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Low Melatonin and Post-COVID Syndrome: Unveiling SIBO as a Potential Pre-Cancerous Condition in the Post-Pandemic Era

Alexandre Tavartkiladze[1,2,3*], Gaiane Simonia[1,2], Ruite Lou[3], Pati Revazishvili[1,2], Maia Maisuradze[1], George Mamukashvili[1], Givi Zumbadze[1], Tamar Japaridze[1], Tatia Potskhoraia[1], Pirdara Nozadze[1,2], George Dundua[1] and David Egiazarov[1]

[1]*Institute for Personalized Medicine, Tbilisi, Georgia.*

[2]*Tbilisi State Medical University, Georgia.*

[3]*Department of Biotechnology, Foconsci Chemical Industry, Shandong, China .*

Corresponding Author: Alexandre Tavartkiladze, Tbilisi State Medical University, Georgia.

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Abstract

The COVID-19 pandemic has left an indelible mark on global health, with millions experiencing not only the acute effects of SARS-CoV-2 infection but also long-term sequelae collectively referred to as post-COVID syndrome or long COVID. Among its multifaceted impacts, the gastrointestinal system has emerged as a significant area of concern. This study explores the potential link between post-COVID syndrome and the development of small intestinal bacterial overgrowth (SIBO), focusing on mechanisms involving melatonin dysregulation, chronic inflammation, and dysbiosis. The findings suggest that post-COVID SIBO could represent a novel pre-cancerous condition, underscoring the urgent need for improved diagnostic and therapeutic strategies. An observational cohort study was conducted on 33 healthy individuals aged 17 to 69 years, who had no prior symptoms of SIBO before SARS-CoV-2 infection. Preventive baseline tests in 2019 included assessments of melatonin and melatonin sulfate levels, pro-inflammatory cytokines, stool analysis for dysbiosis, and tumor markers. In 2023, post-COVID, 18 participants developed SIBO symptoms, while 15 remained asymptomatic. The study revealed significant reductions in blood melatonin concentrations and 24-hour urinary melatonin sulfate levels across all participants ($p < 0.01$). However, this reduction was more pronounced in the SIBO-positive group, accompanied by marked elevations in pro-inflammatory cytokines such as IL-6, TNF-α, IL-12, and IL-17. These findings highlight a strong inverse correlation between melatonin levels and inflammatory cytokines ($r = -0.68$, $p < 0.01$). Stool analyses indicated severe dysbiosis in SIBO-positive participants, characterized by an overgrowth of pathogenic bacteria and reduced microbial diversity. In contrast, SIBO-negative individuals exhibited only mild to moderate dysbiosis.

Notably, tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19.9) were elevated in SIBO-positive individuals, raising concerns about potential early carcinogenic processes linked to chronic inflammation and microbial dysbiosis. No such elevations were observed in the SIBO-negative group. These findings suggest that SIBO, particularly in the context of post-COVID syndrome, may serve as a pre-cancerous condition necessitating early diagnosis and intervention. The study identifies several mechanisms potentially linking post-COVID syndrome to SIBO. Melatonin dysregulation, driven by post-COVID desynchronosis, appears to play a central role. As a regulator of circadian rhythms, melatonin impacts gastrointestinal motility, immune function, and gut microbiome composition. Reduced melatonin levels may impair gut motility, disrupt microbial balance, and exacerbate systemic inflammation, creating a conducive environment for bacterial overgrowth. Furthermore, chronic inflammation and increased intestinal permeability associated with dysbiosis amplify the risk of tumorigenesis, as evidenced by elevated tumor markers. This research highlights the clinical and research implications of post-COVID SIBO. Healthcare providers must remain vigilant for gastrointestinal symptoms in post-COVID patients and prioritize early diagnostic strategies, such as comprehensive breath tests, biomarker assessments, and stool analyses. Therapeutic interventions, including melatonin supplementation, probiotics, and targeted antimicrobial therapies, may mitigate the progression of SIBO and its associated complications. Additionally, the integration of advanced technologies, such as artificial intelligence and microbiome analysis, could revolutionize SIBO diagnostics and enhance precision medicine approaches. In conclusion, this study emphasizes the importance of recognizing post-COVID SIBO as a new and potentially

pre-cancerous condition. By addressing melatonin dysregulation, chronic inflammation, and dysbiosis, healthcare providers can improve outcomes for millions of patients globally. Further research is essential to validate these findings and develop innovative strategies to prevent and treat SIBO, ultimately reducing its impact on global population health and mitigating the risks of cancer development.

