

## Hard water and heart: the story revisited

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**Abstract :** A lower incidence of cardiovascular diseases has been observed in areas with hard water. However, numerous debates and controversies prevailed over time. Some scientists had been trying to correlate cardio-protective factor of hard water while others were working on the toxic factor of soft water with this geo-selective predisposition to cardiovascular events. Now the factor unanimously agreed upon can be concluded as Magnesium. The proofs in favour of Magnesium(Mg) come from studies reporting (i) sudden deaths in areas with Mg deficient drinking water, (ii) low myocardial Mg content in sudden death cases, (iii) cardiac arrhythmias & coronary artery vasospasms being precipitated by Mg deficiency and (iv) intravenous Mg reducing the risks of Arrhythmias & deaths immediately after Acute Myocardial Infarction. Magnesium is a structural component of cardiac muscle and is required by as many as 1300 enzymes for different biochemical reactions. It is an important co-factor for ATPase; hence, is needed in every cell. Mg modulates cellular events involved in inflammation and is important for proteolytic enzymes, which counteract inflammation.

The modern processed food, softened drinking water and over reliance on ready to eat food thus avoiding fruits & green leafy vegetables is an important cause of Mg deficiency. The deficiency of Mg has been reported to cause increase in inflammatory cytokines, endothelial damage and dyslipidemia; all of which are the centre stage for the development of Atherosclerosis, the thickening & hardening of arterial walls. Magnesium, which seems to be the wonder ion can be used for supplementation & fortification. This can prove to be an efficient, effective, replicable and cost effective model for preventing many diseases particularly cardiovascular diseases through public health interventions.

**Key words:** atherogenesis; atherosclerosis;; cytokines; dyslipidemia; total dissolved solids (TDS); vascular cell adhesion molecules (VCAMs).

### I. Introduction

We all know that the cardiovascular diseases are on an increasing trend. During the last five decades, there has been a sharp increase in the prevalence of cardiovascular diseases and sudden ischemic heart disease (IHD) deaths. [1] Atherosclerotic vascular disease continues to be the leading cause of death in the Western world. [2] According to the Centre for Disease Control and Prevention (CDC), approximately 61.8 million people in the United States have heart disease. The American Heart Association reports that approximately 870,000 people died from the condition in 2004. Heart disease contributes to approximately 40% of all deaths. The morbidity status as per National Health Interview Survey, 2009 mentions the number of non-institutionalized adults with diagnosed heart disease as 12% in United States. [3] There is an increasing morbidity and mortality due to cardiovascular death in the developing countries as well. Reasons for increasing IHD could be multifactorial - growing affluence, urbanization, changing lifestyle, unhealthy dietary habits, inactivity, genetics, environment, toxin exposure, dietary deficiency, dietary excess or the water we drink.

Chemical composition of water depends to a great extent on the chemical composition of geological substrata. There is reason for suspecting the chemical composition of the environment to be involved in aetiology of cardiovascular disease as there were reports that in some countries the prevalence of cardiovascular and cerebrovascular diseases may be associated with the type of geological substratum.[4] A negative correlation between hardness of drinking water and cardiovascular diseases has been reported by number of studies in Japan, United States, England, Finland, Sweden, Canada, South Africa etc.[5,6,7,8,9,10,11] In most large-scale studies, an inverse relationship between the hardness of drinking-water and cardiovascular disease (CVD) has been reported. However, no such association has been found in some studies, and in those involving small geographical areas a clear association is often not found. [12,13]

Hard water is the water that has high mineral content. It has high concentrations of calcium and magnesium ions. These ions enter a water supply by leaching from minerals of rocks and soil. Common calcium-containing minerals are limestone (calcium carbonate) and chalk (calcium sulphate). A common magnesium mineral is dolomite, which also contains calcium. TDS, total dissolved solids, is a measurement of all the minerals in drinking water. TDS not only includes calcium and magnesium (the hardness factors), but also zinc, copper, chromium, selenium and so on. Rainwater and distilled water are soft, because they contain few ions.

Although hard water can pose serious problem in industrial settings and hardness is monitored to avoid breakdown in expensive equipment, hard water is generally said to be not harmful to health. The World Health Organization says that “there does not appear to be any convincing evidence that water hardness causes adverse health effects in humans.” [13]

According to the U.S. National Academy of Sciences by 1977 there had been more than 50 studies, in nine countries, that had indicated an inverse relationship between water hardness and mortality from cardiovascular disease. [14] Housewives dislike hard water because it does not lather well or does not taste good, but they may not be knowing that it may prolong their lives, and more especially their husbands. [15]

## **II. Harder the water softer the arteries**

In 1953, Watanabe reported that the death-rate from apoplexy in Japan, compared with those in U.S.A., Britain and Germany, was extraordinary high. Also there was a notable geographical difference in the death-rate from apoplexy which appeared to be due to the environmental difference rather than the racial or heritable one. In 1957, an important Japanese study by Kobayachi showed that when hardness of drinking water went up, the rate of death from cardiovascular disease went down. [5]

