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METAL IONS IN BIOLOGICAL SYSTEMS

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Compendium on Magnesium and Its Role in Biology, Nutrition, and Physiology

MARCEL DEKKER, INC. New York and Basel

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Dietary Magnesium and Drinking Water: Effects on Human Health Status

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1. INTRODUCTION

The increased interest in human magnesium nutrition is a relatively recent phenomenon. The next section will examine the factors contributing to this aroused interest.

2. DIETARY Mg INTAKE

2.1. Trends During 1909—1965

Flink [1] reviewed developments in the metabolic magnesium field during recent decades and commented: "Until the mid 1960s, textbooks of medicine and of biochemistry devoted a few lines or a paragraph to a disclaimer of [any] clinical importance of magnesium". One of the factors that helped to focus more attention on magnesium was the appearance of the 1964 monograph by Seelig [2] whose emphasis was on the inadequate dietary magnesium intake in the Western world. Figure 1 illustrates how the per capita magnesium intake in the United States decreased steadily during the period 1909—1965, i.e., from 410 to 340 mg/day. This decrease has been primarily attributed to a 50% drop in the consumption of grain products during this period [3]. Table 1 shows that of all the traditional staples in the North American diet, whole-grain cereals are the most abundant source of magnesium.

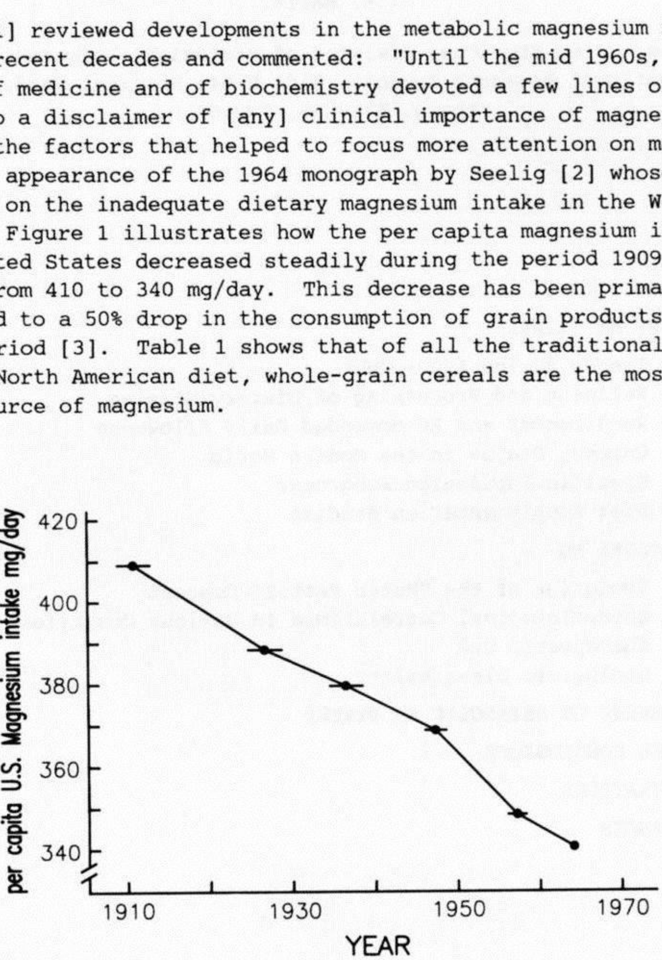

FIG. 1. Decrease in the per capita intake of magnesium in the United States during the period 1909—1965. (Compiled from the data of Ref. 3.)

TABLE 1

Magnesium Content of Common Foods (mg/kg)

Food item	Mg
Cocoa, chocolate, soybeans	1500–4500
Nuts	1300–4100
Whole grains	1000–2000
Dark green leafy vegetables, apricots, dates, clams, crab, shrimp	500–1000
Fish, oysters, green vegetables, bananas, raisins, corn, potatoes, cheese	250–500
Meats	160–250
Eggs, milk, cream	120–140
Salad vegetables	<150
Fruit	<110

Source: Summarized from Ref. 2. Additional data is available in Ref. 4.

