinogen, azoxymethane [48].

Using a similar approach to Newmark's, our own studies examined the effects of a calcium-rich, multi-mineral natural product (Aquamin®) derived from the skeletal remains of red marine algae on colon tumor formation in C57BL/6 mice. Consistent with the findings of Newmark et al. [44,46] we also demonstrated a significant reduction in tumor incidence with mineral supplementation [49,50]. In our studies, animals maintained on a rodent chow diet, had a colon polyp incidence of 18% (16 of 90 mice).

In animals fed a Western-style diet without the mineral supplement, the incidence of polyp formation was 29% (26 of 90) while in littermates fed the Western-style diet with supplementation, the incidence was 2% (2 of 90). Of note, when the tumors were examined histologically, several of the lesions in the Western diet-fed mice proved to be invasive carcinomas. No invasive tumors were seen in mice fed either the rodent chow diet or the calcium-supplemented Western-style diet. These data, thus, suggest that supplementation may affect tumor progression as well as tumor formation. Also of note, all of the diets in our studies contained vitamin D (120 IU/kg), suggesting that in the absence of an adequate supply of calcium, this amount of vitamin D, by itself, was not effective.

Although suppression of growth-regulating signaling pathways or effects on carcinogenic bile acids might explain anti-carcinogenicity in the colon, a reduction in chronic inflammation could have broader effects. Our own studies not only demonstrated reduced colon polyp formation but also showed that mineral supplementation protected mice against bone loss [51,52] and reduced the incidence and severity of ulcerative dermatitis [53]. Perhaps most interesting, during the course of our studies, we observed a high incidence of liver tumor formation in mice on the Western-style diet [54]. Unlike what was observed with colon polyps (where both males and females were susceptible), virtually all of the liver tumors were in males. When these lesions were examined histologically, they encompassed a wide range of presentations - from large non- regenerative and regenerative hyperplastic nodules to premalignant hepatic adenomas and fully-malignant hepatocellular carcinomas. Other manifestations of liver injury, i.e., inflammation, and ballooning degeneration of hepatocytes, along with areas of necrosis and fibrosis - were also observed. In male mice on the mineral-supplemented Western diet, tumor formation was substantially reduced (48% incidence without supplement versus 12% incidence in supplement-fed mice, against a background incidence of 16% for male mice on the rodent chow diet). Inflammation and hepatocyte necrosis were also reduced.

As part of the study, serum calcium levels were assessed in mice from each diet group. In male mice on the supplemented Western-style diet, the average calcium level was 10.1 ± 0.7 mg/dl, while in mice on the un-supplemented diet; the average was 9.5 ± 1.3 mg/dl. Since serum calcium levels are tightly controlled between approximately 9-10 mg/dl, these values put the calcium-supplemented animals at the high end of the normal range while the un-supplemented mice were at a level midway between the upper and lower normal range values. In the same study, male mice maintained on rodent chow diet (containing a comparable amount of calcium to that in the supplemented Western diet [5.25 mg/kg of diet]) also had serum calcium levels at the upper end of the normal range (9.9 ± 1.3 mg/dl). Of interest, female mice had higher levels of serum calcium than males under all conditions. In females, serum calcium levels were 10.9 ± 1.3 mg/dl, 10.9 ± 1.0 mg/dl and 11.4 ± 0.8 mg/dl on the un-supplemented and supplemented Western-style diets and rodent chow diet, respectively). Thus, liver disease and low serum calcium values appear to be correlated.

Of interest, while liver injury was confined almost entirely to males, both male and female mice on the Western-style diet gained excess weight, and demonstrated serum chemistry abnormalities. These were not affected by calcium-supplementation.

Thus, we hypothesize that it is not up-stream consequences of the Western diet that are mitigated by calcium, but the later events that produce overt injury. While our studies may have been the first to document the beneficial effects of calcium in the liver, previous studies have shown a reduction in liver fibrosis by vitamin D [55]. The beneficial effects of vitamin D were presumed to reflect interference with transforming growth factor-β signaling, with little regard to its role in calcium uptake and utilization.

If these findings can be extrapolated to humans, they open up a new avenue for prevention of liver injury occurring as a consequence of poor nutrition. A public health strategy that focuses on preventing the consequences of fatty liver disease rather than targeting the formation of fatty changes per se may prove to be more effective.

Certainly, targeting down-stream consequences of steatosis along with steatosis, itself, should be considered. Finally, while these findings are in the context of the Western- style diet, liver injury due to viral infection as well as alcoholic liver disease may also be amenable to a similar interventional approach. The up-stream initiators of tissue damage are different, but all share common, down-stream patho-physiological mechanisms [56].

How circulating calcium protects the liver is not fully understood. We postulate a similar mechanism to what has been suggested in the colon - i.e., that in the presence of calcium, hepatocyte differentiation occurs, limiting excessive proliferation (and injury), while promoting barrier formation (Figure 1). This, of course, will need to be established experimentally.

