

Original Research

Attenuation of Blood Glucose by the Ketone Monoester (R)-3-betahydroxybutyrate Glyceride in Healthy Male Sprague Dawley Rats in Response to a Standard Oral Glucose Tolerance Test

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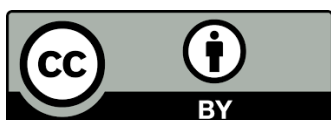
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Academic Editor: Cristiano Capurso

Special Issue: [Nutrition, Carbohydrate Intake and Health](#)



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Abstract

Efficient glucose uptake by peripheral tissue is important for individuals who desire to maintain optimal wellbeing. Various methods to regulate postprandial blood glucose have been reported in the research literature, however, few have examined the effect of ketone esters on blood glucose levels. The present study evaluated blood glucose following the administration of an oral glucose tolerance test, with and without ketone esters delivered at two different dosages, in a sample of healthy Sprague-Dawley rats. We hypothesized that the ketone esters would lower the glucose Area Under the Curve (AUC) in response to oral glucose ingestion, in a dose dependent manner. A single dose ketone monoester (Tecton Ketone) was given to healthy male Sprague-Dawley (SD) rats 30 minutes prior to glucose administration to determine the blood glucose response to an oral glucose tolerance test (OGTT). Twenty-four SD rats were randomly assigned equally to four groups (two control and two ketone). Blood was analyzed for glucose pre-treatment, before glucose loading at baseline, and at 30, 60, 90 and 120 minutes after glucose loading. Ketone esters at 20 g HED significantly reduced the AUC for blood glucose (by ~21%) compared to glucose-loading control. In this group, the most robust differences occurred at the 30- and 60-minute post ingestion times—with an approximate 50% reduction at 30 minutes post ingestion ($p < 0.05$) and low variability in response. Although blood ketone levels were not assessed, the preliminary results from this study demonstrate that ketone esters at 20 g HED attenuate the glycemic response to an OGTT in animals, suggesting that ketone esters may one day be promising not only for those with impaired glucose tolerance but also for healthy individuals who seek enhanced glucose regulation. More research is needed in this area, especially in human subjects, to evaluate the generalizability of these findings.

Keywords

Ketones; ketone esters; glucose tolerance; blood sugar; athletes; glycogen

1. Introduction

Glucose, which is derived from the breakdown of carbohydrates in the diet, serves as the primary energy substrate for cells throughout the body and plays a central role in cellular metabolism [1]. In humans, the topology of need states where proper glucose maintenance (i.e., euglycemia) is paramount is described by three categories: 1) healthy individuals with low to moderate activity, 2) individuals who are not considered to be healthy (i.e., those with diseases), and 3) healthy individuals with a moderate to high level of activity, some of whom may identify as athletes.

In healthy, moderately active individuals, maintaining balanced blood glucose levels is crucial for sustaining energy and supporting tissue demands [2]. The brain is heavily reliant on glucose for energy, and cognitive impairments can arise, such as reduced concentration and memory, if glucose

levels are insufficient [3]. Stable glucose levels also support efficient metabolism, optimal nutrient storage, and utilization while preventing the adverse effects of hyperglycemia and hypoglycemia [4]. Improved glucose uptake enhances glycogen resynthesis after exercise, benefiting metabolic processes [5], and may promote better body composition by reducing insulin secretion for glucose uptake [6].

Managing blood glucose is particularly critical for pre-diabetic or individuals with diabetes, given the rising prevalence of diabetes and its associated healthcare costs [7, 8]. In the U.S., nearly 40 million people (about 11% of the population) have diabetes, and over 100 million adults live with prediabetes [7]. Diabetes is linked to severe health issues [9], including cardiovascular disease [10], kidney disease [11], neuropathy [12], and microvascular complications such as amputation and blindness [13, 14].

Fortunately, diabetes prevention and management are achievable through structured exercise, (which significantly enhances glucose disposal [15]), a nutrient-dense diet with appropriate caloric intake, and potentially a lower-carbohydrate ketogenic diet [16, 17]. Strategic nutrient supplementation can also complement whole-food intake.

