Diabetes Ther (2025) 16:2333–2349
https://doi.org/10.1007/s13300-025-01819-3

ORIGINAL RESEARCH

Protective Role of Serum β-Hydroxybutyrate in Early Diabetic Kidney Disease: A Longitudinal Study

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Received: September 1, 2025 / Accepted: October 21, 2025 / Published online: November 1, 2025

ABSTRACT

***Introduction*:** β-Hydroxybutyrate (βHB), the most stable form of ketone bodies, has exhibited protective effects in metabolic and chronic diseases. This study aimed to assess the association between fasting serum βHB levels, measured at baseline in drug-naïve state, and the risk of proteinuria in patients with newly diagnosed type 2 diabetes.

***Methods*:** In this longitudinal study involving 280 patients, baseline fasting serum βHB levels, urine protein parameters, and metabolic parameters were evaluated. To monitor the development of albuminuria (spot urine albumin-to-creatinine ratio ≥ 30.0 mg/gCr) or proteinuria (spot urine protein-to-creatinine ratio > 0.15 g/gCr), patients with normal baseline levels were followed for a mean of 2.40 ± 1.40 years.

***Results*:** Patients were classified into the highest tertile of baseline serum βHB level group and two other lower tertiles. The highest tertile group (median fasting serum βHB: 0.30 mmol/l) had a significantly lower incidence of proteinuria (6.90% vs. 24.3%, $p = 0.028$) and nonalbumin proteinuria (6.67% vs. 22.9%, $p = 0.031$) compared to the lower two tertiles. Higher baseline βHB levels were associated with a reduced risk of proteinuria (hazard ratio 0.313, 95% confidence interval 0.110–0.891), adjusted for confounders.

***Conclusion*:** Higher baseline fasting serum βHB levels are linked to a lower risk of proteinuria in newly diagnosed type 2 diabetes, suggesting its potential as a protective metabolic marker in early diabetic kidney disease.

Keywords: Albuminuria; β-Hydroxybutyrate; Diabetic kidney disease; Nonalbumin proteinuria; Proteinuria; Type 2 diabetes

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13300-025-01819-3.

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Key Summary Points

Why carry out this study?

β-Hydroxybutyrate (βHB), the most stable form of ketone bodies, has exhibited protective effects in metabolic and chronic diseases.

Diabetic kidney disease (DKD) is a significant complication in type 2 diabetes, often marked by albuminuria or proteinuria, and its pathogenesis involves inflammation and oxidative stress.

This study aimed to determine whether baseline circulating βHB provides protection against the incidence of albuminuria or proteinuria in newly diagnosed type 2 diabetes.

What was learned from the study?

Individuals with higher baseline circulating βHB levels showed a significantly lower incidence of proteinuria and nonalbumin proteinuria over a 2.40-year follow-up, with no observed effect on albuminuria development.

Higher baseline circulating βHB levels were associated with poorer glycemic control and reduced insulin secretory function but also with improved insulin sensitivity.

Baseline circulating βHB levels in individuals with newly diagnosed type 2 diabetes could support early risk stratification and management of DKD, highlighting its protective role in renal function.

INTRODUCTION

Under normal physiologic state, β-hydroxybutyrate (βHB), the most stable form of ketone bodies, is synthesized in the liver from free fatty acids and serves as a convenient source of energy to peripheral tissues, particularly the brain, heart, and skeletal muscles, during prolonged fasting or exercise [1]. In the context of diabetes, ketone bodies are often unfavorably regarded, primarily because of their link to diabetic ketoacidosis. Conversely, recent studies suggest that circulating βHB, in the range of nutritional ketosis where the body uses fat and ketone bodies for energy instead of carbohydrates, may offer beneficial effects on metabolic and chronic diseases, including neurodegenerative diseases, heart failure, and cancer, as βHB not only acts as a metabolite but also plays important roles in cellular signaling by suppressing senescence and inflammation [1–3].

Diabetic kidney disease (DKD) is a major complication and the leading cause of end-stage kidney disease (ESKD) in the US, affecting 20–40% of adults with diabetes [4]. It is clinically diagnosed by the presence of albuminuria and/or reduced estimated glomerular filtration rate (eGFR) without other causes of primary kidney damage in individuals with diabetes [5]. Although the exact mechanism of DKD has yet to be fully elucidated, processes such as oxidative stress, advanced glycation end-products, autophagy, and apoptosis are known to contribute to its pathogenesis [6–10].

Whether circulating βHB concentration is associated with the prevalence and development of DKD remains unclear. A cross-sectional study of 1388 patients with type 2 diabetes demonstrated a J-shaped relationship between circulating βHB levels and DKD risk [11]. Another retrospective study of 955 patients with type 2 diabetes identified a U-shaped relationship between serum βHB levels and DKD prevalence [12]. However, because these studies are cross-sectional, causal relationships between circulating βHB levels and kidney function in type 2 diabetes cannot be determined.

Considering that βHB regulates intracellular signaling to suppress inflammation and senescence, which play crucial roles in the pathophysiology of chronic kidney disease (CKD) [13], investigating the association between circulating βHB levels and the development of albuminuria and proteinuria in patients with type 2 diabetes through a longitudinal study is valuable. In this study, we explored the potential association between circulating βHB levels and the incidence of albuminuria or proteinuria by enrolling newly diagnosed, drug-naïve patients with type 2 diabetes.

