Original Article

Metabolic and Hormonal Adaptations to Ketogenic Diet in Central Indian Adults: A Case-Control Study

Chelikam Rohini[1], Syed Liyakath Ali[2], C. Kishore Kumar[1], M. Anil Kumar[3]

[1]Assistant Professors, Department of Physiology, Takshashila Medical College & Hospital, Ongur, Tindivanam, Tamil Nadu, India. [2]Associate Professor, Department of Physiology, Takshashila Medical College & Hospitals, Ongur, Tamil Nadu, India. [3]Assistant Professor, Department of Biochemistry, Pondicherry Institute of Medical Sciences, Puducherry, India

Abstract

Background: The ketogenic diet (KD) induces nutritional ketosis through drastic carbohydrate restriction, profoundly altering gastrointestinal hormone secretion and metabolic signaling. This study systematically examines KD's effects on key gastric hormones (ghrelin, gastrin, cholecystokinin, glucagon-like peptide-1, motilin) and systemic ketone levels (β-hydroxybutyrate) in Central Indian adults, representing a population gap in ketogenic research. **Material and Methods:** In this prospective case-control study conducted January 2023–December 2024 at Index Medical College (n=264; 132 KD group, 132 controls), healthy adults aged 18-50 years (BMI 18.5-29.9 kg/m²) followed either monitored KD (10% carbohydrates, 70% fats, 20% proteins; <50g carbs/day) or standard Indian diet for 8 weeks. Fasting and postprandial gastric hormones plus plasma β-hydroxybutyrate (BHB) were quantified via ELISA and enzymatic assays at baseline and 8 weeks. Dietary compliance was verified through weekly ketone strips and food diaries. Data analysis used SPSS v28 (paired/independent t-tests, Pearson correlations; $p<0.05$). **Results:** The KD group achieved nutritional ketosis (BHB: 0.3±0.1 to 1.8±0.4 mmol/L, $p<0.001$). Significant hormonal adaptations included fasting ghrelin suppression (-28.4%, 856±142 to 613±118 pg/mL, $p<0.001$), gastrin elevation (+18.2%, 42.3±8.2 to 50.0±9.1 pg/mL, $p=0.002$), postprandial CCK increase (+42.1%, 18.5±4.2 to 26.3±5.1 pg/mL, $p<0.001$), GLP-1 reduction (-22.7%, 24.8±5.6 to 19.2±4.8 pg/mL, $p=0.001$), and motilin elevation (+31.5%, 156±28 to 205±34 pg/mL, $p<0.001$). Strong BHB-hormone correlations emerged (ghrelin: $r=-0.62$, $p<0.001$; CCK: $r=0.59$, $p<0.001$). Controls showed minimal changes (all $p>0.05$). **Conclusion:** KD induces a characteristic enteroendocrine signature in Central Indian adults—ghrelin suppression with gastrin/CCK/motilin elevation and GLP-1 reduction—directly correlated with ketosis depth. These adaptations optimize high-fat digestion, enhance satiety signaling, and accelerate gastric motility, offering mechanistic insights for metabolic and gastrointestinal applications in non-Western populations.

Keywords: Ketogenic diet, ghrelin, gastrin, cholecystokinin, glucagon-like peptide-1, motilin, β-hydroxybutyrate, nutritional ketosis, gastric hormones.

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Introduction

The ketogenic diet (KD)—characterized by <5-10% calories from carbohydrates, 70-80% from fats, and 15-20% from proteins—induces nutritional ketosis, where β-hydroxybutyrate (BHB >0.5 mmol/L) becomes the primary energy substrate, replacing glucose-dependent metabolism.[1] Beyond its established efficacy in refractory epilepsy and obesity management, KD exerts profound effects on gastrointestinal physiology by altering enteroendocrine cell signaling pathways.[2]

Five key gastric hormones orchestrate digestive and metabolic responses that are fundamentally altered under ketogenic conditions:

1. Ghrelin (secreted by gastric X/A-like cells): Known as the "hunger hormone," ghrelin typically rises preprandially to stimulate appetite and falls postprandially in response to nutrient intake, particularly carbohydrates. Chronic KD adherence has been shown to suppress baseline ghrelin levels via fat-mediated counter-regulatory mechanisms involving CCK and GLP-1.[3]
2. Gastrin (secreted by antral G-cells): This hormone stimulates gastric acid secretion by activating parietal cell H^+/K^+-ATPase activity. Dietary protein and fat are known enhancers of gastrin release, suggesting potential upregulation during KD.[4]
3. Cholecystokinin (CCK) (secreted by duodenal I-cells): A primary fat-sensing hormone that mediates ileal brake mechanisms, gallbladder contraction, pancreatic enzyme secretion, and gastric accommodation. High-fat meals potently stimulate CCK release.[5]
4. Glucagon-like peptide-1 (GLP-1) (secreted by intestinal L-cells): This incretin hormone, primarily responsive to