2.2. Refining and Processing of Dietary Staples

Another factor that contributes to a lowered dietary intake of magnesium is the refining and/or processing of foods. Table 2 shows that the preponderance (>80%) of the magnesium is removed during the extraction of white sugar, flour, starch, and during the polishing of rice. Similarly, Table 3 illustrates that from 17 to 61% of the magnesium can be lost during the culinary preparation of a food item.

2.3. Requirement and Recommended Daily Allowance

The topic of Recommended Daily Dietary Allowance (RDA) has recently been reviewed [9]. The recommendations are based on long-term "balance studies" [1,10] which involve a measurement (or calculation) of

TABLE 2

Loss of Magnesium During Refining/Processing of Foods

Ref.	Food item	Magnesium (mg/kg dry weight)	% Magnesium lost
[5]	Molasses	250	0
	White sugar	2	99.2
[6]	Molasses	170	0
	White sugar	2	98.8
[7]	Wheat	1670	0
	Flour	210	87.4
[5]	Wheat	1502	0
	Flour	299	80.1
[5]	Corn	644	0
	Starch	22	96.6
[5]	Unpolished rice	1477	0
	Polished rice	251	83.0

TABLE 3

Effect of Food Preparation on Magnesium Loss

Food item	Magnesium (mg/kg)	% Magnesium lost
Potatoes: baked in skin	290	0
boiled	240	17
Peas: fresh	330	0
boiled	210	36
Carrots: raw	120	0
cooked	70	36
Cabbage: raw	170	0
boiled	70	59
Brussels sprouts: raw	280	0
boiled	110	61

Source: Calculated from data in Ref. 8.

the daily dietary intake along with subtraction of daily excretory losses via urine and feces; thus, the resultant provides the "balance", which can be positive or negative.

In a comprehensive 1964 evaluation of replicate long-term balance studies in 74 men and 71 women, Seelig [2] had recommended a daily magnesium intake of 6 mg/kg. Figure 2 presents the data obtained in two more recent balance studies [11,12] involving a total of 63 adults, i.e., 43% of the total number surveyed in Seelig's prior assessment. Because the average body weight of U.S. adults has been estimated to be 70 kg for men and 55 kg for women [9], Seelig's recommended 6 mg/kg is equivalent to a magnesium requirement of 420 mg/day for men and 330 mg/day for women. In terms of Fig. 2, the Seelig recommendation would mean that only one man and one woman would be in negative magnesium balance, i.e., 3% of the 63 persons.

In the United States, the current RDA for magnesium is 350 mg/day for men and 300 mg/day for women (see Table 4). According to Fig. 2, this would mean that two men and four women would be in negative balance, i.e., 9.5% of the 63 subjects.

In Canada the current RDA is 240 mg/day for men and 190 mg/day for women [13]. Figure 2 reveals that this would mean eight men and

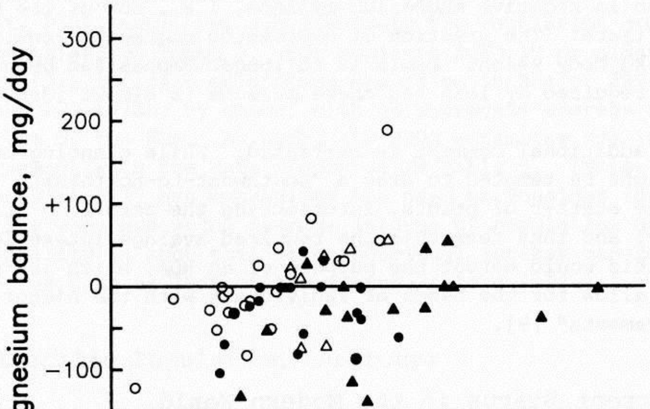

FIG. 2. Magnesium balance studies in individuals. Jones et al. [11]: Δ = men; O = women. Lakshmanan et al. [12]: ▲ = men; ● = women.

