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β-hydroxybutyrate: An Early Predictor of Success in Type 2 Diabetes Remission During Dietary Intervention

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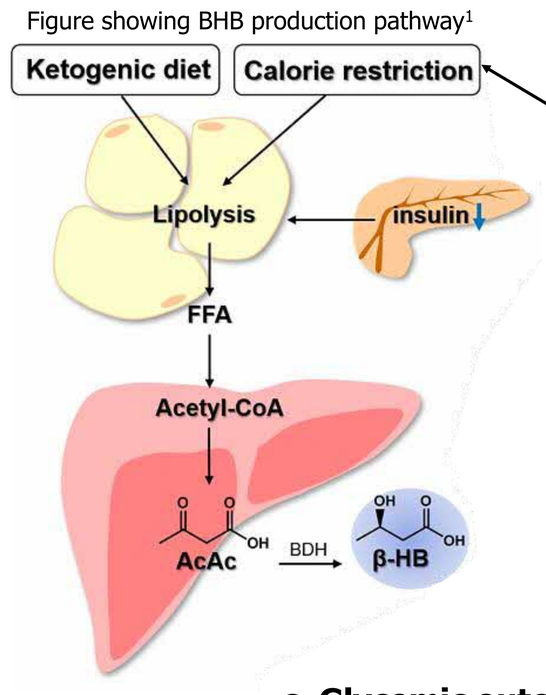
1. BACKGROUND & AIM

- Serum β-hydroxybutyrate (BHB) is the predominant ketone body produced during carbohydrate restriction. It represents a metabolic shift from glucose to fat utilization[1].
- Serum BHB level is measured in patients following a Very Low-Calorie Diet (VLCD) to assess for dietary adherence[2] and to distinguish nutritional ketosis from diabetic ketoacidosis[3].
- Recent studies suggest modest increase in ketone bodies reduced risk of type 2 diabetes (T2D) in patients with impaired fasting glucose and had greater HbA1c reduction in new-onset T2D patients after 6 months of treatment[4].
- Proposed mechanism behind was BHB acts as a signalling substance, reducing oxidative stress, regulating gluconeogenic gene expression and modulating pathways that improve insulin resistance[5].
- However, the association of modestly increased serum BHB during early phase of VLCD and outcomes in T2D remission is underexplored.
- We hypothesized that early BHB elevation during dietary intervention would predict T2D remission success.
- **OBJECTIVE:** To investigate the relationship between BHB levels and T2D remission outcomes in patients undertaking 12 weeks of total diet replacement (TDR)

2. METHODS

a. Programme recruitment criteria and process (started in Jul 2022)

Figure showing BHB production pathway[1]



TDR (12 weeks)
Very Low-Calorie Diet (800kcal/day)

Per serving
- 200 kcal
- 18g CHO
- 20g protein

x 3

- Stop glucose & blood pressure lowering medications
- 2 serves vegetables/day
- 1 teaspoon oil/day

Inclusion criteria:
- Aged 21–65 years old
- T2D duration 0–10 years
- Body Mass Index (BMI) 27–45 kg/m²
- HbA1c≥6.0% (on glucose-lowering meds) or ≥6.5% (on diet control)

36 participants who completed Phase 1 of the programme were analysed.

b. BHB measurement

Point-of-Care testing for BHB at week 2 of TDR following withdrawal of medications that may affect BHB production

c. Glycemic outcomes

- (Primary) T2D remission, defined as HbA1c<6.5% without glucose-lowering medications at end of TDR
- (Secondary) Absolute HbA1c change from baseline to end of TDR