Address for correspondence: Dr. Chelikam Rohini, Assistant Professor, Department of Physiology, Takshashila Medical College & Hospital, Ongur, Tindivanam, Tamil Nadu, India
E-mail: rohini.chelikam@takshashila.edu.in

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carbohydrate intake, slows gastric emptying, enhances insulin secretion, and promotes satiety. Carbohydrate restriction during KD is expected to reduce GLP-1 secretion.[6]

5. Motilin (secreted by duodenal M-cells): This hormone drives the migrating motor complex (MMC) during fasting states, coordinating interdigestive gastric and small bowel contractions. Its role may be amplified in low-carbohydrate dietary states.[7]

While Western studies have documented isolated effects of KD on individual hormones, no research has comprehensively profiled this complete hormonal axis in Indian populations, who exhibit unique dietary patterns (traditional high-carbohydrate baseline diets), genetic polymorphisms (e.g., FTO variants affecting appetite regulation), and gut microbiome composition distinct from Western cohorts.[8] This investigation—utilizing the established Index Medical College KD cohort previously studied for gastric motility/function and immunity—exclusively examines hormonal and metabolic endpoints not addressed in prior publications.

We hypothesized that KD would induce coordinated hormonal adaptations: ghrelin suppression (reducing appetite), gastrin/CCK/motilin elevation (optimizing fat digestion and motility), and GLP-1 reduction (accelerating gastric emptying)—with direct correlations with blood BHB levels, mediated via HCAR2/GPR109A receptor signaling in enteroendocrine cells.

Materials and Methods

Study Design and Setting

This prospective case-control study was conducted from January 2023 to December 2024 at the Department of Physiology, Index Medical College Hospital and Research Centre, Malwanchal University, Indore, Madhya Pradesh, India. The study protocol received approval from the Institutional Ethics Committee (IEC/IMCH/2022/45) and was conducted in accordance with the Declaration of Helsinki. The trial was registered with the Clinical Trials Registry of India (CTRI/2023/04/052134). All participants provided written informed consent before enrollment.

Study Participants

Inclusion Criteria:

- Adults aged 18-50 years
- Body Mass Index (BMI) 18.5-29.9 kg/m²
- Willing to adhere to the assigned dietary intervention for 8 weeks
- Able to provide informed consent
- No antibiotic use in preceding 3 months

Exclusion Criteria:

- Known gastrointestinal disorders (inflammatory bowel disease, peptic ulcer disease, celiac disease, chronic pancreatitis)
- Diabetes mellitus requiring insulin therapy
- Chronic use of medications affecting gastric motility (prokinetic agents, anticholinergics)
- Pregnant or lactating women
- Recent antibiotic use (<3 months prior to enrollment)
- Immunocompromised status (HIV, active malignancy, immunosuppressive therapy)
- History of eating disorders
- Severe hepatic or renal dysfunction

Sample Size Calculation

Sample size was estimated based on previous literature indicating moderate-to-large effect sizes (Cohen's d=0.5-0.7) for hormonal changes in response to dietary interventions. Using an expected effect size of d=0.5, an alpha level of 0.05, and a statistical power of 80%, the calculated sample size was 128 participants per group. Accounting for an estimated 10% dropout rate, a total of 264 subjects were enrolled (132 in each group).

Dietary Interventions

Ketogenic Diet Group (n=132): Participants followed a strictly monitored ketogenic diet comprising <50g carbohydrates per day, corresponding to approximately 10% of total calories from carbohydrates, 70% from fats, and 20% from proteins. Individualized meal plans were developed by registered dietitians using culturally appropriate Indian foods, including:

- Fat sources: Ghee (clarified butter), coconut oil, olive oil, nuts (almonds, walnuts, macadamia), seeds (flaxseed, chia), full-fat paneer, cream
- Protein sources: Eggs, fish (salmon, mackerel), chicken, mutton, paneer, Greek yogurt
- Low-carbohydrate vegetables: Spinach, cauliflower, broccoli, cabbage, bell peppers, mushrooms, zucchini
- Restricted/eliminated: All grains (rice, wheat, roti), legumes (dal), starchy vegetables (potatoes), fruits (except insignificant amounts of berries), sugar, honey.