Further evidence for water hardness came with a study of British towns observed between 1951 and 1961, a time of rising cardiovascular disease. The towns whose water supply became softer during that decade experienced a 20 percent rise in heart disease death rates, while towns with no change in water hardness showed a rise of only 11 percent in such deaths. Towns whose water supply became harder had only an 8 percent rise in heart-disease deaths. [16]

The first major study on drinking water and heart disease was in 1960 by Dartmouth College's Physiologist Henry A. Schroeder in United States. In his paper, ‘Relation Between Mortality from Cardiovascular Disease and Treated water Supplies’, the water in 163 largest cities in the United States was analyzed for 21 constituents and correlated to heart disease. He concluded “some factor either present in hard water, or missing or entering in soft water is associated with higher death rates from degenerative cardiovascular disease.” [17, 6] In fact, when Schroeder began his study, he expected to find that hard water went with hard arteries. He took off from a 1950-51 U.S. Geological Survey study of water supplies for 1315 cities, covering 90% of the urban and 58% of the total population. Dr. Schroeder compared the states' index figures with their mortality and found no relationship with overall death rates. But he found a striking relationship with the death rates from heart-artery diseases. [15] Schroeder, in his subsequent report in 1966, described a similar relationship between water hardness in the same 1950-51 water data and the hypertensive heart disease death rate by state in U.S. whites. [7]

Epidemiologic investigations in Japan, the United States and Great Britain have indicated a higher death rate from cerebrovascular and cardiovascular diseases in areas with soft water than in hard water regions. High sulphate concentration in the river water in Japan has also been positively correlated to death rate in cerebrovascular disease. A study was carried out by Gunnar Bjorck, of Karolinska Institute, Sweden on the relationship between deaths from cardiovascular diseases and various parameters in drinking water in 34 Swedish towns during 1951-60. In this study with more than 25,000 inhabitants, and in addition Visby on the island of Gotland, a similar correlation was found. The results obtained in this study indicated a highly significant negative correlation between the calcium ion concentration and the statistical “other degenerative heart diseases” (Patients not suffering from clear-cut angina pectoris or myocardial infarction, but eventually dying unexpectedly or with heart failure in the absence of valvular heart disease or hypertension). [9] The relationship was stronger for the men than the women. [18, 19]

In Great Britain, the British Regional Heart Study analyzed 253 towns from 1969 to 1973. After adjustment for other factors, they found that soft water areas (around 0.25 mmol/l) had a 10–15% higher cardiovascular mortality than areas of medium hardness (around 1.70 mmol/l). According to them, proper levels of hardness and TDS were two of the beneficial properties in drinking water constituting a healthy

drinking water. They suggest that the ideal amount of hardness was approximately 170 mg/L . [20, 21] In the United States, Greathouse and Osborne studied 4200 adults, ages 25 to 74 in 35 different geographic areas. Their findings, again was less heart disease mortality in hard water areas than in soft water areas. [22, 17]

In 1979 after reviewing fifty studies, Comstock concluded, “there can be little doubt that the associations of water hardness with cardiovascular mortality are not spurious. Too many studies have reported statistically significant correlations to make chance or sampling errors a likely explanation.” He suggests that the reason for this association is due to a ‘deficiency of an essential element or an excess of a toxic one.’ Certainly a combination of both is also possible. [23, 24, 17]

The National Academy of Sciences (NAS) concluded - An optimum conditioning of drinking water could reduce the amount of cardiovascular disease mortality by as much as 15% in the U.S. [25] When looking at the research there is a definite relationship between water hardness and heart disease mortality. They suggested to drink water that has approximately 170 mg/L of hardness; the level found ideal in Great Britain. Second, there is a definite relationship with TDS and heart disease mortality. Higher levels of TDS results in less heart disease. [24] NAS also suggested that proper levels of hardness and TDS are two of the beneficial properties in drinking water constituting a healthy drinking water, like the British Regional Heart Study.

Since the inverse correlation between water hardness and incidence of cardiac fatalities was first reported in 1957, and has since been observed in many regions of the world, it is therefore reasonable to expect that a ‘common factor’ in drinking-water would largely explain this global trend. [26]

### **III. Toxins of soft water vs calcium & magnesium of hard water: controversy resolved**

The mechanism by which hard water may provide protection against cardiovascular disease remains a matter of debate. [27] Medical scientists and doctors naturally wondered what it was in hard water that was protective, or what was it about soft water that was dangerous to hearts. [16] At times acidity of soft water was blamed as it can cause leaching of toxic metals like lead, cadmium etc. Some blamed high sulphate content. Soft water, with a hardness less than about 100 mg/litre, has a greater tendency to cause corrosion of pipes, resulting in the presence of certain heavy metals, such as cadmium, copper, lead, and zinc, in drinking-water. [13] Two principles have constantly been discussed, namely, a toxic effect induced by the contamination of lead or cadmium or a protective effect from the water content of calcium or magnesium. [19] Some researchers believe that very small amounts of a “protective” substance may be present in some water supplies and lacking in others. This unknown substance could have a beneficial effect on the heart in much the same way that minute amounts of fluoride protect the teeth. [26] Out of all two beneficial factors continually stand out - hardness and total dissolved solids. [25,28]

