Calcium and Magnesium in Drinking Water and the Risk of Death From Hypertension

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Many studies have demonstrated a negative association between blood pressure and calcium and magnesium levels. This report examines whether calcium and magnesium in drinking water are protective against hypertension. All eligible hypertension deaths (2336 cases) of Taiwan residents from 1990 through 1994 were compared with deaths from other causes (2336 controls), and the levels of calcium and magnesium in the drinking water of these residents were determined. Data on calcium and magnesium levels in drinking water throughout Taiwan have been obtained from the Taiwan Water Supply Corporation. The control group consisted of people who died from other causes and the controls were pair matched to the cases by sex, year of birth, and year of death. Magnesium levels in drinking water were inversely related to the risk of death from hypertension. The adjusted odds ratios (95% confidence interval) for the highest versus lowest quintiles of exposure was 0.63 (0.47 to 0.84). After adjustment for magnesium levels in drinking water, there was no difference between the groups with different levels of calcium. The results of the present study show that there is a significant protective effect of magnesium intake from drinking water on the risk of hypertension. This is an important finding for the Taiwan water industry and human health. Am J Hypertens 1999; 12:894–899 © 1999 American Journal of Hypertension, Ltd.

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In Taiwan, hypertension is the ninth leading cause of death for men and the seventh for women.[1] The age-adjusted mortality rate for hypertension was 12.27 per 100,000 among men and 12.34 among women in 1995. Also, there is substantial geographic variation in hypertension mortality within the country. Such a geographic distribution may suggest an environmental risk factor.

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Interest concerning the role of calcium and magnesium in human cardiovascular disease was stimulated by ecologic studies that demonstrated an inverse association between water hardness and cardiovascular death rates.[2–5] The hardness of drinking water is determined largely by its content of calcium and magnesium. It is expressed as the equivalent amount of calcium carbonate that could be formed from the calcium and magnesium in solution.

Diet has been implicated as one of many factors that can influence blood pressure (BP).[6] Dietary calcium is the main source of calcium intake. Epidemiologic studies have shown that dietary calcium is inversely associated with BP.[7–12] Studies conducted in several animal models of hypertension have also been consistent in demonstrating a hypotensive effect of calcium supplementation.[13] Magnesium and calcium are the main determinants of water hardness. An inverse re-

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lationship between dietary magnesium and BP has also been reported.[14–19]

In Taiwan, the mean daily intake of dietary calcium is 507 mg. This figure is only 81.9% of the recommended daily intake.[20] The major portion of magnesium intake is through diet, and to a lesser extent by drinking water.[21] There are no available data for assessing the percentage contribution of drinking water to the total magnesium intake in Taiwan. Nonetheless, in the modern world, intake of dietary magnesium is often lower than the recommended dietary amounts of 6 mg/kg/day.[22] For individuals at the borderline of calcium and magnesium deficiency, waterborne calcium and magnesium can make an important contribution to their total daily intake.

Hypertension is one of the most important risk factors for cardiovascular and cerebrovascular diseases, especially stroke. Our recent study found that there is a significant protective effect of magnesium but not calcium intake from drinking water against cerebrovascular disease.[23] The objective of this study was to study the relationship between the levels of calcium and magnesium in drinking water and risk of death from hypertension in Taiwan.

MATERIALS AND METHODS

Study Area Taiwan is divided into 361 administrative districts, which will be referred to herein as municipalities. They are the units that will be subjected to statistical analysis. Excluded from the analysis were 30 aboriginal townships and 9 islets that had different lifestyles and living environments. This elimination of unsuitable municipalities left 322 municipalities for analysis.

Subject Selection Data on all deaths of Taiwan residents from 1990 through 1994 was obtained from the Bureau of Vital Statistics of the Taiwan Provincial Department of Health, which is in charge of the death registration system in Taiwan. For each death, detailed demographic information, including gender, year of birth, year of death, cause of death, place of death (municipality), and residential district (municipality) were recorded on computer tapes. The case group consisted of all eligible hypertension deaths (including deaths caused by essential hypertension (International Classification of Disease, ninth revisions [ICD-9], code 401), hypertensive heart disease (ICD-9 code 402), hypertensive renal disease (ICD-9 code 403), hypertensive heart and renal disease (ICD-9 code 404), and secondary hypertension (ICD-9 code 405)) occurring in people between 50 and 69 years of age.

