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Association between exposure to desalinated sea water and ischemic heart disease, diabetes mellitus and colorectal cancer; A population-based study in Israel

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ABSTRACT

Background: Drinking water (DW) is an important dietary source of magnesium. Recently, Israel has increased its use of desalinated seawater (DSW) as DW country-wide. Its negligible magnesium content, however, raises concern that consumption of DSW may be associated with hypomagnesemia and increase the risk of ischemic heart disease (IHD), diabetes mellitus (DM), and colorectal cancer (CRC).

Objectives: We tested whether there was a change in incidence of negative health outcomes (IHD, DM, and CRC) following the introduction of DSW supply in a population-based ecologic study in Israel.

Methods: A historical prospective analysis was applied to members aged 25–76 during 2004–2013 of Clalit Health Services (Clalit), the largest healthcare provider in Israel, using its electronic medical record database. Multivariable analyses were adjusted for age, sex, socioeconomic status, smoking status, and body mass index.

Results: An increased odds ratio was found for IHD (0.96, 95% CI 0.93–0.99 at baseline and 1.06, 95% CI 1.02–1.11 at the end of the follow-up period), but no time trend was observed.

Conclusions: We found that the risk for IHD increased during the study period. The risks for DM and CRC were unchanged. Long term studies are needed for assessing the risk for CRC due to the long latency. The higher risk for IHD has practical public health implications and raise the need to add magnesium to DSW.

1. Introduction

The availability worldwide of fresh water sources is rapidly diminishing due to climate change and global warming. The perpetually increasing global population combined with a parallel decrease in precipitations jointly deepen the need for fresh water supply. As a form of compensation, desalinated sea water (DSW) has steadily gained credence. In 2015, 150 countries were reported to have operated over 17,000 desalination facilities, daily generating a total of over 80 million cubic meters of drinking water (DW) upon which 300 million people relied (International Desalination Association, 2015).

During the past decade, Israel has massively accelerated the production of DSW. Today, over 50% of Israeli tap water comprises DSW (Koren et al., 2017). It follows, then, that a large Israeli population is exposed to any health effects potentially incurred by DSW (Spungen et al., 2013), specifically with respect to loss of calcium and magnesium. Since both are vital for human health (World Health Organization (WHO), 2005), the WHO recommended in its 2011 report 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" (World Health Organization, 2011, p. 25).

Consequently, in Israel, an expert committee recommends adding calcium to DW and advocates monitoring the long-term effects of magnesium absence in DSW on cardiovascular disease (CVD) (Adin Committee, 2007), which is the major health hazard of magnesium deficiency in developed countries (Ferrandiz et al., 2004). Subsequently, calcium has been added to DSW in Israel, but magnesium has

Abbreviations: DSW, desalinated sea water; DW, drinking water; IHD, ischemic heart disease; DM, diabetes mellitus; CRC, colorectal cancer; CVD, cardiovascular disease; AMI, acute myocardial infarction; BMI, body mass index; SES, socioeconomic status; WHO, World Health Organization; Clalit, Clalit Health Services

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not been added. Magnesium is essential for over 300 metabolic processes, including energy production, protein and nucleic acid synthesis, regulation of vascular tone, and insulin sensitivity (Guerrera et al., 2009). Magnesium deficiency may result in hypertension, cardiac arrhythmia, atherosclerosis, diabetes mellitus (DM), and increased risk for colorectal cancer (CRC) (Markovits et al., 2016; Rasic-Milutinovic et al., 2012; Rosanoff et al., 2012). A recent study has shown a significant increase in all-cause mortality in hospitalized patients in Israel suffering from acute myocardial infarction (AMI), who were living in regions where DSW is the main source of DW (Shlezinger et al., 2016). Due to their researched prevalence, three of these phenomena are further elaborated here: CVD, DM, and CRC.

In a 1992 retrospective review of studies that span a period of 30 years Eisenberg established an association between magnesium deficiency and sudden death (Eisenberg, 1992). The studies were epidemiological and clinical by nature and included human and animal autopsies. Eisenberg suggested a regular supply of magnesium as a possible mean to mitigate the risk of sudden death. Some resolutions to combat this risk included population-level education on the benefits of a magnesium-rich diet, taking magnesium supplements, and enriching DW and food with magnesium.

Numerous reports have demonstrated an inverse association between CVD-related morbidity and mortality and water hardness (e.g., Ferrandiz et al., 2004; Knezović et al., 2014; Kousa et al., 2004, 2006; Luoma et al., 1983; Marque et al., 2003; Punsar and Karvonen, 1979; Rubenowitz et al., 1996, 2000; Rylander et al., 1991; Sauvant and Pepin, 2000; Yang et al., 2006). Of note, Catling and others have calculated a pooled OR of 0.75 for an inverse association between magnesium levels in DW and CVD mortality (95% CI 0.68–0.82; $p < 0.001$). The effect of calcium, however, remained inconclusive (Catling et al., 2008). Additional studies also render controversial the relationship between magnesium and calcium content and CVD risk (Leurs et al., 2010; Maheswaran et al., 1999; Miyake and Iki, 2004; Morris et al., 2008; Rosenlund et al., 2005).

