

Magnesium level in drinking water: its importance in cardiovascular risk

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INTRODUCTION

Of all the cardiovascular risk factors, magnesium now takes first place as judged by the accumulation of epidemiological, pathophysiological, clinical and experimental data, both pharmacological and therapeutic. The "water story" began in 1957 when, after observing a geographical correlation between stroke-associated mortality and river water acidity Kobayashi inferred a possible relationship between the composition of drinking water and cardiovascular diseases. Schroeder checked the validity of the Japanese data statistically and then examined the implications of the phenomenon in the USA. He suggested an inverse relationship between various types of heart diseases and drinking water hardness: drinking soft water increases cardiovascular risk and this effect is reciprocally reduced by hard water consumption (23-26). Numerous studies in all the continents have been devoted to this negative correlation with hardness, involving many statistical units of observation (states, districts, towns), diversification of causes of mortality (general, cardiac, vascular) and multiplications of observed variables (climatic and geographical factors, analytical data on water). This inverse relationship has been confirmed in the majority of the studies and in particular in those done on the largest geographical scale. However the variable relating to water hardness cannot be considered a constant risk since in some studies its effect may be completely absent, the statistical significance of the other ecological variables involved in the water story should not be underestimated (23-26, 34), and other confounding aetiological and atmospheric co-factors (ie amount of rainfall, salt-consumption) which are associated with hardness may play a role. However, the most important aim must be to define clearly the factors in drinking water which may be involved in maintaining the cardiovascular apparatus in satisfactory condition. It is therefore necessary to have an accurate definition of hardness. Hardness is defined by hydrotimetry, ie a measurement which determines the presence of encrusting properties which antagonize vegetable cooking and soap lathering. The bulk of total hardness is made up by Ca and Mg compounds but in some areas salts of other metals are also present in significant amounts: Al, Ba, Fe, Mn, Sr.. Carbonate (or temporary) hardness denotes the proportion of hardness chemically equivalent to the concentration of carbonate - bicarbonate and is thus an index of water alkalinity and buffer capacity. Non carbonate (or permanent) hardness denotes the proportion of hardness attributable to anions such as sulphate or chloride (9, 20, 41, 54). The variables involved in hardness are of three types: (1) Several metals, but mainly Ca and Mg,

determining total hardness ; (2) The buffer capacity and alkalinity of CO_3^{2-} and HCO_3^- in carbonate hardness ; (3) In non carbonate hardness, some of the numerous factors involved in the aggressive and mainly corrosive properties of the water, such as SO_4^{2-} and Cl^- (20, 41). The beneficial and deleterious effects of the multiple macro and trace cations and anions concerned in the measurement of water hardness should be assessed first on the basis of their own properties, then through their reciprocal interactions with Mg (23-26, 54). These water factors only need to be taken into account when they represent quantitatively a significant part of the Recommended Dietary Allowances or if, qualitatively, they constitute a higher bioavailable intake.

I - PROTECTIVE FACTORS (PF) IN DRINKING WATER

I.1 - Accessory PF in drinking water

A significant inverse correlation has been irregularly found between cardiovascular mortality and natural water elements : Ca, K, As, Cu, Fe, Li, Ni, Vanadyl, Zn, CO_3^{2-} , Cr, I, F, Se, Si, Zn (23-26, 71, 48). It is obvious that if the importance of dietary Ca and K is critical, the quantitative part of water Ca and K is rarely substantial (23-26, 28, 30, 38, 39, 43, 51, 64, 66, 73, 75, 79). The Ca level in drinking water has importance in advance of the consumer, since it acts as a crucial anticorrosive substrate of the protective coating deposited on the pipes by well balanced water (25, 26). The inverse correlation between Li and mortality is low and reverses when the partial correlation is calculated. Besides, the lowered carbonate and non carbonate hardnesses are essential components of corrosivity (25, 26, 54). The water contribution of various trace elements, the minimum requirements of which are known (F, I, Cr, Fe, Zn, Cu) may be important (18, 25, 26, 37, 48), but it is difficult to appreciate this contribution when the requirements have not yet been defined.

I.2 - Mg : prominent PF

Among all the factors studied in drinking water, the highest inverse correlation has been observed between Mg and cardiovascular mortality and morbidity. The myocardial Mg level is significantly lower in soft water areas than in hard water areas. The same is found in the heart of the subjects who have died from sudden heart attacks with or without myocardial infarcts (even outside possibly necrosed tissues where the Mg leakage depends on tissue lysis). The strongest correlation concerns fatal arrhythmic seizures (15, 23-26, 34, 50, 53, 54). The importance of the Mg intake in drinking water is both quantitative and qualitative.

