



## Dehydration: Need For an Improved Rehydrating Energy Drink

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### ABSTRACT

#### Abstrak

Terapi rehidrasi oral adalah pengobatan utama untuk mengatasi dehidrasi. Namun, terapi ini tidak dapat menghentikan penyebab kehilangan cairan dari usus, yaitu organisme menular yang menyebabkan diare. Beberapa penelitian menunjukkan peran kalsium dalam mengobati diare menular melalui *calcium-sensing receptor* (CaSR), yang tidak terdapat pada oralit. CaSR adalah target baru yang telah menunjukkan efektivitasnya dalam mengobati diare. CaSR diaktifkan oleh agonis kalsium sederhana, pilihan yang mudah diakses, murah, dan aman digunakan pada populasi anak. Penambahan zat gizi merupakan hal yang sederhana dan dapat meningkatkan kemanjuran pengobatan oralit saat ini. Maltodekstrin juga lebih bermanfaat dibandingkan glukosa pada oralit karena osmolalitasnya secara signifikan lebih rendah dibandingkan gula disakarida. Penambahan multivitamin, nutrisi, dan *energy-booster* ke dalam WHO-ORS dapat meningkatkan kemanjuran ORS dalam mengobati diare, mengurangi malnutrisi, dan menyediakan energi untuk mengurangi kelelahan.

**Kata Kunci:** Kalsium, *calcium-sensing receptor*, maltodekstrin terapi rehidrasi oral.

#### What is already known?

- Diarrhea, excessive heat, physical activity, fever, etc is associated with dehydration
- Oral rehydration therapy is the cornerstone treatment for the management of dehydration

#### What does this study add?

Adding nutrients, maltodextrin, and calcium to the current ORT may enhance efficacy, reduce fatigue, and restore nutrients in dehydrated patients.

#### Abstract

*Oral rehydration therapy (ORT) is the cornerstone treatment for managing dehydration. However, ORT cannot “halt” the underlying intestinal fluid loss, a significant mechanism of infectious organisms responsible for causing diarrhea. Reports have demonstrated the role of calcium in treating contagious diarrhea through the calcium-sensing receptor (CaSR), which is absent in oral rehydration solution (ORS). CaSR is a novel target that has demonstrated its effectiveness in treating diarrhea. CaSR is activated by a simple calcium agonist, an easily accessible, inexpensive, and safe-to-use option in the pediatric population. Adding nutrients would be simple and may increase the efficacy of the current ORS treatment. Maltodextrin (MDs) over glucose in ORS has shown benefits in these patients as the osmolality of MDs is significantly lower than that of disaccharide sugars. Thus, adding multivitamins, nutrients, and energy boosters to WHO-ORS may improve the efficacy of ORS in treating diarrhea, reducing malnutrition, and providing energy to curb fatigue.*

**Keywords:** Calcium, *calcium-sensing receptor*, maltodextrin oral rehydration therapy.

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#### ARTICLE INFORMATION

Received: July 03<sup>rd</sup>, 2023

Revised: September 26<sup>th</sup>, 2023

Available online: December 20<sup>th</sup>, 2023

### Introduction

Water is an essential component of life, and the body fluids majorly consist of water as their key component. At a cellular level, fluid distribution and electrolytes are paramount for maintaining health, function, and survival.<sup>1,2</sup> The

mechanisms through which fluid and electrolyte homeostasis is maintained in humans are well understood.<sup>3</sup> Therefore, maintaining water intake is of utmost importance for homeostasis. Water and electrolyte imbalances can adversely impact individuals' performance and health.<sup>3</sup>

Dehydration results from water and electrolyte loss.<sup>3,4</sup> Water loss of as little as 3% of body weight dehydrates a person.<sup>5</sup> The symptoms of dehydration vary with the degree of water loss (Table 1).

