Review Article

Chronopharmacology of Proton Pump Inhibitors in Irregular Meal Timing: Emerging Implications of Breakfast Skipping in Gastroesophageal Reflux Disease (GERD)

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ABSTRACT

Gastroesophageal reflux disease (GERD) is a highly prevalent gastrointestinal disorder associated with substantial impairment in quality of life and increasing healthcare burden worldwide. Proton pump inhibitors (PPIs) remain the cornerstone of GERD pharmacotherapy; however, a considerable proportion of patients continue to experience persistent reflux symptoms despite standard treatment. Emerging evidence suggests that irregular meal timing, particularly breakfast skipping, may contribute to both GERD pathogenesis and suboptimal therapeutic response to PPIs. This review examines the chronopharmacological relationship between proton pump inhibitor efficacy, circadian regulation of gastric acid secretion, and disrupted meal timing patterns. Circadian rhythms regulate multiple gastrointestinal functions, including gastric acid secretion, lower esophageal sphincter tone, gastric motility, and mucosal defense mechanisms, all of which influence reflux pathophysiology. PPIs exhibit meal-dependent pharmacodynamics, requiring administration prior to food-induced proton pump activation for optimal acid suppression. Breakfast omission disrupts this synchronization, potentially impairing proton pump inhibition, reducing intragastric pH control, and increasing the risk of nocturnal acid breakthrough and refractory GERD symptoms. Additionally, prolonged fasting and circadian misalignment may exacerbate reflux through mechanisms involving transient lower esophageal sphincter relaxations, delayed gastric emptying, autonomic dysregulation, neuroimmune signaling, and gut–brain axis dysfunction. This review further discusses chronotherapeutic strategies, including individualized PPI dosing schedules, split-dose therapy, chrono-nutrition approaches, and the emerging role of potassium-competitive acid blockers in patients with irregular meal timing. Despite growing epidemiological and mechanistic evidence, significant research gaps remain regarding the direct impact of breakfast skipping on PPI pharmacodynamics and GERD outcomes. Future chronopharmacological and precision medicine-based investigations may facilitate more individualized and effective GERD management strategies.

Key words: Gastroesophageal reflux disease; proton pump inhibitors; chronopharmacology; circadian rhythm; meal timing; gastric acid secretion.

Gastroesophageal reflux disease (GERD) is a chronic, multifactorial gastrointestinal disorder characterized by the retrograde movement of gastric contents into the esophagus, resulting in troublesome symptoms such as heartburn, regurgitation, chest pain, chronic cough, and, in severe cases, mucosal injury including erosive esophagitis and Barrett's esophagus [1,2]. GERD represents one of the most prevalent digestive disorders globally, affecting approximately 13% of the world population, with reported prevalence rates ranging from 8% to 33% depending on geographical region, diagnostic criteria, and population characteristics [3,4]. Beyond its clinical manifestations, GERD imposes a considerable socioeconomic burden through increased healthcare utilization, pharmacotherapy costs, diagnostic procedures, reduced work productivity, and substantial impairment in health-related quality of life [5].

The pathogenesis of GERD is complex and involves multiple interacting mechanisms, including transient lower esophageal sphincter (LES) relaxation, impaired esophageal clearance, delayed gastric emptying, gastric acid hypersecretion, esophageal hypersensitivity, and disruption of mucosal defense systems [1,2]. Among these factors, gastric acid exposure remains central to symptom generation and mucosal injury, thereby establishing acid suppression as the primary therapeutic target in GERD management [6]. Consequently, proton pump inhibitors (PPIs), including omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole, have become the cornerstone of pharmacological

Access this article online

Received – 15th Novemer 2024

Initial Review – 28th November 2024

Accepted – 8th December 2024

Quick Response Code

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therapy owing to their superior acid-suppressive efficacy compared with histamine H2-receptor antagonists [6,7]. PPIs exert their therapeutic effect through irreversible inhibition of the gastric H+/K+-ATPase proton pump located on parietal cells, thereby markedly reducing gastric acid secretion and promoting mucosal healing [6].