I.2.1 - Quantitative importance

Water Mg may represent the amount of Mg required to bring an insufficient dietary Mg level to a correct level (23-26, 54). In fact, the adult Mg intake is marginal in developed countries (23-26, 35, 47, 69) and in some cardiovascular disease populations particularly (38, 43, 51, 64, 66, 73, 75). According to the variability of the water intake (tap water, bottled waters, commercialized beverages using tap water in their preparations), and with a consumption ranging from less than 1 litre to 2 litres/day with the corresponding Mg content varying from less than 5 mg to more than 100 mg/litre, the water Mg intake may quantitatively represent the critical contribution allowing the direct control of a marginal intake (3, 25, 26, 54). Indirectly, the Mg level of cooking water also intervenes in the Mg intake. There is an inverse correlation between the Mg loss in the cooked food and the Mg level of the cooking water : the Mg loss in cooked food is lower when the food is cooked in a water with a high Mg content. Nowadays housewives often use hot softened water for cooking : it would be better to use unsoftened tap water (23-26, 60). Furthermore the concept of nutrient density confers special importance on water Mg in the Mg intake of the diet. Usually, Mg intake and calory intake are closely related and the Mg nutritional

density of Mg in most foods rich in Mg is low. Mg in drinking water constitutes a Mg intake whose high nutritional density is ideal since it is ... free from calories ! (4, 31).

I.2.2 - Qualitative importance

Several metals and Mg particularly, ingested in waterborne solution are more readily assimilated by the intestinal tract than the same quantity in food (19). A supplementation study on baboons (*Papio Ursinus*) shows that tap water was more effective in ensuring Mg (or Zn) requirements than dietary supplementation (68). This advantage does not come from a simultaneous water intake, hydration being an efficient means to increase urinary Mg leakage (21). It necessarily results from a higher bioavailability : either increased absorption (better biodisposability) and/or increased utilization, probably linked to the biological significance of the hexahydrated form of Mg (6). Analysis of pharmacological data in normal human beings of LOWIK and BINNERTS, of epidemiological and experimental data of NOVIKOW, and of our own data on membrane permeability (6) allows us to suggest an explanation of the prominent role of Mg in water as a cardiovascular protective factor. The presence of highly bio-available Mg in the intake would avoid the possibility that the neuroendocrine control of Mg homeostasis might be activated by a deficient intake of highly bio-available magnesium, ie a "qualitative" Magnesium deficit, even in the presence of a satisfactory overall Mg intake. Since the various regulatory mechanisms involved in Mg homeostasis are the same as those controlling vasomotor tone and the metabolism of water, Cl, Na, K, P and Ca, it may be presumed that their dysfunction might induce cardiovascular ailments (23-26).

Consequently water Mg intake may intervene in cardiovascular pathology through its quantitative or qualitative properties. The critical quantitative intake of water Mg which palliates marginal Mg deficiency may explain its importance as a protective cardiovascular factor in the case of "absolute" Mg deficit. Mg deficit may induce numerous deleterious effects either directly on the nephro-cardiovascular apparatus or indirectly through the neuro-endocrine apparatus (23-26), but it would be erroneous to attribute to Mg deficit a major role as a hypertensive factor. The studies which attribute an antihypertensive effect to a physiological intake of Mg have confused pharmacological and physiological data (13), have disregarded in vivo data showing that Mg deficiency usually induces hypotension or normotension (1), or have not taken into account the fact that plasma magnesium is generally normal in hypertensive individuals (30) and that normotension is usually the rule during primary Mg deficit (23, 24). It seems very important to discredit the myth that Mg is a major antihypertensive nutrient because of its potentially harmful consequences for health. For example epidemiological studies are necessarily interpreted on the grounds of well established pathophysiological bases. Therefore, as Mg is erroneously considered as a major antihypertensive nutrient, it is presented in the Honolulu heart study as ranking first among other multiple dietary factors showing inverse association with blood pressure. The same epidemiological data could be differently interpreted in the light of our background knowledge of the relationship between Mg and blood pressure (8, 17, 23, 24, 27, 29, 32, 44, 49, 59, 61, 67) and by using the interesting concept of multicollinearity associated with the data concerning the relation between blood pressure and Ca, P, K and particularly Na-sensitivity (38, 64). Though Mg does not appear as a major antihypertensive nutrient, Mg deficit through its numerous noxious actions, both directly on the nephro-cardiovascular apparatus and indirectly through the neuroendocrine apparatus, may sometimes, behave as a cofactor of a hypertensive factor in particular cases. Therefore it is important to prescribe palliative treatment for the deleterious effects on the nephro-cardiovascular apparatus of spontaneous or iatrogenic Mg deficit observed in cardiovascular pathology (23-26, 30, 38, 45, 67).

This quantitative mode of action of water Mg proves useful by supplying an amount of Mg which allows one to obtain a balanced daily Mg intake palliating an "absolute" Mg deficit.