METHODS

Study Design and Participants

In this longitudinal observational study, electronic medical records of patients with newly diagnosed, drug-naïve type 2 diabetes who visited the Severance Diabetes Center, a tertiary care hospital in Seoul, were analyzed using data collected from April 2017 to July 2024. The inclusion criteria were as follows: ≥ 18 years of age, newly diagnosed drug-naïve type 2 diabetes with a glycated hemoglobin (HbA_{1C}) level ≥ 6.5%, and simultaneous measurement of fasting serum βHB, blood glucose parameters, and spot urine albumin-to-creatinine ratio (uACR) or protein-to-creatinine ratio (uPCR) at the initial outpatient clinic visit. The following were excluded: steroid users, patients with concurrent infectious diseases, those who had taken anti-diabetic medication prior to blood and urine sampling at the initial visit, and those who had visited the emergency room for hyperglycemia before their first outpatient clinic visit. The final analysis was conducted on 280 patients among the 337 initially eligible. At the time of the initial outpatient clinic visit, patients underwent a complete physical examination and laboratory assessment, with data on age, sex, height, body weight, and blood pressure retrieved from electronic medical records. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). The overall study design and measurement procedures were consistent with previously reported methodologies [14]. This study was approved by the independent institutional review board of Severance Hospital (4-2024-1469), and the requirement for informed consent was waived owing to its retrospective nature. This study adhered to the tenets of the 1975 Declaration of Helsinki.

Measurements of Blood Gluco-Metabolic Parameters

Fasting blood samples were collected to measure gluco-metabolic parameters after overnight fasting. Postprandial glucose and insulin levels were also measured using blood samples taken 90 min after ingestion of two containers (400 ml total, 400 kcal, 18 g fat, 44 g carbohydrates, and 20 g protein) of a standardized mixed-meal test (Mediwell Diabetic MealTM; Meail Dairies Co., Yeongdong-gun, Chungbuk, Korea) at the initial visit [15]. The HbA_{1C} level was evaluated using high-performance liquid chromatography using a Variant II Turbo instrument (Bio-Rad Laboratories, Hercules, CA, USA; percent coefficient of variation [%CV] of intra-assay variability, b 1.3%). Blood glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and creatinine levels were estimated using a Hitachi 7600-110 automated chemistry analyzer (Hitachi Co., Tokyo, Japan). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation. The eGFR was derived using the Modification of Diet in Renal Disease (MDRD) equation [16]. Serum insulin levels were measured via electrochemiluminescence assay using the Cobas e801 analyzer (Roche Diagnostics GmbH, Penzberg, Germany). Pancreatic insulin secretory function and insulin sensitivity were evaluated using the following indices [17]: homeostatic model assessment of pancreatic β-cell function (HOMA-β) = [(fasting serum insulin [μU/ml] × 20)/(fasting serum glucose [mmol/l] – 3.5)]; insulinogenic index (IGI) = [(postprandial 90 min serum insulin [pmol/l] – fasting serum insulin [pmol/l])/(postprandial 90 min serum glucose [mmol/l] – fasting serum glucose [mmol/l])] [18]; homeostatic model assessment of insulin resistance (HOMA-IR) = [(fasting serum insulin [μU/ml] × fasting serum glucose [mmol/l])/22.5]; quantitative insulin sensitivity check index (QUICKI) = [1/(log(fasting serum glucose [mg/dl]) + log(fasting serum insulin [μU/ml]))] [19].

Serum βHB and Spot Urine Analysis

Using an enzymatic assay with a commercial reagent from Randox Laboratories Ltd. (County Antrim, UK) and the Atellica CH 930 analyzer (Siemens Healthcare Diagnostics, Marburg, Germany), overnight fasting serum βHB concentrations were determined, with a normal reference range of 0.00–0.49 mmol/l. In cases where the

concentration of βHB was below the lower limit of detection for the assay, a value of zero was recorded. Fresh urine samples collected in the morning, after the first voiding, were used to assess urine albumin, total protein, *N*-acetyl-β-D-glucosaminidase (NAG), and creatinine levels in each patient. Urine albumin and total protein levels were measured using immunoturbidimetric methods with an AU680 automated chemistry analyzer (Beckman Coulter, Inc., Brea, CA, USA) and Hitachi 7180 auto analyzer (Hitachi), respectively. Urine NAG levels were measured via a colorimetric method using a reagent from Nittobo Medical (Tokyo, Japan) and a JCA-BM 6010/c automated analyzer (JEOL, Tokyo, Japan). Urine creatinine was measured using the AU680 analyzer via the kinetic Jaffe method. To minimize the influence of variations in kidney function, urine albumin, total protein, and NAG levels were expressed as uACR (mg/gCr), uPCR (g/gCr), and NAG-to-creatinine ratio (uNAG/Cr) (IU/gCr). Albuminuria was defined as uACR ≥ 30.0 mg/gCr, following the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [20], and proteinuria as uPCR > 0.15 g/gCr, based on the normal urine protein excretion threshold of ≤ 0.15 g/day [21]. Urine nonalbumin protein-to-creatinine ratio (uNAPCR) was also indirectly calculated from the difference between uPCR and uACR using the following formula: uNAPCR (mg/gCr) = uPCR (mg/gCr) − uACR (mg/gCr) [22]. Nonalbumin proteinuria (NAP) was defined as uNAPCR ≥ 120.0 mg/gCr, according to previous studies demonstrating its ability to predict CKD progression and accelerated eGFR decline independently of albuminuria in type 2 diabetes [23].

Identification of Incidence of Albuminuria and Proteinuria

We reviewed electronic medical records of patients with normal values for uACR (< 30.0 mg/gCr), uPCR (≤ 0.15 g/gCr), and uNAPCR (< 120.0 mg/gCr) at their initial visit, who had at least one clinic visit and underwent a spot urine test between the initial outpatient clinic visit and July 2024. We evaluated the incidence of albuminuria, proteinuria, and NAP based on uACR, uPCR, or uNAPCR values exceeding the normal range at least once, whereas patients who maintained normal uACR, uPCR, or uNAPCR values on repeated testing were defined as those without such outcomes. Follow-up time was assigned from the date of the initial examination until the date of the first event (development of incident albuminuria or proteinuria) or the date of censoring. Furthermore, we collected data on medication use and HbA_{1C} levels at the time of the event.

