Perspectives on obesity and sweeteners, folic acid fortification and vitamin D requirements

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This review summarizes three controversial areas of clinical practice that were discussed in many articles that appeared in the American Journal of Clinical Nutrition during the author’s tenure as editor in chief.

Controversy 1—obesity and high-fructose corn syrup. The increased frequency of obesity in the US is paralleled by increasing annual consumption of high-fructose corn syrup, an extracted sweetener that is routinely added to soft drinks and to many processed foods in the US diet. Metabolic studies implicate increased fructose consumption in increased body fat and obesity and with increased circulating triglyceride levels and hypercholesterolaemia in children.

Controversy 2—folic acid fortification and supplements. Together with widespread use of supplemental multivitamins, fortification of the US diet with folic acid has resulted in high serum folate levels in much of the population, which may be associated with increased risk of cognitive decline in ageing people with low vitamin B12 status, decreased natural killer T-cell immune function and increased risk of recurrent advanced precancerous colorectal adenomas and breast cancer.

Controversy 3—recommended intakes of vitamin D. Levels of serum 25(OH)D sufficient for fracture prevention are at least 75 nmol/l (30 ng/ml) but cannot be achieved by the current recommended dietary intakes in the US. A recent fracture risk prevention trial showed that the 4-year incidence of all cancers was reduced in US women who received high supplemental doses of both calcium and vitamin D.

Keywords. Obesity, folic acid, vitamin D.

Introduction

On June 30, 2007, I completed an 11-year term as editor in chief of the American Journal of Clinical Nutrition (AJCN). During my tenure, I was able to bring about a number of changes that are summarized in my swan-song editorial that appeared in the June 2007 issue.\(^1\) Between July 1996 and June 2007, the AJCN grew from 950 to 1270 original annual submissions, representing a spectrum of interest areas that included obesity, lipids, carbohydrate metabolism and diabetes, cardiovascular risk, nutritional status, vitamins, minerals, phytochemicals, pregnancy and lactation, growth and development, cancer, nutritional epidemiology and public health and bone metabolism. As the acceptance rate for new original manuscripts fell from 40% to 25% of submissions, the impact factor of the AJCN rose from an average of 3.4 to 6.5 citations for each published article, review and editorial. The most recent impact factor places the AJCN at the top of the list of all peer-reviewed journals related to nutrition and in the middle third of all published scientific journals. The truly international flavour of the AJCN is reflected in the origins of the authors. In 2006, 53% of published original articles came from the US and Canada, while there were 34% from Europe and the remainder from Australia, New Zealand and Asian countries. During my tenure, the AJCN focused on many areas of topical and controversial interest, that include the role of the changed composition of the American diet in the epidemic of obesity in the US, the benefits and potential risks of
folic acid fortification of the diet and changing concepts on the realistic human requirement for vitamin D as a vitamin essential for bone health. I have chosen these three controversies for greater discussion in view of their ongoing topical importance and relevance to both clinical nutrition and public health.

