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Desalinated seawater supply and all-cause mortality in hospitalized acute myocardial infarction patients from the Acute Coronary Syndrome Israeli Survey 2002–2013☆

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ABSTRACT

Background: Consuming desalinated seawater (DSW) as drinking water (DW) may reduce magnesium in water intake causing hypomagnesemia and adverse cardiovascular effects.
Methods: We evaluated 30-day and 1-year all-cause mortality of acute myocardial infarction (AMI) patients enrolled in the biannual Acute Coronary Syndrome Israeli Survey (ACSIS) during 2002–2013. Patients (n = 4678) were divided into 2 groups: those living in regions supplied by DSW (n = 1600, 34.2%) and non-DSW (n = 3078, 65.8%). Data were compared between an early period [2002–2006 surveys (n = 2531) — before desalination] and a late period [2008–2013 surveys (n = 2147) — during desalination].
Results: Thirty-day all-cause-mortality was significantly higher in the late period in patients from the DSW regions compared with those from the non-DSW regions (HR = 2.35 CI 95% 1.33–4.15, P < 0.001) while in the early period there was no significant difference (HR = 1.37 CI 95% 0.9–2, P = 0.14). Likewise, there was a significantly higher 1-year all-cause mortality in the late period in patients from DSW regions compared with those from the non-DSW regions (HR = 1.87 CI 95% 1.32–2.63, P < 0.0001), while in the early period there was no significant difference (HR = 1.17 CI 95% 0.9–1.5, P = 0.22). Admission serum magnesium level (M ± SD) in the DSW regions (n = 130) was 1.94 ± 0.24 mg/dL compared with 2.08 ± 0.27 mg/dL in 81 patients in the non-DSW (P < 0.0001).
Conclusions: Higher 30-day and 1-year all-cause mortality in AMI patients, found in the DSW regions may be attributed to reduced magnesium intake secondary to DSW consumption.

1. Introduction

Climate change and global warming result in limited supply of fresh water.

Deficient supply of fresh water is frequently prevalent in areas with increasing populations and decreasing rainfall. To counteract this and improve fresh water supply, facilities have been built for the desalination of seawater. Over 17,000 desalination plants in 150 countries produce more than 80 million cubic meters of water per day for over 300 million people [1].

Israel began producing desalinated sea water (DSW) in 1978 with a steep increase over the past decade, accounting for about 75% (600 million m^3/year) of the tap water consumption.

The impact of DSW consumption in Israel and globally on public health has not yet been fully assessed. Fresh water from the Israeli National Water Carrier (NWC) is considered "hard," with concentrations of 45–60 mg calcium and 20–25 mg magnesium per liter, desalinated seawater contains little or no calcium or magnesium [1].

The World Health Organization's (WHO) Report on drinking water (DW) states that magnesium is essential for human health [2]. In reviewing health and safety aspects of DSW, the WHO stated that "in circumstances where a supply is moving from a source that has significant levels of calcium and magnesium to low-mineral desalinated water, it would be appropriate to consider remineralizing with calcium and magnesium salts" [3].

Magnesium is a cofactor for more than 300 metabolic reactions in the body and is essential for energy production, protein synthesis, synthesis of nucleic acids, regulating vascular tone and insulin sensitivity

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[4]. The content of magnesium in DW contributes to the daily intake of magnesium; this may be critical for those with reduced magnesium intake from other sources. The consequences of magnesium deficiency are hypertension, cardiac arrhythmias, atherosclerosis, type 2 diabetes and increased risk for colon cancer [5–7]. Optimal consumption of magnesium is important for public health, especially for cardiovascular diseases (CVD), which is the primary cause of mortality in developed countries, with the exception of Japan [8].

Previous studies have reported an inverse relation between water hardness and CVD morbidity and mortality [8–20], whereas some other studies have not found such relationship [21–25]. In a systematic review [26] the pooled OR for inverse association between magnesium levels in DW and cardiovascular (CV) mortality was 0.75 (CI 95% 0.68–0.82, $P < 0.001$). By contrast, the evidence for calcium remained unclear. A large scale study from Japan [27] has showed that dietary magnesium intake was inversely associated with mortality from hemorrhagic stroke in men and with mortality from total and ischemic strokes, coronary heart disease, heart failure and total CVD in women. After adjustment for CV risk factors and sodium intake, the multivariable hazard ratio for the highest vs. the lowest quintiles of magnesium intake was 0.49 (CI 95% 0.26–0.95). An Iranian report [28] shows marked reduction in CV morbidity within one year of increasing the magnesium content in DW. Rosanoff estimates that universal DW and beverages containing moderate to high levels of magnesium (10–100 ppm) could potentially prevent 4.5 million heart disease and stroke deaths per year worldwide [29]. The modern processed food diet which is spreading globally is low in magnesium, thereby accentuating the potential benefit of DW magnesium, especially in areas where insufficient dietary magnesium intake is prevalent.

