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Health effects of desalinated water: Role of electrolyte disturbance in cancer development

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ABSTRACT

This review contends that “healthy” water in terms of electrolyte balance is as important as “pure” water in promoting public health. It considers the growing use of desalination (demineralization) technologies in drinking water treatment which often results in tap water with very low concentrations of sodium, potassium, magnesium and calcium. Ingestion of such water can lead to electrolyte abnormalities marked by hyponatremia, hypokalemia, hypomagnesemia and hypocalcemia which are among the most common and recognizable features in cancer patients. The causal relationships between exposure to demineralized water and malignancies are poorly understood. This review highlights some of the epidemiological and in vivo evidence that link dysregulated electrolyte metabolism with carcinogenesis and the development of cancer hallmarks. It discusses how ingestion of demineralized water can have a procarcinogenic effect through mediating some of the critical pathways and processes in the cancer microenvironment such as angiogenesis, genomic instability, resistance to programmed cell death, sustained proliferative signaling, cell immortalization and tumorigenic inflammation. Evidence that hypoosmotic stress-response processes can upregulate a number of potential oncogenes is well supported by a number studies. In view of the rising production and consumption of demineralized water in most parts of the world, there is a strong need for further research on the biological importance and protean roles of electrolyte abnormalities in promoting, antagonizing or otherwise enabling the development of cancer. The countries of the Gulf Cooperative Council (GCC) where most people consume desalinated water would be a logical place to start this research.

1. Introduction

In his landmark paper, Ames (1979) observed that damage to DNA appeared to be a major cause of most cancers and suggested that natural chemicals in the human diet and the tens of thousands of synthetic chemicals that have recently been introduced into the environment be tested for their ability to damage DNA. Dr. Ames advocated the use of rapid mutagenicity assays to identify environmental mutagens and carcinogens and this seminal study was responsible for shifting the scientific and regulatory emphasis to ‘mutagens as carcinogens’, and led to international quest to find individual chemicals and a few well-defined mixtures (e.g. diesel exhaust) that could be shown to be ‘complete’ carcinogens (i.e., substances that could cause cancer on their own). Advances in cancer biology subsequently revealed the limitations of this approach and have let to the multistage and “hallmarks of cancer” framework which recognizes that the cumulative effects of individual (non-carcinogenic) chemicals acting on different pathways, and a variety of related systems, organs, tissues and cells could plausibly conspire to produce tumors and ultimately malignancies (Casey et al., 2015; Hu et al., 2015; Narayanan et al., 2015). We hypothesize that electrolyte disturbance from exposure to demineralized water can mediate the cancer microenvironment in ways that lead to procarcinogenic outcomes. This review explores the role of dysregulation in electrolyte homeostasis, one of the most recognizable features as well as one of the earliest described hallmarks of cancer (Robey et al., 2015), in enabling cancer genesis, maintenance and progression.

As freshwater resources become scarcer, communities in different parts of world have turned increasingly to “manufacturing” drinking water from desalination or demineralization of seawater. Desalination of sea water and brackish water is growing rapidly and has become the principal source of new fresh (demineralized) water in many parts of the world (Greenlee et al., 2009; Fried and

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Serio, 2012; Lattemann et al., 2010). As of 2013, there were more than 17,000 desalination plants located in 150 different countries. These plants produce about over 80 million cubic meters of water (21.1 billion US gallons) per day. More than 300 million people around the world rely on desalinated water for some or all their daily needs (IDA, 2015). The rate of desalination continues to grow inexorably, driven by worldwide expansion in drought (for example, in California, USA) and the need for water especially in the Arabian Gulf region and China (GWI, 2015). Desalinated water differs from natural waters in the sense that its composition can be controlled whereas natural waters have a very wide range of physical, chemical and biological characteristics that are a matter of climate, geology and chance which are tied to the health of the local population and ecosystems (WHO, 2011a; Mecawi et al., 2013). A logical question in public health is whether the ultimate composition of desalinated and other manufactured "pure" water may have a negative impact on the health of long-term consumers (WHO, 2011a; Rygaard et al., 2011). In this review, we used the "weight of evidence" approach to suggest that chronic ingestion of demineralized water is a potential risk factor for adverse health outcomes.

Chronic ingestion of demineralized water can change the ionic and molecular composition of the extracellular and intracellular fluids resulting in hyponatremia, hypokalemia, hypomagnesemia and hypocalcemia which are very common comorbidities in cancer patients. Such dysregulated electrolyte homeostasis can contribute to multiple stages of tumor development by influencing the tumor microenvironment which consists of a complex of interaction among the extracellular matrix that provides structural and biochemical support, signaling molecules that send messages, blood vessels that feed the tumor, and soluble factors such as cytokines (Casey et al., 2015; Langie et al., 2015). Furthermore, ingestion of water with low levels of sodium, potassium, magnesium and calcium can affect the tonicity and osmolality of body fluids and hence the effective cell volume and blood pressure – thereby creating osmotic stress. Studies on several mammalian cell lines suggest that osmotic stress, regardless of its origin, can cause DNA damage leading to chromosome aberrations; genome malfunction occasioned often is a prerequisite for the development of cancer (Langie et al., 2015; Thompson et al., 2015). This review makes a case that the cumulative effects of aberrant electrolyte homeostasis on different metabolic pathways and a variety of related systems, organs, tissues and cells can produce carcinogenic synergies. The exact mechanism that triggers the procarcinogenic effect needs to be fully explored. This review highlights possible areas for exploratory experiments to validate this hypothesis.