For highly active individuals, glucose regulation is vital to prevent energy deficits that impact performance [18]. Repetitive training and high-level performance create complex metabolic demands, leading to fluctuations in glucose levels. Continuous glucose monitoring (CGM) is increasingly used to track and manage glucose in these individuals [19], but understanding glucose regulation is essential for optimizing energy output and sustaining performance in active individuals such as athletes and warfighters in the military, for example.

In this regard, exogenous ketones have gained significant attention in recent years [20] and may prove valuable both for those who are otherwise healthy and have a high energy demand, as well as for those with impaired glucose tolerance or clinical diabetes. Exogenous ketones have a great deal of clinical potential [21, 22] and, for the person with diabetes, may result in a lowering of blood glucose [23, 24]. The glucose lowering effect appears related to enhanced insulin signaling, an effect that is well established in the research literature [25]. In terms of ketone form, ketone esters have been reported to result in a more rapid and significant elevation in blood ketone levels as compared to ketone salts [26] and other forms [27]. However, more data are needed pertaining to the impact of different ketone forms on blood glucose lowering, with some suggestion of greater effects with ketone monoesters as compared to ketone salts [22], though more recent data indicate little difference between ketone forms [27].

While more scientific interest has certainly been given to the study of blood glucose management in those with diabetes, the findings may have relevance to those without glucose intolerance but who desire optimal glucose disposal for purposes other than simple blood sugar management. Specifically, enhanced glucose uptake can lead to improved glycogen resynthesis following an acute exercise session, and glycogen is associated with multiple beneficial metabolic processes [5]. Likewise, a lower demand for secreted insulin because of improvements in insulin efficiency per unit of glucose and the accompanying changes in body composition resulting from those improvements is additionally of interest to many [6].

While the extant literature demonstrates a lowering in fasting blood glucose following treatment with exogenous ketones, there are few data specific to the postprandial glucose response to carbohydrate feeding, in particular at different dosages of ketones and in healthy individuals. The present study evaluated blood glucose following the administration of an oral glucose tolerance test

(OGTT), with and without ketone esters delivered at two different dosages (chosen from previous dose ranging and chronic work on the ketone molecule under investigation here [21]), in a sample of healthy Sprague-Dawley rats. We hypothesized that ketone esters would lower the glucose area under the curve (AUC) in response to oral glucose ingestion, in a dose dependent manner.

2. Materials and Methods

2.1 Materials

The study was performed during the months of September and October, 2023. Materials were as follows:

2.1.1 Test Item

(R)-3-Hydroxybutyrate glycerides (BHB), previously used in the safety investigation as reported by Dolan et al. [21]. The test material was composed of 93% (R)-3-Hydroxybutyrate glycerides, 5% glycerol, and 1% (R)-3-hydroxybutyrate (Tecton BG, Inc., Alexandria, LA). The composition of the test material was confirmed by gas chromatography (GC) and high-performance liquid chromatography (HPLC). Batch 20221104 was used.

2.1.2 Glucometer & Strips

SD CodeFree™ automatic blood glucose meter (Cat No. 01GM11) and strips (Lot No. CO38429).

2.1.3 D-Glucose

NICE Chemicals, Cat No. G10229.

2.1.4 Experimental Animals

Male Sprague-Dawley (SD) rats (Code CRL:SD) 8-10 weeks old and ~220 g body weight were purchased from Hylasco, Hyderabad, India. Animals were maintained on a normal chow diet throughout the experimental period. Male SD rats were chosen for a number of reasons: 1) to avoid hormonal fluctuations associated with the estrous cycle in female rats which is particularly of interest in metabolic studies [28]; 2) male rats tend to have higher and more consistent glucose levels than females, making male rats a reliable model for studying glucose tolerance [29]; 3) male SD rats have been used extensively in previous research investigating the effects of glucose metabolism and ketones [30].