The association between magnesium deficiency and sudden death was already established in 1992 by Eisenberg, in a review based on studies published over 30 years [30]. These studies included epidemiological, clinical and autopsies as well as animal studies. As a result, it was suggested that a regular supply of magnesium is a possible way to reduce the risk of sudden death. Modalities proposed for this purpose include: education of the population to consume more dietary magnesium, adding magnesium to DW and enrichment of foods with magnesium as well as magnesium supplements.

However, so far there are no reports on the effect of DSW consumption, which lacks magnesium, on CVD morbidity and mortality. Thus, we have evaluated the risk for 30-day and 1-year mortality in patients living in regions where DW predominantly contained DSW compared with those living in regions supplied by standard (non-DSW) DW. Our study is based on data from patients enrolled in the Acute Coronary Syndrome Israeli Survey (ACSIS) 2002–2013.

2. Methods

2.1. Study design and population

The ACSIS registry is a biannual prospective national survey of all patients with acute coronary syndrome (ACS) hospitalized in 25 coronary care units and cardiology wards in all general hospitals in Israel during a 2 month period (March–April) [31,32]. ACSIS recruits only patients residing in Israel in order to allow proper follow-up. Demographic, historic, and clinical data are recorded on pre-specified forms for all patients admitted with a diagnosis of ACS. Admission and discharge diagnoses are recorded as determined by the attending physicians based on clinical, electrocardiographic, and biochemical [elevated creatine kinase (CK)-MB and/or troponin levels] criteria. Patient management is at the discretion of the attending physicians. All patients signed informed consent for the ACSIS trial participation in each medical center.

The current analysis is based on patients presenting with ACS who were enrolled in ACSIS from 2002 through 2013, from 11 coronary care units and cardiology wards, and were treated in hospitals grouped into 2 locations according to regions with and without DSW supply. Patients were grouped as: A. patients ($n = 3078$) who lived in regions with standard (non-DSW) water supply; B. patients ($n = 1600$) who lived in regions where DSW supply was initiated during the study period — with at least 2 years of exposure. The study period was further divided into 2 time frames: early (2002–2006) period when water supply in all regions did not include DSW, and late (2008–2013) period when DSW was the main source of DW supply (>60%) in region B, whereas region A continued to be supplied by non-DSW.

2.2. Endpoints

The primary study endpoint was 1-year all-cause mortality. Secondary endpoints included 30-day all-cause mortality and in-hospital complications; Major adverse cardiac events (MACE) included 30-day mortality, recurrent myocardial infarction (re-MI), post-MI complications, urgent events following discharge, follow-up stent thrombosis, stent thrombosis during hospitalization and stroke during hospitalization.

Mortality data during hospitalization, at 30-days and 1-year were determined for all patients from hospital charts and by matching identification numbers of patients with the Israeli National Population Register. All parameters captured by the registry were defined by protocol.

2.3. Statistical analysis

Characteristics of study participants were compared using χ^2 test for categorical variables and Student's t-test or Wilcoxon rank tests, as appropriate for continuous variables. The Kruskal–Wallis test was used for comparison of non-normally distributed continuous variables.

Multivariate logistic regression analysis was performed to determine association between MACE and independent variables results presented as odds ratio and 95% confidence interval.

The probability of all-cause mortality during 1-year interval was graphically displayed using the Kaplan–Meier method. Cox proportional hazards multivariate-adjusted survival models were used to evaluate the independent effects of DSW and survey period on 30-day and 1-year all-cause mortality, displayed using the forest plot method.

In order to assess the specific contribution of treatment period on all-cause mortality, we created several Cox proportional hazard models with all-cause mortality as the dependent variable and potential confounders as independent variables. The following factors were prespecified as covariates in the multivariate survival models: Age, gender, body mass index (BMI), hypertension, diabetes mellitus, dyslipidemia, family history of coronary artery disease, history of percutaneous coronary intervention (PCI), history of coronary artery bypass grafting (CABG) operation, history of congestive heart failure, smoking, prior stroke, chronic congestive heart failure, prior MI, cardiogenic shock, serum creatinine ≥3 mg/dL and discharge medications.

The effect of the survey period on outcome among patients recruited from DSW and non-DSW regions was assessed by including a DSW-by-

Table 1
Baseline characteristics of patients recruited in the early versus late periods.