One clue: the more alkaline the water, the greater the protective effect on human arteries. This may be because more acid waters, which build up ‘rust in the pipes’ to plague plumbers, also pick up impurities that create ‘rust’ in the body’s pipes. [15] A report by the Oak Ridge National Laboratory, in 1985 found that the calcium and magnesium in hard water reduces the risks of heart attacks and strokes. They studied the well water of 505 Wisconsin farmers, aged 35 to 80, who died from heart attack or stroke, with well water of 854 living Wisconsin farmers who show no clinical evidence of heart disease and found that those who drank soft water suffered from heart disease, whereas, the farmers who drank hard water were, for the most part, free of the problem.

Calcium, one of the components of hard water, can be protective because it makes water less corrosive and less likely to leach toxic trace minerals, such as cadmium and lead, out of metal pipes. [16] Sebastein Marque in their study found a significant relation between calcium levels and cardiovascular disease, when calcium is higher than 94 mg/ l and found protective effect of magnesium between 4 and 11 mg /l . [17]

### **IV. Public health researches**

Bernardi D, et al, in their study from January 1992 to January 1993 found the incidence of sudden cardiac death among the population of Tuscany, Italy, composed of a population of 35,000, to be twice that of the European average. In the examined geographic area a high prevalence of coronary artery disease was verified through the records of the Public Health Service, and through the hospitalization data compared with the national average. Moreover, research was accomplished on physical and chemical properties of drinking water in the same area, and this revealed a very low total hardness due to the paucity of calcium and magnesium salts. [29] Low levels of Mg and calcium, in soft water were correlated with cardiovascular

diseases (CVD), but especially hypertension in white men, 45 to 64 years of age in the United States (U.S.), by Schroeder in 1960. By 1966, he deemed Mg to be the major protective hard water factor. But where water hardness was caused mostly by Ca, as in England, that was the mineral perceived protective in hard water against ischemic heart disease.[7,30]

H. Karppanen et al in their work, 'Correlations between the hardness of drinking water and death rates from Coronary Heart Disease (CHD) in Finland', where CHD rates were very high, also compared the soil contents of some minerals between the areas with the highest and lowest death rates from CHD in Finland. Their report said that selenium has proved to be cardio-protective in several animal studies and death rates from cardiovascular diseases have been reported to be lower in a very high selenium area than in the low selenium area. The selenium content was low in the Finnish soil and also low in the blood of Finns, suggesting possible role of selenium deficiency. [31] Attention was drawn by Karppanen and Neuvonen, in 1973, also to Mg (in soil and water) as protective in southwestern Finland, where the soil and water Mg is three times as high as it is in eastern Finland, and where there is half the Ischemic Heart Disease(IHD) mortality. [31, 30]

Punsar and Karvonen studied mortality from cardiovascular disease and water quality in two areas of Finland and suggested relation of ischemic heart disease to magnesium and chromium. [32] Since the daily intake of calcium is higher in Finland than in most other countries the high death rate from CHD in this country cannot be attributed to a deficiency of calcium. [31]

Studies, in 1997-1999, from Serbia and Taiwan, compared Mg and Ca in drinking water against several arterial diseases affecting the heart or brain, and found that it was Mg, more than Ca, that was protective. Surveys of 65 Serbian municipalities for mineral contents and Cardiovascular Disease (CVD) death rates, reported in 1998, disclosed that areas with drinking water rich in Mg (52-68 mg/L) and poor in Ca (3.5-12.4 mg/L) have very low mortality from CVD, but municipalities poor in Mg (<20 mg/L), and rich in Ca (>80 mg/L) have high CVD death rates. [30]

In a study by Ford ES, data from the 'National Health and Nutrition Examination Survey Epidemiologic Follow-up Study' were used to examine the association between serum magnesium concentration, measured between 1971-1975, and mortality from IHD or all-causes in a national sample of 25-74-year-old participants followed for about 19 years. Serum magnesium concentrations were inversely associated with mortality from IHD and all-cause mortality. [33]

A 2006 WHO expert meeting reviewed the possible protective effect of hard water against cardiovascular disease, and recommended further studies to examine health outcomes in populations that had experienced a change in the hardness of their drinking water supply. Are people who drink "hard" water containing higher levels of calcium and/or magnesium less likely to suffer cardiovascular disease? This is the question that delegates who attended a World Health Organization (WHO) meeting 21-22 January 2008 in Geneva, Switzerland, are now trying to answer once and for all. The aim of the Geneva meeting of January 2008 was to discuss how such a study—ultimately a composite of many smaller studies from different nations—should be performed. Paul Hunter, is a professor of health protection at the University of East Anglia, United Kingdom, whose group has been testing a possible protocol. [27]

## **V. Magnificent magnesium**

Several researchers have suggested that the magnesium present in hard waters has a cardioprotective influence (Schroeder,1960, Parsons *et al.*, 1961; Marier *et al.*, 1963; Bajusz, 1967; Marier, 1968; Holtmeier, 1969; Anderson, 1972). [26]

Magnesium emerged as the most likely 'candidate element' on the basis of several criteria [26] i.e., it was present in more than 10% of the sampled waters; magnesium is a consistent function of the softness-hardness gradient; magnesium represents a significantly-high proportion of the daily intake from other sources; the known metabolic effects of magnesium are consistent with the hardness-mortality trend.