Controversy 1: obesity and high-fructose corn syrup

The incidences of overweight (BMI >25 kg/m² or >95th percentile for same age and sex weight in childhood) and adult obesity (BMI > 30 kg/m²) have increased at alarming rates over the past 15 years in the US and in many European and other developed countries. Statistics from the US Center for Disease Control and Prevention showed that 66.3% of US adults were overweight, including 32.2% who met the criteria for obesity in 2006, each representing a >10% rise in prevalence since 1994, whereas the prevalence of childhood overweight including obesity is nearing 20%. The conventional recognized causes of obesity include predisposing genetic abnormalities and a combination of habitual overeating with inadequate exercise. In a review article published in 2004, Bray and Popkin summarized evidence for a novel concept that the obesity epidemic is caused to a great extent by a shift in the American diet towards increasing emphasis on the use of high-fructose corn syrup (HFCS) as a sweetener. This concept was emphasized by the parallel relationship since 1975 between the increasing prevalence of overweight and obesity and the yearly consumption of HFCS, which represents half of all food sweeteners and is the sole source of sweeteners in soft drinks (Fig. 1). Subsequently, the same authors published a review that indicated that sweetened beverages constitute about half the daily fluid intake and 10% of the calories of the average adult American. As described by Michael Pollan, Professor of Journalism at the University of California Berkeley, increased consumption of HFCS can be traced to the US government’s long-standing food policy which mandates large financial subsidies to American farmers to produce grains including corn, which is used in the manufacture of HFCS that is added to many beverages and processed foods. Because of the US governmental subsidy, processed foods that contain HFCS can be marketed at lower prices than non-processed fresh foods. Coupling relative lower expense with their high caloric density and lower satiety properties, processed foods are in greater use by the poor, who are consequently at greater risk for obesity. Furthermore, a recent study by the US Department of Agriculture found that one in four US adults consumes high caloric fast foods and beverages at least once per day and are at greatest risk of obesity. Nutrition composition data from McDonald’s corporation, a leading purveyor of fast foods, show that a typical meal may include a ‘Big Mac’ hamburger with 540 kCal (with 9 g sugar) a small portion of French fries with 250 kcal and a 32 oz cup of Coca Cola with 310 kCal (all from 86 g sugar as HFCS).

Metabolic evidence for the weight gain and body fat-promoting effects of HFCS and understanding of their metabolic basis has been developed from animal and human experiments. For example, feeding a fructose solution in water increased both body and liver fat in mice compared to feeding a sucrose solution. Unlike glucose which is metabolized by the rate-limiting regulatory enzyme phosphofructokinase, dietary fructose is rapidly converted to glycerol which is the backbone of triglyceride, the circulating and storage form of body fat. In contrast to findings from feeding eucaloric glucose, studies of healthy human volunteers showed that the ingestion of a high-fructose meal at 30% of kCal resulted in lower post-prandial responses of leptin, a satiety hormone, and a higher response of ghrelin, a hormonal inhibitor of satiety, along with a greater increase in serum triglyceride levels. A recent review in AJCN describes the association of elevated uric acid, a principal product of fructose metabolism, with hypertension and renal dysfunction. A study of 74 Swiss children found an association of excessive intakes of fructose-rich sweets with elevated levels of small particle size low-density lipoprotein, which is a predictor of subsequent cardiovascular disease. Current trends in fructose consumption and its metabolic effects are summarized in a recent AJCN editorial. However, an opposing view holds that there is no convincing epidemiological or metabolic relationship between consumption of HFCS and weight gain and is summarized in the findings of a recent consensus conference. Clearly, more definitive prospective studies on the metabolic consequences of HFCS in human subjects will be required to settle this controversy.

