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Therapeutic Efficacy of *β*-Hydroxybutyrate Supplementation on Weight Loss and Glycemic Control in Fasted Obese and Diabetic Mice

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ABSTRACT

The global prevalence of obesity and diabetes necessitates novel therapeutic interventions. Ketone bodies, particularly beta-hydroxybutyrate (BHB), have emerged as promising agents for metabolic management. This study assessed how effective the efficacy of oral beta-hydroxybutyrate (BHB) supplementation on weight loss and glycemic control in a streptozotocin (STZ; 50 mg/kg, intraperitoneal) mouse model of obesity and diabetes induced by a high-fat diet (HFD, which consists of 45% beef tallow, 35% egg yolk, and 20% commercial food pellets) for 21 days under a 16-hour daily fasting protocol. Male Swiss Webster mice were divided into four groups and orally administered: metformin (0.1 mg/g) (positive control), low-dose BHB (3.75 mg/g), high-dose BHB (7.5 mg/g), and water (negative control). All treatments were administered once daily for 14 days. At the end of the treatment period, parameters evaluated included final body weight, fasting blood glucose (FBG) levels in the tail vein on days 0, 1, 7, and 14, and urinary ketone levels via urine sampling. Results demonstrated that high-dose BHB administration induced a significantly reduced body weight ($p < 0.05$) and fasting blood glucose levels ($p < 0.01$), with efficacy comparable to that of metformin. The low-dose BHB group showed a statistically significant improvement in fasting blood glucose (FBG) ($p < 0.05$) but did not significantly reduce body weight. Critically, urinary ketones remained undetectable, indicating no induction of ketoacidosis. These results suggest that oral BHB supplementation, particularly at higher doses, is a safe and effective strategy for improving metabolic outcomes during fasting in obese and diabetic models, positioning it as a viable adjunct therapeutic option.

Keywords: Beta-hydroxybutyrate, Obesity, Diabetes, Fasting, Glucose Control, Weight loss.

Introduction

Obesity and diabetes mellitus are major, interrelated global health challenges, driven by a steady rise in prevalence.[1] By 2035, the global number of people affected by overweight and obesity is projected to exceed 4 billion, up from 2.6 billion in 2020.[2] The International Diabetes Federation (IDF) reported in 2024 that diabetes prevalence reached 11.1% worldwide among adults aged 20-79 (589 million people), with estimates suggesting this will rise to 853 million by 2050.[3] In Indonesia, the 2018 Riskesdas (Indonesia's National Basic Health) survey found an obesity prevalence of 21.8%.[4] The country also ranks in the top ten for diabetes burden, with 10.7 million people affected in 2019.[5] The increasing prevalence of obesity and diabetes has driven the development of various therapeutic and interventional strategies. One non-pharmacological approach that has gained significant attention is intermittent fasting (IF). IF is a dietary intervention that involves periodic calorie restriction, ranging from 12 hours to several days.[6] During periods of low carbohydrate availability, the body shifts to using fat as an energy source via ketogenesis, generating ketone bodies like acetoacetate, beta-hydroxybutyrate (BHB), and acetone, which serve as alternative energy substrates.[7]