A control group was formed using all other deaths, excluding those deaths that were associated with cardiovascular diseases. The deaths excluded were those caused by hypertensive disease (ICD codes 401–405), ischemic heart disease (ICD codes 410 to 414), diseases of pulmonary circulation (ICD codes 415 to 417), other forms of heart disease (ICD codes 420 to 429), cerebrovascular disease (ICD codes 430 to 438), and diseases of the arteries, arterioles, and capillaries (ICD codes 440 to 448). Subjects who died from gastric cancer (ICD code 151) and colorectal cancer (ICD code 153) were also excluded from the control group because of previously reported negative correlation with hardness (calcium or magnesium) levels in drinking water.[24–26] Control subjects were pair matched to the cases by gender, year of birth, and year of death. Each matched control was selected randomly from the set of possible controls for each case. Each case and its matched control had residence and place of death in the same municipality. For controls, the most frequent causes of death were diabetes mellitus (11.0%), liver cancer (9.0%), lung cancer (8.4%), chronic liver disease and cirrhosis (8.0%), diseases of the respiratory system (7.9%), and diseases of the genitourinary tract (5.0%).

Calcium and Magnesium Levels in Drinking Water Information on the levels of calcium and magnesium in each municipality's treated drinking water supply was obtained from the Water Quality Research Center of the Taiwan Water Supply Corporation[27] to whom each waterworks is required to submit drinking water quality data including the levels of calcium and magnesium. They also conduct routine water analyses to assess the suitability of water for drinking from both the sources and at various points in the distribution system. Four finished water samples, one for each season, were collected from each waterworks. The samples were then analyzed by the waterworks laboratory office using standard methods. Because the laboratory office examines calcium and magnesium levels on a routine basis using standard methods, it was thought that the problem of analytical variability was minimal. Among the 322 municipalities, 70 were excluded as they were supplied by more than one waterworks and the exact population served by each waterworks could not be determined. Their details have already been described in earlier publications.[23–26,28] The final complete data consisted of drinking water quality data from 252 municipalities.

Hardness (calcium and magnesium) remains reasonably constant for long periods of time and is a quite stable characteristic of a municipality's water supply.[29] Some information on the levels of water hardness was available for the study areas in 1980. The correlation between 1980 and 1990 hardness levels for the study areas was reasonably high ($r = 0.85$). The waterworks in each municipality received a questionnaire requesting information on whether any changes had occurred in the water supply or the treatment of the water during the past 20 years. No municipalities

were excluded because of changes in water quality (eg, the use of water softeners) during the past few decades. It was believed that the hardness (calcium and magnesium) levels in drinking water have remained reasonably stable. Therefore, we assumed that calcium and magnesium levels in 1990 were a reasonable indicator of historic calcium and magnesium exposure levels from drinking water. Data collected included the mean levels of calcium and magnesium for the year 1990. The municipality of residence for all cases and controls was identified from the death certificate and was assumed to be the source of the subject's calcium and magnesium exposure via drinking water. The levels of calcium and magnesium of that municipality were used as an indicator of exposure to those substances for an individual residing in that municipality.

Statistics In the analysis, the subjects were divided into quintiles according to the levels of calcium and magnesium in their drinking water. The association between hypertension death with calcium and magnesium levels in drinking water was measured using odds ratios (OR) and their 95% confidence intervals (95% CI) from conditional logistic regression models. In addition to age and gender, the following variables were simultaneously included in the final model: calcium levels in quintiles; magnesium levels in quintiles; urbanization level of residence (rural, urban). ORs and their 95% CIs were calculated using the group with the lowest exposure as the reference group.[30] Values of $P < .05$ were considered statistically significant.

RESULTS

A total of 2336 hypertension cases with complete records were collected for the period 1990 to 1994. Of the 2336 cases, 1500 were men and 836 were women. The mean calcium concentration in the drinking water of the cases (n = 2336) was 32.9 mg/L (SD = 20.3). Controls (n = 2336) had a mean calcium exposure of 34.8 mg/L (SD = 19.5). The mean magnesium concentration in the drinking water was 10.9 mg/L (SD = 7.6) for the cases, and 11.2 mg/L (SD = 7.5) for the controls. Both cases and controls had a mean age of 62.9 years. Cases lived in municipalities in which 90.6% of the population was served by a waterworks. For controls this number was 89.8%. Cases had a higher rate (43.6%) of living in metropolitan municipalities than the controls (37.9%) (Table 1).

Table 2 shows the numbers of cases and controls and ORs in relation to calcium levels in their drinking water. Age- and gender-adjusted calcium intake from drinking water was inversely associated with hypertension death risk. This inverse association was not statistically significant except for the comparison involving the group whose calcium exposure was in the second highest quintile with the group with the lowest exposure. The association was even positively, although not significantly, associated with the risk of hypertension in the fully adjusted model. The main variables responsible for the sharp difference between the age- and gender-adjusted and full multivariate model were magnesium levels in drinking water and urbanization level of residence.

