Ketones: the double-edged sword of SGLT2 inhibitors?

Lupsa, B.C., Kibbey, R.G. & Inzucchi, S.E. Diabetologia 66, 23–32 (2023). https://doi.org/10.1007/s00125-022-05815-1

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a class of medications used by individuals with type 2 diabetes that reduce hyperglycaemia by targeting glucose transport in the kidney, preventing its reabsorption, thereby inducing glucosuria. Besides improving HbA1c and reducing body weight and blood pressure, the SGLT2 inhibitors have also been demonstrated to improve cardiovascular and kidney outcomes, an effect largely independent of their effect on blood glucose levels. Indeed, the mechanisms underlying these benefits remain elusive. Treatment with SGLT2 inhibitors has been found to modestly increase systemic ketone levels. Ketone bodies are an ancillary fuel source substituting for glucose in some tissues and may also possess intrinsic anti-oxidative and anti-inflammatory effects. Some have proposed that ketones may in fact mediate the cardio-renal benefits of this drug category. However, a rare complication of SGLT2 inhibition is ketoacidosis, sometimes with normal or near-normal blood glucose concentrations, albeit occurring more frequently in patients with type 1 diabetes who are treated (predominately off-label) with one of these agents. We herein explore the notion that an underpinning of one of the more serious adverse effects of SGLT2 inhibitors may, in fact, explain, at least in part, some of their benefits—a potential 'double-edged sword' of this novel drug category.

Beta-hydroxybutyrate (BHB), a ketone body, is being investigated for its potential role in slowing down aging and promoting longevity. Studies suggest BHB may have anti-aging effects by influencing various biological processes, including senescence, inflammation, and stem cell function.

Here's a more detailed look at the research:

1. Senescence and Vascular Aging:
   - Research indicates that BHB can help prevent vascular senescence in mice.
   - BHB may reduce markers of senescence-associated secretory phenotype (SASP), which is a hallmark of aging.
   - BHB can also diminish the number of senescent vascular cells.
2. Inflammation and Immune Responses:
   - BHB has been shown to reduce inflammation by inhibiting the NLR family pyrin domain-containing protein 3 (NLRP3) inflammasome, a key player in inflammation.
   - BHB may also activate anti-inflammatory pathways, such as the HCAR2 receptor, which can help regulate inflammation.
3. Stem Cell Function:
   - BHB supplementation may help maintain intestinal stem cell function and homeostasis, potentially promoting tissue regeneration.
   - BHB can reduce age- and oxidative stress-induced DNA damage and centrosome abnormalities in stem cells.
4. Lifespan Extension in Model Organisms:
   - Studies in C. elegans (roundworms) have shown that BHB supplementation can extend lifespan.
   - This effect is believed to be linked to mechanisms like HDAC inhibition and activation of stress response pathways.
5. Neuroprotection and Neurological Benefits:
   - BHB may offer neuroprotective effects by protecting against amyloid-beta toxicity (a hallmark of Alzheimer's disease) and reducing alpha-synuclein aggregation (a hallmark of Parkinson's disease).
   - BHB can also help protect the blood-brain barrier and improve cognitive function.
6. Metabolic Regulation and Proteostasis:
   - BHB acts as a signaling molecule that regulates metabolism and gene expression.
   - BHB can modulate histone modification and gene expression by inhibiting HDACs and promoting acetyltransferase activity.

- BHB is also a regulator of proteostasis (the maintenance of protein structure and function), which is important for preventing protein aggregation and degradation during aging.

7. Mechanisms of Action:
   - BHB can exert its effects through various mechanisms, including mitochondrial function, antioxidant effects, and activation of stress response pathways.
   - BHB can also influence cell membrane receptors like HCAR2 and FFAR3, impacting various physiological processes.
8. Potential Therapeutic Applications:
   - BHB supplementation or ketogenic diets may have potential therapeutic applications for age-related diseases, including neurodegenerative diseases and cardiovascular diseases.
   - BHB may also play a role in tissue regeneration and wound healing.
9. Future Directions:
   - Further research is needed to fully elucidate the mechanisms by which BHB contributes to anti-aging and longevity.
   - Studies are needed to determine the optimal BHB levels for promoting health and longevity, as well as to assess potential side effects of BHB supplementation.

In addition, HDAC2, which was found to be inactivated by β-OHB in our study, is essential for promoting heart development and maintaining heart function,[47–49] and downregulation of HDAC2 increases apoptosis in cardiomyocytes.[42] Our in vitro assay showed that β-OHB inhibited HDAC2, with an IC_{50} of 2.4 mM, which is lower than the β-OHB concentrations observed in the human AF heart and in KD-fed and deep-fasted rats (i.e., ~3–4 mM). These results further supported that consumption of a KD induced the accumulation of β-OHB to pathological levels.

GLP-1 agonists and ketosis

These medications slow gastric emptying, increase insulin sensitivity, decrease glucagon, decrease caloric intake, and create a relative calorie deficit (5). GLP-1 agonists cause a state of starvation and deficient oral intake (3). The proposed mechanism for ketoacidosis is starvation ketoacidosis, with reduced insulin levels and increased glucagon levels. Starvation ketoacidosis in the setting of GLP-1 agonist use occurs from decreased caloric intake in patients who are experiencing the gastrointestinal side effects of vomiting, nausea, and diarrhea (6). This causes lipolysis and free fatty acid oxidation through the liver, which increases the production of ketone bodies and eventually causes high anion gap metabolic acidosis. The combination of the mechanism of action discussed above and side effects additively leads to starvation. GLP-1 agonists can induce ketoacidosis in the presence of certain risk factors like dehydration, alcohol use, pancreatitis, and gastroenteritis.