A structured 3-day induction phase under direct supervision was implemented to facilitate ketosis onset and manage potential "keto flu" symptoms. Weekly group counseling sessions were conducted to reinforce dietary adherence and address challenges. Compliance Monitoring: Ketosis verification was performed twice weekly using capillary blood β-hydroxybutyrate measurements (target range: 0.5-3.0 mmol/L) via handheld ketone meters (FreeStyle Precision Neo, Abbott). Detailed 3-day weighed food records were collected bi-weekly and analyzed for macronutrient composition using Indian food composition databases. Participants with adherence <80% (as determined by ketone levels and food logs) were excluded from the final analysis.

Control Group (n=132): Participants maintained a standard Indian diet (SID) based on Indian Council of Medical Research-National Institute of Nutrition (ICMR-NIN) dietary guidelines, comprising approximately 55-60% carbohydrates, 20-25% fats, and 15-20% proteins. The diet included:

- Whole grains (rice, wheat roti/chapati)
- Lentils and legumes (dal varieties)
- Vegetables (diverse variety including starchy types)
- Fruits (2-3 servings daily)
- Dairy products (milk, curd, paneer)
- Moderate fats and oils

Three-day food diaries were collected bi-weekly to confirm adherence to standard dietary patterns and ensure no inadvertent carbohydrate restriction.

Biochemical Measurements

Sample Collection: Blood samples were collected at two time points: baseline (T0, before the dietary intervention) and 8 weeks

(T1, at the end of the intervention). All samples were obtained after an overnight fast of 12 hours at 08:00 hours. For postprandial measurements, participants consumed a standardised 500-kcal mixed test meal, and blood was drawn 120 minutes post-ingestion.

Venous blood (10 mL) was collected in EDTA-containing tubes, immediately placed on ice, and centrifuged within 30 minutes (3000g for 10 minutes at 4°C). Plasma was aliquoted and stored at -80°C until batch analysis to minimise inter-assay variability.

Hormone Assays: All hormones were quantified using validated sandwich enzyme-linked immunosorbent assay (ELISA) kits according to manufacturer protocols:

- Ghrelin (total): Human Ghrelin ELISA Kit (Abcam, ab239706); sensitivity 10 pg/mL; intra-assay CV <6.5%, inter-assay CV <8.2%
- Gastrin: Human Gastrin ELISA Kit (Bio-Rad, MBS269582); sensitivity 5 pg/mL; intra-assay CV <5.8%, inter-assay CV <7.5%
- Cholecystokinin (CCK): Human CCK ELISA Kit (MyBioSource, MBS701278); sensitivity 8 pg/mL; intra-assay CV <7.1%, inter-assay CV <8.9%
- GLP-1 (active): Human Active GLP-1 ELISA Kit (Merck Millipore, EGLP-35K); sensitivity 2 pg/mL; intra-assay CV <5.2%, inter-assay CV <6.8%
- Motilin: Human Motilin ELISA Kit (Elabscience, E-EL-H1453); sensitivity 15 pg/mL; intra-assay CV <6.9%, inter-assay CV <8.5%

All assays were performed in duplicate. Quality control samples (low, medium, and high concentrations) were included in each assay run.

β-Hydroxybutyrate (BHB) Measurement: Plasma BHB concentrations were determined using an enzymatic colorimetric assay kit (Sigma-Aldrich, MAK041) following manufacturer instructions. The assay utilises β-hydroxybutyrate dehydrogenase to convert BHB to acetoacetate, with NADH production measured spectrophotometrically at 450 nm. Sensitivity: 0.01 mmol/L; intra-assay CV <4.8%.

Statistical Analysis: Data were analysed using SPSS Statistics version 28.0 (IBM Corp., Armonk, NY) and R statistical software (version 4.1.0). Continuous variables were assessed for normality using the Shapiro-Wilk test and are presented as mean ± standard deviation (SD). Categorical variables are presented as frequencies and percentages.

Within-group comparisons (baseline vs. 8 weeks) were performed using paired t-tests for normally distributed data or Wilcoxon signed-rank tests for non-normally distributed data.

Between-group comparisons utilised independent t-tests or Mann-Whitney U tests as appropriate.

Effect sizes were calculated using Cohen's d for all significant differences (small: d=0.2-0.5; medium: d=0.5-0.8; large: d>0.8).

Correlation analysis used Pearson's correlation coefficient for normally distributed variables or Spearman's rank correlation for non-normally distributed variables to assess relationships among BHB levels, dietary adherence scores, and hormonal changes.

Statistical significance was set at $p<0.05$ (two-tailed). All tests were pre-specified in the study protocol.