	Early (2002–2006) N = 2531	Late (2008–2013) N = 2147	P-value
Age (±SD), years	63.8 ± 13.1	63.2 ± 13.1	0.07
Female gender	609 (24%)	483 (22.5%)	0.2
BMI (±SD)	27.5 ± 4.4	29.6 ± 20.4	<.0001
Smoking	1352 (53%)	1334 (62%)	<.0001
Diabetes mellitus	873 (34.5%)	856 (40%)	<.0001
Hypertension	1439 (57%)	1396 (65.2%)	<.0001
Dyslipidemia	1467 (58%)	1706 (80%)	<.0001
Family history of coronary artery disease	512 (20.6%)	567 (26%)	<.0001

BMI — body mass index.

survey period interaction-term in the multivariate models. All data analysis was performed using SAS program version 9.3. A 2-sided value of $P < 0.05$ was used for declaring statistical significance.

3. Results

The study population consisted of 4678 patients who were enrolled in the 6 surveys composing the ACSIS 2002–2013. In the 2002–2006 surveys ("early period"), 2531 patients were enrolled, of whom 865 (34%) lived in DSW regions while 1666 (66%) lived in non-DSW regions. In the 2008–2013 surveys ("late period"), 2147 patients were enrolled, of whom 735 (34%) were from DSW and 1412 (66%) from non-DSW regions.

3.1. Baseline characteristics at admission of patients recruited in the early and late periods in the DSW and non-DSW groups

The baseline characteristics of patients from the early versus late period living in both DSW and non-DSW regions are presented in Table 1. Patients recruited in the more recent survey were younger and had significantly higher BMI, smoking, diabetes mellitus, hypertension, dyslipidemia and family history of premature coronary artery disease (CAD). The baseline characteristics of patients recruited in the early and late periods clustered by DSW versus non-DSW regions are presented in Table 2. In both the early and late periods, patients from DSW regions were younger and had lower incidence of congestive heart failure history. In the late period, patients from DSW regions had significantly lower incidence of CAD risk factors before index hospitalization; hypertension, prior PCI, prior CABG and family history of premature CAD, compared with those from non-DSW regions. However, their smoking rate and peripheral vascular disease rate were significantly higher compared with those from the non-DSW regions.

3.2. Admission medications and laboratory results of patients recruited in the early and late periods in the DSW and non-DSW groups

Admission medications in patients from DSW and non-DSW regions are shown in Table 3. In the late period the glucose levels were slightly higher in patients from DSW regions. In the late period both groups (DSW and non-DSW) were homogeneous in terms of renal function, however, serum cholesterol levels were higher in patients recruited in the late period from DSW regions.

3.3. In-hospital complications in patients recruited in the early and late periods in the DSW and non-DSW groups

In-hospital complications were generally lower in patients recruited from DSW regions as well as non-DSW regions who were enrolled in the late compared with the early period, including the incidence of pulmonary edema, cardiogenic shock and anterior wall MI as shown in Table 4. However, anterior wall MI and cardiogenic shock were significantly more common in the late period in patients recruited in the DSW compared with the non-DSW regions. Of note in the late period, patients who lived in non-DSW compared to DSW regions were older, had higher incidence of females, diabetics and family history of premature CAD as well as higher incidence of prior (before hospital admission) heart failure, higher incidence of prior MI, PCI and CABG operations. Nevertheless, their in-hospital complications such as anterior wall MI and cardiogenic shock (both indicators of larger myocardial injury and necrosis) were significantly lower.

3.4. In-hospital care, discharge recommendations and clinical outcome of patients recruited in the early and late periods in the DSW and non-DSW groups

Data on in-hospital care, discharge recommendations and clinical outcome are shown in Table 5. The prevalence of thrombolysis markedly declined in patients recruited in the late period compared with the early period in both the DSW and non-DSW regions, however the reduction was steeper in the non-DSW regions, in the late period. Most patients with ST-elevation myocardial infarction (STEMI) from the early and late periods received primary PCI as the main reperfusion therapy according to practice guidelines. In both the early and late periods the quality index of arrival to reperfusion ("door to balloon time") ≤90 min was not different between groups (DSW and non-DSW). The hospital duration time of patients recruited in the DSW group was significantly higher in both periods. On hospital discharge, clopidogrel prescription was more frequent in the late period in patients from non-DSW compared to DSW regions. Angiotensin-converting enzyme inhibitors, however, were prescribed less frequently for patients recruited from the non-DSW regions compared with those from the DSW region, in both periods.

Despite higher incidence of CAD risk factors in patients recruited from non-DSW regions, the mortality rates were significantly lower both in the 30-day and 1-year follow-up, in the late period but not in the earlier period.

