# Calcium and Magnesium in Drinking-water

## Public health significance

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# Preface

This document identifies knowledge gaps and recommends research priorities in order to build an evidence base to inform decisions on managing "processed" drinking-water. This is important because of increasing consumption of water arising from advanced treatment processes such as desalination and uncertainty about the resulting heatlh implications.

The World Health Organization (WHO) assembled a diverse group of nutrition, medical, epidemiological and other scientific experts and water technologists at the Pan American Health Organization in Washington, DC, USA, on 27–28 April 2006 to address the possible role of drinking-water containing calcium and/or magnesium as a contribution to the daily intake of those minerals. The overarching issue addressed was whether consumption of drinking-water containing a relatively small contribution to total daily dietary intake of calcium and/or magnesium would provide positive health benefits, especially with respect to cardiovascular disease mortality (the so-called "hard water cardiovascular disease benefits hypothesis"), in the population, particularly in people whose dietary intake was deficient in either of those nutrients. The meeting of experts immediately followed the International Symposium on Health Aspects of Calcium and Magnesium in Drinking Water, which was organized by NSF International and the International Life Sciences Institute in Baltimore, MD, USA.

The impetus for the meeting originated from the process for developing WHO guidance for health and environmental aspects of water desalination, which was initiated by the WHO Regional Office for the Eastern Mediterranean, located in Cairo, Egypt. The meeting was also intended to contribute to the Fourth Edition of the WHO *Guidelines for Drinking-water Quality* (to be published in 2010) in respect to nutrients in drinking-water and water hardness as they influence drinking-water quality and health.

The nutritional essentiality and benefits from sufficient dietary intakes of calcium and magnesium are well established but quantitatively imprecise. Many of the ecological epidemiological studies conducted since the mid-1950s have supported the hypothesis that extra magnesium and/or calcium in drinking-water can contribute to reduced cardiovascular disease and other health benefits in populations. However, most of those studies did not cover total dietary intake and other important factors. Several analytical epidemiological studies that were conducted supported the hypothesis that magnesium correlated best with beneficial effects on cardiovascular mortality rates.

The goal of the meeting of experts was to elucidate the role of drinking-water as a contributor to total daily intake of calcium and magnesium and to determine whether there is a plausible case that drinking-water could be an important health factor, especially for cardiovascular disease mortality, at least for people whose dietary intake is deficient in either of those nutrients. The report of the meeting of experts is the first chapter in this volume.

The remaining chapters provide background information on the scientific, nutritional and technological issues that were discussed by the meeting of experts and the symposium participants and that contributed to the report of the meeting of experts. Among the numerous issues addressed were the concentrations and distributions of minerals in drinking-water worldwide, nutritional requirements, biochemical and biomedical aspects of minerals in the body, technologies such as water softening and desalination that significantly alter the mineral composition of drinking-water, the desirability and feasibility of remineralization for stabilization and potential benefits, and the availability of information on water composition so that the public can make informed judgements with respect to their options for bottled water, softened water and naturally soft water. It is hoped that this publication will advance knowledge and contribute to further discussions on these and related issues in this area.

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Finally, WHO would like to express its condolences to the family and colleagues of Dr. Hirotoshi Morii, physician, researcher on osteoporosis and emeritus professor at Osaka City University, who passed away unexpectedly shortly before the International Symposium on Health Aspects of Calcium and Magnesium in Drinking Water. He would have been a session chairman at the symposium and a member of the meeting of experts.

# List of acronyms and abbreviations

| | |
|---|---|
| AI | Adequate Intake |
| ATP | adenosine triphosphate |
| COX-2 | cyclo-oxygenase-2 |
| CVD | cardiovascular disease |
| DRI | Dietary Reference Intake |
| EAR | Estimated Average Requirement |
| FAO | Food and Agriculture Organization of the United Nations |
| GCC | Gulf Cooperation Council |
| HIV | human immunodeficiency virus |
| IFN-γ | interferon-gamma |
| IHD | ischaemic heart disease |
| IL | interleukin |
| iNOS | inducible nitric oxide synthase |
| IOM | Institute of Medicine (USA) |
| iPTH | intact parathyroid hormone |

| | |
|---|---|
| IU | International Unit |
| L-NAME | $N^G$-nitro-L-arginine methyl ester |
| LPS | lipopolysaccharide |
| mRNA | messenger ribonucleic acid |
| NF-KB | nuclear factor-Kappa B |
| NHANES | National Health and Nutrition Examination Survey (USA) |
| NMDA | *N*-methyl-D-aspartate |
| NOS | nitric oxide synthase |
| NTU | nephelometric turbidity unit |
| OR | odds ratio |
| PAF | platelet-activating factor |
| POE | point of entry |
| POU | point of use |
| PTH | parathyroid hormone |
| RDA | Recommended Dietary Allowance |
| RNI | Recommended Nutrient Intake |
| ROS | reactive oxygen species |
| RR | relative risk; risk ratio |
| SD | standard deviation |
| SEM | standard error of the mean |
| SI | Saturation Index |
| SMase | sphingomyelinase |
| SP | substance P |
| TDS | total dissolved solids |
| TIC | total inorganic carbon |
| TNF-α | tumour necrosis factor-alpha |
| UL | Tolerable Upper Intake Level |
| USA | United States of America |
| VSM | vascular smooth muscle |
| WHO | World Health Organization |

# 1

# Expert consensus

*Meeting of Experts Report*

## 1.1 INTRODUCTION

Both calcium and magnesium are essential to human health. Inadequate intake of either nutrient can impair health. Recommended daily intakes of each element have been set at national and international levels.

Food is the principal source of both calcium and magnesium. Dairy products are the richest sources of dietary calcium, contributing over 50% of the total calcium in many diets. Some plant foods, including legumes, green leafy vegetables and broccoli, can also contribute to dietary calcium, but the content is lower than in dairy products, and the bioavailability of calcium in plant foods can be low if the concentration of oxalate or phytate is high. Dietary sources of magnesium are more varied; dairy products, vegetables, grain, fruits and nuts are important contributors.

Individuals vary considerably in their needs for and consumption of these elements. Available evidence suggests that, because of food habits, many people in most countries fail to obtain from their diets the recommended intakes of one

or both of these nutrients. While the concentrations of calcium and magnesium in drinking-water vary markedly from one supply to another, mineral-rich drinking-waters may provide substantial contributions to total intakes of these nutrients in some populations or population subgroups. Water treatment processes can affect mineral concentrations and, hence, the total intake of calcium and magnesium for some individuals.

On the basis of the findings of the World Health Organization (WHO) meeting of experts held in Rome, Italy, in 2003 to discuss nutrients in drinking-water (WHO 2005), the present group focused its consideration on calcium and magnesium, for which, next to fluoride, evidence of health benefits associated with their presence in drinking-water is strongest. The present group also noted that the issue of fluoride was addressed by the Rome meeting in detail and adopted its review and recommendations (see below). In addition, the group concluded that other elements may also have health relevance and should be considered by future groups.

## 1.2 CALCIUM

Over 99% of total body calcium is found in bones and teeth, where it functions as a key structural element. The remaining body calcium functions in metabolism, serving as a signal for vital physiological processes, including vascular contraction, blood clotting, muscle contraction and nerve transmission.

Inadequate intakes of calcium have been associated with increased risks of osteoporosis, nephrolithiasis (kidney stones), colorectal cancer, hypertension and stroke, coronary artery disease, insulin resistance and obesity. Most of these disorders have treatments but no cures. Owing to a lack of compelling evidence for the role of calcium as a single contributory element in relation to these diseases, estimates of calcium requirement have been made on the basis of bone health outcomes, with the goal of optimizing bone mineral density. Calcium is unique among nutrients, in that the body's reserve is also functional: increasing bone mass is linearly related to reduction in fracture risk.

### 1.2.1 Osteoporosis

Osteoporosis is a condition of skeletal fragility characterized by low bone mass and by microarchitectural deterioration of bone tissue, with a consequent increase in risk of fracture. Calcium is the largest constituent of bone, comprising 32% by weight. A large body of primary evidence from randomized controlled trials shows that increasing calcium intake, especially in those who have had habitually low calcium intakes, increases bone mass during growth and

reduces bone loss and fracture risk late in life. Osteoporosis is one of the most prevalent of age-related diseases.

### 1.2.2 Kidney stones

The relationship between calcium intake and the incidence of kidney stones is dependent on whether calcium is consumed with food or separately. Calcium that reaches the lower small intestine actually protects against kidney stones by binding oxalic acid (a precursor to common kidney stones) in foods and reducing its absorption. Calcium ingested from water together with food would have the same effect. Epidemiological evidence is strong that dietary calcium reduces the incidence of kidney stones. In contrast, the results of a large randomized trial[1] suggest an increased risk of kidney stones associated with calcium supplements, possibly because the calcium was not ingested with food or the supplements were taken by those who exceeded the upper level of 2500 mg/day.

### 1.2.3 Hypertension and stroke

Hypertension (high blood pressure) is a risk factor for several diseases. It is an important health problem especially in developed countries, but also in developing countries. Although hypertension is multifactorial in origin, adequate calcium intake has been associated with lowered risk of elevated blood pressure in some, but not all, studies. A clear mechanism has not been identified. Dairy products, more than calcium, per se, have been associated with reduced blood pressure in randomized prospective studies and with reduced risk of stroke in prospective studies.

### 1.2.4 Insulin resistance

Insulin resistance is associated with type 2 diabetes mellitus, the prevalence of which is escalating with the rise in obesity worldwide. Dietary calcium may be implicated in the etiology of insulin resistance through the fluctuations in calcium-regulating hormones in states of calcium sufficiency and deficiency. This is an area of active research; thus, it is premature to use such a clinical outcome as the basis for deriving recommendations for dietary intake of calcium.

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[1] From the Women's Health Initiative, a 15-year programme established by the United States National Institutes of Health in 1991.

### 1.2.5 Vulnerable populations

Those individuals who avoid dairy products or lack access to them may be at increased risk of calcium deficiency. Formula-fed infants will not normally be at risk from deficient or excess amounts of calcium. Even extremely low or high calcium concentrations in water would not lead to absorption of unphysiological amounts of calcium from infant formula reconstituted with the water. If, however, other feeds are used that do not provide the calcium content of full-strength formula, then water may represent an important source of the mineral for the infants.

### 1.2.6 Excess calcium intakes

To a great extent, individuals are protected from excess intakes of calcium by a tightly regulated intestinal absorption mechanism through the action of 1,25-dihydroxyvitamin D, the hormonally active form of vitamin D. When absorbed calcium is in excess of need, the excess is excreted by the kidney in most healthy people. Concern for excess calcium intake is directed primarily to those who are prone to milk alkali syndrome (the simultaneous presence of hypercalcaemia, metabolic alkalosis and renal insufficiency) and hypercalcaemia. Although calcium can interact with iron, zinc, magnesium and phosphorus within the intestine, thereby reducing the absorption of these minerals, available data do not suggest that these minerals are depleted when humans consume diets containing calcium above the recommended levels. For example, even though high intakes of calcium can exert acute effects on iron absorption, there is no evidence of reduced iron status or iron stores with long-term calcium supplementation.

## 1.3 MAGNESIUM

Magnesium is the fourth most abundant cation in the body and the second most abundant cation in intracellular fluid. It is a cofactor for some 350 cellular enzymes, many of which are involved in energy metabolism. It is also involved in protein and nucleic acid synthesis and is needed for normal vascular tone and insulin sensitivity. Low magnesium levels are associated with endothelial dysfunction, increased vascular reactions, elevated circulating levels of C-reactive protein and decreased insulin sensitivity. Low magnesium status has been implicated in hypertension, coronary heart disease, type 2 diabetes mellitus and metabolic syndrome.

### 1.3.1 Hypertension

Magnesium deficiency has been implicated in the pathogenesis of hypertension, with some epidemiological and experimental studies demonstrating a negative correlation between blood pressure and serum magnesium levels. However, data from clinical studies have been less convincing.

### 1.3.2 Cardiac arrhythmias

Cardiac arrhythmias of ventricular and atrial origin have been reported in patients with hypomagnesaemia. Indeed, a serious cardiac arrhythmia, Torsade de Pointes, is treated with intravenous magnesium therapy.

### 1.3.3 Pre-eclampsia

Pre-eclampsia (defined as hypertension after 20 weeks of gestation) with proteinuria has been treated with magnesium salts for many decades. A recent clinical trial (Altman *et al*. 2002) using magnesium sulfate showed a 50% decreased risk of eclampsia.

### 1.3.4 Atherosclerosis

Animal studies have documented an inverse (protective) relationship between magnesium intake and the rate or incidence of atherosclerosis.

### 1.3.5 Coronary heart disease

In humans, there is evidence for an inverse (protective) relationship between magnesium and coronary heart disease. Three cross-sectional studies have now documented an inverse relationship between the concentration of C-reactive protein (a proinflammatory marker that is a risk factor for coronary heart disease) and magnesium intake or serum magnesium concentration, suggesting that magnesium may have an anti-inflammatory effect.

### 1.3.6 Diabetes mellitus

Several studies have documented the importance of magnesium in type 2 diabetes mellitus. Two recent studies have documented an inverse (protective) relationship between magnesium intake and risk of developing type 2 diabetes mellitus. Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetes mellitus.

### 1.3.7 Magnesium depletion status

Alcoholism and intestinal malabsorption are conditions associated with magnesium deficiency. Certain drugs, such as diuretics, some antibiotics and some chemotherapy treatments, increase the loss of magnesium through the kidney.

### 1.3.8 Hypermagnesaemia

The major cause of hypermagnesaemia is renal insufficiency associated with a significantly decreased ability to excrete magnesium. Increased intake of magnesium salts may cause a change in bowel habits (diarrhoea), but seldom causes hypermagnesaemia in persons with normal kidney function.

### 1.3.9 Gastrointestinal function

Drinking-water in which both magnesium and sulfate are present in high concentrations can have a laxative effect, although data suggest that consumers adapt to these levels as exposures continue. Laxative effects have also been associated with excess intake of magnesium taken in the form of supplements, but not with magnesium in diet.

## 1.4 EPIDEMIOLOGICAL EVIDENCE

A large number of studies have investigated the potential health effects of drinking-water hardness. Most of these have been ecological epidemiological studies and have found an inverse relationship between water hardness and cardiovascular mortality. Inherent weaknesses in the ecological epidemiological study design limit the conclusions that can be drawn from these studies.

Based on identified case–control and cohort studies,[1] there is no evidence of an association between water hardness or calcium and acute myocardial

[1] Case–control and cohort studies are more useful than ecological epidemiological studies for investigating cause-and-effect relationships. Seven case–control studies and two cohort studies of acceptable quality investigating the relationship between calcium or magnesium and cardiovascular disease or mortality were identified in the literature. Of the case–control studies, one addressed the association between calcium and acute myocardial infarction and three the association between calcium and death from cardiovascular disease. None found a positive or inverse correlation between calcium and either morbidity or mortality. Two examined the relationship between magnesium and acute myocardial infarction, finding no association. Five examined the relationship between magnesium and cardiovascular mortality; while some failed to yield statistically significant results, collectively they showed similar trends of reduced cardiovascular

infarction or deaths from cardiovascular disease (acute myocardial infarction, stroke and hypertension). There does not appear to be an association between drinking-water magnesium and acute myocardial infarction. However, the studies do show a negative association (i.e. protective effect) between cardiovascular mortality and drinking-water magnesium. Although this association does not necessarily demonstrate causality, it is consistent with the well known effects of magnesium on cardiovascular function.

## 1.5 DRINKING-WATER

Water is essential for hydration and, therefore, for life. It is also very important in food preparation and cooking, sanitation and hygiene and a wide range of other uses. Drinking-water supply has a primary objective of protecting human health, including ensuring access to adequate quantities of safe water. It has been estimated that approximately 17% of the world's population uses water from unprotected and remote sources, 32% from some form of protected source and 51% from some sort of centralized (piped) system to the dwelling or plot. Of the latter, a small but increasing proportion applies some form of treatment within the home. Individual water consumption occurs both at home and elsewhere, such as at schools and workplaces. Drinking-water is consumed not only as water per se but also in beverages and incorporated into foodstuffs. In response to increasing global and local water scarcity, there is increasing use of sources such as recovered/recycled waters, harvested rainwater and desalinated waters.

### 1.5.1 Conditioning of water for piped distribution

Conditioning of water, including central softening and stabilization, may be necessary to reduce corrosion of piping materials and/or scaling effects in installations and to improve consumer acceptability. Corrosion and scaling can be associated with adverse effects on health (from leachates such as lead) and the environment (from leachates such as copper if the water is not conditioned) and reduced lifespan of the distribution network and appliances using water. When conditioning is done, the target is normally to achieve bicarbonate equilibrium, suitable pH and alkalinity and limited concentrations of sulfate,

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mortality as magnesium concentrations in water increased. Statistically significant benefits (where observed) generally occurred at magnesium concentrations of about 10 mg/l and greater. The cohort studies examined the relationship between water hardness (rather than calcium or magnesium content) and cardiovascular disease or mortality and found no association.

nitrate and chloride. Modification of calcium and magnesium concentrations in drinking-water for health reasons must comply with the technical requirements to provide water suitable for distribution and must not compromise disinfection.

### 1.5.2 Organoleptic considerations

Dissolved minerals contribute to the taste of drinking-water to varying degrees. Acceptability of water will usually depend on the individual user's taste and familiarity. Especially high or low mineral content may be considered unpalatable by consumers. Concentrations of calcium and magnesium in water that are detectable by consumers are typically above those that are considered manageable in drinking-waters.

### 1.5.3 Desalination

A rapidly growing technique for producing new water is desalination of seawater and brackish water, in which water with a high dissolved solids content is converted to water with a very low dissolved solids content. This water is stabilized before distribution in order to avoid corrosion of piped distribution systems. Practices in stabilization typically involve blending the desalinated water with un-desalinated source water (seawater or naturally occurring brackish groundwater) or adding minerals and alkalinity from, for example, limestone. The stabilization process modifies the water composition, potentially reintroducing sodium, chloride and miscellaneous salts, depending on the source. Typically, if 1% seawater is used for post-treatment blending, this would introduce magnesium at approximately 12–17 mg/l and calcium at approximately 4–5 mg/l into the finished water.

Stabilization practices should ensure that the overall process does not significantly reduce total intake of nutrients such as calcium, magnesium and fluoride. Based on local circumstances, public health authorities may wish to set a requirement to further modify final drinking-water composition in light of overall mineral nutrition.

### 1.5.4 Water reuse

Globally, there is extensive indirect wastewater use, in that the water is extracted from sources that have inputs from wastewater discharges. Planned indirect potable reuse of wastewater, where wastewater discharges are sited close to drinking-water extraction points, is a growing source of drinking-water in some localities. For such planned reuse, enhanced treatment steps are usually employed.

The total dissolved solids content of domestic wastewater is greater than that of the original drinking-water. In some settings, the wastewater is treated by membrane technologies to reduce the levels of total dissolved solids, as well as for purification. If groundwater recharge or groundwater storage is part of the process, additional stabilization may be needed after withdrawal of the water and prior to its distribution.

Treatment and stabilization practices should ensure that the overall process does not significantly reduce total intake of nutrients such as calcium, magnesium, fluoride and others below recommended values. Based on local circumstances, water suppliers and public health authorities may wish to further modify final drinking-water composition in light of overall mineral nutrition.

### 1.5.5 Packaged water

Packaged waters, which can be spring or mineral waters or bottled tap waters, form an increasingly utilized source of drinking-water in both developed and developing countries. Because of extreme variation in the mineral composition of marketed bottled waters, with levels of total dissolved solids ranging from almost zero to several thousand milligrams per litre and with a similar variation in concentrations of essential elements, the public should have access to information on the mineral composition of bottled or packaged water.

### 1.5.6 Naturally soft water

Naturally soft water can have aggressive properties towards the piping material through which it is distributed. To avoid adverse health, environmental and economic effects due to the corrosion of piping materials, the water is normally conditioned or stabilized. Frequently, this involves increasing the alkalinity and/or adding corrosion-inhibiting substances (e.g. phosphates) in some form. The choice for the most appropriate conditioning technology will depend on local circumstances (e.g. water quality issues, piping materials, corrosion). Based on local circumstances, water suppliers and public health authorities may wish to further modify drinking-water composition in light of overall mineral nutrition.

### 1.5.7 Collected rainwater

Rainwater collection refers to collection at the household or local community level for local use. Rainwater is soft and usually slightly acidic. If it is distributed through a piped system, the same considerations as for naturally soft

water apply. In some settings, marble chips (calcium carbonate) are added to rainwater storage tanks. This will contribute to calcium intake and corrosion prevention.

### 1.5.8 Point-of-entry and point-of-use devices

Point-of-entry ion exchange (water softener) devices are used in some households to remove hardness (calcium, magnesium) and iron from water. Each divalent ion (e.g. $Ca^{2+}$ or $Mg^{2+}$) in the water is replaced by two sodium ions. Softening will have several aesthetically beneficial effects inside the home, such as reducing scaling in pipes, fixtures and water heaters and improving laundry and washing characteristics, but it also increases the sodium content of the drinking-water.

Point-of-use reverse osmosis and distilling devices remove virtually all the minerals from the input water, functioning as a final barrier against potential trace-level contaminants that may be present, as well as removing nutrients. While this water need not be conditioned if materials not subject to corrosion are used after the treatment, the resultant drinking-water is devoid of all minerals. Use of these devices may result in the reduction of the overall intake of nutrient minerals by the consumers in the households.

Users of these devices should be made aware of the changes in mineral composition that arise and the possible consequences for total nutrient intake and human health. For example, those who sell or install these devices may be encouraged to bring to the attention of the users of these devices the possibility of reduced intake of minerals and various means for their replacement.

Additionally, the manufacturers of these devices may provide a suitable bypass of a portion of this water to maintain some level of these minerals in the water actually consumed (e.g. to a kitchen tap) or develop and add an appropriate remineralizing unit in the water line prior to the point of consumption.

### 1.5.9 Further Issues

Any addition of minerals to water supplies must not lead to overall intakes that exceed recommended maximum intakes.

All suppliers of water, whether through a piped distribution system or packaged/bottled waters, should make available to the consumer information on the mineral content of their water in order to enable development of guidance to vulnerable subgroups. Similar information should be provided by manufacturers of domestic water treatment devices that alter mineral content.

There are a number of possible approaches to ensuring that there is calcium/magnesium sufficiency in populations, including high-risk groups.

These would include dietary education, the introduction of supplementary sources of calcium/magnesium, including in fortified or manufactured foods and bottled water, introduction in manufactured drinking-water or modification of drinking-water. However, different approaches will be appropriate according to local requirements and circumstances in different parts of the world.

Health authorities may wish to consider appropriate requirements for consumer information in the context of overall nutritional guidelines and cost–benefits of alternative interventions.

## 1.6 FLUORIDE IN REMINERALIZED DRINKING-WATER

*Although fluoride was not discussed at length, the meeting of experts agreed to carry forward the relevant recommendation from the 2005 WHO "Nutrients in Drinking Water" report, which is summarized here.*

Most drinking-waters contain some fluoride. Fluoride is present in seawater at concentrations of about 1.2–1.4 mg/l, in groundwater at concentrations ranging from 0 to about 67 mg/l and in surface waters sometimes at concentrations as low as 0.1 mg/l or less. Demineralization and some other treatment processes will reduce levels of fluoride.

Excessively high levels of fluoride intake cause crippling skeletal fluorosis and possibly increased bone fracture risk. Ingestion of excess fluoride during tooth development, particularly at the maturation stage, may also result in dental fluorosis. These effects may be mitigated by co-exposure to some minerals, such as calcium or magnesium.

The recommended value for artificial fluoridation of water supplies is generally between 0.5 and 1.0 mg/l and depends upon the volume of drinking-water consumed daily and the uptake of and exposure to fluoride from other sources. The WHO drinking-water guideline value for fluoride is 1.5 mg/l. Where dental caries risk is high or increasing, authorities may consider addition of fluoride to the demineralized public water supply to between 0.5 and 1.0 mg/l, but other factors should also be considered. In countries where dental health awareness in the public is very high and alternative vehicles for fluoride (e.g. fluoridated toothpaste) are widely available and widely used, a decision to not fluoridate the water would likely be of little consequence. On the other hand, in developing and developed countries where public dental health awareness in some population groups (e.g. lower income) might be much lower, drinking-water containing fluoride at concentrations of 0.5–1.0 mg/l would be important for dental health. A decision to use demineralized water as a drinking-water source without addition of fluoride during remineralization will depend upon the concentration of fluoride in the existing local supply, the prevalence of risk

factors for dental caries (including sugar consumption), oral hygiene practices and dental care, the level of public dental health awareness and the presence of alternative vehicles for fluoride intake available to the whole population.

## 1.7 KEY KNOWLEDGE GAPS AND RESEARCH RECOMMENDATIONS

Recommendations for research to fill key knowledge gaps are listed below. All studies involving human subjects must, of course, follow appropriate ethical guidelines for human research studies.

1. **Develop better information on global intakes of magnesium (by country) and population-specific intake requirements.**

*Rationale*: Data on calcium intake and calcium requirements have recently been compiled for numerous countries. However, comparable information is not readily available for magnesium. Knowledge of local dietary intake of calcium and magnesium from both food and water sources relative to needs is fundamental to decisions about whether water might be a useful source of these nutrients.

2. **Determine the bioavailability of calcium and magnesium from various types of drinking-water in the contexts of the usual diets of people in both healthy and vulnerable population groups.**

*Rationale*: Controlled feeding studies employing waters of defined composition are needed to determine calcium and magnesium net retention, the influence of anions on excretion of calcium and magnesium and functional measures of health in response to increasing doses of calcium and magnesium in water. It would be of further value to test the efficacy of varying concentrations of magnesium and calcium in water as a component of diets in which minerals are likely well absorbed (i.e. low in oxalates and phytates) compared with those high in these inhibitors of mineral absorption to provide context for the heterogeneity of diets consumed worldwide.

3. **Conduct well designed epidemiological studies to elucidate the health implications of waterborne calcium and magnesium.**

*Rationale*: Additional analytical epidemiological studies of improved design (case–control or cohort) are required to elucidate the relationship between

calcium and/or magnesium in drinking-water and health outcomes. Such studies should assess the consumption of calcium and magnesium from both diet and water. Data should also be collected on recognized cardiovascular risk factors, such as smoking, blood lipids and physical activity. Study populations should have a range of drinking-water concentrations to give an adequate range of calcium and magnesium exposures. Studies utilizing cardiovascular death as an end-point should consider multiple types of cardiovascular end-points (e.g. stroke or sudden cardiovascular death) and set up criteria to reduce health end-point misclassification. Biomarkers for calcium and magnesium status should be developed and utilized.

Historical data for health outcomes should be examined in communities that have experienced significant changes in water composition to determine whether related changes in disease rates have occurred. Health outcomes should be monitored in communities where planned changes in water supply or treatment would alter the calcium and/or magnesium concentrations; this should include the use of biomarkers of both exposure and effect. These community intervention studies should be conducted in multiple communities with a wide range of exposures and over different time periods.

Previously conducted cohort studies should be examined to determine whether any may be suitable for reanalysis to determine relationships between serum magnesium levels and drinking-water composition.

Ongoing and planned prospective cohort studies should be examined to determine the feasibility of including a water exposure component, particularly in studies with the potential to examine multiple health outcomes (e.g. cardiovascular disease, osteoporosis and cancer).

**4. Identify vulnerable subgroups for which low intakes of calcium and magnesium present the greatest health risks.**

*Rationale*: Large numbers of people avoid or lack access to dairy products and other foods that are rich in calcium and/or magnesium. These groups should be identified and the associated health risks determined with attention to the threshold intakes associated with low risk. Such high-risk individuals should be the first to benefit from minerals provided via drinking-water or other means of supplementing mineral intakes.

**5. Improve the scientific basis for estimating human magnesium requirements and assessing magnesium status.**

*Rationale*: While experimental magnesium deficiency in humans has been shown to alter heart rhythm, impair carbohydrate metabolism and perturb calcium metabolism, the scientific basis for estimating magnesium requirements is weak. Estimations of human magnesium requirements by metabolic balance studies need to be augmented by measurement of fractional magnesium absorption and by concurrent compartmental analysis of magnesium stable isotope tracer kinetics. Compartmental analysis can yield information about pool sizes and rates of transfer between pools, and parameters deduced from such models can be used as markers of magnesium nutritional status. Magnesium kinetics have been characterized in adolescent girls. Such studies are needed for other vulnerable age–sex groups.

Current tools available for assessing calcium and magnesium status provide little information about the rate of intake, the physiologically functional pools and, for magnesium, the body burden. This limits the informative value of studies of both controlled clinical trials and epidemiological investigations. These purposes will be served by developing biomarkers that are responsive to the rates of intake of each nutrient and that can help to better define the physiologically "normal" reference range for serum magnesium.

**6. Determine the effects of marginal magnesium intakes on risk factors for chronic disease.**

*Rationale*: There is a need for studies designed to assess the interrelationships between dietary magnesium intakes, indicators of magnesium status and risks of osteoporosis, diabetes and heart disease. These efforts should address the health impacts of suboptimal magnesium status such as are typical throughout the world (intakes ~160 mg/day) and should include explicit efforts to develop accurate and specific biomarkers of magnesium status.

- ***Osteoporosis.*** Available data suggest that magnesium deprivation can increase calcium imbalance and lead to an abnormal redistribution of tissue calcium, such that there may be increased risk of soft tissue (including aorta) calcification, despite concurrent bone degradation. Controlled feeding studies in humans are needed to determine the effects of marginal magnesium intakes on bone turnover, as supplementation studies have indicated that magnesium treatment can suppress serum biomarkers associated with bone turnover (osteocalcin, C-terminus of type I procollagen peptide, type I telopeptide), while marginal magnesium status increased serum 25-hydroxyvitamin D.
- ***Diabetes.*** Because all kinases and other ATP-related enzymes and channels regulating insulin action are dependent on magnesium, it is not

surprising that serum magnesium concentrations have been found to be decreased in non-diabetic subjects with metabolic syndrome and that hypomagnesaemia is a common feature in subjects with type 2 diabetes mellitus. Whether low intracellular magnesium content is secondary to or precedes insulin resistance is unclear; however, recent evidence suggests that subclinical magnesium deficiency may precipitate a diabetic state. Studies are needed to determine the role of subclinical magnesium status in diabetes risk. These should include measures of glycosylated haemoglobin (haemoglobin $A_{1c}$), an indicator of glycaemic control that has been found to respond to oral magnesium supplementation and to correlate negatively with serum ionized magnesium or serum total magnesium in persons with type 2 diabetes mellitus.

- ***Cardiovascular health.*** In light of the epidemiological evidence for a relationship between magnesium and cardiovascular health, studies are needed to determine whether subclinical magnesium deficiency increases cardiovascular disease risk, particularly by affecting early inflammatory or oxidative stress indicators, such as substance P, interleukin-1, tumour necrosis factor-α and C-reactive protein, each of which has been found to respond to magnesium deprivation in animal models and/or to vary inversely with serum magnesium.

7. **Re-examine both older and recent hypotheses that water low in total dissolved solids or acidic water increases excretion of some nutrients from the organism.**

*Rationale*: Various experimental and epidemiological studies on humans and animals published in the former Soviet Union and the Russian Federation since the 1960s indicated that consumption of demineralized or low-mineral water may lead to both acute and chronic changes in metabolism of certain minerals and to higher incidence of several diseases. Recent experiments from Sweden tested similar hypotheses, such as that consumption of acidic water (which is usually water low in mineral content) enhances excretion of magnesium from the body.

## 1.8 REFERENCES

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# 2

# Overview of global dietary calcium and magnesium intakes and allowances

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## 2.1 INTRODUCTION

Calcium and magnesium are important nutrients in the development and maintenance of human health. These dietary components (as well as phosphorus) are most strongly associated with the development of strong bones and teeth and are essential to cardiovascular function. Approximately 99% of the body's calcium stores are found in bones and teeth, with small amounts in the tissues and body fluids necessary for muscle contraction, nerve transmission and glandular secretions. A smaller portion (50–60%) of the body's magnesium is found in bone. Magnesium is a cofactor for over 350 enzyme reactions, many of which involve energy metabolism. It is also involved in protein and nucleic acid

synthesis and is needed for normal vascular tone and insulin sensitivity. Both dietary calcium and dietary magnesium may play a role in the etiology of osteoporosis and cardiovascular disease (IOM 1997).