Ethical Considerations: The study was conducted in accordance with ethical principles for medical research involving human subjects. All participants provided voluntary written informed consent after a detailed explanation of study procedures, potential risks, and benefits. Participants were free to withdraw at any time without prejudice. Confidentiality was maintained through coded identifiers. Adverse events were monitored and managed appropriately.

Results

Table 1: Baseline Characteristics

Parameter	KD Group (n=132)	Control Group (n=132)	p-value
Age (years)	34.6 ± 7.8	34.1 ± 8.0	0.62
Sex (Male/Female)	68/64	70/62	0.78
BMI (kg/m²)	25.1 ± 2.8	25.0 ± 2.9	0.85
Fasting BHB (mmol/L)	0.3 ± 0.1	0.2 ± 0.1	0.12
Fasting ghrelin (pg/mL)	856 ± 142	849 ± 138	0.78
Fasting gastrin (pg/mL)	42.3 ± 8.2	41.8 ± 8.0	0.76
Postprandial CCK (pg/mL)	18.5 ± 4.2	18.2 ± 4.0	0.69
Postprandial GLP-1 (pg/mL)	24.8 ± 5.6	24.5 ± 5.4	0.75
Fasting motilin (pg/mL)	156 ± 28	154 ± 27	0.67

[Table 1] Baseline demographic and biochemical characteristics of study participants. Values are mean ± SD. Statistical comparisons were performed using independent t-tests. No significant differences were observed between groups at baseline (all $p>0.05$).

Both groups were well-matched at baseline with no significant differences in demographic characteristics (age, sex distribution, BMI) or any hormonal/metabolic parameters (all $p>0.05$), confirming successful randomisation and group comparability.

Achievement of Nutritional Ketosis

The KD group demonstrated robust achievement of nutritional ketosis, with plasma BHB levels increasing from 0.3±0.1 mmol/L at baseline to 1.8±0.4 mmol/L at 8 weeks (mean change +1.5±0.4 mmol/L, $p<0.001$, Cohen's d=4.5). This represents a 500% increase in circulating ketone bodies. In contrast, the control group showed minimal change (0.2±0.1 to 0.3±0.1 mmol/L, $p=0.21$).

By week 2, 92% of KD participants achieved target ketosis (BHB ≥0.5 mmol/L), with this proportion maintained throughout the intervention period. Mean dietary adherence score in the KD group was 87±9% based on combined ketone monitoring and food diary analysis.

Table 2: Hormonal Adaptations After 8 Weeks

Hormone	KD Base	KD 8wk	%Δ	Control Base	Control 8wk	%Δ	p-inter	Cohen's d
Ghrelin (pg/mL)	856±142	613±118	-28.4	849±138	832±135	-2.0	<0.001	1.84
Gastrin (pg/mL)	42.3±8.2	50.0±9.1	+18.2	41.8±8.0	42.1±7.9	+0.7	0.002	1.12
CCK (pg/mL, post)	18.5±4.2	26.3±5.1	+42.1	18.2±4.0	18.7±4.1	+2.7	<0.001	1.95
GLP-1 (pg/mL, post)	24.8±5.6	19.2±4.8	-22.7	24.5±5.4	24.1±5.3	-1.6	0.001	1.38
Motilin (pg/mL)	156±28	205±34	+31.5	154±27	157±28	+2.0	<0.001	1.72

[Table 2] Changes in gastric hormone concentrations after 8-week dietary intervention. Base = Baseline; 8wk = 8 weeks; %Δ = percent change; p-inter = p-value for intergroup comparison of change scores; post = postprandial measurement. All within-group KD changes: $p<0.01$; all within-group control changes: $p>0.05$. Effect sizes (Cohen's d) calculated for intergroup differences in change scores, indicating large effects ($d>0.8$) for all hormones.

The KD group exhibited marked and statistically significant alterations in all five gastric hormones examined:

Ghrelin: Fasting ghrelin concentrations decreased by 28.4% (856±142 to 613±118 pg/mL, $p<0.001$), while controls showed minimal change (-2.0%, $p=0.18$). The intergroup difference was highly significant ($p<0.001$, $d=1.84$).

Gastrin: Fasting gastrin levels increased by 18.2% (42.3±8.2 to 50.0±9.1 pg/mL, $p<0.001$) in the KD group versus essentially no change in controls (+0.7%, $p=0.62$)—intergroup comparison: $p=0.002$, $d=1.12$.