Despite their established clinical efficacy, approximately 20–30% of GERD patients continue to experience incomplete symptom relief or persistent reflux symptoms during standard PPI therapy [8]. This therapeutic variability has prompted increasing interest in factors beyond intrinsic drug potency that may influence treatment outcomes, including dosing schedule, circadian variation in gastric acid secretion, lifestyle behaviors, and meal timing patterns [9,10]. Current clinical guidelines recommend administering PPIs approximately 30–60 minutes before the first meal of the day, typically breakfast, to ensure optimal drug absorption and synchronization with postprandial proton pump activation [11]. However, the growing prevalence of irregular eating behaviors, particularly breakfast skipping, may compromise this pharmacodynamic synchronization and contribute to suboptimal acid suppression.

Recent decades have witnessed profound lifestyle and dietary behavioral changes associated with urbanization, occupational stress, academic pressures, shift work, intermittent fasting practices, and altered social routines [12,13]. Among these behavioral patterns, breakfast skipping has emerged as an increasingly common habit, particularly among adolescents, university students, healthcare workers, and shift-based occupations, with prevalence estimates ranging between 20% and 60% depending on demographic characteristics and study definitions [14,15]. Importantly, accumulating epidemiological and clinical evidence indicates that breakfast skipping is independently associated with increased GERD prevalence, higher symptom frequency, and greater reflux severity [16,17]. Several mechanisms have been proposed to explain this association, including prolonged fasting-induced gastric acid accumulation, delayed gastric emptying, altered lower esophageal sphincter physiology, impaired gastrointestinal motility, autonomic imbalance, and circadian disruption of gastrointestinal function [18,19].

The interaction between meal timing and drug response can be more comprehensively understood through the framework of chronopharmacology, a specialized branch of pharmacology that investigates how biological rhythms influence drug absorption, distribution, metabolism, excretion, and pharmacodynamic efficacy [20,21]. Circadian rhythms, regulated by central and peripheral biological clocks, exert substantial influence on gastrointestinal physiology, including gastric acid secretion, gastrointestinal motility, hormone release, and digestive enzyme activity. Gastric acid secretion itself follows a distinct circadian pattern, with variations occurring throughout the day and night in response to feeding behavior, neurohormonal regulation, and autonomic nervous system activity [9,10]. Consequently, disruption of regular meal timing may interfere with both physiological acid regulation and the time-dependent therapeutic efficacy of PPIs.

Emerging evidence further suggests that breakfast skipping may contribute to GERD pathogenesis through mechanisms involving the gut–brain axis and neuroimmune signaling pathways. Prolonged fasting and circadian misalignment may alter vagal signaling, stress hormone secretion, inflammatory cytokine release, and gastrointestinal sensory processing, thereby exacerbating reflux symptoms and visceral hypersensitivity [18,19]. These observations highlight the possibility that irregular meal timing may not only influence disease pathophysiology but also impair pharmacological responsiveness to acid-suppressive therapy.

2. Circadian Regulation of Gastric Acid Secretion

2.1 Molecular Mechanisms of the Gastric Circadian Clock

Circadian rhythms are endogenous, approximately 24-hour biological oscillations that regulate a broad spectrum of physiological processes in virtually all mammalian tissues and organ systems [22]. At the molecular level, circadian rhythmicity is driven by transcription-translation feedback loops involving core clock genes, including CLOCK, BMAL1, Period (PER1, PER2, PER3), and Cryptochrome (CRY1, CRY2) [23]. The central circadian pacemaker residing in the suprachiasmatic nucleus (SCN) of the hypothalamus integrates environmental light-dark cues to synchronize peripheral clocks throughout the body, including those in the gastrointestinal tract [24]. Clock gene expression has been documented in gastric parietal cells, enterochromaffin-like (ECL) cells, and gastric smooth muscle, suggesting intrinsic circadian control of acid-secretory machinery at the cellular level [25].

Gastric acid secretion exhibits well-documented circadian oscillation, with basal acid output reaching its nadir in the early morning hours and peaking during the evening, typically between 22:00 and 02:00 hours [26]. This nocturnal acid surge is mediated by elevated vagal activity, increased histamine release from ECL cells, and circadian variation in gastrin secretion from G-cells of the antrum [27]. The physiological significance of this nocturnal acid peak lies in its contribution to nocturnal GERD symptoms, esophageal mucosal injury during sleep, and the well-recognized clinical phenomenon of nocturnal acid breakthrough despite PPI therapy [28].