Nutrient recommendations are derived using a variety of approaches. Often estimation of an average requirement is based on a biological distribution curve for a specific end-point in a defined healthy population. If this distribution is normal, the mean requirement of the population is the average requirement. If the distribution is not normal, the data could be transformed, and the median intake is then the average requirement. This "requirement" value is adjusted to accommodate interindividual variation for the derivation of a recommended value ("allowance") that will meet the physiological needs of most individuals in the population. Nutrient intake values for individuals are derived from the variations in nutrient requirements and nutrient intakes of the specific population. This derivation reflects an application of the average requirement.

This chapter provides an overview of the global recommended dietary calcium and magnesium intakes and allowances.

## 2.2 REFERENCE INTAKES

Nutrient-based dietary standards were first established in the United States in the early 1940s (Mertz 2000). The current reference intake values for calcium and magnesium, as described in the Dietary Reference Intakes (DRIs) established by the United States Institute of Medicine (IOM 1997), are composed of four different values and are defined as follows:

- *Estimated Average Requirement (EAR)*: The nutrient intake value that is estimated to meet the requirement defined by a specified indicator of adequacy in 50% of the individuals in a life stage or gender group.
- *Recommended Dietary Allowance (RDA)*: The average daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (97–98%) individuals in a life stage and gender group. Generally derived from the EAR using a 10% coefficient of variation as a default in the absence of nutrient-specific data on variability in the target population.
- *Adequate Intake (AI)*: An estimate of the average nutrient intake by a group or groups of healthy people within a designated age, life stage and/or gender group. It is derived from the observed intakes of apparently healthy individuals in the subgroup of interest. AI values are established when there are insufficient data to derive an EAR, as was the case for calcium.

- *Tolerable Upper Intake Level (UL)*: The maximum level of a total chronic daily intake of a nutrient that is unlikely to pose risks of adverse effects to the most sensitive members of a healthy population.

Table 2.1 lists the AIs for calcium and the AIs, EARs and RDAs for magnesium from the DRI report of 1997 (IOM 1997).

Table 2.1. DRI values for calcium and magnesium (from IOM 1997)

| | Calcium intake (mg/day) | Magnesium intake (mg/day) | | |
|---|---|---|---|---|
| Group | AI | AI | EAR | RDA |
| 0–6 months | 210 | 30 | | |
| 7–12 months | 270 | 75 | | |
| 1–3 years | 500 | | 65 | 80 |
| 4–8 years | 800 | | 110 | 130 |
| 9–13 years | 1300 | | 200 | 240 |
| 14–18 years | 1300 | | 340/300[a] | 410/360[a] |
| 19–50 years | 1000 | | 330/255[a] | 400/310[a] |
| >50 years | 1200 | | 350/265[a] | 400/310[a] |
| **Pregnancy** | | | | |
| <18 years | 1300 | | 335 | 400 |
| 19–30 years | 1000 | | 290 | 350 |
| 31–50 years | 1000 | | 300 | 360 |
| **Lactation** | | | | |
| <18 years | 1300 | | 300 | 360 |
| 19–30 years | 1000 | | 255 | 310 |
| 31–50 years | 1000 | | 265 | 320 |

[a] Male/female.

## 2.3 DIETARY INTAKES OF CALCIUM AND MAGNESIUM

A number of different dietary assessment methods have been utilized in studies to describe dietary intakes around the world. These approaches include food frequency questionnaires, 24-h recall, food diaries and market basket analysis. Each of these methodologies has its inherent limitations but provides a snapshot of intakes for healthy populations as well as populations at risk for nutrient insufficiency.

Data on the dietary intakes of calcium and magnesium collected from a variety of dietary studies published after the 1997 DRI report (IOM 1997) are summarized in Tables 2.2 and 2.3. The studies ranged from those that tested hypotheses related to specific nutrients and chronic diseases such as hypertension or diabetes to those used to monitor nutrient intakes by specific populations. Not only were different approaches employed in assessing dietary intake, but the studies also varied in the population group samples (e.g. adults, children or infants; males, females or mixed sexes). For the most part, the studies selected did not involve dietary intervention. If data were abstracted from an intervention study, only those for the control population or the study population before intervention were used. Although some of the studies selected involved measured use of supplements, the information on intake that included the supplements was not used for this report. A number of recent reports, however, provide data on supplement consumption in the United States (Radimer *et al*. 2004; Archer *et al*. 2005).

Table 2.2. Reported ranges for calcium and magnesium intakes in the United States and Canada compared with the recommended amounts set out as an AI or EAR[a]

| | Calcium intake (mg/day) | | Magnesium intake (mg/day) | |
|---|---|---|---|---|
| Group | AI | Dietary intake | EAR | Dietary intake |
| Adults (>18 years) | 1000–1200 | 466–880 | 255–265 female<br>330–350 male | 168–319 |
| Adolescents (9–18 years) | 1300 | 685–1390 | 200–340 | 164–185 |
| Children (1–8 years) | 500–800 | 723–857 | 65–110 | 148–187 |
| Infants (<1 year) | 210–270 | 372–842 | 30–75 (AI) | 33–140 |

[a] Sources: Millen *et al*. 1997; Humphries *et al*. 1999; Bell *et al*. 2002; Heaney *et al*. 2002; Johnson *et al*. 2002; Abbott *et al*. 2003; IOM 2003; Mrdjenovic and Levitsky 2003; Frary *et al*. 2004; Lancaster *et al*. 2004; Lappe *et al*. 2004; Bounds *et al*. 2005; Gilmore *et al*. 2005; Song *et al*. 2005; Townsend *et al*. 2005; Briefel *et al*. 2006; Daida *et al*. 2006.

## 2.2.1 Intakes in the United States and Canada

The 2005 *Dietary Guidelines for Americans* (United States Department of Agriculture and United States Department of Health and Human Services 2005) reported that less than 60% of adult men and women in the United States met the AI values for calcium and magnesium, and both calcium and magnesium were listed as nutrients consumed in amounts low enough to be of concern.

Many children aged 9 years and older had intakes below the EAR for magnesium. Median calcium intake was well below the AI for females beginning at 9 years of age, although risk of deficiency cannot be determined using an AI. Female adolescents aged 14–18 years demonstrated the most severe shortfalls in intake for both magnesium and calcium (Suitor and Gleason 2002). Table 2.2 provides an overview of reported intakes of calcium and magnesium in the United States and Canada in the years between 1997 and 2006.

Table 2.3. Reported ranges for or usual calcium and magnesium intakes by adults in countries other than the United States[a]

| Country/area | Calcium intake (mg/day) | Magnesium intake (mg/day) |
|---|---|---|
| Canada | 757–1320 | 209–279 |
| France | 881–1003 | 284–377 |
| Guam | 743 ± 575 | 270 ± 131 |
| Indonesia | 342 | Not determined |
| Israel | 548–733 | 228–270 |
| Japan | 660 ± 185 | Not determined |
| Malaysia | 255–333 | Not determined |
| Myanmar | 498 | Not determined |
| Pakistan | 508 ± 139 | Not determined |
| Philippines | 390 | Not determined |
| Singapore | 482 | Not determined |
| South Africa | 438–577 | 228–285 |
| Spain | 1267 | 366 |
| United Kingdom | 755–1267 | Not determined |
| Viet Nam | 488 | Not determined |
| Adult DRI | 1000–1200 (AI) | 255–265 female (EAR)<br>330–350 male (EAR) |

[a] Sources: Monge-Rojas 2001; Galan *et al*. 2002; Troppmann *et al*. 2002; Jodral-Segado *et al*. 2003; Pobocik *et al*. 2003; Akhter *et al*. 2004; Nakamura *et al*. 2004; Charlton *et al*. 2005; Reimer *et al*. 2005; Shahar *et al*. 2005; Tee and Florentino 2005.

## 2.2.2 Global intakes

The survey data on adult intakes of magnesium are more varied than those for calcium. Estimates made on a regional basis indicate a wide variation in dietary calcium intakes, with the lowest intakes occurring in developing nations, particularly those in Asia, as displayed in Table 2.3. Higher calcium intakes are apparent in Europe and North America, largely due to the greater contributions from animal products. Magnesium data from countries other than the United

States are limited but suggest that dietary magnesium values are more uniform across cultures than those for calcium. However, dietary magnesium intakes are still only marginally adequate when compared with the EAR for magnesium. Similarly, the data demonstrate high variability in calcium and magnesium contributions from drinking-water, reflecting the mineral content of the source water (Galan *et al*. 2002; Jodral-Segado *et al*. 2003).

## 2.4 BIOAVAILABILITY OF NUTRIENTS

The biological effects of a nutrient are heavily dependent on its bioavailability. A number of key factors determine the bioavailability of a nutrient. These factors, which must be taken into account when determining nutrient intake values, may include the chemical form in which the nutrient is presented to the intestinal absorptive surface, the presence of competing foods or drugs in the intestinal lumen, the concentration of food constituents (such as phytates and other chelating agents) that bind to the nutrient and make it unavailable for absorption, intestinal transit time and enzyme activity. The underlying nutritional status of an individual can also play a role in determining the level of absorption of a specific nutrient. The bioavailability of nutrients may also be affected by the presence of other nutrients, as a nutrient may affect not only the absorption of other nutrients, but also their transport, tissue uptake, function and metabolism. Hence, concurrent ingestion of several nutrients may result in synergistic, antagonistic or threshold effects. The effect of a single nutrient or of multiple nutrients on bioavailability should be evaluated separately unless no interactive or threshold effects can be found.

The basis of recommended daily allowances for calcium and magnesium varies between agencies. In many cases, the derivation of the recommended intakes is not always clearly delineated; in some cases, values have been simply adopted by one agency from the recommendations of another agency. A review of reports finds that recommended intakes for a specific age and/or sex group can vary widely. For example, in a review of calcium recommendations for infants, children and youth (SCF 2003), recommended intakes for infants aged 6–12 months ranged from 270 to 650 mg/day and for children 1–4 years of age ranged from 350 to 800 mg/day. If, ideally, we are to globally harmonize nutrient-based dietary recommendations, an essential first step will be to determine a standard approach or model upon which to derive estimates of nutrient needs. Sometimes it is valuable to conduct analyses using several approaches to determine if they yield a similar estimate of nutrient requirement, thereby providing more confidence in the value derived.

## 2.5 OVERVIEW OF APPROACHES TO ESTABLISH RECOMMENDED INTAKES FOR CALCIUM AND MAGNESIUM

### 2.5.1 Calcium

#### *2.5.1.1 Calcium intake data*

For infants in the first half year of life, intake of mineral from a predicted average volume of human milk is the basis for recommended intakes used in most dietary standard reports. Such an approach supports the WHO (1996) and multicountry recommendation of exclusive breastfeeding for the first 6 months of life. From 6 to 12 months, the recommended intakes are usually based on the amount consumed from a standard volume of human milk plus reported intakes from solid foods. Because such an approach does not rely on a physiological or functional outcome, but rather an observed intake in normal healthy infants, the model is that of an adequate intake in contrast to an estimated average requirement or recommended daily intake.

#### *2.5.1.2 Metabolic balance*

Data from metabolic balance studies are frequently used to determine the intake of mineral that will provide for zero balance in adults or the amount required for growth, as estimated from accretion of calcium in bone in children and youth. Problems in utilizing data from metabolic balance studies to derive estimated requirements include the lack of an appropriate adaptation period, consideration of the impact of dietary factors on bioavailability of the minerals and a lack of dose–response data. The design of metabolic balance studies must provide a sufficient duration of study to allow for systemic and intestinal adaptation to variations in intake of mineral, which may include measurement of hormonal homeostatic changes in response to intake or interaction effects with other nutrients or food components in the diet (see chapter 9).

For calcium, the approach taken by the joint United States/Canadian report on DRIs (IOM 1997) was the intake required to achieve maximal calcium retention based on calcium retention data from published reports of balance studies that were conducted over a range of calcium intakes. For each age group, the data were modelled to determine an estimate of calcium intake that provided a desirable retention rate of calcium, which varied by life stage. The desirable calcium retention in the DRI report was estimated based on peak bone mineral accretion, which for calcium was 282 mg/day in males and 212 mg/day in females between 9 and 19 years of age. Application of these estimates of

calcium accretion to both the maximal retention model and a factorial model resulted in similar values, which were then adopted as AI recommendations of 1300 mg for children 9 through 18 years of age (IOM 1997). The Belgian recommendations are just slightly lower, at 1000 mg for children 11–14 years of age and 1200 mg/day for those 15–18 years of age (De Backer 2003). In reports such as *Recommended Dietary Allowances for the Caribbean* (Committee of the Expert Group on Caribbean Food and Nutrition Surveillance System 1994), lower recommendations for calcium were made for adolescents (900 mg/day) and adults (700 mg/day) on the premise that the population is primarily of African origin, is fairly active and gets adequate amounts of sunshine and thus may not need as much calcium for bone health. The Finnish recommendations are also lower, at 900 mg for both males and females 10–17 years of age (National Nutrition Council 1999). The recent recommendations from Mexico (Bourges *et al.* 2005) and Australia (National Health and Medical Research Council 2006) parallel those in the DRI report (IOM 1997), with the exception that the Australian report recommends 1300 mg of calcium per day (compared with 1200 mg) for adults over 50 years of age.

Appreciable differences in the RDAs for calcium for every age group exist among selected South-east Asian countries (Indonesia, Malaysia, Philippines, Singapore, Thailand and Viet Nam). In setting the RDAs for most South-east Asian countries, currently published reports were extensively consulted, including the 2002 Expert Consultation on Recommended Nutrient Intakes for Vitamins and Minerals of the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) (FAO/WHO 2002), the United Kingdom Department of Health's Dietary Reference Values (Expert Group on Vitamins and Minerals 2003) and the recommendations of the DRI committee (IOM 1997). Given the habitually low intake of calcium by South-east Asian women, the South-east Asian RDAs throughout pregnancy and lactation were set at 1000 mg/day (Tee and Florentino 2005). This amount is 300 mg/day above the South-east Asian RDA for non-pregnant women (Tee and Florentino 2005) but is the same as that recommended by FAO/WHO (2002) and the DRI committee (IOM 1997) for pregnant women.

### *2.5.1.3 Factorial model*

Another approach to setting recommended intakes for calcium utilizes the factorial model, which is based on summing tissue accretion based on body weights and known bone and/or lean tissue content of the mineral for children and also for the fetus and mother in pregnancy, or for milk nutrient secretion and maternal needs in lactating women. Data from metabolic balance studies have been applied to derive obligatory losses as the principal determinant of requirement in a factorial model. While data exist to estimate obligatory faecal

and urinary loss (estimated to be 160 mg/day for adults), there are no reliable data on losses through sweat or sloughed skin or the small amount for consolidation of bone in the third decade (SCF 1993). For growing children and youth, other reports have also considered the calcium needs for bone accrual in establishing recommended intakes using a factorial model. The value applied for absorptive efficiency may also vary between reports, but is usually of the order of 30–35% for adults and 40% for children.

Using this approach, the Scientific Committee on Food of the European Commission placed recommended intakes for males 11–17 years of age at 1000 mg/day and for females at 800 mg/day (SCF 1993), while the DRI report set the recommended AI at 1300 mg/day for both sexes (IOM 1997). In pregnancy, recent studies demonstrated that adaptive maternal responses include increased efficiency of absorption of calcium (via upregulation of the active hormone of vitamin D, which then upregulates intestinal calcium absorption); thus, there was no evidence for higher intake needs than for non-pregnant women (IOM 1997). Similarly, in lactation, biological adjustments during lactation and after weaning result in no excess bone loss to cover the calcium secreted into milk, so again the DRI report (IOM 1997) recommended intakes as for non-pregnant women. In dietary standards published prior to the late 1990s, additional calcium intakes are sometimes recommended during pregnancy (Committee of the Expert Group on Caribbean Food and Nutrition Surveillance System 1994) and lactation (SCF 1993; Committee of the Expert Group on Caribbean Food and Nutrition Surveillance System 1994), but these pre-date the studies upon which the DRI recommendations were made.

#### *2.5.1.4 Extrapolation models*

When biological data are not available to estimate recommendations, extrapolation models adjusted for mean population-based body weights for age and sex are applied to derive values for young children from recommendations for adults or older children, or for older adults, by extrapolating up from younger adult values. This is particularly true for older infants (7 months to 2 years) and for children of preschool and school ages. Consideration should be given to the difference across life stages in nutrient needs, not only for maintenance metabolism, but also for obligate losses and for growth, which are particularly large during the phases of rapid growth in infancy, the preschool growth spurt and the pubertal growth spurt (Koletzko *et al.* 1998). In extrapolating nutrient recommendations for younger adults up to those for older adults, adjustment is usually based on reference body weights of the two age groups, but such a direct extrapolation does not account for differences in absorption or excretion of nutrients owing to degenerative processes, metabolic rate or activity levels. This

underlines the importance of obtaining metabolic balance data on healthy individuals across the various life stages.

Models used for extrapolations include calculations based on body size or metabolic turnover. In the first case, nutrient requirement is estimated to be directly proportional to total body weight using age- and sex-appropriate reference body weights, but these will vary between countries. Also, such an extrapolation does not allow for variations between age groups in metabolic rate, energy intake or basal metabolic rate. Extrapolation of values from adults down to younger ages is often based on metabolic turnover, adjusting the values derived for adults to the 0.75 power of body mass, which corrects for metabolic differences related to body weight (Kleiber 1947; West *et al*. 2002). The assumption inherent in this method is that the maintenance needs of the nutrient, expressed with respect to metabolic weight, are similar for adults and children. For calcium, the only application of an extrapolation model was for adults aged >70 years, as this was derived by extrapolating up from the values for desirable retention of 51- to 70-year-olds.

### *2.5.1.5 Epidemiological or intervention studies*

Nutrient–disease relationships, such as with osteoporosis, hypertension, cardiovascular disease and diabetes, were considered by several agencies for one or both of calcium and magnesium, but the evidence was not sufficiently compelling to be applied in the derivation of the recommended intakes for calcium in any reports of which we are aware. Nutrient–disease relationships are discussed in detail in other chapters (see chapters 5, 6 and 9). While the primary indicator used in the DRI report (IOM 1997) was desirable calcium retention for specific age groups, data from controlled clinical trials that studied the effect of calcium intake on bone mass were reviewed where data were available for children and older adults.

In dietary standards such as the DRI report (IOM 1997), an association between lifelong calcium intake and risk of osteoporosis or fracture in later life could not be established as a criterion to set recommended intakes. The presence of a myriad of confounding variables that impact on bone accrual during growth, maintenance during adulthood and rate of loss in later life makes it impossible to draw a direct relationship between dietary calcium and bone status. Such variables include weight-bearing physical activity, vitamin D status (which is dependent on sun exposure and dietary intake of fortified foods) and genetics, such as the vitamin D receptor polymorphisms. To our knowledge, all current dietary standards base their recommendations for calcium intake on metabolic data.

## 2.5.2 Magnesium

### *2.5.2.1 Magnesium intake data*

As with calcium for infants in the first half year of life, intake of magnesium from a predicted average volume of human milk is the basis for recommended intakes used in most dietary standard reports. From 6 to 12 months, the recommended intakes are usually based on the amount consumed from a standard volume of human milk plus reported intakes from solid foods.

### *2.5.2.2 Magnesium balance*

For adults, the amount of magnesium intake needed to maintain "zero balance" is a key criterion for setting recommended intakes. Similar to the issues raised for calcium, consideration must be made for duration of time to adapt to varying intakes of minerals, for dietary components that might reduce absorption of magnesium, such as phytates, and for loss of magnesium through sweat, skin or menses. In the DRI report (IOM 1997), intakes of magnesium that provided for zero or slightly positive magnesium balance were used to derive the EARs. When an EAR value was expressed on a body weight basis, mean reference weights were then applied to give a value in milligrams per day. A similar approach was used by the Scientific Committee on Food of the European Commission (SCF 1993). For some reports (Committee of the Expert Group on Caribbean Food and Nutrition Surveillance System 1994; IOM 1997; National Nutrition Council 1999), the recommended intake for males is greater than that for females, whereas other reports (SCF 1993) provide only one value or a range of recommended intakes for both sexes. The recommendations for magnesium in the recent Mexican report (Bourges *et al*. 2005) parallel those of the DRI report (IOM 1997). Magnesium was not one of the "core nutrients" included in the South-east Asia RDAs; hence, RDAs have yet to be set for this nutrient in South-east Asia (Tee and Florentino 2005).

### *2.5.2.3 Factorial method*

Accretion of magnesium during growth can be derived using body composition values obtained from cadavers. To our knowledge, such data have not been applied in current reports. For pregnancy, a factorial method was used for the DRIs in the joint United States/Canadian report (IOM 1997), by assuming a magnesium content of 470 mg/kg lean body mass, a gain of 7.5 kg lean mass during pregnancy and an absorption efficiency of 40%. This summed and rounded to 35 mg/day of *additional* magnesium required during pregnancy. This value is then added to the EAR for age so that for pregnant women aged 19–30

years, the EAR is 290 mg/day. Because variance in requirements cannot be determined from the available data for pregnant women, a coefficient of variation of 10% was assumed to account for individual variability in requirements. The RDA for magnesium of 350 mg/day was thus established for pregnant women 19–30 years of age. For lactation, enhanced bone resorption and reduced urinary magnesium loss cover the extra needs for magnesium excreted in milk; thus, no additional intake was recommended (SCF 1993; IOM 1997).

#### *2.5.2.4 Extrapolation models*

When balance data are not available for specific age groups, estimates of magnesium needs are extrapolated from those for other age groups. For example, in the DRI report (IOM 1997), recommendations for the 1- to 3-year and 4- to 8-year age groups were extrapolated from balance data in older children, adjusting for reference body weight.

#### *2.5.2.5 Epidemiological or intervention studies*

Low magnesium status has been implicated in hypertension, coronary artery disease, type 2 diabetes mellitus, pre-eclampsia and metabolic syndrome. Nutrient–disease relationships are discussed in detail in other chapters (see chapters 5, 6 and 9). The primary indicator used in the DRI report (IOM 1997) for magnesium for older children and adults was metabolic balance studies.

## 2.6 OVERVIEW OF UPPER LEVELS OF INTAKE FOR CALCIUM AND MAGNESIUM

### 2.6.1 Defining upper levels of intake

The DRI report defines the upper level (UL) as "the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all apparently healthy individuals in the specified life stage group. As intake increases above the UL, the potential risk of adverse effects may increase" (IOM 1998a). The Food and Nutrition Board of the United States Institute of Medicine's Subcommittee on Upper Reference Levels of Nutrients, after much deliberation, selected a risk assessment methodology on which to base its assessment of the ULs (NRC 1983). To use a UL to characterize population nutrient intakes, one needs to know the actual usual intake of the nutrient, which is often difficult, as accurate assessment of nutrient intake is limited to the number of available data on supplement use, and because food composition data are quickly outdated as new products appear on the market. Additionally,

deriving the ULs for various populations is challenging because of genetic diversity among individuals in populations and individuals' different stages of life. The UL was further defined by the DRI committee as the "tolerable upper intake level" in order to convey the concept that upper intake levels derived by risk assessment methodology were tolerable but were not to be portrayed as the desirable intakes to be achieved. This decision is consistent with principles elaborated by WHO for the establishment of ULs for xenobiotic substances found in foods and at present represents a global consensus approach (Ministère de l'Economie et des Finances *et al*. 1995; Nordic Council of Ministers 1995; IOM 1997, 1998b, 2000a,b, 2004; Expert Group on Vitamins and Minerals 2003; SCF 2003; FAO/WHO Technical Workshop on Nutrient Risk Assessment 2006). Table 2.4 provides the ULs for calcium and magnesium as set by national and regional authorities.

### 2.6.2 Upper level of intake for calcium

Values for the ULs in the DRI reports from the United States and Canada have been set for 14 elements and 8 vitamins and are provided for at least some population subgroups. The safe or tolerable upper level of intake above which habitual intake may produce an adverse health effect was set at 2500 mg/day for calcium in some reports (IOM 1997; SCF 2003; Bourges *et al*. 2005; National Health and Medical Research Council 2006), but the critical adverse effect chosen as the basis for the UL (e.g. milk alkali syndrome) is not consistent among agencies. Also considered as limiting adverse effects of excessive calcium intakes were kidney stone formation and the interaction of calcium with the absorption of other essential minerals. Risk of excessive calcium intake from food and supplements is not highly likely based on previous population-based dietary survey data; however, with the increase in calcium-fortified foods and diversity of supplements, ongoing surveillance of population intakes is vital. The estimated UL of 2500 mg for adults (from diet and supplementary sources) is considered to be a conservative estimate. The available data were judged to be inadequate for deriving a UL for pregnant and lactating women.

### 2.6.3 Upper level of intake for magnesium

The UL for magnesium was established based solely on dietary supplement intake levels as opposed to intakes from food. No adverse effect could be established for food-based mineral. Osmotic diarrhoea was chosen as the most sensitive toxic manifestation of excess magnesium intake as a result of excessive

intake from supplements in a sugar base. This indicator was consistently used across reports (IOM 1997; Expert Group on Vitamins and Minerals 2003; SCF

Table 2.4. Upper levels for calcium and magnesium intake, by national/regional authority (adapted from FAO/WHO Technical Workshop on Nutrient Risk Assessment 2006)

| Nutrient | United States/Canada: IOM (1997) | United Kingdom: Expert Group on Vitamins and Minerals (2003) | European Union: SCF (2003) |
|---|---|---|---|
| Calcium from diet and supplementary sources | Adults >19 years: 2500 mg/day (62.5 mmol/day)<br>Children 1–18 years: 2500 mg/day (62.5 mmol/day)<br>Infants 0–12 months: It was not possible to establish a UL for supplementary calcium or for calcium from diet | Insufficient data to establish ULs<br>Guidance level:<br>• Supplemental calcium doses up to 1500 mg/day would not be expected to result in any adverse effect, but higher doses could result in adverse gastrointestinal symptoms in a few people<br>• An estimate for total calcium intake has not been made, as the effect is related to calcium in supplemental doses | Adults: 2500 mg/day (62.5 mmol/day) |
| Magnesium from supplementary sources[a] | Adults: 350 mg/day (14.6 mmol/day)<br>Children >8 years: 350 mg/day (14.6 mmol/day)<br>Children 4–8 years: 110 mg/day (4.6 mmol/day)<br>Children 1–3 years: 65 mg/day (2.7 mmol/day)<br>Infants: It was not possible to establish a UL for supplementary magnesium | Insufficient data to establish ULs | All age groups: 250 mg/day (10.4 mmol/day) |

[a] No adverse effects have been associated with the ingestion of magnesium from food sources. Osmotic diarrhoea results from excess consumption of magnesium-containing products.

2003) to establish a UL of 250–350 mg/day for magnesium. For children, there is a paucity of research-based data, so UL values are most often extrapolated

down from UL values set for adults or no UL is set, as in infants (see Table 2.5). The UL for pregnant and lactating women is set at 350 mg/day, as no increased susceptibility to adverse effects was noted in this population. In patients with certain clinical conditions, intake levels above 350 mg/day may be beneficial in the clinical setting (IOM 1997). The prevalence of excessive intakes, above the UL, for both calcium and magnesium is extremely low in the United States, at less than 5% of the population. However, it is important to maintain surveillance of the use of supplemental forms of these nutrients as well as calcium-fortified products in the marketplace. For both magnesium and calcium, sensitive subpopulations exist that may be particularly susceptible to high intakes.

Table 2.5. Adverse health effects considered and used in setting ULs for calcium and magnesium, by report (adapted from FAO/WHO Technical Workshop on Nutrient Risk Assessment 2006)

| | Information provided relative to the adverse effect | | |
|---|---|---|---|
| Adverse effect | United States/ Canada: IOM (1997) | United Kingdom: Expert Group on Vitamins and Minerals (2003) | European Union: SCF (2003) |
| **Calcium** | | | |
| *Adults* | | | |
| Milk alkali syndrome | Summary of case reports | Not available / no UL set | Intervention trials without adverse effects |
| *Infants and children* | | | |
| Applicability of extrapolation to other groups | Also applicable to 1–18 years, pregnancy, lactation | Guidance value for supplemental intake 1500 mg/day (37.5 mmol/day) | Not applicable to children and adolescents |
| **Magnesium** | | | |
| *Adults* | | | |
| Osmotic diarrhoea | Summary of intervention studies | Summary of intervention studies | Summary of intervention studies |
| *Infants and children* | | | |
| Applicability of extrapolation to other groups | Extrapolation for body weight 1–8 years, also applicable in pregnancy and lactation | Guidance level for supplemental intake 400 mg/day (16.7 mmol/day) | Applicable to supplemental intake, applicable to children >4 years |

## 2.7 SUMMARY

Great heterogeneity exists in the formulation of dietary recommended intakes for calcium and magnesium, and future recommendations should ideally be based on established and common methodologies for respective age groups. Based on the survey data available, it is clear that very large numbers of people consume levels of these minerals that are insufficient to support even the most conservative estimates of their physiological needs. Additionally, very few studies have considered drinking and cooking waters in terms of their potential contributions to total calcium/magnesium intakes, and it is critical that this information be gathered to provide more accurate assessments of population intakes.

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# 3

# The mineral composition of water and its contribution to calcium and magnesium intake

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## 3.1 INTRODUCTION

Traditionally, drinking-water has been drawn from streams, lakes and rivers, collected directly from rainwater or extracted from groundwater sources such as wells. Advances in technology have offered other approaches, such as desalination of ocean water, melting of ice and reclamation of used water by membranes and other advanced techniques. Different water quality issues have to be faced when utilizing these different water resources. Some of these are at present largely neglected in water quality regulations. One important issue that deserves attention is the low mineral intakes from foods and water that are

common in many parts of the world. Today, subclinical deficiencies of iron, magnesium, zinc and calcium prevail in both the developed and developing worlds. Although dozens of geographical studies have been conducted on minerals in drinking-water and their relationships to various diseases, their daily intakes and status of deficiencies as well as their health consequences are still inadequately understood.

This chapter attempts to provide some background information on drinking-water composition in different parts of the world. Studies from world regions are also briefly reviewed with regard to minerals in drinking-water and their known and potential health effects.

## 3.2 DRINKING-WATER IN DIFFERENT REGIONS

### 3.2.1 WHO Western Pacific and South-East Asia Regions

Historically, "drinking-water" was often regarded as water without pathogenic microbial or obvious anthropogenic or chemical contamination. Many people assumed that such "clean" water was harmless. Thus, typically, only a few chemical elements that were assumed to define water quality were routinely analysed in most Asian nations. Minerals such as calcium, magnesium and zinc still are not normally on the regulatory monitoring list.

The drinking-water resources in Asia are diverse and include piped and non-piped supplies. Most drinking-water is piped, but ditches, ponds, springs and rivers are important in some regions, accompanied by rainwater collection and wells. The mineral contents of water from most Asian drinking-water supplies are generally in the range of 2–80 mg/l for calcium ($Ca^{2+}$) and below 20 mg/l for magnesium ($Mg^{2+}$). Several epidemiological investigations on the possible associations between the risk of gastrointestinal tract cancers and minerals in drinking-water, in particular hardness, have been well reported. Studies by Yang and his colleagues showed that there was an inverse relationship between water hardness and various diseases, including coronary mortality, cerebrovascular disease and gastrointestinal tract cancers in Taiwan, China; however, the specific concentrations of calcium, magnesium and other minerals that made up the total water hardness were not given in these reports (Yang *et al.* 1996, 1997, 1999; Yang 1998; Yang and Hung 1998).

A few previous studies have looked at the relationship between pregnancy outcome and magnesium nutritional intake and found that magnesium supplementation could have beneficial effects on prenatal outcome. A study was carried out by Yang *et al.* (2002a) to examine the relationship between the levels of magnesium in drinking-water and the risk of delivering a child of very low birth weight (birth weight less than 1500 g). There was a significant trend

towards a decreased risk of having a child of very low birth weight with increasing magnesium levels in drinking-water (Yang *et al*. 2002a). It was hypothesized that magnesium supplementation can reduce smooth muscle contractibility and tone and that this effect can be clinically manifested by a reduction in blood pressure and a reduction in the incidence of premature delivery. A similar study was conducted on the relationship between the levels of calcium in drinking-water and the risk of delivering a child of very low birth weight by the same group in Taiwan, China. The results suggest that there is significant protective effect of calcium intake from drinking-water on the risk of delivering a very low birth weight baby (Yang *et al*. 2002b).

Punjab is a typical large state in north-eastern India, neighbouring Pakistan. People in this region relied on groundwater as a drinking-water source. Kumar *et al.* (2006) studied the water from 24 different locations and noted that there was a large variation in mineral contents in the well water, with a range of 8–343 mg/l for calcium and 5–235.6 mg/l for magnesium. This study suggests that even for groundwater from similar geographical locations, the mineral contents can vary markedly.

