

**Rolling revision of the WHO Guidelines for
drinking-water quality**

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**Studies of mineral and cardiac health in
selected populations**

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Studies of Minerals and Cardiac Health in Selected Populations

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1 INTRODUCTION

Cardiovascular diseases are, as a group, the leading cause of death in western countries. Sudden death from cardiovascular disease accounts for over 300,000 deaths per year in the U.S. (Eisenberg *et al.* 1992). Because of the importance of cardiovascular disease, major efforts have been made to identify risk factors and to take steps to reduce these risks.

There is an increasing body of evidence that drinking water hardness and elevated concentrations of certain minerals in hard water may reduce the risk of cardiac death and, in particular, the risk of sudden cardiac death. Recent interest has focused on deficits in dietary magnesium. In developed countries, these deficits are potentially compounded by use of medications, such as diuretics, that further reduce body stores of magnesium (McLean 1994). There is also concern that increased use of calcium supplements to prevent osteoporosis may alter the ratio of calcium to magnesium intake, further exacerbating the deficiency in magnesium intake. Since calcium and magnesium compete for absorption, there is concern that increasing calcium intake without also increasing magnesium intake can result in a deficit of magnesium. The optimal ratio of calcium to magnesium is unknown. In this chapter, the plausibility of a relationship between waterborne and dietary magnesium ingestion and cardiac disease is discussed, primary in terms of persons who are on magnesium therapy or participate in rigorous exercise. In particular, can studies of these two high-risk populations provide evidence for or against the hypothesis of a causal relationship between water hardness and the risk of cardiovascular disease?

2 MAGNESIUM DEFICIENCY

In theory, it should be relatively easy to determine whether a population has a deficit in magnesium or calcium intake and whether drinking water levels of either mineral significantly affect total intake. However, of more direct interest for public health intervention is whether individuals who have certain heart diseases have a deficiency of magnesium body stores or whether they have too much calcium intake relative to their magnesium intake.

It is difficult to identify magnesium deficiencies because serum and tissue magnesium levels are not correlated. Perhaps, the lack of a correlation is because magnesium can readily move between bone, muscle, soft tissues, and other body compartments. About 53% of the total body stores of magnesium are in the bone, 27% in muscle, 19% in soft tissue, 0.5% in erythrocytes and 0.3% in serum (McClean 1994), but it is difficult to measure tissue levels and assess magnesium deficiency levels in any individual. This difficulty limits efforts to relate magnesium deficiency to heart disease.

Another major problem in assessing magnesium deficiencies is that magnesium interacts with both calcium and potassium, so that a deficiency or excess of one can affect the others. The effect of adequate magnesium intake is to maintain cellular levels of both magnesium and potassium. Magnesium is needed for the sodium/potassium pump. A magnesium deficiency may impair the ability of cells to pump sodium out of the cell and to pump potassium into the cell. Prescription diuretics can deplete magnesium and potassium (Wester 1987).

Magnesium and calcium are also antagonistic for blood coagulation. Magnesium inhibits coagulation while calcium promotes the process. It is possible that calcium to magnesium ratios of much greater than 2 to 1 can interfere with coagulation as well as other processes (Wester 1987).

In clinical and population studies where magnesium tissue levels can be measured, evidence of hypomagnesemia is commonly found. Hypomagnesemia occurs in about 65% of intensive care unit patients (Fink 1981) and in 11% of the general population (Ryzen *et al.* 1985). The clinical manifestations of hypomagnesemia include neuromuscular hyperactivity, psychiatric disturbances, calcium/potassium abnormalities and cardiac effects (Wong *et al.* 1983). An experimental study of magnesium depletion in humans found that plasma magnesium levels fell to 10%-30% of previous levels. The primary symptoms of the depletion were neurologic signs (e.g. Trousseau sign, personality change, tremor and fasciculation), however, anorexia, nausea and apathy were also

reported. All symptoms reverted to normal following reinstatement of magnesium (Shils 1969).

Other clinical data support a relationship between magnesium and cardiovascular function. Deficiencies in magnesium have been shown to cause an increase in cardiac arrhythmias (Reinhardt 1991). Lower levels of magnesium were found in the heart muscle of persons who died suddenly from ischemic heart disease compared to people who died from other causes (Chipperfield & Chipperfield 1978). Supplementing magnesium intake for patients with arrhythmias often controls the arrhythmias.

3 PROTECTIVE EFFECTS OF MAGNESIUM

Epidemiological studies have repeatedly indicated that a benefit of magnesium is to reduce the occurrence of sudden death from cardiovascular disease. Singh (1990) conducted an intervention study using two cohorts at high risk of cardiovascular disease morbidity and mortality. One cohort (206 subjects) was given a magnesium-enriched diet and the other (194 subjects) remained on their usual diet. The magnesium-enriched diet contained 1,142 mg/day whereas the usual diet contained 418 mg/day of magnesium. The high magnesium diet included 880 mg/day calcium whereas the low magnesium diet included 512 mg/day of calcium. The occurrence of sudden death was 1.5 times more common in the usual-diet group. This finding is consistent with prior studies showing low intake of magnesium is associated with arrhythmias (Singh 1990).