SGLT2 inhibitors in Heart Failure

In heart failure patients on SGLT2 inhibitors, the level of ketosis is typically mild, within the range of 1-3 mmol/L. This level is considered a therapeutic range for ketone bodies and is achieved by SGLT2 inhibitors increasing circulating ketone levels. However, the ketogenic effect of SGLT2 inhibitors is less pronounced than with a ketogenic diet.

Mechanisms of Ketogenesis:

SGLT2 inhibitors increase circulating ketone levels by shifting fuel consumption from glucose to fat oxidation. This "perceived fasting state" promotes hepatic ketogenesis. Elevated ketone levels, within the therapeutic range, may contribute to the cardioprotective effects of SGLT2 inhibitors in heart failure. Some studies suggest ketones may improve myocardial efficiency and energy production.

Comparison to Ketogenic Diets: While SGLT2 inhibitors can induce ketosis, the increase in ketone levels is generally less pronounced compared to a ketogenic diet. Ketogenic diets lead to a more significant increase in serum ketone body levels.

Potential Risks:

A rare but serious complication of SGLT2 inhibitors, especially in patients with type 1 diabetes, is euglycemic diabetic ketoacidosis (DKA), which can occur with normal or near-normal blood glucose levels. The risk of DKA is higher in the presence of a ketogenic diet.

Beta Hydroxybutyrate in Aging and Longevity Research

What is Beta Hydroxybutyrate?

Beta hydroxybutyrate is one of three ketone bodies produced during the process of ketogenesis. When the body is in a state of low carbohydrate availability, such as during fasting or ketogenic dieting, it starts converting fatty acids into ketone bodies, including acetoacetate, acetone, and beta hydroxybutyrate. BHB is the most abundant ketone body and serves as an alternative energy source for the brain and muscles when glucose levels are low.

Mechanisms of BHB in Aging

1. Mitochondrial Function and Energy Production

Mitochondria, the powerhouse of the cell, play a crucial role in aging. BHB enhances mitochondrial function by increasing the efficiency of ATP production. Research has shown that BHB can improve mitochondrial biogenesis and reduce the production of reactive oxygen species (ROS), which are harmful byproducts of cellular respiration that contribute to aging (Veech, 2004).

2. Epigenetic Regulation

BHB influences gene expression through epigenetic mechanisms. It acts as a histone deacetylase (HDAC) inhibitor, promoting the acetylation of histones and thereby modulating the transcription of genes involved in longevity and stress resistance. This epigenetic regulation can enhance cellular function and promote a healthier aging process (Shimazu et al., 2013).

3. Inflammation Reduction

Chronic inflammation is a hallmark of aging and is linked to various age-related diseases. BHB has anti-inflammatory properties that can mitigate the effects of aging. By inhibiting the NLRP3 inflammasome, BHB reduces the secretion of pro-inflammatory cytokines, thus protecting against the inflammatory damage associated with aging (Youm et al., 2015).

4. Autophagy and Cellular Maintenance

Autophagy is a cellular process that degrades and recycles damaged organelles and proteins. It is essential for maintaining cellular health and function. BHB has been shown to induce autophagy, thereby promoting cellular repair and longevity. Studies suggest that BHB can activate pathways that lead to increased autophagic activity (Li et al., 2017).

Evidence from Research Studies

Animal Studies

Animal models have provided significant insights into the effects of BHB on aging. Research on rodents has demonstrated that a ketogenic diet, which elevates BHB levels, can extend lifespan and improve

health markers associated with aging. For instance, a study by Roberts et al. (2017) found that mice on a ketogenic diet showed increased longevity and reduced incidence of age-related diseases.

Human Studies

Human studies are still in their early stages, but preliminary evidence is promising. Clinical trials have explored the effects of ketone supplementation on cognitive function and metabolic health in older adults. A study by Newman et al. (2019) reported that ketone supplementation improved cognitive performance in elderly participants, suggesting a potential role for BHB in mitigating cognitive decline.

Cellular Studies

Cellular studies have also shed light on the mechanisms by which BHB influences aging. Research on cultured cells has shown that BHB can enhance cellular resilience to stress and damage. For example, a study by Cheng et al. (2020) found that BHB-treated cells exhibited improved resistance to oxidative stress and better maintenance of cellular homeostasis.

Potential Applications and Future Directions

The potential applications of BHB in aging and longevity research are vast and varied:

1. Dietary Interventions

Dietary approaches such as ketogenic diets or intermittent fasting could be employed to elevate endogenous BHB levels, thus promoting health and longevity. Long-term studies are needed to assess the feasibility and safety of these interventions.

2. Supplementation

Exogenous ketone supplements, such as BHB salts or esters, could be developed to provide a more controlled and consistent elevation of BHB levels. Clinical trials are essential to determine the optimal dosing and long-term effects of BHB supplementation.

3. Therapeutic Strategies

BHB could be integrated into therapeutic strategies for age-related diseases. Its anti-inflammatory and neuroprotective properties make it a promising candidate for conditions such as Alzheimer's disease, Parkinson's disease, and metabolic disorders.

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