2.1.5 Acclimatization

The animals were acclimatized for at least five days to laboratory conditions and were observed for clinical signs once daily. Veterinary examination of all the animals was performed on the day of receipt and prior to the start of the treatment.

2.1.6 Environmental Conditions

Animals were housed in an environmentally monitored air-conditioned room maintained at a temperature of 20 ± 3°C, a relative humidity of 30 to 70%. Air changes of 10-15 per hour were maintained in the experimental room with 12 h dark and 12 h light cycle. Temperature and humidity were recorded once daily.

2.1.7 Housing

Animals were kept in the same group, with a maximum of two to three animals per cage and housed in standard polycarbonate cages. The cages were fitted with a stainless-steel mesh top grill with facilities for holding pelleted food and drinking water bottle.

2.1.8 Food and Water

The pellet feed was provided *ad libitum* throughout the acclimatization and experimental period. Standard rodent maintenance diet with a branded formula (5L79) from Charles River Laboratories for rats was procured (Lot No. 08MAR20231) from Hyalasco Pvt. Ltd. and provided to study animals. Reverse osmosis water was provided *ad libitum* throughout the experiment period.

2.2 Ketone Treatment and Randomization

Healthy male SD rats were grouped and allocated to their respective treatment groups using a body weight-based stratified randomization. The details of study design and animal allocation are below and shown in Figure 1.

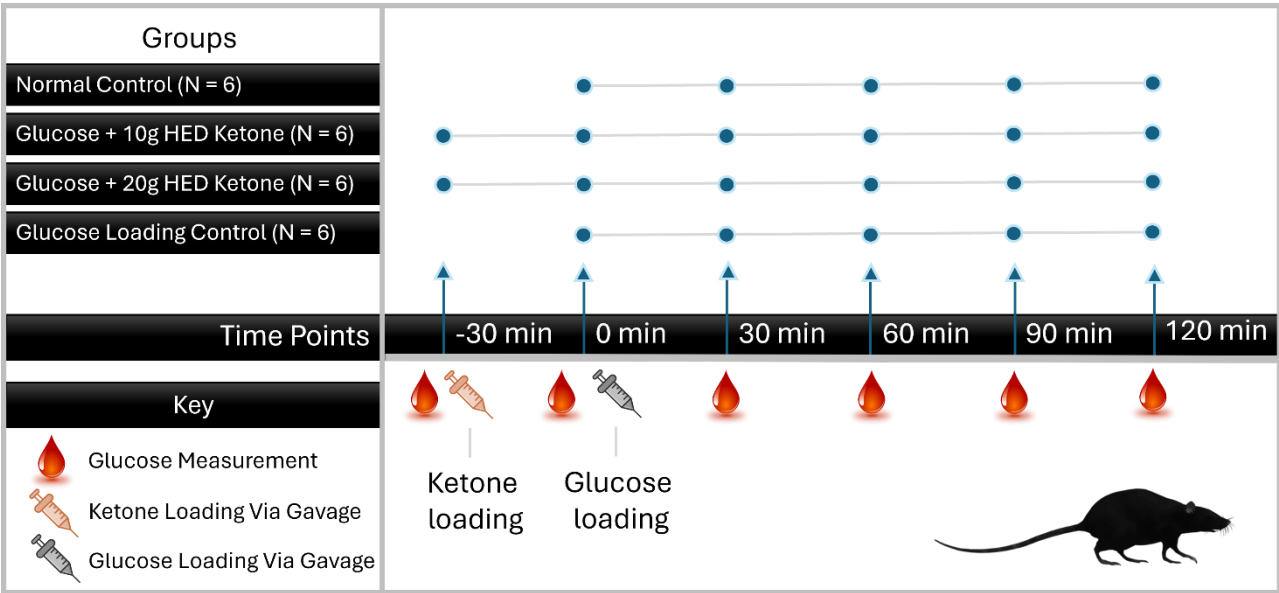


Figure 1 Study schema of experimental design. Figure shows the groups of SD rats including the time points for ketone loading by oral gavage, as well as glucose loading. For each group, it shows the OGTT time points where blood was collected for each rat. N: number of animals per group.