The potential value of Mg in water was first reported in 1697 by Grew in England, who advised the use of epsom salts (Mg sulfate), not only for its cathartic effects, but for use in calcific uroliths, diabetes, headaches, and several neuromuscular complaints. Except for brief mention of 'cardialgia' - which Grew referred to as 'heartburn and other such pains' (?angina), and its diuretic effects, he made no mention of water-borne Mg in CVD. [30]

Although statistically significant inverse relationship was present between water hardness and mortality from cardiovascular disease for both sexes, mortality caused by ischemic heart disease was inversely related to the magnesium content, particularly for the men. [19]

In a Canadian study, Anderson et al found that in cases dying of accidents, the Mg content of heart muscle was found to be higher in hard than in soft water regions. They analysed 350 tissue samples from 161 autopsy cases and revealed that myocardial magnesium was 6% lower in 'cardiac death' patients from soft-water localities, in comparison with hard-water regions; also, myocardial magnesium in all 'cardiac death' tissues averaged 22 % lower than in the group of non-cardiac fatalities. [26] Anderson found no significant differences between the cities with soft and hard water in the mean myocardial concentrations of calcium, zinc, copper, chromium, lead or cadmium.[10]

Crawford and Crawford (1967) compared cardiac lesions found in a very soft water area (Glasgow) and in a very hard water area (London) in two comparable series of medicolegal necropsies - men who had died from an accident and men who had died suddenly and unexpectedly from ischemic heart-disease. The findings in both these series suggest an increased susceptibility of the myocardium and a 33% lower magnesium content in coronary arteries of sudden-death cardiac cases in soft-water regions. [8,26]

A similar 12 to 15% lower heart-muscle magnesium content in sudden-death cardiac cases has also been reported in Britain (Chipperfield and Chipperfield, 1973; Behr and Burton, 1973). [26] Damaged areas of hearts from people who had died of heart disease had 40 to 50 percent less magnesium than undamaged areas of the same hearts. [16]

Leary et al from South Africa also reported similar significant negative correlation between the incidence of death apparently due to IHD and the magnesium content of drinking water. [11] A study by Ferrandiz et al provides statistical evidence of the relationship between mortality from cardiovascular diseases and hardness of drinking water. This relationship was stronger in cerebrovascular disease than in ischemic heart disease, was more pronounced for women than for men, and is more apparent with magnesium than with calcium concentration levels. [18]

In Finland especially in eastern areas the soil contents of several minerals, including magnesium are very low, the mortality rates from CHD were high.[31] In a study in 1960, when Finland had a high rate of CVD, the Finnish immigrants in North Dakota, an area where Mg content of water was very high, had virtually the same dietary and lifestyle habits, and could be assumed to share the same basic hereditary characteristics as their relatives in Finland, but surprisingly, had less than half the incidence of heart disease and a longer average life expectancy. It was time to take magnesium seriously. [16]

It is now becoming clear that a lower than normal dietary intake of Mg can be a strong risk factor for hypertension, cardiac arrhythmias, ischemic heart disease, atherogenesis and sudden cardiac death. Deficits in serum magnesium appear often to be associated with arrhythmias, coronary vasospasm and high blood pressure. Experimental animal studies suggest interrelationships between atherogenesis, hypertension (both systemic and pulmonary) and ischemic heart disease. [34]

Data coming from epidemiologic, autopsy, clinical, and animal studies suggest that: (1) Sudden death is common in areas where community water supplies are Mg-deficient; (2) Myocardial Mg content is low in people who die of sudden death ; (3) Cardiac arrhythmias and coronary artery vasospasm can be caused by Mg deficiency and (4) Intravenous Mg reduces the risk of arrhythmia and death immediately after acute myocardial infarction. [35]

## **VI. How does magnesium help**

It is becoming clear that Mg exerts multiple cellular and molecular effects on cardiac and vascular smooth muscle cells which explain its protective actions. [34] Magnesium is a vital structural component of all muscle cells, and the heart comprises of mainly muscle. Each molecule of myosin has an atom of magnesium in it. The availability of magnesium within the heart affects the rhythm of the heart both directly and indirectly by controlling potassium and calcium levels. This also affects the conduction system. Blood vessel muscle cells need healthy amounts of magnesium to relax properly after each contraction. They can become stiff and inflexible if their magnesium gets too low. [16] Intracellular mononuclear cell magnesium is a better indicator of the magnesium status of the heart than intracellular red blood cell magnesium. [36]

