Calcium and vitamin D deficiencies: a world issue?[1]

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> "I don't want to achieve immortality through my work ... I want to achieve it through not dying."
>
> Woody Allen

The search for immortality has preoccupied human society since the dawn of time. Whether it be the elixir of life or a panacea to cure all disease, the human mind continues to believe that there exists a simple way to ensure freedom from disease and maximum quality of life. Today the situation is no different, except that the quest has been intensified by continuing developments in modern biology suggesting that modification of fundamental life processes, i.e. at the genome, could cure and prevent most human ailments, including ageing. While there is some basis for this belief, an understanding of higher levels of biological organization has resulted in the life span continuing to increase throughout most human societies, albeit faster in industrialized economies than in developing ones. Paradoxically, this success has led to even greater concern among people who, having attained the possibility of long life, are afraid to lose it. Further support for this hope results from recent discoveries made in nutrition that have led the public to believe that there are simple things that will ensure a long, quality life. This belief in nutritional panaceas has become almost a dogma; as Florence King, a United States author, has said, in reference to vitamin tablets, "I swallow it, therefore it is".

Unfortunately, the tendency is to think of these outcomes in terms of single nutrients, rather than in the matrix of a complex diet; a thought process not limited to the public, but shared, unfortunately, by some of our colleagues. Thus we continue to look for the magic bullet which will provide the equivalent of the medieval panacea and elixir of life. The nature of this bullet tends to change, depending on which nutrient occupies the most lines in the newspapers. Today the principals include beta-carotene, ascorbic acid, vitamin E and, of course, calcium. Vitamin D is often included in this credo because of its association with calcium.

To a significant extent, the mushrooming interest in calcium and vitamin D is a function of the extended life span of our populations. In large measure, this has occurred because of the ability of modern medicine to control and cure most acute infectious diseases, although this has become problematic with the appearance of new pathogens. Like peeling an onion, extension of life has brought its own set of health issues, including osteoporosis, coronary artery disease, certain cancers and so on. For calcium (and vitamin D), osteoporosis is the principal, but not sole, issue. A number of publications have addressed the possible role of calcium in the prevention of disorders other than osteoporosis, such as colon cancer, hypertension and pre-eclampsia in pregnancy.

One of the outcomes of this research has been the recognition that the need for calcium is the end-point of a series of complex events. Osteoporosis, for example, has been shown to be a function of bone mass attained in the first two or three decades of life and the rate of bone loss in later years. While calcium has been shown to be supportive of ensuring optimal bone mass and delaying or reducing the rate at which bone is lost, other factors seem to play a much more important role.

Several consistent threads emerge from the data relating calcium to bone disease. First, there is a significant body of evidence suggesting that calcium intake influences bone mass and hip fracture. Second, in those studies that involve a direct comparison of the effects of oestrogen replacement and calcium supplementation on bone mass, the oestrogen effect is usually much more marked. Recent work has demonstrated that oestrogen is necessary to maintain balance between osteoclastic and osteoblastic activity in bone. With decreasing oestrogenic activity, osteoclastic apoptosis decreases, while that of the osteoblast increases. Dietary calcium supplementation will only be effective in arresting that component of bone loss that is due to inadequate calcium intake and will not have much primary influence on the profound effects of oestrogen deficiency on bone metabolism.

The role of vitamin D is more indirect, serving to increase calcium absorption without necessarily having a direct effect on bone growth. It has been argued that vitamin D has an effect only when deficient in the diet.

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The data relating calcium to hypertension and colonic cancer are also complex and not well understood.

Given the probability that increased dietary calcium and vitamin D could help in reducing the incidence of osteoporosis, hypertension and so on, the other side of the coin also has to be evaluated. What are the adverse effects of increased calcium and vitamin D intake? Concern about the toxicity of high calcium intakes has been concentrated on nephrolithiasis and mild-alkali syndrome. Over the last two decades, a substantial number of papers have attempted to determine the relationship between stone formation and calcium intake. The difficulty of demonstrating this association has led to escalating doubt on the part of many investigators of the primary role of calcium in nephrolithiasis. Nevertheless, there are studies that suggest that in certain individuals, increased dietary calcium and vitamin D can lead to stone formation and, to a lesser extent, to other aspects of hypercalcification such as aortic calcification. One of the more interesting observations in these studies is that other substances, such as sodium, may play an important and direct role in the development of stones by competing with calcium for receptors in the kidney.