TABLE 4

Recommended Daily Dietary Allowances (RDA) in the United States

Subjects	Age, etc.	Magnesium (mg/day)
Males	19 or older	350
	15–18	400
	11–14	350
Females	11 or older	300
	pregnant or lactating	450
Children	7–10	250
	4–6	200
	1–3	150
Infants	0.5–1.0	70
	0–0.5	50

Source: Compiled from data in Ref. 9.

eight women in negative magnesium balance, i.e., 25% of the 63 individuals. (*Note*: The practice of expressing magnesium requirements on a "per kg body weight" basis is no longer emphasized because the magnesium required by lean and obese persons is almost identical [11,14].)

One additional comment is warranted: While glancing at Fig. 2, some might be tempted to draw a "southwest-to-northeast" line through the scatter of points, intersecting the zero line at about 250 mg/day, and thus term this the required average intake for adults. However, this would defeat the purpose of an RDA, which is "set high enough to allow for the needs of individuals with the highest nutrient requirements" [9].

2.4. Current Status in the Modern World

Table 5 summarizes the results obtained in surveys of magnesium intakes by average citizens consuming self-selected normal diets during 1970–1987 in various regions of the modern world. In the tabulation, the U.S. RDA is used as a common reference point for all the studies. The highest magnesium intakes (over 400 mg/day) were in the Irish Republic, and were attributed to a proportionately large intake of whole grain cereals and breads that was *double* the amount consumed in Boston in 1970 [15]. Therefore, the 1970 Irish diet resembles the 1909 U.S. diet which supplied a per capita magnesium intake of 410 mg/day (see Fig. 1 and Sec. 2.1 of this chapter).

Table 5 also shows that the magnesium intake is 67–77% of the U.S. RDA in West Germany, England, and in some regions of North America. But elsewhere, the magnesium intake is often less than two-thirds of the RDA. And even in those regions where the magnesium intake is somewhat in excess of 300 mg/day, the subjects tend to be in negative balance (see notes to Table 5). The lowest magnesium intakes of barely 50% of the RDA are in Newfoundland and Japan, and both regions have a very high prevalence of hypertension and cerebrovascular mortality [18,28]. In a recent survey of 61 dietary variables in 615 men from the Honolulu region, dietary magnesium emerged with the strongest correlation (inverse) with blood pressure [29].

Overall, the data of Table 5 indicate that the magnesium intake in the modern world ranges all the way from borderline adequacy down to about 50% of the recommended intake.

Table 6 summarizes a large-scale 1977–1978 study conducted by the U.S. Department of Agriculture (USDA) in which more than 37,000 individuals in the 48 conterminous states were surveyed by means of a 3-day "dietary recall" questionnaire. It can be seen that only 25% of the individuals had a magnesium intake equaling or exceeding the RDA, whereas 39% had an intake of less than 70% of the RDA. The group with the lowest magnesium intake consisted mostly of teenagers and adults [30], and these are precisely the population groups already emphasized in Table 5. For subjects aged 19 or older, the USDA data [31] indicate an average magnesium intake of 299 mg/day by men and 220 mg/day by women, with an aggregate average adult intake of 78% of the RDA. As such, the USDA estimates are in reasonable agreement with the data presented in Table 5. (*Note*: A recent recommendation [27] has emphasized the need to consider individual variability when assessing average intakes of population groups. The variability is such that some individual intakes can be as low as 41% or as high as 184% of the average intake [12].)

2.5. Specific Population Subgroups

Adult diets in hospitals or in long-term care institutions can provide as little as 169 or 220 mg of magnesium per day [14,32,33]. Recent studies have shown that 20% of such patients can have a low serum magnesium status [34–36] and that clinical symptoms of magnesium depletion are greatest in ill patients [33,36] and are most prevalent among the acutely ill [37]. It has also been reported that patients can develop hypomagnesemia during their hospital stay [37] and that 50% of patients can have intracellular magnesium deficiency [38]. The symptoms include neuromuscular, cardiovascular, and psychiatric manifestations [34,36]. For more details about the