2.2 Circadian Regulation of Broader Gastrointestinal Function

Beyond acid secretion, circadian rhythms exert pervasive regulatory influence over gastrointestinal physiology. Gastric emptying rate varies with time of day, with more rapid emptying observed in the morning compared to the evening, a pattern governed by both autonomic innervation and enteric

clock gene expression [29]. Intestinal motility, regulated by the interstitial cells of Cajal and enteric nervous system neurons, also exhibits circadian periodicity, with migrating motor complexes showing time-of-day variation [30]. Epithelial permeability of the gastrointestinal mucosa, tight junction protein expression, and mucus secretion are subject to circadian modulation, influencing mucosal defense against acid and pepsin [31].

Esophageal physiology is similarly influenced by circadian factors. LES tone, which is the primary mechanical barrier against gastroesophageal reflux, exhibits diurnal variation, with lower sphincter pressures documented during nighttime sleep [32]. Esophageal acid clearance, dependent on peristaltic contraction amplitude and salivary bicarbonate secretion, is markedly impaired during sleep, prolonging mucosal acid contact time and increasing the risk of esophagitis [33]. Disruption of circadian synchronization — whether through shift work, social jetlag, or irregular feeding schedules — impairs this coordinated gastrointestinal homeostasis and predisposes individuals to symptomatic GERD and its complications [34].

3. Pharmacology and Chronopharmacology of Proton Pump Inhibitors

3.1 Mechanism of Action

PPIs are prodrugs that require acidic pH for conversion to their active sulfonamide form within the secretory canaliculi of gastric parietal cells [12]. Once activated, they form covalent disulfide bonds with cysteine residues (primarily Cys813 and Cys822) of the alpha-subunit of the H+/K+-ATPase pump, resulting in irreversible inhibition of acid secretion [35]. Because PPIs exclusively inhibit pumps that are actively secreting acid at the time of drug administration, their efficacy is fundamentally dependent on the proportion of proton pumps stimulated by meal-related vagal and hormonal signals [14]. New pump synthesis occurs within 24 to 48 hours, necessitating once-daily or twice-daily dosing for sustained acid suppression.

The pharmacokinetic profile of PPIs is characterized by a short plasma elimination half-life of approximately 1 to 2 hours, making their duration of acid suppression considerably longer than predicted by plasma concentration alone due to covalent pump inhibition [36]. PPIs undergo extensive first-pass hepatic metabolism primarily via cytochrome P450 enzymes CYP2C19 and CYP3A4, with significant inter-individual pharmacokinetic variability attributable to CYP2C19 genetic polymorphisms [37]. Poor metabolizers exhibit substantially higher plasma PPI concentrations and greater acid suppression compared to extensive metabolizers, highlighting the importance of pharmacogenomic factors in treatment optimization [38].

3.2 Timing of Administration and Pharmacodynamic Optimization

The critical importance of meal-related timing for PPI efficacy has been established through multiple pharmacokinetic-pharmacodynamic studies. Administration 30 to 60 minutes before the first meal of the day optimizes drug delivery to the systemic circulation, coinciding with meal-stimulated proton pump activation, thereby maximizing the proportion of inhibited pumps [14,39]. Studies using 24-hour intragastric pH monitoring have demonstrated that patients who take PPIs without a preceding meal achieve significantly lower intragastric pH values and reduced time with pH greater than 4 compared to those who take their medication before a standardized breakfast [40].

Split-dose regimens, involving administration before breakfast and before the evening meal, have been shown to produce superior 24-hour acid suppression compared to once-daily dosing in patients with incomplete response to standard therapy, particularly for control of nocturnal acid secretion [41]. The pharmacodynamic rationale for split dosing rests on the activation of newly synthesized proton pumps by the evening meal, providing a second window of optimal drug-pump interaction [42]. These findings underscore the meal-dependent nature of PPI pharmacodynamics and the potential therapeutic consequences of meal skipping.