This brings us to a vital issue. Interaction among nutrients, "the balanced diet", has always been a theoretical dietary concept expressed more in research paradigms than in much of contemporary media dietary advice. The relationships of calcium and magnesium, calcium and phosphorus, calcium and sodium, and calcium and zinc are very well known. Recent papers suggest that calcium has an inhibitory effect on iron absorption in humans. Yet, with the exception of calcium and phosphorus, little attention is paid to these relationships when media dietary advice is developed.

The determination of calcium and vitamin D requirements is further complicated by the recognition that there may be racial and ethnic differences in calcium needs. Several recent papers have suggested that Africans have a higher bone density and therefore may be more resistant to osteoporosis even though calcium intake in Africa is substantially less than in other parts of the world. Nevertheless, to some extent, osteoporosis and other diseases associated with calcium are widespread throughout the world.

FORTIFICATION

Given the ubiquitous nature of diet-associated disorders, recommendations have been made for the widespread fortification of food with those nutrients that are believed to be deficient in human diets, or for which levels above the recommended dietary allowance (RDA) may be helpful in preventing chronic disease. Calcium has been high on the lists of nutrients recommended for fortification. There are, however, important scientific and policy issues that must be resolved before programmes for fortification can be considered. In a recent publication, Walter Mertz listed the data needs, constraints and limitations for fortification programmes. He identified five general areas: human requirements and nutritional status; bioavailability; interactions among nutrients; interactions of fortification nutrients with carrier foods; and the safe upper limits (or upper reference levels) for these nutrients. While all need to be discussed and incorporate areas of disagreement, the domain of greatest controversy is the establishment of upper reference levels or nutrient toxicity.

Although extensive experience has been attained in safety evaluations of food additives, we are far from this level of sophistication in our evaluation of the risks associated with the use of nutrients. This lag is a result of many factors, not the least of which is the general view that nutritional patterns associated with normal diets cannot represent any particular hazard to humans. While this is generally true, a substantially modified food supply which involves fortified foods, supplements and constructed and fabricated foods offers real possibilities for exceptions to this complacent view. Another important issue is that we do not fully understand the implications of modified patterns of nutrient consumption. Until recently, nutrition studies focused primarily on the impact of deficiency states. Today nutritionists are beginning to understand that the contemporary health problem is usually not classical deficiency but, rather, excess. The fortification of a food for the prevention of one chronic disease may exacerbate another. The chronic impact on health of the distortion of the diet resulting from public belief in the daily dietary revelations in the press is not well understood. With few exceptions, the data concerning nutrient safety refer to acute toxicity. What is not understood is the chronic impact of distorted nutrient patterns on such areas as metabolism, genetic expression, behaviour, immune function, physical performance and the capacity of the organism to deal with a wide spectrum of xenobiotics.

Perhaps the best approach to the problem of making appropriate policy decisions concerning issues as profoundly important as fortification is the development of appropriate models to predict the risk associated with these actions. Recently the Food and Nutrition Board of the United States National Academy of Sciences has been examining the development of such a model in attempting to establish upper reference levels for nutrient use as part of

its programme to restructure the United States RDAs. If useful information is to be provided to policy-makers for fortification programmes, not only do we have to understand the risk of not fortifying foods, we must compare that with the risk of fortification. In other words, the issue is not risk versus benefit, but rather, risk versus risk. The problem of comparing benefits in one set of units with risk in another is, at best, difficult. Risk versus risk comparisons allow the use of similar units, therefore providing for more rational and useful recommendations. Moreover, such models must also consider that nutrients do not exist in a pristine state, but rather in a complex matrix called food, containing other nutrients and non-nutrients that may have important effects on the utilization and metabolism of the nutrient. Excellent examples are the relationship between sodium and calcium in the aetiology of nephrolithiasis, and calcium and iron absorption.