Table 2
Baseline and admission characteristics of patients recruited in the early and late periods in the DSW and non-DSW groups.

	Early (2002–2006)			Late (2008–2013)		
	DSW N = 865	Non-DSW N = 1666	P-value	DSW N = 735	Non-DSW N = 1412	P value
Age (±SD) (years)	63 ± 12	64 ± 13	0.01	62.4 ± 13	63.5 ± 13	0.05
Female gender	216 (25%)	393 (21%)	0.44	144 (20%)	339 (24%)	0.02
BMI (±SD)	27.3 ± 4	27.5 ± 4.4	0.19	30.6 ± 5	29 ± 15	0.08
Diabetes mellitus	309 (36%)	564 (34%)	0.35	286 (39%)	550 (40%)	0.55
Hypertension	467 (54%)	972 (58.4%)	0.03	457 (62%)	939 (66%)	0.05
Dyslipidemia	468 (54%)	999 (60%)	0.005	571 (78%)	1135 (80%)	0.22
Family history of coronary artery disease	164 (19%)	348 (21%)	0.17	173 (25%)	394 (29%)	0.02
Smoking	473 (54.7%)	879 (52.8%)	0.35	505 (68.7%)	829 (58.7%)	<0.001
Chronic renal failure	80 (9%)	215 (13%)	0.06	107 (15%)	181 (12%)	0.25
History of congestive heart failure	52 (6%)	169 (10%)	<0.001	36 (5%)	127 (9%)	<0.001
History of myocardial infarction	208 (24%)	515 (31%)	<0.001	207 (28%)	434 (31%)	0.25
History of angina	301 (34%)	712 (42%)	<0.001	292 (39%)	546 (38%)	0.64
History of PCI	169 (20%)	375 (21%)	0.26	211 (21%)	477 (34%)	0.02
History of CABG	76 (9%)	174 (11%)	0.8	52 (7%)	151 (11%)	0.006
PVD	96 (11%)	152 (9%)	0.11	94 (13%)	93 (7%)	<0.001

BMI — body mass index, PCI — percutaneous coronary intervention, CABG — coronary artery bypass grafting, PVD — peripheral vascular disease, ACEI — angiotensin converting enzyme inhibitors, ARB — angiotensin receptor blocker.

Table 3
Admission medications and laboratory results of patients recruited in the early and late periods in the DSW and non-DSW groups.

	Early (2002–2006)			Late (2008–2013)		
	DSW N = 865	Non-DSW N = 1666	P-value	DSW N = 735	Non-DSW N = 1412	P-value
Admission medications						
Aspirin	847 (98%)	1538 (92%)	<0.001	703 (96%)	1384 (98%)	0.001
Beta-blockers	733 (85%)	1318 (80%)	<0.001	610 (83%)	1122 (80%)	0.04
Statins	640 (74%)	1318 (79%)	0.002	697 (95%)	1321 (94%)	0.19
Clopidogrel	663 (77%)	998 (60%)	<0.001	573 (78%)	1130 (80%)	0.26
Anticoagulants	28 (3%)	42 (3%)	0.31	35 (5%)	63 (5%)	0.75
Nitrates	273 (47%)	445 (40%)	0.01	291 (40%)	256 (18%)	<0.001
ACEI/ARB	704 (81%)	1098 (61%)	<0.001	617 (84%)	1073 (74%)	<0.001
Laboratory results						
Creatinine (±SD)	1.2 ± 0.93	1.3 ± 0.94	0.001	1.4 ± 4.7	1.8 ± 7.8	0.22
GFR (±SD)	99.12 ± 181	71 ± 87	<0.001	92 ± 417	85 ± 349	0.6
Glucose mg/dL (±SD)	163 ± 83.5	166 ± 88	0.55	162.7 ± 96.6	155 ± 83	0.07
Peak K (IU/L) (±SD)	1014 ± 2355	1044.8 ± 2011	0.73	752 ± 1101	705 ± 1224	0.4
Cholesterol-total (±SD)	195 ± 46	193 ± 47	0.45	183 ± 47	178 ± 46	0.04
LDL (±SD)	122 ± 40	117 ± 40	0.01	111 ± 40	108 ± 40	0.1
HDL (±SD)	42 ± 15	41 ± 13	0.1	39 ± 11	38 ± 12	0.7

ACEI — angiotensin converting-enzyme inhibitors, ARB — angiotensin receptor blocker, GFR — glomerular filtration rate, LDL — low density lipoprotein; HDL — high density lipoprotein, CK — creatine kinase.