TABLE 5

Surveys of Magnesium Intake from Self-Selected Diets in the Modern World

Year and ref.	Locality	Subjects	Age	Magnesium (mg/day) Av. Mg intake	Magnesium (mg/day) U.S. RDA	Intake as % of RDA
1970 [15]	Eire (rural)	152 men	20–>60	472	350	135
	Eire (city)	887 men	20–>60	415	350	119
	Boston	955 men	20–>60	262	350	75
1972 [16]	West Germany	1852 men	—	235	350	67
1973 [17]	England	Adults	—	250	325	77
1978 [18]	Newfoundland	83 men	—	189	350	53
		105 women	—	143	300	48
1978 [19]	Montreal	15 men	Students	247	350	71
		15 women	Students	224	300	75
1979 [20]	Indiana	76 girls	12–14	231	300	77
		25 girls	12–14	<200	300	<67

1980 [21]	France	5 surveys	Adults	260–325	325	80–100
1980 [22]	Kentucky	148 adults	60–89	<217	325	<67
1981 [23]	Seattle	40 women	19–35	<200	300	<67
1981 [24]	Fairbanks	28 women	Students	<200	300	<67
1984 [12]	Maryland	16 men	20–53	323	350	92[a]
		18 women	20–53	234	300	78
1986 [25]	Japan	20 men	—	186	350	53
1987 [26]	Maryland	Blacks				
		20 men	21–65	214	350	61
		20 women	21–65	186	300	62
1987 [27]	Australia	195 men	65–75	346	350	99[b]
		136 women	65–75	318	300	106[b]

[a]Despite the relatively high magnesium intake, the subjects were in negative balance.
[b]Approximately 40% of the subjects were in negative magnesium balance in relation to the Australian RDA, which is set at 90% of the U.S. RDA [27].

TABLE 6

Pattern of Dietary Magnesium Intake in the 1977–1978 USDA Survey

Mg intake as % of RDA	% of surveyed population (n = 37,785)
100 or >	25
70–99	36
<70	39

Source: Data taken from Ref. 30.

clinical symptomatology of magnesium depletion, readers are advised to consult comprehensive sources [8,39,40].

A similar situation exists in cases of pregnancy and/or lactation, where the magnesium intake can be as low as 142 or 205 mg/day [41-43]. The symptomatology is as was described in the preceding paragraph. The pregnancy (and pediatric) aspects of a low magnesium status have been reviewed [8,41].

At this juncture, it is relevant to point out that increased urinary loss of magnesium can be caused by digitalis [44-46], or by long-term use of various diuretics [46-48], or by chronic intake of alcohol [49]. When any of the foregoing factors are combined with a low dietary magnesium intake, the adverse metabolic consequences are exacerbated.

Persons involved in strenuous athletics can have a suboptimal magnesium intake. In the United States, female ball players [50] and gymnasts [50,51] had a magnesium intake of only about two-thirds or less of the RDA. Among female distance runners, the magnesium intake was 92% of the RDA for those who menstruated regularly but was only 55% of the RDA for those who were amenorrheic [52]. Among males, the proportion of soccer players [53] and college wrestlers [54] with a low magnesium intake (<70% RDA) was 50 and 64%, respectively, at midseason. In Italy, it was reported that 54% of the athletes lack magnesium and that the cause was a lack of magnesium in sports diets [55]. Similarly, in France it had been concluded that sports diets lack magnesium, and it was also emphasized that football players require a magnesium intake of 8 mg/kg/day [56]. Prolonged exertion such as that involved in a marathon hike or run can cause a drop of 0.15–0.20 mM/liter in the serum magnesium concentration [57-59]. Therefore, if the serum magnesium level is initially at the lower end of the "normal" range (i.e., 0.75 mM/liter), prolonged exertion can render the participants hypomagnesemic [58,60]. Such cases have been reported in Italy [55], South Africa [60], and the United States [61], where the symptoms of spontaneous cramps and carpopedal spasms, etc., were abolished after magnesium supplementation. The consensus of reviewers in Italy [55], France [56], Canada [62], and the United States [63] is that a suboptimal magnesium status has a negative effect on athletic performance.