Magnesium is a necessary catalyst for all sorts of life reactions. Among the enzymes that have been studied intensively, over 300 need magnesium directly and a 1000 indirectly. One especially important reaction that needs magnesium is the one that controls the production of the molecule adenosine triphosphate (ATP). Literally every energy-consuming reaction in life involves ATP and thus needs magnesium to proceed. No wonder low magnesium can affect the heart and its blood vessels. [16]

Evidence in experimental animals strongly suggest a role of magnesium in the aetiology of dyslipidaemia and atherosclerosis. The concentrations of chylomicrons, VLDL (Very Low Density Lipoproteins) and LDL (Low Density Lipoproteins) -bad fat are higher in Mg-deficient rats, but the concentration of HDL(High Density Lipoproteins)- good fat, is less than in controls. Mg deficiency potentiates the effect of stress since catecholamines release is increased in Mg-deficient animals. Stress is a major contributing factor to ill health, particularly cardiovascular diseases and atherosclerosis, and there are possible connections between stress and altered lipoprotein metabolism. [36]

### **VII. Low magnesium and atherogenicity**

Atherosclerosis is a well-known precursor of ischemic heart disease, stroke and sudden cardiac death. Atherosclerosis is no longer considered a disorder due to abnormalities in lipid metabolism. In fact, the inciting event of atherosclerosis is likely an inflammatory insult that occurs decades before the disease becomes clinically apparent. [2]

Dr. Andrzej Mazur and team at Milan University confirmed that magnesium modulates cellular events involved in inflammation. [37,16] They have shown in experimentally induced magnesium deficiency in rats that after only a few days a clinical inflammatory syndrome develops and is characterized by leukocyte and macrophage activation, release of inflammatory cytokines and excessive production of free radicals. Because magnesium acts as a natural calcium antagonist, the molecular basis for inflammatory response is probably the result of modulation of intracellular calcium concentration.

It seems that without the inflammation elevated cholesterol is not a threat after all. When magnesium levels fall researchers note a profound increase of inflammatory cytokines present, along with increased levels of histamine. Inflammation contributes to the pro-atherogenic changes in lipoprotein metabolism, endothelial dysfunction, thrombosis, hypertension and explains the aggravating effect of magnesium deficiency.

As magnesium levels drop off so do the activities of crucial biological magnesium sensitive enzymes, the proteolytic enzymes which counteract the inflammation. Most if not all of these enzymes are mediated by magnesium. The problem is, after around age 25, our production of these enzymes drops off almost completely so there is nothing to tell the body to stop the inflammation. Enzymes also clean the blood of excess fibrin that causes the blood to thicken, which sets us up for clots, which can cause heart attack or stroke.

The atherosclerotic process is characterized, in its earliest stages, by perturbations in endothelial function. One of the earliest sign of magnesium deficiency is degeneration of the sub-endothelium. [2] The arterial damage resulting from Mg deficiency has been extensively reviewed. This includes intimal thickening, thinning and fragmentation of the elastic membrane and calcification. An increase in the Ca content of the cardiovascular system occurs as a general consequence of Mg depletion, as intracellular magnesium deficiency may cause an increase in intracellular Na and Ca and a loss of K. The mechanisms responsible for the pathological consequences of Mg deficiency may be mediated by lipid peroxidation products. [38,39]

Atherosclerotic lesions are composed of three major components. The first is the cellular component comprised predominately of smooth muscle cells and macrophages. The second component is the connective tissue matrix and extracellular lipid. The third component is intracellular lipid that accumulates within macrophages, thereby converting them into foam cells. Atherosclerotic lesions develop as a result of inflammatory stimuli, subsequent release of various cytokines, proliferation of smooth muscle cells, synthesis of connective tissue matrix, and accumulation of macrophages and lipid. [2]

Evidence is accumulating for a role of Mg in the modulation of serum lipids and lipid uptake in macrophages, smooth muscle cells and the arterial wall.[34] Earlier studies indicate that Mg deficiency enhances vascular lipid infiltration in rats, rabbits and monkeys on atherogenic diets. Recent studies confirm

that Mg deficiency can intensify cardiovascular lipid deposition and lesions in animals on atherogenic diets and that dietary Mg supplementations prevents atherosclerosis. [39]

Atherosclerosis is likely initiated when endothelial cells over-express adhesion molecules in response to turbulent flow in the setting of an unfavourable serum lipid profile. Animals fed a pro-atherogenic diet rapidly over express vascular cell adhesion molecule-1 (VCAM-1). Li demonstrated that expression of VCAM-1 on endothelial surfaces was an early, and necessary, step in the pathogenesis of atherosclerosis. Increased cellular adhesion and associated endothelial dysfunction then 'sets the stage' for the recruitment of inflammatory cells, release of cytokines and recruitment of lipid into the atherosclerotic plaque. [2,40]