Cholecystokinin (CCK): Postprandial CCK demonstrated the largest relative increase, rising 42.1% (18.5±4.2 to 26.3±5.1 pg/mL, $p<0.001$) in the KD group compared to 2.7% in controls ($p=0.35$). This yielded the largest effect size ($p<0.001$, $d=1.95$).

GLP-1: Postprandial active GLP-1 decreased by 22.7% (24.8±5.6 to 19.2±4.8 pg/mL, $p<0.001$) in the KD group, while controls showed a negligible change (-1.6%, $p=0.52$). Intergroup: $p=0.001$, $d=1.38$.

Motilin: Fasting motilin increased by 31.5% (156±28 to 205±34 pg/mL, $p<0.001$) in the KD group versus stable levels in controls (+2.0%, $p=0.41$). Intergroup: $p<0.001$, $d=1.72$.

All between-group differences demonstrated large effect sizes (Cohen's d >0.8), indicating clinically meaningful hormonal adaptations specifically attributable to the ketogenic dietary intervention.

Table 3: Correlation Analysis: BHB and Dietary Adherence with Hormonal Changes

Parameter	BHB Correlation (r, p-value)	Diet Adherence (r, p-value)
Δ Ghrelin	-0.62, <0.001	-0.51, <0.001
Δ Gastrin	+0.48, <0.001	+0.42, 0.001
Δ CCK	+0.59, <0.001	+0.55, <0.001
Δ GLP-1	-0.45, <0.001	-0.39, 0.001
Δ Motilin	+0.53, <0.001	+0.47, <0.001

Table 3: Pearson correlation coefficients for relationships between hormonal changes (Δ = change from baseline to 8 weeks) and plasma β-hydroxybutyrate levels or dietary adherence scores in the KD group (n=132). All correlations are statistically significant at $p<0.001$ or $p=0.001$.

Strong linear relationships emerged between the degree of ketosis (plasma BHB levels) and the magnitude of hormonal changes in the KD group:

- Ghrelin suppression correlated strongly and negatively with BHB ($r=-0.62$, $p<0.001$), indicating greater ketosis associated with more pronounced appetite hormone suppression
- CCK elevation showed robust positive correlation with BHB ($r=+0.59$, $p<0.001$)
- Motilin increased moderately strongly with BHB ($r=+0.53$, $p<0.001$)
- Gastrin elevation demonstrated moderate positive correlation ($r=+0.48$, $p<0.001$)
- GLP-1 reduction correlated moderately with BHB ($r=-0.45$, $p<0.001$)

Similarly, dietary adherence scores (percentage compliance with KD macronutrient targets) showed significant correlations with all hormonal changes, though slightly weaker than those with BHB. No significant correlations were observed in the control group between dietary parameters and hormonal changes (all $r<0.10$, $p>0.30$).

These dose-response relationships strongly suggest that ketone bodies themselves, rather than confounding dietary factors, directly mediate the observed hormonal adaptations.

Discussion

This study provides the first comprehensive profiling of gastric hormone adaptations to the ketogenic diet in a Central Indian population, revealing a consistent and mechanistically coherent pattern of enteroendocrine remodelling. The principal findings—marked ghrelin suppression, elevation of gastrin/CCK/motilin, reduced GLP-1, and strong correlations with ketosis depth—offer novel insights into the hormonal mechanisms underlying KD's metabolic effects in non-Western populations.

Ghrelin Suppression and Appetite Regulation

The 28.4% reduction in fasting ghrelin observed in our KD group (effect size $d=1.84$) aligns closely with findings from Sumithran et al.'s landmark study, in which sustained weight loss via KD was associated with attenuated compensatory ghrelin elevation compared with conventional caloric restriction.[3] This suppression is counterintuitive, as carbohydrates are the primary postprandial suppressors of ghrelin secretion, yet chronic high-fat feeding appears to reset ghrelinergic tone fundamentally.

Multiple mechanisms may explain this adaptation. First, sustained elevation of CCK and other satiety signals from

chronic fat intake may chronically desensitize ghrelin-secreting X/A-like cells in the gastric fundus via paracrine feedback.[9] Second, ketone bodies themselves, particularly BHB, may directly suppress ghrelin gene expression via epigenetic mechanisms, including histone deacetylase (HDAC) inhibition.[10] Our strong negative correlation between BHB and ghrelin changes ($r = -0.62$, $p < 0.001$) supports direct ketone-mediated effects.

Third, altered gut microbiota composition under KD (as documented in our prior publication) may influence ghrelin secretion via short-chain fatty acid (SCFA) signaling. However, the direction of this effect remains unclear.[11] The reduction in ghrelin likely contributes substantially to KD's appetite-suppressing effects despite the high caloric density of fats, helping explain the improved satiety and reduced energy intake commonly reported by KD adherents.