3.5. Temporal trends in outcome among patients recruited in the DSW and non-DSW regions

Consistent with the above findings, Kaplan–Meier survival analysis shows that in the early period the 1-year mortality rates were similar in patients recruited from DSW regions compared with patients from non-DSW regions (Fig. 1A). By contrast, in the late period the 1-year mortality in patients recruited from DSW regions was significantly higher compared with those in the non-DSW regions (Fig. 1B).

Multivariate analysis adjusted for confounders listed in the Methods section demonstrated a higher risk of 30-day all-cause-mortality in patients from DSW regions compared to the non-DSW regions only in the late period (HR = 2.35 CI 95% 1.33–4.15, P < 0.001) while in the early period there was no significant difference (HR = 1.37 CI 95% 0.9–2, P = 0.14) (Fig. 2A). Furthermore, there was a significantly higher 1-year all-cause mortality in the late period in patients from DSW compared to non-DSW regions (HR = 1.87 CI 95% 1.32–2.63, P < 0.0001) while in the early period there was no significant difference (HR = 1.17 CI 95% 0.9–1.5, P = 0.22) (Fig. 2B).

3.6. MACE

The crude rates of MACE were higher in the DSW group, compared with the non-DSW group in the early period, and similar between groups in the late period, as shown in Table 5. However, multivariate logistic regression modeling, after adjustment for confounders listed above, showed a higher MACE score in patients from DSW regions compared with those residing in the non-DSW regions, at the late period compared with the early period (OR = 2.04 CI 95% 1.48–2.8, P < 0.0001). However, in patients from non-DSW regions, there was no significant difference between the two periods (OR = 1.19 CI 95% 0.93–1.52, P = 0.16).

3.7. Serum magnesium levels and magnesium supplements

Serum magnesium levels on hospital admission were available in 211 of 268 ACS patients (from 4 hospitals) in the year 2013 (130 patients recruited in 2 hospitals in the DSW regions and 81 from patients recruited in 2 hospitals in the non-DSW regions). Serum magnesium levels (M ± SD) were significantly lower in patients recruited from DSW regions compared to the non-DSW regions (1.94 ± 0.24 mg/dL vs. 2.08 ± 0.27 mg/dL, respectively; P < 0.0001) (Fig. 3).

Data on magnesium supplementations were not collected in our patient population. However, in a questionnaire conducted in 150 consecutive first AMI patients from both DSW and non-DSW regions in 2015, intake of magnesium supplementations was reported in only by 8% of the patients.

4. Discussion

Throughout the early period (2002–2006) of the study, while there was no seawater desalination in Israel, the 30-day survival and 1-year survival were not significantly different in ACS patients from DSW and

Table 4
In-hospital complications of patients recruited in the early and late periods in the DSW and non-DSW groups.

	Early (2002–2006)			Late (2008–2013)		
	DSW N = 865	Non-DSW N = 1666	P-value	DSW N = 735	Non-DSW N = 1412	P-value
Anterior MI	330 (38%)	544 (33%)	0.005	210 (29%)	320 (23%)	0.009
High degree AVB	33 (4%)	38 (2.3%)	0.02	19 (3%)	31 (2.2%)	0.56
New LBBB	10 (1%)	24 (1.4%)	0.55	1 (0.2%)	3 (0.3%)	0.77
New RBBB	13 (1.5%)	32 (2%)	0.44	12 (3%)	12 (1.3%)	0.05
Cardiogenic shock	39 (4.5%)	50 (3%)	0.05	31 (4%)	33 (2.3%)	0.01
Pulmonary edema	104 (12%)	163 (10%)	0.08	44 (6%)	67 (4.7%)	0.21
Major bleeding	7 (0.8%)	19 (1%)	0.4	10 (1.4%)	28 (2%)	0.3
Free wall rupture	6 (0.7%)	9 (0.5%)	0.63	2 (0.3%)	3 (0.2%)	0.7
Pericarditis	7 (0.8%)	17 (1%)	0.6	4 (0.5%)	7 (0.5%)	0.87
Tamponade	2 (0.2%)	6 (0.4%)	0.58	2 (0.3%)	4 (0.3%)	0.96

MI — myocardial infarction, AVB — atrioventricular block, LBBB — left bundle branch block, RBBB — right bundle branch block, EF — ejection fraction.

Table 5
In-hospital care, discharge recommendations and clinical outcome of patients recruited in the early and late periods in the DSW and non-DSW groups.