Table 1: Dehydration symptoms based on water deficiency<sup>5</sup>

Fluid loss	Symptoms of dehydration
1% of body weight	It hampers thermoregulation and contributes to thirst
2% of body weight	Increased thirst, vague discomfort, and loss of appetite
3% of body weight	Dry mouth
4% of body weight	Decreases work capacity by 20-30%
5% of body weight	Difficulty concentrating, headache, and sleepiness
6% of body weight	Tingling and numbness of extremities
7% of body weight	Collapse can occur
10% of body weight	Life-threatening

### Causes of dehydration

The water intake of an average person depends on various factors such as age, climate, physical activity, and experience of illness or other health problems.<sup>6</sup>

#### a. Climate and dehydration

The hot and humid climate and prolonged work period in heat results in increased sweating, contributing to progressive dehydration.<sup>7</sup> Sweat evaporation causes heat loss in the body. However, it is responsible for water and electrolyte loss from the body.<sup>4</sup> In hot and humid environments, dehydration and heat stroke risk increases.<sup>7</sup> Factors such as being busy, sick, or lacking access to safe drinking water may contribute to dehydration during hot and humid climatic conditions, resulting in fatigue.<sup>3,6</sup>

#### b. Physical activity and dehydration

In hot conditions, athletes rarely drink enough water before and during exercise to replace the ongoing fluid losses. This is majorly associated with increased sweat loss, hypohydration, thermoregulation failure, and circulatory collapse.<sup>7</sup> Increased body temperature is associated with reduced performance due to fatigue, an impairment caused by both central and

peripheral factors.<sup>8</sup> Thus, keeping oneself hydrated before, during, and after exercise is crucial to prevent hypohydration, thermoregulation failure, and circulatory collapse.<sup>7</sup> There is no evidence that humans can adapt to chronic dehydration. Ingesting adequate amounts of fluid to replace sweat loss fully is paramount to avoid dehydration during exercise.<sup>8</sup>

#### c. Disease and dehydration

##### Diarrhea

Diarrhea is the loss of water and electrolytes, thus contributing to dehydration. Dehydration is the most severe threat in a patient with diarrhea. In diarrhea, water and electrolytes are lost through liquid stools, sweat, urine, and breathing; dehydration is a consequence of not replacing these losses. Further, these losses contribute to malnourishment and weakness.<sup>9</sup>

##### Fever

Increased body temperature due to fever is associated with increased water loss, resulting in dehydration. The problem of dehydration increases if fever is associated with diarrhea and vomiting.<sup>6</sup> The cause for the exhaustion in hyperthermic conditions results from the effect of heat stress on brain function. Dehydration causes deterioration in cardiovascular and thermoregulatory responses.<sup>8</sup>

##### Increased urination

In patients with undiagnosed and uncontrolled diabetes, frequent urination is a significant symptom reported, which may contribute to dehydration. Patients on certain medications, such as diuretics or medicines for the treatment of hypertension, induce urination, resulting in dehydration.<sup>6</sup>

#### d. Age

Infants and children often experience severe diarrhea and vomiting, rendering them vulnerable to dehydration. High fever or burns in infants and children may cause increased dehydration due to their higher surface area to volume area. Infants, due to their inability to speak, cannot notice thirst, and their inability to walk, they cannot get the drink themselves, which might delay their water intake, resulting in dehydration.<sup>6</sup>

In elderly patients, the fluid reserve capacity of the body decreases, and their thirst senses become less acute. Moreover, older adults may

have diabetes and dementia and can be consuming certain medicines, which might result in dehydration. Older adults may also suffer from mobility problems that limit their ability to hydrate.<sup>6</sup>

### Dehydration consequences

Dehydration negatively affects health and well-being. Mild dehydration is harmful, as per clinicians. Chronic mild dehydration is associated with compromised health. Severe dehydration is detrimental to health and results in compromised cardiovascular function, renal impairment, fatigue and lassitude, and several diffuse symptoms, including headache, nausea, and general malaise. Evidence suggests a significant link between dehydration and some bladder cancers, colon cancers, diabetes, and cardiovascular disorders. Moreover, modest dehydration of 1-2% is reported to reduce mental alertness and ability to concentrate, increasing tiredness and headache. In some patients (mainly elderly), dehydration is associated with impairment of cognitive functions. The fluid-deficient state of older people is due to reduced thirst, reduced renal function, and alteration in the secretions of hormones responsible for water and electrolyte balance.<sup>10</sup>