Keywords: Post-COVID Syndrome, Small Intestinal Bacterial Overgrowth (SIBO), Melatonin Dysregulation, Chronic Inflammation, Gut Dysbiosis, Tumor Markers, Pre Cancerous Conditions

1. Introduction

The COVID-19 pandemic, driven by the SARS-CoV-2 virus, has become a defining global health crisis of the 21st century. While the acute manifestations of COVID-19, including respiratory distress, systemic inflammation, and multi-organ failure, have received significant attention, an increasing body of evidence highlights the lingering effects of the virus. Collectively termed post-COVID syndrome or long COVID, these persistent conditions affect millions worldwide, profoundly impacting their quality of life and posing challenges to healthcare systems globally. Post-COVID syndrome encompasses a broad spectrum of symptoms that can persist for weeks to months following the resolution of acute infection, with some individuals experiencing long-term complications affecting various organ systems, including the cardiovascular, neurological, and gastrointestinal systems. Among these, gastrointestinal complications such as small intestinal bacterial overgrowth (SIBO) are gaining attention due to their complex interplay with post-COVID immune dysregulation, inflammation, and metabolic alterations.

SIBO is a condition characterized by an abnormal overgrowth of bacteria in the small intestine, leading to symptoms such as bloating, abdominal discomfort, diarrhea, malabsorption, and nutritional deficiencies. Its pathogenesis is multifactorial, involving disruptions in gut motility, the intestinal microbiota, and local immune responses. Recent research has identified potential associations between viral infections, including COVID-19, and the onset of SIBO. These associations are thought to be mediated by mechanisms such as chronic inflammation, intestinal dysbiosis, and disrupted gut barrier function. Additionally, alterations in biological rhythms and melatonin metabolism—key regulators of gastrointestinal and systemic health—may play a critical role in the development of post-COVID SIBO.

Melatonin, a hormone primarily secreted by the pineal gland, is a master regulator of circadian rhythms, with downstream effects on sleep, metabolism, immune function, and oxidative stress. Beyond its central role in regulating the sleep-wake cycle, melatonin exhibits potent antioxidant, anti-inflammatory, and immunomodulatory properties, making it a critical molecule in maintaining gastrointestinal health. Melatonin production is known to be highly sensitive to environmental and physiological disruptions, such as stress, infection, and inflammation. Post-COVID syndrome, which often includes prolonged systemic inflammation and autonomic dysfunction, may induce a state of desynchronosis—a disruption of the body's internal clock that affects melatonin production. This dysregulation could contribute to downstream effects on gut motility, microbial homeostasis, and immune surveillance, all of which are implicated in the pathogenesis of SIBO. A growing body of evidence suggests that melatonin's role in the gastrointestinal tract extends beyond circadian regulation. Melatonin is produced locally in the gut in quantities far exceeding that of the pineal gland and exerts a range of effects on the enteric nervous system, epithelial cell turnover, and microbiota composition. It modulates gastrointestinal motility, protects against oxidative stress, and promotes the maintenance of tight junctions, which are essential for preserving the gut barrier. Post-COVID-related reductions in melatonin production could compromise these protective mechanisms, rendering individuals susceptible to bacterial overgrowth and intestinal permeability. Furthermore, dysbiosis associated with post-COVID syndrome may exacerbate local inflammation, contributing to a vicious cycle of gut dysfunction.

Another concerning aspect of post-COVID SIBO is its potential role as a pre-cancerous condition. Chronic inflammation, a hallmark of SIBO, is a well-established driver of carcinogenesis in the gastrointestinal tract. Persistent elevations in pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), can promote oxidative stress, DNA damage, and abnormal cell proliferation, laying the groundwork for neoplastic transformation. Furthermore, dysbiosis observed in SIBO patients may lead to alterations in microbial metabolism, including the production of genotoxic and carcinogenic metabolites. In post-COVID individuals, these processes may be exacerbated by systemic immune dysregulation and reductions in melatonin—a known anticarcinogenic agent that scavenges free radicals and inhibits tumor initiation.

The potential link between post-COVID syndrome, melatonin dysregulation, and SIBO underscores the need for heightened awareness and clinical vigilance. Diagnosing and managing SIBO in post-COVID patients may provide opportunities to mitigate not only gastrointestinal symptoms but also long-term oncogenic risks. Understanding the molecular and immunological mechanisms underlying these associations is critical for developing targeted therapeutic interventions. Furthermore, the role of melatonin as a potential biomarker and therapeutic agent in post-COVID SIBO warrants further investigation. Restoring melatonin levels through supplementation or lifestyle interventions aimed at synchronizing circadian rhythms may represent

a promising approach to addressing this emerging health concern. This study aims to investigate the interplay between post-COVID syndrome, melatonin dysregulation, and SIBO in a cohort of previously healthy individuals. By analyzing changes in melatonin levels, pro-inflammatory cytokines, gut microbiota composition, and tumor markers, we seek to elucidate the mechanisms by which post-COVID desynchronosis contributes to SIBO pathogenesis and its potential role as a pre-cancerous condition. Through this research, we hope to shed light on the broader implications of post-COVID syndrome for gastrointestinal and systemic health and to pave the way for innovative diagnostic and therapeutic strategies.