	Early (2002–2006)			Late (2008–2013)		
	DSW N = 865	Non-DSW N = 1666	P-value	DSW N = 735	Non-DSW N = 1412	P-value
In-hospital care						
Primary PCI for STEMI	348 (69%)	658 (67%)	0.41	525 (71%)	964 (68%)	0.13
Thrombolysis	93 (35%)	265 (54%)	<.0001	43 (15%)	11 (2.7%)	<0.001
CABG until discharge	48 (5.5%)	78 (4.7%)	0.34	25 (3.4%)	40 (2.8%)	0.46
Primary PCI within 90 min from ER arrival with STEMI	588 (68%)	1232 (74%)	0.07	485 (66%)	1002 (71%)	0.13
Hospital duration (days) (±SD)	8.7 ± 9.2	6.7 ± 5.2	<.0001	7 ± 6.5	5 ± 5	<0.001
Discharge recommendations						
Statins	678 (93%)	1293 (93%)	0.8	655 (77%)	1349 (82%)	0.001
Aspirin	803 (94%)	1493 (91%)	0.003	698 (95.2%)	1333 (95.4%)	0.9
Clopidogrel	565 (66%)	945 (58%)	<.0001	462 (63%)	946 (68%)	0.03
Beta blockers	690 (81%)	1289 (78%)	0.17	582 (79%)	1067 (76%)	0.1
ACE inhibitors/ARB	675 (79%)	1065 (65%)	<.0001	581 (79%)	998 (71%)	<0.001
Clinical outcomes						
30-day all-cause mortality	53 (6.1%)	90 (5.4%)	0.46	44 (6%)	49 (3.5%)	0.006
1-year all-cause mortality	112 (13%)	186 (11.2%)	0.17	72 (10%)	102 (7.3%)	0.04
MACE at 30-days	191 (22%)	247 (15%)	<.0001	87 (12%)	156 (11%)	0.58

CABG — coronary artery bypass grafting operation; ER — emergency room, MACE — Major adverse cardiovascular events, PCI — percutaneous coronary intervention; STEMI — ST-elevation myocardial infarction.

non-DSW regions. By contrast, in the later period (2008–2013), following seawater desalination, both 30-day survival and 1-year survival were significantly reduced in patients from the DSW compared with the non-DSW regions. To the best of our knowledge, this is the first report of an association between DSW supply for DW and mortality in ACS patients.

Water hardness contains magnesium and calcium ions. Many studies have examined the association between cardiovascular mortality and water hardness. However, the results have been inconsistent. Numerous studies have shown an inverse relation between water hardness and CVD morbidity and mortality [8–20].

By contrast, a Swedish study from 2005 does not support previous reports of a protective effect on myocardial infarction from water with higher levels of hardness [25]. A long-term British cohort study from 2007 suggests that neither high water hardness, nor high calcium or magnesium intake appreciably protects against CVD [24].

Studies were performed on the relationship between water hardness, magnesium and calcium with CVD, of tap water from various sources. To the best of our knowledge there are no reports on the impact of using DSW, which are deficient in magnesium and calcium, on population health. While calcium is added to DSW in Israel, there is no enrichment of magnesium. Thus, a large part of the Israeli population consumes DW with low magnesium content. This creates a unique opportunity to study the health implications of low magnesium intake secondary to seawater desalination.

There is no clear latency period between exposure and adverse health effects. Some authors pointed out that 1-year is sufficient to produce observable magnesium effects [16], while others have indicated that longer periods of observations are needed [33]. However, in our study the exposure period was at least 2 years.

According to the WHO, the recommended daily magnesium dose for an adult is about 400 mg for men and 300 mg for women [2]. Studies show that daily magnesium intake by the population is inadequate and the average daily consumption in Israel for adults is 228–270 mg, which is less than 70% of the recommended daily dose for men [34]. According to WHO recommendations (2005), in regular climatic conditions and effort, the daily water intake for children, adult women and men is 1, 2.2 and 2.9 L respectively. Under conditions of warm climate and hard work the recommended daily water consumption is 4.5 L [3]. While standard tap water contains 20–25 mg of magnesium per