TABLE 1. CHARACTERISTICS OF THE STUDY POPULATION

Characteristics	Cases	Controls	*P*
Total no. of subjects	2336	2336	
No. of enrollment municipalities	252	252	
Sex (%)			
Male	1500 (64.2)	1500 (64.2)	
Female	836 (35.8)	836 (35.8)	
Mean age (years) (SD)*	62.9 ± 5.0	62.9 ± 5.0	
Mean calcium concentration (SD)	32.9 ± 20.3	34.8 ± 19.5	.08
Mean magnesium concentration (SD)	10.9 ± 7.6	11.2 ± 7.5	.13
Drinking water served by waterworks (%)	90.6 ± 15.6	89.8 ± 16.3	.18
Urbanization level of residence (%)*			
Metropolitan	1019 (43.6)	885 (37.9)	
City	405 (17.3)	473 (20.2)	
Town	624 (26.7)	613 (26.2)	
Rural	288 (12.3)	365 (15.6)	.001

* *The urbanization level of each municipality was based on the urban–rural classification scheme of Tzeng and Wu.*[43]

The OR in relation to magnesium levels in drinking water are shown in Table 3. Magnesium intake from drinking water was significantly inversely associated with hypertension death risk in a model controlling for age and gender. The ORs for the highest versus the lowest quintile of magnesium intake from drinking water was 0.80 (95% CI 0.67 to 0.95). In the multivariate model, the inverse association was somewhat stronger. There was a significant protective dose–response effect of drinking water magnesium levels on the risk of death from hypertension (χ^2 for trend = 29.05, $P < .001$). The increased magnesium group had a 27% to 37% lower risk of death from hypertension.

DISCUSSION

This study used a death certificate-based case-control study and a drinking water quality ecology study to examine the relationship between hypertension mortality and calcium and magnesium exposure from drinking water in Taiwan. The results of the present study show that there is a significant protective effect of magnesium intake from drinking water for the risk of hypertension.

TABLE 2. ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR HYPERTENSION DEATH BY CALCIUM LEVELS IN DRINKING WATER, 1990–1994

	Calcium (mg/L [median])				
	4–11.3 (7.4)	11.4–30.0 (20.2)	30.1–37.3 (34.6)	37.4–53.4 (43.3)	53.5–81.0 (60.5)
No. of cases	498	473	453	423	489
No. of controls	443	473	459	498	463
Crude odds ratio*	1.00	0.88 (0.74–1.06)	0.87 (0.73–1.05)	0.76 (0.63–0.91)‡	0.93 (0.78–1.12)
Adjusted odds ratio†	1.00	1.23 (0.94–1.62)	1.32 (0.98–1.78)	1.12 (0.83–1.51)	1.26 (0.92–2.02)

* *Odds ratio adjusted for age (50–59, 60–69 years) and sex (male, female).*

† *Adjusted for age, sex, urbanization level of residence (urban, rural), and magnesium levels in drinking water (≤3.8, 3.9–8.2, 8.3–11.1, 11.2–16.3, ≥16.4).*

‡ P = *.003.*

Despite their inherent limitations[31] studies on the ecologic correlation between mortality and environmental exposures have been used widely to generate or discredit epidemiologic hypotheses. The completeness and accuracy of a death registration system should be evaluated before any conclusion based on the mortality analysis is made. Because it is mandatory to register death certificates at local household registration offices and as the household registration information is verified annually through a door-to-door survey, the death registration in Taiwan is very complete. Although causes of death may be misdiagnosed or misclassified, the problem has been minimized through the improvement in the verification and classification of causes of death in Taiwan since 1972. Furthermore, Taiwan is a small island with a convenient communication network, and the accessibility of medical service facilities is comparable among study municipalities. Mortality data differences between the municipalities in this study do not appear to result from systematic differences in recording and codification.

Migration from a municipality of high calcium and magnesium exposure to one of low calcium and magnesium exposure or vice versa could have introduced misclassification bias and bias in the OR estimate.[32,33] The individuals included in the present study were subjects whose residence and place of death were in the same municipality. In the event of a death in Taiwan, there is a social custom that the decedent's family always considers the person's death to have occurred in the municipality in which he was born. Therefore, the decedent's residence, place of birth, and place of death are likely to be listed as the same municipality, although the place of birth information was not available for this data set. We believe that this ameliorates the migration problem. Also all the subjects used for the present study were at least 50 years old, and it is assumed that the elderly are more likely to remain in the same residence and, therefore, that most of their lifetime was spent at the address listed on the death certificate.