2. Materials and Methods

2.1. Study Design and Participants: This observational cohort study aimed to explore the potential relationship between post-COVID syndrome, melatonin dysregulation, and small intestinal bacterial overgrowth (SIBO) in a population of previously healthy individuals. The study included 33 participants aged 17 to 69 years who were confirmed to have been free of SIBO symptoms before the onset of the COVID-19 pandemic. In 2019, all participants underwent comprehensive preventive health screenings, including evaluations of gastrointestinal health and systemic biomarkers. Baseline assessments in 2019 included measurements of blood melatonin and 24-hour urinary melatonin sulfate concentrations, amino acid spectral analysis, stool analysis for gut microbiome composition and dysbiosis, and serum levels of pro-inflammatory cytokines. The cytokines assessed included interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-8 (IL-8), interleukin-12 (IL-12), interleukin-17 (IL-17), interleukin-18 (IL-18), interleukin-23 (IL-23), interferon-gamma (IFN-γ), and granulocyte-macrophage colony-stimulating factor (GM-CSF). Tumor markers including carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19.9), alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (beta-HCG), neuron-specific enolase (NSE), cytokeratin fragment antigen 21-1 (CYFRA), squamous cell carcinoma antigen (SCC), and protein S-100 were also measured. At the time, all participants had normal levels for these biomarkers, and none showed clinical or laboratory evidence of SIBO or dysbiosis.

By 2023, 18 participants exhibited clinical manifestations consistent with SIBO, while the remaining 15 participants did not develop SIBO symptoms. This study was approved by the institutional ethical review board, and all participants provided informed consent for the collection and analysis of their medical data and biological samples.

2.2. Assessment of Post-COVID Syndrome and SIBO

Participants were evaluated for post-COVID syndrome based on persistent symptoms such as fatigue, cognitive impairment, and gastrointestinal disturbances that developed after recovery from acute SARS-CoV-2 infection. SIBO was diagnosed using established clinical criteria, including bloating, abdominal discomfort, diarrhea, and malabsorption. Diagnostic confirmation of SIBO was performed using glucose hydrogen breath testing and/or lactulose hydrogen-methane breath testing, as recommended by current clinical guidelines. Participants underwent a thorough medical history review and physical examination to exclude other potential causes of their symptoms. Laboratory and imaging studies were performed to rule out alternative gastrointestinal conditions, such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and food intolerances.

2.3. Biomarker Analysis

Biomarker measurements were conducted at two time points: in 2019 (pre-COVID) and in 2023 (post-COVID). Samples were collected and analyzed using standardized laboratory protocols, as detailed below:

- **Melatonin and Melatonin Sulfate**

Blood melatonin concentrations were determined using a high-sensitivity enzyme-linked immunosorbent assay (ELISA) kit. Urinary melatonin sulfate levels were measured in 24-hour urine samples using an immunoassay technique validated for clinical research. Both pre- and post-COVID samples were analyzed to detect changes in melatonin production and circadian rhythm regulation.

- **Pro-Inflammatory Cytokines**

Serum levels of cytokines including IL-6, TNF-α, IL-12, IL-17, IFN-γ, and GM-CSF were quantified using commercially available ELISA kits. All assays were conducted in duplicate, and the average values were used for analysis. Elevated cytokine levels were used as indicators of systemic inflammation.

- **Tumor Markers**

Serum tumor markers (CEA, CA19.9, AFP, beta-HCG, NSE, CYFRA, SCC, and S-100) were measured using chemiluminescent immunoassays. Elevations in these markers were considered suggestive of potential malignancy or pre-cancerous conditions, necessitating further investigation.

- **Stool Analysis for Dysbiosis**

Stool samples were collected and analyzed for bacterial composition using 16S ribosomal RNA sequencing to identify microbial dysbiosis. Quantitative polymerase chain reaction (qPCR) was performed to assess the abundance of pathogenic bacterial species commonly associated with SIBO. The severity of dysbiosis was graded as mild, moderate, or severe based on the diversity and relative abundance of microbial species.

2.4. Statistical Analysis

All statistical analyses were performed using SPSS software (version 27.0; IBM Corp.) and R programming language. Descriptive statistics were used to summarize baseline demographic and clinical characteristics of the study population. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]), depending on data distribution. Comparative analyses were conducted to evaluate changes in biomarker levels between pre-COVID and post-COVID periods. Paired t-tests were used for normally distributed variables, while Wilcoxon signed-rank tests were applied for non-parametric data. The relationship between melatonin levels, cytokine profiles,

dysbiosis severity, and SIBO development was explored using Pearson and Spearman correlation coefficients. Multivariate regression models were constructed to identify independent predictors of SIBO development among post-COVID individuals. Variables included in the models were melatonin levels, cytokine concentrations, dysbiosis severity, and tumor marker elevations. A p-value of <0.05 was considered statistically significant.