Statistical Analyses

Patients were divided into two groups based on tertiles of fasting serum βHB levels at the initial visit (designated as baseline serum βHB) because absolute βHB thresholds defining 'low' and 'high' in non-ketoacidotic states have not been standardized: low (first and second tertiles) and highest (third tertile). For all continuous variables, a normality test was conducted. The study participant characteristics were analyzed by group using a two-sample Student's *t*-test or Mann-Whitney U test for continuous variables and Pearson χ^2 test for categorical variables. Correlations between baseline serum βHB levels, uACR, uPCR, and other variables were analyzed using Pearson's or Spearman's correlation coefficients. For longitudinal analysis, we assessed the relationships between baseline serum βHB levels and the development of incident albuminuria, proteinuria, or NAP over time. Patients with normal uACR (< 30.0 mg/gCr), uPCR (≤ 0.15 g/gCr), or uNAPCR (< 120.0 mg/gCr) values at their initial visit were categorized into low and highest baseline βHB groups. Differences in the occurrence of these outcomes between the groups were analyzed using Kaplan-Meier curves and the log-rank test. Cox regression analyses were conducted to model the relationships among incident albuminuria, proteinuria, and NAP and metabolic parameters, including baseline serum βHB levels. All statistical analyses were conducted using SPSS version 27.0 for Windows (IBM Corp., Armonk, NY, USA). Statistical significance was set at $p < 0.05$.

RESULTS

Baseline Characteristics According to Baseline Fasting Serum βHB Levels in Patients with Newly Diagnosed Type 2 Diabetes

In Table 1, the baseline demographic and laboratory data for the 280 study participants (180 men and 100 women) are presented. Patients were classified into two groups based on the tertiles of baseline serum βHB levels: the lower two tertiles ($N=192$) and the highest tertile ($N=88$, defined as fasting serum βHB levels > 0.16 mmol/l). The median fasting serum βHB levels for each group were 0.00 mmol/l and 0.30 mmol/l, respectively. The mean age in the highest baseline βHB group was slightly lower at 51.5 ± 15.0 years compared to 54.9 ± 12.1 years in the low baseline βHB group, with no statistically significant difference ($p=0.064$). BMI was slightly lower in the highest baseline βHB group (25.7 vs. 26.4 kg/m^2); however, this difference was also not statistically significant ($p=0.073$). Additionally, no significant differences were noted in the systolic or diastolic blood pressure between the groups. Concerning laboratory parameters, the highest baseline βHB group had significantly higher HbA_{1C} (9.45 vs. 7.70%, $p<0.001$) and postprandial 90 min serum glucose (223.0 vs. 201.5 mg/dl, $p=0.042$) levels compared to the low baseline βHB group. Fasting serum glucose levels were higher in the highest baseline βHB group without statistical significance ($p=0.067$). No significant differences were noted in lipid profiles, serum creatinine, and eGFR (MDRD). For insulin secretion and sensitivity measures, HOMA-β ($p=0.002$) and the IGI ($p=0.003$) were significantly lower in the highest baseline βHB group, suggesting reduced insulin secretory function. However, QUICKI, representing insulin sensitivity, was significantly higher in the highest baseline βHB group (0.32 vs. 0.31, $p=0.034$). In newly diagnosed patients with type 2 diabetes, the baseline uACR, uPCR, uNAPCR, and uNAG/Cr values in the drug-naive state revealed no differences according to baseline serum βHB levels.

Baseline Fasting Serum βHB Levels Are Correlated with Elevated Blood Glucose Levels, Reduced Insulin Secretory Function, and Enhanced Insulin Sensitivity

Simple correlations between baseline serum βHB levels and numerous clinic-laboratory parameters were analyzed (Table S1). βHB levels were inversely correlated with age ($r=-0.170$, $p=0.004$), suggesting that younger individuals with type 2 diabetes may have enhanced fatty acid oxidation capacity, consistent with findings from a previous study [24]. Positive correlations were observed with blood glucose parameters, including HbA_{1C} ($r=0.369$, $p<0.001$), fasting serum glucose ($r=0.140$, $p=0.019$), and postprandial 90 min serum glucose ($r=0.188$, $p=0.004$) levels, indicating higher βHB levels are associated with elevated glycemic levels. Inverse correlations with HOMA-β ($r=-0.233$, $p<0.001$) and the IGI ($r=-0.233$, $p<0.001$) suggest reduced insulin secretory function, while a positive correlation with QUICKI ($r=0.170$, $p=0.004$) indicates enhanced insulin sensitivity. No significant correlations were observed between βHB levels and baseline uACR, uPCR, uNAPCR, and uNAG/Cr values in drug-naive, newly diagnosed patients with type 2 diabetes.

A Higher Baseline fasting Serum βHB Level Predicts a Lower Incidence of Proteinuria and NAP in Patients with Type 2 Diabetes

This study explored the relationship between baseline serum βHB levels and the incidence of albuminuria and proteinuria in patients with normal baseline levels (Fig. 1). During a 2.40 ± 1.40-year follow-up, albuminuria developed in 12.7% (8 of 63) of patients in the highest baseline βHB group and 18.9% (25 of 132) in the low baseline βHB group, with no significant difference observed (Kaplan-Meier and log-rank test, $p=0.502$) (Fig. 1a). Proteinuria occurred in 6.90% (4 of 58) of patients in the highest baseline βHB group compared to 24.3% (34 of 140) in the low baseline βHB group, demonstrating a significant difference ($p=0.028$) (Fig. 1b). Furthermore, owing to the discrepancy in

Table 1 Baseline characteristics of study participants according to baseline fasting serum βHB levels ($N = 280$)