Given the intricacy of the problem, what then is the standard of scientific evidence that should be used to determine when it is or is not appropriate for major public health actions, such as fortification, to be taken? In other words, we need to examine the standard for data upon which such changes will be made.

It has often been said that surety is a fundamental goal of modern science. The scientific method is assumed to provide for a system by which data and hypothesis are checked, rechecked, evaluated and re-evaluated. This constant process of pruning and rebuilding is essential for knowledge to increase and for science to advance. There is a tendency, however, for experimental scientists who are not responsible for public health issues to look for a degree of absolutism in scientific relationships that, while appropriate for evaluating an experimental hypothesis, may only serve to delay the implementation of important public health actions. This is true, I believe, because there is a dichotomy between academic science and public health science regarding the nature of the words "sufficient scientific evidence". Generally speaking, as scientists we are trained continually to question data and hypothesis. Scientific papers are riddled with "possibles", "probables", "could possiblies", phrases that are essential to the recognition that scientific "truth" is an ephemeral concept. Such "truth" almost always is as stable as the next scientific journal. When we recognize this in science and recognize it to such an extent that its philosophical premise becomes ingrained into our psyches, we are rarely able to say we believe without reservation that any proposed relationship is unequivocally demonstrated. This tentative attitude, essential to academic science, is not always an acceptable position for a public health scientist. In the collection of information concerning a public health problem, public health scientists must make what I like to call "the leap of faith". They must believe that the data are sufficiently convincing to take a public health action, even though doubts may remain. If they delay in taking that action, they run the danger of imperilling the health of substantial numbers of people. For the academic scientist, no such compelling force exists. Any doubt is sufficient to withhold full acceptance of a relationship. This dichotomy between academic and public health science and the consequent lack of agreement on the meaning of the word "sufficient" often creates a conflict between public health scientists and the professional community and, in turn, confusion for the public.

What then should the standard of evidence be? For public health scientists the standard of evidence for any particular action varies. It depends in large measure on how potentially important the action is to maintaining the public health, as well as on the potential for a counterproductive effect to occur. In other words, if the risk of doing is considerably less than the risk of not doing, then it becomes an appropriate action for public health agencies to take. This often occurs under conditions in which the academic scientist will correctly say that the data are insufficient to support the hypothesis. There is a real possibility for this to occur in our current efforts to exploit the role of diet in the modification of chronic disease, such as in the current discussion of calcium fortification. Nevertheless, as long as the harm done by the action is low or minimal, the fact that the activity ultimately has little effect on public health does not necessarily make it an inappropriate decision at the time. On the other hand, I must offer an important caveat. The very nature of public health decisions makes it necessary that we do not overstate the potential of the actions that are promoted. What we need is rationality and moderation in this process. We must also recognize the responsibility of being as assiduous in identifying and estimating the risks of doing as we are in promoting. Moreover, implicit in such public health decisions is the belief that the option of lowest risk is taken. Thus, for nutrient modification of the diet, dietary advice is less risky than fortification which, in turn, is less risky than supplement use.

It is surprising how difficult it has been to develop widely acceptable data relating diet and chronic disease, such as calcium and osteoporosis. In spite of epidemiological and animal studies supporting many of these relationships, focused human clinical studies have often been negative or at best equivocal. There is no good explanation for this. It has become a truism in nutrition to

describe the relationship between diet and chronic disease as multifactoral in an effort to indicate its complexity. In general, however, when we describe an event as multifactoral, we mean not only that many factors are involved in its aetiology, but also that each of the factors interacts with the other dietary and non-dietary components of the environment. Although we speak of this relationship, traditional experimental designs tend to ignore it. In the case of the relationships between diet and chronic disease, it is almost certain that several factors have to vary simultaneously for a response to be observed. The metabolic and physiologic relationships among nutrients suggest this as a possibility. Equally important may be the fact that the primary disease-related factors are ubiquitous in the environment. The role of diet, then, becomes important in modulating the expression of these primary factors, rather than providing a direct effect. It is not surprising, therefore, that using traditional experimental approaches, results obtained may be less powerful than we expect. Indeed, it may be that only long-term prospective multinutrient studies are capable of exploring these relationships. Such studies are expensive and tedious and not often performed. If this hypothesis is true, then much greater emphasis must be placed on creative animal and epidemiological studies in the development of public policy. Equally important, however, it emphasizes the need for continuing research in these areas; it demands that much greater support be given to exploring the relationships between nutrients and other factors in modification of the disease process, particularly at the cellular and genetic levels.