Magnesium is required in higher quantities during the rapid growth phase in children. Its level in the groundwater in Kerala, India, is low and is believed to cause magnesium deficiency, especially in children from the lower socio-economic groups who also suffer from nutritional insufficiency. Nair and colleagues (1995) compared the serum and erythrocyte magnesium levels of schoolchildren from high and low socioeconomic classes. The results showed that serum and erythrocyte magnesium levels were significantly lower in both boys and girls from low socioeconomic groups who consumed groundwater and who had lower body mass indices.

An attempt was made to determine whether an association existed between hardness of water and certain cardiovascular diseases in indigenous populations who drink untreated water collected directly from rivers. Blood pressure was measured in persons living in villages along the banks of the Wogupmeri River in Papua New Guinea. The calcium content of the river water was found to decrease as the river flows downstream, whereas the blood pressure of the villagers living along this river increased as the river flows downstream (Masironi *et al*. 1976). The results of this investigation tend to be in line with more recent findings of a beneficial effect of hard water on cardiovascular parameters (Yang 1998).

Analysis of water hardness in major Australian cities by the Australian Water Association (http://www.awa.asn.au) shows a range from very soft (Melbourne) to very hard (Adelaide). Total hardness as calcium carbonate (in mg/l) is as

follows: Melbourne, 11.3–14.0; Sydney, 39.4–60.1; Perth, 30–198; Brisbane, 100; Adelaide, 101–216; Hobart, 6–50; Darwin, 22–38.

### 3.2.2 WHO Eastern Mediterranean and African regions

Very few studies have been conducted in African and eastern Mediterranean countries on minerals and water supplies and consumption. Historically, these regions have relied on springs, rivers and wells as water sources. Based on limited data from these regions, mineral contents of well waters are generally higher than those of surface waters. Today, many of these countries rely on desalinated seawater as a source of drinking-water. This water is frequently obtained by mixing distilled water with low-salinity groundwater to obtain water suitable for drinking.

A survey of trace elements, including magnesium, but not calcium, was conducted by al-Saleh and al-Doush (1998) in Riyadh, Saudi Arabia. This city is supplied mainly with desalinated seawater and water from deep wells. The study found that the household drinking-water contained magnesium at concentrations ranging from 0.78 to 0.88 mg/l, suggesting that the concentration of this trace element in drinking-water is minimal. Olajire and Imeokparia (2001) investigated several ions in water samples from the Osun River, a main water source for a large population of eastern Nigeria, in addition to several groundwater sources in this region. The calcium concentration in the Osun River ranged from 2 to 60.8 mg/l, whereas the concentration in groundwater sources ranged from 3 to 52 mg/l.

### 3.2.3 WHO Region of the Americas

Significant variations exist in the mineral content of tap water sources among North American cities. In general, the levels of $Ca^{2+}$ and $Mg^{2+}$ were higher among those cities supplied by groundwater sources than among those using surface water sources. Tap water sources that contained higher levels of $Ca^{2+}$ generally also contained high levels of $Mg^{2+}$. Azoulay *et al*. (2001) found that, of the 12 states of the United States and three provinces of Canada in their study, the mineral levels were highest in Arizona, California, Indiana and Texas. In addition, variations were also found in mineral content of different water sources within the same city. Calcium levels, for example, varied from 9 to 60 mg/l among the three water sources in San Jose, California. In Los Angeles, California, magnesium levels varied from 5 to 29 mg/l.

In Canada, the Canadian Shield does not leach many minerals into the water, resulting in very soft groundwater and surface water. However, the moraine material on which the Prairie provinces are located (mainly Saskatchewan and

Manitoba) contains high quantities of calcium and magnesium, often as dolomite; these minerals are readily soluble in the groundwater, which contains high concentrations of trapped carbon dioxide from the last glaciation. In these parts of Canada, the total hardness (in calcium carbonate equivalent) frequently exceeds 200 mg/l if groundwater is the only source of potable water. Some typical values are as follows: Calgary, Alberta, 165 mg/l; Saskatoon, Saskatchewan, <140 mg/l; Toronto, Ontario, 121 mg/l; Vancouver, British Columbia, <5 mg/l.

### 3.2.4 WHO European Region

In northern Europe, groundwater exploitation has expanded considerably over the last two centuries. A significant proportion of western and central Europe now receives drinking-water from groundwater sources in addition to surface water. Residents in Italy, Iceland, Austria, Denmark and Lithuania consume close to 90% of their water from groundwater sources, whereas people in France, Sweden and Finland consume up to 50%, close to that of people from the Netherlands and Germany, at 50–70%. The contribution of groundwater to drinking-water supply in the United Kingdom ranges from 30% to 35%; in Norway, it is about 15% (Reimann and Banks 2004).

According to Sjors and Gunnarsson (2002), the range of calcium in natural groundwater is normally from 1 to 100 mg/l. This variation of calcium concentration obviously depends on the original well water and the composition of the bedrock.

Information from the United Kingdom's Drinking Water Inspectorate (2004) shows that drinking-water in England is generally considered to be "very hard", with most areas of England, particularly the east, exhibiting hardness (as calcium carbonate equivalent) above 200 mg/l. Wales, Cornwall and parts of north-west England are softer-water areas, with hardness ranging from 0 to 200 mg/l.

## 3.3 COMMERCIALLY AVAILABLE BOTTLED WATERS

From being a generic natural resource, water has been processed, packed, labelled and branded. The sophistication of the water purification process as well as packaging, branding and marketing costs make bottled drinking-water expensive on a unit basis, while its consumption is increasing in most regions.

Bottled water consumption has been steadily growing in all parts of the world for the past 30 years, and it is now the most dynamic sector of the entire food and beverage industry. Globally, consumption has increased by an average of

12% per year, in spite of its high unit price compared with tap water. The consumption of bottled water in Sweden, for example, increased from 92 million litres to 161 million litres from 1992 to 2001 (Rosborg *et al*. 2005). The annual per capita consumption of bottled water in the United States increased from less than 30 litres in 1991 to almost 42 litres in 1996 (Ferrier 2001). However, the fastest growing markets are in Asia and the Pacific, with an annual increase of 15% for the period 1999–2001 (Ferrier 2001). In newer markets such as India, bottled water consumption is increasing by as much as 50% annually (Ferrier 2001).

Currently, an average of 15 litres of bottled water is consumed per year per person. Among populations in different regions, western Europeans are the world's major bottled water consumers (85 litres per person per year), consuming nearly half of the world's bottled water. Within Europe, Italians drink more bottled water than other Europeans, at 107 litres per year per inhabitant on average (Ferrier 2001).

In North America, partly because of concern that certain contaminants of tap water may have adverse health effects, consumption of tap water has decreased and intake of bottled water has increased. One in five households, or 54% of Americans, regularly drink bottled water in the United States. Asian consumers bought an average 11.0 litres per person in 2004, while those in the GCC countries purchased more than triple this figure, at 36.5 litres (Ferrier 2001).

### 3.3.1 Quality of bottled water

Internationally recognized standards for food (which includes bottled/packaged water) are produced by the Codex Alimentarius Commission, which is jointly sponsored by WHO and the Food and Agriculture Organization of the United Nations (FAO). Separate standards are provided for natural mineral waters (CAC 1997) and for bottled/packaged drinking-waters other than natural mineral waters (CAC 2001). The WHO *Guidelines for Drinking-water Quality* are the basis for derivation of the standards for all bottled/packaged waters. The Codex standards describe the product and its labelling, composition and quality factors, including limits for certain chemicals, hygiene and packaging. The Codex Codes of Practice for Collecting, Processing and Marketing of Natural Mineral Waters and for Bottled/Packaged Drinking Waters (Other than Natural Mineral Waters) provide guidance to the industry on a range of matters concerning good manufacturing practices. Although Codex Alimentarius Commission standards and recommendations are not strictly mandatory, Codex health and safety requirements are recognized as representing the international consensus for consumer protection. It should be noted that neither Codex standard refers specifically to calcium or magnesium.

Natural mineral water is defined by Codex as water characterized by its content of certain mineral salts and their relative proportions and the presence of trace elements or other constituents that is obtained directly from natural or drilled sources from underground water-bearing strata with a constant composition and collected under conditions that guarantee the original microbiological purity and chemical composition of essential components. Natural mineral water may be naturally carbonated, non-carbonated, decarbonated, fortified by carbon dioxide or carbonated (CAC 1997). Bottled/packaged drinking-water other than natural mineral water is water that may contain minerals, naturally occurring or intentionally added; may contain carbon dioxide, naturally occurring or intentionally added; but shall not contain sugars, sweeteners, flavourings or other foodstuffs. Bottled/packaged drinking-waters may be either water defined by origin or prepared water (CAC 2001).

There are differences between the United States and Europe on some labelling criteria that apply to packaged water. In the United States, the terms used on the labels of packaged waters to describe their characteristics, origin and treatment methods include (natural) mineral water, spring water, purified water, artesian water and sparkling water (Table 3.1). In the United States, the Food and Drug Administration defines natural mineral water as having a minimum total dissolved solids concentration of 250 mg/l and deriving from a protected underground water source. Spring water, in comparison, need not have a constant mineral composition and is usually cheaper. Purified water is taken from lakes, rivers, underground springs or municipal tap water supplies and has been treated, often by reverse osmosis and ozonation, prior to bottling.

More than half (59%) of the commercial bottled water drunk in the world is purified water, the remaining 41% being primarily spring water or natural mineral water. Bottled water's popularity has a number of causes. In Asia and Latin America, population growth and problems with local water quality and supply are the biggest factors. Currently, 1.1 billion people worldwide lack access to improved water sources, and about 1.6 million children under the age of five die each year from diseases brought on by lack of safe drinking-water and adequate sanitation. Thus, bulk packaging has made bottled water more attractive in some parts of the world. Prompted by advertising, many consumers buy bottled water as an alternative to soft drinks and alcohol, as it is perceived to be safer than tap water or because it tastes better than tap water. Interestingly, even in countries where there is access to safe public drinking-water, people spend up to 1000 times more on a unit cost basis for bottled water than for tap water. Changes in lifestyle also explain this increase in bottled water sales. In the United States, bottled water is considered a food product and must meet applicable food packaging and quality regulations of the Food and Drug Administration. Tap

water, in contrast, is regarded as a utility and must meet Environmental Protection Agency standards.

Table 3.1. Types of bottled water in the United States

| Type | Description |
|---|---|
| Mineral water (natural) | Water containing a minimum total dissolved solids level of 250 mg/l, originating in an underground water table or deposit. Mineral water is distinguished from other types of water by its constant level and relative proportions of minerals and trace elements at the point of emergence from the source. No minerals may be added to this water. |
| Spring water | Bottled water derived from an underground formation from which water flows naturally to the surface of the earth. Spring water must be collected only at the spring or through a borehole tapping the underground formation feeding the spring. Spring water collected through a borehole must have all the physical properties, before treatment, and be of the same composition and quality as the water that flows naturally to the surface of the earth. |
| Purified water | Water produced by distillation, deionization, reverse osmosis or other suitable process that meets the definition of purified water in the 23rd revision of the United States Pharmacopoeia. |
| Artesian water | Water from a well that taps an aquifer in which the water level is higher than the top of the aquifer. |
| Sparkling water | Water that, after treatment and possible replacement of carbon dioxide, contains the same amount of carbon dioxide that it had at the source (not to be confused with soda water, seltzer water or tonic water). |

Source: Based on the United States Food and Drug Administration (http://www.cfsan.fda.gov/~lrd/FCF165.html), which has established specific regulations for bottled water in Title 21 of the *Code of Federal Regulations* (21 *CFR*). These regulations include the identity standard (21 *CFR* § 165.110[a]), which defines different types of bottled water, such as spring water and mineral water, and the quality standard (21 *CFR* §165.110[b]), which establishes allowable levels for contaminants (chemical, physical, microbial and radiological) in bottled water.

Although commercially bottled waters are generally of good microbiological quality, they are not exempt from some contaminants. In a test conducted on over 1000 bottles of 103 brands, the Natural Resources Defense Council of the United States (NRDC 1999) found that most of the bottled waters were of good quality, although levels of chemical or non-pathogenic bacterial contaminants exceeded those in tap water in about one third of the bottled waters tested. Indeed, for some countries, rules for bottled water are weaker than national potable water regulations. Regulated and certified bottled water is required to be tested for bacteria and chemical contaminants. In some countries, the regulations

for bottled water do not require examination for thermotolerant (faecal) coliforms, as do those for municipal tap water.

The situation could be worse in developing countries. For example, in India, there is a general lack of standards for bottled water, hygiene requirements for the containers and a mandatory system for testing and monitoring bottled water quality and safety (Radhakrishna *et al.* 2003), with 65% of bottlers simply pumping water from a bore well or even municipal water supplies. A 2001 report from the Consumers' Foundation in Taiwan, China, claimed that 80% of bottled water and mineral water sold in Taiwan, China, is unfit for human consumption (http://www.taipeitimes.com/News/front/). According to the Consumers' Foundation, the bottled water and mineral water industry is insufficiently regulated. Many local bottled water manufacturers failed to pass the Foundation's test, because bacteria levels in the water were high.

### 3.3.2 Minerals in bottled water

Because drinking-water may be an important source of mineral intake, the shift in consumption from tap water to bottled water may have important implications in health and disease. The contribution of water to calcium and magnesium intake depends on the amount of the minerals in the water and the amount of water consumed.

The variation in the mineral content of bottled waters in different parts of the world is tremendous, and few of them have an optimal mineral profile. Given the extensive consumption of bottled water, the question naturally arises as to the long-term impact of the varying chemical composition of these waters on human health. Chemical analyses of bottled water are not usually provided at all, or only for selected parameters. Consumers are faced with difficulty in interpreting the information that does exist on the bottled water label. For instance, none of the samples treated by reverse osmosis displayed information on total dissolved solids levels (Pip 2000).

Garzon and Eisenberg (1998) first showed that there is a large variation in mineral contents of commercially available bottled waters. The magnesium content of bottled water available in North America ranged from 1 to 120 mg/l, and the calcium content ranged from 1 to 240 mg/l, whereas bottled waters that are commercially available in Europe ranged in concentration from 0 to 546 mg/l for calcium and from 1 to 126 mg/l for magnesium. A comprehensive follow-up study by Azoulay and colleagues (2001) on a wide range of commercially available bottled waters suggested that the mineral levels varied tremendously in bottled waters sold in North America. Generally, the bottled waters imported from Europe contained higher mineral levels than local bottled

waters. It is believed that mineral intake from spring waters among North Americans is minimal, as only some North American mineral waters contain high calcium and magnesium levels.

Rosborg *et al*. (2005) studied the concentrations of about 50 metals and ions in 33 different brands of bottled waters on the Swedish market. Ten of the brands showed calcium concentrations of ~10 mg/l and magnesium levels of <3 mg/l, implying that they could be soft water in origin. Furthermore, a large variation in the concentrations, especially of macroelements such as $Ca^{2+}$, $Mg^{2+}$, $Na^{+}$, $K^{+}$ and $Cl^{-}$, was found in the bottled waters. The concentrations of calcium and magnesium in tap water and bottled water in different parts of the world are summarized in Table 3.2.

Table 3.2. Calcium and magnesium contents of tap water and bottled water in different parts of the world

| | $Ca^{2+}$ concentration (mg/l) | | | $Mg^{2+}$ concentration (mg/l) | | |
|---|---|---|---|---|---|---|
| | Mean | Median | Range | Mean | Median | Range |
| (a) Surface water sources (*n* = 36) | 34 ± 21 | 36 | 2–83 | 10 ± 8 | 8 | 0–29 |
| (b) Groundwater sources (*n* = 8) | 52 ± 24 | 48 | 26–85 | 20 ± 13 | 12 | 2–48 |
| (a) Spring water (*n* = 28) | 18 ± 22 | 6 | 0–76 | 8 ± 18 | 3 | 0–95 |
| (b) Mineral water (*n* = 29) | 100 ± 125 | 8 | 3–310 | 24 ± 42 | 7 | 1–130 |
| (a) Low-mineral water (*n* = 40) | 60 ± 40 | 54 | 4–145 | 16 ± 19 | 14 | 1–110 |
| (b) Medium-mineral water (*n* = 26) | 262 ± 139 | 217 | 78–575 | 64 ± 37 | 56 | 9–128 |
| (c) High-mineral water (*n* = 7) | 60 ± 59 | 33 | 5–176 | 16 ± 20 | 9 | 4–60 |
| (a) Distilled water (*n* = 9) | NA | 0 | 0–0.1 | NA | NA | NA |
| (b) Mineral water (*n* = 4) | NA | 12 | 0.2–20.8 | NA | NA | NA |
| (c) Imported mineral water (*n* = 12) | NA | NA | 12–199 | NA | NA | NA |

NA, Not available

Source: Summarized data based on Garzon and Eisenberg (1998), Von Wiesenberger (1999) and Azoulay *et al*. (2001).

## 3.4 WATER LOSS, WATER INTAKE AND DIETARY SOURCES OF WATER

A review of the research designed to define the fluid requirements of humans increases one's appreciation for the complexity of the issue. A multitude of intra- and interindividual factors influence water requirements. The impracticality of establishing a general total water requirement was reiterated in the *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (IOM 2004):

> Given the extreme variability in water needs, which are not solely based on differences in metabolism, but also in environmental conditions and activity, there is not a single level of water intake that would ensure adequate hydration and optimal health for half of all apparently healthy persons in all environmental conditions.

### 3.4.1 Water loss

For sedentary to moderately active individuals under temperate conditions, water lost from the body includes respiration, urinary and faecal losses and evaporation. Water lost via sweating is usually low in temperate, sedentary conditions, but profuse sweating can be a major source of water and electrolyte loss for persons exercising or labouring in extreme heat and/or humidity. During physical exertion, sweating presents the most highly variable water loss. Sweat rates can reach 3–4 litres per hour and vary significantly between individuals. In addition to inherent individual differences, sweat production is also affected by intensity and duration of exertion, age, sex, level of conditioning, heat acclimatization, air temperature, humidity, wind velocity, cloud cover and clothing.

### 3.4.2 Water intake

Several basic considerations are required to determine the potential benefit of minerals in drinking-water. One is the volume of water consumed. Numerous factors affect both water requirements and water consumption. Data from studies determining the fluid requirements of people under a variety of conditions are abundant. Total daily fluid requirements have been shown to range from as little as 2 litres per day to 16 litres per day, depending on the work load and the level of heat stress.

Reference values of water required for hydration for female and male adults and children under average conditions are 2.2, 2.9 and 1 litres/day, respectively; 4.5 litres/day for all three segments under manual labour conditions at high

temperature; and 4.8 litres/day during pregnancy and 3.3 litres/day during lactation (Howard and Bartram 2003).

The most significant conclusions that can be drawn from an examination of water intake studies are the limited scientific data and the magnitude of the variability within and among individuals. Of interest is not only the wide range of intakes for total water, but also the variance in the water content of the food consumed. For example, total water intake by males 31–50 years of age who participated in the third United States National Health and Nutrition Examination Survey (NHANES III) was 2100 ml/day for the 5th percentile and 6340 ml/day for the 95th percentile. Total water intake from food for the same population was 372 ml/day for the 5th percentile and 1251 ml/day for the 95th percentile. Understanding the diversity of people's diets, the numerous factors that affect requirements and the fact that euhydration can be achieved with a wide range of water intakes is paramount to answering the question, "How much fluid do I need to drink?"

Most countries do not include water in their dietary reference values, nor are water intake data available for most countries or populations. Data from the United States NHANES and two German surveys were compared and contrasted (Manz and Wentz 2005). The German surveys included one on children, the German Dortmund Nutritional and Anthropometric Longitudinally Designed Study, and one on adults, the Cooperative Study: Nutrition Survey and Risk Factor Analysis. Compared with the German population, the population of the United States had a higher intake of total water (from fluids and food) and a higher urinary volume, which was interpreted as a more favourable hydration status. In view of the negative effects of chronic mild hypohydration on several diseases and physiological, physical and cognitive functions, the interest in establishing population reference values for total water intake is increasing.

### 3.4.3 Dietary sources of water

Water is ingested as water in food (inherent and/or added during preparation) and water in beverages. Table 3.3 shows the water content of a variety of foods and beverages. Metabolic water (water produced during the metabolism of food) is also a source of water, although the amount is relatively small. By far the most important source of water is from beverages, including drinking-water.

The types of beverages consumed can have a significant impact on the nutrient intake of an individual or population. Water is an essential nutrient and is provided by all beverages. Many beverages, however, are also sources of other essential nutrients. For example, in addition to water, fruit and vegetable juices and milk provide significant amounts of essential vitamins and minerals.

Drinking-water can be a significant source of minerals, depending on the mineral content and the volume consumed.

Table 3.3. Water content of select foods and beverages (adapted from Grandjean and Campbell 2004)

| Food and beverages | % water |
|---|---|
| **Beverages** | |
| Water, brewed tea, brewed coffee, diet soft drinks, canned/bottled tea, sports drinks, lemonade, vegetable juice | 90–100 |
| Milk (skim, 1%, 2%, whole, chocolate), soft drinks (regular), fruit juice, fruit drinks | 85–90 |
| **Soup** | |
| Clear broth, French onion, vegetable beef, minestrone, tomato, cream of mushroom (made with water) | 90–95 |
| Chicken noodle, chunky minestrone, chunky soups, tomato, cream of mushroom (made with milk) | 80–90 |
| **Fruits and vegetables** | |
| Strawberries, melons, grapefruits, peaches, pears, oranges, apples, grapes, cucumbers, lettuce, celery, tomatoes, cabbage, broccoli, onions, carrots | 80–85 |
| Banana, potatoes, corn | 70–75 |
| **Dairy** | |
| Cottage cheese and yoghurt | 75–80 |
| Pudding, milkshake, eggnog | 70–75 |
| Ice cream | 50–60 |
| Cheese | 40–50 |
| **Grains** | |
| Cooked cereals | 85–90 |
| Rice and pasta | 65–80 |
| Breads, bagels, biscuits | 30–45 |
| Ready-to-eat breakfast cereals | 2–5 |
| **Meat, fish and eggs** | |
| Fish and seafood | 70–80 |
| Eggs (scrambled, fried, poached), omelette, egg substitute | 65–80 |
| Beef, chicken, lamb, pork, turkey, veal | 45–65 |
| Jerky, bacon | 15–30 |
| **Mixed dishes** | |
| Stew, pasta and meat dishes, casseroles (with meat and meatless), meatloaf, tacos, enchiladas, macaroni and cheese, vegetarian quiche | 60–80 |
| Pizza | 50–60 |

Table 3.3 *(continued)*

| Food and beverages | % water |
|---|---|
| **Meal replacement drinks** | |
| All liquid drinks for weight loss, muscle gain, meal replacement | 70–85 |
| **Snacks, candies, confections** | |
| Chips, pretzels, candies, crackers, puffs, dried fruit, popcorn | 1–10 |
| **Seeds and nuts** | 1–5 |
| **Sauces, gravies and dips** | |
| Sauces and gravies | 50–85 |
| Dips (salsa, sour cream–based, bean) | 70–90 |

## 3.5 SWEAT LOSS AND CALCIUM AND MAGNESIUM BALANCE

It is known that minerals (e.g. calcium, iron, magnesium, manganese, potassium, sodium, zinc, phosphorus, copper, molybdenum) are lost in sweat, and a significant amount of research in this area has been conducted over the last several decades. The vast majority of studies have examined sodium and potassium loss and repletion. A handful of studies have examined calcium and magnesium in sweat.

A study conducted to determine changes in bone mineral content in members of a men's college basketball team found that total body bone mineral content in the men decreased 3.8% from preseason to midseason, increased 1.1% in the off-season and decreased an additional 3.3% during summer practice (Klesges *et al*. 1996). One of several findings of the study was that calcium lost in sweat averaged 422 mg per training session. However, the amount of calcium lost decreased over time (e.g. 624, 462 and 179 mg on days 1, 2 and 3), owing to decreases in both the amount of sweat and the calcium concentration per litre of sweat. This would be consistent with the decrease in sodium loss seen with acclimatization.

The significance of sweat-related calcium loss comes into clear focus when one realizes that the net intestinal absorption of calcium in non-pregnant adults averages only about 10%. Thus, extra sweat loss of 200 mg could require an additional oral intake of as much as 2000 mg if the skeleton is to be protected. The general unfeasibility of such increases in calcium intake explains both the bone loss recorded across the practice and playing season and the protection afforded by calcium supplement tablets (Klesges *et al*. 1996).

A study on three healthy young men assessed mineral losses in sweat and the relation of each mineral to balance and requirements (Consolazio *et al*. 1963). Chemical analyses of the food composites, urine, faeces and sweat were performed for five minerals, which included magnesium. Results showed that magnesium sweat excretion averaged 2.3 mg/h and, unlike some other minerals, did not decrease appreciably during acclimatization. The researchers also found that the sweat loss did not greatly affect the magnesium balance due to an extremely high retention of magnesium.

## 3.6 ABSORBABILITY OF CALCIUM AND MAGNESIUM IN WATER

Interest in water as a source of minerals has prompted studies on the bio-availability of calcium and magnesium and water's potential nutritional contribution.

### 3.6.1 Calcium

Using a dual-label stable isotope technique, Couzy *et al*. (1995) compared the absorption and urinary excretion of calcium from carbonate- and sulfate-rich water with those of calcium from milk in women 21–36 years of age. Nine women completed two study periods during which the subjects ate the same diet for the first 3 days. On the 4th and 5th days, the subjects consumed either milk or calcium- and sulfate-rich water. Calcium from the calcium- and sulfate-rich water was as well absorbed and retained as the calcium from milk.

A review of published and unpublished data (Heaney 2006) showed that the absorbability of the calcium in the waters tested is comparable to the absorbability of calcium in milk when studied under similar conditions (see Figure 3.1). Heaney (2006) concluded that the calcium in high-calcium mineral waters is highly absorbable and that mineral water consumption can potentially account for a substantial fraction of total daily calcium intake, noting that high-calcium water functions much like a supplement — i.e. it provides basically a single nutrient (or, at most, two, in the case of the bicarbonate-rich waters). By contrast, milk, the comparator source most widely used to evaluate the absorbability of other calcium sources, provides, in addition to its calcium, a broad array of other nutrients important for total body as well as skeletal health.

However, given the demonstrated good absorbability of calcium in drinking-water, it seems clear that high-calcium waters can make an appreciable contribution to total intake. One litre of a water containing ~300 mg of calcium per litre will provide an amount of calcium equal to one dairy serving. There is

evidence that the counter-ion accompanying calcium (principally sulfate or bicarbonate) affects retention of the absorbed calcium to a small extent, but the same is true for food sources of calcium. Thus, depending upon the volume consumed, a medium- to high-calcium mineral water can make a useful contribution to total daily calcium intake.

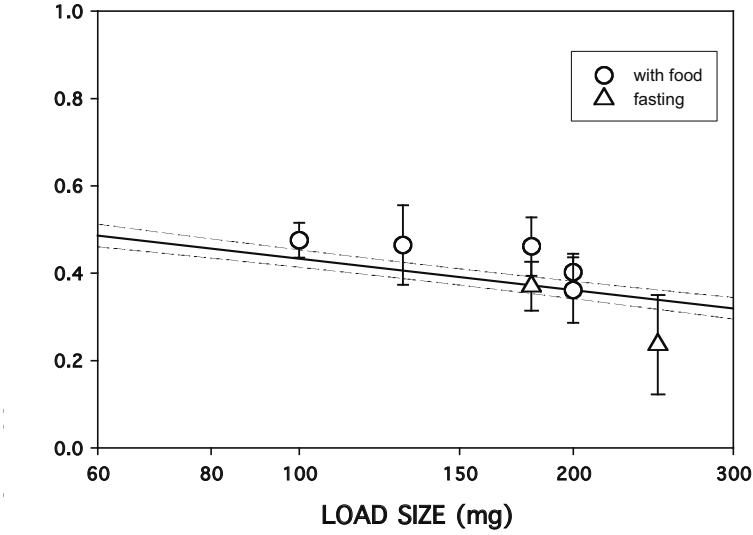


Figure 3.1. Fractional absorption from seven studies of high-calcium mineral waters. The regression line is plotted for historical data for milk calcium, ingested as part of a meal and studied over a wide range of load sizes. It is the least squares, best-fit line with its 95% confidence limits. (The actual data points to which this line is fitted are not shown.) Circles represent mean values in studies in which the water was ingested as part of a test meal, and triangles, studies in which the water was ingested fasting and without co-ingested food. Error bars for the individual studies are ±2 SEM (from Heaney 2006).

To determine if a high-calcium mineral water would replete both water and calcium lost during physical exertion, a study was conducted on male triathletes to assess the acute effects of an intensive endurance cycling exercise on biochemical bone markers (Guillemant *et al*. 2004). Consumption of 972 mg of calcium given in 2 litres of water just prior to and during exercise completely eliminated the increase in osteoclastic bone resorption (calcium loss) observed in the control group given low-calcium water (9 mg/l).

Elevated concentrations of intact parathyroid hormone (iPTH) induce an increase in bone turnover, which is accompanied by increased bone loss. Oral intake of calcium increases serum calcium and lowers iPTH concentrations. A

study was conducted on healthy young men to determine if high-calcium mineral water (344.7 mg/l) is an efficient additional source of dietary calcium and to elucidate its effect on serum iPTH concentration and bone resorption (Guillemant *et al*. 2000). Results showed that a moderate dose of calcium (172 mg of elemental calcium), provided by consuming 0.5 litre of water, inhibited iPTH secretion and bone resorption. The authors concluded that drinking calcium-rich mineral water several times a day could be recommended, because it would provide both supplemental calcium and adequate hydration in addition to the inhibitory effect on iPTH secretion and bone resorption.

### 3.6.2 Magnesium

To determine magnesium bioavailability from magnesium-rich mineral water (110 mg/l), women aged 25–45 years consumed, in a cross-over design, water with or without a meal (Sabatier *et al*. 2002). Absorption of magnesium was 45.7 ± 4.6% from the water alone and was significantly greater when the water was consumed with a meal (52.3 ± 3.9%), a relative difference of 14.4%. Furthermore, magnesium retention was also significantly greater (11.0%) when the water was consumed with a meal. The researchers concluded that regular consumption of magnesium-rich mineral water could make a valuable contribution to magnesium requirements.

Another study examined the bioavailability of magnesium from mineral water, with men aged 25–42 years as subjects (Verhas *et al*. 2002). Each subject completed two sessions: in one, they consumed 300 ml of water containing 1.2 mmol magnesium, and in the other, the magnesium was injected intravenously. Dietary intake was assessed prior to initiation of the study and in a weekly diary during the study. The mean bioavailability was 59.1 ± 13.6%. The range of absorption was 36.1–84.8%, with absorption being significantly inversely correlated with age.

Data on the absorbability of magnesium from water are sparse. However, the same considerations as specified for calcium should be applied to determine the relative contribution of waterborne magnesium. In both children and adults, fractional intestinal magnesium absorption is inversely proportional to the amount of magnesium ingested, but is always substantially greater than net absorption of calcium, averaging about 50%. Hence, one can expect the absorbability of magnesium from waters to be at least as good as that of magnesium from food.

Among healthy adults in the United States, dietary intake of magnesium is limiting, with more than 60% of men and women more than 19 years of age consuming less than the Estimated Average Requirement (EAR) of 330–350

and 255–265 mg/day, respectively (Moshfegh *et al*. 2005). Although magnesium is widely distributed in foods, its content is highly variable. Foods such as unrefined grains and nuts have high magnesium concentrations, whereas meats, starches and dairy products have reduced levels. Forty-five per cent of dietary magnesium in the United States comes from fruits, vegetables, grains and nuts, with about 30% contributed from milk, meat and eggs (Pennington and Young 1991). Beverages are a variable source of magnesium, with higher concentrations in wine, intermediate levels in milk and beer and lower concentrations in tap and bottled water (Lukaski 1995).

Magnesium intake can be appreciably influenced by water consumption (Marier 1990; IOM 1997). Because the magnesium concentration of tap water is related to the degree of hardness (e.g. calcium and magnesium contents), it has been estimated that drinking-water can contribute 40–100 mg/day (Marier 1990). Bottled water can also supply a significant amount of magnesium (30 mg/day) (Marier 1990). Thus, water may be a significant source of magnesium, accounting for 29–38% of the EAR for adults.

## 3.7 THE POTENTIAL CONTRIBUTION OF DRINKING-WATER TO HUMAN NUTRITION

Drinking-water is 100% water, with the water content of other beverages ranging from 85% to 100% (see Table 3.2). Although research is limited, the studies reviewed herein underscore that mineral-rich water can contribute to calcium and magnesium intake, balance and overall nutrition. Several factors will determine the relative nutritional contribution on both an individual and a population basis, including the amount of mineral per volume, the volume consumed and the frequency and regularity of consumption.