In Taiwan, the mean daily intake of dietary calcium is 507 mg. This figure is only 81.9% of the recommended daily intake.[20] The mean calcium concentration in Taiwan's drinking water is 34.7 mg/L. This figure would contribute, on average, 13.7% to an individual's total dietary calcium intake, given a daily consumption of 2 L of water. One may hypothesize that waterborne calcium can make an important con-

TABLE 3. ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR HYPERTENSION DEATH BY MAGNESIUM LEVELS IN DRINKING WATER, 1990–1994

	Magnesium (mg/L [median])				
	1.5–3.8 (3.5)	3.9–8.2 (7.0)	8.3–11.1 (9.1)	11.2–16.3 (13.5)	16.4–41.3 (19.4)
No. of cases	570	435	438	388	505
No. of controls	476	458	461	413	528
Crude odds ratio*	1.00	0.79 (0.66–0.95)	0.80 (0.67–0.95)	0.79 (0.65–0.95)	0.80 (0.67–0.95)
Adjusted odds ratio†	1.00	0.73 (0.57–0.93)	0.66 (0.50–0.87)	0.67 (0.50–0.89)	0.63 (0.47–0.84)
				χ^2 for trend = 29.05, $P < .001$	

* *Odds ratio adjusted for age (50–59, 60–69 years) and sex (male, female).*

† *Adjusted for age, sex, urbanization level of residence (urban, rural), and calcium levels in drinking water (≤11.3, 11.4–30.0, 30.1–37.3, 37.4–53.4, ≥53.5).*

tribution to the total daily intake for subjects with insufficient calcium intake. However, controlling for magnesium levels eliminates the perceived effect of calcium levels on hypertension mortality. The reason for not finding a protective effect of calcium on risk of hypertension death may be the fact that calcium and magnesium levels in the drinking water are highly correlated (correlation coefficient, 0.65). This may create collinearity in the regression model making it difficult to detect the effect of calcium.

In the general population, the major proportion of magnesium intake is through diet, and to a lesser extent via drinking water (in Sweden, generally <5% is from drinking water).[21] There is no available data for assessing the percentage that drinking water contributes to the total magnesium intake in the present study. Nonetheless, in the modern-day world, intake of dietary magnesium is often lower than the recommended dietary amount of 6 mg/kg/day.[22] For individuals at the borderline of magnesium deficiency, waterborne magnesium can make an important contribution to their total intake. In addition, the loss of magnesium from food is lower when the food is cooked in magnesium-rich water.[34] Another reason why magnesium in water can play a critical role is its higher bioavailability. Magnesium in water appears as hydrated ions, which are more easily absorbed than magnesium in food.[22,35] The contribution of water magnesium among persons who drink water with high magnesium levels could thus be crucial in the prevention of magnesium deficiency.

The significant association between mortality from hypertension and the levels of magnesium in drinking water is supported by knowledge of the functions of magnesium. A recently proposed hypothesis suggests that an impairment of the cell membrane sodium transport system is responsible for the increased total peripheral resistance found in essential hypertension.[36] Magnesium is an enzyme (Na/K-ATPase) activator and regulates cellular energy metabolism, vascular tone, and cell membrane ion transport. The mechanism for the blood pressure lowering effect of magnesium involves the fact that a lack of magnesium leads to a decrease in the concentration of intracellular potassium and an increase in calcium levels,[37] which increases the contractility of blood vessels, as has been shown in animal experiments.[38]

Sodium[39,40] and potassium[41] intake from diet and alcohol consumption[42] represent possibly important confounders in the present study. There is unfortunately no information available on these variables for individual study subjects and they could not be adjusted for directly in the analysis. However, there is no reason to believe that there would be any correlation between these confounders and the levels of magnesium in the water. It is also unlikely that there would be a direct relationship between other risk factors and the level of magnesium in drinking water. Also fear of hypertension should not deter anyone from drinking water with low magnesium levels.

In conclusion, the results of the present study show that there may be a significant protective effect of magnesium intake from drinking water on the risk of hypertension. This is an important finding for the Taiwan water industry and human health risk assessment. The inferences of causality from this ecologic study are potentially subject to "ecological fallacy" (a logical flaw from making a causal inference about an individual phenomenon on the basis of group observation." Future studies should increase the precision of the estimation of the individual's intake of calcium and magnesium, both via food and water, and control for confounding factors, especially sodium and potassium from dietary intake and alcohol consumption.

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