	Low baseline βHB group ($N = 192$)	**Highest baseline βHB[a] group ($N = 88$)**	***p* value**
Demographic parameters			
Age (years)	54.9 ± 12.1	51.5 ± 15.0	0.064
Male sex [*N* (%)]	123 (64.1)	57 (64.8)	0.908
Female sex [*N* (%)]	69 (35.9)	31 (35.2)	
BMI (kg/m^2)	26.4 (24.2–28.9)	25.7 (22.7–28.1)	0.073
Systolic blood pressure (mmHg)	131.5 ± 16.7	128.5 ± 15.3	0.166
Diastolic blood pressure (mmHg)	83.2 ± 11.1	81.2 ± 10.4	0.169
Gluco-metabolic parameters			
HbA_{1C} (%)	**7.70 (6.90–9.50)**	**9.45 (7.90–11.7)**	**< 0.001**
AST (IU/l)	25.0 (19.0–34.0)	26.0 (19.0–33.8)	0.968
ALT (IU/l)	29.0 (19.0–44.0)	28.0 (19.3–40.8)	0.912
Fasting glucose (mg/dl)	133.0 (120.0–176.3)	149.0 (119.0–220.5)	0.067
Postprandial 90 min glucose (mg/dl)	**201.5 (169.0–248.3)**	**223.0 (183.5–271.3)**	**0.042**
Total cholesterol (mg/dl)	189.0 (158.0–222.0)	196.0 (147.0–225.0)	0.869
HDL cholesterol (mg/dl)	45.0 (39.0–50.0)	43.0 (37.0–50.8)	0.467
LDL cholesterol (mg/dl)	115.8 ± 41.3	116.8 ± 50.1	0.874
Triglyceride (mg/dl)	143.0 (104.0–223.0)	130.0 (96.8–203.0)	0.343
Creatinine (mg/dl)	0.84 (0.70–1.00)	0.85 (0.67–0.98)	0.739
eGFR (MDRD) (ml/min/1.73 m^2)	87.5 (75.4–102.8)	89.8 (79.4–104.5)	0.344
Uric acid (mg/dl)	5.10 (4.00–6.18)	5.20 (4.23–6.40)	0.374
Albumin (g/dl)	**4.60 (4.30–4.70)**	**4.60 (4.40–4.80)**	**0.043**
HOMA-β (%)	**49.1 (26.7–85.2)**	**38.2 (18.5–57.4)**	**0.002**
IGI (pmol/mmoL)	**0.62 (0.30–1.18)**	**0.41 (0.08–0.84)**	**0.003**
HOMA-IR	4.00 (2.37–5.94)	3.53 (1.98–5.15)	0.112
QUICKI	**0.31 ± 0.03**	**0.32 ± 0.04**	**0.034**
Fasting serum βHB (mmol/l)	**0.00 (0.00–0.11)**	**0.30 (0.20–0.60)**	**< 0.001**
Spot urine parameters			
uACR (mg/gCr)	16.5 (7.25–40.8)	13.7 (8.63–49.5)	0.900
uACR ≥ 30.0 mg/gCr [N (%)]	60 (31.3)	25 (28.4)	0.631
uPCR (g/gCr)	0.10 (0.08–0.14)	0.10 (0.08–0.16)	0.783
uPCR > 0.15 g/gCr [N (%)]	42 (21.9)	22 (25.0)	0.443

Table 1 continued

	Low baseline βHB group ($N = 192$)	Highest baseline βHB[a] group ($N = 88$)	*p* value
uNAPCR (mg/gCr)	87.9 (64.3–109.4)	90.2 (66.8–121.5)	0.419
uNAPCR ≥ 120.0 mg/gCr [N (%)]	38 (19.8)	20 (22.7)	0.459
uNAG/Cr (IU/gCr)	6.52 (4.64–9.66)	5.57 (4.02–9.02)	0.321

Bold values indicate statistical significance. Two-sample Student's *t*-test or Mann-Whitney U test was used for continuous variables and a Pearson χ^2 test for categorical variables; continuous variables are described as mean ± SD for parametric variables and as median (interquartile range) for nonparametric variables

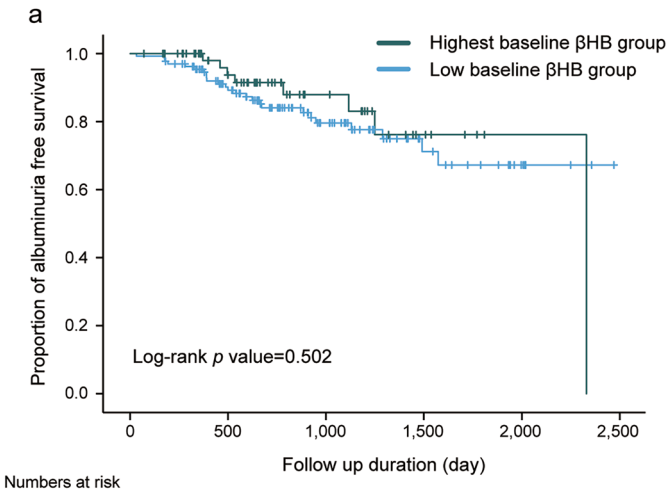
ALT alanine aminotransferase, *AST* aspartate aminotransferase, *βHB* beta-hydroxybutyrate, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, HbA_{1C} glycated hemoglobin, *HDL* high-density lipoprotein, *HOMA-β* homeostatic model assessment of pancreatic β-cell function, *HOMA-IR* homeostatic model assessment of insulin resistance, *IGI* insulinogenic index, *LDL* low-density lipoprotein, *MDRD* Modification of Diet in Renal Disease, *N* number of patients, *QUICKI* quantitative insulin sensitivity check index, *SD* standard deviation, *uACR* urine albumin-to-creatinine ratio, *uNAG/Cr* urine *N*-acetyl-β-D-glucosaminidase-to-creatinine ratio, *uNAPCR* urine nonalbumin protein-to-creatinine ratio, *uPCR* urine protein-to-creatinine ratio

[a]The highest tertile of baseline fasting serum βHB refers to levels > 0.16 mmol/l

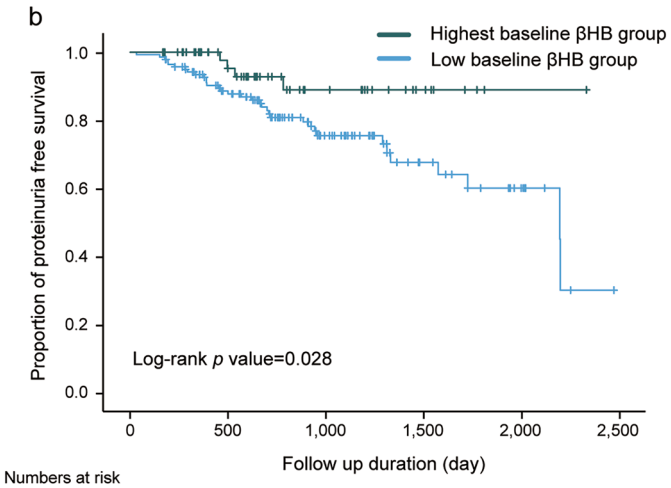
albuminuria and proteinuria incidence, we also analyzed the incidence of NAP. Baseline uNAPCR level was moderately correlated with uNAG/Cr, which is present in the proximal tubule epithelial cells and serves as a renal tubular damage marker ($r = 0.484$, $p < 0.001$) (Figure S1). NAP developed in 6.67% (4 of 60) of patients in the highest baseline βHB group and 22.9% (33 of 144) in the low baseline βHB group, demonstrating a significant difference ($p = 0.031$) (Fig. 1c).