3.3 Chronotherapeutic Principles Applied to PPI Therapy

Chronopharmacology posits that optimizing the timing of drug administration relative to biological rhythms can enhance therapeutic efficacy, minimize adverse effects, and improve patient outcomes [7]. For PPIs, chronotherapeutic considerations encompass both the circadian rhythm of acid secretion and the individual's meal timing pattern as determinants of optimal dosing strategy [8]. Patients with predominantly nocturnal symptoms may benefit from evening PPI dosing before dinner, which targets the physiological nadir of LES pressure and the peak of circadian acid secretion during sleep [43]. Conversely, patients with daytime predominant symptoms are best served by pre-breakfast administration.

Emerging evidence from chronopharmacological studies suggests that circadian variation in gastric acid secretion, parietal cell sensitivity to PPIs, and hepatic CYP enzyme activity collectively produce time-dependent differences in PPI pharmacodynamics that may have clinical relevance in populations with disrupted meal timing [44]. The therapeutic implications extend beyond the timing of medication to encompass broader behavioral modifications, including regularization of meal schedules, avoidance of late-night eating, and management of circadian dysregulation as adjunctive strategies in GERD management [45].

4. Breakfast Skipping and GERD: Pathophysiological Connections

4.1 Epidemiology and Determinants of Breakfast Skipping

Breakfast skipping has become increasingly prevalent across diverse demographic groups, with rates varying from approximately 10% to 60% depending on age group, geographic region, occupational status, and definitional criteria employed [18,19]. Among adolescents, breakfast omission rates of 20% to 30% have been documented in developed nations, driven by time constraints, sleep inertia, and weight management beliefs [46]. In adult populations, breakfast skipping is particularly prevalent among healthcare workers, shift employees, single-person households, and urban professionals, where irregular work schedules and meal timing disruption are endemic [17,47]. A comprehensive meta-analysis of studies across 47 countries reported that breakfast skipping was associated with a twofold increased risk of metabolic syndrome, providing a broader metabolic context for its gastrointestinal consequences [48].

Breakfast skipping is frequently intertwined with other GERD risk factors, including obesity, sedentary lifestyle, high-fat dietary patterns, and increased alcohol and caffeine consumption, creating complex and interrelated pathophysiological interactions [20,49]. Importantly, several prospective cohort studies have identified breakfast skipping as an independent predictor of GERD development after controlling for confounding variables, suggesting direct mechanistic effects on esophagogastric physiology beyond those attributable to associated dietary patterns [21,50].

4.2 Mechanisms Linking Breakfast Skipping to GERD Pathophysiology

The pathophysiological mechanisms by which breakfast skipping may exacerbate GERD are multifactorial and mutually reinforcing. Prolonged nocturnal and morning fasting substantially extends the duration of gastric acid accumulation in the absence of food's buffering and diluting effect, resulting in elevated intragastric acidity throughout the fasting period [51]. This fasting-associated hyperacidity increases the concentration gradient favoring acid reflux across a relatively hypotonic LES, particularly during the morning hours when basal LES pressure is physiologically reduced.

Fasting also alters the pattern of gastric motility, promoting phase III migrating motor complexes that increase transient LES relaxations (TLESRs), the predominant mechanism underlying gastroesophageal reflux events [52]. Prolonged fasting increases circulating ghrelin concentrations, which stimulate gastric acid secretion and motility, potentially amplifying reflux frequency [53]. Conversely, the large, calorie-dense meals frequently consumed later in the day by breakfast skippers produce pronounced gastric distension, which is a potent trigger for TLESRs and reflux episodes [54].

Delayed gastric emptying, compounded by the consumption of large, high-fat meals in the absence of an earlier meal, prolongs the period of gastric distension following eating, further increasing reflux risk [55]. Cortisol, which peaks in the early morning in alignment with the circadian rhythm, promotes gastric acid secretion and heightens esophageal mucosal susceptibility to acid injury; breakfast skipping disrupts the normal postprandial attenuation of this cortisol-acid secretion coupling [56]. At the cellular level, circadian misalignment induced by irregular meal timing impairs tight junction integrity in the esophageal epithelium, reducing mucosal resistance to acid-mediated injury [57].