The following test groups were used: n = 6 per group:

- Normal control group (no glucose and no ketones)
- Glucose + 10 g HED Ketone (30 minutes prior to glucose challenge)
- Glucose + 20 g HED Ketone (30 minutes prior to glucose challenge)
- Glucose loading control (no ketones)

Groups of 6 male SD rats (average weight: 220 ± 20 g) were fasted overnight (about 16 hours) and the ketone test article was administered via gavage 30 minutes before oral glucose loading (2 g/kg body weight). Ketone was delivered 30 minutes prior to oral glucose loading in accordance with previous human subjects research [31]. Ketone was administered on a per unit body weight (kg) basis, where the exact amount of ketone for each animal was calculated based on the individual respective body weight at the time of dosing. The animal equivalent dose (amount/kg) was scaled from the specified human equivalent dose via allometric scaling using the species (rat) specific body surface area-based conversion factors. Specified HED to be tested in this glucose tolerance test were 10 g and 20 g ketone per adult (average body weight of 70 kg), as these dosages are commonly used by humans in a free-living environment. These doses were also confirmed via animal testing previously published by Dolan et al. [21].

2.3 Blood Collection and Analysis

Blood was collected from the tail vein, and blood glucose was measured by glucometer with a biosensor-strip based method [using 2 separate Automatic Blood Glucose Monitoring Systems (01GC110) of the make SD CodeFree™ (qualified accuracy that meets ISO15197:2013 standards) from SD Biosensors, Republic of Korea] at -30 (pre-treatment), 0 (before glucose loading), 30, 60, 90 and 120 minutes after glucose loading (a standard timeline for OGTT). The area under the curve over 120 min (AUC 0-120 min) was determined. In addition, the peak blood glucose was compared at all time-points.

2.4 Statistical Analysis

The data were entered in a Microsoft® Excel spreadsheet for organization and then exported to a statistical software program (GraphPad Prism; Version 10.0, San Diego, CA, USA) for further statistical analyses. A one-way ANOVA was used to test the significance between means of respective control versus treatment groups. The data were further subjected to Dunnett's test for multiple comparisons. All results are expressed as the Mean $\pm$ Standard Deviation (SD) and presented in tables and/or figures. All differences were considered statistically significant if $p \leq 0.05$ (Level of significance is indicated by * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ versus control, which is noted where appropriate).

2.5 Overview, Compliance, and Ethics Statement

This study was performed at Vipragen Biosciences Private Limited. The guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) were followed and the laboratory (Registration number 1683/PO/RcBiBt/S/13/CPCSEA) following all ethical practices as described in the guidelines for animal care and accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International, USA. This study

was approved by the Institutional Animals Ethics Committee (IAEC) of the test facility – VIP/IAEC/0/2022.

3. Results

All 24 animals successfully completed the study and blood samples for each time point were successfully obtained from all the groups (4 groups × 6 animals per group). These results are shown in Figure 2.