Jeanette A.M Maier et al report the up-regulation of Vascular Cell Adhesion Molecule-1 (VCAM-1) after Mg deficiency. VCAM-1 is responsible, at least in part, of the increased adhesion of monocytoid U937 cells to the endothelial cells grown in low magnesium. In addition, endothelial migratory response is severely impaired. They found that low Mg concentrations reversibly inhibit endothelial proliferation, and this event correlates with a marked down-regulation of the levels of CDC25B (M-phase inducer phosphatase). The inhibition of endothelial proliferation is due to an up-regulation of interleukin-1 (IL-1). In conclusion, their results demonstrate a direct role of low magnesium in promoting endothelial dysfunction by generating a pro-inflammatory, pro-thrombotic and pro-atherogenic environment that could play a role in the pathogenesis cardiovascular disease. [41]

Ferre S et al in their recent study published in 2010\_report that endothelial cells cultured in low magnesium rapidly activate NFkB (nuclear factor kappa-light-chain-enhancer of activated B cells), an event which is prevented by exposure to the anti-oxidant trolox. It is well known that NFkB activation correlates with marked alterations of the cytokine network. This study, shows that exposure of endothelial cells to low magnesium increases the secretion of RANTES, interleukin 8 and platelet derived growth factor BB, all important players in atherogenesis. [42]

A study showed that adults who consume less than the recommended amount of magnesium are 1.48 to 1.75 times more likely to have elevated C-reactive protein. This finding offers yet another reason why those who are magnesium deficient have increased rates of cardiovascular disease. [43]

Burton M. Altura et al in their experiments also showed that VSMCs (Vascular smooth muscle cells) exposed to low Mg resulted in the de novo synthesis of ceramide; the lower the Mg, the greater the synthesis of ceramide. [44] Ceramides are one of the component lipids of sphingomyelin, one of the major lipids in the lipid bilayer of cells, hence are found in high concentrations within the cell membranes. For years, it was assumed that ceramides and other sphingolipids found in the bilayer cell membrane were purely structural elements. Now it is known that ceramide can actually act as a signalling molecule. The most well-known functions of ceramides as cellular signals include regulating the differentiation, proliferation, programmed cell death (PCD), and apoptosis (Type I PCD) of cells. In a related study Burton M Altura et al tested the hypothesis that a short-term dietary deficiency of magnesium (21 days) in rats would result in the upregulation of the two major subunits of serine palmitoyl-CoA-transferase, SPT 1 (serine palmitoyl transferase) and SPT 2 - the rate-limiting enzymes responsible for the de novo biosynthesis of ceramides, in left ventricular, right ventricular, and atrial heart muscle and abdominal aortic smooth muscle, as well as induce a reduction in serum sphingomyelin concomitant with the release of mitochondrial cytochrome c (Cyto c) in these tissues. The data suggest that Mg deficiency, most likely, causes a biosynthesis of ceramides via two pathways in cardiovascular tissues, viz., via the activation of serine palmitoyl-CoA-transferase and sphingomyelinase, which lead to apoptotic events via intrinsic and extrinsic pathways. Even Low levels of drinking water Mg were cardio- and vasculoprotective. [45]

Several studies have indicated an inverse relationship between omega-3 fatty acids - such as EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) and the risk of cardiovascular disease and cardiac death. People with magnesium deficiency cannot properly metabolize these important fatty acids, EPA and DHA which are vital to heart health.

A study by Shivkumar et al demonstrated for the first time that magnesium deficiency significantly ( $P < 0.001$ ) increases levels of thiobarbituric acid - reactive substances in the aorta of rats, significant reduction (54%,  $P < 0.001$ ) in the activity of superoxide dismutase and catalase (37%,  $P < 0.01$ ) and a 19% increase in net fractional rates of collagen synthesis ( $P < 0.05$ ) suggesting that magnesium deficiency may

trigger a wound healing response, involving oxidative injury and growth stimulation, in the vascular system. [46]

The noxiousness of corrosive waters is mainly due to two toxic metals lead and cadmium which have cumulative toxicity on particularly the nephro-cardiovascular system. Magnesium appears as a competitive inhibitor of both polluting metals on different sites and particularly during combined intoxication. [47]

### **VIII. Magnesium deficiency**

Many patients may have normal serum magnesium levels but be intracellularly depleted. [48] The modern processed foods is high in fat, especially saturated fat; high in cholesterol; and high in sugar and salt, among other things. But not emphasized and not many of us know is that such a diet is low in magnesium. [49] Magnesium is present in ionized form in water and may have better bioavailability than solid foods. [17]

According to Frantisek Kozisek, head of the National Reference Centre for Drinking Water in Prague, Czech Republic- "Cooking food in soft water also tends to remove magnesium, calcium, and other essential elements from food, making matters worse." Kozisek has already proposed that levels of calcium and magnesium in drinking water be set at 40–80 mg/L and 20–30 mg/L, respectively. [27]