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BHB, the most abundant and stable circulating ketone body, serves not only as an energy source but also has therapeutic potential for metabolic disorders such as obesity and diabetes.[8] In managing obesity, BHB contributes to hunger suppression by reducing ghrelin levels. In diabetes, BHB inhibits hepatic gluconeogenesis, thereby lowering blood glucose levels.[9] However, endogenous ketone production typically requires prolonged fasting or intense physical activity, making it challenging to achieve physiologically relevant levels.[10] Exogenous ketones provide a rapid and convenient way to elevate blood ketone levels. After ingestion, exogenous ketones are absorbed into the bloodstream and distributed to various tissues (such as the brain, heart, muscles, and kidneys), where they are metabolized in the mitochondria to produce adenosine triphosphate (ATP) as acetyl-CoA.[10,11] However, excessive accumulation of ketones can lead to adverse effects, including ketoacidosis and potentially life-threatening blood pH imbalances, which necessitate careful dosing and monitoring.[12] Previous studies have demonstrated several essential findings regarding exogenous BHB supplementation. Research has shown that BHB administered as esters or salts can effectively raise blood ketone levels and induce ketosis without requiring dietary changes.[5] Clinical studies indicate that ketone salt supplements can reduce hepatic fat in overweight or obese individuals without causing significant side effects.[13] Animal studies have further confirmed these results, reporting elevated BHB levels accompanied by substantial reductions in glucose concentrations and only minimal alterations in fat metabolism.[14] However, it is noteworthy that when BHB supplementation was combined with ketogenic diets, it showed no significant advantage for weight loss compared to placebo-controlled diets.[15] While these studies have contributed valuable insights into BHB's metabolic effects, most have focused on its administration alongside ketogenic dietary regimens. Therefore, this study seeks to examine the effects of BHB supplementation specifically under fasting conditions in obese and diabetic animal models. The objectives of this study are: (1) to evaluate the impact of exogenous BHB supplementation on body weight reduction during fasting; (2) to assess its efficacy in improving

glycemic control; and (3) to monitor potential adverse effects through regular ketone measurements. This approach aims to address an essential gap in the current literature by examining BHB's therapeutic potential in the context of intermittent fasting, thereby informing the development of more effective management strategies for obesity and diabetes.

Materials and Methods

Materials

The materials used in this study included magnesium beta-hydroxybutyrate (BulkSupplements®, USA), streptozotocin (bioWORLD®, USA), metformin HCl (Hexpharm Jaya, Indonesia), distilled water, sodium chloride 0.9% (BBraun®, Indonesia), a glucometer (Sinocare®, Indonesia), blood glucose test strips (Sinocare®, Indonesia), alcohol swabs (Onemed, Indonesia), and urinary ketone test strips (Medimed, China.

Animals

This study was conducted in accordance with protocols approved by the Animal Experiment Ethics Committee of the University of Yayasan Pendidikan Imam Bonjol (YPIB), Majalengka (Approval No. 274/KEPK/EC/X/2024). Male Swiss Webster mice (*Mus musculus*) weighing 20-30 g were procured from Pahlepi Mouse House, a laboratory animal breeding facility located in Tasikmalaya, Indonesia. The mice were housed in groups of three to five per cage and kept on a 12-hour light/dark schedule. Following this, they were randomly assigned to one of four experimental groups: the positive control group (metformin 0.1 mg/g), the low-dose BHB group (magnesium beta-hydroxybutyrate 3.75 mg/g), the high-dose BHB group (magnesium beta-hydroxybutyrate 7.5 mg/g), and the negative control group (distilled water).

Induction of Obesity

Obesity was induced in the mice by administering a high-fat diet (HFD) for 21 days post-acclimatization. The HFD, prepared daily to avoid spoilage, was formulated as a mixture of 45% beef fat, 35% egg yolk, and 20% commercial food pellets, modifying an established method.[16] Spoilage was prevented by preparing the HFD fresh daily. Following the induction period, the mean body weights from before and after were compared. Obesity confirmation was based on the Lee index, a value calculated from body weight and naso-anal length; an index exceeding 300 indicated obesity.[17]

Induction of Diabetes

Diabetes was induced via a single intraperitoneal injection of streptozotocin (STZ) at a dose of 50 mg/kg,[18] which was prepared in sodium citrate buffer. This method was adapted from a literature source.[19,20] To determine fasting blood glucose (FBG), blood was taken from the tail vein and analyzed using a glucometer (Sinocare®) immediately before and 72 hours after STZ administration. Mice with blood glucose levels >126 mg/dL were classified as diabetic.[21]

Experimental Procedure

After confirming that the mice were obese and diabetic, they were randomly assigned to treatment groups (n = 4 per group) and underwent a 14-day intervention regimen. All groups received daily oral treatments for 14 days at 07:00**,** accompanied by a 16-hour fasting period (from 17:00 to 09:00) to enhance metabolic effects. Physiological monitoring included daily body weight measurements at 08:30 and fasting blood glucose assessments through tail vein sampling on days 0, 1, 7, and 14. The values obtained on day 0 served as baseline data before the intervention began. Additionally, urinalysis for ketone detection was performed at the same time points. Urine samples were collected spontaneously, as the volume required to wet the reactive area on the urine ketone test strip was minimal.