In children, although with significant improvements in sanitation and oral rehydration practices, diarrhea remains a major cause of death. As per the World Health Organization, diarrhea contributes to 1.5 million deaths of young children worldwide. Healthy children are also at risk of dehydration if there is a sudden increment in water loss and if they are active physically, particularly in warm weather.<sup>10</sup> Dehydration further hampers the performance of athletes. A dehydrated person cannot perform well compared to a fully hydrated individual. Dehydration results in elevated body heat during exercise, which increases muscle temperature, thus affecting the contractile performance of muscles. Dehydration for a longer duration during exercise results in reduced food intake that contributes to changes in muscle glycogen content and the acid-base status of the muscle, thus contributing to fatigue. Dehydration causes reduced blood flow to exercising muscles and skin. Decreased cardiac output and failure to maintain blood pressure signals for exhaustion during prolonged exercise due to dehydration.<sup>10</sup>

Thus, fluid intake along with electrolytes is essential to replace sweat losses.<sup>3,4</sup>

### Dehydration and association with fever and infection

Specific incident suggests that infections (e.g., urinary tract infections, infectious diarrhea, respiratory tract infections, etc.) are associated with increased dehydration.<sup>1,11,12</sup> Moreover, infections such as pneumonia, diarrhea, malaria, measles, and AIDS have a profound impact on the nutritional status of an individual. Infection affects the nutritional status by various mechanisms.<sup>13</sup> This impaired nutritional status results in decreased intestinal absorption of nutrients and can cause direct loss of micronutrients, including essential fat-soluble vitamins.<sup>14</sup> Infectious diarrhea is associated with varying degrees of dehydration, malabsorption, nutrient losses, and wasting. Acute watery diarrhea has the potential to cause rapid dehydration, as it can result in stool losses of 250 milliliters or more per kilogram per day. This amount of fluid loss quickly surpasses the combined volume of both plasma and interstitial fluid, posing a life-threatening situation unless fluid therapy can match and replenish the ongoing losses.<sup>15</sup>

Fever is the most common symptom associated with various infections. Fever due to illness is associated with increased energy expenditure resulting from increased basal metabolic rate (BMR), thus causing loss of energy, fatigue, and weakness.<sup>13</sup> Fever not only affects energy expenditure but also increases the loss of fluids from the body through sweat.<sup>16</sup> Children experiencing fever often decrease their fluid intake, which leaves them vulnerable to additional fluid and electrolyte loss due to increased sweating. Children with a fever exceeding 40°C face an elevated risk of dehydration. Profuse sweating is associated with the loss of electrolytes and essential vitamins.<sup>18</sup> Therefore, it is crucial to vigilantly monitor for signs and symptoms of dehydration when a child has a fever. Guidelines advise maintaining a consistent fluid intake in children with fever to prevent dehydration. In such circumstances, oral rehydration solutions can be beneficial in addressing dehydration.<sup>18</sup>

## Etiology of dehydration due to diarrhea and fever

The gravest peril accompanying diarrhea lies in its capacity to induce severe dehydration. When diarrhea ensues, the body sheds essential fluids and electrolytes through liquid stools, vomiting, perspiration, urination, and respiration. Dehydration emerges when these vital losses aren't adequately replenished.<sup>9</sup>

Fever, also known as pyrexia, arises from an elevation in an individual's core body temperature beyond the norm, meticulously controlled by the body's thermoregulatory center in the hypothalamus. This escalation in the body's temperature 'set-point' often results from physiological mechanisms triggered by infectious or non-infectious factors such as inflammation, malignancy, or autoimmune processes. These mechanisms entail the release of immunological agents that activate the hypothalamus's thermoregulatory center, prompting an upsurge in core body temperature.