Vegetarian diets can provide an abundant supply of magnesium. In Sweden, vegetarian diets provided a magnesium intake of 615 mg/day for men and 468 mg/day for women [64]. Similar results were obtained in a U.S. study showing that vegetarian diets provide a magnesium intake of 480–570 mg/day whereas lactovegetarian diets provide somewhat less, i.e., 366–560 mg/day [65]. Concern has been expressed about the possible limited bioavailability of nutrients from fiber-rich diets [65]. Recent studies of humans [66] and animals [21,67] ingesting diets supplemented with wheat bran have shown that its high magnesium content (i.e., 4400 mg/kg) compensates for any reduced absorptivity. There is, however, evidence that the magnesium content of roasted peanuts is poorly absorbed by humans [68].

2.6. Diet Supplementation Studies

In Section 2.4 there was mention of a recent Honolulu study in which dietary magnesium provided the strongest correlation (inverse) with blood pressure [29]. Also mentioned was the low magnesium intake in Japan and Newfoundland, both of which are regions with a high prevalence of hypertension. The same situation exists in Finland where a magnesium-supplemented table salt has been formulated which provides 10 mg of magnesium per gram of salt. The at-home use of this salt was assessed in 85 hypertensive adults during a 6-month period, and the result was a blood pressure decrease averaging 7/2 mm Hg [69]. In Hungary, supplementation of cafeteria meals, providing an extra 160 mg/day of magnesium to each of 74 workers during a 6-week period, resulted in a blood pressure decrease averaging 15/10 mm Hg [70]. A corollary study involved a 160 mg/day magnesium supplement to 190 young adult students during a 7-month period, and this resulted in improved scholastic achievement and enhanced ability to cope with examination stress, etc. [70]. The fact that oral magnesium supplementation of magnesium-deficient persons can improve brain performance, concentration, and stress tolerance has been reported in other studies [34].

The foregoing examples are indicative of an inadequate metabolic magnesium status in the modern world and also illustrate some of the beneficial effects of oral magnesium supplementation. The following segment on the waterborne magnesium aspect will provide additional insights.

3. WATERBORNE Mg

3.1. Evolution of the "Water Factor" Concept

The story began in Japan some 30 years ago, where cerebrovascular mortality was found to be directly related to low-carbonate, acidification-prone waters whose high SO_4/CO_3 ratios were attributable to Japan's geology [71]. Such corrosive waters can be expected to solubilize toxic trace metals from geological strata [72] and also from plumbing conduits [73,74]. The implicated Japanese waters were soft waters whose total hardness averaged 42 ppm $CaCO_3$ [75]. Here, it must be noted that a total hardness of 100 ppm $CaCO_3$ denotes a water containing 1×10^{-3} M of Ca + Mg, and this concentration is intermediate between "hard" and "soft" designations [18].

However, a comprehensive 1960 U.S. survey found that the SO_4/CO_3 factor did not apply to the overall pattern in the United States, but *did* find an inverse correlation between state averages for waterborne total hardness and metropolitan "all-causes" mortality, which was largely attributable to an effect on cardiovascular diseases [76]. Thus, the stage was set for 15 years of controversy revolving around two schools of thought: either soft waters induced a harmful effect or, conversely, hard waters conferred a protective effect.

3.2. Epidemiological Correlations in Various Countries

In 1961, British researchers confirmed the inverse correlation between cardiac-related mortality and waterborne total hardness, and also obtained comparably similar correlation coefficients for waterborne calcium and carbonate but not sulfate, although the SO_4/CO_3 aspect was not explored; and because British waters tend to be devoid of magnesium, no significant correlation was obtained relating to waterborne magnesium [77]. It has since been pointed out that the epidemiological data in Britain can best be explained on the basis of toxic trace element contamination in corrosive soft waters of low carbonate content [78]. As such, the British situation resembles Japan as well as the one encountered in the Monongalia region of West Virginia, where coal-mining activity abounds along with waters having a high SO_4/CO_3 ratio [79,80]. In this regard, it is relevant to mention that many British soft waters occur in acidic peaty areas [78] and that toxic plumbosolvency has been discussed as a chronic problem in Britain [73].