When we compared baseline and event-time clinic-laboratory parameters based on the occurrence of incident proteinuria (Table 2) or NAP (Table S2), patients who maintained normal proteinuria or NAP levels during follow-up had considerably higher baseline serum βHB levels and a greater proportion in the highest baseline βHB tertile compared to those with incident cases. Conversely, there were no significant differences in age at diabetes diagnosis, sex, BMI, eGFR (MDRD), and insulin secretion and sensitivity measures. Given that glucagon-like peptide 1 (GLP-1) receptor agonists reduce the progression of albuminuria in DKD [25, 26], GLP-1 receptor agonist use at the event was collected and showed no significant difference between the incident proteinuria or NAP and non-event groups, likely reflecting the low overall frequency of use in this study population. Those with incident proteinuria or NAP exhibited poorer glycemic control at the time of the event.

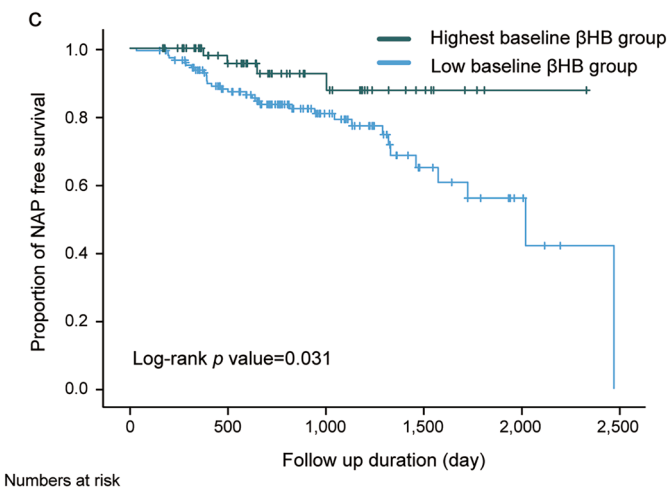
In the subgroup not receiving sodium-glucose cotransporter 2 (SGLT2) inhibitors—given their potential to increase serum βHB—proteinuria occurred in 8.33% (4 of 48) in the highest baseline βHB group and 20.3% (25 of 123) in the low baseline βHB group; however, the difference was not statistically significant ($p = 0.223$; data not shown). The following factors may explain this finding: (1) reduced sample and event counts; (2) higher SGLT2 inhibitor use among those with incident proteinuria (23.7% vs 11.3%, $p = 0.045$; Table 2), reflecting preferential prescribing to higher-risk patients. Excluding these users disproportionately removes higher-risk patients, introducing selection bias that attenuates between-group differences and reduces precision.



Numbers at risk						
Highest group	63	43	19	7	1	0
Low group	132	98	49	19	7	0



Numbers at risk						
Highest group	58	39	17	7	1	0
Low group	140	104	50	20	9	0



Numbers at risk						
Highest group	60	40	19	7	1	0
Low group	144	105	50	16	5	0

◂**Fig. 1** Kaplan-Meier curves for the development of incident albuminuria ($N = 195$) (**a**), proteinuria ($N = 198$) (**b**), and NAP ($N = 204$) (**c**) according to the highest tertile versus the lower two tertiles of baseline fasting serum βHB levels. Incident albuminuria is defined as a baseline uACR < 30.0 mg/gCr that progresses to ≥ 30.0 mg/gCr, while incident proteinuria is defined as a baseline uPCR ≤ 0.15 g/gCr that progresses to > 0.15 g/gCr. Incident NAP is defined as a baseline uNAPCR < 120.0 mg/gCr that progresses to ≥ 120.0 mg/gCr. The highest tertile of baseline fasting serum βHB refers to levels > 0.16 mmol/l. *βHB* beta-hydroxybutyrate, *N* number of patients, *NAP* nonalbumin proteinuria, *uACR* urine albumin-to-creatinine ratio, *uNAPCR* urine nonalbumin protein-to-creatinine ratio, *uPCR* urine protein-to-creatinine ratio

Higher Baseline Fasting Serum βHB Levels Are Independently Associated with a Reduced Risk of Proteinuria and NAP

Cox regression analyses explored the association between the highest tertile of baseline serum βHB and incident proteinuria or NAP (Table 3). In unadjusted model 1, the highest tertile of baseline serum βHB demonstrated a significantly reduced hazard ratio (HR) for incident proteinuria (HR 0.331, 95% confidence interval [CI] 0.117–0.934). This protective effect remained consistent in model 2 (adjusted for age at the time of event and sex, HR 0.331, 95% CI 0.117–0.934) and model 3 (further adjusted for medication use, HR 0.313, 95% CI 0.110–0.891). In the fully adjusted model 4, which included HbA_{1C} levels at the time of event, the effect was attenuated but remained suggestive (HR 0.379, 95% CI 0.131–1.097). Similarly, an analysis of incident NAP in 204 patients demonstrated a reduced risk in those with higher baseline serum βHB levels, although statistical significance was attenuated after adjusting for angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use in model 3 and HbA_{1C} levels at the time of event in model 4. These findings highlight a reduced risk of proteinuria and NAP in patients with higher baseline serum βHB levels.