An interesting recent study (Abbot *et al.* 2003) tracked 7,172 men in the Honolulu Health Program. Baseline measurements were made between 1965 and 1968. Over a 30-year period follow-up 1,431 men developed CHD. There was a statistically significant increased risk of CHD in men in the lowest versus the highest quintiles of baseline magnesium intake after adjusting for other dietary and non-dietary cardiovascular disease risk factors both of which were also ascertained at baseline. They did not present data on both calcium and magnesium intake for the various quintiles, making it impossible to determine the calcium to magnesium ratio. An interesting finding, however, was that systemic hypertension decreased with increasing magnesium intake. Unfortunately, in assessing the effects of both calcium and magnesium, some papers have adjusted for blood pressure, which appears to be an intermediate outcome of increased magnesium intake. By adjusting for such an intermediate outcome one can falsely conclude that calcium is protective but that magnesium has no effect on heart disease risks. In reality the effect of magnesium on heart disease could be through its effect on lowering blood pressure (Iso *et al* 1999).

Two case-control studies reported protective effects of magnesium for cardiovascular diseases in women (Rubenowitz *et al.* 1999) and for men and women (Rubenowitz *et al.* 2000). Since the case-control and cohort design provide persuasive evidence of a causal relationship, these studies are particularly important, and their results significantly increase the level of confidence in the relationship between magnesium exposure and cardiovascular disease. The highest quartile received 9.9 mg/liter or more drinking water magnesium versus less than or equal to 3.4 mg/liter magnesium in the lowest or comparison group. The odds ratio for the highest exposure group was 0.70 (95% C.I. 0.50-0.99).

3.1 Magnesium Therapy

Another approach to assessing the contribution of magnesium to cardiac health is to examine the therapeutic effects of administering magnesium. Although these magnesium levels are much higher than found in water or the diet, the studies can provide supportive evidence of protective effects and possible adverse effects at deficient levels. Magnesium therapy has been tested as a treatment for people with a known or suspected myocardial infarction. A review (Teo *et al.* 1993) of randomised clinical trials of the role of magnesium in reducing mortality from acute myocardial infarction reported a statistically significant reduced relative risk, an odds ratio of 0.61 (95% C.I. 0.48-0.76). The Leicester Intravenous Magnesium Intervention Trial of suspected myocardial infarction (Woods *et al.* 1994) used a double-blind protocol that started injection before any thrombolytic therapy was used. They found a 21% reduction in mortality from ischaemic heart disease (95% C.I. 5%-35%) and a 16% reduction in all cause mortality (95% C.I. 75-9%).

Even in the absence of hypomagnesemia, magnesium is often used for treatment of pre-eclampsia (Sadeh 1989, Isiri *et al.* 1984) and asthma (Okayama *et al.* 1987). It is also an accepted therapy for cardiac arrhythmias (McLean *et al.* 1994). However, there are questions whether much of the benefit of the magnesium therapy results from correcting magnesium deficiency caused by other therapies such as digitalis and diuretics.

Unfortunately, the success of magnesium in treating patients for these diseases does not provide sufficient evidence that it would be successful in preventing the diseases. We do not know the mode of action for its effectiveness and thus, do not know whether the effectiveness of therapeutic magnesium results from correcting a deficiency in body stores of magnesium or some other reason.

3.2 Calcium, Copper, and Zinc Deficiencies

The relationship between minerals, trace elements and cardiovascular outcomes appears to be rather complex. High levels of serum calcium have been positively correlated with adverse cardiovascular outcomes (Lind *et al.* 1988), but a deficiency of calcium is also related to an elevated risk of hypertension (Cutler *et al.* 1990). Elevated serum copper levels have been suggested as a risk factor for cardiovascular disease (Iskra *et al.* 1993). There may be relationships between absorption of magnesium and each of these other elements. One study that considered serum levels of many of these elements found that only high serum copper and low serum zinc were associated with an increased risk of cardiovascular mortality. No associations with serum calcium or magnesium and mortality risk were apparent in this study (Reunanen *et al.* 1996). However, as discussed earlier, serum levels may not be good indicators of cellular levels of these elements (Reunanen *et al.* 1996). Furthermore calcium and magnesium serum levels may fluctuate more than cellular levels.

3.3 Magnesium, Strenuous Exercise, and Sudden Cardiac Death

In this case, the question is whether water hardness or elevated dietary magnesium intake can reduce the risk of sudden cardiac death among people involved in modest to rigorous exercise. This is important because there is considerable evidence that exercise reduces the risk of premature mortality and physicians encourage most of their patients to maintain a program of regular exercise (Carter and Phillips 1969). However, during exercise there is also an increase risk of sudden death (Northcote 1985). Inactive men have a 56-fold increased risk of death during periods of during vigorous exercise than during other periods (Siscovick 1984).