By the mid-1970s, more than 50 studies had been done on the "water factor" in various regions of the world. But, as can be gleaned in the compilations of two reviews [81,82], only two-thirds of the surveys had demonstrated a meaningful association between human health and drinking water composition [18]. One of the reasons for the inconsistent observations was the sole reliance on the total hardness designation as the only index of water composition. However, it has been shown that waters of almost identical total hardness can differ enormously in their respective proportions of calcium and magnesium [18]; in fact, magnesium can account for as little as 10% and as much as 89% of the total hardness designation [83]. The U.S. National Academy of Sciences has recommended that the emphasis should be on the individual chemical constituents of water instead of sole reliance on hardness measurements [84].

Meanwhile, the epidemiological pattern in the United States had provided information about the importance of waterborne magnesium, i.e.,

- The high-mortality regions had almost no magnesium in the drinking water, whereas the water in the low-mortality localities tended to contain more than 10 mg/liter [85].
- The water in the 25 cities with the lowest death rates for coronary disease contained 70% more magnesium and 30% less calcium [86] than the national average [76].
- In the low-mortality localities, the correlation coefficient for waterborne calcium was only 60% of that for magnesium [86].
- It was shown that the water factor is correlated with dietary magnesium [87].
- Hard waters can contribute as much as 27% of the dietary intake of magnesium [88].

It was in 1975 that a coast-to-coast Canadian survey of more than 500 drinking waters found that magnesium provided the strongest correlation (i.e., inverse) with mortality [89]; the correlation for calcium was only 65% as strong, and was much weaker for the other elements (antimony, cadmium, chromium, cobalt, copper, lead, lithium, mercury, molybdenum, nickel, silver, zinc). Another 1975 report involved analysis of seven elements (calcium, magnesium, cadmium, chromium, copper, lead, zinc) in nonnecrosed myocardial tissue from 161 autopsy cases in Ontario; moreover, the samples were classified as to whether the subjects had resided in a soft- or a hard-water locality, and whether they had died from cardiac ischemia or noncardiac causes [90]. Only magnesium provided a significant correlation with the softness-hardness gradient (2 vs 29 mg/liter of magnesium), i.e., the myocardium of soft-water residents contained 6% less magnesium than found in subjects from hard-water localities, irrespective of whether they had died from heart attacks or from noncardiac causes. When it is realized that ischemic heart fatalities have been associated with a 12—24% decrease in the magnesium content of nonnecrosed myocardial tissue [83,91], it can be appreciated that a 6% debit in the myocardium of soft-water residents is a hefty proportion of the magnesium loss associated with sudden death [83]. It was subsequently shown that the soft-water Ontario regions can experience 30% more sudden death ischemic heart fatalities than seen in the hard-water localities [92].

Confirmation has come from a study of South African whites living in 12 communities whose waterborne magnesium ranges from 1 to 45 mg/liter, and where the death rate from Ischemic Heart Disease (IHD) was found to be inversely proportional to waterborne magnesium [93,94]. Also, a report comparing two towns in Polish Silesia has demonstrated how a higher waterborne magnesium concentration is associated with a lower male mortality rate from myocardial infarction and/or cardiovascular diseases [95]. Meanwhile, a study of the water factor in 24 Texas communities had found that waterborne magnesium and/or urinary magnesium provided an inverse correlation with both hypertension and hypertensive heart disease, whereas the waterborne or urinary sodium/magnesium *ratio* was directly correlated with the same diseases [28,96]; accordingly, the authors concluded that "the most mortality protection would seem to be ingestion of magnesium" [96]. Similarly, a study in the Soviet Union compared residents of four communities whose waterborne magnesium ranged from 2 to 26 mg/liter and was inversely correlated with blood pressure; also, there was a greater prevalence of electrocardiogram (ECG) abnormalities at 11 mg/liter than at 26 mg/liter, along with an increased frequency of cardiac arrhythmias at 5 and 2 mg/liter [94,97]. Thus, as previously suggested [94], it seems that the waterborne magnesium factor is a global phenomenon.