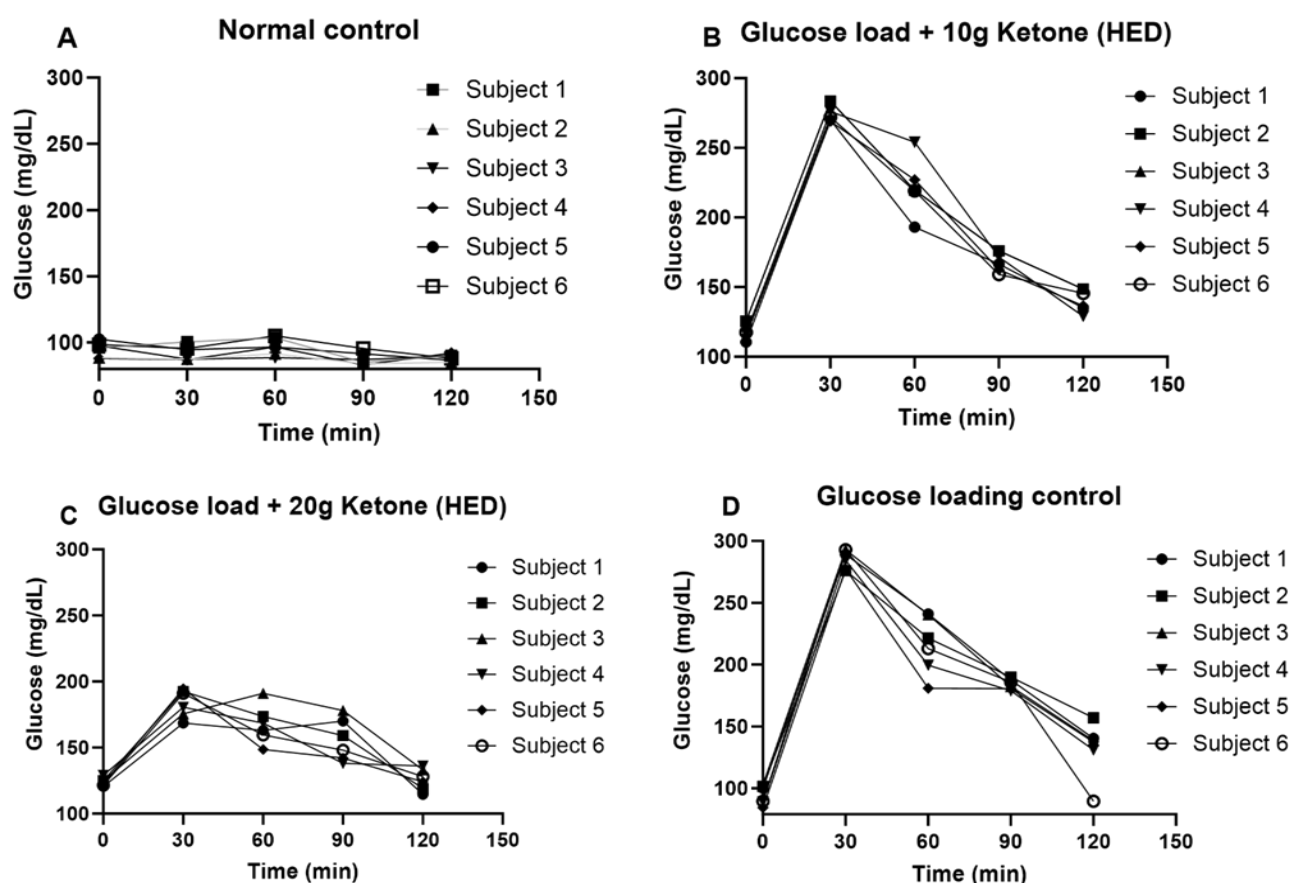


Figure 2 Blood glucose values against time points in different test groups (“subjects” represent animals in each group): (A) Normal control with no glucose loading, (B) 10 g HED ketone plus glucose load, (C) 20 g HED ketone plus glucose load, and (D) glucose loading control. Raw values for each subject (animal 1-6) in each plot (A-D) are presented in Table S1 with mean and standard deviation at each time point.

Regarding the blood glucose data, values for animals receiving the dose of 20 g HED ketone esters were significantly lower as compared to the glucose loading control ($p < 0.05$). The most pronounced difference occurred at the 30-minute post ingestion time, when values were approximately 50% lower for the ketone ester group. A highly similar response was observed for all animals exposed to the 20 g HED dose of ketone esters, indicating little variability across animals. With the 10 g HED dose, no statistically significant difference was noted between glucose-loading control ($p > 0.05$).

Figure 3A shows group mean blood glucose data for each time point (-30 to 120 minutes). The glucose loading control and glucose load plus 10 g HED ketone groups showed nearly identical responses at each time point. However, when the animals were challenged with a 20 g HED ketone

load at time point -30 minutes and then given a glucose load at time point 0 minutes, there was a noticeable attenuation of blood glucose levels.