Gastrin Elevation and Gastric Acid Secretion

The 18.2% increase in fasting gastrin ($d=1.12$) represents a moderate but significant elevation, consistent with our previous finding of increased gastric acid output in this cohort. Gastrin stimulates parietal cell acid secretion by binding to CCK-B receptors and activating the H^+/K^+-ATPase proton pump.[4]

Several factors likely contribute to elevated gastrin under KD. Dietary protein is a well-established stimulus for antral G-cell gastrin release, as amino acids directly activate calcium-sensing receptors on G-cells.[12] Additionally, high-fat intake promotes bile acid secretion and duodenal acidification, which can reflexively stimulate gastrin release. The correlation between BHB and gastrin elevation ($r=+0.48$, $p<0.001$) suggests ketone bodies may also directly or indirectly enhance gastrin secretion, possibly via modulation of somatostatin tone (the primary inhibitor of gastrin).[13]

Clinically, modest gastrin elevation optimizes protein digestion in the high-protein context of KD and may enhance mineral absorption (iron, calcium, zinc), dependent on acidic pH. However, sustained hypergastrinemia could theoretically increase the risk of gastroesophageal reflux disease (GERD) or, in extreme cases, parietal cell hyperplasia, warranting monitoring in long-term KD users.

CCK Surge and Fat-Adaptive Responses

The 42.1% elevation in postprandial CCK ($d=1.95$)—the most robust hormonal change observed—directly reflects the high-fat content of KD meals. CCK is secreted by duodenal I-cells in direct proportion to fatty acid chain length and concentration in the intestinal lumen.[5] Long-chain fatty acids, abundant in KD, are particularly potent CCK secretagogues.

Elevated CCK serves multiple adaptive functions under KD:

1. Ileal brake activation: CCK slows gastric emptying and small bowel transit to optimize fat digestion and absorption, preventing malabsorption
2. Pancreatic enzyme secretion: CCK stimulates lipase and co-lipase release, essential for triglyceride hydrolysis
3. Gallbladder contraction: Promotes bile acid delivery for fat emulsification
4. Satiety signaling: CCK acts on vagal afferents and central nervous system receptors to promote meal termination and satiety.[14]

The strong positive correlation between BHB and CCK ($r=+0.59$, $p<0.001$) suggests ketone bodies may potentiate CCK responses, possibly via effects on I-cell sensitivity or CCK receptor expression. This finding correlates with our prior observation of increased stool fat content in the KD group, as even maximally stimulated pancreatic lipase cannot achieve complete fat digestion when intake exceeds ~100-150g/day.

GLP-1 Reduction and Accelerated Gastric Emptying

The 22.7% reduction in postprandial active GLP-1 ($d=1.38$) directly reflects the absence of carbohydrate stimulus, as intestinal L-cells are primarily activated by glucose and other monosaccharides via SGLT-1 transporters and sweet taste receptors.[6] This finding has important implications for gastric motility and glucose homeostasis.

GLP-1 is a potent inhibitor of gastric emptying via central and peripheral mechanisms, mediating the nutrient brake that prevents rapid nutrient delivery to the small intestine.[15] Its reduction under KD removes this inhibitory brake, contributing to the accelerated gastric emptying we previously documented in this cohort (gastric emptying half-time reduction of 11.1 minutes, $p<0.001$). This acceleration may initially seem counterintuitive given simultaneous CCK elevation but represents a balanced adaptation—CCK slows proximal emptying while GLP-1 reduction permits distal passage.

From a metabolic perspective, GLP-1 reduction may seem disadvantageous given its insulinotropic and glucose-lowering effects. However, in the context of sustained carbohydrate restriction and ketosis, insulin requirements are minimal, and GLP-1's glucose-regulatory role becomes less critical. Some studies suggest that ketone bodies may partially substitute for GLP-1's metabolic benefits via direct effects on pancreatic beta cells.[16]

Motilin Elevation and Interdigestive Motility

The 31.5% increase in fasting motilin ($d=1.72$) represents a novel finding not previously documented in KD studies. Motilin orchestrates the migrating motor complex (MMC), particularly phase III high-amplitude contractions that "sweep" the stomach and small bowel during fasting to prevent bacterial overgrowth and stasis.[7]

Enhanced motilin under KD may serve adaptive purposes. First, the low fiber content of most KD formulations reduces intraluminal bulk, potentially predisposing to stasis without compensatory motility enhancement. Elevated motilin may counteract this by maintaining robust interdigestive contractility. Second, high-fat meals typically suppress motilin and MMC activity during digestion; chronically elevated baseline motilin may ensure rapid return of cleansing contractions between meals. The positive correlation between BHB and motilin ($r=+0.53$, $p<0.001$) suggests direct effects of ketones on duodenal M-cells or motilin gene expression. This finding aligns with clinical observations that KD rarely causes constipation despite low fiber, possibly due to enhanced neuromotor activity mediated by motilin and other factors.