## 3.8 CONCLUSION

This chapter attempts to illustrate the inherent variations in the mineral content of drinking-water and briefly review the potential contribution of drinking-water to calcium and magnesium intake. As summarized in Table 3.2 in section 3.3, in some geographical areas, the magnesium and calcium contents of drinking-waters (including tap and bottled waters) are extremely low and may provide little supplementation towards a person's daily requirement. Physiologically, waterborne minerals are in ionic form, which tend to be easily absorbed by the human gastrointestinal tract; thus, water can be an important source of mineral intake. Furthermore, waterborne magnesium is known to be more bioavailable than magnesium obtained from foods and thus may be more important clinically (Durlach *et al.* 1985). Although certain minerals in water may be useful in

providing essential micronutrients, such as calcium, magnesium and zinc, so far there are no guidelines on minimum concentrations of these minerals in drinking-water.

Globally, owing to the growing concern that certain constituents or contaminants of potable water may affect health, consumption of tap water has decreased and consumption of bottled water has increased significantly over the last two decades. However, the quality of bottled waters available throughout the world varies tremendously. European bottled waters tend to contain higher levels of minerals than North American tap and bottled waters. In contrast, most of the local Asian bottled waters are low in all minerals, as they are usually obtained through membrane treatment, reverse osmosis or distillation. Some countries have national standards for bottled water, and some have national certification schemes; the Codex Alimentarius Commission of the FAO and WHO (http://www.codexalimentarius.net/web/index_en.jsp) provides international standards for bottled/packaged water and bottled mineral water. Based on existing knowledge and the fact that bottled water constitutes an increasing market in the world and may affect health, we can see the urgent need for more appropriate recommendations for mineral concentrations in bottled water. While chemical and microbial contaminants continue to be a global concern of drinking-water suppliers, efforts are obviously needed to reorient and set new and better priorities for drinking-water practices, including potential benefits.

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# 4

# Identifying magnesium deficiency: A diagnostic dilemma

*R.J. Elin*

The assessment of magnesium status provides a challenge to clinical medicine and biomedical technology. Blood is the tissue of choice used in clinical medicine for the assessment of most analytes. For many of the analytes, the concentration in the blood offers information about extracellular and intracellular status. This is not the case for magnesium. Serum and red blood cell magnesium concentrations have been shown to be poor predictors of intracellular magnesium concentration. Thus, the assessment of magnesium status becomes difficult, since approximately 99% of the total body magnesium is in bone and intracellular in soft tissue.

The definition of magnesium deficiency seems simple, but it is complicated by the lack of available clinical tests for the assessment of magnesium status. Ideally, we would define magnesium deficiency as a reduction in the total body magnesium content. Tests should be available to identify which tissues are deficient and the state of magnesium in these tissues. Unfortunately, this definition of magnesium deficiency is incompatible with current technology.

Thus, from a practical sense, magnesium deficiency has been defined by clinical medicine as a serum magnesium concentration below the reference interval for the laboratory. There are problems with this functional definition. Certainly, there are individuals with a serum magnesium concentration within the reference interval that have a total body deficit for magnesium. This is especially likely when an individual has a chronic, marginally negative magnesium balance, as the serum concentration may be supported by magnesium from other tissue pools, particularly bone. However, clinical medicine has chosen to use the serum magnesium concentration as the standard for magnesium deficiency, imperfect as it may be.

Is the reference interval established by clinical laboratories valid to diagnose magnesium deficiency? Using data from the first National Health and Nutrition Examination Survey (NHANES I) in the United States and a United States population of 15 820 between the ages of 1 and 74 years, Lowenstein and Stanton (1986) established the reference interval (central 95th percentile) for the serum magnesium concentration of 0.75–0.955 mmol/l. This study used atomic absorption spectroscopy, the reference method for determining serum magnesium, and is scientifically and statistically valid. However, we do not know what percentage of this population had an inadequate intake of magnesium and may have been magnesium deficient. Thus, the lower limit of the reference interval may have been flawed by having subjects in the "normal" population that were deficient in magnesium.

How likely is it that a significant portion of the population in the NHANES I study had an inadequate intake of magnesium? The intake of magnesium by the average citizen of the United States has progressively declined over the past century (Marier 1982; Ford and Mokdad 2003). The processing of food and the shift to a higher percentage of fast food, which is essentially devoid of magnesium, in the diet have effected this progressive decreased intake of magnesium. Thus, similar to the situation with cholesterol, the reference interval for the serum magnesium concentration as established by the laboratory may not adequately identify those individuals with magnesium deficiency, since the lower limit of the reference interval is flawed, being too low for health (Liebscher and Liebscher 2004). To correct this problem, it is recommended that the reference interval for the serum magnesium concentration be established by evidence-based medicine for health, similar to the process that was used for cholesterol. This would then alert physicians to patients who have a magnesium deficiency based on their serum magnesium concentration and enable them to adjust their diet for a greater intake of magnesium or consider oral supplementation with magnesium. This is where the magnesium concentration of the drinking-water is very important. In theory, the higher the magnesium content of

the drinking-water, the greater the intake of magnesium for the subject, which would lessen the risk of disease entities associated with magnesium deficiency.

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# 5

# Magnesium deficiency: Clinical and experimental aspects

*W.B. Weglicki*

## 5.1 INTRODUCTION

The average diet in the United States is deficient in magnesium (Pao and Mickle 1981; Lichton 1989; see also Table 2.2 in chapter 2). A survey of mean daily magnesium consumption revealed that intake was only 68% of the Recommended Dietary Allowance (RDA) of magnesium for adult women and 80% of the RDA for adult men (National Research Council 1989; for RDAs, see Table 2.1 in chapter 2). The *average* pregnant woman in the United States consumes only 34–58% of her RDA for magnesium (Franz 1987). Data on the dietary intake of magnesium collected from a variety of dietary studies and summarized in Table 2.3 of chapter 2 suggest that the situation is similar in many other countries of the world.

## 5.2 HYPOMAGNESAEMIA: CLINICAL ASPECTS

Hypomagnesaemia is common in hospitalized patients: in one study, 63% of intensive care patients exhibited hypomagnesaemia, and 45% of patients with acute myocardial infarction had hypomagnesaemia (Dubey and Solomon 1989). In acutely ill patients, the mortality rate of those with hypomagnesaemia was double that of the normomagnesaemic group (Rubeiz *et al*. 1993). In the case of chronic severe hypomagnesaemia in a child, congenital magnesium wasting due to nephropathy led to progressive dilated hypertrophic cardiomyopathy and, ultimately, to his death at age 14 (Riggs *et al*. 1992). Hypomagnesaemia also occurs in other segments of the population — diabetics, alcoholics, those infected with human immunodeficiency virus-1 (HIV-1) (Moseson *et al*. 1989) and those receiving magnesium-wasting drugs — leading to overt hypomagnesaemia.

Symptoms of hypomagnesaemia are diverse and include muscle cramps, extra heart beats and neuromuscular irritability associated with convulsions in very severe cases. However, no specific pattern of symptoms/signs is clearly diagnostic for hypomagnesaemia, which has been defined by clinical medicine as a serum magnesium concentration below the reference interval for a laboratory.

## 5.3 DIETARY MAGNESIUM DEFICIENCY: ANIMAL STUDIES

Severe dietary magnesium deficiency leads to profound hypomagnesaemia and diverse pathology in animal models: myocardial necrosis, neuromuscular hyperexcitability, arrhythmia, hyperirritability, erythema, haemorrhagic skin lesions, enhanced atherosclerosis, increased indices of oxidative injury (including decreased red blood cell glutathione) and enhanced myocardial susceptibility to ischaemia–reperfusion stress (Kramer *et al.* 1997). Investigations into the pathological mechanism of magnesium deficiency in rodents led to the discovery that circulating levels of the proinflammatory neuropeptide, substance P (SP), were significantly elevated. This early neuropeptide release probably emanated from sensory motor neuron fibres, which are rich in neuropeptides. The significant rise in plasma SP preceded increases in circulating white blood cells and other circulating inflammatory mediators (Weglicki *et al.* 1994). This neuropeptide may be inducing many of the later inflammatory/oxidative events that eventually promote cardiomyopathy.

Moderate dietary magnesium deficiency also induces significant systemic inflammation. Others have reported increases in prostaglandin $E_2$ (Soma *et al.*

1998), circulating histamine (Kraeuter and Schwartz 1980) and erythema (Classen *et al.* 1993) in moderately magnesium-deficient rodents. Moreover, rats fed a moderately magnesium-deficient diet displayed hypersensitivity to an applied catecholamine stress (Kantak 1988; Uthringer *et al*. 1988; Atrakchi *et al*. 1992). Nitric oxide (NO·) is generally thought to have beneficial cardiovascular effects (Moncada *et al*. 1991; Rubanyi *et al*. 1991; Huie and Padmaja 1993; Jun *et al*. 1994), but cytotoxicity has also been reported (Beckman *et al*. 1990; Mulligan *et al*. 1991; Cazevieille *et al*. 1993; Radi *et al*. 1994; White *et al*. 1994). SP can induce endothelial cell NO· production (Persson *et al*. 1991) and enhance NO· production *in vivo* during magnesium deficiency. NO· production, as measured by both plasma nitrate and nitroso-haemoglobin (complex of NO· and haem iron) formation, was shown to increase during severe magnesium deficiency (Mak *et al.* 1995a,b) and was blocked by a relatively low dose of the nitric oxide synthase (NOS) inhibitor, $N^G$-nitro-L-arginine methyl ester (L-NAME). Rock *et al.* (1995) also reported NO· elevations in severe magnesium-deficient rats.

In our study, we observed a loss of red blood cell glutathione during the 2nd week of magnesium deficiency (Mak *et al.* 1996); inhibition of NOS (by L-NAME) attenuated depletion of red blood cell glutathione, suggesting a pro-oxidant role for NO· during magnesium deficiency. With a mouse model (C57B6 mice) of moderate magnesium deficiency, we recently found a >3-fold increase in the levels of inducible nitric oxide synthase (iNOS) mRNA (reverse transcriptase–polymerase chain reaction technique) in the liver after 7 weeks. Thus, the data suggest that sustained increase in NO· production due to iNOS induction may occur during magnesium deficiency and that this may contribute to oxidative stress.

The neuronal *N*-methyl-D-aspartate (NMDA) receptor/channel complex enhances the entry of substantial amounts of calcium, which is an important mediator of both neuromodulator release (including that of SP) and tissue injury. The NMDA complex is blocked by $Mg^{2+}$ in a voltage-dependent manner (McIntosh 1993). The protection afforded by specific NMDA receptor/channel blockers suggests that hyperactivation of this complex contributes to injury. Dizocilpine (MK-801), a non-competitive NMDA receptor/channel blocker, was shown to prevent noise-mediated seizures (Pierson and Swann 1991; Nakamura 1997) and depress the acoustic startle reflex (Miserendino and Davis 1993) in magnesium-deficient rats. Others (Dubray and Rayssiguier 1997; Dubray *et al.* 1997) have reported that magnesium deficiency–induced hyperalgesia in rats was decreased in a dose-dependent manner by persistent treatment with MK-801. Findings from recent studies with MK-801-treated rats are also consistent with NMDA complex involvement in magnesium deficiency pathology. Several

studies have also shown that magnesium therapy can ameliorate neuronal injury (Kass *et al*. 1998).

Overall, these data suggest that magnesium deficiency causes systemic hyperactivation of the magnesium-gated NMDA receptor/channel complex, which leads to early release of the proinflammatory neuropeptide, SP, triggering a cascade of proinflammatory/pro-oxidative events in multiple tissues/organs and altering susceptibility to subsequent stresses.

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# 6

# Magnesium and hypertension

*R.M. Touyz and B. Sontia*

## 6.1 INTRODUCTION

Magnesium is an essential element that is critically involved in cardiac and vascular function. Small changes in extracellular $Mg^{2+}$ levels ($[Mg^{2+}]_e$) and/or intracellular free $Mg^{2+}$ concentrations ($[Mg^{2+}]_i$) have significant effects on cardiac excitability and on vascular tone, contractility, reactivity and growth (Laurant and Touyz 2000; Touyz and Yao 2003). Increased concentrations of extracellular magnesium cause vasodilation, improve blood flow, decrease vascular resistance, increase capacitance function of peripheral, coronary, renal and cerebral arteries and attenuate agonist-induced vasoconstriction, whereas decreased concentrations cause contraction, potentiate agonist-evoked vasoconstriction and increase vascular tone (Laurant *et al*. 1997; Yoshimura *et al*. 1997; Laurant and Touyz 2000; Touyz and Yao 2003).

## 6.2 MAGNESIUM AND EXPERIMENTAL HYPERTENSION

Hypomagnesaemia and decreased tissue content of magnesium have been demonstrated in various experimental models of hypertension (Ameen *et al*. 1991; Laurant *et al*. 1995; Saito *et al*. 1995; Mahboob *et al*. 1996). In experimental models with severe hypertension, $[Mg^{2+}]_i$ is negatively correlated and intracellular free calcium concentration ($[Ca^{2+}]_i$) is positively correlated with systolic blood pressure; $[Mg^{2+}]_i$ and $[Ca^{2+}]_i$ are inversely associated (Adachi *et al*. 1993; Kisters *et al*. 2001), suggesting that $[Mg^{2+}]_i$ may be involved in blood pressure regulation by competing with calcium effects. Mechanisms underlying magnesium deficiency in experimental hypertension are unclear but could relate to altered intestinal magnesium absorption (Wells and Agrawal 1992), defective cellular magnesium handling and increased renal magnesium loss (Berthelot *et al*. 1987; Gilles-Baillien and Cogneau 1992).

Long-term magnesium deficiency in experimental animals potentiates responses to vasoconstrictor agents, attenuates responses to vasodilator agents, increases vascular tone and elevates blood pressure (Ameen *et al*. 1991; Laurant *et al*. 1999). Some of these effects may be due to endothelial dysfunction (Laurant and Berthelot 1994). Magnesium deficiency is associated with vascular structural changes, including decreased lumen diameter and increased media-to-lumen ratio, indicative of medial hypertrophy and vascular remodelling, which are characteristic features of vascular changes in hypertension (Berthon *et al*. 2002). Hypomagnesaemia also promotes vascular inflammation and oxidative stress in hypertension, which are ameliorated by antioxidant treatment (Touyz *et al*. 2002).

However, dietary magnesium loading during the prehypertensive stage and the developing stage of hypertension in spontaneously hypertensive rats prevents the rise in blood pressure (Berthelot and Esposito 1983; Touyz and Milne 1999). These data suggest that oral magnesium may be beneficial in preventing further blood pressure elevation if magnesium is given at a critical period during the development of hypertension.

## 6.3 MAGNESIUM AND HUMAN HYPERTENSION

Epidemiological studies have linked hypertension and cardiac disease with “soft water”, low in magnesium, and protection against cardiovascular disease with “hard water”, high in magnesium (Geleijnse *et al*. 2005). The relationship between dietary magnesium intake and blood pressure in humans was first demonstrated in the Honolulu Heart Study (Joffres *et al*. 1987) and later by

many epidemiological and clinical investigations that supported the hypothesis that increased magnesium intake contributes to prevention of hypertension and cardiovascular disease (Whelton and Klag 1989; Van Leer *et al*. 1995; Simons-Morton *et al*. 1997). Data from large, well conducted prospective studies on nutrition and blood pressure in populations from the United States and the Netherlands suggested that magnesium-rich diets may reduce blood pressure levels, especially in older individuals (Ascherio *et al*. 1996; Geleijnse *et al*. 1996). A large retrospective study that assessed the magnesium and calcium content of drinking-water in subjects who died from hypertension and in those who died from other causes demonstrated that magnesium levels in drinking-water were inversely related to the risk of death from hypertension (Yang and Chiu 1999). Results from the cross-sectional Atherosclerosis Risk in Communities study on 15 000 middle-aged citizens of the United States demonstrated a negative correlation between dietary and serum magnesium levels and both systolic and diastolic blood pressure (Kao *et al*. 1999). The recent data from the third and fourth National Health and Nutrition Examination Surveys (NHANES III and NHANES IV) in the United States suggested that the negative association between mineral intake and blood pressure was valid and persisted over two decades (Townsend *et al*. 2005; Ueshima 2005). These epidemiological studies together with experimental evidence suggest physiological relationships between $Mg^{2+}$ and blood pressure and pathophysiological associations between $Mg^{2+}$ deficiency and hypertension.

Hypertensive patients who are hypomagnesaemic were found to require a greater number of antihypertensive medications compared with normomagnesaemic patients (Whang *et al*. 1982). A relationship has also been described between the renin–angiotensin system, magnesium and blood pressure. High-renin hypertensive patients have significantly lower serum magnesium levels than normotensive subjects (Resnick *et al*. 1983), and serum magnesium is inversely associated with plasma renin activity (Resnick *et al*. 1983). Recent studies have also reported a negative dependency between $[Mg^{2+}]_i$ and arterial compliance in humans: the lower the $[Mg^{2+}]_i$, the stiffer the blood vessels and the greater the blood pressure (Resnick *et al*. 1997). However, some studies found no differences in serum magnesium levels or in $[Mg^{2+}]_i$ in hypertensive patients (Cappuccio *et al*. 1985; Ferrara *et al*. 1992), whereas others reported increased erythrocyte $[Mg^{2+}]_i$ in patients with essential hypertension (Sasaki *et al*. 2000). Furthermore, some epidemiological studies failed to show an association between magnesium intake and blood pressure or cardiovascular disease (Whelton and Klag 1989; Rosenlund *et al*. 2005). It is evident that not all hypertensive patients are hypomagnesaemic, and not all patients with magnesium deficiency are hypertensive.

There are subgroups of hypertensive patients who consistently demonstrate altered magnesium metabolism. These include individuals of African descent, obese patients, patients with severe or malignant forms of hypertension and those with metabolic syndrome (Touyz *et al*. 1995; Delva *et al*. 1998; Corica *et al*. 1999).

## 6.4 MAGNESIUM AND PRE-ECLAMPSIA

Magnesium is the most frequently used treatment in the management of pre-eclampsia and eclampsia in the United States (Lucas *et al*. 1995; The Eclampsia Collaborative Group 1995; Corica *et al*. 1999). In fact, the recent findings of the Magpie trial demonstrated that magnesium sulfate halves the risk of eclampsia and probably reduces the risk of maternal death; magnesium sulfate is now considered the therapy of choice in the management of pre-eclampsia and eclampsia (Altman *et al*. 2002).

Data relating to serum magnesium concentrations in pre-eclampsia are conflicting, with some studies failing to demonstrate any differences between pre-eclampsia and uncomplicated pregnancy (Frenkel *et al*. 1994; Sanders *et al*. 1998) and others reporting decreased serum and intracellular magnesium levels in pre-eclampsia (Seydoux *et al*. 1992). Some investigations found total magnesium levels to be higher in pre-eclamptic women (Kisters *et al*. 1990). Although the exact role of magnesium in the pathogenesis of pre-eclampsia remains obscure, it has been suggested that magnesium can be used as a predictive tool for pre-eclampsia.

## 6.5 THE THERAPEUTIC ROLE OF MAGNESIUM IN HYPERTENSION

In general, data from clinical trials of magnesium therapy in hypertension have been disappointing. Some studies reported significant blood pressure–lowering effects of oral or intravenous magnesium treatment (Widman *et al*. 1993; Itoh *et al*. 1997; Kawasaki *et al*. 1998), and magnesium supplementation to patients already receiving diuretics or other antihypertensive agents appears to reduce blood pressure further (Dyckner and Wester 1983; Katz *et al*. 1999). However, other trials failed to demonstrate any hypotensive action of magnesium supplementation (Cappuccio *et al*. 1985; Ferrara *et al*. 1992), and results from the Trials of Hypertension Prevention showed no benefit of magnesium therapy in 698 patients followed for 6 months (Yamamoto *et al*. 1995). Studies that have consistently shown a beneficial effect of magnesium treatment were performed

in black patients, those with established hypomagnesaemia, those with diuretic-associated hypertension and those for whom magnesium was supplemented long term (Lind *et al*. 1991; Ford 1998). Magnesium is also therapeutically effective in lowering blood pressure in many forms of secondary hypertension as well as in pre-eclampsia (Mason *et al*. 1996; Jurcovicova *et al*. 1998). Thus, although this cation may not be a universally effective antihypertensive agent, it may benefit a subgroup of patients with hypertension.

## 6.6 CONCLUSIONS

Despite strong epidemiological and experimental data supporting a role for low magnesium in the pathogenesis of hypertension, clinical observations and clinical trials have provided controversial and often conflicting results. Moreover, the therapeutic value of magnesium in the management of hypertension is still unclear. Before making definitive therapeutic recommendations on the use of magnesium in the management of hypertension, well controlled, long-term therapeutic trials in carefully characterized hypertensive patients are needed. However, the potential benefits of magnesium are recognized, and the current European, United States, Canadian and international guidelines have included maintenance of adequate dietary magnesium intake as a recommendation for lifestyle modifications for hypertension prevention management (Stergiou *et al*. 2004; Khan *et al*. 2005).

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# 7

# Atherosclerosis and magnesium

*B.M. Altura and B.T. Altura*

## 7.1 MAGNESIUM AND ATHEROGENESIS

Several studies have demonstrated in animal models that magnesium deficiency accelerates components of the atherogenic process (Altura *et al.* 1990; Rayssiguier *et al.* 1993; Maier *et al.* 2004). The nuclear factor-Kappa B (NF-KB) pathway is one of the signalling pathways turned on in atherogenesis in response to proinflammatory cytokines (e.g. tumour necrosis factor-alpha [TNF-α], interleukin-1 [IL-1] and IL-18), as well as activation of Toll-like receptors (Tedqui and Mallat 2006). Activation of the NF-KB pathway is a dominant player in the inflammatory process found in atherogenesis via its regulation of proinflammatory cytokines, adhesion molecules, chemokines, growth factors and inducible enzymes, such as cyclo-oxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) (De Martin *et al.* 2000). Once activated and translocated to the nucleus, binding to kB enhancer elements takes place on specific genes, and transcription will be promoted. Studies have demonstrated that NF-KB is activated in peripheral and cerebral vascular smooth muscle (VSM) cells

exposed to lower than normal $Mg^{2+}$ concentrations (Altura *et al*. 2003a,b; Altura and Altura 2007) and is associated with increased levels of several transcription factors, including c-Fos and c-Jun (Altura *et al*. 2003a,b; Altura and Altura 2007), needed for VSM cell differentiation, growth and transformation, as seen in the atherosclerotic process (for review, see Tedqui and Mallat 2006).

Diverse bioactive lipids have been observed and identified in the atherosclerotic plaque, including the inflammatory mediator platelet-activating factor (PAF), PAF-like lipids, oxidized phospholipids, lysophosphatidylcholine and several sphingolipids (Tedqui and Mallat 2006). Morrill *et al*. (1997, 1998) showed that exposure of peripheral and cerebral VSM cells to lowered levels of $Mg^{2+}$ results in production of PAF-like lipids, a breakdown of membrane neutral sphingomyelinase (SMase) and release of a number of bioactive sphingolipids, including several ceramides. SMase and several sphingolipids, including physiologically derived ceramides, when tested in the intact cerebral and intestinal microvasculatures *in vivo*, result in vasospasm concomitant with endothelial sticking of white blood cells followed by rupture and emigration of these elements into the extravascular spaces (Altura *et al*. 2002). Such *in situ* evidence is suggestive of a role for sphingolipids in the developing atherogenic process.

It has been shown that both endothelial cells and VSM cells, when exposed to low levels of $Mg^{2+}$, can result in rapid formation of malondialdehyde and reactive oxygen species (ROS) (Dickens *et al*. 1992; Weglicki *et al*. 1992; Morrill *et al*. 1997, 1998; Rock *et al*. 1998; Yang *et al*. 2000; Altura *et al*. 2003a,b). Recently, it was demonstrated that when peripheral and cerebral VSM cells are exposed to hydrogen peroxide, hydroxyl radical (·OH) and peroxynitrite, they will undergo apoptosis (6–24 h) in a concentration-dependent manner (J. Li *et al*. 2003a,b, 2004a,b; W. Li *et al*. 2004), and low-magnesium environments were observed to potentiate these apoptotic processes (Li *et al*. 2007). It is thought that defects in the clearance of apoptotic cells can promote and perpetuate proinflammatory factors and, thus, the atherogenic process (for review, see Tedqui and Mallat 2006).

## 7.2 VASCULAR SPASM AND ISCHAEMIC HEART DISEASE

Arterial vasospasm may be a major factor leading to cardiovascular disorders, and a number of mechanisms have been proposed for localized coronary vasospasm. These include 1) passive and active influences on vessel calibre, e.g. changes in VSM cell tone; 2) endothelial-dependent mechanisms (e.g. mechanical injury of endothelial cells and/or loss of endogenous vasodilator substances such as nitric oxide); 3) non-endothelial mechanisms (e.g. increased sympathetic

activity; release of vasoactive substances such as histamine, angiotensin II; hypersensitivity of coronary VSM resulting in spontaneous phasic contractile activity); and 4) alterations in divalent cation metabolism (see below).

Certain drugs, such as digitalis and other cardiac glycosides, and many diuretics, which are commonly used to treat ischaemic heart disease (IHD) and hypertension, result in wasting of $K^+$ and $Mg^{2+}$ (Duarte 1968; Ryan *et al.* 1980; Cohen and Kitzes 1983; Mountokakis 1983; Cohen *et al.* 1984; French *et al.* 1984; Altura and Altura 1985; Li *et al.* 2007). Many of the IHD patients treated with these drugs become susceptible to cardiac arrhythmias and sudden death, probably attributed to the tissue and cellular deficits in $K^+$ and $Mg^{2+}$. A large body of clinical and experimental evidence indicates that irrespective of the myocardial syndrome (IHD, sudden death IHD, myocardial infarction, unstable angina, ventricular fibrillation), all are associated with myocardial and coronary arterial losses of $K^+$ and $Mg^{2+}$ and gains of $Na^+$ and $Ca^{2+}$ (for reviews, see Iseri *et al.* 1952; Dyckner and Wester 1981; Altura and Altura 1982, 1984, 1985; Mountokakis 1983; Cohen *et al.* 1984). Experimental evidence suggests that $Mg^{2+}$ may be the first cation to be lost in the myocardium and coronary arterial VSM cells in a hypoxically induced injury to the heart (Iseri *et al.* 1952; Dyckner and Wester 1981; Altura and Altura 1982, 1984, 1985).

Using perfused working rat hearts and $^{31}P$-nuclear magnetic resonance spectroscopy, Altura *et al.* (1993) showed that low extracellular $Mg^{2+}$ levels, similar in concentration to those found in patient sera with IHD, resulted in deficits in intracellular $Mg^{2+}$, reduction in coronary blood flow, reduction in cardiac output, lowered myocardial cell ATP and lowered levels of creatine phosphate. Such events seem to lead to ROS (Freedman *et al.* 1990; Weglicki *et al.* 2001) and ferrylmyoglobin, an additional tissue-damaging ROS (Wu *et al.* 1994).

Can evidence be found, clinically, to implicate low serum or tissue levels of $Mg^{2+}$ in the diseases discussed above? Using $Mg^{2+}$ ion-selective electrodes, researchers have shown that patients with congestive heart failure, IHD, strokes, type 2 diabetes mellitus, hypertension, renal transplants and end-stage renal disease all exhibit lowered levels of ionized magnesium in sera and red blood cells (B.T. Altura and Altura 1991, 1994, 1997; Markell *et al.* 1993a,b; Altura and Lewenstam 1994; Altura *et al.* 1994; B.M. Altura and Altura 1995).

## 7.3 CONCLUSIONS

Until relatively recently, it was not believed that magnesium played any role in maintaining normal cardiovascular functions and dynamics. However, this was due to a number of factors: poorly designed experiments; an absence of

methodology needed to measure, precisely, the free ionized magnesium rather than total magnesium in tissues, cells, organs and body fluids; and a poor appreciation of the progressive shortfalls in magnesium dietary intake (in foodstuffs, beverages and water) since the turn of the past century.

This minireview serves to fill in several of these gaps in knowledge and provides a scientific-medical basis for a link between magnesium deficiency, atherogenesis and cardiovascular diseases. The experimental and clinical studies reviewed above lead us to believe that in order to prevent or ameliorate vascular- and cardiac-related disorders, our diets and/or drinking-water (and beverages) should be supplemented with magnesium. For the diets, the available data suggest that the total magnesium intake must be at least 450–500 mg/day, and drinking-water should contain a minimum of 25–50 mg/l (at present, in the United States, many of our potable water sources contain <10 mg/l). At the turn of the past century, we were ingesting, in the United States, about 450–500 mg of magnesium per day; at present, we are ingesting about 175–248 mg/day — thus, a considerable shortfall. Corrections of these deficits should perforce lead to healthier bodies, less cardiovascular diseases and longer lifespans.

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# 8

# Health significance of calcium and magnesium: Examples from human studies

*G.F. Combs, Jr and F.H. Nielsen*

## 8.1 ROLES OF CALCIUM AND MAGNESIUM IN NUTRITION AND HEALTH

Calcium and magnesium play important roles in bone structure, muscle contraction, nerve impulse transmission, blood clotting and cell signalling. Some 99% of body calcium is in the bone, which is 40% calcium. That this pool is regulated at apparently lower priority than cellular calcium pools results in impairments in bone mineralization as the main features of calcium deficiency. Accordingly, calcium-deficient children show rickets, the condition of under-mineralized bone resulting in structural deformities of growing bones, while bone undermineralization in adults is involved in osteoporosis with associated

increases in fracture risk. Magnesium deficiency affects neurological and neuromuscular function, resulting in anorexia, muscular weakness, lethargy and unsteady gait. These clinical signs are not common but have been reported in cases with low magnesium intakes coupled with excessive magnesium losses due to prolonged diarrhoea.

It is clear that the calcium intakes of many people do not meet their calcium needs. This is the case for most children and all adults in developing countries and for most adults in industrialized ones. The widespread nature of calcium undernutrition almost certainly contributes to the emergence of rickets in the developing world and to prevalent osteoporosis (best characterized in developed countries) in many countries. In recent years, rickets has been reported in at least 21 countries (Pettifor *et al*. 1978; Okonofua *et al*. 1991; Oginni *et al*. 1996; Banajeh *et al*. 1997; Muhe *et al.* 1997; Thacher *et al*. 1997, 1999, 2000; Kreiter *et al*. 2000; Majid Molla *et al*. 2000; Fraser and Tserendolgor 2001; Harris *et al*. 2001; Karim *et al*. 2001). It is prevalent in south-eastern Bangladesh, where it appears to affect some 4% of children. Fischer *et al*. (1999) found cases in this area to show normal plasma 25-hydroxycholecalciferol levels, which suggests that their rickets is of the calcium deficiency type.

It is estimated that three quarters of United States residents also do not consume Recommended Dietary Allowance (RDA) levels of magnesium, based on dietary recommendations derived from a small number of metabolic balance studies of non-deficient individuals. The lack of well controlled studies also has made it difficult to establish an evidence-based recommended intake or requirement for magnesium. The most recent recommendations of the Food and Nutrition Board of the United States Institute of Medicine (IOM 1997) were based on usual dietary intakes not associated with adverse effects and a poorly controlled balance study (Lakshmanan *et al*. 1984). Accordingly, the Estimated Average Requirements (EARs) and RDAs (IOM 1997) have been questioned. The Scientific Committee for Food of the European Commission (SCF 1993) had opted to set only an acceptable range (150–500 mg/day) of magnesium intake for adults, and the FAO/WHO Expert Consultation (2002), finding no evidence for magnesium deficiency in humans consuming less than United States RDA levels, set the Recommended Nutrient Intake (RNI) for magnesium arbitrarily (e.g. that for 19- to 65-year-old women at 220 mg/day). Hunt and Johnson (2006) compiled magnesium balance data from some 20 controlled feeding studies conducted at the Grand Forks Human Nutrition Research Center; their analysis suggested that magnesium balance was achieved at approximately the RNI level set by the FAO/WHO Expert Consultation (2002). It is clear that very large numbers of people consume levels of magnesium and calcium that are insufficient to support even the most conservative estimates of their physiological needs.

The experiments described below were approved by the appropriate institutional review boards: the calcium intervention trial in Bangladesh by the Human Subjects Committees of Cornell University, Dhaka University and the University of North Dakota[1]; and the controlled magnesium feeding studies by the Human Subjects Committee of the University of North Dakota.[1]

## 8.2 CALCIUM INTERVENTION STUDY

In order to determine the role of calcium in endemic rickets in south-eastern Bangladesh, Combs and Hassan (2005) conducted studies of the local food system followed by a calcium intervention trial with high-risk susceptible children living in a rickets-endemic area. These were done in Cox's Bazaar District, Bangladesh. Most families in affected communities consumed few, if any, calcium-rich foods; consequently, their calcium intakes were very low (Figure 8.1). In particular, the high-risk children consumed less than a quarter of levels recommended in the United States (IOM 1997).