DISCUSSION

This study found the relationships among baseline fasting serum βHB levels, metabolic parameters, and the risk of proteinuria in newly diagnosed drug-naive patients with type 2 diabetes, identifying three major outcomes: (1) patients with higher baseline βHB levels exhibited concurrent poorer glycemic control, reduced insulin secretory function, and better insulin sensitivity, but no link was found with baseline uACR, uPCR, or uNAPCR; (2) higher βHB levels were associated with a considerably lower incidence of proteinuria and NAP over approximately 2.40 years, with no impact on albuminuria; (3) higher βHB levels independently reduced the risk of proteinuria, even after adjustments, while HbA_{1C} remained the strongest determinant. These findings underscore the complex metabolic effects of βHB and its potential protective role against renal complications.

Regarding baseline glucometabolic characteristics, patients in the highest tertile of baseline serum βHB levels exhibited significantly worse glycemic profiles, characterized by higher fasting and postprandial serum glucose as well as HbA_{1C} levels, including reduced insulin secretory function. This aligns with prior findings indicating that elevated ketone body levels, as markers of an altered or compensatory metabolic state, correlate with dysregulated glucose metabolism [27]. Interestingly, QUICKI values indicated enhanced insulin sensitivity in the highest baseline βHB group, suggesting that, while high serum βHB is associated with poor glycemic control, compensatory mechanisms for the decreased insulin secretory function might improve peripheral insulin sensitivity. Our analyses revealed no significant correlations between serum βHB levels and cardiovascular risk factors such as blood pressure or lipid profile, indicating that the role of βHB in newly diagnosed patients with drug-naïve type 2 diabetes may be more pronouncedly linked to glucose metabolism than to general cardiovascular risk factors.

Regarding the discrepancy in the development of albuminuria and proteinuria—that is, the protective effect of high baseline serum βHB on the incidence of proteinuria and NAP but not

Table 2 Comparison of baseline fasting serum βHB levels and other characteristics according to incident proteinuria development ($N = 198$)

	Incident proteinuria: not developed ($N = 160$)	Incident proteinuria: developed ($N = 38$)	*p* value
At baseline			
Age (years)	53.6 ± 12.4	55.0 ± 13.3	0.534
Male sex [*N* (%)]	107 (66.9)	23 (60.5)	0.459
Female sex [*N* (%)]	53 (33.1)	15 (39.5)	
BMI (kg/m^2)	26.2 ± 3.88	26.9 ± 4.57	0.326
eGFR (MDRD) (ml/min/1.73 m^2)	88.7 (79.4–100.6)	89.1 (77.2–105.6)	0.711
HOMA-β (%)	46.5 (27.0–77.9)	44.1 (23.7–85.6)	0.917
IGI (pmol/mmoL)	0.63 (0.24–1.13)	0.47 (0.26–1.00)	0.895
HOMA-IR	3.59 (2.25–5.36)	3.17 (1.79–5.80)	0.370
QUICKI	0.32 ± 0.03	0.33 ± 0.04	0.260
Fasting serum βHB (mmol/l)	**0.10 (0.00–0.20)**	**0.00 (0.00–0.14)**	**0.028**
Highest tertile of fasting serum βHB[a] [*N* (%)]	**54 (33.8)**	**4 (10.5)**	**0.005**
At the time of event			
SGLT2 inhibitor use, yes [*N* (%)]	**18 (11.3)**	**9 (23.7)**	**0.045**
GLP-1 receptor agonist use, yes [*N* (%)]	5 (3.13)	4 (10.5)	0.071
ACE inhibitor or ARB use, yes [*N* (%)]	39 (24.4)	12 (31.6)	0.361
HbA_{1C} (%)	**6.60 (6.20–6.90)**	**6.90 (6.50–7.30)**	**0.001**

Bold values indicate statistical significance

Two-sample Student's *t*-test or Mann-Whitney U test was used for continuous variables and a Pearson χ^2 test for categorical variables; continuous variables are described as mean ± SD for parametric variables and as median (interquartile range) for nonparametric variables. Incident proteinuria is defined as a baseline uPCR ≤ 0.15 g/gCr that progresses to > 0.15 g/gCr

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *βHB* beta-hydroxybutyrate, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *GLP-1* glucagon-like peptide 1, HbA_{1C} glycated hemoglobin, *HOMA-β* homeostatic model assessment of pancreatic β-cell function, *HOMA-IR* homeostatic model assessment of insulin resistance, *IGI* insulinogenic index, *MDRD* Modification of Diet in Renal Disease, *N* number of patients, *QUICKI* quantitative insulin sensitivity check index, *SD* standard deviation, *SGLT2* sodium-glucose cotransporter 2, *uPCR* urine protein-to-creatinine ratio

[a]The highest tertile of baseline fasting serum βHB refers to levels > 0.16 mmol/l

albuminuria—the following explanations may be plausible. In this study, the participants were newly diagnosed with type 2 diabetes, indicating a short duration of diabetes. Albuminuria, reflecting glomerular capillary wall permeability, precedes GFR decline in kidney disease [28] and is a valuable marker for populations both with and without diabetes, linking early kidney damage with cardiovascular risk and mortality, even at levels below microalbuminuria [29]. However, because DKD involves diverse mechanisms, including tubular changes driven by hypoxia, renin-angiotensin-aldosterone system activation, and growth factors, as well as glomerular

Table 3 Cox regression analyses for incident proteinuria or NAP development

	Hazard ratios (95% CI)	
	Highest tertile of baseline fasting serum βHB[a] (0 = no, 1 = yes)	
	Incident proteinuria (*N* = 198)	Incident NAP (*N* = 204)
Model 1	**0.331 (0.117–0.934)**	**0.336 (0.119–0.952)**
Model 2	**0.331 (0.117–0.934)**	**0.337 (0.119–0.958)**
Model 3	**0.313 (0.110–0.891)**	0.373 (0.128–1.084)
Model 4	0.379 (0.131–1.097)	0.448 (0.149–1.342)

Bold values indicate statistical significance. Incident proteinuria is defined as a baseline uPCR ≤ 0.15 g/gCr that progresses to > 0.15 g/gCr. Incident NAP is defined as a baseline uNAPCR < 120.0 mg/gCr that progresses to ≥ 120.0 mg/gCr