Let us return for a moment to the issue of risk assessment for nutrients. It has not always been true that risk assessment was an acceptable way of estimating the safety of additives in food. The change in attitude of most regulatory scientists towards quantitative risk assessment came about for two reasons. First, there was increasing recognition that scientific knowledge and experience were sufficient to support the identification of hazards. Second, there was the recognition of safety as a continuous rather than a dichotomous concept. Today, for food additives, toxicologists are trying to evaluate substances or products in terms of the magnitude of the risk they impose, not simply in terms of "up or down" or "yes or no" judgements. At the same time, it is important to remember that safety, considered in this way, is a societally derived point on a continuum. Thus the concept of significant risk becomes, in part, the result of consideration of social, political and economic factors. This, in turn, influences which phenomena we intend to investigate, how hard we are to look for them and how acceptable is their occurrence. While this has become recently recognized in the evaluation of chemical food additives, it has always been true for nutrients. The modification of the nutrient pattern to maintain health has always been a complex policy issue, depending to an extent on the economics and public health policy of the countries involved. What is required now is the development of a model that would allow us to perform risk assessments independent of these policy decisions, providing risk managers objective evaluations which could then be used to develop policy.

Returning to the issue of fortification as a strategy for the prevention of chronic disease, it is important to understand that the early enrichment programmes were based upon evidence of deficiency of a nutrient in a substantial segment of the population. Throughout the years, this principal has remained the pillar of fortification policy. Decisions concerning nutrient addition were relatively simple to make in the days when frank deficiency diseases such as pellagra and rickets were widespread in the population. Certainly in the industrialized world, these diseases, fortunately, no longer afflict large masses of people. In terms of fortification, the shift from deficiency disease prevention to health promotion offers a complex realm in which the scientific data are woefully insufficient. It raises the most fundamental question as to whether fortification of foods with nutrients is the most desirable approach to health promotion or whether it is better to rely on advice to the public to improve diets or on modification of nutrient patterns in foods, for example. Scientific data with respect to these issues are few, and if the scientific community were polled it is unlikely that there would be a consensus.

We must keep in mind that when fortification is practised, several problems may arise. The loss of control over what is occurring in the total food supply is a primary threat. If random fortification or widespread use of supplements in addition to fortification should occur, it could create imbalances or excesses in the food supply. Calcium is again a case in point. Recently, based on the recommended United States dietary guidelines, the possible total dietary intake of calcium was calculated assuming that all foods known to be fortified or that had been fortified with calcium were consumed. It was estimated that, under these conditions, calcium consumption could exceed 4 g per day. Consider this in relation to the recommendation of the United States National Institutes of Health (NIH) Consensus Conference on Calcium and Osteoporosis that calcium intake should not exceed 2 g per day.

Another possibility is to put increasing pressure on the agricultural production part of the system to develop and to