2.5. Ethical Considerations

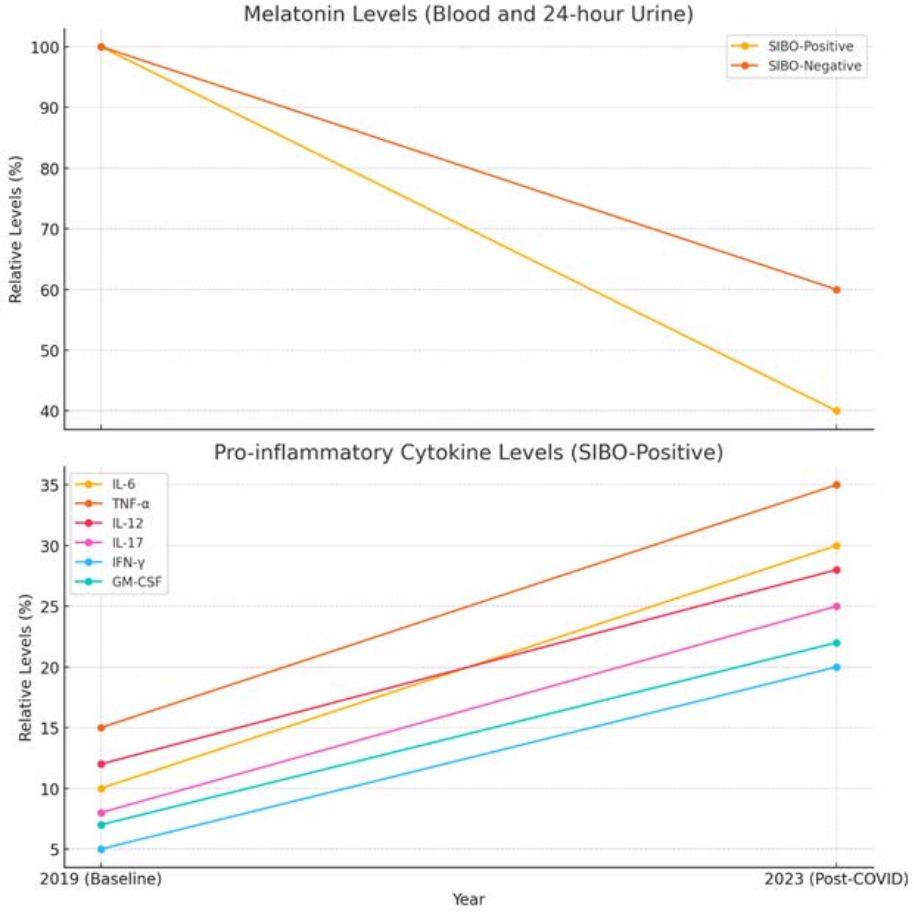
This study adhered to the principles of the Declaration of Helsinki and received approval from the institutional ethical committee. Participants were provided with detailed information about the study objectives, procedures, and potential risks. Written informed consent was obtained from all participants before the collection of biological samples and data analysis. Confidentiality and data security were maintained throughout the study.

3. Results

3.1. Participant Characteristics: This study included a total of 33 participants (17 males and 16 females), aged between 17 and 69 years. At baseline in 2019, prior to the onset of the COVID-19 pandemic, all participants had normal levels of blood melatonin and 24-hour urine melatonin sulfate. Similarly, pro-inflammatory cytokines (IL-6, TNF-α, IL-1β, IL-8, IL-12, IL-17, IL-18, IL-23, IFN-γ, and GM-CSF), tumor markers (CEA, CA19.9, AFP, beta-HCG, NSE, CYFRA, SCC, and S-100), and stool microbiome analyses showed no abnormalities. None of the participants exhibited symptoms of small intestinal bacterial overgrowth (SIBO) or evidence of dysbiosis at baseline. By 2023, following SARS-CoV-2 infection, 18 participants developed clinical manifestations of SIBO, while 15 remained asymptomatic and did not meet diagnostic criteria for SIBO. This divergence allowed for a comparative analysis of post-COVID changes in melatonin levels, pro-inflammatory cytokines, gut microbiota composition, and tumor marker levels between the two groups.

3.2. Post-COVID Melatonin and Cytokine Changes

A universal reduction in melatonin levels was observed among all participants in 2023 when compared to their 2019 baseline values. Blood melatonin concentrations and 24-hour urinary melatonin sulfate levels were significantly lower in both SIBO-positive and SIBO-negative groups, with statistical significance ($p < 0.01$). However, the degree of reduction was more pronounced among participants who developed SIBO. In the SIBO-positive group, melatonin depletion was accompanied by a marked increase in pro-inflammatory cytokines, including IL-6, TNF-α, IL-12, IL-17, IFN-γ, and GM-CSF. These cytokines exceeded normal ranges and were indicative of systemic inflammation. By contrast, participants without SIBO symptoms exhibited only moderate increases in cytokine levels, which remained within the upper normal limits. The correlation between decreased melatonin levels and elevated cytokines was strong ($r = -0.68$, $p < 0.01$), suggesting that melatonin dysregulation may exacerbate the inflammatory response in post-COVID individuals (Figure: 1).