Model 1, unadjusted

Model 2, adjusted for age (years), sex (0 = male, 1 = female)

Model 3, adjusted for age (years), sex (0 = male, 1 = female), SGLT2 inhibitor use (0 = no, 1 = yes), ACE inhibitor or ARB use (0 = no, 1 = yes), GLP-1 receptor agonist use (0 = no, 1 = yes)

Model 4, adjusted for age (years), sex (0 = male, 1 = female), SGLT2 inhibitor use (0 = no, 1 = yes), ACE inhibitor or ARB use (0 = no, 1 = yes), GLP-1 receptor agonist use (0 = no, 1 = yes), HbA_{1C} (%)

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *βHB* beta-hydroxybutyrate, *CI* confidence interval, *GLP-1* glucagon-like peptide 1, *HbA_{1C}* glycated hemoglobin, *N* number of patients, *NAP* nonalbumin proteinuria, *SGLT2* sodium-glucose cotransporter 2, *uNAPCR* urine nonalbumin protein-to-creatinine ratio, *uPCR* urine protein-to-creatinine ratio

[a]The highest tertile of baseline fasting serum βHB refers to levels > 0.16 mmol/l

damage, albuminuria alone may not adequately reflect the early stages of DKD [30–34]. The tubular hypothesis indicates that proximal tubule injury may precede glomerular damage in DKD [35], underscoring the growing attention on tubular damage markers as early indicators of DKD progression [36–38]. Furthermore, under normal protein loss conditions, urine albumin constitutes a small portion of total protein but becomes predominant as proteinuria increases. For instance, albumin accounted for only 21% of the total protein in individuals with low uPCR levels but rose to 73% in those with higher uPCR levels in a general population study, indicating that nonalbumin proteins predominate during stages of lower proteinuria excretion [39, 40]. This study demonstrates that increased serum βHB levels in newly diagnosed patients with type 2 diabetes are protective against proteinuria rather than albuminuria, likely because of the prevalent characteristics of early-stage DKD in this study population.

In our study, we indirectly calculated and adopted NAP as a marker of renal tubular damage. Several urinary proteins reflecting tubular damage, such as fatty acid-binding protein (FABP), NAG, neutrophil gelatinase-associated lipocalin (NGAL), and kidney injury molecule 1 (KIM-1), have been proposed as complementary markers for albuminuria in DKD. However, no single marker has revealed sufficient evidence or cost-effectiveness to replace albuminuria, and assessing multiple biomarkers individually is impractical. In this context, total proteinuria, including NAP, serves as a practical and efficient screening tool, especially for patients with type 2 diabetes without albuminuria or at high risk for CKD progression [41]. NAP encompasses various renal tubular biomarkers, including liver FABP, NGAL, and KIM-1, and has revealed significant correlations with these markers in patients with type 2 diabetes [42]. In fact, an expert consensus report indicated that uPCR is nearly as effective as uACR for predicting the risk of ESKD, although uACR is generally preferred owing to

its higher standardization across clinical laboratories [43]. NAP has been identified as a key marker for predicting DKD progression, with a Korean research team first reporting this correlation [44]. In 237 patients with type 2 diabetes, uNAPCR was linked to annual eGFR decline and remained a prognostic marker for DKD progression, even in patients with normoalbuminuria or an eGFR ≥ 60 ml/min/1.73 m^2, indicating its utility in the early stages of DKD. These findings collectively demonstrate that NAP is a valuable marker for evaluating DKD progression, particularly in patients who might be overlooked when relying solely on albuminuria as a diagnostic and prognostic tool.

As revealed in our analysis, an elevated fasting serum βHB level in a drug-naïve state may indicate impaired insulin secretion and resulting hyperglycemia [1]. Previous studies found that high-normal circulating βHB levels (0.12–0.30 mmol/l [11]; 0.09–0.27 mmol/l [12]) were associated with the lowest DKD risk, despite blood glucose levels progressively increasing with higher circulating βHB levels. However, both studies lacked causal evidence owing to their cross-sectional design. In our longitudinal study, the highest baseline βHB group (0.30 [0.20–0.60] mmol/l), mostly within the high-normal range (assay upper limit 0.49 mmol/l), revealed protective effects against proteinuria and NAP, consistent with previous findings that high-normal circulating βHB levels protect the kidney. Elevated circulating βHB levels enhance glomerular filtration, with proximal tubule βHB concentrations equaling plasma levels and most filtered βHB being reabsorbed in the renal tubules [45]. βHB utilization by the kidney and heart is proportional to circulating levels [46, 47]. Hyperinsulinemia inhibits renal tubular reabsorption of βHB via the SIRT3/SMCT1 pathway [48]. In this study, higher circulating βHB levels were associated with decreased insulin secretion, potentially enhancing both βHB production and renal utilization. Although ketosis and hyperglycemia often coexist in patients with type 2 diabetes, the findings of the present study suggest that high-normal circulating βHB levels may mitigate the harmful effects of hyperglycemia on the kidney, although the range of βHB levels associated with renal protective effects still requires further research.