distribute more widely new strains of food having nutrient patterns that are considered to be more optimal for the prevention of chronic disease. The success of agricultural research and food science and technology in providing an abundant food supply aimed at solving the problems of hunger and deficiency has led in part to a host of new issues, concerns and questions which must be addressed by appropriately directed research. Enhanced productivity is still an important worldwide goal for agriculture, but the situation today demands a changing emphasis towards greater concern for the safety and nutritional quality of the diet, rather than emphasis only on its quantity. The picture is that the optimal utilization of scientific research related to chronic diseases and its associated public health concerns requires that scientific research related to food production must be formulated with nutritional consequences in mind. In other words, as it becomes increasingly apparent that the pattern of diet and its nutritional quality play an essential role in ensuring the total quality of life, health needs will also have to be considered as a major component in food policy and planning. Health policy and agricultural policy will have to be integrated to produce national and international food policy. However, this will place further pressures on the scientific community to produce new products that are more consistent with our developing understanding of the requirements for maintaining and improving health. It is important to note that this revolution in health, nutrition and agriculture is not occurring in a national vacuum. Important nutrition-related research is being done throughout the world, and the need for international cooperation is obvious. Governments in the more developed countries must consider how best to transfer agricultural, safety and nutritional technologies to less developed regions of the world, narrowing the increasing gap between the rich and the poor and thus contributing to the peace and stability of the world.

To return to the initial question of this discussion, is there a worldwide need to increase calcium and vitamin D intake? If so, what is the best way to accomplish it? I, unfortunately, do not have the answer. It seems clear that a relationship exists between calcium and several chronic diseases. It is not clear whether this relationship is primary or indirect. For example, calcium intake is lowest in Africa, yet osteoporosis, while it exists, is of a lower incidence than in other parts of the world. On the other hand, demonstrable problems exist if intake is excessive – a paradox. Whatever recommendations are made, they must consider all aspects of the risk associated with these actions.

In any case, it is clear that the next several decades will represent a revolution in the way we grow, process and distribute food. It is also clear that it is no longer possible for us to consider separately the various components of the national food supply. We have seen nutrition, food science, food safety and agricultural policy all evolving from basically independently directed disciplines to a point where it is essential that they be integrated to produce coherent food policy. We will have to consider agricultural needs, health and nutritional needs, safety needs and food technology needs simultaneously. Only in this way can we ever develop an understanding of the entire gestalt of the problem.

It is also clear that research in these areas is on the very cutting edge of science. Many times we pass over the frontier between what we know and what we would like to know. Clearly what we need is more research directed towards better understanding of these important problems, including studies of the interrelationship of science and food policy. Unfortunately, it seems that each new scientific observation results in a compelling force to change the policies that are in place or in development. This is not surprising. Science is a destabilizing force in policy, and new science is always difficult to incorporate in the development of food policies that have inherently great inertia. Perhaps T.S. Eliot was right. In 1934, he wrote in his poem “The Rock”, “Where is the wisdom we have lost in knowledge? Where is the knowledge we have lost in information?”. Perhaps it is inappropriate for us to try to integrate everything we know into the development of public health policy. Yet I firmly believe that if we do not use the best science available we will not fulfil our mission to ensure, to all the people in the world, health and a high quality of life. ♦

Summary/Résumé/Resumen

Calcium and vitamin D deficiencies: a world issue?

Increasing life expectancy has led to growing interest in diseases associated with the ageing process. One of the most intensely studied disorders is osteoporosis. Osteoporosis is an end result of a complex series of events in which the relative importance of dietary calcium is unclear. The literature contains many conflicting references to the efficacy of calcium supplementation or fortification in prevention and mitigation of osteoporosis. The issue is complicated by the suggestion that increased dietary calcium intake can cause a number of adverse biological effects.

While in general the trends suggest an inverse relationship between calcium intake and the incidence of osteoporosis, this relationship is not always as strong as theory predicts. In some countries, relatively low intakes of calcium do not result in high incidence of osteoporosis. Part of the explanation may be that other factors such as hormone levels and exercise may be of more importance than dietary calcium. These are not always measured, particularly in epidemiological studies. Nevertheless, it has been proposed that calcium fortification to mitigate osteoporosis be considered on a widespread basis. The development of a fortification policy must be based on rigorous criteria that embrace both positive and adverse consequences. The consideration is not of risk versus benefits, but of risk versus risk. The evaluation of calcium as a possible candidate for worldwide fortification involves most of the vital policy issues associated with diet and nutrition and requires the development of data at the frontiers of contemporary nutritional research.

Carences en calcium et vitamine D: un problème mondial?