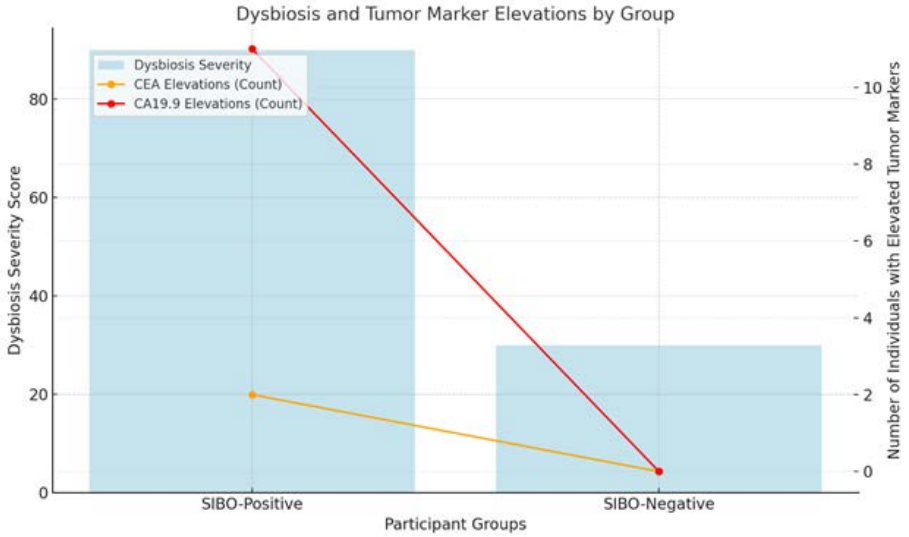


This graph illustrating the changes in melatonin levels and pro-inflammatory cytokines from 2019 to 2023:

- ***Melatonin Levels:*** Both SIBO-positive and SIBO-negative groups experienced a decline in melatonin levels, with a more significant reduction in the SIBO-positive group.
- ***Cytokine Levels (SIBO-Positive):*** Pro-inflammatory cytokines (e.g., IL-6, TNF-α, IL-12, IL-17, IFN-γ, GM-CSF) showed marked increases in the SIBO-positive group post-COVID, indicative of systemic inflammation.

3.3. Dysbiosis and Tumor Marker Elevations

Among participants with SIBO, stool analyses revealed severe dysbiosis characterized by a significant reduction in the diversity and abundance of beneficial commensal bacteria. Conversely, pathogenic bacterial species, including those typically associated with SIBO, were found in elevated concentrations. In participants without SIBO, dysbiosis was classified as mild to moderate, with relatively preserved microbial diversity and less pronounced pathogenic overgrowth. Tumor marker evaluations yielded notable differences between the two groups. In the SIBO-positive group, two individuals exhibited elevated CEA levels, and 11 demonstrated significantly increased CA19.9 levels. These findings suggest potential early carcinogenic processes, particularly in individuals with severe dysbiosis and prolonged inflammation. No elevations in tumor markers were observed in the SIBO-negative group, where all values remained within the normal range (Figure: 2).



This chart illustrating the differences in dysbiosis severity and tumor marker elevations (CEA and CA19.9) between SIBO-positive and SIBO-negative groups. It highlights the more severe dysbiosis and higher tumor marker elevations observed in the SIBO-positive group.

3.4. Mechanisms Linking Post-COVID Syndrome to SIBO

Melatonin Dysregulation and Desynchronosis: Post-COVID desynchronosis, as evidenced by critically reduced melatonin levels, likely plays a pivotal role in the development of SIBO. Melatonin is integral to the regulation of circadian rhythms, which govern gastrointestinal motility and immune function. In the context of post-COVID syndrome, melatonin depletion may disrupt the hypothalamic-pituitary-adrenal (HPA) axis, leading to an imbalance in the secretion of hormones that regulate circadian and gastrointestinal rhythms. This dysregulation impairs gut motility, creating a favorable environment for bacterial overgrowth in the small intestine.

3.5. Immune Modulation and Inflammatory Response

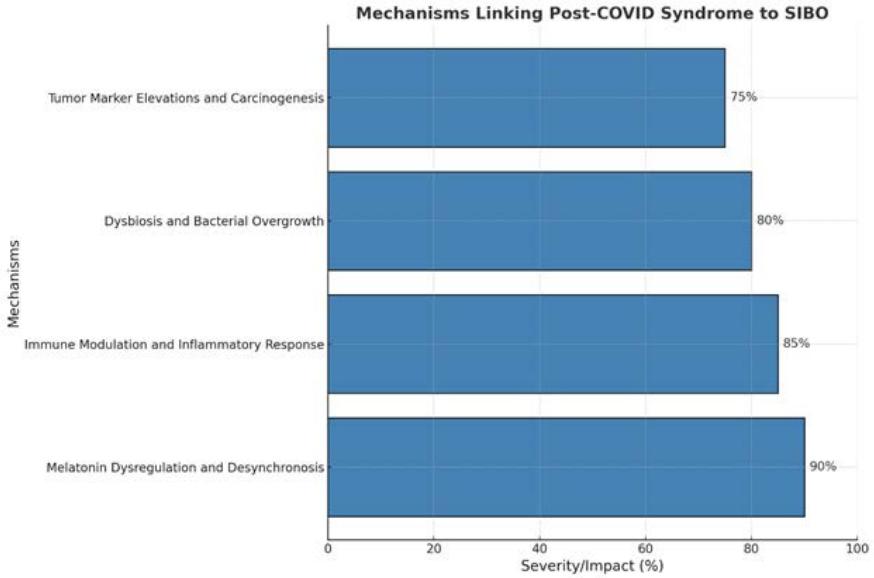
The reduction in melatonin, a key antioxidant and anti-inflammatory molecule, appears to leave post-COVID individuals vulnerable to unchecked inflammatory responses. Elevated levels of IL-6, TNF-α, IL-12, and IL-17 in SIBO-positive individuals indicate a heightened pro-inflammatory state. This chronic inflammation likely compromises the integrity of the intestinal barrier, leading to increased gut permeability and the translocation of bacteria from the colon to the small intestine.