Calcium supplementation to mitigate health consequences of the western-style diet: Possibilities and limitations

To the extent that the Western-style diet is a problem of calcium-deficiency, the solution would seem obvious - provide a sufficient amount of calcium, preferably as part of a healthful diet, but as a supplement where dietary improvement fails. The use of calcium supplements (alone and in conjunction with other nutrients) is already widespread. Their primary use is in prevention of bone loss and osteoporosis, but people utilize calcium supplements to reduce risk of colon polyp formation or to mitigate other health concerns. Without minimizing the value of calcium supplementation, there are a number of issues that should be considered. Beyond the usual - bioavailability and tolerability - is the potential for adverse consequences at high doses. For example, a meta-analysis of calcium supplement use data concluded that a risk of cardiovascular events did exist for the highest doses of supplement use [57]. An association between calcium supplement intake (self-reported) and macular degeneration in the elderly has also been reported [58]. Perhaps more troubling is the positive correlation in some studies between calcium intake and prostate cancer [59-61]. Whether the benefits of calcium supplement use outweigh potential risks has to be determined; sometimes on a case by case basis. Equally important is the reality that no critical nutrient, including calcium, functions in a vacuum. How well calcium from any source performs depends on the presence (at appropriate levels) or

absence of other nutrients. Importance of vitamin D to calcium uptake from the gastrointestinal tract and at the cellular level is well-known [18-21].

Less well-known but, perhaps, equally important is the level of other important minerals. Magnesium, for example, has little chemo-preventive activity by itself, but the ratio of magnesium to calcium has been shown to be important for calcium chemoprevention in the colon [62]. Magnesium is probably not unique. However, since magnesium is present in substantial amounts, it is possible to establish this interaction by creating an experimental deficiency and measuring the consequences. This is not the case with other potentially important divalent or trivalent cationic trace elements; some of which are present in truly "trace" amounts. The lanthanide elements constitute one such group. The lanthanides, because of their similarity to calcium in terms of orbital size and electronic configuration [63,64], interact with calcium-binding sites on proteins, often with higher affinity than calcium itself. Calcium channel proteins [65-67] and proteins that are part of calcium-exchangers [68] have been shown to bind lanthanide elements - leading to either enhanced or inhibited function (altered calcium influx-efflux). The extracellular calcium-sensing receptor (CaSR) is another calcium-binding protein capable of high-affinity lanthanide binding [69-71]. This protein, which is sensitive to tiny changes in the extracellular calcium concentration, plays a critical role in colon epithelial cell growth control [72-76]. Our own past studies have shown that in the presence of gadolinium (lanthanide family member), there is a "left-shift" in the response to calcium. That is, CaSR is up-regulated [73,74] and growth-suppression occurs at lower calcium concentrations than would otherwise occur [77].

While many experimental approaches have utilized gadolinium as a representative of the lanthanide family, we conducted a survey study in which all 14 naturally-occurring lanthanide elements were compared for ability to suppress epithelial cell proliferation [78]. Only three members in the entire family (terbium, dysprosium and ytterbium) failed to have significant activity at a concentration of 100 μM. At the other extreme, the most potent lanthanides (thulium, gadolinium and samarium) had activity at 5-10 μM. The capacity to modify response to calcium was not seen with several other divalent or trivalent cationic trace elements including aluminum, iron (ferrous and ferric), cobalt, copper, nickel, magnesium, manganese and zinc. Thus, the lanthanides appear to function through a mechanism that is not shared by many other cationic trace elements. This is not to suggest, however, that the lanthanides are unique. Two relatively abundant cationic elements (barium and strontium) are CaSR activators [70,71,79]. Of interest, it appears that strontium activation of CaSR and activation by calcium do not lead to identical signaling events-providing a rationale for potential co-operativity [80].

The question is not whether certain minor trace elements can modulate responses to calcium, but whether they are present (as a group) at circulating levels or tissue levels sufficient to accomplish this task *in vivo*. With the lanthanides, at least, this question will be difficult to address since the *in vivo* levels of individual lanthanide elements are low and not routinely measured. One can assume, perhaps, that since many of these trace elements are nutritionally associated with calcium, a diet that is deficient in calcium might also be deficient in these other trace elements, as well. The implication is that the mineral composition of a healthy diet cannot easily be duplicated in a supplement; no matter how well-thought-out it is. Alternatively, there are multi-mineral-containing natural products available, and it would be premature to suggest that these cannot provide benefit if used appropriately. In the interest of evidence-based medicine, additional studies will be needed to address this issue.

Conclusion

The Western-style diet has a number of features that make it unhealthy. While the focus of this work is on minerals (in particular, calcium), there is no doubt that the high content of saturated fat and processed carbohydrate underlies much of what is wrong with the diet. Our intent is not to minimize this. Rather, the intent is only to point out that in addition to saturated fat and processed carbohydrates; the Western-style diet is also lacking an adequate amount of calcium (and, presumably, other trace elements that are found in the same foods as calcium). A calcium-deficiency is an independent risk factor for many of the same chronic illness associated with the Western-style diet, and it is not unreasonable to hypothesize that the lack of dietary calcium (and, perhaps, other essential trace elements) may contribute to several of the chronic diseases associated with the Western-style diet. That having been said, what is the potential for mitigating these health issues by providing a supply of essential minerals (calcium, of course, but also other trace elements that support calcium's beneficial activities), either through dietary modification or as a supplement if dietary improvement fails? That, in our opinion, is still an open question, and one worth addressing.

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