Ketone-Mediated Mechanisms: HCAR2/GPR109A Signaling

The consistent, strong correlations between plasma BHB levels and all five hormonal changes (r ranging from -0.62 to +0.59, all $p<0.001$) strongly implicate ketone bodies as direct mediators

rather than mere biomarkers. BHB functions not only as an energy substrate but also as a signaling molecule via the G-protein-coupled receptor HCAR2 (also known as GPR109A), expressed on immune cells, adipocytes, and notably, enteroendocrine cells.[17]

HCAR2 activation by BHB triggers multiple downstream effects:

- Modulation of intracellular cAMP levels
- Altered hormone gene transcription via HDAC inhibition
- Changes in calcium signaling affecting vesicle exocytosis
- Anti-inflammatory signaling via NF-κB pathway inhibition.[18]

Our findings suggest that chronic HCAR2 activation on gastric/intestinal enteroendocrine cells may coordinate the observed hormonal pattern. Specifically, BHB may suppress ghrelin transcription in X/A-like cells while enhancing gastrin, CCK, and motilin secretion from G-, I-, and M-cells, respectively. GLP-1 reduction is likely primarily due to the absence of a glucose stimulus rather than to direct ketone effects on L-cells.

This represents a novel physiological axis—the "ketone-gut hormone axis"—warranting further mechanistic investigation using in vitro enteroendocrine cell models and HCAR2 knockout animal studies.

Novel Insights in the Indian Population Context

Unlike Western populations, which may transition to KD from moderate-carbohydrate baseline diets (typically 40-50% carbohydrates), our Indian participants shifted from traditional high-carbohydrate patterns (55-65% carbohydrates from rice, wheat, and legumes). This more dramatic macronutrient transition may explain why the magnitude of certain hormonal changes—particularly ghrelin suppression and CCK elevation—appears somewhat greater in our cohort compared to published Western studies. Additionally, genetic factors prevalent in Indian populations may modulate hormonal responses. Polymorphisms in the FTO (fat mass and obesity-associated) gene, present in approximately 25% of Indians, influence ghrelin sensitivity, and appetite regulation.[8] Whether FTO variants predict differential hormonal responses to KD represents an important future research direction for personalized nutrition. The gut microbiome differences between Indians and Westerners—particularly the higher baseline Prevotella abundance in Indians—may also influence hormonal adaptations via microbe-derived metabolites that affect enteroendocrine function.[19] Our prior microbiome analysis in this cohort revealed substantial restructuring under KD; integrating microbiome and hormone data could reveal novel diet-microbe-host interactions.

Clinical and Therapeutic Implications

These hormonal adaptations offer mechanistic insights for several clinical applications:

Obesity and Weight Management: The combination of ghrelin suppression (reduced hunger), CCK elevation (enhanced satiety), and GLP-1 reduction (less delayed gastric emptying, preventing discomfort) creates a hormonal milieu favorable for sustained caloric restriction without hunger. This helps explain KD's superiority over isocaloric low-fat diets for short- to medium-term weight loss.[20]

Gastroparesis: Patients with delayed gastric emptying might benefit from KD's GLP-1-reducing effect, potentially accelerating transit. However, the CCK elevation could be counterproductive, suggesting careful individualization.

Post-Bariatric Surgery: Following Roux-en-Y gastric bypass, exaggerated GLP-1 responses contribute to reactive hypoglycemia. KD might attenuate this via reduced GLP-1 secretion, though clinical trials are needed.

GERD Management: Elevated gastrin raises theoretical concerns about reflux, yet clinical evidence suggests KD may improve GERD symptoms, possibly via weight loss and reduced intra-abdominal pressure, outweighing acid effects.[21]

Functional Dyspepsia: The coordinated hormonal changes—accelerated emptying from reduced GLP-1, enhanced acid from gastrin, improved interdigestive motility from motilin—might benefit some dyspepsia patients, though CCK elevation could exacerbate symptoms in hypersensitive individuals.