Children are particularly vulnerable to health risks from ingestion of demineralized water. For the most part they drink when given the opportunity and can readily over-hydrate their optimal needs by continuing to drink water or some other liquids such as soda (often low in minerals) or fruit juice (made with demineralized water). Over time, the chronic lack of optimal water intake could create metabolic conditions that can promote epigenetic changes and tumorigenesis later in life. Any delayed health effects from drinking of water by children has to be of some concern.

2. Dysregulation of water and electrolyte homeostasis after ingestion of demineralized water

Since pure desalinated water has unsavory and undesirable attributes that can affect the water distribution system, effort is generally made to stabilize and reduce its corrosivity using lime or limestone and/or some blending with groundwater (WHO, 2005, 2011b; Birnhack et al., 2011). The post-treatment processes often result in products with varying chemical characteristics and it is remarkable that currently there are few regulatory guidelines specific to the quality of desalinated water that gets to the consumer's tap (WHO, 2005). Such desalinated or demineralized water (whether delivered from the tap or sold in bottles) often contain <10 mg/L of sodium, <15 mg/L of calcium, <5 mg/L of magnesium, <3 mg/L of potassium and less than 50 mg/L of total hardness (Whelton et al., 2007; Lahav and Birnhack, 2007; WHO, 2010; Dieter, 2011; Rygaard et al., 2011; Al Nouri et al., 2014). By comparison, typical concentrations in human serum are 15–25 mg/L for magnesium, 45 mg/L for calcium, 137–196 mg/L for potassium and over 3000 mg/L for sodium. Conversion of ingested water into extracellular and intracellular fluids is a complicated phenomenon. Nevertheless, there is evidence to suggest that ingestion of such demineralized water can lead to loss of these cations in urine through the osmoregulatory processes in the hypothalamic-pituitary-adrenal (HPA) axis as well as the adrenergic nervous (ANS) and renin-angiotensin-aldosterone (RAAS) systems (reviewed by Verbalis (2003)). The regulatory responses can culminate in concordant appearance of hypokalemia, hypomagnesemia, hypozincemia, and hyposelenemia which are common pathophysiological features of many cancers (Weber et al., 2010; Rosner and Dalkin, 2014). While the role of electrolyte hypometabolism on tumor pathogenesis is unknown, there is a suggestion that hyponatremia, hypokalemia and hypomagnesemia are important determinants of the outcome of tumors in patients (Onitilo et al., 2007).

Most of the body burden of sodium (about 65% or 2500 mmol) is located in extracellular fluid, whereas only about 8% or 300 mmol of sodium is intracellular and the remainder of the body's sodium (about 25–30% or 1000 mmol) is stored in bone (Giebisch and Windhager, 2005). Serum sodium and its accompanying anions, mainly chloride and bicarbonate, are the major osmotically active substances in the extracellular fluid, and therefore play a paramount role in the control of extracellular and intracellular volume conditions (Giebisch and Windhager, 2005). Consumption of demineralized water has been shown to create both extracellular and intracellular electrolyte imbalances which can lead to spilling of large amounts of sodium, potassium, calcium, magnesium and other trace minerals into the urine, feces and sweat (WHO, 2005, 2011a). In addition, the dilutional effect on the concentration of solutes (osmolytes) in the extracellular fluids would create hypotonicity which causes the cells to swell initially as water diffuses into them to maintain osmolality equilibrium between the intracellular and extracellular fluids (Verbalis, 2003; Miltiadous et al., 2008; Popkin et al., 2010). This causes a change (increase) in blood volume and arterial blood pressure (an osmotic stress) which the cells must quickly avoid (Fig. 1) using a combination of thirst sensation and by balancing the body's electrolyte (mainly sodium) content using two major pathways – the "affector" and "effector" systems (Verbalis, 2003; Popkin et al., 2010). The affector (or sensing) system monitors whether there is too much, too little, or just the right content of sodium. It does this through the baroreceptors in the aortic arch, carotid arteries, atria, brain, and liver. If the sodium content is incorrect, the effector systems is brought into play and uses the renin-angiotensin-aldosterone, catecholamine, and vasopressin systems to change the sodium retention and blood pressure (Popkin et al., 2010). The atrial natriuretic peptide (ANP) system is also involved in renal sodium loss (Bourque et al., 2008; Sterns et al., 2013). These osmoregulatory systems prevent plasma sodium concentration from rising above 142 mEq/L or falling below 135 mEq/L. A change in plasma sodium concentration by as little as 1–2% (with a corresponding change in plasma osmolality) causes cell volume receptors ("osmoreceptors") to respond by activating the stress regulatory system (Verbalis, 2003; Schrier et al., 2013; Sterns et al., 2013; Rivard et al., 2013). What this means is that ingestion of desalinated water does not