A supply of water Mg may also protect the nephrocardiovascular apparatus because of its qualitative mode of action. Even in the case of quantitatively sufficient daily Mg intake, water Mg, through its high degree of bioavailability can reduce the activation of the neuroendocrinoregulatory mechanisms of Mg homeostasis by a genuine "relative" Mg deficit due to a deficient intake of the highly bioavailable Mg of water Mg. This beneficial effect may arise from the role of these neuroendocrine mechanisms in the control of the metabolism of water, Cl, Na, K, P and Ca and vasomotor tone (Fig. 1).

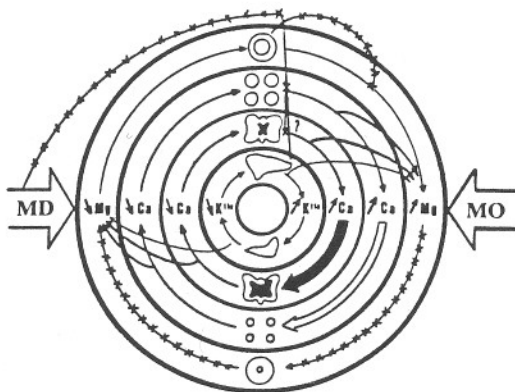


Figure 1 - General diagram of the endocrine feedback control of humoral disorders due to alterations in magnesium metabolism. In J. Durlach, 1988 (24).

"Absolute" and "relative" magnesium deficit (MD) induces increased secretion of several neurohormones which are pathogenic for the cardiovascular system, ie adrenaline, insulin and PTH, and it also induces a decrease in secretion of CT, a hormone with protective properties for the cardiovascular system. In addition, MD induces other neurohormonal or metabolic disturbances which may have deleterious consequences, for example increased production of renin and aldosterone, calcinosis, dyslipidaemias and alterations in haemostasis. An adequate intake of water Mg may in particular palliate "absolute" marginal MD with a critical supply over the marginal intake, and/or qualitatively palliate a "relative" MD by supplying Mg of high bio-availability.

II - NOXIOUS FACTORS (NF) IN DRINKING WATER

II.1 Natural NF

A significant and direct correlation has been irregularly found between cardiovascular risk and Na (23-26, 28, 42). However this correlation is not consistent (30, 42, 43, 64) and even inverse correlation may be observed (11, 51). These data agree with the notion of salt-sensitive hypertension with hyporeninaemia and salt-insensitive or salt-resistant hypertension with normo- or hyper-reninaemia. These clinical forms of essential hypertension present with abnormalities of plasma water and electrolytes and variations of plasma volume which are closely linked with disturbances of calcium-phosphorus regulating hormones (10, 11, 16, 42, 52, 56, 58, 65, 66). Chloride, the anionic component of salt, seems to play an important role, together with sodium, in the harmful effects involved in salt-sensitive hypertension. This fact calls into question

the innocuous nature of chlorination processes in water treatment (22, 46, 76-78, 80). It is obvious that the amount of Na and Cl in drinking water is not a major part of their intake in the diet, but in salt-sensitive hypertension it is difficult to reduce the 50 % contribution to the total sodium intake which is provided by meat and dairy products. It is worthwhile, however, avoiding the consumption of artificially softened water or mineral waters rich in sodium.

A direct but irregular correlation has also been found between cardiovascular morbidity and other natural elements of the mineral content of drinking water (Ca, P, Zn) (25, 26, 30), but usually these deleterious effects have been observed in association with markers of dysregulation of metabolisms : \downarrow Ca^{2+} and \uparrow Ca total in blood, hypercalciuria, hypophosphataemia and alterations of calcium and phosphorus controlling hormones (12, 16, 23, 24, 30, 39, 42, 51, 58, 62, 63, 66, 79). This notion of the dysregulation of these controlling hormones explains how sometimes a treatment which reduces the phosphate load of the arterial wall may be useful in hypertension (62, 63) ; and how sometimes phosphate therapy may be used as a palliative of hypophosphataemia, which is inversely related to blood pressure. Phosphorus reduces hypercalciuria and therefore increases the level of Ca^{2+} in the blood, probably through a reduction in synthesis of $1-25(\text{OH})_2\text{D}_3$ (23, 24). Evidently water intake represents only a small part of the overall intake of these natural noxious factors.

II.2 - Polluting "factors" and RYZNAR Index

- In the "water story" an important role is played by corrosivity. This physical factor of water solubilizes toxic metals in the geological layers or in the pipes (25, 26, 54). One should distinguish between aggressivity : the capacity of water to attack calcium carbonate, well defined in the Langelier Index ($\text{IL} < 0$ = aggressive water) and corrosivity : its ability to corrode metals, as defined by the Ryznar Index ($\text{IR} > 7$ = corrosive water). We have proposed that the RYZNAR Index should be systematically used in epidemiological studies on the relationship between drinking water and health (25, 26).