The lowest mortality rate in the United States has been said to be in western Texas [96], although a similar claim could be made for Nebraska [8,85]. In Canada the lowest mortality rates are in the prairie provinces [74]. All of these regions abound in high waterborne magnesium concentrations and are part of a geological-hydrological zone extending from the Mexican border northward through western Texas and Nebraska, and onward into the Canadian prairie region [98].

3.3. Therapeutic Use

Magnesium-rich mineral waters have recently been used for therapeutic purposes. Thus, a magnesium dosage of 90 mg/day for 15 days was effective in abating neuromuscular hyperexcitability [99]. Also, a magnesium dosage alternating from 67 to 134 mg/day for 3 months improved the condition of asthmatics [100,101]. Such dosages are close to the 160 mg/day dietary supplements already discussed in Sec. 2.6 and are similar to the dietary shortfall of many of the population groups listed in Table 5.

3.4. Biological Plausibility

The cardioprotective function of magnesium has been emphasized in books [8,39,40] and has also been the topic of several reviews [91, 102-108]. In a 1981 critique of the "water story", it was stated that the magnesium hypothesis has strong biological plausibility that is well substantiated by experimental and clinical evidence, but that the supporting epidemiological evidence is weak [109]. However, a current review concludes that the evidence (including the epidemiology) is persuasive, and recommended that magnesium infusion in heart infarct patients should become part of the routine treatment [108].

4. ASSESSMENT OF METABOLIC Mg STATUS

There are several analytical methods for the measurement of magnesium [110], although atomic absorption appears to be the method of choice [39]. In serum, the normal range of magnesium concentrations is 0.75—1.05 mM/liter [39]. Hypermagnesemia is most often seen in severe renal failure and has been the theme of a comprehensive review [111]. At the other extreme, hypomagnesemia has been described as "probably the most underdiagnosed electrolyte deficiency in current medical practice" [112]; for example, in the "Multiple Risk Factor Intervention Trial" no attempt was made to consider the role of a low serum magnesium status, nor of tissue magnesium depletion or the influence of the waterborne magnesium factor [113]. It is important to emphasize that a normal serum magnesium level can be maintained despite the presence of intracellular magnesium depletion [114], as was seen during the Canadian studies of the water story [115]. The intracellular status can be assessed by means of the "magnesium load test", which involves the measurement of urine magnesium and as such is suitable for use as a nontraumatic screening procedure [116]. A recent report has discussed the various tests available for the assessment of metabolic magnesium status [110].

5. OVERALL CONCLUSIONS

Dietary magnesium intake in North America has decreased throughout the present century.

The current magnesium intake in the modern-day world ranges from borderline adequacy down to 50% of the recommended intake.

Subgroups of the population having low magnesium intakes are adults who are hospitalized or in long-term-care institutions; also women who are pregnant or lactating. Also, persons with chronic intake of digitalis, diuretics, or alcohol are prone to excessive urinary loss of magnesium.

Sports diets lack magnesium and this can have a negative effect on athletic performance.

Vegetarian diets can provide an abundant supply of magnesium, provided that the ingredients are reasonably well absorbed.

The beneficial effect of dietary magnesium supplementation attests to an inadequate metabolic magnesium status in the modern world.

Residents of localities having low-magnesium drinking waters are subject to intracellular magnesium depletion at the cardiac site, along with a high prevalence of myocardial infarct fatalities.

The cardioprotective waterborne magnesium factor has been observed in Canada, the United States, South Africa, Poland, and the Soviet Union, and is therefore a global phenomenon.

Magnesium-rich mineral waters have been used successfully in therapy.

The cardioprotective function of magnesium is indisputable.

If the dietary magnesium intake was generally adequate in the modern world, it would be impossible to detect the waterborne magnesium effect.

ABBREVIATIONS

ECG electrocardiogram
IHD ischemic heart disease
RDA recommended daily allowance
USDA United States Department of Agriculture

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