Beyond the Peak: Comparing the Duration and Quantity of Ketones from Three BHB Supplements

STUDY BACKGROUND

Ketones are the alternative fuel source used by the body when glucose is depleted or in short supply. This generally occurs when on a low-carb, high-fat diet like the ketogenic diet or during long periods of fasting. However, exogenous ketones (bioidentical to what the body produces) can now be produced that duplicate the results of a ketogenic diet and can deliver the benefits of ketones without the rigorous compliance required for sustaining a ketogenic diet.

Multiple studies show promising evidence that using ketones for energy can improve numerous health markers including decreased inflammation[1], improved mental clarity[2], faster weight loss[3] increased performance, recovery, lowering of stress and increased satiety[4].

Research is ever-evolving and continues to confirm the optimal health and performance benefits of using ketones in dietary health and well-being, providing a new frontier of being able to take advantage of the benefits of ketones either in a glucose depleted or glucose fed state, thus emulating metabolic flexibility.

With the capability of administering exogenous ketones comes the debate of dosage and ketone levels. This has prompted some debate within scientific circles about whether a higher peak of blood ketones or quantity/duration directly correlates to better results when it comes to emulating ketosis and its potential benefits. Here's a breakdown of the arguments:

Arguments for Higher Peak Ketones:

- **Deeper Ketosis:** Some experts suggest that higher peak ketone levels might indicate a more intense state of ketosis, potentially leading to enhanced metabolic or treatment effects.

- **Individual variability:** Individuals may respond differently to varying ketone levels, believing higher readings might align with better outcomes. It is unknown whether high peaks pose higher risks such as ketoacidosis.

Arguments For Sustained Ketone Duration Levels:

- **Duration Matters:** More researchers argue that the total amount of time you spend in ketosis (greater than 0.5 mmol/L being the nutritional ketosis threshold) is more important and therapeutic than reaching a transient absolute peak value.

- **Adaptation:** The body adapts quickly to using ketones for fuel over time. Consistently elevated ketones suggest better metabolic adaptation and quicker entry into a state of metabolic flexibility.

Unfortunately, there are few credible studies specifically comparing the metabolic effects or benefits of varying peak ketone levels within an induced state of nutritional ketosis. Much of the current understanding is speculative and is based on theoretical models and observational findings.

However, in looking at evolutionary evidence, our hunter-gatherer ancestors wouldn't have benefited from a system prone to dramatic swings in ketone production, but rather, evolution would have favored a more stable, efficient system capable of maintaining a sustained state of ketosis during periods of low food availability. This aligns more with the concept of duration being the key factor in unlocking the true potential of mimicking ketosis with the use of exogeneous ketones.

While the anecdotal belief that a higher peak might suggest a more robust metabolic response, it's evolutionary history that points to the total time spent in ketosis, along with the total quantity of ketones delivered by the supplement, that we believe provides a much more accurate and substantiated picture of metabolic adaptation and flexibility.

STUDY PURPOSE

Currently, testing surrounding ketone supplementation often emphasizes peak blood ketone levels. This study is designed to go “beyond the peak” measurement to determine how the different forms of BHB substances or precursors perform in terms of duration and quantity (AUC, the total amount of ketones present in the blood over time) rather than just measuring peak ketone elevation in order to gain a much clearer understanding of ways to optimize ketone supplementation strategies to support health and well-being by measuring their effects of ketone quantity and duration of ketone elevation.

Our study hypothesis is that the quantity of ketones provided by these three different BHB substances and precursors generate similar amounts of blood ketones over a two-hour period of time within a defined level of ketosis, which is above 0.5mmol/liter when dosed at the same mmol dosing levels.

STUDY PROTOCOL

Since exogenous ketones can be used directly for the creation of ATP energy, we wanted to discover which exogenous BHB substances best produced ketones in the human body. In November of 2022, Axcess Global Sciences and NNB Nutrition designed and conducted a ketogenic PK study for the purpose of assessing the effects of each of three BHB substances (R-BHB liquid acid, R-1,3-butanediol BHB diester and R-1,3-butanediol), also referred in the marketplace as D-BHB liquid acid, 1,3-butanediol BHB diester and 1,3-butanediol) in their ability to produce ketones using equivalent m/mols doses.

The study was conducted on 32 ICR mice randomly divided into 4 groups. The mice were administered one of the exogenous BHB substances orally (gavage volume was 0.2 mL/10 g per mouse). The mice blood ketogenic level was measured at 0, 15, 30, 60, 90, and 120 min with the blood ketogenic meter. The ketogenic level of exogenous BHB substances was determined by measuring the body ketone concentration in the mice.

The study measured (1) the ketone levels at 0, 15, 30, 60, 90, and 120 min over the duration of two hours after administration and (2) the quantity of ketones generated above the 0.5 m/mol level (ketosis), the AUC, (Area Under the Curve). The study was constructed under the theoretical hypothesis that when all three exogenous BHB substances are dosed at an equivalent m/mol dosage, they will produce molar equivalent quantities of R-BHB ketones in the blood.