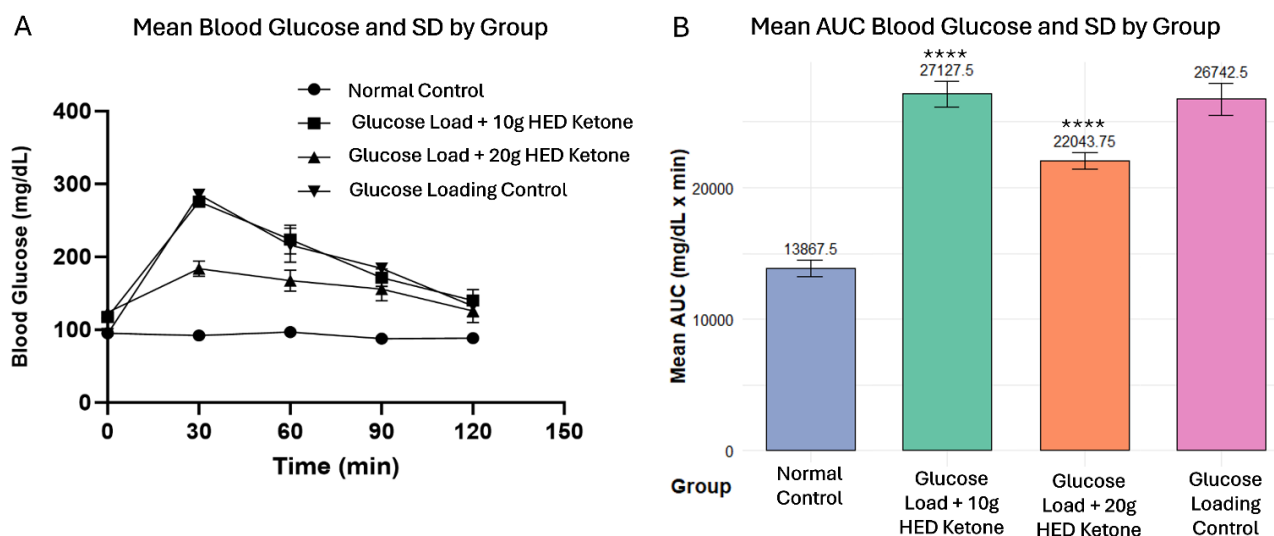


Figure 3 Summary of OGTT data from different test groups. (A) mean blood glucose (with SD) by time point for each group. Compared to glucose loading control group, blood glucose levels were significantly lower in 20 g HED Ketone group. In 10 g HED Ketone group, glucose levels were similar to glucose loading control. (B) mean AUC blood glucose (with SD) for each group. When AUC was analyzed for each group, the 20 g HED ketone was significantly decreased from the glucose loading control ($p < 0.0001$), while the 10 g HED ketone exhibited a response like the glucose loading control. All results have been expressed as the Mean $\pm$ Standard Deviation (SD). **** $p < 0.0001$.

Figure 3B shows the mean AUC for the four groups with standard deviation. Importantly, when the active group (glucose load + 20 g HED ketone) was compared to the glucose loading control, a mean difference of -4698.8 mg/dL $\times$ min was found within a -6013.46 to -3384.04 95% confidence interval (CI). This is a 21% decrease in AUC blood glucose levels for that group comparison.

Table 1 shows a Dunnett's multiple comparison test for relevant groups. There was a significant difference between the ketone treated groups ($p < 0.0001$), indicating a dose response. Similarly, there was a significant difference between the glucose loading control and the 20 g HED ketone dose ($p < 0.0001$). Cohen's d was calculated for this group comparison (glucose loading control and the 20 g HED ketone dose) and was found to be 4.46 with a 95% CI of 2.24 to 6.67. For Cohen's effect size analysis, anything above the threshold of 0.8 is considered to be large, thus, 4.46 is very large and positive. The effect size between the ketone groups (10 g HED ketone and 20 g HED ketone) was also found to be large and positive at 5.65 (95% CI of 3 to 8.31), which further exemplifies the strength of the dose response finding.