There are a number of articles reporting sudden deaths during marathon races, while playing squash or during other sporting events. Studies of sudden deaths of males during athletic events have generally found that the deaths were triggered rather than caused by the exercise (Marion 2003). In general, cardiac abnormalities were found that could explain the death (Marion 2003). The situation is less clear for women. The majority of sudden cardiac deaths in women occur in the absence of obvious risk factors. Furthermore, the rate of sudden cardiac deaths among women is increasing. There have, unfortunately, been few rigorous studies of mineral intake or serum or cellular mineral levels of women suffering sudden cardiac death.

Also there are few studies of the effects of strenuous exercise on non-fatal events. An interesting analysis of the metabolic effects of strenuous exercise was conducted in Israel (Stendig-Lindberg *et al.* 1989). Healthy young men received 6 months of physical training. They participated in a rigorous march

and were screened for a large number of metabolic parameters. Of all the parameters measured, the primary change was in serum magnesium concentration. Although serum magnesium did not change immediately following the march, it declined at 72 hours, and it remained lower at 18 days and at 3 months. Another study by the same authors (Stendig-Lindberg *et al.* 1991) found the same change in serum magnesium in a different group of young males participating in vigorous exercise. A study conducted by Corrado (2001) found that young athletes in Padova, Italy had 2.5 times the risk of sudden death than non-athletes. This occurred despite routine medical and ECG screening of these young athletes. Stendig-Lindberg (1992) speculated that sudden death in athletes during exertion is 'mediated' by the effects of persistent magnesium deficiency.

Given both the added risks and benefits of exercise on health, more information is needed to better understand the physiological effects of exercise and to identify both risk factors and approaches to minimize the health risks from exercise. Considering the limited data available, people involved in moderate to vigorous exercise may be at risk of mineral imbalances, particularly magnesium. An added concern is that the U.S. Centers for Disease Control and Prevention (www.cdc.gov/od/oc/media/pressrel/r010301.thm) reported that sudden cardiac deaths are increasing in young people, especially young women. Reasons for the increase are unknown at this time.

4 SUMMARY AND CONCLUSIONS

There are many potential implications from the studies of minerals in drinking water and health effects. The most convincing findings, to date, have been relationships between the occurrence of sudden cardiac death and deficits in magnesium intake. Sudden death is a significant cause of cardiovascular death, and many of these deaths are believed to be related to arrhythmias and coronary artery vasospasm. Thus, the benefits of magnesium in hard water are likely to be significant.

The problem with the current body of evidence is the complexity of the interrelationship between potassium, calcium and magnesium intake and other risk factors for cardiac death (i.e., the web of causation). The interpretation of current study results allows several conflicting hypotheses to be consistent with the available data, and it is possible to convince oneself that magnesium is an important as well as an unimportant risk factor for cardiovascular risks. For example, the Task Force on Sudden Cardiac Death of the European Society of Cardiology (Priori *et al.* 2001) reported that some studies of supplemental magnesium administration showed a 45% reduction in all-cause mortality, with

most of the reduction due to a reduce risk of death from congestive heart failure. However, the Task Force also cautioned that more recent studies have not been able to confirm earlier findings showing a 45% reduction in mortality. The Task Force suggested that differences in observed results between the earlier and later studies may be due to the fact that initiation of the magnesium therapy was delayed in the later studies. Even though not all studies show a benefit, many indicate that small increases in magnesium intake may result in reduced risks of sudden cardiac death. If so, it is possible that relatively modest increases in water or food magnesium levels might result in considerable benefits with minimal risks of adverse effects.

For any large-scale intervention program where magnesium is added to drinking water, one must also consider the possibility that some persons may be harmed by the addition of magnesium to the diet. However, high dose intravenous administration for individuals with heart disease is considered to be safe (Horner, 1991) suggest that low-dose supplementation of magnesium in drinking water is likely to have a significant margin of safety.

In considering possible magnesium supplementation, Eisenberg et al. (1992) raise several important concerns including: how should the supplementation occur (e.g., through drinking water or food or by treating individuals) and how long must it be conducted before a benefit is apparent? Legal and liability issues with magnesium supplementation of water or food should also be considered. Given the special health risks of people over age 40 who participate in vigorous sports, the balancing of risks and potential benefits from magnesium supplementation may be different than for the general population. Also, since supplementation could be done for specific individuals, it may be easier to exclude individuals who may suffer adverse health effects from magnesium supplementation. Although this might best be accomplished through dietary supplementation, ensuring that sufficient magnesium is in the drinking water would more effectively reach a large number of people with a minimum of cost. An important question, however, is what are the minimum and maximum levels of magnesium that should be considered for drinking water.

Additional low-cost observation studies should be conducted to expand the available data on the protective effects of magnesium. Randomised placebo-controlled trials of magnesium supplementation may also be feasible, especially in high-risk populations. These studies could provide the information needed to plan future large-scale efforts to more conclusively resolve the relationships between water hardness, magnesium intake and cardiovascular risks and assist public health officials in selecting optimum, safe levels that could be added to demineralised water.

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