- Some polluting metals or metalloids have toxic effects which may concern the nephro-cardiovascular apparatus : As, Co, Cr, F, Mg, Mn, Zn, V^{5+} (2, 14, 25, 26, 55, 70).

- The noxiousness of corrosive waters is mainly due to two toxic metals, Pb and Cd, which have cumulative toxicity.

In areas where drinking water is corrosive, the main origine of chronic lead poisoning is water lead pollution (7, 23-26, 36, 40). Water pollution is a less important aetiological factor in chronic Cd poisoning, which is more often correlated with tobacco smoking (23-26, 72). Even low levels of Cd and Pb have detrimental cumulative effects on the cardiovascular system (25, 26). Mg is a competitive inhibitor of Pb and Cd in the isolated amnion, but on different sites (5, 25). Mg deficiency increases while Mg load decreases toxicity of these two polluting metals. The target of this antagonism seems to be cellular since neither absorption nor urinary leakage are concerned in it (23-26, 33, 57, 59, 72, 74).

Mg does not appear to be a panacea which antagonizes all noxious agents, but it seems to be an antagonist of the two main polluting metals which induce the nephro-cardiovasotoxicity of some corrosive drinking waters.

III - NEW PERSONAL DATA

Our studies on the permeability of the isolated human amnion, estimated by the measurement of ionic conductance and ionic flux (25) complete the preceding data and are summed up in the following two tables (MS = maternal side ; : FS = fetal side) :

	<u>MS</u>	<u>FS</u>		<u>MS</u>	<u>FS</u>
Mg Cl ₂	S - B	S - B	Mg Acetate	S - B	S - B
Mg SO ₄	S	B	Mg Citrate	S - B	S - B
Mg Lactate	S	S - B	Mg Nitrate	S	B

Table 1 : Effects of the magnesium salts on the amniotic membrane expressed in terms of screening (S : reduction of the permeability) and binding (B : increase of the permeability).

These results show first that water Mg exhibits better tissue bioavailability probably linked to the hexahydrated form of Mg and, secondly, that the action of Mg in water is not due to its hydrated structure only, but also, to its relationship with the anion present in the medium (6).

	<u>MS</u>	<u>FS</u>		<u>MS</u>	<u>FS</u>
Mg - Pb	na	CI	Mg - Co	na	na
Mg - Cd	CI	na	Mg - As	na	na
Mg - Hg	nCI	nCI	Mg - Cr	na	na
Mg - Al	A	A	Mg - Mn	Ac	Ac

Table 2 - Relationship between Mg and noxious cations on the external membrane sites obtained after the measurement of the variation of the conductance (na = no action ; nCI = non competitive inhibition ; CI = competitive inhibition ; A = activation with independent fixation ; Ac = activation on the same site. coupling activation).

Mg does not antagonize all noxious agents but reverses the effects of the two main polluting metals, Pb and Cd (5) which are responsible for the renal and cardiovascular toxicity of some corrosive drinking waters. Since Pb and Cd are involved at different sites, Mg may have a common action on both, though it is more active against Pb than against Cd.

The fact that the amnion is a particularly leaky and non-excitabile membrane limits the scope of our conclusions about the general properties of membranes. However in spite of the heterogeneity of the effects, some conclusions can be drawn : (1) The effect of water Mg may be due to the hexahydrated form in connection with the linked anion ; (2) Water Mg may antagonize Pb and Cd on the plasma membrane, particularly during combined intoxication .

CONCLUSION

- Among the numerous variables involved in the "water story" Mg appears preeminent. Its importance is both quantitative and qualitative. The critical quantitative intake of water Mg may palliate an "absolute" Mg deficit and its multiple consequences particularly on the nephrocardiovascular apparatus . Even in the case of a balanced daily Mg intake, water Mg may qualitatively act on the nephrocardiovascular apparatus by palliating a genuine "qualitative" Mg deficit due to a deficient amount of highly bioavailable Mg. It reduces the activation of the neuroendocrine regulatory mechanisms of Mg homeostasis which also control the metabolisms of water, Cl, Na, K, P and Ca and the regulation of vasomotor tone.
- Corrosivity is the other main factor of the "water story". Mg appears as a competitive inhibitor of the two main noxious polluting agents : Pb and Cd.
- It is advisable to have 30 mg/litre of Mg in drinking water. If the water is not corrosive, it is not advisable to enrich it with Mg in the course of the processing since its corrosivity index would also increase. A Mg salt can only be added after the water has been collected. If the water is corrosive, it will be filtered in processing stations through an anticorrosive filter with optimum Mg/Ca ratio (25, 26) to ensure the highest Mg/Ca ratio in tap water with the best anticorrosive power.

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