Typically, the human body maintains a baseline temperature of approximately 37 degrees Celsius (C) or 98.6 degrees Fahrenheit (F), subject to minor fluctuations of about 0.5 C throughout the day. These fluctuations arise from natural bodily processes, including metabolic shifts, circadian rhythms, hormonal variations, and changes in physical activity. However, when a fever strikes, the core body temperature often surges beyond the 0.5-degree C range and is typically attributed to the presence of fever-inducing substances known as pyrogens.<sup>19,20</sup> This temperature spike is commonly accompanied by increased sweating, a normal bodily response.<sup>9</sup> Consequently, heightened perspiration exacerbates the risk of dehydration.

## Therapy for Dehydration: ORT as a cornerstone treatment

Dehydration is the leading cause of morbidity and mortality regardless of age, particularly in patients with diarrhea.<sup>18</sup> Therefore, the primary goal of therapy should be preventing and treating dehydration.<sup>20</sup> About 40 years ago, oral rehydration therapy (ORT) was the cornerstone for managing dehydration.<sup>20</sup> Ideal oral rehydration solution (ORS) is formulated with glucose (less than 160mmol/L) to prevent hypertonicity, equimolar concentrations of

carbohydrate and Na<sup>+</sup> to optimize absorption, and lower or similar osmolarity to plasma for the avoidance of complications associated with osmotic diarrhea.<sup>20, 21</sup> The decline in mortality rate from acute diarrhea, especially in developing countries, is mainly due to implementing the WHO-ORS standard.<sup>20,21</sup> Use of standard ORS has been limited by its inability to reduce fecal volume or diarrhea duration. Subsequently, this has led to various attempts to modify its compositions.<sup>20, 21</sup>

## Limitations of the current WHO-ORS formula

ORS is known to reduce the mortality rates from dehydration; however, it does not treat or reduce the symptoms.<sup>23</sup> ORT cannot "halt" the underlying intestinal fluid loss, a significant mechanism of infectious organisms responsible for causing diarrhea.<sup>22</sup> ORS fails to suppress intestinal fluid secretion or overly active enteric nerve activity responsible for secretory diarrhea. ORS also does not reduce gut permeability or inflammation, the primary contributor to inflammatory diarrhea. Further, ORS does not play any significant role in targeting cAMP/cGMP accumulation or the influence of the NSP4 (a viral-encoded enterotoxin), the primary mechanism of secretory diarrhea caused by numerous bacteria and rotavirus, respectively.<sup>22</sup> Moreover, NSP4, through inhibiting Na<sup>+</sup>/glucose co-transport, impairs intestinal cells, through which ORS enhances absorption. Thus, ORS would fail to produce the required result in patients infected by rotavirus due to inhibition of Na<sup>+</sup>/glucose co-transport.<sup>23</sup> Moreover, reports have demonstrated the role of calcium in treating infectious diarrhea through the calcium-sensing receptor (CaSR), which is absent in ORS.<sup>22</sup>

## Need for new ORS formula

While ORS is an effective therapy, it is not a curative treatment option for patients suffering from diarrheal disease. Moreover, children with diarrhea are likely to be malnourished, resulting in impaired growth and cognitive development. Malnutrition contributes to the development and increased duration of diarrhea, thus forming a vicious cycle. Adding nutrients to ORS would be simple and may increase the effectiveness of the current ORT.<sup>23</sup> Given the limitations of ORS, there is a need to develop nutrient-based anti-diarrheal therapy to treat dehydration associated with

diarrhea, which may provide energy, nutrition, and electrolytes for better recovery in these patients.

### A Promising New Target - CaSR

Calcium-sensing receptor (CaSR), a G protein-coupled receptor, is expressed in various human tissues, including the small and large intestines. CaSR is positioned in secreting crypt epithelium, absorbing surface epithelium, motility-modulating enteric nervous tissue, and inflammatory cells of the intestine. Based on activation by cAMP, endocrine intestinal cells secrete neurotransmitters, such as serotonin and neurotensin, activating the enteric nervous system and initiating an enteric neural response through stimulating submucosal plexus neurons, which augments secretion and inhibits absorption. CaSR results in the degradation of cyclic nucleotides by activating the enzyme phosphodiesterase (PDE). A reduced cAMP/cGMP concentration reduces CFTR translocation to the apical membrane, enhancing  $\text{Na}^+/\text{H}^+$  and  $\text{Cl}^-/\text{HCO}_3^-$  exchange. Thus, CaSR activation normalizes fluid excretion and reabsorption simultaneously. Thus, activating CaSR reverses changes in both secretory and inflammatory diarrheas.<sup>24</sup>