Integration with Prior Findings

These hormonal data integrate coherently with our previously published findings in this cohort. The 11.1-minute reduction in gastric emptying time we reported is mechanistically explained by GLP-1 reduction (removing the brake) despite CCK elevation (partial brake). Enhanced gastric acid output aligns with elevated gastrin levels. The gut microbiota restructuring (reduced diversity, elevated F/B ratio) likely influences and is influenced by these hormonal changes through bidirectional gut-microbe-hormone crosstalk.

This multi-level dataset—hormones (present study), motility/function, immunity, and microbiota (prior publications)—offers an unusually comprehensive view of KD's physiological effects, demonstrating coordinated adaptations across digestive, endocrine, immune, and microbial systems.

Strengths and Limitations: Strengths include the relatively large sample size (n=264), a prospective, controlled design, rigorous dietary adherence monitoring via objective ketone measurements, comprehensive hormonal profiling using validated assays, a focus on an understudied population, and integration with prior multi-system data from the same cohort.

Limitations warrant acknowledgment: The 8-week duration captures acute-to-subacute adaptations but not long-term steady-state or potential reversibility. We measured total ghrelin rather than acylated (active) ghrelin, though both correlate closely. Hormones were assessed under standardized conditions (fasting, fixed test meal), which may not fully reflect free-living responses to variable meals. We did not perform gastric aspirate sampling to correlate hormone levels with direct acid output. Genetic polymorphisms (e.g., FTO, leptin receptor) were not assessed, limiting the ability to identify responder phenotypes. Single-center design and the Central Indian population may limit generalizability to other Indian regions or populations.

Future Research Directions

Several important questions emerge from this work:

1. Long-term hormonal trajectory: Do these changes persist, attenuate, or amplify with prolonged KD (6-12 months)? Are they reversible upon diet cessation?
2. Mechanistic studies: Direct investigation of HCAR2/GPR109A signaling in human enteroendocrine cell lines; ketone effects on hormone gene transcription and secretion

3. Genetic stratification: Do FTO, MC4R, or other polymorphisms predict differential hormonal responses? Can genotype guide KD personalization?
4. Microbiome-hormone axis: How do gut microbiota changes causally influence hormonal adaptations? Do probiotics or prebiotics modulate responses?
5. Clinical trials: Prospective studies in gastroparesis, GERD, functional dyspepsia, and post-bariatric hypoglycemia testing therapeutic potential
6. Modified KD formulations: Do fiber-supplemented, Mediterranean, or plant-based ketogenic variants produce different hormonal profiles? Can formulations optimize benefits while minimizing potential concerns?
7. Sex and age differences: Our cohort included both sexes but was not powered for stratified analysis; do hormonal adaptations differ by sex or age?

Conclusion

This study demonstrates that an 8-week ketogenic diet induces a characteristic and coordinated enteroendocrine signature in healthy Central Indian adults, characterized by ghrelin suppression (-28.4%), gastrin elevation (+18.2%), CCK surge (+42.1%), GLP-1 reduction (-22.7%), and motilin increase (+31.5%)—all with large effect sizes and strong correlations to ketosis depth (BHB levels).

These hormonal adaptations are mechanistically coherent, optimizing the gastrointestinal system for high-fat nutrient processing: enhanced acid secretion (gastrin) and pancreatic enzyme release (CCK) facilitate fat digestion; reduced hunger (ghrelin) and enhanced satiety (CCK) support caloric restriction; accelerated gastric emptying (GLP-1 reduction) balances fat-induced slowing (CCK elevation); and enhanced interdigestive motility (motilin) prevents stasis despite low fiber.

The strong BHB-hormone correlations implicate ketone bodies as direct signaling molecules mediating these adaptations, likely via HCAR2/GPR109A receptor pathways on enteroendocrine cells. This represents a novel "ketone-gut hormone axis" warranting further mechanistic investigation.

Importantly, the magnitude of adaptations observed in this Indian cohort—particularly the elevation of the F/B ratio from our microbiome study and the hormone changes reported herein—suggests population-specific responses shaped by distinct baseline diets, genetics, and microbiomes. This underscores the critical importance of conducting dietary intervention research in diverse populations rather than extrapolating from Western studies.

These findings provide mechanistic insights into KD's metabolic benefits, inform clinical applications in obesity, gastroparesis, and other conditions, and highlight the need for careful monitoring, potential mitigation strategies, and individualized approaches to optimize both therapeutic benefits and physiological adaptation during ketogenic dietary interventions in Indian and other non-Western populations.

Future research integrating genetics, microbiomics, metabolomics, and hormonal profiling will advance precision nutrition approaches, enabling personalized ketogenic protocols that maximize benefits while minimizing risks for diverse individuals and populations.

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Conflicts of interest

There are no conflicts of interest.

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