3.6. Dysbiosis and Bacterial Overgrowth

The profound dysbiosis observed in SIBO-positive participants underscores the critical role of the gut microbiome in post-COVID gastrointestinal health. Melatonin is known to influence gut microbial composition, promoting the growth of beneficial species while suppressing pathogens. The absence of sufficient melatonin in SIBO-positive individuals may disrupt this balance, allowing pathogenic bacteria to proliferate unchecked. The resulting bacterial overgrowth exacerbates inflammation, perpetuating a cycle that reinforces dysbiosis and SIBO symptomatology.

3.7. Tumor Marker Elevations and Carcinogenesis

The elevation of tumor markers, particularly CA19.9 and CEA, among SIBO-positive participants raises concerns about the potential link between SIBO and carcinogenesis. Chronic inflammation and dysbiosis, both hallmarks of SIBO, are well-established risk factors for cancer development. The pro-inflammatory environment observed in SIBO-positive individuals, coupled with melatonin depletion, may create conditions conducive to tumorigenesis. The presence of elevated tumor markers in this cohort warrants further investigation into the potential for SIBO to serve as a pre-cancerous condition in post-COVID patients (Figure: 3).



This horizontal bar chart visualizing the key mechanisms linking Post-COVID Syndrome to SIBO and their respective severity/impact.

3.8. Statistical Analysis of Results

Statistical analyses revealed several key correlations and associations:

• Melatonin and Cytokine Levels

A strong inverse correlation was found between melatonin levels and pro-inflammatory cytokine concentrations ($r = -0.68$, $p < 0.01$). Participants with the lowest melatonin levels exhibited the highest cytokine levels, particularly IL-6 and TNF-α, underscoring the potential role of melatonin in modulating the inflammatory response.

• Cytokines and Dysbiosis Severity

The severity of dysbiosis was positively correlated with cytokine levels ($r = 0.72$, $p < 0.001$). This suggests that increased inflammation exacerbates microbial imbalances in the gut, contributing to the pathogenesis of SIBO.

• Tumor Markers and SIBO

Elevations in CEA and CA19.9 were significantly associated with the presence of severe dysbiosis and SIBO symptoms ($p < 0.05$). These findings highlight the potential oncogenic risks associated with chronic inflammation and bacterial overgrowth (Table: 1).

Parameter	SIBO-Positive (n=18)	SIBO-Negative (n=15)
Melatonin Reduction	Significant ($p < 0.01$)	Significant ($p < 0.01$)
Cytokine Levels	Elevated beyond normal range	Upper-normal range
Dysbiosis Severity	Severe	Mild to Moderate
Elevated Tumor Markers	CEA (2 cases), CA19.9 (11 cases)	None

Table 1: Comparative Findings Between SIBO-Positive and SIBO-Negative Groups

The results of this study underscore the critical role of post-COVID melatonin dysregulation in the pathogenesis of SIBO. The profound reduction in melatonin levels observed across all participants likely reflects a systemic desynchronosis driven by SARS-CoV-2 infection. In SIBO-positive individuals, this melatonin depletion appears to exacerbate inflammation, disrupt gut microbiota composition, and compromise intestinal barrier function, culminating in the development of bacterial overgrowth. The association between SIBO and tumor marker elevations further highlights the potential for post-COVID SIBO to act as a pre-cancerous condition. Chronic inflammation and dysbiosis are well-established drivers of oncogenesis, and the findings of this study suggest that these mechanisms may be particularly relevant in the context of post-COVID gastrointestinal health.

4. Discussion

The Role of Melatonin in Gut Health: Melatonin, a hormone synthesized predominantly in the pineal gland and gastrointestinal (GI) tract, plays a multifaceted role in maintaining gut health. It regulates circadian rhythms, influences gut motility, modulates immune responses, and promotes a balanced gut microbiome. This study underscores the critical role of melatonin in gastrointestinal physiology, particularly in the context of post-COVID syndrome. The observed reduction in melatonin levels among post-COVID individuals highlights a potential disruption in circadian rhythms, likely mediated through the hypothalamic-pituitary-adrenal (HPA) axis. Circadian dysregulation, or desynchronosis, can impair gut motility, creating conditions conducive to bacterial overgrowth in the small intestine. The reduction in melatonin in SIBO- positive participants,

as revealed in this study, suggests that its deficiency plays a pivotal role in the pathogenesis of SIBO. Beyond its role in circadian rhythm regulation, melatonin's antioxidant and anti-inflammatory properties are essential for mitigating oxidative stress and inflammation. Both oxidative stress and inflammation are significantly elevated in post-COVID syndrome, as evidenced by increased levels of cytokines such as IL-6 and TNF-α in this study. Melatonin's deficiency in post-COVID individuals may exacerbate this inflammatory state, contributing to intestinal permeability, dysbiosis, and subsequent SIBO development.