Statistical Analysis

The collected data were analyzed using IBM SPSS and GraphPad Prism (version 9.5.1 [733]). Statistics is used to analyze the data collected. Data normality was evaluated using the Shapiro-Wilk test, while variance homogeneity was assessed with Levene's test. Comparisons before and after induction within the same groups were made using a paired sample t-test. A two-way repeated measures ANOVA, supplemented by Dunnett's post-hoc test, was applied for multiple comparisons. A result was deemed statistically significant if the p-value was below 0.05.

Results and Discussion

This study examined the effects of exogenous BHB supplementation on body weight, blood glucose levels, and the potential risk of ketoacidosis in obese diabetic mice under fasting conditions. Obesity was induced using an HFD composed of standard chow, egg yolk, and beef fat, designed to emulate human dietary patterns that contribute to metabolic syndrome. This composition, rich in saturated fats and high in caloric density, effectively triggered rapid weight gain and visceral adiposity. Each component served a distinct metabolic function: the standard chow provided essential macronutrients, egg yolk contributed additional lipids, and beef fat, being a primary source of saturated fat, promoted triglyceride synthesis and fat accumulation.[22,23] After 21 days of ad libitum feeding, the animals exhibited significant weight gain, with Lee index values exceeding 300, confirming the establishment of an obesity phenotype associated with disrupted energy homeostasis.

The anthropometric data during the obesity induction period are shown in Table 1. The final body weights were significantly higher ($p < 0.05$) than the initial measurements, indicating that the HFD effectively contributed to obesity development. Similarly, Lee index values were significantly higher ($p < 0.05$) in all groups compared with the initial measurements. Following the 21-day HFD treatment period, all mice in each group exhibited Lee index values above 300, confirming that all subjects in this study developed obesity according to established criteria.

Table 1: Body Weight and Lee Index Changes in Different Groups During Obesity Induction Period

Groups	Body Weight (g)		Lee index	
	Initial	Final	Initial	Final
MET	24.5 ± 1.55	27.48 ± 2.32*	305.51 ± 5.60	317.08 ± 7.78^
KS1	26.75 ± 1.55	30.40 ± 1.57*	295.23 ± 3.92	308.20 ± 4.74^
KS2	28.75 ± 2.59	30.28 ± 2.74*	315.64 ± 11.46	321.24 ± 13.01^
WTR	31 ± 2.48	33.90 ± 2.56*	298.67 ± 1.91	307.83 ± 2.43^

* Significantly different from initial body weight within the same group ($p < 0.05$)

^ Significantly different from the initial Lee index within the same group ($p < 0.05$)

MET, metformin (positive control); KS1, ketone supplementation 3.75 mg/gBW; KS2, ketone supplementation 7.5 mg/gBW; WTR, distilled water (negative control).

Obese mice induced with HFD were administered STZ to cause metabolic dysfunction. As shown in Table 2, while most mice developed hyperglycemia (FBG > 126 mg/dL), variability in response was observed, which may be attributed to several factors. The statistically significant elevation in blood glucose levels ($p < 0.05$) confirms the model's validity, while the observed variability mirrors the heterogeneous presentation of diabetes.

To simulate the pathophysiology of diabetes, the obese mice were subsequently administered STZ, a β-cell cytotoxic agent. A moderate dose of STZ was used to induce partial dysfunction in pancreatic β-cells while preserving some insulin secretory capacity**;** this scenario is typical for type 2 diabetes mellitus (T2DM) in the context of obesity-induced insulin resistance.[24] This dual induction approach successfully created a metabolic environment reflective of diabetes, evidenced by significantly elevated FBG levels post-STZ injection. Thus, the model provided a robust framework for evaluating the combined effects of fasting and BHB supplementation on metabolic regulation.