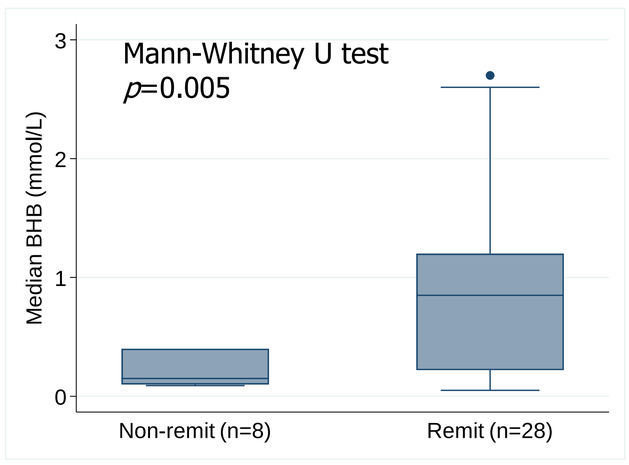
3. RESULTS

a. Baseline characteristics of participants by T2D remission status

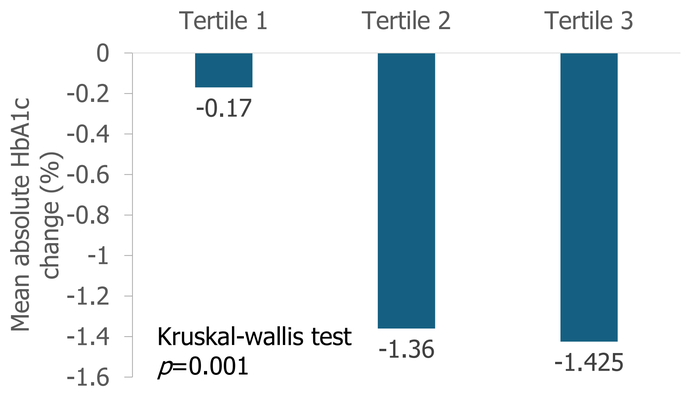
Variables	All (n=36)	Non-remit (n=8)	Remit (n=28)	*p* value
Age (years)	42 ±10	45 ± 8	41 ± 10	0.271
Male, n (%)	22 (61.1)	3 (37.5)	19 (67.9)	0.120
Ethnicity, n (%)				
Chinese	18 (50.0)	2 (25.0)	16 (57.1)	0.258
Malay	5 (13.9)	2 (25.0)	3 (10.7)	
Indian	7 (19.4)	3 (37.5)	4 (14.3)	
Others	6 (16.7)	1 (12.5)	5 (17.9)	
T2D duration (years)	3 (1 – 5)	3.3 (1.5 – 6)	3 (1 – 5)	0.859
BMI (kg/m²)	33.9 ± 3.9	31.5 ± 3.6	34.5 ± 3.7	0.052
SBP (mmHg)	131 ± 11	130 ± 12	132 ± 11	0.714
HbA1c (%)	7.1 ± 1.3	8.1 ± 1.2	6.8 ± 1.2	**0.009**
TG (mmol/L)	1.46 (1.18 – 2.08)	1.47 (1.20 – 2.62)	1.46 (1.18 – 1.94)	0.761

SBP: systolic blood pressure, TG: triglycerides

b. BHB levels by T2D remission status



c. Change in HbA1c after TDR by BHB tertiles



Median BHB tertile 1, 2 and 3 levels were 0.1, 0.6, and 1.4 mmol/L, respectively

d. Association of BHB with glycemic outcomes

	Unadjusted Coefficient (95% CI), *p* value	Adjusted* Coefficient (95% CI), *p* value
Outcome: T2D remission (Modified Poisson regression)		
BHB (continuous)	**1.26 (1.03 – 1.52), 0.021**	**1.29 (1.11 – 1.50), 0.001**
BHB (categorical)		
Tertile 1	Reference	Reference
Tertile 2	1.29 (0.71 – 2.31), 0.402	1.55 (0.97 – 2.46), 0.066
Tertile 3	1.71 (1.06 – 2.78), 0.029	**1.82 (1.20 – 2.75), 0.005**
Outcome: Absolute HbA1c change (Linear regression)		
BHB (continuous)	0.53 (0.20 – 0.85), 0.002	**0.36 (0.20 – 0.52), <0.001**
BHB (categorical)		
Tertile 1	Reference	Reference
Tertile 2	1.19 (0.29 – 2.09), 0.011	0.79 (0.32 – 1.25), 0.002
Tertile 3	1.26 (0.36 – 2016), 0.007	0.89 (0.44 – 1.34), <0.001

*Adjusted for age, sex, and baseline HbA1c

- Modified Poisson regression analysis revealed that one-unit increase in natural-log transformed BHB levels elevated likelihood of remission by **26% (95% CI:1.03–1.52, p=0.021)** in the unadjusted model. The relationship persisted after controlling for age, sex, and baseline HbA1c **(risk ratio:1.29, 95% CI:1.11–1.50, p=0.001).**
- BHB tertile 3 also independently predicted remission **(risk ratio: 1.82, 95% CI:1.20–2.75, p=0.005).**
- Linear regression confirmed an independent association between higher BHB levels and greater HbA1c reduction **(coefficient:0.36, 95% CI:0.20–0.52, p<0.001).**

4. DISCUSSION & CONCLUSIONS

- This study showed that early elevated BHB levels detected at week 2 of TDR significantly predict successful T2D remission and greater reduction in HbA1c after 12 weeks of TDR.
- This result showed that BHB level potentially serving as a useful early biomarker representing enhanced fat metabolism and therapeutic response, as well as serving as a source of motivation for participants to adhere to dietary intervention.
- Hence, monitoring BHB could provide valuable insights for modifying clinical and dietary intervention and help to identify individuals who are more likely to respond favorably to dietary intervention.

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