The effects of a low intake of magnesium can be worsened by the high levels of fat, sugar, sodium, and phosphate in our diets as well as, ironically, by the use of calcium supplements, which has become widespread because of our awareness of calcium's value for bone health. [16] Another reason that many people are magnesium deficient is that they drink bottled water or softened water. In the old days everyone drank well water or water from streams, both of which contain large amounts of magnesium. Magnesium is removed when water is softened and it is not in large amounts in most of the bottled waters that are available. In developed countries risk of magnesium deficiency is compounded by the use of diuretics and calcium supplementation for osteoporosis which alters Ca /Mg ratio and causes relative Mg deficiency. [50]

After National Academy of Sciences (NAS) report indicated nearly 80% of Americans were deficient in magnesium, a small group of mineral water bottlers pressured the Food & Drug Administration to establish a minimum standard for magnesium levels in drinking water, a move that scientists confirm would save hundreds of thousands of lives annually and reduce health care costs by billions of dollars. [51]

Our diets and lifestyles are much different from our ancestors. Living in a modern industrialized country the food is processed (depletes mineral content by 80%); drinking water is softened (bottled water is usually very mineral deficient); beverages are made from de-ionized water (often phosphated); and the soils our fruits and vegetables come from are lower in magnesium than 75 years ago. [36] Green vegetables such as spinach are good sources of magnesium because the centre of the chlorophyll molecule contains magnesium. Some legumes (beans and peas), nuts, seeds, and whole, unrefined grains are also good sources of magnesium. Refined grains are generally low in magnesium. [43]

### **IX. Role of magnesium supplementation**

Mg has long been used for parenteral treatment of convulsions and hypertension of eclampsia. There are case reports of relief from angina for prolonged periods following Magnesium supplementation.[52] There are case reports of immediate relief from myocardial infarction and congestive cardiac failures (CCF). [53,52] In fact, a majority of patients referred for the treatment of CHF have ambient ventricular arrhythmias, which are frequently linked to hypomagnesemia. Magnesium administration can reduce the amount of digitalis required in these patients and, thus, decrease the risk of its toxicity. [53]

Dietary magnesium supplementation will not reduce cholesterol. It will however, help maintain the elasticity of arteries and has been reported to raise the amount of HDL. This in turn reduces LDL/HDL ratio and reduces the risk of heart attack. In addition, magnesium prevents the deposition of calcium along the arterial wall at points of micro-injury. Thus magnesium may play a crucial role in the prevention of both atherosclerosis and arteriosclerosis. [54]

A pilot phase 6 month open trial of oral magnesium supplementation in nine ischemic heart disease patients with low erythrocyte magnesium levels led to significant increases of erythrocyte magnesium in these patients, and to an impressive decrease of anginal attacks and nitrate consumption, as well as to a lesser



degree of ST segment depression on surface ECG (electrocardiogram) obtained at exercise testing in seven patients. [55]

Myocardial infarction is the typical example of a painful illness where stress induces magnesium depletion. In double blind *vs* placebo studies on oral magnesium supplementation for angina pectoris, beneficial effects were shown: either through a lesser requirement or nitroglycerin or in a group of patients with ischemic heart disease through control of the deleterious concomitant dyslipidaemia. [47]

A Core Study revealed a consistent adverse effect of high body mass index and excess salt intake on BP (blood pressure) and a beneficial effect of magnesium on blood pressure. [56]

B T Altura et al in their study, have examined the effects of variation in dietary Mg on the atherogenic process. Oral supplementation of rabbits fed a high cholesterol diet (1% or 2%) with the Mg salt magnesium aspartate hydrochloride (Magnesiocard) (i) lowers the level of serum cholesterol and triglycerides in normal (25-35%) as well as atherosclerotic (20-40%) animals and (ii) attenuates the atherosclerotic process markedly. In addition, they found that dietary deficiency of Mg augments atherogenesis markedly and stimulates (or activates) macrophages of the reticuloendothelial system. Evidence is presented to indicate that the hypercholesterolemic state may cause the loss of Mg from soft tissues to the serum, thereby masking an underlying Mg deficiency. [57]

Stroke patients in Los Angeles County are participating in a study to determine whether magnesium can protect the brain from damage. Los Angeles County paramedics will administer intravenous magnesium sulfate to patients being transported to the hospital.

Marx and Neutra evaluated the published data and suggested the potential value of increasing magnesium intake and that addition of magnesium to water might be an intervention to lower IHD and may save many lives annually and reduce hospital cost. [58,30] How much better it would be to prevent much of the damage from heart disease by treating the magnesium deficiency that underlies all of its symptoms, giving the body the simple nutrient it needs for healthy hearts and blood vessels. [16]

There are literally hundreds of physiological reasons to proclaim magnesium the ultimate heart medicine; its involvement in hundreds of enzyme reactions is just a start. Its use as an anti inflammatory makes magnesium absolutely indispensable to not only heart patients but also to diabetics, neurological and cancer patients as well

## **X. Conclusion**

It has been proved beyond doubt that there is a definite and consistent correlation between Magnesium and cardiovascular health. The modern processed food, softened drinking water and over reliance on ready to eat food thus avoiding fruits & green leafy vegetables is an important cause of Mg deficiency. The deficiency of Mg has been reported to cause increase in inflammatory cytokines, endothelial damage and dyslipidaemia; all of which are the centre stage for the development of atherosclerosis, the thickening & hardening of arterial walls.