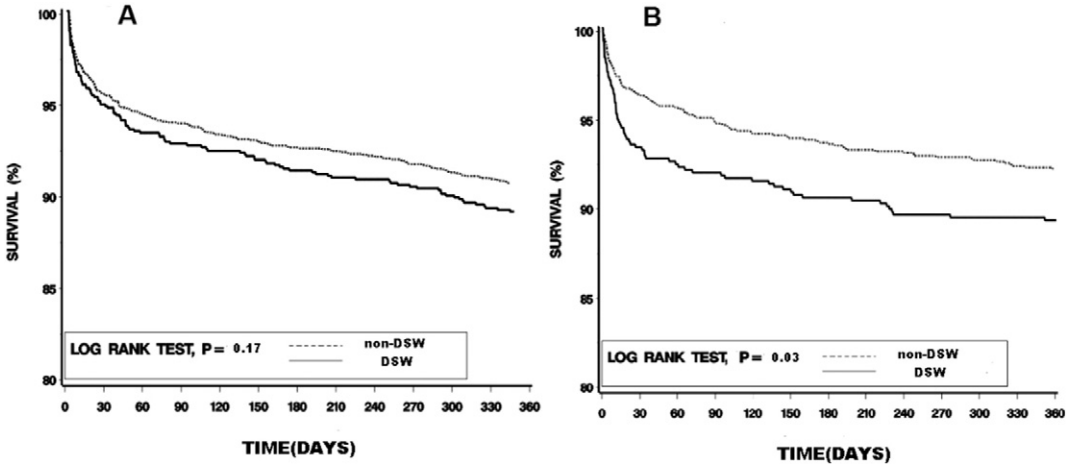

Fig. 1. A — 1-year survival stratified by DSW regions for 2002–2006 period. B — 1-year survival stratified by DSW regions for 2008–2013 period. Comparison of Kaplan–Meier 1-year survival curves between patients in the desalinated sea water and non-desalinated sea water regions in the early period (A) (P = 0.17) and late period (B) (P = 0.03).

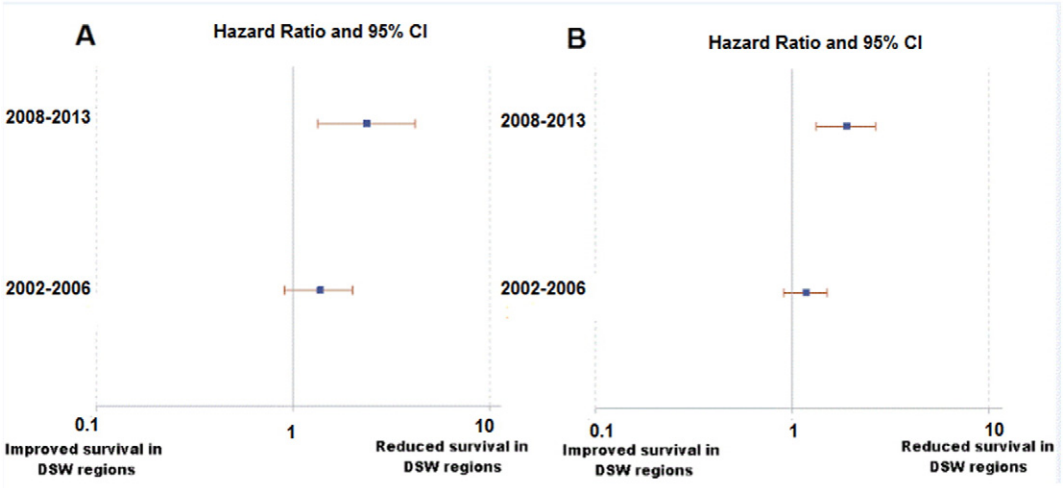

Fig. 2. A — Comparison of 30-day survival in patients in the DSW regions in reference to patients in the non-DSW regions. B — Comparison of 1-year survival in patients in the DSW regions in reference to patients in the non-DSW regions. Adjusted Hazard ratios for 30-day (A) and 1-year all-cause mortality (B) in patients recruited from the early and late periods, adjusted for clinical variables. The horizontal bars show the 30-day (A) and 1-year (B) survival in patients in the desalinated sea water regions in reference to the non-desalinated sea water regions (HR = 1); the HR for 30-days was 1.37 (CI 95% 0.9–2, P = 0.14) for the years 2002–2006, and 2.35 (CI 95% 1.33–4.15, P < 0.001) for the 2008–2013 period. Corresponding HRs for the 1-year survival were 1.17 (CI 95% 0.9–1.5, P = 0.22) and 1.87 (CI 95% 1.32–2.63, P < 0.0001) respectively.

liter, DSW contains very little magnesium or does not contain at all [1]. According to these data, standard tap water contributes about 20% to daily magnesium intake. In a recent paper from Spain, the estimated fraction of daily magnesium recommendations provided by water consumption in adults was 7.5–17%, if the magnesium water concentration is 15–30 mg/L [35]. Thus, supply of DSW as the main source of DW may farther aggravate magnesium deficiency.