4.3 Clinical and Epidemiological Evidence

Multiple epidemiological studies have established statistically significant associations between breakfast skipping and GERD prevalence, symptom frequency, and severity scores. A large cross-sectional study involving over 19,000 Japanese adults found that breakfast omission was independently associated with a 1.4-fold increased risk of GERD symptoms after multivariate adjustment [20]. A prospective investigation of Korean adults reported that irregular meal timing, including breakfast skipping, predicted new-onset erosive esophagitis on follow-up endoscopy [21]. Population-based studies from Europe and North America have similarly documented associations between meal irregularity and GERD symptom burden [6,16].

In pediatric and adolescent populations, breakfast skipping has been associated with higher rates of functional dyspepsia and GERD-like symptoms, suggesting developmental implications of disrupted meal timing for esophagogastric physiology [58]. Among shift workers, who frequently skip or delay morning meals due to inverted sleep-wake cycles, GERD prevalence rates are reported to be 2 to 3 times higher than in daytime workers, with poorer PPI treatment responses observed [17,34]. These clinical observations collectively support the hypothesis that breakfast skipping constitutes a modifiable behavioral risk factor for GERD development and therapeutic failure.

5. Impact of Irregular Meal Timing on PPI Efficacy

5.1 Impaired PPI Activation in Breakfast-Skipping Patients

The fundamental pharmacodynamic consequence of breakfast skipping for PPI therapy is the uncoupling of drug absorption from meal-stimulated proton pump activation. When PPIs are administered in the habitual 30 to 60 minutes before breakfast window, but the patient subsequently omits or significantly delays breakfast, the drug reaches therapeutic plasma concentrations during a period of minimal acid secretory activity [14,39]. Under these conditions, the proportion of H+/K+-ATPase pumps actively secreting acid at the time of drug administration is substantially reduced, resulting in fewer covalent drug-pump interactions and proportionally diminished acid suppression [35,40].

Studies using ambulatory intragastric pH monitoring in patients with varying meal patterns have demonstrated that time with intragastric pH above 4, a validated surrogate marker of acid suppression adequacy for GERD management, is significantly lower in patients who take PPIs without a subsequent meal compared to those who consistently eat breakfast after medication [40,59]. The clinical correlate of this pharmacodynamic impairment is reflected in higher symptom scores, increased antacid rescue medication consumption, and lower rates of esophagitis healing in patients with irregular meal timing [60].

5.2 Nocturnal Acid Breakthrough and Sleep-Related Reflux

Nocturnal acid breakthrough (NAB), defined as the occurrence of intragastric pH below 4 for periods exceeding 1 hour during nighttime, represents a clinically important form of PPI treatment failure that disproportionately affects patients with irregular meal timing [28,61]. NAB occurs in approximately 50% to 70% of patients on once-daily PPI therapy and is driven by the physiological nocturnal acid surge, new proton pump synthesis since the last PPI dose, and the absence of meal-related acid buffering during sleep [28]. In patients who skip breakfast, the timing mismatch between PPI administration and meal stimulation may compound nocturnal acid suppression inadequacy by reducing daytime intragastric pH control and altering the pool of inhibited pumps available to buffer the nocturnal surge [43,61].

Nocturnal GERD has particular clinical significance due to its association with esophagitis development, Barrett's esophagus, sleep fragmentation, and reduced health-related quality of life [62]. Prolonged nocturnal acid exposure also predisposes to laryngopharyngeal reflux, dental erosion, and chronic respiratory conditions, including asthma and chronic cough [63]. Strategies to mitigate nocturnal acid breakthrough in patients with irregular meal timing include split-dose PPI therapy, evening administration before dinner, addition of bedtime H2-receptor antagonists, and behavioral modification to regularize meal timing [41,64].

5.3 Circadian Misalignment, Shift Work, and Refractory GERD

Shift workers represent a clinically important population in which circadian misalignment, irregular meal timing, and GERD pathophysiology converge to produce suboptimal treatment outcomes [17,34]. Shift work is associated with chronic circadian disruption, social jetlag, altered cortisol and melatonin rhythms, disrupted sleep architecture, and systematic displacement of meal timing relative to internal biological time [65]. These overlapping disruptions create a syndromic state of heightened GERD risk and PPI pharmacodynamic impairment that may account for the disproportionately high rates of refractory GERD symptoms observed in this population.