Controversy 2: folic acid fortification and supplements

Folate, a water soluble vitamin, plays a central role in cellular metabolism by regulating nucleic acid incorporation into DNA and, in a vitamin B12-dependent reaction, is a methyl donor for methionine metabolism and the epigenetic regulation of the expressions of many genes. Clinically, folate deficiency is associated with abnormal embryonic development and increased risks of neural tube defects (NTDs), anaemia due to delayed generation of red blood cells, elevated homocysteine levels with increased risk for cardiovascular diseases and, owing to its interaction with vitamin B12, with increased risk of cognitive decline in ageing. On the basis of abundant evidence that newborn NTD that occurred
at a rate of 6 per 10,000 live births in the US are related to maternal folate deficiency. In 1998, the US government adopted a public health policy to fortify all grain products with folic acid at a dose of 150 μg/100 g, which was considered sufficient to increase daily folate intake to its requirement of 400 μg/day. Subsequently, the incidence of US newborn NTDs was reduced by about 20%, and the incidence of low serum folate levels (<3 ng/ml) in childbearing age women was reduced from 21% to less than 1% (Fig. 2). However, at the same time, the frequency of high serum folate level (>20 ng/ml) in children and older adults increased from 5 and 7% to 42 and 38%. Several studies have addressed concerns that elevated levels of circulating folate may have deleterious health effects. A study of immune function in postmenopausal women found that natural killer (NK) T-cell activity was influenced by the consumption of supplemental folic acid at levels of at least 400 μg/day. NK activity is important in defense against infection as well as surveillance and elimination of nascent cancer cells and was decreased by 25% of normal levels among women who consumed diets adequate in folate that were supplemented with folic acid, 78% of whom were found to have un-metabolized folic acid in the blood. Because of their metabolic interactions, both folate and vitamin B12 interact in protection against anaemia and cognitive decline. A study that evaluated relationships between vitamin B12 and folate status according to their serum levels in over 1500 elderly subjects found that low B12 with normal folate status (20% of the group) doubled the risk of anaemia from 3.5% to 7% and increased the risk of dementia from 18% to 25%. However, the incidences of anaemia and dementia in those with low B12 but high folate status due to supplement use (3.3% of the group) were significantly increased to 15% and 45% of subjects, respectively. Several recent large clinical trials have shown relationships between the use of supplemental folic acid and increased cancer risk. For example, a 10-year prospective study of more than 25,000 postmenopausal women found an overall 19% increased incidence of breast cancer among those taking supplemental folic acid, while there was a 32% increased risk of breast cancer among women in the highest quintile of folate intake from both diet and supplements. These data contrast with those from a 9-year prospective study of more than 11,000 subjects in Sweden, a country with no folic acid fortification, that showed a 40% decrease in breast cancer incidence in those receiving the highest dietary folate intake. A prospective study of more than 1000 men and women followed by colonoscopic surveillance for 10 years after surgical resection of colorectal cancer found a 52% greater risk of recurrent high-grade dysplastic adenomas in those taking folic acid supplements (10.9%), compared to those taking placebo (4.3%).

There are several postulated mechanisms for increased disease risk among individuals taking folic acid supplements with resultant high serum folate levels and
the frequent occurrence of un-metabolized folic acid in the circulation. First, since folic acid shares cellular transport mechanisms with physiological methylenetetrahydrofolate (MTHF) in most tissues, high circulating folic acid could compete for the cellular transport of MTHF that is necessary for normal metabolic reactions. In this regard, a recent study demonstrated that the gene expression levels of cellular folate transporters were reduced after incubation of human intestinal and renal cells with high concentrations of folic acid. Second, the presence of high intracellular levels of folic acid could promote the synthesis and utilization of higher levels of MTHF which, through its B12-dependent pathway for DNA synthesis, could deplete B12 that is ultimately required for brain uptake and maintenance of cognitive function. Third, while low levels of folate enhance DNA instability and may increase the initiation of cancer, excessively high folate levels may promote the proliferation of dormant cancer cells, especially in the context of reduced NK cell anti-cancer cell surveillance, resulting in a U-shaped cancer risk paradigm for both ends of the folate status spectrum. Fourth, high intracellular folate levels could promote enhanced gene methylation and silencing, which, in the case of tumour suppressor genes, would have the net effect of enhancing carcinogenesis. Much more needs to be learned about potential mechanisms for folic acid toxicity and cellular dysfunction.

Controversy 3: recommended intakes of vitamin D

The main physiologic function of vitamin D is to maintain calcium absorption and homeostasis in the body, and the principal signs of its deficiency are osteoporosis and bone fracture in adults, skeletal developmental deformity in newborns and maintenance of lower extremity function in the elderly. The forms of vitamin D include vitamin D3 (cholecalciferol), which circulates in the blood and is derived from photosynthesis, fish oils, egg yolks, fortified milk and dietary supplements. Vitamin D2 (ergocalciferol) is derived from dietary plant sources and is converted to vitamin D3. Vitamin D3 is less well absorbed and plays a much lesser metabolic role than vitamin D3.