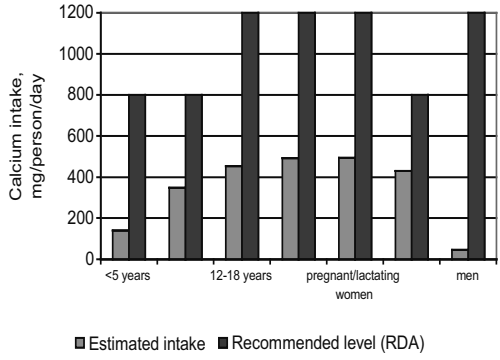


Figure 8.1. Estimated calcium intakes in a rickets-endemic area, Cox's Bazaar District, Bangladesh.

On the basis of that finding, Combs *et al.* (2005) conducted a 13-month-long, double-blind, clinical trial with 1- to 5-year-old children randomized to several treatments consisting of a milk powder–based dietary supplement given daily, 6 days per week. These included treatments providing 50, 250 or 500 mg of calcium per day, with physical, radiographic and biochemical indicators of bone

[1] Contractor to the Grand Forks Human Nutrition Research Center.

health being the primary end-points. Combs *et al.* (2005) screened a total of 1749 1- to 5-year-old children, some 13% of whom, over the 7 months before the start of the intervention, had developed physical signs of rickets. A total of 119 children remaining asymptomatic after that were randomized to the treatments and followed for 13 months. After that period, none showed rachitic leg signs or radiological evidence of active rickets, and all showed carpal ossification normal for age after that intervention, suggesting that even the lowest supplement of calcium (50 mg/day) was useful in supporting normal bone development in this high-risk population.

## 8.3 MAGNESIUM FEEDING STUDIES

A series of controlled feeding studies was conducted to describe the quantitative need for magnesium and determine whether simple nutritional magnesium deficiency may affect cardiovascular and/or bone health (Hunt *et al.* 1997; Nielsen 2004; Nielsen *et al.* 2007a,b). These studies involved female postmenopausal volunteer subjects who resided in the metabolic unit of the Grand Forks Human Nutrition Research Center. Medical, psychological and nutritional evaluations showed that all subjects were in good health. Each experiment was conducted for about 6 months, during which time subjects consumed weighed amounts of all foods and beverages, provided in a 3-day rotating menu composed of foods found often in a developed country–type diet that were low in magnesium. Generally, the diets provided about 10% of their energy as protein, 54–58% as carbohydrate and 35–36% as fat. Supplements were used to ensure adequacy of nutrients present in low or in unknown quantities in the diet. Energy intakes were adjusted in 840-kJ increments to maintain body weight within 2% of admission weight. The diets were formulated to provide 600–800 mg of calcium and about 150 mg of magnesium per day. While other elements were included as variables in these studies, each study followed a depletion–repletion design with respect to magnesium, using a low-magnesium diet containing about 110 mg of magnesium per day to effect magnesium deprivation and a magnesium gluconate supplement (200 mg of magnesium per day) to effect magnesium repletion. Each study used a small number of subjects (postmenopausal women) randomized to the low-magnesium diet or supplemented diet for an initial period, followed by assignment to the other diet during a subsequent period according to a Latin-square design.

Diet samples, total urine and faeces were collected daily and analysed for magnesium, calcium and phosphorus by inductively coupled argon plasma emission spectroscopy after dilution (urine) or nitric–perchloric acid digestion

(diets, faeces). Magnesium balance was calculated as the difference between dietary intake and faecal plus urinary excretion.

### 8.3.1 Magnesium experiment 1

Eleven subjects were equilibrated to an intake of approximately 310 mg of magnesium per day using supplemental magnesium gluconate. They were then randomized into groups receiving low magnesium (109 mg/day) with or without supplemental magnesium (200 mg/day) and with or without an aluminium supplement (1000 mg/day) in 24-day treatment periods. Measured during the final 12 days of each treatment period, magnesium balance was positive during magnesium deprivation and increased (67 mg/day) during magnesium replenishment (Table 8.1). The change in magnesium status was associated with an increase in calcium balance from 21 to 145 mg/day during periods of magnesium deprivation — an unexpected finding, as magnesium deprivation has been shown to impair bone formation in experimental animals (Hunt *et al.* 1997). In fact, magnesium deficiency depressed serum parathyroid hormone and 1,25-dihydroxycholecalciferol, the biologically active form of vitamin $D_3$, in rats (Rude *et al.* 2005); reductions in these hormones are associated with impaired calcium conservation by the kidney and/or intestine.

Table 8.1. Magnesium and calcium balance data[a] from a modified Latin-square-designed experiment with deficient and adequate dietary magnesium and boron as well as aluminium supplementation as variables (Magnesium experiment 1)

| | Balance data (mg/day) | |
|---|---|---|
| Variable | Basal diet | Magnesium-supplemented diet |
| **Magnesium balance** | | |
| Dietary magnesium | 109 ± 15 | 340 ± 19 |
| Faecal magnesium | 32 ± 13 | 150 ± 51 |
| Urinary magnesium | 70 ± 12 | 123 ± 33 |
| Magnesium balance | +7 | +67 |
| **Calcium balance** | | |
| Dietary calcium | 580 ± 53 | 616 ± 69 |
| Faecal calcium | 314 ± 127 | 430 ± 148 |
| Urinary calcium | 121 ± 49 | 165 ± 108 |
| Calcium balance | +145 | +21 |

[a] Data from Hunt *et al.* (1997); analyses of samples obtained the last 12 days of each 24-day magnesium deprivation/supplementation treatment period.

## 8.3.2 Magnesium experiment 2

Thirteen subjects were equilibrated for 21 days to a diet that provided about 318 mg of magnesium per day prior to randomization to the low-magnesium (118 mg/day) diet with or without supplemental magnesium gluconate (200 mg of magnesium per day) and with or without a boron supplement (3 mg/day) in 42-day treatment periods. Magnesium balance during the last 12 days of each period was positive during magnesium supplementation but negative during magnesium restriction, an effect apparently moderated by reduced urinary magnesium excretion (Table 8.2). Magnesium deprivation decreased urinary calcium excretion, although calcium balance appeared to increase in periods of low dietary magnesium (Table 8.3) (Nielsen 2004).

Table 8.2. Effect of magnesium depletion and repletion on magnesium and calcium balance[a] (Magnesium experiment 2; from Nielsen 2004)

| | Balance data (mg/day) | | | | | |
|---|---|---|---|---|---|---|
| | Low magnesium | | Magnesium supplemented | | | |
| Variable | Low boron | High boron | Low boron | High boron | Pooled SD | Magnesium effect *P* value |
| **Magnesium balance**[b] | | | | | | |
| Dietary magnesium | 116 | 119 | 321 | 317 | | |
| Faecal magnesium | 60 | 51 | 177 | 170 | 25 | 0.0001 |
| Urinary magnesium | 74 | 74 | 141 | 137 | 8 | 0.0001 |
| Magnesium balance | −18 | −6 | +3 | +10 | 21 | 0.003 |
| **Calcium balance**[b] | | | | | | |
| Dietary calcium | 695 | 708 | 715 | 702 | | |
| Faecal calcium | 524 | 518 | 532 | 520 | 70 | 0.84 |
| Urinary calcium | 161 | 165 | 180 | 180 | 15 | 0.0003 |
| Calcium balance | +10 | +25 | +4 | +3 | 63 | 0.45 |

[a] Based on analyses of samples obtained the last 24 days of each 42-day dietary treatment period.

[b] Data based on all 42 days of each treatment period; magnesium deprivation significantly increased calcium balance (33 vs 10 mg/day; $P < 0.04$).

## 8.3.3 Magnesium experiment 3

Further experiments were conducted to determine the response of postmenopausal women to magnesium. Eleven women were equilibrated to a diet providing 307 mg of magnesium per day using supplemental magnesium (220 mg/day) before being randomized to the low-magnesium diet (107 mg/day) or the diet supplemented with 220 mg magnesium per day for 72 days, after which

each group was assigned to the opposite treatment for a second 72-day period. Balance determinations were made during the last 36 days of each treatment period. Results showed that magnesium balance was negative (−5 mg/day) when the low-magnesium diet was fed and positive (+54 mg/day) when supplemental magnesium was given; calcium balance was greater during the period of magnesium deprivation (+33 mg/day) than it was during the period of magnesium supplementation (−1 mg/day). Magnesium deprivation also decreased red blood cell membrane magnesium, a putative indicator of body magnesium status (Table 8.4). One subject showed an increase in ventricular premature discharges after 52 days of magnesium deprivation; she was given supplemental magnesium, whereupon her heart rhythm returned to baseline within 14 days (Nielsen *et al*. 2007a).

Table 8.3. Effect of magnesium deprivation and repletion on selected variables with or without supplemental boron (Magnesium experiment 2; from Nielsen 2004)

| | Urine | | Serum | | |
|---|---|---|---|---|---|
| Dietary treatment[a] | K, g/day | P, mg/day | 25-OH-$D_3$, nmol/l | 1,25-OH-$D_3$, pmol/l | Cholesterol, mmol/l |
| Low Mg / Low B | 1.24 | 574 | 61.9 | 59.2 | 6.41 |
| Low Mg / High B | 1.11 | 587 | 72.4 | 62.2 | 6.41 |
| High Mg / Low B | 1.52 | 561 | 58.2 | 69.1 | 6.62 |
| High Mg / High B | 1.32 | 547 | 56.7 | 61.4 | 6.59 |
| Pooled SD | 0.29 | 34 | 14.2 | 8.2 | 0.21 |
| | Analysis of variance *P* values | | | | |
| Mg effect | 0.002 | 0.01 | 0.01 | 0.06 | 0.02 |
| B effect | 0.05 | 0.96 | 0.32 | 0.10 | 0.60 |
| Mg × B | 0.98 | 0.12 | 0.07 | 0.70 | 0.32 |

25-OH-$D_3$, 25-hydroxycholecalciferol; 1,25-OH-$D_3$, 1,25-dihydroxycholecalciferol, the biologically active form of vitamin D

[a] Low Mg = 118 mg/day; high Mg = 318 mg/day; low B = 0.25 mg/day; high B = 3.25 mg/day.

### 8.3.4 Magnesium experiment 4

Thirteen postmenopausal women were fed a low-magnesium diet (101 mg/day) for a targeted 93 days, after which they were to be given supplemental magnesium (200 mg/day) for 42 days. However, heart rhythm changes detected in several subjects prior to the completion of the planned magnesium depletion period necessitated their being given supplemental magnesium (Nielsen *et al*. 2007b). This occurred at 42 days for one subject who also showed a rise in blood pressure. Upon magnesium supplementation, her heart rhythm returned to baseline and hypertension disappeared. Heart rhythm changes were detected for two subjects at 52 days, for one at 64 days and for one at 78 days. In each case,

affected subjects were given supplemental magnesium, as were all unaffected subjects at 78 days. In the case of each affected subject, heart rhythm changes, particularly atrial flutter and fibrillation, which were observed in three subjects, disappeared upon magnesium supplementation and did not reappear (Nielsen *et al*. 2007b).

Table 8.4. Effect of magnesium depletion and repletion on magnesium and calcium balance (Magnesium experiment 3; from Nielsen *et al*. 2007a)

| Variable | Dietary treatment | | Pooled SD | *P* value |
|---|---|---|---|---|
| | Magnesium deprived | Magnesium supplemented | | |
| **Magnesium balance data**[a] | | | | |
| Dietary magnesium, mg/day | 107 | 327 | | |
| Faecal magnesium, mg/day | 60 | 169 | 18 | 0.0001 |
| Urinary magnesium, mg/day | 52 | 104 | 11 | 0.0001 |
| Magnesium balance, mg/day | −5 | +54 | 20 | 0.0001 |
| **Calcium balance data**[a] | | | | |
| Dietary calcium, mg/day | 762 | 767 | | |
| Faecal calcium, mg/day | 570 | 593 | 80 | 0.09 |
| Urinary calcium, mg/day | 160 | 175 | 13 | 0.0001 |
| Calcium balance, mg/day | +33 | −1 | 75 | 0.009 |
| **Other parameters** | | | | |
| Urinary potassium, g/day | 1.58 | 1.64 | 63 | 0.04 |
| Urinary phosphorus, mg/day | 787 | 769 | 49 | 0.03 |
| Serum 25-OH-$D_3$, nmol/l | 84 | 84 | 4 | 0.96 |
| Red blood cell magnesium,[a] nmol/mg protein | 2.51 | 2.67 | 0.02 | 0.05 |

25-OH-$D_3$, 25-hydroxycholecalciferol

[a] Data based on samples collected the last 36 days of each 72-day dietary period.

It is possible that some of these subjects may have entered the study in marginal magnesium status, as might be expected based on the 2001–2002 findings of the United States National Health and Nutrition Examination Survey (NHANES) (Moshfegh *et al.* 2005). If so, then the negative balance shown during the period of magnesium depletion (−3 mg/day) would be expected to exacerbate a mild magnesium deficiency. When the volunteers were supplemented with magnesium, magnesium balance exceeded 48 mg/day (Table 8.5). In this study (Nielsen *et al*. 2007b), magnesium deprivation markedly increased calcium balance (261 mg/day), a finding consistent with the results of the previous experiments.

Table 8.5. Effect of magnesium depletion and repletion on magnesium balance (Magnesium experiment 4; from Nielsen *et al.* 2007b)

| Variable | Dietary treatment | | Pooled SD | *P* value |
|---|---|---|---|---|
| | Magnesium deprived | Magnesium supplemented | | |
| **Magnesium balance data**[a] | | | | |
| Dietary magnesium, mg/day | 108 | 319 | | |
| Faecal magnesium, mg/day | 50 | 162 | 25 | 0.0001 |
| Urinary magnesium, mg/day | 61 | 108 | 8 | 0.0001 |
| Magnesium balance, mg/day | −3 | +48 | 22 | 0.0001 |
| **Calcium balance data**[a] | | | | |
| Dietary calcium, mg/day | 690 | 657 | | |
| Faecal calcium, mg/day | 298 | 297 | 0.96 | NS |
| Urinary calcium, mg/day | 130 | 132 | 0.78 | NS |
| Calcium balance, mg/day | 261 | 228 | 0.04 | 0.05 |
| **Other parameters** | | | | |
| Urinary potassium, g/day | 1.13 | 1.25 | 0.08 | 0.002 |
| Serum cholesterol, mg/dl | 6.10 | 6.67 | 0.28 | 0.0003 |
| Red blood cell magnesium, nmol/mg protein | 3.00 | 3.25 | 0.17 | 0.005 |
| Red blood cell superoxide dismutase (U/mg haemoglobin) | 2973 | 3387 | 438 | 0.03 |

NS, not significant

[a] Based on samples collected the last 36 days of magnesium depletion (78 days) and magnesium repletion (58 days).

These studies suggest that marginal magnesium status, such as found in many apparently healthy citizens in the United States, can increase calcium retention and decrease potassium excretion, potentially affecting cardiac function.

## 8.3.5 Conclusions

These studies demonstrate the responses of different types of human subjects to controlled supplementation with calcium and/or magnesium, both of which are widely underconsumed relative to their physiological needs. For children at risk of developing rickets, owing to their reliance on diets limited in calcium, modest supplements of calcium appear to have significant health value. For apparently healthy adults, metabolic balance studies suggest that intakes less than 100–150 mg of magnesium per day have the potential to adversely affect cardiac function.

These human magnesium balance studies demonstrate the utility of the metabolic balance approach for determining needs for dietary magnesium. Those findings indicate that magnesium intakes in the range of 100–150 mg/day

induce mild to moderate deficits in that mineral, which are associated with increased calcium retention. Should that response involve the accumulation of calcium in soft tissues and increases in intracellular ionized calcium, then the release of pro-inflammatory neuropeptides and enhancement of oxidative stress would be expected (Kramer *et al.* 2003). Such marginal magnesium status may be a factor in osteoporosis by the induction of bone resorption, which has been demonstrated in the rat in response to increased circulating levels of the neuropeptides substance P and tumour necrosis factor-alpha (Rude *et al.* 2005). Moderate magnesium deficiency is also known to increase the excretion of potassium, a finding consistent with changes caused by increased intracellular calcium and adversely affecting heart rhythm. Because many individuals consume less than 150 mg of magnesium per day (Moshfegh *et al.* 2005), it is likely that increasing the magnesium intakes of many individuals may benefit both their bone health and their cardiac function.

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# 9

# Calcium and magnesium: Role of drinking-water in relation to bone metabolism

*C.M. Weaver and J.W. Nieves*

## 9.1 WATER AS A SOURCE OF CALCIUM AND MAGNESIUM

The most concentrated sources of calcium in the diets of most people are dairy products. A high proportion of the calcium intake for much of the world's population is from milk. Therefore, to consider the role of high-calcium water in providing calcium nutrition, it is prudent to compare it with milk for content of calcium and other nutrients, stability and bioavailability. A litre of milk contains 1276 mg calcium, 118 mg magnesium, 1044 mg phosphorus, 35.5 g protein, 1715 mg potassium, 1.35 mg riboflavin and 380 IU vitamin D (in North America). The concentration of calcium in milk is reasonably consistent. In

contrast, the concentration of calcium in water is widely variable. The solubility of the calcium, which influences whether the calcium is ingested or is apparent as precipitate in the bottom of the container, depends on many factors, especially pH and atmospheric carbon dioxide. The presence of anions such as phosphates, nitrates, chlorides and sulfates determines the solid phase of calcium across the pH range at the atmospheric pressure of carbon dioxide present. In contrast, milk pH is controlled within a narrow range by buffering proteins, and the calcium remains stable in solution through complexes with casein micelles. Thus, while water may provide important contributions of calcium and magnesium to the diet, it alone cannot be viewed as a substitute for milk, because of the variability of waters and also because the availability of calcium and magnesium may be more variable than that from milk.

Because magnesium is present in many foods, particularly legumes, vegetables, nuts, seeds, fruits, grains, fish and dairy products, severe magnesium deficiency is rarely seen in healthy people. Magnesium in water is subject to many of the same influences as discussed for calcium.

## 9.2 BIOAVAILABILITY OF CALCIUM AND MAGNESIUM IN WATER

The bioavailability of calcium includes how well calcium is absorbed, retained and utilized in the body. The bioavailability of calcium from water is likely to be influenced by the same factors that affect calcium bioavailability from food, which has been reviewed (Weaver and Heaney 2006). The presence of anions in certain waters can influence the bioavailability of calcium from either water or other sources in the diet.

Calcium absorption is influenced by the load in a meal and matrix effects on the meal. Calcium absorption efficiency decreases with increasing load, although total mass of calcium absorbed continues to increase with load. This phenomenon is related to the multiple pathways for calcium absorption. Transcellular calcium absorption is an active process mediated by vitamin D–induced calcium binding proteins. This is a saturable process as calcium binding sites become occupied, which reduces absorption efficiency with increasing load. Paracellular calcium absorption is a passive, non-saturable process that increases linearly with calcium load.

Consumption of calcium with a meal generally improves calcium absorption by about 5% (Recker 1985). The major inhibitors to calcium absorption from food are oxalate and phytate. Phytate is only modestly inhibitory to calcium

absorption relative to other cations such as zinc, which is more tightly bound to the negatively charged phosphate groups on phytic acid. Oxalate forms insoluble salts with calcium, which reduces calcium absorption 10-fold in spinach compared with calcium in milk and 2-fold in sweet potatoes and beans (Weaver and Heaney 2006). Oddly, soybeans, which are rich in both oxalate and phytate, have only a modest inhibitory effect on calcium absorption.

## 9.3 CALCIUM AND MAGNESIUM ABSORPTION FROM WATER

The typical strategy of estimating calcium absorption from a source is to use a radioactive or stable isotope to label the calcium. The label is measured in the blood or urine, post-ingestion, to estimate absorption. The method successfully estimates calcium absorption only to the extent the label exchanges with the endogenous calcium in the source being studied. In foods, the best measurements of calcium absorption have incorporated the labels endogenously by giving the label to plants during growth or injecting it into a lactating cow prior to milking. Calcium salts used as fortificants can be synthesized with calcium isotopes. However, it is difficult to conceive how the calcium in the groundwater could be intrinsically labelled. Thus, the studies use the extrinsic labelling approach. This involves mixing a soluble form of a calcium isotope into the source. With foods, the extrinsic labelling approach can be validated against an intrinsic labelling approach. The extrinsic labelling approach was validated for estimating calcium absorption from milk (Weaver *et al.* 1997), but vastly overestimated the calcium absorption from spinach, presumably because the extrinsic label does not exchange with calcium oxalate (Weaver and Heaney 1991).

Calcium absorption from high-calcium waters has been studied using the extrinsic labelling approach. Results from five studies are summarized in Table 9.1; in all these studies, calcium absorption from the water was as good as that from milk. However, not enough information about the waters was available for most of the studies to estimate how much of the calcium from the water or the label was in solution or in a solid phase. If some of the calcium in water is in a solid phase when the label is added, the label would take a very long time to equilibrate or may never equilibrate. In that case, the label could be completely in solution and would represent absorption only from the ionized calcium, which likely would overestimate calcium absorption from the water.

Table 9.1. Calcium absorption from high-calcium water using the extrinsic labelling approach

| Study | Calcium load (mg) | Absorption results | Reference |
|---|---|---|---|
| 1 | 100 | 43.3% from milk and 47.5% from Sangemini (Italy) water, $P < 0.05$ | Heaney and Dowell (1994) |
| 2 | 250 | 23.8% from high-sulfate water and 25% from milk / NS | Couzy *et al*. (1995) |
| 3 | 180 | 37% from mineral water and 38–42% from dairy / NS | Van Dokkum *et al*. (1996) |
| 4 | 200 | 34.1–37.0% $CaCl_2$ water (high sulfate vs high bicarbonate) combinations had equivalent absorption | Wynckel *et al*. (1997) |
| 5 | 127 | 22% from water and 23% from milk | Bacciottini *et al*. (2004) |

NS, non-significant

Waters are diverse, with varying amounts of anions present, depending on the source and treatment process. Calcium forms complexes with chlorides, nitrates, bicarbonates, sulfates and hydroxides, as affected by carbon dioxide and pH. As an example, Figure 9.1 shows the percentage of total calcium that is in solution as a function of pH in a low- and high-sulfate water. Panel A shows the formation of calcite as pH increases, when water is at atmospheric (ambient) carbon dioxide pressure. Above pH 8.5, over half of the calcium is removed from solution. Most of this would be colloidally dispersed, but will eventually drop out as "scale" deposits. Panel B shows calcite precipitation expected at elevated carbon dioxide pressure (10 times ambient, which is not unusual in groundwater). Above pH 8.0, increasing amounts of calcium are removed from solution. Sulfate has a rather small impact on the proportion of free calcium in solution, approximately 10% reduction in the example. Small concentrations of phosphate in the water will result in the precipitation of hydroxyapatite, a calcium–phosphorus solid phase. This occurs at pH 7. At the 1 mg phosphate per litre present in the example, the maximum amount of calcium that can be precipitated as hydroxyapatite is 9% of the total calcium. The pH of drinking-water is often maintained above pH 7 to avoid corrosion of pipes. Thus, formation of calcium solid phases is common. We do not know the bio-availability of calcium from the carbonates, hydroxides, oxides or other complexes that can form in water. Furthermore, the calcium complexes may not be consumed if they have precipitated in the container. Böhmer *et al*. (2000) reported the ion concentration of the mineral waters used in all of the studies

except the study by Bacciottini *et al*. (2004). However, neither the pH nor the carbon dioxide pressure was given. Wynckel *et al*. (1997) did report the pH of the three mineral waters their group tested, which was 7–7.2. It would be informative to know the variation in pH and carbon dioxide pressure in mineral waters.

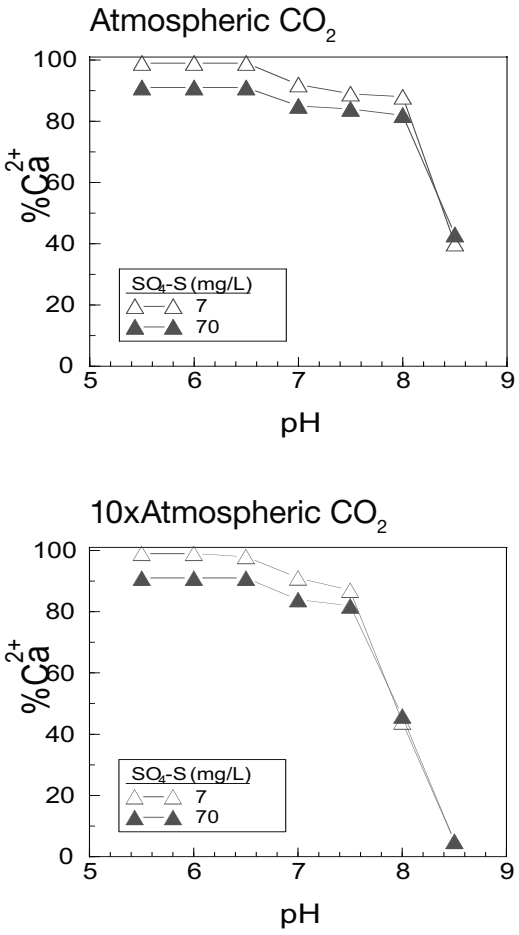


Figure 9.1. Removal of calcium from solution as calcite with increasing pH, carbon dioxide pressure and sulfate content of water. Composition of the drinking-water: Ca, 16 mg/l; Mg, 1.6 mg/l; $SO_4$, either 7 or 70 mg/l; Cl, 35 mg/l; $PO_4$, 1 mg/l; $CO_2$, either 35.5 Pa (upper panel) or 355 Pa (lower panel).

There is less known about the absorption of magnesium from water. Using the extrinsic labelling approach, magnesium appears to be well absorbed, and the absorption is improved when the water is consumed during a meal (Sabatier *et al*. 2002); absorption is also higher in younger individuals (Verhas *et al*. 2002).

A matched case–control analysis reported that depending on the calcium concentration, mineral-rich water might contribute up to one quarter of the total calcium intake and 6–17% of the total daily magnesium intake (Galan *et al.* 2002). Therefore, mineral-rich water may provide an important supplementary contribution to total calcium and magnesium intake.

## 9.4 CALCIUM AND MAGNESIUM RETENTION FROM DRINKING-WATER

Anions in water can influence urinary calcium excretion. Sodium and sulfate both increase urinary calcium losses. In a cross-over study in 37 young women, whose basal diets contained 600 mg calcium supplemented with 480 mg calcium either from milk or from a high-sulfate water in 3-week periods, urinary calcium excretion was significantly greater ($P = 0.001$) when the calcium was ingested from the water than from the milk (3.44 ± 1.21 vs 2.94 ± 1.36 mmol/day) (Brandolini *et al*. 2005). In the same study, several other minerals were measured that were also present in the high-calcium water. In particular, urinary magnesium excretion was higher ($P = 0.0002$) when the magnesium was provided in water compared with milk (3.88 ± 1.75 vs 2.95 ± 0.96 mmol/day). There were no differences in a biochemical marker of bone resorption or parathyroid hormone (PTH), a hormone that increases bone resorption, between the two periods. The authors hypothesized that the increased urinary mineral excretion during the water phase was due to the acidogenic nature of the sulfates. They speculated that if the observed calcium loss was sustained over 30 years, this could translate to 10–15% loss in bone mineral mass, equivalent to one third of the bone loss that occurs after menopause.

## 9.5 EFFECT OF HIGH-MINERAL WATER ON BONE METABOLISM

High-calcium water suppresses PTH both acutely (Guillemant *et al*. 2000) and chronically (Meunier *et al*. 2005) relative to low-calcium water. In the study by Meunier *et al*. (2005), 180 postmenopausal women aged 70.1 ± 4.0 years were randomized to one of four groups: 1) high-calcium water, 2) low-calcium water, 3) high-calcium water plus supplementation with 400 IU of vitamin $D_2$ per day

or 4) a calcium (unspecified salt) plus vitamin $D_3$ supplement for 6 months. Biochemical markers of bone turnover significantly decreased in the group on high-calcium mineral water relative to the group on low-calcium mineral water, by 8.6% for serum osteocalcin, 11.5% for alkaline phosphatase and 16.3% for serum-type collagen C-telopeptide; as well, there was a decrease in serum PTH of 14.1%. The vitamin $D_2$ supplement provided no further benefit. The changes associated with the high-calcium water were similar to those observed with the supplement of calcium plus vitamin $D_3$. In another study by the same group (Guillemant *et al.* 2002), suppression of serum PTH and a bone resorption marker, serum CTX, was compared in three experimental periods: 1) ~600 mg of calcium given as high-calcium mineral water in three divided doses, 2) a single dose of tricalcium phosphate and 3) a low-calcium water in 15 young men using a cross-over design. Initial suppression of these biochemical indices of bone resorption was comparable, which was surprising, given the different initial loads of calcium. However, after the second dose of the high-calcium water, the biochemical indices remained suppressed throughout the test period, whereas the indices returned to the control levels after ingestion of the low-calcium water.

## 9.6 CALCIUM AND BONE MASS

Considerable epidemiological data have been accumulated seeking to evaluate the relationship between calcium intake and bone density. Peak bone mass that is attained during adolescence/young adulthood can be maximized by raising calcium intake to the Adequate Intake (AI) levels recommended by the 1997 Food and Nutrition Board of the United States Institute of Medicine (IOM 1997). To achieve maximal peak bone mass, dietary calcium and its absorption need to be at or above the threshold required for skeletal modelling and consolidation and obligatory losses in urine, faeces and sweat. After growth, calcium is needed to maintain serum calcium, because any decreases are quickly compensated for by increases in PTH and increased bone remodelling, leading to bone loss. Higher calcium intakes have been related to higher bone mass in children, young adults and postmenopausal women in most (64 out of 86) observational epidemiological studies and clinical trials of calcium supplementation (Heaney 2000). However, most individuals do not consume adequate intakes of calcium.

Clinical trials with calcium supplements in children and adolescents have been short term (1–3 years) and have shown an overall positive effect of calcium on bone mass accrual of between 1% and 6% per year in the total body and between 1% and 10% at each skeletal region compared with placebo (Nieves 2002; Matkovic *et al.* 2004). In children, results are often dependent on

pubertal stage. For example, in one recent study, postmenarcheal adolescent girls (<15.5 years of age) with baseline low calcium intakes (<800 mg/day) who were given calcium supplementation (1000 mg/day) had enhanced bone mineral acquisition compared with girls given placebo, especially in girls more than 2 years past the onset of menarche (Rozen *et al*. 2003). A meta-analysis of calcium intake in slightly older premenopausal women concluded that calcium supplementation led to an average increase in bone density at the spine and forearm of 1.1% per year compared with women receiving placebo (Welten *et al.* 1995). However, in most studies, the beneficial effect of added calcium on bone mass disappears when supplementation is halted (Johnston *et al*. 1992; Lee *et al*. 1996), although one trial showed a persistent beneficial effect persisting after 3–4 years (Bonjour *et al*. 1997). These data suggest that adequate calcium intake needs to be maintained throughout childhood, adolescence and young adulthood to have a lasting impact on peak bone mass.

In older individuals, calcium intake has been associated with retaining bone mass. In postmenopausal women, reviews of over 20 studies have concluded that calcium supplementation can decrease bone loss by approximately 1% per year (Nordin 1997). In a meta-analysis of 13 trials, calcium induced significant mean gains in bone mass (or slowed loss of bone mass) of 0.6% at the forearm, 3% at the spine and 2.6% at the femoral neck (Mackerras and Lumley 1997). A more recent meta-analysis found that in 15 trials, calcium-induced changes in bone mass were increases of 1.66% at the lumbar spine and 1.64% at the hip (Shea *et al*. 2002). Therefore, calcium supplementation has been shown to be effective in retarding bone loss in postmenopausal women. The beneficial effect of calcium intake on bone mass in postmenopausal women may be modified by several factors, including age, number of years since menopause, baseline calcium intake before supplementation and possibly physical activity level. In addition, the effect of calcium may be greater at the sites with more cortical bone (Suzuki *et al*. 2003; Ho *et al*. 2004), in elderly and late postmenopausal women and in women with low baseline calcium intakes. In large enough doses, calcium can reduce the higher PTH levels and lower the rate of bone remodelling (McKane *et al*. 1996). Calcium supplementation appears to improve the efficacy of anti-resorptive therapy, such as hormone replacement therapy, on bone mass (Nieves *et al*. 1998).