Table 1 Dunnett's multiple comparisons test and Cohen's effect size test for AUC values of blood glucose. For each comparison, the reference level is noted. For the Dunnett's multiple comparison test and Cohen's effect size, significance level and effect size magnitude are noted for context.

Dunnett's multiple comparisons test for AUC values of OGTT	Mean Diff. (mg/dL × min)	95% CI of Diff. (mg/dL × min)	Adjusted <i>p</i> Value	Significance Level	Cohen's <i>d</i>	Cohen's 95% CI	Effect Size Magnitude
Glucose Loading Control (ref) vs. Glucose load + 10 g HED ketone	385	-929.7 to 1699.70	0.8	ns	-0.32	-1.51 to 0.87	Small, Negative
Glucose Loading Control (ref) vs. Glucose load + 20 g HED ketone	-4698.8	-6013.46 to -3384.04	<0.0001	****	4.46	2.24 to 6.67	Large, Positive
10 g HED ketone (ref) vs. 20 g HED ketone	5083.75	-6399.68 to -3767.82	<0.0001	****	5.65	3 to 8.31	Large, Positive

Ref: reference value, AUC: area under the curve, OGTT: oral glucose tolerance test, Diff: difference, CI: confidence interval.

4. Discussion

In the current study, the following key findings were observed: 1) exogenous ketone ester administration at 20 g HED in healthy male SD rats was associated with a reduction in the AUC for blood glucose of ~21% compared to glucose-loading control, with the most robust differences occurring at the 30 and 60 minute post ingestion times—an approximate 50% reduction at 30 minutes post ingestion (Figure 3); 2) The response observed for all animals exposed to the ketone esters had little variability (as evidenced by low SD in those groups), as can be seen in Figure 2 (Panel C, in particular); and 3) exogenous ketone ester administration at 10 g HED did not yield an effect on blood glucose, as compared to glucose loading control.

The study demonstrates that ketone esters attenuate the glycemic response to an OGTT in a sample of healthy male SD rats at 20 g HED. This effect has been previously reported in human subjects, although the magnitude of glucose lowering was roughly half of that reported in the present study [31], i.e., 11% vs. 21% reduction. This discrepancy may be related to noted differences in comparing the effects of ketones in animals vs. human subjects. However, it is also possible that the unique metabolic behavior of the ketone ester used in the present investigation could also be responsible for the more robust findings. Interestingly, the study by Myette-Côté and colleagues [31] used a dosage of 482 mg/kg body weight of ketone esters, and subjects had an average body mass of 96 kg—equating to an average ketone dose of 46 grams, which is more than double the HED used in the present investigation but with a much lower glucose lowering effect. With such an improved glucose lowering ability of the Tecton Ketone used in the present study, it is certainly plausible that the type of ketone ester used could have played a role in these differing outcomes (e.g., (R)-3-hydroxybutyl (R)-3-hydroxybutyrate used in the study by Myette-Côté et al. [31]). Future studies with more data, including the comparison of various ketone forms, is warranted.

While a single dose of 20 g HED yielded a positive effect, we failed to observe a similar effect at the lower dosage of 10 g HED. It is possible that a certain threshold for blood BHB may be needed prior to glucose loading for glycemic effects to occur and the lower dosage of ketone esters was not able to generate this increase in blood BHB. Unfortunately, a measure of blood BHB was not included in this study, which can be viewed as a limitation. That said, recent anecdotal evidence (unpublished findings) supports an attenuation in the glycemic response when ketone esters precede glucose ingestion in a human model. While not observed in a controlled laboratory setting, these observations warrant further investigation.

Exogenous ketones are increasing in popularity, possibly due to the increased awareness of, and adherence to, a ketogenic diet [32]. Exogenous ketones have been suggested for use as a metabolic therapy [33], reported to increase blood and muscle oxygenation [34], support the brain during times of energy crisis [35], and can lower blood glucose [23]. Related to the latter point, there have been several studies demonstrating a lowering in fasting blood glucose following either adherence to a low carbohydrate ketogenic diet or use of exogenous ketones [17, 22]. That effect is fairly well-described, where a significant rise in BHB following ketone ingestion led to a concomitant lowering in blood glucose—a finding that is more pronounced for ketone ester vs. ketone salt [22].