Vitamin D deficiency can occur through insufficient exposure to sunlight by persons living at elevated latitudes, elderly and other stay-at-homes, darker skinned persons and in persons living in cultures that practice extensive skin covering. A recent AJCN study of ethnic effects on vitamin D status in pregnant women residing in The Hague, Netherlands, found deficient blood levels in 8% of white Caucasian Dutch women, compared to low levels in more than 60% of women of Moroccan or Turkish origin. Since these authors used an unconventional low cut-off point for the normal 25-hydroxyvitamin D (25[OH]D) level (25 nmol/l or 10 ng/ml), the incidence of vitamin D deficiency is probably much higher in pregnant Dutch women of all ethnicities than in women living at lower latitudes who are exposed to more sunlight. Another study found that 51% of elderly Dutch men and women had serum 25(OH)D levels less than 50 nmol/l (20 ng/ml), which is a marginal cut-off point (see below) and that time spent outdoors, lower body weight and ingestion of fatty fish and fortified margarine were the main determinants for adequate vitamin D status in The Netherlands. The authors point to the need for adequate vitamin D supplementation in countries such as The Netherlands where vitamin D deficiency is a risk due to limited food fortification and direct sun exposure due to its far northern latitude.

In recent years, it has become apparent that the recommended daily allowances for vitamin D intakes adopted by the US (200 i.u./day for all up to age 50, 400 i.u./day for age 50–70 and 600 i.u./for those over age 70) are set at unrealistically low levels for the prevention of osteoporosis and bone fractures. This controversy has been extensively aired in several AJCN review articles that focus on optimal daily doses to assure serum levels of 25(OH)D that are consistent with prevention of bone fractures, and the urgent need to revise current recommended daily intakes is summarized in a recent AJCN review. For example, Heaney pointed out that while most laboratory ranges for normal levels of serum 25(OH)D extend from about 37.5 to 100 nmol/l (15 ng/ml to 40 ng/ml), a composite of studies indicate that the maximal physiological absorption of calcium is not reached below serum 25(OH)D levels of at least 80 nmol/l (32 ng/ml). An extensive meta-analysis of 12 randomized control trials established relationships between bone mineral density and serum 25(OH)D levels in more than 13 000 US adults enrolled in the US National Health and Nutrition Examination Survey, who were grouped by age younger and older than 50 years. As shown in Fig. 2, while there was some discrepancy according to race, optimal bone mineral density values were obtained at serum 25(OH)D levels near 100 nmol/l (40 ng/ml). The same study showed that the daily intake of at least 1000 i.u. vitamin D was associated with blood levels of 25(OH)D at 75 nmol/l in just half the subjects with optimal bone mineral density, suggesting need for higher intakes to sustain adequate bone health. Whereas the US Food and Nutrition Board established 2000 i.u. as the upper limit of tolerable daily vitamin D intake, an extensive review of multiple studies found that toxicity manifest by hypercalcaemia and hypercalciuria was not evident at daily doses as high as 10 000 i.u.

Vitamin D has important properties that extend beyond optimization of calcium absorption and bone health. For example, vitamin D enhances lower extremity strength essential for minimizing falls among the elderly. In ~4100 US adults over aged 60, a cut-off
for optimal speed of walking 8 feet occurred in those with serum 25(OH)D levels above 80 nmol/l (32 ng/ml). Decreased incidences at inverse proportion to serum 25(OH)D levels have been noted for a wide variety of cancers, including prostate and colorectal cancer. A recent AJCN study found a 4-year decreased incidence of a variety of cancers including breast, colon, lung and uterus among 1179 women enrolled in a fracture prevention study who received 1100 i.u. vitamin D with supplemental calcium.

Summarizing, these three controversies were extensively aired during my tenure as the editor in chief of the AJCN. Considerable evidence was published to support emerging concepts that (i) the increasing addition of HFCS to the US diet may contribute substantially to the epidemic of obesity and its associated co-morbidities; (ii) that folic acid fortification of the US diet together with widespread use of multivitamin supplements that routinely contain folic acid may have multiple deleterious effects including reduced immune surveillance for cancer, a greater incidence of cognitive defects in the elderly and the proliferation of nascent cancer cells; and (iii) that the current US dietary reference intakes for vitamin D are set too low to influence the incidence of osteoporosis and bone fractures.

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