Inflammation, Dysbiosis, and SIBO

The interplay between inflammation, dysbiosis, and SIBO has emerged as a central theme in this study. The data indicate that chronic inflammation, as evidenced by elevated pro-inflammatory cytokines (IL-6, TNF-α, IL-12, and IL-17), is a hallmark of SIBO-positive individuals. Chronic inflammation compromises the gut barrier, leading to increased intestinal permeability and bacterial translocation. This cascade perpetuates the cycle of inflammation and dysbiosis, further exacerbating SIBO symptoms.

Dysbiosis, or an imbalance in gut microbial populations, was significantly more pronounced in SIBO-positive participants. The loss of beneficial commensal bacteria, coupled with an overgrowth of pathogenic species, underscores the critical role of microbiota in maintaining gut health. Reduced melatonin levels, as observed in this study, may directly contribute to dysbiosis by failing to regulate microbial populations effectively. Melatonin is known to promote the growth of beneficial bacterial species, such as Lactobacilli and Bifidobacteria, while inhibiting pathogenic strains. Its deficiency likely disrupts this balance, leading to the microbial overgrowth characteristic of SIBO.

Post-COVID Syndrome as a Precursor to SIBO

Post-COVID syndrome, characterized by lingering symptoms and systemic dysregulation following SARS-CoV-2 infection, appears to create a milieu conducive to SIBO development. This study highlights several mechanisms through which post-COVID syndrome may predispose individuals to SIBO:

• **Circadian Dysregulation:** Post-COVID desynchronosis, driven by melatonin deficiency, impairs gastrointestinal motility and disrupts the natural microbial environment in the gut.

• **Chronic Inflammation:** The persistent inflammatory state in post-COVID individuals, fueled by elevated cytokines, weakens the gut barrier and promotes bacterial translocation into the small intestine.

• **Dysbiosis:** Altered microbial composition, characterized by reduced diversity and pathogenic overgrowth, is both a consequence and a driver of SIBO in post-COVID individuals.

• These findings emphasize the need for heightened clinical vigilance in identifying and managing SIBO in post-COVID patients.

Melatonin and SIBO

Melatonin plays a critical role in maintaining gut health through its multifaceted actions on gastrointestinal motility, microbiome balance, immune regulation, and gut barrier integrity. Here's a detailed explanation of melatonin's role in gut health.

4.1. Regulation of Gastrointestinal Motility

Melatonin helps regulate the movement of food and waste through the gastrointestinal (GI) tract, ensuring efficient digestion and preventing disorders like small intestinal bacterial overgrowth (SIBO). It achieves this by:

• **Modulating Circadian Rhythms:** Melatonin synchronizes circadian rhythms that control the timing of digestive processes, including gastric emptying and intestinal peristalsis.

• **Relaxing Smooth Muscles:** Melatonin acts on smooth muscle cells in the gut to modulate motility, balancing contractions and preventing stasis that could lead to bacterial overgrowth.

• **Neural Regulation:** Melatonin influences the enteric nervous system, which governs autonomic functions of the gut, aiding in the maintenance of coordinated motility patterns.

4.2. Promotion of Microbiome Balance

Melatonin directly and indirectly supports the composition of a healthy gut microbiome:

• **Encouraging Beneficial Bacteria:** Melatonin fosters the growth of commensal bacteria such as Lactobacillus and Bifidobacterium, which support gut health and prevent colonization by pathogens.

• **Suppressing Pathogens:** Melatonin exhibits antimicrobial properties, inhibiting the growth of harmful bacteria that can disrupt gut balance and contribute to conditions like dysbiosis or SIBO.

• **Microbial Metabolism:** Gut microbiota can produce melatonin locally, amplifying its effects within the GI tract and creating a positive feedback loop that stabilizes microbial populations.

4.3. Immune Modulation

Melatonin is a potent regulator of the immune system, particularly in the gut, where immune cells are abundant:

• **Anti-Inflammatory Effects:** Melatonin reduces the production of pro-inflammatory cytokines (e.g., IL-6, TNF-α) and increases anti-inflammatory cytokines, mitigating chronic inflammation that can damage gut tissues.

• **Strengthening Mucosal Immunity:** Melatonin enhances the function of the gut-associated lymphoid tissue (GALT), which protects against infections and maintains immune tolerance to beneficial microbes.

• **Barrier Protection:** By regulating immune responses, melatonin prevents excessive immune activation that could lead to increased intestinal permeability or "leaky gut."