A review of 16 observational studies assessing hip fracture and calcium intake found that an increase in usual calcium intake of 1 g/day was associated with a 24% reduction in the risk of hip fracture (Cummings and Nevitt 1997). A recent prospective cohort study did not show an association between dietary calcium and vitamin D intake and fracture in a cohort of Swedish women aged 50–85 years (Michaelsson *et al*. 2003). In a follow-up of the cohort from the

Nurses' Health Study, a prospective investigation into the risk factors for major chronic diseases in over 100 000 women aged 34–59 in 1980 (Feskanish *et al.* 2003), an adequate vitamin D intake was associated with a lower risk of hip fracture, although neither milk intake nor a high-calcium diet was associated with hip fracture reduction. A meta-analysis of observational studies relating calcium intake to fracture risk (Xu *et al*. 2004) also failed to show any association between calcium intake and hip fracture, although there was a suggestion that individuals with extremely low calcium intake may be at increased fracture risk. However, data from randomized trials are much less prone to bias than the previously discussed observational studies. Two randomized clinical trials, which evaluated calcium supplementation alone, found vertebral fractures to be reduced by 28% and symptomatic fractures to be reduced by 70% in the calcium-supplemented group (Reid *et al*. 1995; Recker *et al*. 1996). Significant reductions in fracture (26–54% reduction in hip and non-spine fracture rates) have also been seen in those randomized clinical trials where calcium was given in conjunction with vitamin D (Nieves 2002), and it also appears that a minimum daily dose of 800 IU of vitamin D would be required for fracture efficacy (Bischoff-Ferrari *et al*. 2005).

## 9.7 MAGNESIUM AND BONE MASS

There have been several studies that have shown that higher intakes of magnesium are related to higher bone mass (Wang *et al*. 1971; Yano *et al.* 1985; Freudenheim *et al*. 1986; Angus *et al*. 1988; Houtkooper *et al*. 1995; Michaelsson *et al*. 1995; New *et al*. 1997, 2000; Ryder *et al*. 2005). Several small epidemiological studies have found that higher magnesium intakes are associated with higher bone mineral density in elderly men and women (Rude and Olerich 1996; Durlach *et al*. 1998; Tucker *et al*. 1999). There have been only small controlled clinical trials of magnesium supplementation (Nielsen 1990; Stendig-Lindberg *et al*. 1993) that were primarily effective in increasing bone mineral density in magnesium-depleted subjects. There is little evidence that magnesium is needed to prevent osteoporosis in the general population. Overall, observational and clinical trial data concerning magnesium and bone density or fractures are inconclusive; in fact, one recent study from the Women's Health Initiative (a 15-year programme of women's health established by the United States National Institutes of Health in 1991) reported that higher intakes of magnesium were associated with a higher risk of wrist fracture (Jackson *et al*. 2003).

## 9.8 HIGH-MINERAL WATER AND BONE MINERAL DENSITY

Whether calcium and magnesium intakes could be improved with drinking-water and whether this could have an impact on bone health are unknown. There is some evidence that high-calcium water is beneficial to bone. Spine mineral density was significantly ($P$ = 0.03) higher in 175 women aged 30–70 years living in Sangemini, a region of central Italy, who drank the local high-calcium water (318 mg/l), compared with 80 women in the same region who drank low-calcium water (<60 mg/l). The estimated difference in calcium intake from an assessment of diet and water was 258 mg/day on average (Costi *et al*. 1999). In an evaluation of calcium ingested from water and hip bone mineral density in French women ($n$ = 4434) aged 75 years or older, an increase in calcium of 100 mg/day from drinking-water was associated with a 0.5% increase in femoral bone density (Aptel *et al*. 1999).

## 9.9 CONCLUSIONS

The bioavailability of calcium from water is likely subject to the same influences as for calcium bioavailability from food. Therefore, divided doses throughout the day promote calcium absorption efficiency, which would suggest that the habit of sipping on water throughout the day is preferential to bolus consumption of food sources of calcium. There is indication that calcium from high-calcium water (and calcium from other sources) is beneficial to bone health by suppressing bone resorption. Little is known about magnesium bioavailability from the diet, including water. Current evidence for a role of magnesium in bone health is quite weak. While high-mineral waters may provide supplemental calcium and magnesium to the diet, they are not able to serve as a main source of these nutrients with the variation in content and solubility.

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# 10

# Epidemiological studies and the association of cardiovascular disease risks with water hardness

*R. Calderon and P. Hunter*

## 10.1 THE HARD WATER–CARDIOVASCULAR DISEASE HYPOTHESIS

Since the mid-1950s, there has been a steady source of epidemiological studies evaluating the relationship of water hardness to cardiovascular disease. The first paper to call attention to the marked geographic variation in death rates from heart disease appeared in 1956. Analysing death rates for the United States from 1949 to 1951, Enterline and Stewart (1956) noted that place of residence might be an important risk factor for cardiovascular disease.

The World Health Organization held an expert meeting in Rome, Italy, in November 2003 to address a number of questions relating to the nutrient

composition of drinking-water and the possibility that drinking-water could in some circumstances contribute to total dietary nutrition (WHO 2005). Calderon and Craun (2005) reviewed the epidemiological studies of water hardness and cardiovascular disease published before 1980, and Monarca *et al.* (2005) reviewed the studies of water hardness and cardiovascular and other diseases published from 1980 to 2002. Because different kinds of epidemiological studies have been conducted during the past 35 years, close attention should be paid to the problem of interpreting their results.

The first part of this chapter describes important aspects of epidemiological studies to help readers better understand what each study design can contribute to our understanding of the possible benefits that may be attributed to hard water. The second part of the chapter reviews those epidemiological studies that have examined the association of cardiovascular disease risks with water hardness.

## 10.2 OVERVIEW OF EPIDEMIOLOGICAL METHODS, STRENGTHS AND WEAKNESSES

### 10.2.1 Types of epidemiological studies

Observational epidemiological studies are either descriptive or analytical (Table 10.1). Descriptive epidemiology is important for summarizing disease information (e.g. cardiovascular disease mortality) to help assess demographic and geographical patterns of disease and develop hypotheses about disease etiologies. Analytical epidemiology is used to test specific hypotheses. Ecological (also called geographical, correlational or aggregate) studies explore possible associations between health statistics, demographic measures and risk factors or exposures (e.g. environmental or water quality measures). The ecological study is relatively inexpensive and easy to conduct, but the associations that are observed must be cautiously interpreted (Greenland and Robins 1994a,b; Piantadosi 1994; Poole 1994). It must be remembered that the health, exposure and demographic statistics characterize population groups rather than the individuals within the groups. The group may not be the appropriate unit of study, and serious errors can result when it is assumed that inferences from an ecological analysis pertain to the individuals within the group. Neither theoretical nor empirical analyses have offered consistent guidelines for the interpretation of results from ecological studies. Although correlation coefficients can be obtained from ecological studies, a reliable quantitative estimate of risk cannot.

Table 10.1. Types of observational epidemiological studies (adapted from Monson 1990)

| Descriptive studies | Analytical studies |
|---|---|
| Disease surveillance/surveys | Cross-sectional |
| Ecological | Longitudinal |
| | • Cohort or follow-up |
| | • Case–control |

Analytical epidemiological studies are able to provide information about possible causal associations and the magnitude of the risk (Monson 1990). In contrast to ecological studies, individuals within a population group or geographic area are studied. For each study participant, information is obtained about his or her disease, his or her exposure to possible risk factors and other important individual behaviours or characteristics. Analytical studies can be either longitudinal or cross-sectional. In a longitudinal study, a time sequence can be inferred between exposure and disease; that is, it can be determined whether the exposure precedes the disease. In a cross-sectional study, the data on exposure and disease relate to the same time period, and this may present a problem when studying diseases with a long latency period. Longitudinal studies are of two distinct, opposite approaches. The cohort study (also called a follow-up study) begins with an exposure or characteristic of interest and seeks to determine disease consequences of the exposure or characteristic. The case–control (also called case–referent or case–comparison) study begins with a disease or health condition of interest and seeks information about exposures and risk factors.

In a case–control study, individuals enter the study solely on the basis of disease status without knowledge of their exposure status. A single disease or health outcome (e.g. cardiovascular mortality, blood lipid levels) is studied. Persons with the disease or outcome are selected within a defined geographical area or from selected hospital(s), clinic(s) or a specified cohort. A comparison group of individuals in which the condition or disease is absent (the controls or referents) is also selected, preferably randomly, from the same population from which the cases arise. Existing or past attributes and exposures thought to be relevant in the development of the disease are determined for all cases and controls. Because previous exposures are studied, a case–control study is sometimes called a retrospective study. The frequency of exposure is compared for individuals with and without the disease to determine possible associations with the disease being studied. This study design is usually more efficient than the cohort study, requires fewer study participants for adequate statistical power and is often considered as the first option when studying risk factors. Information about relevant individual exposures or behaviour (e.g. smoking, use of hard or soft water and, where water is consumed, calcium and magnesium

exposures) is obtained by interview and/or measurement. Often, information must be obtained by questioning a surviving spouse. It may be difficult to accurately assess exposures that may have occurred many years ago and to ensure that the quality and accuracy of information about exposures are similar for cases and controls.

Individuals are selected for the cohort solely on the basis of the presence or absence of certain characteristics, a specific event or their exposure status (e.g. water hardness; high, moderate or low levels of calcium or magnesium in water). A fundamental requirement is that the investigator should not know the disease status of any individual when the cohort is assembled. Morbidity or mortality incidence is then determined for the diseases of interest, and rates are compared for the exposed and unexposed groups in the cohort. An advantage of this study is that more than one health-related outcome or disease can be studied. A cohort can be based on currently defined exposures and followed forward in time or based on historical exposures, if available. For diseases with a long latency period, it may be possible to assemble a historical cohort based on known exposures at some previous point in time. For example, if a cohort could be established based on known drinking-water exposures (e.g. to water hardness) in 1970, over 30 years of exposure would have already occurred, and the follow-up period could be relatively short.

A special kind of cohort study, the community intervention study can be conducted when a community changes water treatment or sources to improve its water quality. Both individual-level and group-level disease and water exposure information can be collected in this type of study. Community intervention studies helped demonstrate the effectiveness of water fluoridation in preventing dental caries. Advantages of this type of study include the following: a time-series analysis can be conducted; water quality is changed at all places where persons may consume water (e.g. home, school, work, restaurants), minimizing exposure misclassification; and a large number of routinely collected community health surveillance data can be evaluated. A major difficulty and limitation of cardiovascular disease studies is that the latency period to effect a detectable change in disease risk may require many years of follow-up, and the population demographics and behaviours may change significantly over time. Since the studies must be conducted in areas considering changes, the areas may not be optimal in terms of water quality or population characteristics.

### 10.2.2 Random and systematic error

The association observed in each study type should be evaluated to assess possible random and systematic error (Table 10.2). The likelihood that a positive association is due to random error can be assessed by calculating the level of

statistical significance ("*p*" value) or the confidence interval. In epidemiology, the confidence interval is the preferred measure of random error because it provides a range of possible values for the risk estimate. It should be remembered, however, that random error or chance can never be completely ruled out as the explanation for an observed result and that statistical significance does not imply causality, biological significance or lack of systematic error.

Table 10.2. Interpreting epidemiological associations

| Lack of random error (precision) | Lack of systematic error (validity) |
|---|---|
| Study size and statistical power | Selection bias |
| | Misclassification bias |
| | Observation bias |
| | Confounding bias |

Systematic error or bias affects the validity of an observed association. Systematic error can occur in the design and conduct of the study, leading to a false or spurious association or a measure of risk that departs systematically from the true value. Systematic error should be avoided or controlled; in some instances, its effect may be assessed.

Error can be introduced by observation, selection, misclassification and confounding biases. Selection bias occurs when criteria used to enrol persons into the study are not comparable for exposed and unexposed individuals or cases and controls. Observation bias occurs when disease or exposure information is collected differently from the groups being studied (e.g. cases and controls). Selective or differential recall of cases or controls about their exposure will also result in a biased estimate of risk.

An erroneous diagnosis of disease or erroneous classification of a study participant's exposure will result in misclassification bias. The probability of misclassification can vary in either a differential or non-differential manner among the groups being studied. Non-differential misclassification will almost always bias a study towards not observing an association when one may actually be present or underestimating the magnitude of the association. Differential misclassification bias can result in associations that either under- or overestimate the magnitude of risk. In environmental epidemiological studies where the magnitude of the association is often small, accurate assessment of exposure is critical, as the impact of misclassification can be severe. The imprecise nature of the water hardness estimate presents a potential for exposure misclassification bias in cardiovascular studies.

Confounding bias may convey the appearance of an association; that is, a confounding characteristic rather than the suspected cause or exposure may be responsible for all or much of the observed association. A confounder is a

characteristic that can cause or prevent the disease and is associated with the exposure being evaluated. Cigarette smoking is a potential confounder that should be assessed in studies of drinking-water and cardiovascular disease risks. Confounding bias does not necessarily result from any error of the investigator. It is potentially present in all epidemiological studies and must always be considered as a possible explanation for any observed association. If a risk factor or characteristic has no association with exposure or disease, that factor or characteristic cannot confound the association between exposure and disease. To avoid confounding, investigators may employ a technique known as matching. For example, controls may be selected to have similar characteristics as cases (e.g. age, smoking status). Not to be confused with a confounding bias, effect modification refers to a change in the magnitude of the effect of a putative cause (Monson 1990). The possible interactive effects of smoking and a drinking-water factor are an example of effect modification that should be assessed for cardiovascular disease risks.

### 10.2.3 Strength of association

The magnitude of the risk ratio or relative risk can help investigators assess the spurious nature of an observed association. Based on epidemiological experience (Monson 1990), it is difficult to interpret weak associations, or a relative risk of less than 1.5 (Table 10.3). One or more confounding characteristics can lead to a weak association between exposure and disease, and it is usually not possible to identify and adequately measure or control weak confounding bias. In contrast, a large relative risk is unlikely to be completely explained by an unidentified or uncontrolled confounding factor. The magnitude of a relative risk, however, has no bearing on the possibility that an association is due to observation, selection or misclassification bias. Any of these biases can lead to a total misrepresentation of an observed association. If a relative risk of less than 1.5 is observed in an environmental epidemiological study, a thorough assessment should be made to identify possible uncontrolled confounding.

Table 10.3. Assessing the strength of an epidemiological association (adapted from Monson 1990)

| Relative risk | Strength of association |
|---|---|
| 1.0 | None |
| >1.0 – <1.5 | Weak |
| 1.5–3.0 | Moderate |
| 3.1–10.0 | Strong |
| >10.0 | Infinite |

### 10.2.4 Causality of an association

The interpretation of epidemiological data should be made with caution and in the context of all relevant scientific information about the disease and its etiology. No single epidemiological study, even one with little systematic error, can provide a definitive answer about the exposure–disease association. Results from several studies of different design and different population groups allow a more definitive conclusion, and it may be necessary to consider studies in both the general and special populations. Judging causality in epidemiology is based on guidelines (Hill 1965; Rothman 1986; Beaglehole *et al*. 1993), which include:

- *Temporal association*: Exposure must precede the disease, and in most epidemiological studies this can be inferred. When exposure and disease are measured simultaneously, it is possible that exposure has been modified by the presence of disease.
- *Strength of association*: The larger the relative risk or odds ratio, the less likely the association is to be spurious or due to confounding bias. However, a causal association should not be ruled out simply because a weak association is observed.
- *Consistency*: Repeated observation of an association under different study conditions supports an inference of causality; however, its absence does not rule it out.
- *Specificity*: A putative cause or exposure leads to a specific effect. The presence of specificity argues for causality, but its absence does not rule it out.
- *Biological plausibility*: When the association is supported by evidence from clinical research or basic sciences (e.g. toxicology, microbiology) about biological behaviour or mechanisms, an inference of causality is strengthened.
- *Dose–response relationship*: A causal interpretation is more plausible when an epidemiological gradient is found (e.g. higher risk is associated with larger exposures).
- *Reversibility*: An observed association leads to some preventive action, and removal or reduction of the exposure leads to a reduction of disease or risk of disease.

Epidemiologists have debated how scientific evidence should be evaluated in an attempt to better understand causal inferences. Even when repetitions of an association are observed, questions may remain as to whether these associations really constitute an “empirical demonstration that serves as a valid platform for (causal) inference” or whether “the process is still steeped in uncertainty”

(Rothman 1986). Thus, when environmental policy-makers and regulators are confronted with epidemiological associations that suggest the need for action, they must be aware of the uncertainties about causality. Scientific evidence is often conflicting, and the type of evidence or studies that are considered in the evaluation must be given due weight based on the issues mentioned previously (i.e. study design, study precision and study validity).

## 10.2.5 Web of causation

Many diseases have multiple exposures or risk factors that cause the disease or increase the disease risk, and the disease process is often a complex one. This complexity is evident in the example conceptual model that might be used to describe the relationship between water exposures and other risk factors for cardiovascular disease (Figure 10.1). This model is often referred to as the web of causation (Rockett 1994). It places less emphasis on the role of the agent or water contaminant in favour of other factors that may be important in the onset of disease. Epidemiologists have found lower cardiovascular disease mortality in areas where water hardness (e.g. levels of calcium and magnesium) is high, and some studies have associated water constituents with decreased blood pressure. The use of a dotted line for water exposures in Figure 10.1 suggests that additional evidence may be warranted.

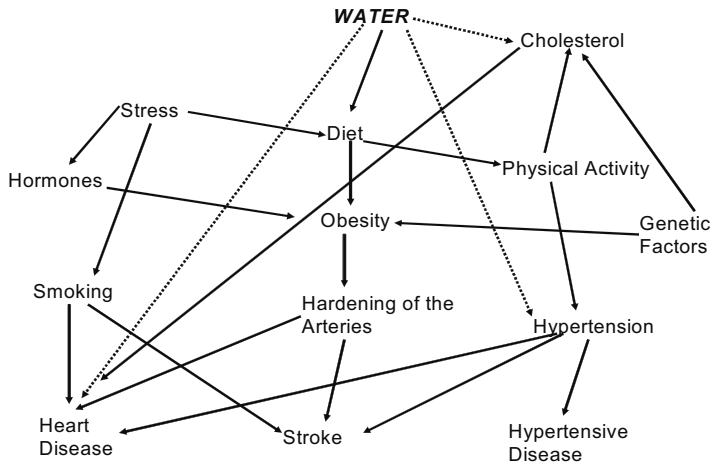


Figure 10.1. Web of causation applied to cardiovascular disease (adapted from Rockett 1994).

### 10.2.6 Conclusions

Results of ecological studies are useful to identify emerging problems, to develop specific hypotheses for study by analytical studies and, in some instances, to evaluate health conditions and control programmes. Results from analytical studies can provide evidence of a causal association between exposure and disease and estimates of the magnitude of risk, but the studies must be carefully designed and conducted. Because small risks have usually been observed in environmental epidemiological studies, it is extremely important to consider the effects of misclassification bias and confounding on the interpretation of the associations reported for water hardness and cardiovascular disease.

When considering epidemiological evidence for the hard water–cardiovascular disease hypothesis, it is important to critically evaluate each study to determine the quality and amount of information it can contribute to the evaluation of an association's causality and magnitude of risk. At present, sufficient information should be available to assess the causality of the observed association and estimate the benefits that may be attributed to hard water or a specific constituent found in hard water.

## 10.3 THE ASSOCIATION OF CARDIOVASCULAR DISEASE RISKS WITH WATER HARDNESS

We have summarized information published in recent reviews of the epidemiological studies of cardiovascular disease and drinking-water hardness and calcium and magnesium levels (Catling *et al*. 2005; Monarca *et al*. 2006). The results of these studies are briefly described below.

### 10.3.1 Epidemiological studies published from 1957 to 1978

More than 50 ecological (geographical correlation) studies were published from 1957 to 1978. Studies were conducted in the United States, the United Kingdom, Ireland, Canada, Sweden, the Netherlands, Finland, Italy, Romania, Czech Republic, Germany, Japan, Australia and Hungary. Populations in 21 cities around the world were also studied. Comstock (1979a,b) reviewed these studies based on size of geographical areas (national or international; province or state; county, borough or city).

### 10.3.2 Epidemiological studies published after 1978: ecological studies

Twenty ecological studies (Masironi *et al.* 1979; Scassellati Sforzolini *et al.* 1979; Pocock *et al.* 1980; Zielhuis and Haring 1981; Leary *et al.* 1983; Lacey and Shaper 1984; Leoni *et al.* 1985; Smith and Crombie 1987; Grillo *et al.* 1989; Flaten and Bolviken 1991; Gyllerup *et al.* 1991; Rylander *et al.* 1991; Nerbrand *et al.* 1992, 2003; Yang *et al.* 1996; Maheswaran *et al.* 1999; Sauvant and Pepin 2000; Marque *et al.* 2003; Miyake and Iki 2003; Kousa *et al.* 2004) were reviewed (Table 10.4). Some studies took into account potential confounders such as socioeconomic status, income or climate (Pocock *et al.* 1980; Gyllerup *et al.* 1991; Yang *et al.* 1996; Maheswaran *et al.* 1999; Nerbrand *et al.* 1992, 2003; Miyake and Iki 2003).

Ten studies reported a statistically significant inverse (i.e. protective) association between drinking-water hardness and cardiovascular disease mortality (Masironi *et al.* 1979; Pocock *et al.* 1980; Leary *et al.* 1983; Lacey and Shaper 1984; Leoni *et al.* 1985; Rylander *et al.* 1991; Yang *et al.* 1996; Sauvant and Pepin 2000; Marque *et al.* 2003; Kousa *et al.* 2004). When calcium and magnesium were evaluated separately, similar associations with cardiovascular disease mortality were frequently found for each. Four of these studies estimated the effect of drinking-water hardness. A 7.5% reduction of cardiovascular disease mortality in men for 100 mg/l increased water hardness was reported in England and Wales (Lacey and Shaper 1984). In Finland (Kousa *et al.* 2004), the risk of acute myocardial infarction decreased 0.56% for each 10 mg/l increase in water hardness. A 10% increase in the risk of ischaemic heart disease mortality was reported in municipalities in Taiwan, China (Yang *et al.* 1996), with <75 mg/l water hardness compared with those with >150 mg/l hardness. In France (Marque *et al.* 2003), a 10% reduction of the relative risk for cardiovascular disease and ischaemic heart disease mortality and a 14% reduction of the relative risk for stroke mortality were found for the highest compared with the lowest concentrations.

Six of the remaining 10 studies found either a very small inverse association or no association (Scassellati Sforzolini *et al.* 1979; Zielhuis and Haring 1981; Smith and Crombie 1987; Gyllerup *et al.* 1991; Maheswaran *et al.* 1999; Kousa *et al.* 2004). In Norway (Flaten and Bolviken 1991), ischaemic heart disease and stroke mortality rates increased with increased drinking-water magnesium, but these findings are questionable, since virtually all municipalities in the study had soft water.

Table 10.4. Ecological (geographic correlation) studies on the relationship between cardiovascular diseases or stroke and hardness and/or calcium/magnesium concentration of drinking-water

| Reference | Country, area and population age | Period | Drinking-water parameters | CVD or stroke mortality | Results |
|---|---|---|---|---|---|
| Masironi *et al.* (1979) | Europe, 17 towns, 45–64 years | 1974 | Total hardness[a] 32–354 mg/l | AMI incidence | M & F: $r = -0.46$ |
| Scassellati Sforzolini *et al.* (1979) | Italy, Umbria Region, 12 municipalities | 1967–1976 | Total hardness | Mortality for: | |
| | | | | IHD | M & F: $r = +0.28$ |
| | | | | Stroke | M & F: $r = -0.07$ |
| | | | Calcium concentration | Mortality for: | |
| | | | | IHD | M & F: $r = +0.37$ |
| | | | | Stroke | M & F: $r = -0.05$ |
| | | | Magnesium concentration | Mortality for: | |
| | | | | IHD | M & F: $r = -0.26$ |
| | | | | Stroke | M & F: $r = -0.28$ |
| Pocock *et al.* (1980) | Great Britain, 253 municipalities, 35–74 years | 1969–1973 | Total hardness[a] 10–528 mg/l | Mortality for CVD | M & F: $r = -0.67$ |

Table 10.4 *(continued)*

| Reference | Country, area and population age | Period | Drinking-water parameters | CVD or stroke mortality | Results |
|---|---|---|---|---|---|
| Zielhuis and Haring (1981) | The Netherlands, 30 communities, ≥30 years | 1977 | Calcium concentration | Mortality for: | |
| | | | 16–117 mg/l | IHD | M: $r = -0.01$ F: $r = -0.11$ |
| | | | | Stroke | M: $r = -0.14$ F: $r = -0.12$ |
| | | | Magnesium concentration | Mortality for: | |
| | | | | IHD | M: $r = -0.19$ F: $r = -0.10$ |
| | | | 1–15 mg/l | Stroke | M: $r = -0.02$ F: $r = -0.07$ |
| Leary *et al.* (1983) | South Africa, 12 districts, all ages | 1978–1982 | Magnesium concentration | Mortality for IHD | White M: $r = -0.68$* |
| | | | 1–45 mg/l | | |
| Lacey and Shaper (1984) | England and Wales, 14 areas, 45–74 years | 1968–1972 | Total hardness[a] | Mortality for CVD | M: 7.5% reduction of mortality for 100 mg/l increase of hardness* |
| | | | 19–409 mg/l | | |
| Leoni *et al.* (1985) | Italy, Abruzzo Region, 11 water supplies in four provinces, 45–64 years | 1969–1978 | Total hardness[a] | Mortality for: | |
| | | | 105.6–443.5 mg/l | CVD | M & F: $r = -0.55$* |
| | | | | IHD | M & F: $r = -0.59$* |
| | | | | Stroke | M & F: $r = -0.24$ |

Table 10.4 *(continued)*

| Reference | Country, area and population age | Period | Drinking-water parameters | CVD or stroke mortality | Results | |
|---|---|---|---|---|---|---|
| Smith and Crombie (1987) | Scotland, 56 districts, 35–64 years | 1979–1983 | Total hardness[a]<br>0–180 mg/l | Mortality for IHD | M: $r = -0.17$ | |
| Grillo *et al.* (1989) | Italy, Sicily Region, 12 municipalities | 1980–1982 | Total hardness<br>NR | Mortality for:<br>CVD<br>IHD<br>Stroke | <br>M & F: $r = -0.55$<br>M & F: $r = +0.50$<br>M & F: $r = -0.60$ | |
| Flaten and Bolviken (1991) | Norway, 97 municipalities, all ages | 1974–1983 | Calcium concentration<br>0.44–21.7 mg/l | Mortality for:<br>IHD<br>Stroke | <br>NR<br>NR | <br>NR<br>NR |
| | | | Magnesium concentration<br>0.08–2.64 mg/l | Mortality for:<br>IHD<br>Stroke | <br>M: $r = +0.33$***<br>M: $r = +0.22$** | <br>F: $r = +0.23$*<br>F: $r = +0.35$** |
| Gyllerup *et al.* (1991) | Sweden, 259 municipalities (males only), 40–64 years | 1975–1984 | Total hardness[a]<br>54.3–92.5 mg/l | Mortality for AMI | Inverse association, with lower relevance after adjusting for cold climate | |
| | | | Magnesium concentration<br>NR | Mortality for AMI | Inverse association, with lower relevance after adjusting for cold climate | |

Table 10.4 *(continued)*

| Reference | Country, area and population age | Period | Drinking-water parameters | CVD or stroke mortality | Results | |
|---|---|---|---|---|---|---|
| Rylander *et al.* (1991) | Sweden, 27 municipalities, 45–64 years | 1969–1978 | Total hardness[a] | Mortality for: | | |
| | | | 14.32–370.53 mg/l | IHD | M: $r = -0.60$*** | F: $r = -0.45$** |
| | | | | Stroke | M: $r = -0.48$* | F: $r = -0.37$* |
| | | | Calcium concentration | Mortality for: | | |
| | | | 3.4–131 mg/l | IHD | M: $r = -0.47$** | F: $r = -0.41$* |
| | | | | Stroke | M: r = −0.52* | F: $r = -0.32$ |
| | | | Magnesium concentration | Mortality for: | | |
| | | | | IHD | M: $r = -0.62$** | F: $r = -0.45$** |
| | | | 0.57–15.0 mg/l | Stroke | M: $r = -0.16$ | F: $r = -0.49$ |
| Nerbrand *et al.* (1992) | Sweden, 76 municipalities, 45–74 years | 1969–1983 | Total hardness[b] | Mortality for: | | |
| | | | 1–216 mg/l | IHD | M*** | F* |
| | | | | Stroke | M*** | F*** |
| | | | Calcium concentration | Mortality for: | | |
| | | | NR | IHD | M** | F*** |
| | | | | Stroke | M | F*** |

Table 10.4 *(continued)*

| Reference | Country, area and population age | Period | Drinking-water parameters | CVD or stroke mortality | Results | |
|---|---|---|---|---|---|---|
| | | | Magnesium concentration | Mortality for: | | |
| | | | | IHD | M | F |
| | | | NR | Stroke | M | F |
| Nerbrand *et al.* (1992) *(contd)* | | | Total hardness[b] | Prevalence of: | | |
| | | | 36.3–315.0 mg/l | IHD | M: not significant association after adjusting for major risk factors | |
| | | | Calcium concentration | Prevalence of: | | |
| | | | NR | IHD | M: not significant association after adjusting for major risk factors | |
| Yang *et al.* (1996) | Taiwan, 227 municipalities, all ages | 1981–1990 | Total hardness[a] | Mortality for: IHD | RR (95% CI) adjusted for age and urbanization: | |
| | | | <75 mg/l | | 1.096 (1.084–1.108)* | |
| | | | 75–150 mg/l | | 1.045 (1.032–1.058)* | |
| | | | >150 mg/l | | Reference | |

Table 10.4 *(continued)*

| Reference | Country, area and population age | Period | Drinking-water parameters | CVD or stroke mortality | Results |
|---|---|---|---|---|---|
| Maheswaran *et al.* (1999) | England, 305 areas, >45 years | 1990–1992 | Calcium concentration 5–215 mg/l<br>Magnesium concentration 2–111 mg/l | Mortality for AMI | RR (95% CI) for 4-fold increase in calcium and magnesium concentration in drinking-water, adjusted for age and SES:<br>Ca: 0.99 (0.94–1.05)<br>Mg: 1.01 (0.96–1.06) |
| Sauvant and Pepin (2000) | France, Puy de Dôme Department, 52 districts, all ages | 1988–1992 | Total hardness<br>NR | Mortality for:<br>IHD<br>Stroke<br>CVD | <br>M: $r = -0.33$* F: $r = -0.18$<br>M: $r = -0.32$* F: $r = -0.34$**<br>M: $r = -0.34$** F: $r = -0.37$** |
| Marque *et al.* (2003) | France south-west, 69 areas, >65 years | 1990–1996 | Calcium concentration 94–146 mg/l | Mortality for:<br>CVD<br>IHD<br>Stroke | M & F: RR (95% CI) for highest vs lowest tertile adjusted for age:<br>0.90 (0.84–0.96)**<br>0.90 (0.84–0.97)**<br>0.86 (0.77–0.96)* |
| | | | Magnesium concentration | Mortality for: | M & F: RR (95% CI) for highest vs lowest tertile adjusted for age: |

Table 10.4 *(continued)*

| Reference | Country, area and population age | Period | Drinking-water parameters | CVD or stroke mortality | Results |
|---|---|---|---|---|---|
| Marque *et al.* (2003) *(contd)* | | | 11–34 mg/l | CVD | 0.93 (0.86–1.01) |
| | | | | IHD | 0.96 (0.87–1.05) |
| | | | | Stroke | 0.92 (0.80–1.06) |
| Miyake and Iki (2003) | Japan, 44 municipalities, all ages | 1995 | Total hardness[a] | Mortality for stroke | RR (95% CI) adjusted for age, sex, SES, health care status: |
| | | | <46.5 mg/l | | Reference |
| | | | 46.5–51.9 mg/l | | 0.97 (0.91–1.03) |
| | | | >51.9 mg/l | | 0.93 (0.84–1.02) |
| Nerbrand *et al.* (2003) | Sweden, 2 municipalities in the west and east, 40–59 years | 1989–1998 | West | Mortality for:[c] | Mortality rates: |
| | | | Ca: 8.8 mg/l | IHD | M: 21/1000 F: 5/1000 |
| | | | Mg: 0.74 mg/l | CVD | M: 31/1000 F: 11/1000 |
| | | | East | Mortality for: [c] | |
| | | | Ca: 66 mg/l | IHD | M: 10/1000 F: 2/1000 M: 20/1000 F: 6/1000 |
| | | | Mg: 4.1 mg/l | CVD | |
| | | | | | RR (West/East) adjusted for age: |
| | | | | | IHD = M: 2.03**** F: 2.56**** |
| | | | | | CVD = M: 1.56**** F: 1.71**** |

Table 10.4 *(continued)*

| Reference | Country, area and population age | Period | Drinking-water parameters | CVD or stroke mortality | Results |
|---|---|---|---|---|---|
| Kousa *et al.* (2004) | Finland, whole country (males only), 35–74 years | 1983, 1988 and 1993 | Total hardness[a] (mg/l): | Incidence of AMI per year | Age standardized incidence per 100 000 |
| | | | <30.6 | | 562.1* |
| | | | 30.6–93.08 | | 469.5* |
| | | | >93.08 | | 437.6* |
| | | | | | Overall effect: 1% reduction of mortality for an increase of 20 mg/l of total hardness |

AMI, acute myocardial infarction; Ca, calcium; CI, confidence interval; CVD, cardiovascular diseases; F, females; IHD, ischaemic heart diseases; M, males; Mg, magnesium; NR, not reported; r, correlation coefficient; RR, relative risk; SES, socioeconomic status

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.000\,01$; otherwise, $P > 0.05$; $P < 0.10$ for Masironi *et al.* (1979)

[a] Total hardness in mg/l of calcium carbonate ($CaCO_3$).