Kanadhia et al. indicate that lower magnesium concentrations in DW correlate with low serum magnesium [36]. Low serum magnesium concentrations predict cardiovascular and all-cause mortality [37] and are associated with an increased risk of coronary heart disease (CHD) mortality and sudden cardiac death [38,39]. Serum magnesium levels were not inspected in the ACSIS study, but we know that serum magnesium levels are inversely proportional to glucose levels and we determined that in the late period the glucose levels were slightly higher (P = 0.07) in patients recruited from DSW regions, which was not the case in the early period. Also, in our study the admission serum magnesium levels of the 211 patients (out of 268) who were recruited in 2013 in 4 hospitals, were significantly lower in patients from DSW regions compared with patients from the non-DSW regions. The effect of magnesium supplements on these differences is unlikely as only 8% of patients recently recruited

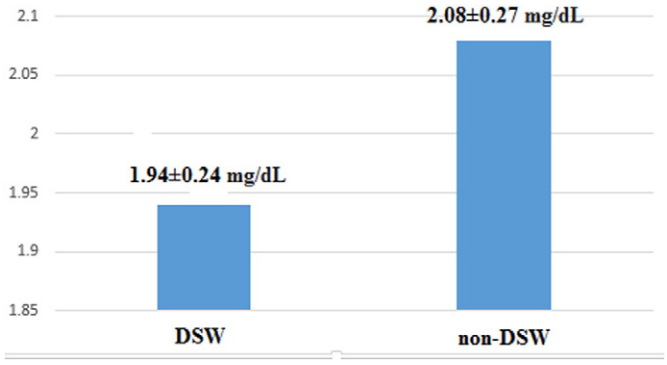

Fig. 3. Serum magnesium levels ± SD in admission in patients from DSW regions vs. non-DSW regions. Admission serum magnesium levels (M ± SD) in 130 patients recruited from the desalinated sea water regions (1.94 ± 0.24 mg/dL) and 81 patients recruited from the non-desalinated sea water regions (2.08 ± 0.27 mg/dL) (P < 0.0001).

for the ACSIS study, in hospitals from both regions, received daily magnesium supplements.

In addition to the direct effect of reduced magnesium intake by consuming DW supplied by DSW, consumption of crops irrigated by DSW could further contribute to hypomagnesemia. Although magnesium levels in crops irrigated by DSW have not yet been studied in depth, Yermiyahu et al. pointed out that after farmers used DSW for irrigation, magnesium deficiency symptoms appeared in crops, including tomatoes, basil and flowers [1].

Recently, the Scientific Report of the 2015 Dietary Guidelines Advisory Committee (DGAC), Advisory Report to the US Secretary of Health and Human Services and the Secretary of Agriculture found that in a representative sample of the US population ages 2 years and above magnesium (as well Vitamins A, D, E, C, folate and calcium) is under consumed. The DGAC suggests that the US population should increase consumption of foods rich in magnesium [40].

A positive correlation between CHD and the estimated calcium and magnesium ratio in the diet has also been suggested in several countries [41].

An internal report of the Israeli Ministry of Health estimated that "DW supply with deficient magnesium in DSW is expected to result in excess mortality of about 250 Israelis from CVD, annually. If DSW is supplied to 27.3% of the population, annual AMI mortality will be expected to rise from 1417 to 1682. However, adding magnesium to DSW in concentrations of 10, 20 and 30 mg/l will reduce annual AMI mortality to 1507, 1464 and 1425 respectively" [42]. In reality, the proportion of the Israeli population which received DSW has increased steeply, approaching 75% in 2016, so that the earlier estimated excess CVD mortality of about 250 Israelis annually from the consumption of DSW, should be up-scaled by a factor of 2.7.

Further research is needed to estimate the actual mortality attributed to DSW consumption in Israel, on a national level. Data of the present study may have a potential impact on the health implications, particularly regarding cardiovascular disease, from the consumption of DSW globally. With the trend of global warming in parallel to the increase in global population, the demands for DW supply are expected to increase the production and consumption of DSW.

Our study has several limitations, this was a retrospective cohort analysis and not an interventional prospective analysis. Individual assessment of DSW consumption was not done in patients recruited for this study. However, the comparison between groups of patients

residing in the same regions, and served by the same hospitals, before and after initiation of DSW consumption, and the large sample size gives power to the study. The absence of systematic data on serum magnesium levels is a limitation and requires further prospective study to assess the correlation between DSW consumption, serum magnesium levels and cardiovascular health.

In conclusion, magnesium is essential to human health. While lack of magnesium in DW was associated with increased cardiovascular morbidity and mortality, this question has not been previously studied in a population that consumes DSW, deficient in magnesium. Higher 30-day and 1-year all-cause mortality in AMI patients, found in patients residing in regions with DSW supply in our study, may be attributed to reduction in magnesium intake secondary to using DSW. Large prospective studies are needed to evaluate the potential health implications of using DSW, as a major source of DW, since the increasing global demands for DW result in a steep increase of the production and usage of DSW as a major source for DW.

Conflict of interest

The authors state that no conflict of interest exists regarding the possible publication of this article.

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