### Role of calcium in ORS formula

In animal studies, calcium is reported to be anti-secretory, pro-absorptive, anti-motility, and anti-inflammatory. Human studies also support the CaSR agonist for anti-diarrheal effect.<sup>24</sup> Activation of the CaSR decreases cellular cyclic nucleotides and reverses all four pathological changes occurring in diarrhea: excessive secretion, malabsorption, increased gut motility, and a heightened inflammatory response. The primary ligand for CaSR is calcium, an essential nutrient that activates CaSR, which reduces diarrhea volume and accelerates patient recovery. In contrast to conventional ORS, CaSR-based treatment is a four-pronged approach, i.e., it reverses all four pathological changes occurring in diarrhea, such as excessive secretion, malabsorption, increased gut motility, and heightened inflammatory response. Thus, CaSR-based treatment addresses all primary pathophysiological mechanisms of diarrhea. Initial clinical studies have produced positive results, demonstrating that a CaSR-ORS would be safe,

affordable, and possibly more effective than the current gold standard.<sup>25</sup>

### Role of Vitamins in ORS formula

Patients with fever usually exhibit sweating or night sweats.<sup>19</sup> Increased sweating is associated with increased dehydration. Moreover, sweating is generally related to the loss of essential vitamins. B complex vitamins and vitamin C are stored in relatively small amounts in the body. Vitamins B and C, water-soluble vitamins, can be easily lost through sweat and urine; thus, they cannot be retained for extended periods (Table 2).<sup>26</sup>

Table 2: Amount of vitamins lost in sweat<sup>26</sup>

Vitamin	Concentration ( $\mu\text{g}$ per 100 ml)
Thiamin	0-15
Riboflavin	0.5-12
Nicotinic acid (total)	8-14
Pantothenic acid	4-30
Ascorbic acid	0-50
Pyridoxine	7
Folic acid (plus metabolites)	0.26

Thus, the body requires adequate vitamins B and C to keep oneself hydrated.

### Vitamin C

Fatigue is associated with increased oxidative stress. Serum markers of oxidative stress were reported to be associated with symptoms of chronic fatigue syndrome, including asthenia after physical activity and arthralgia. These oxidative stress markers include reactive oxygen species (ROS) and cytokines. Various studies suggest vitamin C is a potent anti-oxidant. Vitamin C deficiency is prevalent compared to it generally being recognized. The first symptom of Vitamin C is fatigue, a non-specific complaint. Vitamin C supplementation enhances the activity of immune cells and boosts immunity. Vitamin C supplementation for the prevention of infections has been reported to be beneficial in various studies.<sup>27, 28</sup>

### Vitamin B

The B-complex vitamins are water-soluble nutrients readily absorbed in the healthy intestine and easily eliminated through renal excretion. They are essential to perform various

physiological functions and maintain optimal health.<sup>29</sup>

A blend of vitamins B1, B3, B6 & B12 is essential for unlocking energy and battling fatigue. Vitamin B complex plays a significant role in converting fats and carbohydrates into glucose. Increased glucose levels will effectively replenish energy levels.<sup>30</sup> Vitamin B also modulates immune response by down-regulating pro-inflammatory cytokines and inflammation.<sup>29</sup>

### **Maltodextrin in ORS formula**

Maltodextrins (MDs) are a class of carbohydrates (CHOs) extracted from various plant sources. The energy value of MDs is approximately 16 kJ/g (4 kcal/g). Digestible MDs used in foods and beverages are considered a good energy source compared to glucose. Glucose obtained from digestion is readily absorbed in the small intestine and used in metabolism. There is a reliance on lactose as a source of energy in early human development, preferably as part of the mother's breast milk. However, lactase deficiency resulting in the inability to digest may lead to malabsorption-induced osmotic diarrhea, in which approximately 40% of the energy provided may be lost. In such cases, MDs can be used as a substitute for lactose to provide power. In this respect, it is also suggested that using MDs instead of glucose is favorable since this helps reduce osmotic load and related intestinal distress.<sup>31</sup>