[b] Total hardness expressed as mg/l of calcium carbonate ($CaCO_3$) estimated by authors.

[c] Study of 207 inhabitants found positive association for calcium and systolic blood pressure; inverse association for calcium in drinking-water and low-density lipoprotein and total cholesterol; no association for magnesium and major cardiovascular disease risk factors.

### 10.3.3 Epidemiological studies published after 1978: case–control studies

Associations between cardiovascular disease mortality and calcium or magnesium in drinking-water were investigated in Finland, Taiwan, China, and Sweden (Table 10.5) (Luoma *et al*. 1983; Rubenowitz *et al*. 1996, 1999, 2000; Yang 1998; Yang and Chiu 1999; Rosenlund *et al*. 2005). Five of the seven studies (Luoma *et al*. 1983; Rubenowitz *et al*. 1996, 2000; Yang 1998; Yang and Chiu 1999) found a statistically significant inverse association between magnesium levels in drinking-water and mortality risks for acute myocardial infarction, stroke or hypertension; one study found a significant inverse association between acute myocardial infarction and both calcium and magnesium levels (Rubenowitz *et al*. 1999). Investigators considered major cardiovascular disease risk factors in two studies (Rubenowitz *et al*. 2000; Rosenlund *et al*. 2005); these were the only studies that found no significant association with either mineral.

### 10.3.4 Epidemiological studies published after 1978: cohort studies

Neither of the two cohort studies (Punsar and Karvonen 1979; Comstock *et al*. 1980) considered major cardiovascular disease risk factors (Table 10.6). Punsar and Karvonen (1979) conducted a 15-year follow-up of 1711 men resident in two rural areas of Finland; all used private well water. Mortality due to coronary heart disease was almost twice (14.7% vs 8.7%) as high in the area with lower drinking-water magnesium. Among 1126 men who submitted a household water sample for analysis, those who died of coronary heart disease had significantly lower mean levels of drinking-water magnesium compared with those alive at the end of the study.

In Washington County, Maryland, USA, Comstock *et al*. (1980) found no consistent association between water hardness and cardiovascular disease mortality. Water samples from 1569 households were analysed for total hardness. An analysis that accounted for socioeconomic characteristics and cigarette smokers showed no significant trend of cardiovascular disease mortality with water hardness. A reduced risk of mortality for arteriosclerotic heart disease was found in men but not women.

Table 10.5. Case–control studies on the relationship between cardiovascular diseases and hardness and/or calcium/magnesium concentrations of drinking-water

| Reference | Country, area, year | Population | Age (years) | Drinking-water parameters (years of analysis) | Odds ratio (95% CI) | |
|---|---|---|---|---|---|---|
| Luoma *et al.* (1983) | Finland; south-eastern region; 1974–1975 | 58 males with AMI, alive or dead (cases)<br>58 males (hospital controls)<br>50 males (population controls) | 37–64 | Ca concentration (1974–1975) | OR unadjusted: Hospital controls | OR unadjusted: Population controls |
| | | | | <16 mg/l | 0.73 (0.22–1.99) | 0.56 (0.25–1.28) |
| | | | | 16–18 mg/l | 0.77 (0.30–1.91) | 1.07 (0.48–2.42) |
| | | | | 19–20 mg/l | 0.91 (0.35–2.36) | 1.64 (0.73–3.85) |
| | | | | >20 mg/l | Reference | Reference |
| | | | | Mg concentration (1974–1975) | OR unadjusted: Hospital controls | OR unadjusted: Population controls |
| | | | | <1.2 mg/l | 2.00 (0.69–6.52) | 4.67 (1.30–25.32)* |
| | | | | 1.2–1.5 mg/l | 1.11 (0.41–3.10) | 2.29 (0.88–6.58) |
| | | | | 1.6–3.0 mg/l | 1.00 (0.36–3.08) | 1.63 (0.62–4.52) |
| | | | | >3.0 mg/l | Reference | Reference |

Table 10.5 *(continued)*

| Reference | Country, area, year | Population | Age (years) | Drinking-water parameters (years of analysis) | Odds ratio (95% CI) |
|---|---|---|---|---|---|
| Rubenowitz *et al.* (1996) | Southern Sweden, 17 municipalities; 1982–1989 | 854 males dead for AMI (cases)<br>989 males dead for cancer (controls) | 50–69 | Ca concentration (1982–1989) | OR age-adjusted: |
| | | | | <34 mg/l | Reference |
| | | | | 34–45 mg/l | 0.88 (0.65–1.19) |
| | | | | 46–81 mg/l | 0.84 (0.64–1.10) |
| | | | | ≥82 mg/l | 1.06 (0.82–1.38) |
| | | | | Mg concentration (1982–1989) | OR age-adjusted: |
| | | | | <3.6 mg/l | Reference |
| | | | | 3.6–6.8 mg/l | 0.88 (0.66–1.16) |
| | | | | 6.9–9.7 mg/l | 0.70 (0.53–0.93)* |
| | | | | ≥9.8 mg/l | 0.65 (0.50–0.84)* |

Table 10.5 *(continued)*

| Reference | Country, area, year | Population | Age (years) | Drinking-water parameters (years of analysis) | Odds ratio (95% CI) |
|---|---|---|---|---|---|
| Yang (1998) | Taiwan, China, 252 municipalities with single water source; 1989–1993 | 17 133 males and females dead from stroke (cases)<br>17 133 males and females dead from other causes, excluding CVD (controls) | 50–69 | Ca concentration (1990) | OR adjusted for age and sex: |
| | | | | <24.4 mg/l | Reference |
| | | | | 24.4–42.3 mg/l | 1.5 (0.99–1.11) |
| | | | | 42.4–81.0 mg/l | 0.95 (0.88–1.01) |
| | | | | Mg concentration (1990) | OR adjusted for age and sex: |
| | | | | <7.3 mg/l | Reference |
| | | | | 7.4–13.4 mg/l | 0.75 (0.65–0.85)* |
| | | | | 13.5–41.3 mg/l | 0.60 (0.52–0.70)* |
| Rubenowitz *et al.* (1999) | Southern Sweden, 16 municipalities; 1982–1983 | 378 females dead from AMI (cases)<br>1368 females dead from cancer (controls) | 50–69 | Ca concentration (1982–1983) | OR adjusted for age and Mg: |
| | | | | ≤31 mg/l | Reference |
| | | | | 32–45 mg/l | 0.61 (0.39–0.94)* |
| | | | | 46–69 mg/l | 0.71 (0.49–1.02) |
| | | | | ≥70 mg/l | 0.66 (0.47–0.94)* |

Table 10.5 *(continued)*

| Reference | Country, area, year | Population | Age (years) | Drinking-water parameters (years of analysis) | Odds ratio (95% CI) |
|---|---|---|---|---|---|
| Rubenowitz *et al.* (1999) *(contd)* | | | | Mg concentration (1982–1983) | OR adjusted for age and Ca: |
| | | | | ≤3.4 mg/l | Reference |
| | | | | 3.5–6.7 mg/l | 1.08 (0.78–1.49) |
| | | | | 6.8–9.8 mg/l | 0.93 (0.64–1.34) |
| | | | | ≥9.9 mg/l | 0.70 (0.50–0.99)* |
| Yang and Chiu (1999) | Taiwan, China, 252 municipalities with single water source; 1990–1994 | 2336 males and females dead from hypertension (cases) 2336 males and females dead from other causes, excluding CVD | 50–69 | Ca concentration (1990) | OR adjusted for age, sex, urbanization and Mg: |
| | | | | 4.0–11.3 mg/l | Reference |
| | | | | 11.4–30.0 mg/l | 1.23 (0.94–1.62) |
| | | | | 30.1–37.7 mg/l | 1.32 (0.98–1.78) |
| | | | | 37.8–53.4 mg/l | 1.12 (0.83–1.51) |
| | | | | 53.5–81.0 mg/l | 1.26 (0.92–2.02) |

Table 10.5 *(continued)*

| Reference | Country, area, year | Population | Age (years) | Drinking-water parameters (years of analysis) | Odds ratio (95% CI) |
|---|---|---|---|---|---|
| Yang and Chiu (1999) *(contd)* | | (controls) | | Mg concentration (1990) | OR adjusted for age, sex, urbanization and Ca: |
| | | | | 1.5–3.8 mg/l | Reference |
| | | | | 3.9–8.2 mg/l | 0.73 (0.57–0.93)*** |
| | | | | 8.3–11.1 mg/l | 0.66 (0.50–0.87)*** |
| | | | | 11.2–16.3 mg/l | 0.67 (0.50–0.89)*** |
| | | | | 16.4–41.3 mg/l | 0.63 (0.47–0.84)*** |
| Rubenowitz *et al.* (2000) | Southern Sweden, 18 municipalities; 1994–1996 | 263 males and females dead from AMI (cases) | 50–74 | Ca concentration (1996) | OR adjusted for age and Mg (highest vs lowest quartiles) |
| | | | | 0–235 mg/l | M & F: 0.89 (0.59–1.33) |
| | | 258 males and females dead from other causes (controls) | | Mg concentration (1996) | OR adjusted for age and Ca (highest vs lowest quartiles) |
| | | | | 0–44 mg/l | M & F: 0.64 (0.42–0.97)* |

Table 10.5 *(continued)*

| Reference | Country, area, year | Population | Age (years) | Drinking-water parameters (years of analysis) | Odds ratio (95% CI) |
|---|---|---|---|---|---|
| Rubenowitz *et al.* (2000) *(contd)* | | 823 males and females surviving after an AMI (cases) | 50–74 | Ca concentration (1996) | OR adjusted for age and Mg (highest vs lowest quartiles) |
| | | | | 0–235 mg/l | M & F: 0.97 (0.78–1.21) |
| | | 853 males and females without AMI (controls) | | Mg concentration (1996) | OR adjusted for age and Ca (highest vs lowest quartiles) |
| | | | | 0–44 mg/l | M & F: 1.16 (0.93–1.45) |
| Rosenlund *et al.* (2005) | Sweden; 1992–1994 | 497 males and females with AMI (cases) | 45–70 | Ca intake from tap water: | OR adjusted for age, gender, smoking, hypertension, DM, SES, physical activity, BMI, job stress (95% CI): |
| | | 677 males and females without AMI (controls) | | <42.4 mg/day | 1.00 |
| | | | | >42.3 mg/day | 1.07 (0.62–1.85) |
| | | | | Mg intake from tap water: | |
| | | | | <6.9 mg/day | 1.00 |
| | | | | >6.9 mg/day | 1.07 (0.63–1.82) |

Table 10.5 *(continued)*

AMI, acute myocardial infarction; BMI, body mass index; Ca, calcium; CI, confidence interval; CVD, cardiovascular diseases; DM, diabetes mellitus; F, females; M, males; Mg, magnesium; OR, odds ratio; SES, socioeconomic status
* $P < 0.05$; *** $P < 0.001$; all others not statistically significant

Table 10.6. Cohort studies of the relationship between cardiovascular diseases and drinking-water hardness and calcium and magnesium levels

| Authors, year of publication | Country and area | Population | Age (years) at recruitment | Period | Cause of death | Drinking-water parameters (years of analysis) | Outcome measure |
|---|---|---|---|---|---|---|---|
| Punsar and Karvonen (1979) | Finland, two rural regions (West Finland and East Finland) | 504 in the west, 622 in the east area with drinking-water Mg data (M) | 49–59 | 1959–1974 (15 years of follow-up) | CHD, others | Mg concentration[a] (1970) | West Finland: |
| | | | | | | 12.7 mg/l | Died of CHD ($n$ = 49/504; 9.7%) |
| | | | | | | 14.2 mg/l | Died of other causes ($n$ = 89/504; 17.7%) |
| | | | | | | 13.6 mg/l | Survivors ($n$ = 366/504 = 72.6%) |
| | | | | | | | East Finland: |
| | | | | | | 3.3 mg/l | Died of CHD ($n$ = 95/622; 15.3%) |
| | | | | | | 3.2 mg/l | Died of other causes ($n$ = 100/622; 16.1%) |

Table 10.6 *(continued)*

| Authors, year of publication | Country and area | Population | Age (years) at recruitment | Period | Cause of death | Drinking-water parameters (years of analysis) | Outcome measure | |
|---|---|---|---|---|---|---|---|---|
| Punsar and Karvonen (1979) *(contd)* | | | | | | 3.6 mg/l | Survivors ($n$ = 427/622 = 68.6%)<br>RR for east vs west:<br>CHD death = 15.3%/9.7%; 1.6* | |
| Comstock *et al.* (1980) | Washington County, Maryland, USA | 30, 534 (M & F) | >25 | 1963–1975 (12 years of follow-up) | AHD | Water hardness: 0 vs 200 mg/l of $CaCO_3$ (1971) | | RR: |
| | | | | | | | M: 7+ years[b] | 0.69 |
| | | | | | | | M: <7 years[b] | 0.86 |
| | | | | | | | F: 7+ years[b] | 1.06 |
| | | | | | | | F: <7 years[b] | 1.73 |

AHD = arteriosclerotic heart disease; Ca, calcium; CHD, coronary heart disease; F = females; M = males; Mg, magnesium; RR = relative risk
* $P < 0.01$ (computed by the authors); otherwise, $P > 0.05$
[a] Mean concentrations of magnesium in the drinking-water of men who died in the study period or were still alive in 1974.
[b] Duration of residence prior to the 1963 census (beginning of the study).

### 10.3.5 A meta-analysis of epidemiological studies

In a systematic review of epidemiological studies, Catling *et al*. (2005) undertook a meta-analysis of case–control studies. They identified only one case–control study linking water hardness and deaths from arteriosclerotic cardiovascular disease, which found no significant association. In contrast, there were six case–control studies linking water magnesium and/or calcium with such deaths. Only one study reported a protective effect of drinking-water calcium on female mortality from acute myocardial infarction (Rubenowitz *et al.* 1996). In contrast, four studies showed a significant protective effect of drinking-water magnesium against mortality from acute myocardial infarction (Rubenowitz *et al.* 1996, 2000), hypertensive disease (Yang and Chiu 1999) and stroke (Yang 1998) for males and females. More recently, another study found no protective effect from water hardness, magnesium or calcium (Rosenlund *et al*. 2005). However, this last study seems to have been conducted in an area with generally low magnesium in the water, and it is doubtful that there would have been sufficient people living in high-magnesium drinking-water areas to see an effect, even if one existed.

The authors of this systematic review distinguished those case–control study papers where the outcome was morbidity from those where the outcome was mortality. It can be seen from Figure 10.2 that the single study of drinking-water calcium and morbidity does not indicate an association; indeed, this was not significant in the original study. The four studies that tested the relationship between drinking-water calcium and mortality from cardiovascular disease also do not support an association (Figure 10.3). From Figure 10.4, there were two case–control studies of drinking-water magnesium and cardiovascular morbidity. Taken together, these studies do not support an effect, and both were non-significant. From Figure 10.5, five case–control studies investigated water magnesium and cardiovascular mortality. Not all of these studies were statistically significant in themselves, and for some there are issues around inadequate control for confounding, but all five showed the same inverse trend, especially at magnesium levels of greater than about 5 mg/l.

The authors of this review concluded that the identified case–control studies do not support an association between water hardness or calcium and cardiovascular disease morbidity or mortality. In contrast, they concluded that water magnesium appears to be inversely associated with cardiovascular mortality but not morbidity (Catling *et al*. 2005).

In the light of this observation, the lack of a significant result for the three cohort studies would not be surprising, given that all three investigated the association with water hardness only.

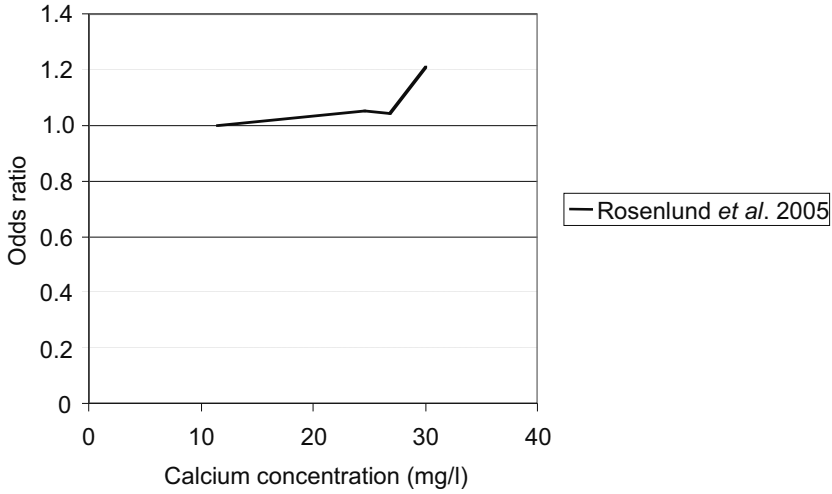


Figure 10.2. Odds ratios of risk of cardiovascular disease in relation to drinking-water calcium (data from Rosenlund *et al*. 2005).

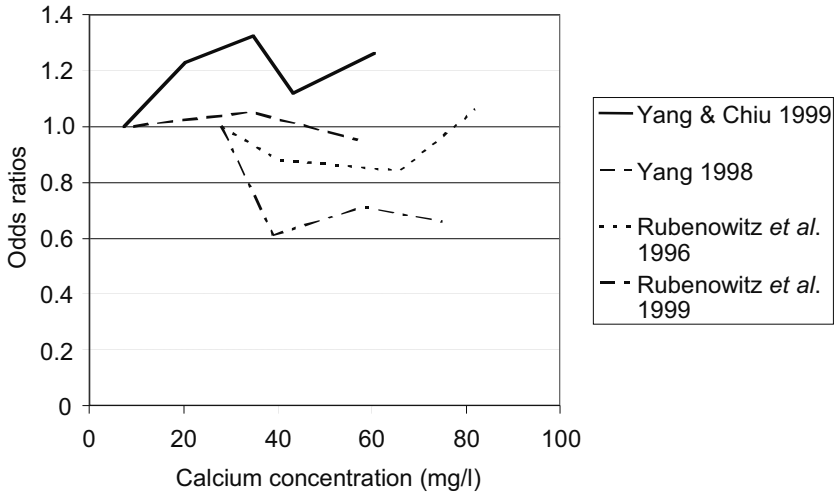


Figure 10.3. Odds ratios of risk of cardiovascular mortality in relation to drinking-water calcium (data from Rubenowitz *et al.* 1996, 1999; Yang 1998; Yang and Chiu 1999).

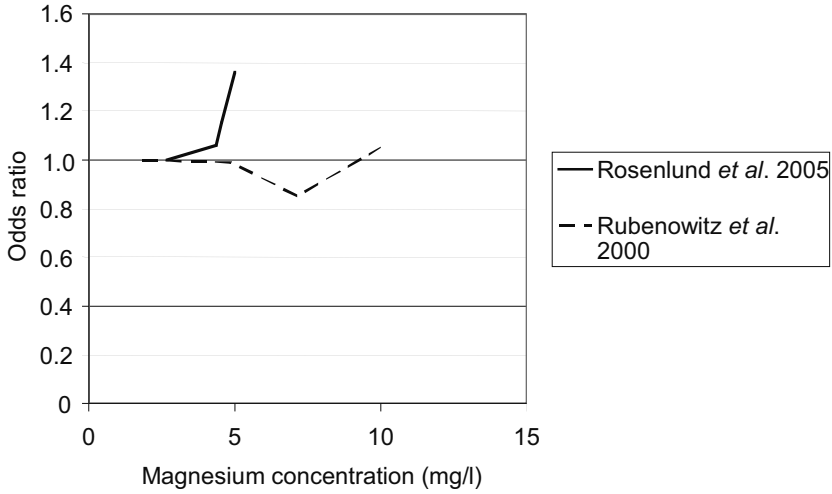


Figure 10.4. Odds ratios of risk of cardiovascular disease in relation to drinking-water magnesium (data from Rubenowitz *et al*. 2000; Rosenlund *et al*. 2005).

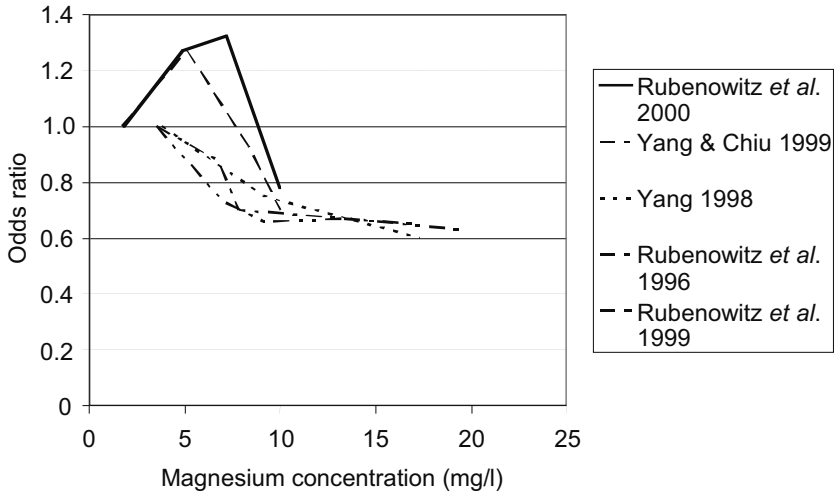


Figure 10.5. Odds ratios of risk of cardiovascular mortality in relation to drinking-water magnesium (data from Rubenowitz *et al*. 1996, 1999, 2000; Yang 1998; Yang and Chiu 1999).

### 10.3.6 Conclusions

Many ecological studies report an inverse (i.e. protective) association between cardiovascular disease mortality and water hardness, calcium or magnesium levels; however, results are not consistent. Various analytical studies report a reduction in cardiovascular disease mortality risk with increasing magnesium levels in drinking-water, but there is little evidence for an association with water hardness or calcium levels.

In conclusion, the epidemiological evidence for the water hardness–cardiovascular disease hypothesis is still not proven. However, at present, the balance of epidemiological evidence supports the link between magnesium and cardiovascular mortality. Such an association is consistent with evidence of the cardiovascular effects of magnesium deprivation and of inadequate magnesium in the diets of people from developing countries, as discussed elsewhere in this book.

Information from toxicological, dietary and epidemiological studies supports the hypothesis that a low intake of magnesium may increase the risk of dying from, and possibly developing, cardiovascular disease or stroke. Thus, not removing magnesium from drinking-water, or in certain situations increasing the magnesium intake from water, may be beneficial, especially for populations with an insufficient dietary intake of the mineral.

This raises a significant policy issue. How strong does the epidemiological and other evidence need to be before society acts to reduce a potential public health threat rather than await further evidence that such a threat is real? Such a decision is a political rather than a purely public health issue. There is a growing consensus among epidemiologists that the epidemiological evidence, along with clinical and nutritional evidence, is already strong enough to suggest that new guidance should be issued.

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# 11

# Alternative hypotheses and knowledge gaps

*J.K. Fawell*

## 11.1 INTRODUCTION

A number of issues surround the evidence concerning the potential impact of "hard water" on public health. These involve alternative interpretations of the data and consideration of whether the consumption of drinking-water containing high or low total dissolved solids (TDS) is a related or separate question (Vajpeyee 2006). There are also other important practical issues relating to the supply of desalinated water, which is an increasingly important source of drinking-water. In the future, the same issues will arise with consideration of expanded indirect or possibly even direct reuse of wastewater that has been treated by reverse osmosis. Finally, there are also practical problems related to the use of water softeners, which can play an important role in reducing lime scale and energy costs.

## 11.2 ALTERNATIVE INTERPRETATIONS AND MECHANISMS RELATING TO THE HEALTH EFFECTS OF HIGH-MINERAL DRINKING-WATER

While there are numerous ecological and a few analytical epidemiological studies of the negative (beneficial) association between calcium and/or magnesium in drinking-water and acute myocardial infarction or acute cerebrovascular events, they all have limitations, whether they find an association or not (Calderon and Craun 2005; Catling *et al*. 2005; Monarca *et al*. 2005; Calderon *et al*. 2006; Hunter 2006). One of the difficulties is that there are usually only limited data on other water components and related factors that could be confounders. There are plausible biochemical mechanisms for calcium and magnesium playing important roles in these and other diseases, and the probability exists that drinking-water can be an important stable supplementary source of these minerals in the event of a population being marginal in calcium and magnesium intake. However, the hypotheses relate to the population level, and relating the findings specifically to higher-risk individuals still remains an important knowledge gap, along with the contribution of calcium and magnesium from drinking-water to total daily dietary intake.

In addition, there are other minerals present in high-TDS water, which is often hard water. While calcium and/or magnesium generally dominate hard waters, the levels and ratios can vary significantly. Many other ions will also be present depending on the source water and the treatment that it has received. These include a wide range of essential/beneficial elements as well as some that may have adverse effects at sufficient levels and others that we know relatively little about. Some examples are vanadium, barium and strontium.

Studies also need to consider alternative sources of water, their mineral content and how these might impact on the total intake of tap water. The rise in the consumption of bottled water in many countries is cited as a possible confounder, but some countries have a long tradition of drinking bottled water. Dietary patterns can also be important; for example, although the consumption of bottled water is high in Italy, so is the consumption of foods that take up a significant amount of tap water in cooking, in this case pasta and rice. Not only is this important, but it should not be assumed that bottled water replaces tap water. In the United Kingdom, there is evidence from surveys commissioned by the drinking water regulator (Drinking Water Inspectorate) that bottled water is not replacing tap water to the extent that it is replacing sugary drinks (United Kingdom Drinking Water Inspectorate 1996).

It is plausible that drinking-water can be an important contributory source of the minerals calcium and magnesium if the population is nutritionally marginal.

However, it is also possible that if the beneficial effect associated with drinking-water minerals is indeed confirmed, it could be due to other essential elements present at low but important concentrations in the drinking-water, rather than to calcium and magnesium. Studies carried out on water minerals for the United Kingdom regional heart study from 1977 to 1980 looked at 26 elements and 36 parameters in total. These data were obtained from tap water samples taken from 1000 homes in over 25 towns with widely differing water hardness. Concentrations of many background minerals, not surprisingly, correlated with calcium and magnesium concentrations (Powell *et al*. 1987). However, the strongest correlation was between vanadium and magnesium. Is the key to the apparent beneficial effects of drinking-water hardness actually another trace element or group of elements that is correlated with hardness and is acting as a confounder in the epidemiological studies?

Many inorganic elements also interact synergistically or antagonistically, and the presence of one may enhance or reduce the absorption or physiological activity of another. This can also apply to other substances in food; while oxalate is known to sequester calcium, it is not clear whether high calcium in water would reduce the calcium sequestering ability of oxalate during the cooking process. Could this be an important contributory factor to the beneficial effects associated with water hardness?

## 11.3 ALTERNATIVE INTERPRETATIONS AND MECHANISMS RELATING TO THE HEALTH EFFECTS OF LOW-MINERAL DRINKING-WATER

The most common proposal for an alternative mechanism for the adverse cardiovascular effects associated with low drinking-water hardness is that soft or low-TDS water is more aggressive to pipes and can lead to high tap water concentrations of toxic metals, particularly lead, which is suspected of raising blood pressure (Vajpeyee 2006). There is, therefore, the basis for a plausible debate. As indicated above, minerals interact in a number of cases to either enhance or reduce the absorption of other minerals or elements. Magnesium and, particularly, calcium are important in this respect, and one possibility is that low calcium/magnesium levels enhance the gastrointestinal absorption of toxic metals, such as lead, from all sources.

While this is apparently plausible, there have been major steps taken to reduce lead exposure from all sources, not just drinking-water. The fact that a beneficial effect of calcium and/or magnesium is still being reported from a country such as Finland (Kousa *et al*. 2004), which has taken significant steps to

reduce exposure to lead and other toxic metals, would tend to militate against the toxic metal theory. However, since the majority of acute myocardial infarction cases are in older individuals, it is probable that they were exposed to the higher lead levels prevalent in the 1940s and 1950s. The argument could be made that this resulted in damage at an early age that was not fully manifest until later. However, the data on lead and blood pressure would not seem to support this view. In addition, there have been studies examining changes in water hardness; where a protective effect of hardness on acute myocardial infarction is observed, the impact of a change in water hardness seems to be quite rapid, implying that the mechanism is current rather than historical damage (Lacey and Shaper 1984).

In addition, the study of water contaminants and constituents associated with the British Heart Study and mentioned above (Powell *et al*. 1987) demonstrated the large impact of first-draw water, compared with fully flushed samples, on levels of metals from plumbing. These included lead along with copper, zinc and nickel. The correlations between metal concentration and the softness of the water were clear in first-draw samples but not obvious for fully flushed samples. Since most water that will be consumed will obviously not be first draw, then the differences in the contribution of metals in soft and hard water will be significantly reduced.

While naturally soft water can be significantly more aggressive, the same concern has been levelled at artificially softened water in which calcium and magnesium ions are replaced by sodium ions. However, this concern appears to be without proper foundation (Harrison 2006). There are significant differences in the characteristics of naturally soft waters and artificially softened waters. While naturally soft water contains lower TDS, usually has a low pH and often has an excess of carbon dioxide over alkalinity, this is not true of artificially softened water. As a consequence, although there is an absence of calcium and magnesium ions due to their replacement by sodium ions (which could have its own consequences for some persons), the water is not necessarily aggressive and would not give rise to increased levels of corrosion products from plumbing materials. In particular, the level of bicarbonate in artificially softened water is high, and the buffering capacity of the water is also high.

There are other possible explanations that are less well supported by evidence but which have also not been particularly well studied. The first is that soft waters sometimes have higher levels of humic and fulvic acids from the types of catchments that are often associated with soft water. These organic acids are precursors for the formation of a wide range of by-products from the disinfection of drinking-water with chlorine. It is also conceivable that the key contaminants in soft waters could be disinfection by-products. Although the possible effect of chlorination by-products on heart disease, and acute

myocardial infarction in particular, has not been well studied, the limited studies available do not support this contention. In particular, no plausible mechanism has been identified, and, like the situation with toxic metals, there have been substantial efforts made to significantly reduce the concentrations of chlorination by-products in drinking-water.

It has been reported from studies in eastern Europe that drinking-water with a very low mineral content has a negative impact on the gastrointestinal tract (Kozisek 2005), although no mechanism has been clearly elucidated. Such an effect could, in theory, change the gastrointestinal absorption of minerals, and/or toxic metals, from other sources, particularly food. However, there remain a number of uncertainties relating to the potential for ingestion of low-mineral water to have an impact on the gastrointestinal tract. While there is a need to obtain additional data on the actual effect, it remains uncertain whether this would be an effect on the gastrointestinal tract itself or on the short-term physiology of the gastrointestinal tract. There are some other important considerations. The studies seem largely to have been carried out under conditions of exercise and water stress, and this may lead to unusual conditions. For example, assuming adequate dietary intake of ions and minerals, under such conditions would rehydration with low-mineral water lead to loss of minerals from the gastrointestinal mucosa, or would the key be replacement of minerals lost through sweating and diuresis? Currently there appear to be few studies that would provide answers or even partial answers, except in relation to sports medicine, which also provides relatively extreme conditions.

## 11.4 WHAT IS NEEDED?

The potential for minerals in drinking-water to provide even a small protective effect with regard to acute myocardial infarction or acute cerebrovascular events is an important one in view of the number of worldwide deaths from these causes. However, in order to make the best use of this knowledge and to either make appropriate interventions or provide information to the public, it is necessary to determine whether this effect is real and to be much more certain of the mechanism by which the effect operates. It is, therefore, important that we have a combination of studies, with a multidisciplinary approach, that include both clinical and epidemiological investigations.