L'accroissement de l'espérance de vie a suscité un intérêt croissant pour les maladies associées au processus de vieillissement. L'ostéoporose et le rôle du calcium dans l'alimentation sont parmi les sujets les plus étudiés. Il n'est pas étonnant que l'ostéoporose soit le résultat final d'une suite de phénomènes complexes où l'importance relative du calcium dans l'alimentation n'est pas clairement déterminée. Les publications ne s'accordent guère sur l'efficacité d'une complémentation en calcium pour prévenir et limiter les effets de l'ostéoporose. La question est d'autant plus complexe que certains affirment qu'un apport accru de calcium peut entraîner nombre d'effets négatifs.

En général, tout semble indiquer qu'il existe un rapport inverse entre apport calcique et incidence de l'ostéoporose, mais ce rapport n'est pas toujours aussi clair que ne le laisse penser la théorie. Dans certains pays, un apport relativement faible en calcium n'entraîne pas une augmentation sensible de l'ostéoporose. D'autres facteurs (secrétions hormonales ou activité physique, par exemple) joueraient un rôle plus important que le calcium dans l'alimentation. Or, ces facteurs ne sont pas toujours mesurés, notamment lors des études épidémiologiques. On propose pourtant, un peu partout dans le monde, d'enrichir les aliments en calcium pour réduire le risque de cette maladie. La mise en œuvre d'une telle politique se doit d'être fondée sur des critères rigoureux prenant en considération les conséquences à la fois positives et négatives. Car il ne s'agit pas de mesurer les risques par rapport aux avantages possibles, mais plutôt d'évaluer les risques actuels par rapport à d'autres risques éventuels. Lorsqu'on évalue le bien-fondé d'un enrichissement en calcium des produits alimentaires au niveau mondial, ce sont la plupart des questions vitales de politique touchant à l'alimentation et à la nutrition qui sont en jeu et on a besoin de nouvelles données situées aux frontières de la recherche nutritionnelle contemporaine.

¿Son las carencias de calcio y vitamina D un problema mundial?

El aumento de la esperanza de vida ha provocado un creciente interés por las enfermedades asociadas con el proceso de envejecimiento. Uno de los trastornos más estudiados ha sido la osteoporosis y la función del calcio alimentario. Esto no es de extrañar, dado que la osteoporosis es el resultado final de una serie compleja de acontecimientos en los que no está clara la importancia relativa del calcio alimentario. La bibliografía sobre este tema contiene muchas referencias contradictorias a la eficacia de la suplementación de calcio para la prevención y mitigación de la osteoporosis. La sugerencia de que una ingesta de calcio alimentario bastante próxima a los niveles propuestos en los Estados Unidos puede causar diversos efectos biológicos negativos viene a complicar aún más las cosas. Y la situación

se hace todavía más confusa cuando se contempla desde una perspectiva mundial. Aunque en general los datos existentes indican una relación inversa entre la ingesta de calcio y la incidencia de la osteoporosis, esta relación no es siempre tan clara como prevé la teoría. Así pues, en algunos países, ingestas de calcio relativamente bajas no dan lugar a un aumento considerable de la incidencia de la osteoporosis. Puede que el problema se deba en parte a que otros factores, como los niveles hormonales y el ejercicio, tal vez desempeñen una función más importante que el calcio alimentario. Estos factores no siempre se tienen en cuenta, sobre todo en los estudios epidemiológicos. Además, la osteoporosis no es la única consecuencia funcional de la carencia de calcio. No obstante, se ha propuesto que se estudie la suplementación de calcio para mitigar la osteoporosis a nivel mundial. La elaboración de una política de enriquecimiento generalizada de los alimentos deberá basarse en criterios rigurosos que tengan en cuenta las consecuencias tanto positivas como negativas. El problema no consiste en confrontar los riesgos con los beneficios, sino unos riesgos con otros. La evaluación del calcio como posible candidato para el enriquecimiento a nivel mundial implica casi todas las cuestiones decisivas de política asociadas con la alimentación y la nutrición y exige la elaboración de datos en las fronteras de la investigación nutricional contemporánea. ♦