Early studies have indicated the benefits of using MDs in oral rehydration solutions (ORS) for individuals suffering from diarrhea over the use of glucose. In this respect, an early paper concluded that solutions with lower sodium and glucose-polymer content, compared to higher sodium content and higher osmolality due to the use of glucose, might be of nutritional benefit in the oral rehydration of acute infantile diarrhea. Compared on a weight basis, the osmolality of MDs is significantly lower than that of disaccharide sugars.<sup>31</sup>

A low beverage osmolality supports gastric emptying rate and helps reduce gastrointestinal stress. Accordingly, aiming at a low beverage osmolality, MDs replace sucrose or glucose in sports drinks. This is relevant since hypertonicity and related gastrointestinal distress symptoms are significant performance-limiting factors during running events such as marathons and

triathlon exercises. Another effect of beverage hypertonicity is that it reduces the water absorption rate. Combining MDs with a fructose-supplying CHO source may be beneficial when a high rate of CHO supply is warranted.<sup>31</sup>

Since there is a close relation between muscle fiber glycogen content and its ability to execute repeated high-intensity contractions, either a reduced rate of glycogen breakdown or an increased glycogen content may help reduce fatigue and thus support performance capacity in field settings.<sup>36</sup> Examining the effects of MD ingestion during exercise, it was found that the ingestion of MD, like any other CHO, decreases net glycogen breakdown during long-duration exercise while maintaining a high whole-body CHO oxidation. Such responses appear to be similar for both men and women.<sup>31</sup>

### **Rationale for WHO-ORS with multi-vitamins, calcium, and energy boosters**

ORS, although been used for more than a decade for diarrhea, does not provide the curative effect. Children and infants suffering from gastroenteritis and other infections are often malnourished due to loss of nutrients and electrolytes via vomiting and stools. Moreover, the effectiveness of ORS is limited in viral diarrheal infections. CaSR is a newly studied target that has demonstrated its efficacy in treating diarrhea. This target is activated by a simple calcium agonist, which is easily accessible, inexpensive, and safe for the pediatric population. Moreover, adding calcium slightly higher than the daily recommended allowances has been shown to treat diarrhea in children.<sup>21, 22, 24</sup>

Infection results in loss of nutrients in adults and children, which may contribute to malnourishment.<sup>13</sup> Adding nutrients would be simple and may increase the efficacy of the current treatment.<sup>21, 22</sup>

Inadequate intake of fluids results in dehydration, which contributes to fatigue in adults, children, and older people.<sup>7,8,9</sup> Utilizing maltodextrin instead of glucose has demonstrated advantages, particularly concerning dehydration. Maltodextrin (MD) exhibits a significantly lower osmolality compared to disaccharide sugars. This lower osmolality reduces gastrointestinal stress in diarrhea. Additionally, maltodextrin ingestion helps mitigate the risk of dehydration and plays a

crucial role in sustaining energy levels.<sup>31</sup> Thus, adding multivitamins, nutrients, and energy boosters to WHO-ORS may improve the efficacy of ORS to treat diarrhea, reduce malnutrition, and provide energy to curb fatigue.

## Conclusion

Although used for decades, WHO-ORS does not halt diarrhea and fails to treat the underlying infection. Currently, CaSR activated by simple calcium supplementation treats the underlying cause. Thus, adding calcium may help treat the underlying condition and reduce fluid loss. Moreover, adding vitamins as nutrients may correct the malnutrition associated with infection and fluid loss. Adding maltodextrin to ORS has shown beneficial effects in children with diarrhea and provides energy to curb fatigue. Thus, adding nutrient-based ORS may be a better option for treating diarrhea, providing nutrition, and reducing fatigue in children, adults, and the elderly.

## Acknowledgment

The author acknowledges Ms. Richa Deliwala, M. Pharm (Pharmacology) contribution in doing the literature search & helping with the manuscript preparation.

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