Postprandial blood glucose was lowered in response to an oral glucose challenge, which is a novel finding. This may be of great relevance, first, to humans with healthy glucose control who desire to maintain lower and more stable blood glucose and insulin levels throughout the day. Second, this may be of value to those who wish to optimize performance and recovery, or who wish to extend

operations in the field under high operational demands (e.g., athletics, warfighters, or other occupations demanding significant physical exertion). Third, the finding of blunting the oral glucose response may be important in those with impaired glucose regulation, such as in diabetes. If this finding is generalizable to humans, it may provide health benefits by diminishing the glucose load from a meal and reducing the sustained exposure of tissues to elevated glucose.

The present study has a number of limitations that should be addressed in future research. First, the results may not be generalizable to female rats nor to humans. Second, future research should examine additional analytes associated with glucose regulation such as insulin and peptide C, blood BHB to confirm the ketone dynamics, indices of insulin signaling relevant to glucose uptake and glycogen synthesis, and determination of glucose clearance and glycogen content into muscle and liver tissues. This level of detail would allow for further exploration into the mechanistic underpinnings of how ketone intervention attenuates blood glucose levels. As such, the findings presented herein should be considered preliminary until more research is conducted to confirm and expand the findings mentioned above.

5. Conclusions

The results from this study suggest that preloading with ketone esters may attenuate the blood glucose response in animals exposed to an oral glucose challenge. Specifically, these results indicate a dose-dependent response to ketones, as evidenced by a 21% decrease in blood glucose AUC as a result of preloading with 20 g HED ketone dose when compared to the glucose loading control (mean blood AUC difference: -4698.8 mg/dL × min and $p < 0.0001$). Notably, this response was not observed in the 10 g HED ketone dose.

Future animal studies involving female rats will be required to confirm the generalizability based on sex. Follow up clinical studies, ideally involving different dosages of ketone esters and the quantification of circulating BHB levels and other relevant analytes, are needed to confirm this hypothesis as well as the mechanistic dynamics underlying the particular phenomena of glucose attenuation presented in this study. Although the present study convincingly demonstrates the impact of the Tecton ketone ester on postprandial glycemia, obtaining data from human subjects will strengthen these findings and may lead to clinical and non-clinical recommendations for the use of ketone esters as a nutritional tool to modulate glucose uptake and utilization following carbohydrate-rich feedings.

Author Contributions

Conceptualization: A.R.K., V.T., K.K., K.K., M.R.H. and A.C.; Data curation: M.R.H.; Formal analysis: M.R.H. and V.V.V.; Funding acquisition: M.R.H. and V.V.V.; Investigation: M.R.H. and V.V.V.; Methodology: R.J.B., A.R.K., V.T., K.K., K.K., M.R.H. and A.C.; Project administration: M.R.H. and V.V.V.; Writing – original draft: R.J.B. and K.K.; Writing – review & editing: A.R.K., V.T., K.K., M.R.H., V.V.V., C.S., M.S., B.J.F., N.A., and A.C.

Funding

Funding for this work was provided in part by Tecton BG, Inc.

Competing Interests

A.M.C. is an employee of Tecton BG, INC. R.J.B. is a consultant for Tecton BG, INC. C.M.S. and M.A.S. are advisors to Tecton BG, INC. M.R.H., V.V.V., K.K.K., K.V.K., A.R.K., V.C.T., B.J.F., and N.A.A. have no reported conflicts related to this work.

AI-Assisted Technologies Statement

The authors declare that no AI technologies were used in the writing of this manuscript.

Additional Material

The following additional materials are uploaded at the page of this paper.

1. Table S1: Individual Values for All Animals in all Groups with Mean and SD.

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