Poor magnesium content in modern processed food further emphasizes the potential benefits of magnesium in DW, especially in areas where prevalent nutritional habits rely mainly on a magnesium-poor diet. Rosanoff (2013) estimated that global consumption of DW and beverages containing moderate to high levels of magnesium (10–100 ppm) would have the power to prevent as much as 4.5 million heart diseases and stroke deaths per year. Indeed, Gharedaghi et al. (2014) showed a marked reduction in CVD morbidity in an Iranian province after increasing the magnesium content in DW for one year. Similarly, a recent meta-analysis of case-control studies showed a protective effect of magnesium in DW for CVD, with an effect size of 0.75 (95% CI 0.66–0.86; $p = 0.000$) (Gianfredi et al., 2017). However, high heterogeneity and certain publication bias limit the robustness and generalizability of these findings. A large-scale Japanese study showed an inverse association between magnesium intake and mortality from hemorrhagic stroke in men and ischemic strokes, coronary heart disease, heart failure, and total CVD in women (Zhang et al., 2012). A multivariable hazard ratio of 0.49 (95% CI 0.26–0.95) was found for the highest vs. lowest quintiles of magnesium intake, after adjusting for CVD risk factors and sodium intake.

Another disease that seems to be influenced by magnesium intake is DM. A case-control study (Yang et al., 1999), which had a heavy impact on the Taiwanese water industry and human health, showed magnesium intake provided an important protective effect against DM mortality. Similarly, Longstreet et al. (2007) studied magnesium as a candidate contributor to DM in Australian Aboriginals and Torres Strait Islanders based on magnesium content of DW and diet. They explored additional climate and socioeconomic status (SES) properties potentially influencing properties on magnesium intake, such as temperature, rainfall, education, employment, and income. They reported a strong correlation between the magnesium content of DW and DM-related mortality, supporting their hypothesis that low magnesium dietary intake, characterized by low DW magnesium content, can elevate DM-mortality risk in the endemic population of Queensland. In contrast, a register-based Finnish study (Kousa et al., 2011) did not conclusively demonstrate an association of well water magnesium content with the geographical variation of DM while an earlier study (Joslyn et al., 1990) has altogether failed to find a direct effect of magnesium in DW on DM.

The relationship between DSW and cancer was studied extensively. In their recent review, Nriagu et al. (2016) focused on the Arabian Gulf region population, which relies on DSW as its primary source of DW. The authors comment on the potential risk for cancer development from consuming DSW, proposing that DSW can critically upset the body's electrolyte balance due to its low concentrations of calcium, sodium, potassium, and magnesium, ultimately leading to tumorigenesis and full-fledged cancer. The direct causal relation linking DSW and cancer, however, is yet to be proven. More specifically, in a Taiwanese case-control study on CRC (Yang et al., 1997) no evidence was found for a significant relationship between magnesium levels in DW and CRC whereas calcium intake from DW showed a significant protective effect. Further evidence suggests the presence of other substances is required in order to observe the influence of magnesium on CRC. For example, data of a case-control study based on Taiwanese death certificates across a 5-year period (from 2003 to 2007) shows that low magnesium in DW is associated with CRC-related deaths when nitrate content is high in DW (Chiu et al., 2010). Similarly, Kuo et al. (2010), who have gathered data from 53 municipalities in Taiwan, concluded that while trihalomethanes alone did not influence the risk of CRC-related death, their combination with lower magnesium levels in DW evidently works in favor of CRC development.

Despite the vast research demonstrating various adverse health effects of low magnesium and calcium content in DW and the sharp increase in the utilization of DSW globally, only a few studies were conducted exploring the association between DSW and health outcomes. The impact of exposure to DSW on the incidence of ischemic heart disease (IHD), DM, and CRC morbidity is as yet under-explored; this, together with the inconclusive results of previous studies on poor magnesium content in DW and diet, prompted us to investigate changes in incidence of IHD, DM, or CRC among a population residing in a region where DSW is the main source of DW.

2. Methods

2.1. Study area and population

This is a large historical prospective cohort study conducted on data from 2004 to 2013 that was extracted from the electronic medical record database of Clalit Health Services (Clalit), the largest health fund in Israel. Members of Clalit represent a geographically and socioeconomically diverse population of over 4 million patients, both inpatients and outpatients, with less than 1% attrition per year (Shmueli et al., 2007). Furthermore, Clalit has a single, comprehensive, universally adopted electronic medical record system in which all members' health care data is compiled into a single data warehouse, including diagnoses, laboratory measurements, and medication usage. This system thus provides an opportunity to capture incidence of new diseases at the population level.

450,174 members were included in the cohort if they were 25–74 years of age (inclusive) as of index date and had been members in Clalit for at least two consecutive years prior, to increase the completeness of the dataset, the final model includes only those members with available smoking, body mass index (BMI) and demographic data (Fig. 1). Members whose primary care clinic changed to a region of a different type of water supply during the course of the study were excluded. This study was approved by Clalit's ethical review committee.