Therefore, there is need to educate medical & public health communities as well as the general public about the benefits of magnesium and to know the composition of foods, water and beverages that they consume. Magnesium, which seems to be the wonder ion can be used for supplementation & fortification. Bottled water and beverages can be fortified to provide supplemental mineral as required. In addition, the morbidities and mortalities due to Ischemic Heart Diseases and other cardiac problems caused by deficiency of Magnesium can be averted by appropriate and timely therapies involving adequate magnesium intake by persons at risk. This can prove to be an efficient, effective, replicable and cost effective model for preventing many diseases particularly cardiovascular diseases through public health interventions.

Based on the comprehensive review of the varied literature including individual & institutional researches and scientific comparative studies, it is clear in no uncertain terms that the magnesium plays crucial, important and decisive role for cardioprotective action of the hard water.

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**Table 1: Important Studies related to Magnesium, Hard Water and Coronary Heart Diseases.**

S.	Year of Study	Study Conducted By	Country	Report
1	1697	Grew	England	Advised the use of Epsom Salt (Magnesium Sulphate). [60]
2	1951-60	Bjorck	Karoliska Institute, Sweden	Highly significant correlation between calcium ion and heart disease. [9]
3	1957	Kobayashi	Japan	Relation of Cerebrovascular Accidents and Sulphate : Bicarbonate Ratio [5]

4	1960	Schroeder	USA	The inverse correlation of death rates from certain cardiovascular diseases and water hardness was present and were significant for hypertensive heart disease and for arteriosclerotic heart disease in both sexes. [6]
5	1966	Schroeder	USA	No trace element of 19 measured was found highly correlated with hypertensive and arteriosclerotic heart disease [7]
6	1967	Crawford & Crawford	UK	Lower Magnesium Contents of Coronary Arteries of Sudden Cardiac Death Cases. [8]
7	1969-73	British Regional Heart Study	Great Britain	10 to 15 % more cardiovascular deaths in soft water areas. [21]
8	1971-75	Ford ES	USA	Inverse relation of Serum Magnesium and IHD and all cause Mortality. [33]
9	1973	H Karppanen et al	Finland	Correlation of drinking water hardness, magnesium and low selenium with CHD. [31]
10	1973	Chipperfield & Chipperfield	-	Lower Cardiac Muscle Magnesium content in Sudden Death Patients. [26]
11	1973, 75	Anderson et al	Canada	Low myocardial Magnesium in Cardiac Death patients from soft water areas. [10]
12	1979	Punsar & Karvonen	Finland	Relation of IHD to Magnesium and Chromium. [32]
13	1980	Greathouse & Osborne	USA	Less heart disease in hard water areas. [22]
14	-	Oak Ridge National Lab.	USA	More heart disease in farmers drinking soft water. [61]
15	1983	Leary et al	South Africa	Negative correlation of Magnesium content of drinking water and IHD. [11]
16	1989	Sherman Bloom	Mississippi, USA	Magnesium depletion causes increased intracellular Na <sup>+</sup> and Ca <sup>++</sup> and loss of K <sup>+</sup> [38]
17	1990-96	Sebastien Marque	France	Significant relation between calcium and cardiovascular disease. [17]
18	1991	B.M. Altura, B.T. Altura	USA	Deficiency of magnesium is related with arrhythmia, coronary vasospasm and high blood pressure. [34]
19	1992-93	Bernardi D et al	Tuscany, Italy	IHD and low hardness of drinking water. [29]
20	2003	Frantisek Kozisek	Serbia & Taiwan	Magnesium is more protective than calcium for CVD. [63]
21	2004	Ferrandiz J et al	Spain	Stronger correlation of cerebrovascular disease than IHD with hard water, more prominent in women than men, more apparent with Magnesium than Calcium [18]
22	2005	Mark A Crowther	Canada	Atherosclerosis is initiated by inflammation [2]
23	2010	Burton M Altura et al	New York, USA	Magnesium deficiency increases Ceramide synthesis [59]
24	2010	Burton M Altura et al	New York, USA	Magnesium deficiency upregulates serine palmitoyl transferase [44]
25	2011	Slavica Stevanovic et al	Serbia	High death rate from CVD in areas poor in Magnesium although rich in Calcium. [62]

**Table 2 : Water hardness and ranges of mineral concentrations.**

<b>S.No.</b>	<b>Water Quality</b>	<b>Range of Mineral Concentration</b>
1	Soft	0 to 60 mg / litre
2	Moderately hard	61 to 120 mg / litre
3	Hard	121 to 180 mg / litre
4	Very hard	> 181 mg /litre