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WHO Meeting of Experts on the Possible Protective Effect of Hard Water Against Cardiovascular Disease

Washington, D.C., USA

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Final Statement

The World Health Organization (WHO) assembled a diverse group of nutrition, medical and epidemiological scientific experts and water technologists at the Pan American Health Organization in Washington, D.C., USA, on 27–28 April 2006 to address questions in regard to 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 contribution to total daily dietary intake of calcium and/or magnesium would provide positive health benefits in the population.

The impetus for the meeting originated from the process for developing guidance for health and environmental aspects of water desalination, which was initiated by the WHO Eastern Mediterranean Regional Office. It is also intended to contribute to the Fourth Edition of the WHO *Guidelines for Drinking-water Quality* in respect to nutrients in drinking-water and water hardness as they impact on drinking-water quality and health. A Meeting of Experts met in Rome in November 2003 and developed the report *Nutrients in Drinking Water*,[1] which was the precursor to the present meeting report.

Introduction

Both calcium and magnesium are essential to human health. Inadequate intake of either nutrient can impair health. Standards for 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*[2] 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

[1] World Health Organization (2005) *Nutrients in Drinking Water.* Geneva, World Health Organization, Water, Sanitation and Health. 186 pp. Available at: http://www.who.int/water_sanitation_health/dwq/nutrientsindw/en/index.html

[2] Italicized terms are defined in the glossary at the end of the text.

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 WHO expert meeting held in Rome in 2003 to discuss nutrients in drinking-water, the present group focused its consideration on calcium and magnesium, for which evidence of health benefits associated with their presence in drinking-water is strongest. The group also noted that the issue of fluoride was addressed by the Rome meeting in detail (see below) and accepted that other elements may also have health relevance and should be considered by future groups.

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.

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.

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 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[3] 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.

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

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*.

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.

Vulnerable populations

Those individuals who avoid dairy products or lack access to them may be at risk of calcium deficiency. Formula-fed infants will not normally be at risk from deficient or excess amounts of calcium, as 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 to the infants.

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.

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 the *metabolic syndrome*.

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.

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.

Preeclampsia

Preeclampsia (defined as hypertension after 20 weeks of gestation) with proteinuria has been treated with magnesium salts for many decades. A recent trial[4] using magnesium sulfate showed a 50% decreased risk of eclampsia.

Atherosclerosis

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

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.

Diabetes mellitus

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

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.

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.

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

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[4] The Magpie Trial Collaborative Group (2002) Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet, 359: 1877–1890.

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.

Epidemiological evidence

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

Based on identified *case–control* and *cohort studies*,[5] there is no evidence of an association between water hardness or calcium and acute myocardial 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.

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 is 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.

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[5] Case–control and cohort studies are more useful than ecologic 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 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.

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 life span 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, 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.

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.

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 approximately 12–17 mg/l of magnesium and 4–5 mg/l of calcium 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 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.

Reuse water

Globally, there is extensive indirect wastewater reuse, 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.

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.

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.

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.

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 non-corrosive materials 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 mineral intake and alternative 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.

Further recommendations

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

All suppliers of water, whether or not 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 vary 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.

Fluoride in remineralized drinking-water

Although fluoride was not discussed at length, the expert group 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 remove 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 for fluoride is 1.5 mg/l.

Where 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 public dental awareness 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 data), 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.

Key knowledge gaps and research recommendations

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: *Analytical epidemiological studies* of improved design (case–control or cohort) are required to elucidate the relationship between calcium and 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 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 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 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 subclinical 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. 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 type 2 diabetics.

- ***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 enhances excretion of some nutrients from the organism.

Rationale: Various experimental and epidemiological studies on humans and animals published in Russia 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.

Glossary

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.

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 person 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.

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 (weather events), sociopolitical (changes in water treatment) or medical (immunization, behaviour modification).

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

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.

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 the metabolic syndrome are at increased risk of coronary heart disease, stroke, peripheral vascular disease and type 2 diabetes.

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

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. 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.

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.

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.

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.