A prospective observational study of healthcare workers found that those working rotating night shifts had significantly higher GERD symptom scores and lower intragastric pH time above 4 on PPI therapy compared to day-shift workers, independent of PPI dose and adherence [66]. Experimental circadian misalignment protocols in healthy volunteers have demonstrated impaired gastric acid suppression during simulated shift-work schedules, suggesting a direct mechanistic effect of biological clock disruption on PPI pharmacodynamics [67]. The management of GERD in shift workers requires individualized chronotherapeutic approaches that account for the patient's current work schedule and meal timing pattern rather than defaulting to standard pre-breakfast dosing recommendations.

6. Clinical Implications and Personalized Therapeutic Strategies

6.1 Patient Education and Behavioral Modification

Comprehensive patient education regarding the pharmacodynamic rationale for meal-coupled PPI administration is a fundamental component of effective GERD management that is frequently underprioritized in clinical practice [15,68]. Patients should receive clear, evidence-based counseling explaining that PPIs must be taken 30 to 60 minutes before a meal — not simply at a fixed time each day — to maximize therapeutic efficacy. Dietary counseling addressing the importance of regular meal timing, avoidance of prolonged fasting periods, reduction of large evening meals, and moderation of known reflexogenic foods and beverages should be integrated into GERD management plans [69].

Behavioral interventions targeting breakfast skipping have demonstrated effectiveness in improving metabolic and gastrointestinal outcomes in several clinical trials, providing a therapeutic rationale for recommending breakfast reinstatement as part of GERD management [70]. Structured meal timing programs, consistent with the principles of chrono nutrition, the alignment of food intake with circadian biology may offer complementary benefits to pharmacotherapy by restoring the meal-stimulated pharmacodynamic milieu essential for optimal PPI function [71].

6.2 Chronotherapeutic Optimization Strategies

For patients with predominant nocturnal GERD symptoms, evening PPI dosing before dinner may provide superior nocturnal acid control compared to standard morning administration, by inhibiting the newly synthesized proton pumps activated by the evening meal and exerting more proximal pharmacodynamic coverage of the nocturnal acid surge [43,72]. Split-dose therapy, administering PPIs before breakfast and before dinner, consistently outperforms once-daily morning dosing for 24-hour pH control in patients with partial response to standard therapy and represents a well-validated chronotherapeutic strategy [41,73].

The addition of a bedtime H2-receptor antagonist to PPI therapy can temporarily suppress nocturnal acid breakthrough by blocking histamine-mediated pump activation that occurs independently of meal stimulation during the night [64]. However, tachyphylaxis to this approach develops within weeks due to H2-receptor upregulation, limiting its role to short-term symptomatic relief [64]. Potassium-competitive acid blockers (P-CABs), such as vonoprazan, which inhibit H+/K+-ATPase through a reversible, potassium-competitive mechanism and achieve more rapid and consistent acid suppression without a meal requirement, may represent an important therapeutic advance for patients with irregular meal timing and PPI pharmacodynamic impairment [74,75].

6.3 Precision Medicine and Future Therapeutic Directions

The integration of precision medicine approaches into GERD management offers promising avenues for individualization of acid-suppressive therapy. Chronotype assessment, characterizing whether a patient is a morning or evening type, may inform optimal PPI dosing time, as chronotype influences the circadian phase of peak acid secretion and meal timing preferences [76]. Digital health technologies, including wearable sensors capable of continuous monitoring of circadian biomarkers such as skin temperature, heart rate variability, and physical activity rhythms, may enable clinician-guided personalization of PPI dosing schedules based on objective circadian phenotyping [77].

Pharmacogenomic profiling of CYP2C19 metabolizer status has demonstrated clinical utility in guiding PPI dose selection and may be particularly valuable in patients with suboptimal responses to standard regimens [37,38]. Point-of-care CYP2C19 genotyping is increasingly feasible and cost-effective and may be incorporated into refractory GERD assessment protocols. Artificial intelligence-based clinical decision support tools that integrate patient-reported meal timing data, symptom diary information, chronotype assessment, and pharmacogenomic profiles may facilitate evidence-based, chronotherapy-informed PPI prescribing in routine clinical practice [78].