The body weight changes of the mice throughout the 14-day treatment

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are presented in Figure 1. The results indicate that all treatment groups experienced weight loss during the fasting period. We used a two-way repeated-measures ANOVA and found a significant interaction between the time factor and the treatment factor ($F_{42, 168} = 1.677$, $p = 0.0117$), suggesting that the effects of both BHB supplementation and metformin on weight loss varied with treatment duration. Additionally, a highly significant time effect was observed ($F_{2.231, 26.77} = 22.01$, $p < 0.0001$), confirming that body weight changes progressed throughout the experimental period.

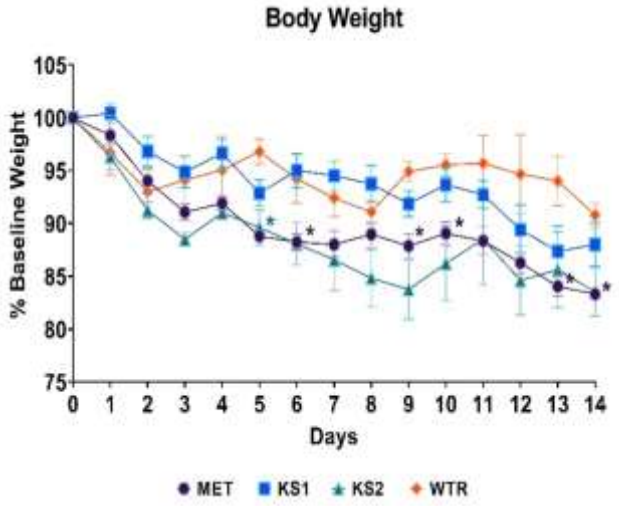

Figure 1: Effects of ketone supplementation on body weight MET, metformin (positive control); KS1, ketone supplementation 3.75 mg/gBW; KS2, ketone supplementation 7.5 mg/gBW; WTR, water (negative control). * Significantly different from initial body weight within the same group ($p < 0.05$).

Post-hoc analysis showed that the positive control group and the KS2 (ketone supplementation 7.5 mg/gBW) group achieved statistically significant weight reduction compared to the negative control at specific time points. Although the KS1 group showed a decreasing trend in body weight, these changes were not statistically significant compared with the negative control group.

The experimental data presented in Figure 2 demonstrate statistically significant differences in FBG levels across all treatment groups during the study period. Statistical analysis using a two-way repeated measures ANOVA showed a significant interaction between time and treatment ($F_{6, 27} = 4.121$, $p = 0.0046$, indicating differential treatment effects over time. Additionally, a strong main effect of time was observed ($F_{2.418, 21.76} = 31.35$, $p < 0.0001$), reflecting consistent changes in glucose levels over the course of the experiment.

Post-hoc analysis revealed distinct response patterns among the treatment groups. The positive control group showed significant reductions in FBG at all time points ($p < 0.05$). The KS1 (ketone supplementation 3.75 mg/gBW) group also demonstrated glucose-lowering effects, but these were statistically significant only on days 7 and 14 of treatment. More pronounced effects were observed in the KS2 (ketone supplementation 7.5 mg/gBW) group. Analysis using the Friedman test confirmed significant treatment effects ($p = 0.0009$), and Dunn's post-hoc tests identified specific reductions on days 7 and 14 ($p < 0.01$). In contrast, the negative control group exhibited only minor, non-significant fluctuations in FBG levels throughout the observation period.

During the intervention period, all groups underwent a 16-hour fasting protocol. Even in the absence of pharmacological or nutritional treatment, the negative control group experienced notable weight reduction.