STUDY RESULTS

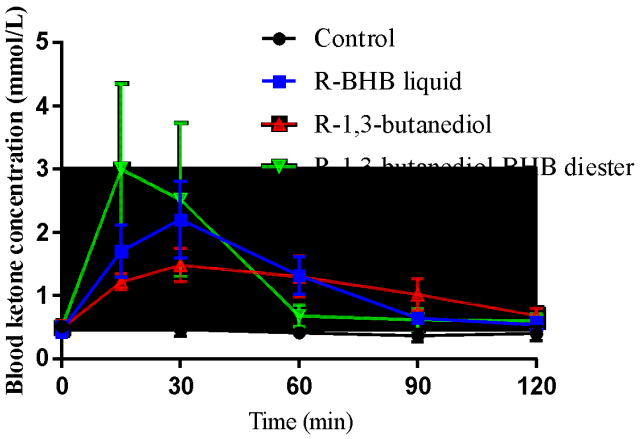

Figure 1. Conventional measurement of ketone levels of R-BHB liquid, 1,3-butanediol, and 1,3-butanediol BHB diester over 2 hours

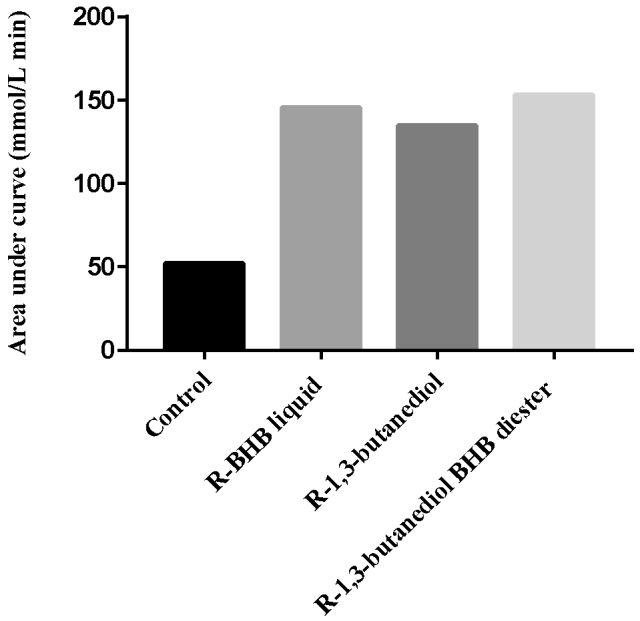

Figure 2. AUC measurement (evaluating total quantity of ketones in the blood over two hours) of R-BHB liquid acid, 1,3-butanediol, and 1,3-butanediol BHB diester

STUDY DISCUSSION

The study results confirmed our study hypothesis that equivalent m/mol doses of each exogenous BHB substance produces near equivalent amounts of ketones over two hours after administration, with some differences in peak levels and timing in ketone levels.

Measuring Ketone Levels at Time Intervals:

The R-1,3-butanediol BHB diester reached its ketone level peak at 15 minutes, with ketone levels quickly tailing off at the 60-minute mark. R-BHB liquid acid and R-1,3-butanediol reached their ketone level peak at 30 minutes with R-BHB liquid acid having a higher peak than 1,3 butanediol. Both R-BHB liquid acid and R-1,3 butanediol remained elevated beyond R-1,3-butanediol BHB diester at 80 minutes. R-1,3 butanediol had the lowest peak of the three BHB substances, but remained elevated the longest.

All three BHB substances remained elevated above the control at 120 minutes. Although the peak value of the R-1,3-butanediol BHB diester was higher than R-BHB liquid acid and R-1,3-butanediol, the R-1,3-butanediol BHB diester also saw the most rapid decline in blood ketone levels. R-1,3-butandiol had the lowest peak value, but its decline rate was slowest. R-BHB liquid acid had the greatest median peak and elevation of the three BHB substances.

Measuring Quantity of Ketones Over Time (Area Under the Curve):

Taking into account the different ketone level peaks and declines" (shape of the curve) of the three BHB substances, we computed the quantity of ketones generated by each BHB substance to be relatively equivalent. The R-1,3-butanediol BHB diester and R-BHB liquid acid were rather identical with the R-1,3-butanediol registering a slightly lower quantity. However, in comparing quantities of ketones statistically, all three BHB substances resulted in similar ketone amounts AUC (Area Under the Curve).

STUDY SUMMARY

First, that each BHB substance has its own PK curve in their ability to raise ketone levels and then maintain those ketone levels throughout a ketogenic state over 120 minutes.

The second and primary finding of the study, the final quantity of R-BHB ketones produced by each of the three exogenous BHB substances were statistically equivalent.

FUTURE RESEARCH NEEDED

While this study provided valuable insights into the peak and AUC values of R-BHB from three different sources, it did not account for the potential impact of S-BHB (also known in the marketplace as L-BHB). Emerging research suggests S-BHB plays a crucial role in energy production, metabolic regulation, and cellular signaling. Therefore, we are initiating a Phase 2 study to directly compare peak values and AUC of S-BHB to the R-BHB sources examined here. Preliminary data and prior research on S-BHB leads us to hypothesize that S-BHB may exhibit higher peak and larger AUC values when measured in the blood than its R-BHB counterparts.

However, measuring blood ketone levels alone is insufficient to fully understand the efficacy of BHB supplements. While these measurements confirm a state of ketosis, they do not reveal the efficiency with which different BHB sources generate usable energy (ATP). A comprehensive evaluation must consider the entire process, from absorption to intracellular metabolism.

Therefore, future research needs to reach beyond the measure of blood BHB levels to assess the ATP values and energy costs associated with converting BHB from various sources into BHB that enter the bloodstream. This holistic approach will provide a more accurate understanding of the net ATP yield from different BHB sources, ultimately guiding the development of more effective ketone supplements.

References:

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[3]Paoli A et al. Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. 2013 June 26

[4] Bazzano L et al. Effects of Low-Carbohydrate and Low-Fat Diets. 2014 September 2