7. Research Gaps and Future Directions

Despite the compelling mechanistic and epidemiological evidence reviewed above, direct clinical evidence specifically addressing the impact of breakfast skipping on PPI pharmacodynamics and GERD outcomes remains limited, representing a significant gap in the literature. Existing studies on meal timing and GERD have primarily focused on epidemiological associations rather than controlled pharmacodynamic investigations, and few have examined the specific effect of breakfast omission on intragastric pH profiles in patients on PPI therapy.

Randomized controlled trials examining the effect of structured meal timing interventions on PPI pharmacodynamic endpoints, including 24-hour intragastric pH profiles, symptom scores, and esophagitis healing rates, are critically needed. These trials should incorporate continuous intragastric pH monitoring as an objective pharmacodynamic endpoint and should stratify patients according to meal timing pattern, chronotype, and CYP2C19 metabolizer status to enable subgroup analyses relevant to precision medicine applications [79]. Head-to-head comparisons of standard pre-breakfast PPI dosing versus meal-timing-adapted chronotherapeutic regimens in patients with irregular meal patterns would provide the highest quality evidence for clinical guideline development.

Mechanistic studies examining the effects of prolonged fasting on parietal cell circadian clock gene expression, proton pump synthesis and membrane trafficking, and the molecular pharmacodynamics of PPI activation in the context of circadian disruption would advance the fundamental science underlying the clinical observations reviewed here [80]. Translational research linking circadian biomarker profiles measurable through minimally invasive wearable technologies to PPI pharmacokinetic and pharmacodynamic parameters may enable the development of clinically actionable chronopharmacological models for individualized GERD management. Large prospective cohort studies incorporating detailed dietary recall, meal timing assessment, objective circadian phenotyping, and GERD outcome measures are required to establish causality and refine individualized management recommendations.

CONCLUSION

GERD remains a prevalent, chronic gastrointestinal disorder with significant impact on patient quality of life and healthcare systems globally. While PPIs are highly effective agents for acid suppression, their efficacy is fundamentally meal-dependent, rendering them vulnerable to pharmacodynamic impairment in patients with irregular meal timing. Breakfast skipping, an increasingly common behavioral pattern in modern populations, represents a clinically meaningful but underrecognized contributor to GERD pathogenesis and PPI therapeutic failure through multiple interacting mechanisms including prolonged fasting hyperacidity, circadian desynchronization, increased transient LES relaxations, impaired nocturnal acid suppression, and disruption of the meal-stimulated pharmacodynamic milieu essential for proton pump activation.

Chronopharmacology provides an integrative framework for understanding these complexities and offers actionable insights for optimizing acid-suppressive therapy. Clinicians should incorporate assessment of meal timing patterns and breakfast habits into routine GERD evaluation and counsel patients about the pharmacodynamic consequences of meal skipping on PPI efficacy. Chronotherapeutic strategies including split-dose therapy, meal-timing-adapted dosing, and behavioral interventions targeting regular eating schedules should be considered as components of individualized,

precision GERD management, particularly for patients with documented irregular meal patterns, shift work schedules, or refractory symptoms on standard therapy.

Future research should prioritize randomized controlled trials and mechanistic studies directly addressing the effects of meal timing on PPI pharmacodynamics, incorporating objective circadian phenotyping, pharmacogenomic profiling, and advanced intragastric pH monitoring technologies. The integration of digital health tools, chrono nutrition principles, and precision pharmacotherapy holds considerable promise for improving outcomes in the substantial proportion of GERD patients who currently experience suboptimal therapeutic responses.

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How to cite this article: Rayappan VA, Alwin Simon M. Chronopharmacology of Proton Pump Inhibitors in Irregular Meal Timing: Emerging Implications of Breakfast Skipping in Gastroesophageal Reflux Disease (GERD). Indian J Pharm Drug Studies. 2024; 3(4):147-155.

Funding: None; *Conflicts of Interest: None Stated*