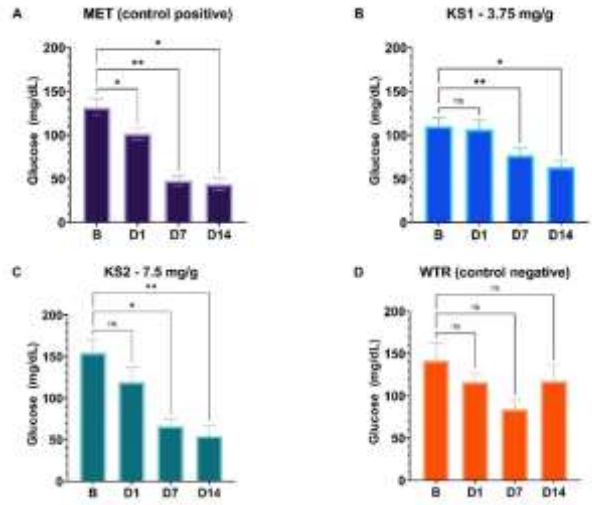

Figure 2: Effects of ketone supplementation on blood glucose levels. (A) MET (metformin, positive control) significantly reduced glucose levels over time. (B) KS1 (ketone supplementation 3.75 mg/gBW) showed a gradual decrease in glucose levels, with a significant reduction by day 7 and 14. (C) KS2 (ketone supplementation 7.5 mg/gBW) resulted in a more pronounced glucose-lowering effect by day 7 and 14. (D) WTR (distilled water, negative control) showed no significant reduction in glucose levels. Data are presented as mean ± SEM. *$p < 0.05$; **$p < 0.01$; ns, not significant.

This finding aligns with prior research showing that intermittent fasting stimulates the body to stimulate the body to generate more short-chain fatty acids (SCFAs) and enhance the release of glucagon-like peptide-1 (GLP-1), while also enhancing gut microbial activity. These hormonal responses suppress appetite, improve satiety, and facilitate lipolysis, thereby contributing to body weight reduction.[25] Although this study did not measure blood ketone levels, the results are consistent with prior research demonstrating that even an 8-hour fast can elevate serum ketone levels and induce ketosis.[26] Endogenous ketosis enhances lipolysis, mobilizing free fatty acids from adipose tissue for energy production and thereby facilitating weight loss.[27] This metabolic shift likely supported energy demands during caloric restriction and helps to explain the weight loss observed in the fasting-only group.

The metformin-treated group, included as a positive control, exhibited the most substantial reductions in both body weight and FBG levels. The well-established metabolic advantages of metformin are mainly driven by the activation of AMP-activated protein kinase (AMPK), which increases fatty acid oxidation,[28] decreases hepatic gluconeogenesis,[29] and improves insulin sensitivity.[30] Additionally, metformin has been shown to downregulate fibroblast growth factor 21 (FGF21), which is a hormone secreted by the liver and known to be involved in fat accumulation and dyslipidemia.[31] This dual action contributes to both glycemic control and improved lipid metabolism, underscoring metformin's efficacy in addressing the core features of diabetes and obesity.

Comparable therapeutic outcomes were observed in the high-dose BHB supplementation group (KS2), whereas the lower-dose group (KS1) showed more modest effects. BHB appears to help reduce obesity through multiple biological pathways, including stimulation of mitochondrial β-oxidation,[32] suppression of de novo lipogenesis, and promotion of and stimulating the browning process of white adipose tissue (WAT), transforming it into thermogenic brown adipose tissue (BAT) that burns calories,[33] a transformation associated with increased lipid oxidation and energy expenditure. These processes work synergistically to reduce adiposity and support weight loss during fasting.

Table 2: Changes in Fasting Blood Glucose Levels in Different Groups During Diabetes Induction Period

Groups	FBG (mg/dL)	
	Initial	Final
MET	70 ± 10.61	131.50 ± 10.05*
KS1	101 ± 11.26	109.75 ± 9.94*
KS2	79.25 ± 10.14	154.75 ± 15.56*
WTR	100.75 ± 11.01	141.75 ± 21.31*

* Significantly different from initial FBG within the same group ($p < 0.05$). FBG, fasting blood glucose; MET, metformin (positive control); KS1, ketone supplementation 3.75 mg/gBW; KS2, ketone supplementation 7.5 mg/gBW; WTR, distille water (negative control)

In addition to its peripheral metabolic effects, BHB also influences the neuroendocrine regulation of appetite. This compound helps control hunger signals in the brain by suppressing the production of two key appetite-stimulating molecules neuropeptide Y (NPY) and agouti-related peptide (AgRP) in the hypothalamus, while simultaneously enhancing the secretion of anorexigenic hormones such as cholecystokinin (CCK) and suppressing the secretion of the orexigenic hormone ghrelin.[34] These hormonal shifts likely contributed to reduced food-seeking behavior and caloric intake in the BHB-treated groups, even before fasting, thereby reinforcing its role in appetite suppression and energy balance.