In both in vitro and animal models, several studies have reported the protective effects of βHB on kidney pathology [49, 50]. Although fatty acid oxidation is the principal energy source in renal proximal tubular cells under physiological conditions [51], its activity declines with renal dysfunction [52–54]. In diabetes, kidneys appear to favor ketone-body metabolism—evidenced by enrichment of ketone-body pathways, upregulation of *HMGCS2* (the rate-limiting enzyme in ketogenesis), and downregulation of ketolytic genes in rodent DKD [55]. Thus, moderately elevated βHB within the physiological range may help sustain renal energetics when fatty-acid β-oxidation is impaired, suggesting that upregulated renal ketogenesis could represent a compensatory—and potentially renoprotective—adaptation in DKD [56, 57]. Chronic inflammation in renal tissue represents a key pathological basis underlying the development of DKD [7, 26, 58]. In a previous study [59], β-hydroxybutyrate dehydrogenase 1 (BDH1), a mitochondrial enzyme mediating ketone-body utilization, was downregulated in db/db mouse kidneys and human diabetic kidneys, and in high glucose- or palmitic acid-treated human kidney-2 (HK-2) cells, and its loss led to increased reactive oxygen species production and activation of the IL-1β and IL-18 inflammatory pathway. In contrast, BDH1 overexpression or βHB supplementation activated nuclear factor erythroid 2-related factor 2-dependent antioxidant signaling and attenuated inflammation. However, several studies have suggested that βHB may exert potentially deleterious effects on renal pathology. In db/db mice, renal *HMGCS2* was markedly upregulated; in rat proximal tubule cells, βHB induced TGF-β1 and collagen I expression and promoted epithelial-to-mesenchymal transition, indicating profibrotic signaling [60]. In another study, exposure to βHB induced hypertrophy in HK-2 cells and inhibited cell proliferation through activation of the TGF-β/Smad3 pathway, partly mediated by oxidative stress and accompanied by increased collagen production [61]. The authors suggest that better glycemic control may lessen the adverse effects of hyperketonemia,

as ketone body levels rise with hyperglycemia and decline when glucose improves. Thus, the optimal βHB range for renal protection warrants further investigation. SGLT2 inhibitors activate SIRT1 and AMPK pathways, promoting ketogenesis, mitochondrial homeostasis, and autophagy while reducing oxidative stress, offering renoprotective benefits in diabetic nephropathy [62]. In DKD models, 1,3-butanediol, a ketone body precursor, and empagliflozin demonstrated renoprotective effects by inhibiting the hyperactivation of mTORC1, which is a key contributor to podocyte and proximal tubular epithelial cell damage in hyper-nutrient states, highlighting ketone bodies as endogenous inhibitors critical for renal protection [63]. In summary, βHB may help restore renal energy metabolism while reducing oxidative stress and inflammation [58, 64].

Protective effects of ketogenic diets in DKD have been reported in several studies. In mice [65], an 8-week ketogenic diet reversed albuminuria and reduced oxidative stress-related gene expression in DKD, with higher βHB, lower glucose, and unchanged body weight; benefits were attributed to improved glycemia. In a pilot study involving individuals with advanced DKD (eGFR < 40 ml/min/1.73 m^2), a 12-week very-low-calorie ketogenic diet produced significant weight loss and improvements in glycemic and insulin-resistance markers, with a reduction in albuminuria, likely through amelioration of upstream metabolic derangements (hyperglycemia, insulin resistance, obesity-related mechanisms) [66]. Collectively, any renoprotective effects of ketogenic diets in DKD may represent composite metabolic changes—including weight loss and improved glycemic control—rather than the effect of βHB per se [67]. Furthermore, major guidelines advise caution regarding ketogenic diets in type 2 diabetes, citing possible LDL cholesterol increases; risks of hypoglycemia, ketoacidosis, and nutrient deficiencies; adherence challenges; and uncertain long-term safety [68, 69]. Thus, the ketogenic diet warrants cautious interpretation, and well-controlled, longer-term trials are needed before it can be recommended for DKD.

The present study has several strengths. First, to our knowledge, this is the first study to explore the longitudinal relationship between baseline serum βHB levels and the development of DKD assessed by albuminuria or proteinuria. Second, baseline serum βHB levels were measured in drug-naïve patients to reflect intrinsic ketogenesis without medication influence on insulin or glucagon secretion. However, this study also has some limitations. First, using real-world outpatient data from newly diagnosed type 2 diabetes—an environment in which serum βHB is not routinely tested—our study likely had a modest sample size and low event rate; even so, the highest tertile of baseline serum βHB retained an adjusted, directionally consistent protective association. Second, incident albuminuria or proteinuria was defined by a single measurement, potentially including transient cases, but inpatient data were excluded to reduce the impact of intercurrent illness. Third, we considered only the glucose- and blood pressure-lowering drugs used at the time of the event but not the changes during follow-up, which could affect the incidence of albuminuria or proteinuria. Finally, in this study, the mean follow-up period was relatively short (~ 2.40 years).

CONCLUSION

This study highlights the potential of baseline serum βHB measurements as an early marker for identifying patients at an elevated risk of DKD, especially proteinuria, supporting the inclusion of metabolic profiling in traditional risk assessments. Strategies that maintain a relatively high circulating βHB concentration within the physiological range may protect the kidney by restoring renal energy metabolism and reducing oxidative stress and inflammation. Further investigation is warranted to define the circulating βHB concentration range most robustly associated with renoprotective outcomes in type 2 diabetes.

ACKNOWLEDGEMENTS

We thank the participants of the study.

Author Contributions. Conceptualization: So Ra Kim, Byung-Wan Lee. Data curation: So Ra Kim, Minyoung Lee, Yong-ho Lee. Formal analysis: So Ra Kim, Minyoung Lee, Yong-ho Lee. Investigation: So Ra Kim, Minyoung Lee, Yong-ho Lee. Methodology: Eun Seok Kang, Bong-Soo Cha, Byung-Wan Lee. Project administration: Eun Seok Kang, Bong-Soo Cha, Byung-Wan Lee. Supervision: Byung-Wan Lee. Validation: Eun Seok Kang, Bong-Soo Cha. Visualization: So Ra Kim, Minyoung Lee. Writing—original draft: So Ra Kim, Byung-Wan Lee. Writing—review & editing: So Ra Kim, Minyoung Lee, Yong-ho Lee, Eun Seok Kang, Bong-Soo Cha, Byung-Wan Lee. All authors reviewed and approved the final manuscript.

Funding. No funding or sponsorship was received for this study or publication of this article, the authors will be paying the rapid service fee.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. So Ra Kim, Minyoung Lee, Yong-ho Lee, Eun Seok Kang, Bong-Soo Cha, and Byung-Wan Lee have nothing to disclose.

Ethical Approval. This study was approved by the independent institutional review board of Severance Hospital (4-2024-1469) and the requirement for informed consent was waived owing to the retrospective nature of the study. This study adhered to the tenets of the 1975 Declaration of Helsinki.

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