Clearly, as there are a substantial number of ecologic epidemiological studies already available, this is not the way forward. There is, therefore, a need for more suitable analytical epidemiological studies that have wider objectives. These studies need to consider the nutritional status of the populations studied in detail, since this has largely been ignored to date. The studies also need to

consider the age and risk profiles of the study group, because these have an impact not only on the incidence of the clinical events under scrutiny, but also on the mineral nutrition of the individuals within the study population.

There are also a number of water factors that need to be considered in any such studies. It is essential that a wider range of elements in water and drinking-water parameters, such as bicarbonate and organic matter, be taken into consideration. The concentrations of toxic metals or other metals from plumbing will vary according to individual buildings; in many countries, however, data are available that would enable reasonable estimates of exposure to plumbing-derived metals to be made in conjunction with data on water consumption habits, such as use of first-draw water for drinking. Alternative sources of fluid intake are also important, including intake from foods, along with the mechanism of fluid intake, such as drinking tap water in the form of tea, as boiling will change the mineral composition to some extent.

An opportunity exists to study populations who have been using desalinated water for long periods as a drinking-water source. This opportunity is also likely to be expanded in the immediate future.

There are many potential confounders, not least because the disease states leading to the clinical events are of a multifactorial nature, so the potential for confounding needs to be considered very seriously.

## 11.5 PRACTICAL CONSIDERATIONS

There are a number of very important practical and ethical considerations regarding the information available. Much depends on the weight of the evidence available for a positive effect and the weight of the evidence for the mechanism by which this effect occurs. Any information and advice concerning calcium and/or magnesium in drinking-water also need to be placed in the context of overall dietary intake and sufficiency of mineral intake. However, any proposal to change current practice will need to gain widespread support among practitioners and must take into account local sensitivities, political realities and consumer perception.

The most important drinking-water-related question involves adding back minerals removed in desalination or in fresh water treated by reverse osmosis or ion exchange softening of hard water. It is possible to stabilize desalinated and reverse osmosis–treated water with regard to corrosion without necessarily adding significant quantities of calcium and magnesium ions, but the question arises as to whether calcium and magnesium should be added as part of the process to potentially produce additional benefits. Although the optimum levels of these ions remain to be generally agreed, it would seem that there is a strong argument for taking this approach. One common stabilization approach has been

to add lime; another is to add back about 1% of treated source seawater/brackish water to the desalinated water. This contributes magnesium and other salts. The primary issue for specific mineral addition is whether there would be additional costs and whether such costs were significant. The problem of what final concentration to aim for has been addressed by Israel in relation to large desalination projects to provide secure water supplies in a water-stressed region (Adin *et al*. 2006). In this case, the decision has been taken to add calcium ions as part of the process of stabilization. The amount added is 25 mg/l as $Ca^{2+}$, providing an additional 50 mg/day of calcium for a 2-litre intake of drinking-water, either as drinks or in water absorbed into food during cooking. This decision was taken after consideration of a number of requirements in meeting the desired quality of water. These include calcium carbonate precipitation potential higher than 3 mg/l, alkalinity higher than 80 mg/l (as calcium carbonate), calcium higher than 80 mg/l (as calcium carbonate; 32 mg/l as $Ca^{2+}$) and lower than 120 mg/l (as calcium carbonate; 48 mg/l as $Ca^{2+}$), pH lower than 8.5 and turbidity lower than 0.5 NTU. These standards will provide water that is closer to the quality of the limited supplies that the desalination programme will replace.

## 11.6 SUMMARY

An overview of the current situation is as follows:

- A large number, but not all, of epidemiological studies have identified apparent negative (beneficial) associations between hardness or calcium and/or magnesium concentrations and the incidence of ischaemic heart disease, but the ecological epidemiological study associations tend to be fairly weak. The strongest negative (beneficial) association appears to be with magnesium and cardiovascular disease mortality, as was borne out by several analytical studies (Yang 1998; Rubenowitz *et al*. 2000).
- There are deficiencies in all of the studies, and there needed to be an objective evaluation. This has been carried out by Catling *et al*. (2005).
- The benefits of minerals in drinking-water need multidisciplinary consideration that includes a broader nutritional component.
- It appears that because of the variation and the multifactorial nature of the health end-points, simple definitive answers are unlikely.
- There are a number of significant practical issues that need to be taken into account in implementing any findings from this research, and these are the impetus for developing better data.

- There is a need to consider whether there should be addition of calcium and magnesium ions to desalinated water or water treated by reverse osmosis to be used as a drinking-water source as part of the necessary process of stabilization. Adverse effects are unlikely, and positive benefits are possible. There would seem to be adequate evidence to suggest that this should be considered on a project-by-project basis, taking into account both practicalities and cost; however, it would be helpful to provide better advice on the optimum levels to be added.

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# 12

# Water production, technical issues and economics

*Perialwar (Regu) Regunathan*

## 12.1 CENTRAL SOFTENING

The issue of having calcium and magnesium in finished drinking-water can be of importance not only for those water suppliers that utilize desalination processes, but also for the broader water industry internationally. The Global Water Research Coalition, as representative of many water-related research institutes worldwide, has prepared a review on the reasons and criteria for softening and conditioning (Mons *et al*. 2007). It recommends that in addition to nutrition, other health-related and other pertinent aspects should be considered. Both very soft and very hard water can interact with piping materials, which may negatively impact the water quality and the integrity of the piping system. It is therefore important that those other considerations, including the optimal composition of piped drinking-water to prevent corrosion and scaling, are taken into account.

In several countries, softening is sometimes applied centrally (e.g. Netherlands, Germany, Belgium, France, United States). Point-of-entry (POE) softening at the individual residence is the most frequently applied method of softening. Central softening of drinking-water offers public health and environmental benefits. Moreover, consumer comfort is increased, and there are also several financial benefits for the consumer.

Reasons for central softening include:

- reduced exposure to trace metals due to reduced corrosion of plumbing in the distribution system and household plumbing;
- reduced costs because of reduced consumption of detergents and energy as well as lessened need to use private softeners;
- fewer discharges to the environment (e.g. less detergents, less leaching of copper, less salt usage by private softeners, lower use of chemical inhibitors); and
- better consumer comfort due to better looking clothes, glassware, etc.

It is essential to arrive at an optimal composition of the drinking-water to be distributed, and the central aspects of this optimal composition of the public drinking-water should include:

- calcium–carbonic acid equilibrium;
- a non-corrosive pH; and
- sufficient alkalinity.

First of all, the water will need to be in calcium–carbonic acid equilibrium. This means that the Saturation Index (SI) should be close to 0. The preferred range for SI values is $-0.2 < SI < +0.3$. In this region of SI, the corrosion of cement pipe will be minimal, while at the same time the scaling effects will be low as well. Figure 12.1 presents the bandwidth of the preferred SI range.

Secondly, to keep the metal-dissolving properties of the water sufficiently low, the pH needs to be maintained in an optimal range. Upper and lower pH limits are indicated in Figure 12.1. In hard water, it will not be possible to have a sufficiently high pH, because the water will then become supersaturated with respect to calcium carbonate and cause scaling. Allowing for a sufficient pH increase, together with the need to have water in calcium–carbonic acid equilibrium, necessitates the softening of water. On the other hand, it should be recognized that the efficacy of chlorine disinfection decreases as pH increases, and it is especially weak beyond about pH 7–8.

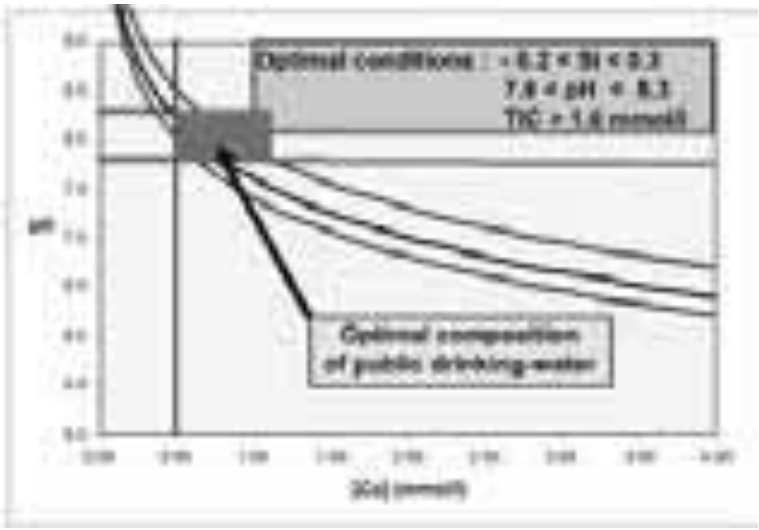


Figure 12.1. Bandwidth of the optimal composition of drinking-water (TIC, total inorganic carbon) (from Mons *et al*. 2006).

### 12.1.1 Water treatment practices in the Netherlands

Central softening has been applied in the Netherlands since the late 1970s. Almost all drinking-water in the Netherlands is conditioned to prevent corrosion and excessive calcium carbonate scaling. In approximately 50% of the production capacity of the country, softening is required to achieve the required water quality. All of the 101 million cubic metres of water supplied annually by Waternet, the municipal water supply company of Amsterdam, is softened, as well as large percentages of the water supplies in the other regions of the country. Naturally soft waters are often treated to add some calcium carbonate alkalinity by having these waters flow through "marble filters".

Softening is mainly done in *pellet softeners*. It is initiated by the addition of a base, calcium hydroxide or sodium hydroxide. Calcium carbonate will crystallize at the surface of sand grains present in a fluidized bed. The sand grains will grow until they are approximately 1 mm in size. These grains are extracted from the fluidized bed periodically, and new sand grains are added. Several design variations of the reactors exist, but all are based on the same approach with the same end goals.

*Nanofiltration*, a membrane filtration technique, is also applied in several utilities to produce low-hardness permeate, which is then aerated and mixed with untreated raw water. The pH is corrected for optimal water composition.

Table 12.1 gives an overview of the values of hardness-related water quality parameters attained in these efforts to produce an optimum composition of water. The pellet softening process reduces the calcium carbonate content in the water, leaves the magnesium concentration unchanged and increases the sodium concentration (where sodium hydroxide is used as base). Furthermore, the scaling potential of the water is reduced significantly.

Table 12.1. Water quality parameters of several raw and treated drinking-water supplies in the Netherlands (from Hofman *et al.* 2006)

| | | Waternet (Leiduin) | | Vitens (Rodenmors) | | Brabant Water (Nuland) | |
|---|---|---|---|---|---|---|---|
| | | Pellet softener, NaOH | | Nanofiltration | | Pellet softener, $Ca(OH)_2$ | |
| Parameter | Unit | Raw | Treated | Raw | Treated | Raw | Treated |
| Ca | mg/l | 76.8 | 43.1 | 100 | 53 | 94 | 56 |
| Mg | mg/l | 9.7 | 9.5 | 6.3 | 3.5 | 5.9 | 6.1 |
| Total hardness | mmol/l | 2.3 | 1.49 | 2.8 | 1.5 | 2.5 | 1.6 |
| Na | mg/l | 46.6 | 76.4 | 34 | 21 | 99 | 77 |
| Cl | mg/l | 87.2 | 93.5 | 9 | 11 | 153 | 108 |
| $HCO_3^-$ | mg/l | 197.0 | 157.2 | 341 | 200 | 308 | 199 |
| $SO_4^{2-}$ | mg/l | 52.5 | 52.1 | 10 | 5 | 21 | 13 |
| pH | | 7.89 | 8.35 | 7.0 | 7.9 | 7.3 | 7.8 |
| $TACC_{90}$[a] | mmol/l | | 0.32 | 0.95 | 0.5 | | 0.97 |
| SI | | 0.37 | 0.48 | −0.2 | +0.26 | 0.04 | 0.16 |
| Cu solubility | mg/l | 2.21 | 1.21 | 4.6 | 1.3 | 3.59 | 1.55 |
| Pb solubility | µg/l | 166 | 102 | 298 | 168 | 249 | 179 |

[a] $TACC_{90}$ is theoretical calcium carbonate scaling potential at 90 °C.

One of the main reasons for the introduction of central softening was the potential environmental and health effects of copper and lead releases. Significant reductions in copper and lead solubility were experienced by the processes of softening and nanofiltration, as can be seen in the values for the three regions shown in Table 12.1. Copper concentrations are below the standard in the Netherlands of 2 mg/l at the tap. For lead, 90% of the observations were below the standard of 10 µg/l. However, conditioning alone has not been

sufficient to comply with the lead standard, as 10% of samples showed higher than the standard level of 10 µg/l. Therefore, use of lead pipe materials in the distribution system has been banned by the authorities. The occasional high lead values found (up to 200 µg/l) are probably due to the presence of old lead pipes in house installations that are outside of the control of the water supply company.

Central softening at large scale is relatively inexpensive. On average, the costs are approximately € 0.02 per cubic metre. When central softening is applied on a smaller scale, the cost can, however, increase to approximately € 0.25 per cubic metre. An average family (annual use 100 $m^3$) will therefore pay approximately € 2 to € 25 extra for their drinking-water due to the introduction of softening. The overall cost savings, resulting from lower maintenance on warm water equipment, less detergent use, reduced staining of sanitary fittings and less energy demand, are estimated at about € 20 to € 300 per year. Thus, softening has been shown to be economical even in small utilities.

In the Netherlands, as in some other countries, the amount of naturally very soft groundwater is a significant portion of the total available drinking-water. In many cases, marble filtration is applied or milk of lime is added to reach the optimum water composition and only for conditioning of the drinking-water to reduce copper and lead solubility. Marble filtration adds only calcium in drinking-water, not magnesium.

*Marble filtration* at large scale is relatively inexpensive: it is estimated at € 0.04 per cubic metre. At smaller scale, the cost increases to approximately € 0.10 per cubic metre. Table 12.2 shows the effect of marble filtration on the water quality for two cases. From this table, it can be concluded that naturally very soft water has about the same level of calcium (after marble filtration) as water softened by central softening. The final water quality depends on the saturation level of the raw water.

This section shows that 20 years of experience with central softening and conditioning of drinking-water in the Netherlands have provided health and environmental benefits at affordable costs. Also, consumers benefit from having softened water at their tap because it reduces their overall costs and improves their comfort.

## 12.2 BOTTLED WATER AND BEVERAGES

The Codex Alimentarius Commission provides an international consensus on the quality and composition of bottled/packaged waters of all types. There are differences between the United States and Europe on some labelling criteria that apply to packaged water. In the United States, the terms used on the labels of packaged waters to describe their characteristics, origin and treatment methods

are *artesian water*, *groundwater*, *spring water*, *mineral water, drinking-water* and *purified water*, which includes *distilled water* and *deionized water*. More detailed descriptions of these types of bottled water are given in Table 3.1 in section 3.3.

Table 12.2. Examples of the effect of marble filtration on water composition in the Netherlands (from Hofman *et al.* 2006)

| | | Vitens (Eerbeek) | | Brabant Water (Vessem) | |
|---|---|---|---|---|---|
| | | Marble filtration | | Marble filtration | |
| Parameter | Unit | Raw | Treated | Raw | Treated |
| Ca | mg/l | 21 | 35 | 22 | 60 |
| Mg | mg/l | 1.8 | 1.8 | 5.8 | 5.8 |
| Total hardness | mmol/l | 0.6 | 0.9 | 0.79 | 1.74 |
| $SO_4^{2-}$ | mg/l | 11 | 11 | 65 | 65 |
| $HCO_3^-$ | mg/l | 35 | 95 | 40 | 140 |
| pH | | 6.6 | 7.9 | 6.1 | 7.7 |
| SI | | −2.3 | −0.3 | −2.7 | −0.1 |
| Cu solubility (calculated) | mg/l | 1.7 | 0.4 | 3.5 | 2.2 |
| Pb solubility (calculated) | µg/l | 324 | 141 | 395 | 169 |

In the European Union, there are three main types of bottled waters: natural mineral water, spring water and prepared water (see also section 3.3). Traditionally, and backed up by centuries of historical background, Europe has developed the market chiefly based upon natural mineral water. Natural mineral water means microbiologically wholesome water, originating in an underground water table or deposit. Natural mineral water can be distinguished from ordinary drinking-water by its nature, by certain effects and by its original state.

Natural mineral waters often contain calcium and magnesium as well as other elements and ions. The composition of a natural mineral water is a characteristic that cannot be modified; hence, there are no two identical mineral waters. Moreover, no treatment can be applied to natural mineral water besides the removal of unstable elements such as iron and manganese, which can further precipitate in the bottle once the product is in the market.

Spring waters are waters intended for human consumption in their natural state and bottled at the source, and they must comply with certain regulatory provisions for human consumption.

Prepared waters are waters subjected to specific treatments to make them compliant with European Union drinking-water regulations, or just to modify their original composition, mostly for acceptability aspects.

Table 12.3 shows the mineral content in thermal and mineral waters from Austria, Belgium, Czech Republic, France, Germany, Hungary, Italy, Slovak Republic and Switzerland. It is important to point out that the highest mineral contents correspond to thermal (spa) or medicinal waters, which are not always bottled.

Table 12.3. Mineral content in thermal and mineral waters from various European countries (from Molas 2006)

| | Mineral content (mg/l) | | |
|---|---|---|---|
| | Maximum | Minimum | Mean |
| $Ca^{2+}$ | 28 826 | 1.8 | 549 |
| $Mg^{2+}$ | 5 430 | 0.02 | 177 |
| $Na^{+}$ | 122 500 | 0.8 | 5 684 |
| $K^{+}$ | 5 493 | 0.2 | 106 |
| $HCO_3^{-}$ | 9 319 | 5 | 975 |
| $Cl^{-}$ | 198 000 | 0.14 | 9 211 |
| $SO_4^{2-}$ | 52 890 | 0.9 | 1 180 |

Unlike the mineral waters shown above, concentrations of calcium and magnesium in European bottled waters usually lie within the following ranges: $Ca^{2+}$, 1.5–600 mg/l; $Mg^{2+}$, 0.5–90 mg/l.

If and when supplementation is considered appropriate, the key considerations in supplementing minerals in bottled water are:

- potential health benefits;
- taste;
- product stability;
- quality of the salts;
- industrial procedures; and
- cost.

Consumer taste preferences play a leading role in determining choice of a mineral water. When the composition is changed, sensory perception also changes, which may lead to an immediate reaction of acceptance or rejection by the consumer.

When considering the addition of salts to a water intended for bottling, the concentrations that can be added without exceeding the solubility of the salts in the water at 20 ºC must be calculated so as to prevent precipitation in the bottle. Solubility can be improved if water is carbonated, as lower pH usually enhances solubility. Chlorides and sulfates of both calcium and magnesium can be used to

supplement bottled water with minerals; their carbonate salts have low solubility in water at 20 ºC.

The procedure for adding minerals to water is quite simple. A mother solution can be prepared in water in a clean reservoir under constant stirring using the same water that will be in the product. The mother solution can also be pasteurized. A pump can be used to inject a portion of the mother solution either directly on-line or to a feed tank maintained under agitation to avoid precipitation of salts. Water with minerals added is then bottled using conventional bottling machines.

To add 20 mg of calcium and 20 mg of magnesium to a specific water, the cost would rise by US$ 0.002 22 per litre of product (US$ 2.2 per 1000 litres) if prepared from calcium sulfate and magnesium chloride or by US$ 0.001 98 per litre of product (US$ 1.98 per 1000 litres) if prepared from calcium chloride and magnesium sulfate. These costs do not include the costs of electricity and mixers/pasteurizers.

## 12.3 IMPACTS ON THE HOME WATER TREATMENT INDUSTRY

The point-of-use (POU) or point-of-entry (POE) industry in the United States, Europe and other regions of the world produces and markets POE softeners and POU reverse osmosis and distiller units to consumers. These products reduce or totally remove calcium and magnesium present in the incoming waters. While the bottled water industry is not traditionally viewed as a part of POU/POE industry, it is part of the home water provision industry and is often similarly affected by the same rules or regulations.

The recommendations of a World Health Organization expert meeting (WHO 2005) were reviewed by the United States and European home water industry with general concerns and questions due to the potential effects of these recommendations on this industry and its current operations in the marketplace. Each of the industry groups responded separately to the expert group's recommendations with its own questions and concerns.

One important point raised by the POU/POE industry was the difference between naturally soft or low total dissolved solids (TDS) waters and softened waters. Many of the epidemiological studies have compared health outcomes of consuming naturally soft versus hard waters. However, no known study has compared consumption of hard waters versus softened waters. There are significant composition differences between naturally soft waters and softened waters.

Another point pertained to possible benefits of the concurrent removal of some regulated contaminants by POU/POE treatment methods. Those contaminants are present only in trace levels in drinking-waters supplied by the utilities, as the utilities need to reduce them below Maximum Contaminant Levels or Maximum Allowable Limits stipulated by the different countries. However, the levels of these contaminants are usually not at zero, partly because such an extent of reduction in all the treated waters is usually too expensive. Use of certified devices in reducing these contaminants from only the water that is ingested (i.e. drinking-water at the household tap) can possibly further reduce risks in some cases (principally for "non-threshold chemicals").

A POU reverse osmosis membrane system removes almost all the calcium and magnesium in source waters. If properly maintained, a POU reverse osmosis membrane system with an activated carbon filter can also yield drinking-water virtually free of many organic and inorganic chemicals of potential concern. In addition to removing calcium, magnesium and also fluoride, the membrane barrier can reduce many inorganic and particulate contaminants to near detection limits, such as arsenic, perchlorate, lead, copper, radium-226/228, selenium, chromium, turbidity, barium, cadmium, protozoan cysts, TDS, nitrate/nitrite, sodium and sulfate.

Similarly, a POU distiller can remove virtually all inorganic chemicals, including calcium and magnesium, along with volatile and non-volatile organics. Volatile organics can be reduced by these devices with a good venting system or by a carbon filter at the outlet of the product water.

A POE softener is generally considered as an aesthetic device removing hardness ions, but it can also remove other divalent cations from drinking-waters. While some softeners are also certified for their ability to remove barium and radium-226/228, they can also remove copper, cadmium, iron, manganese and other trace-level divalent cations.

The balancing of the potential beneficial aspects of these devices against the potential harm of reducing the calcium and/or magnesium and fluoride levels to below the recommended thresholds in drinking-waters is worthy of consideration.

Acceptance of the "hard water–cardiovascular disease benefits" hypothesis by health experts can lead to several different actions by segments of the water industry as a whole. Some will need to take strong actions, while others may have a set of options:

- Utilities with demineralized waters might be guided to add recommended levels of calcium and magnesium.
- Cities with naturally "soft" water supplies may face a dilemma in the form of a conflict between the possible need to add the recommended

levels of calcium and/or magnesium and the economy of such action, even if they are not required to do so by their country's laws. The benefit–cost balance of such additions must take into consideration that only a small fraction of the water supply that is used as drinking-water requires this treatment, but all 100% will end up being treated. Many of the cities may not undertake such a treatment simply for economic reasons. However, consumers may not be satisfied and may choose other means, such as fortified bottled water.

- The POU/POE industry would need to re-evaluate how to realign some of its products and activities.
- The bottled water industry would have the opportunity to augment its product lines with mineralized waters, as some are already doing.

Softener manufacturers and installers may choose to adopt a variety of approaches, even though none of them is desirable in their point of view, although some are already practised:

- a separate hard water line to the kitchen sink;
- a small bypass to achieve target hardness levels in the cold water;
- a new POU mineralization unit under the kitchen sink with a separate tap; and
- hot water softening only in lower-hardness areas.

The POU industry might also develop products capable of adding target amounts of calcium and/or magnesium to drinking-waters of all kinds. These products can be used in naturally "soft" waters to add minerals just to the drinking-water used in households. The same devices can also be used as add-on devices after the POU reverse osmosis/distiller systems or as a unit under the sink to add minerals to softened water. These products may, however, present a challenge due to the intermittent nature of their use and the tendency of these chemical compounds to solidify and not yield consistent concentrations of minerals in the effluent waters.

The cost of such a product will also be dependent to some degree on the cost of the minerals used in the devices, the quantity of the mineral addition and the mechanism used to introduce minerals into the waters. The unit cost of the minerals is low and has been estimated at US$ 0.002 per gram of calcium and US$ 0.004 per gram of magnesium. Assuming addition of 30 mg of calcium and 10 mg of magnesium, then the cost per litre of water consumed will be only US$ 0.0001.

In spite of the technical feasibility, many in the home water treatment industry are anxiously monitoring the possible outcome of the discussions, because they still have several concerns, including the following:

- although not health experts, some are not convinced of the scientific validity of the conclusions;
- the issue of differences between "soft" and softened water;
- the public's potential negative perceptions about all types of drinking-waters with lower hardness levels;
- stigma on the industry associated with removing elements beneficial to the consumers;
- potential uninformed regulatory response in different countries and regions; and
- concern about potential uneven treatment of or impact on some segments of the water industry compared with others.

Their concerns should be kept in mind in the public health guidance deliberations to make sure that the most beneficial and scientifically supportable conclusions are made.

## 12.4 SUMMARY

Properly softened waters can have public health, economic, environmental and customer comfort benefits. Controlled central water softening as practised in the Netherlands and some other locations appears to reduce lead and copper corrosion, increase the pH and reduce the potential for scaling in cold and hot water plumbing components. Their practice leaves a certain amount of calcium in treated waters, but has no impact on magnesium concentrations. Additionally, marble filtration can be used to increase pH, alkalinity and calcium concentrations in naturally soft waters (but without an increase of magnesium concentrations).

Addition of calcium and magnesium to bottled water is a process that can be easily undertaken with only minor effects on costs. Taste preferences will determine consumer choices of products probably more than other factors, although a segment would be expected to opt for mineral fortified waters.

Addition of calcium and magnesium after the POU/POE installations or to naturally soft waters in a home presents some technical difficulties that would need to be resolved. Some manufacturers have already developed some products to add calcium and magnesium to water. The differences between naturally "soft" waters and softened waters have been pointed out. So, while health

studies comparing soft and hard waters may be valid, they may not apply to softened waters because of their different compositions (i.e. higher sodium and TDS and probably lower corrosivity). There is a need to balance the potential beneficial aspects of those POU and POE devices that concurrently remove trace contaminants against the potential negative effects of reducing the calcium and/or magnesium and fluoride levels to below the recommended levels in drinking-waters.

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# Glossary

*Adequate Intake (AI)* is an estimate of the average nutrient intake by a group or groups of healthy people within a designated age, life stage and/or sex group. It is derived from the observed intakes of apparently healthy individuals in the subgroup of interest. AI values are established when there are insufficient data to derive an Estimated Average Requirement (EAR).

*Analytical epidemiological studies* are designed to examine specific hypothesized causal relationships. Individuals in the study population may be classified according to absence or presence (or future development) of specific disease and according to risk factors that may influence disease occurrence. Types of analytical study are cohort and case–control.

*Association* is the dependence between two or more events, characteristics or variables (e.g. exposure and disease). Variables are associated if one is more (or less) common in the presence of another variable or when they occur more

frequently together than expected by chance. Association and relationship are often used interchangeably. Association does not necessarily imply cause–effect between the events or variables.

*Bioavailability* refers to the proportion of an ingested nutrient (from foods or nutritional supplements) that is absorbed and utilized through normal metabolic pathways in specific organs or tissues.

*Case–control studies* are retrospective, analytical, observational epidemiological studies of persons with the disease of interest (cases) and a suitable comparison or reference group of persons without the disease (controls). The relationship of a risk factor to the disease is examined by comparing the cases and the controls in terms of how frequently the factor is present.

*Causality* is relating causes to their effects. Evidence from biology, biochemistry, and toxicology is necessary in addition to a body of epidemiological research. Causes can be necessary (the cause must always precede the effect) and/or sufficient (the cause inevitably initiates or produces the effect). Considerable debate often accompanies the determination of causal inferences from epidemiological associations.

*Cohort studies* are analytical, observational epidemiological studies of large numbers of people over a long period of time, comparing rates of illness in groups that differ by risk factors. These studies can be retrospective, prospective or bidirectional.

*Community intervention studies* are experimental epidemiological studies in which the intervention is allocated in an entire community. The intervention can be natural (e.g. weather events), sociopolitical (e.g. changes in water treatment) or medical (e.g. immunization, behaviour modification).

*Confidence interval* is a computed interval, with a specified probability, that contains the estimated value of a parameter (e.g. relative risk or odds ratio). The boundaries of a confidence interval are the confidence limits. The specified level of confidence is usually 95%, but the investigator can select another level. A 95% confidence interval around an estimated parameter should contain the population parameter value in 95 out of 100 replicated studies.

*Ecological epidemiological studies* are descriptive epidemiological studies based upon populations or groups of people, rather than individuals.

*Estimated Average Requirement (EAR)* is the nutrient intake value that is estimated to meet the requirement defined by a specified indicator of adequacy in 50% of the individuals in a life stage or sex group.

*Extrinsic labelling* is a procedure in which a tracer is mixed with the test substance. In measurements of calcium bioavailability, for example, the calcium label or tracer is simply mixed with the final food product. Extrinsic labelling does not always yield reliable results due to the difference between the chemical forms of the calcium tracer and the calcium in food products, in this example, which can affect bioavailability.

*Functional* in this context refers to the fact that the body's reserve of calcium held in the bone is not simply a reservoir or storage area for excess body calcium but actually performs an important role in health protection.

*Intrinsic labelling* is a procedure in which simple labelled compounds are provided to a plant, for example, or simple organic molecules are added to animal feed, and natural processes such as photosynthesis and metabolism are allowed to proceed, producing a full range of products in a manner that is no different from normal food production.

*Metabolic syndrome* is characterized by a group of metabolic risk factors, including excessive fat tissue in the abdomen, insulin resistance or glucose intolerance, raised blood pressure and elevated C-reactive protein in the blood. People with metabolic syndrome are at increased risk of coronary heart disease, stroke, peripheral vascular disease and type 2 diabetes mellitus.

*Multifactorial origin* means simply that many factors are involved in causing the disease of interest.

*Null hypothesis* is the statistical hypothesis that one variable has no association with another or that two or more population distributions do not differ.

*Probability or "p" value* is, under the assumption that the null hypothesis is true, a statement of the probability of obtaining as association or difference as extreme as or more extreme than the one observed in the study. Investigators set their own significance levels, but in most instances a study result whose probability value is less than 5% (1 in 20 chance or $p < 0.05$) is deemed statistically significant or unlikely to have occurred by chance.

*Prospective studies* are studies in which data collection and the events of interest occur after individuals are enrolled.

*Randomized controlled trials* (or *Randomized prospective studies*) are prospective, experimental epidemiological or clinical studies using primary data (i.e. the original study data). Individuals are randomly allocated to two or more treatment groups, and the outcomes of the groups are compared after sufficient follow-up time. Differences in outcome may be attributed to the treatment, rather than to the characteristics of individuals forming the treatment groups.

*Recommended Dietary Allowance (RDA)* is the average daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (97–98%) individuals in a life stage and sex group. It is generally derived from the Estimated Average Requirement (EAR) using a 10% coefficient of variation as a default in the absence of nutrient-specific data on variability in the target population.

*Retrospective studies* are studies in which all events of interest have already occurred and data are generated from historical records (secondary data) and from recall.

*Risk factor* is an exposure, characteristic or aspect of personal behaviour that is associated with an increased probability of a health-related condition(s) or disease(s), not necessarily a causal explanation. Age, behaviour, occupation and smoking are risk factors for many diseases and must be considered along with the exposure being studied.

*Signalling* is a function of certain molecules in cells, including calcium ions, cyclic nucleotides and various protein kinases and phosphatases. Intracellular events are often triggered by external or extracellular signals, by means of the binding of an extracellular signalling molecule to a receptor that faces outward from the membrane. The extracellular signal is then converted to an intracellular signal, which triggers the intracellular event.

*Statistical power* is the probability that a study will demonstrate a statistically significant result at a specified value when a true difference or association exists (i.e. the null hypothesis is rejected when it is false). A study's power is determined by several factors, including frequency of the condition being studied, the magnitude of effect and sample size.

*Tolerable Upper Intake Level (UL)* is the maximum level of a total chronic daily intake of a nutrient that is unlikely to pose risks of adverse effects to the most sensitive members of a healthy population.

*Water hardness* is a measure of the concentration of divalent cations that contributes to scale formation and soap curd. In most water supplies, calcium and magnesium are the predominant contributors to hardness. Water considered to be moderately hard contains about 60–120 mg/litre as calcium carbonate.

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**Can calcium and magnesium ('hardness') in drinking water contribute to preventing disease?**

**This book documents the outputs of an unprecedented group of experts assembled by the World Health Organization to address this question. It includes their comprehensive consensus view on what is known and what is not about the role and possible health benefit of calcium and magnesium in drinking-water.**

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