Importantly, this study also aimed to determine the impact of BHB supplementation on glycemic control. While fasting alone led to inconsistent reductions in FBG, with levels rebounding by the end of the intervention, the addition of BHB, particularly at higher doses, resulted in more stable and sustained reductions. This anti-hyperglycemic effect is believed to be mediated through several mechanisms: activates G-protein-coupled receptors (GPCRs) on pancreatic beta cells to boost insulin secretion; suppression of adipocyte lipolysis via GPR109A receptors, thereby reducing gluconeogenic substrates; and inhibition of L-alanine release from muscle tissue, a key gluconeogenesis precursor.[8,10] These coordinated actions limit hepatic glucose production and promote glycemic stability, positioning BHB as a potentially valuable adjunct in diabetes therapy.

Given BHB's ketone-based nature, a significant concern during its administration is the potential risk of ketoacidosis, a serious condition characterized by excessive ketone accumulation and metabolic acidosis. To address this concern, urinary ketone levels were monitored regularly. The results indicated no detectable ketones in urine samples across all treatment groups, including those receiving BHB. This finding suggests that neither the fasting protocol nor exogenous BHB supplementation induced pathological ketone accumulation. The absence of urinary ketones can be attributed to BHB's high metabolic utility and rapid peripheral oxidation, with only about 1.5% of administered BHB excreted renally.[27] These results are consistent with prior studies and indicate that BHB, when administered in controlled doses under intermittent fasting conditions, does not pose a risk of ketoacidosis. Nevertheless, complementary assessment of blood ketone levels would provide a more comprehensive evaluation of ketone metabolism and safety.

Urinary ketone levels were measured quantitatively using commercial urine test strips (Medimed, China), which use the sodium nitroprusside reaction.[35] In this method, urinary acetoacetate forms a purple complex with sodium nitroprusside. Throughout the experimental period, all urine samples from the mice (n = 4 per group) showed undetectable ketone levels, as indicated by the test strips failing to change color. These results suggest that the combination of intermittent fasting and exogenous BHB supplementation did not lead to ketoacidosis, even in the diabetic animal model. The consistent negative results across all treatment groups (see Table 3) further support the metabolic safety of the administered protocol.

Table 3: Urinary Ketone Levels in Different Groups During Treatment Period

Groups	Urine ketone level
MET	Negative
KS1	Negative
KS2	Negative
WTR	Negative

*MET, metformin (positive control); KS1, ketone supplementation 3.75 mg/gBW; KS2, ketone supplementation 7.5 mg/gBW; WTR, distilled water (negative control)

The conclusions of this study demonstrate that fasting alone does not result in significant improvements in weight or glycemic control through endogenous ketosis and hormonal modulation. However, the addition of exogenous BHB significantly enhances these effects, particularly at higher doses, with outcomes comparable to those of metformin treatment. Moreover, the absence of detectable urinary ketones suggests that BHB administration under the studied conditions does not trigger ketoacidosis, supporting its safety profile. These results highlight BHB's potential as an adjunctive or alternative intervention for managing obesity and diabetes, particularly in therapeutic strategies that integrate dietary restriction or intermittent fasting.

Conclusion

The present study demonstrates that beta-hydroxybutyrate supplementation exerts significant metabolic effects in obese diabetic mice under fasting conditions. Our results reveal three key observations: First, administration of beta-hydroxybutyrate at the higher dose (7.5 mg/g) significantly reduced body weight, with particularly notable effects observed by day 5 of treatment. Second, both tested doses (3.75 mg/g and 7.5 mg/g) effectively lowered fasting blood glucose levels, achieving statistical significance by days 7 and 14 of the intervention period. Importantly, urinary ketone monitoring throughout the study confirmed the safety of beta-hydroxybutyrate supplementation, as no cases of ketoacidosis were observed despite the fasting conditions. Collectively, these results suggest that beta-hydroxybutyrate supplementation, particularly at the higher dose, may represent a potential therapeutic strategy for controlling metabolic parameters in diabetes and obesity while maintaining ketone concentrations within the physiological range.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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