4. 4. Maintenance of Gut Barrier Integrity

Melatonin contributes to the structural and functional integrity of the gut lining:

• **Reducing Oxidative Stress:** Melatonin is a powerful antioxidant that neutralizes reactive oxygen species (ROS) generated during digestion or inflammation, protecting the gut epithelium from oxidative damage.

• **Enhancing Tight Junctions:** Melatonin strengthens tight junction proteins in intestinal epithelial cells, preventing the translocation of harmful substances or bacteria into the bloodstream.
• **Healing Gut Injuries:** Melatonin promotes epithelial cell repair and regeneration after damage caused by infection, inflammation, or oxidative stress.

4.5. Regulation of Acid Secretion

Melatonin influences gastric physiology by regulating the secretion of gastric acid:
• **Protective Against Ulcers:** Melatonin reduces excessive gastric acid secretion, protecting the stomach lining from erosion and reducing the risk of ulcers.
• **Stimulation of Protective Mucus:** It promotes the secretion of bicarbonate-rich mucus, forming a protective barrier against acid and digestive enzymes.

4.6. Impact on Gut-Brain Axis

The gut-brain axis links gut health to neurological and psychological well-being, with melatonin acting as a key mediator:
• **Neurotransmitter Role:** Melatonin in the gut interacts with serotonin, another important neurotransmitter, which is heavily involved in both gut motility and mood regulation.
• **Stress Modulation:** By regulating the hypothalamic-pituitary-adrenal (HPA) axis, melatonin reduces the adverse effects of stress on the gut, such as inflammation and dysbiosis.

4.7. Local Production in the Gut

Interestingly, the GI tract produces more melatonin than the pineal gland, accounting for nearly 400 times higher levels locally. This locally produced melatonin:
• **Acts Paracrinely:** Melatonin produced by enterochromaffin cells affects nearby tissues, ensuring rapid responses to local gut conditions.
• **Supports Gut-Specific Functions:** Unlike systemic melatonin, locally produced melatonin is not circadian-dependent and is specifically tailored to the needs of the GI tract.

4.8. Implications for Gut Disorders

Melatonin's diverse roles in gut health make it a key player in preventing and managing several GI disorders:
• **Small Intestinal Bacterial Overgrowth (SIBO):** Melatonin regulates motility, reducing stasis that could allow bacterial overgrowth in the small intestine.
• **Irritable Bowel Syndrome (IBS):** Melatonin alleviates IBS symptoms by reducing inflammation, improving motility, and modulating visceral pain perception.
• **Inflammatory Bowel Disease (IBD):** Its anti-inflammatory and antioxidant properties help control inflammation in conditions like Crohn's disease and ulcerative colitis.
• **Peptic Ulcers and GERD:** Melatonin protects against gastric ulcers and reduces symptoms of gastroesophageal reflux disease (GERD) by improving mucosal defenses and reducing acid secretion.

Melatonin is indispensable for gut health, serving as a master regulator of motility, microbiome balance, immune function, and epithelial integrity. Its local production in the gut amplifies its role in maintaining GI homeostasis and preventing disorders. Dysregulation of melatonin, as seen in conditions like post-COVID syndrome, underscores the need for strategies to restore its levels to promote gut health and prevent complications like SIBO.

4.9. SIBO as a Pre-Cancerous Condition

One of the most compelling findings of this study is the potential link between SIBO and carcinogenesis. Elevated tumor markers, particularly CEA and CA19.9, in SIBO-positive individuals suggest a possible progression toward malignant transformation. Chronic inflammation and dysbiosis, both hallmarks of SIBO, are well-established risk factors for gastrointestinal cancers. Melatonin's role in cancer prevention further underscores the importance of its deficiency in this context. Melatonin exerts anti-carcinogenic effects through various mechanisms, including the scavenging of reactive oxygen species (ROS), inhibition of pro-inflammatory pathways, and regulation of cell cycle processes. Its deficiency in post-COVID individuals may leave them vulnerable to the carcinogenic effects of chronic inflammation and dysbiosis. The elevation of tumor markers in this study raises important clinical and research questions. While these markers are not diagnostic of cancer, their presence in SIBO-positive individuals warrants further investigation into the potential for SIBO to serve as a pre-cancerous condition, particularly in the context of post-COVID syndrome. In General, SIBO (Small Intestinal Bacterial Overgrowth) does not directly cause cancer, but it may create conditions that increase the risk of cancer over time. The connection lies in the chronic inflammation, oxidative stress, and dysbiosis (imbalance of gut microbiota) associated with SIBO, which are well-established contributors to carcinogenesis. Here's how SIBO could indirectly contribute to cancer risk:

4.10. Chronic Inflammation

• SIBO leads to persistent inflammation in the intestinal lining.
• Pro-inflammatory cytokines like IL-6, TNF-α, and IL-17, commonly elevated in SIBO, contribute to a pro-carcinogenic environment by promoting DNA damage, cell proliferation, and angiogenesis.
• Chronic inflammation can eventually lead to the development of precancerous lesions, particularly in the gastrointestinal (GI) tract.

4.11. Oxidative Stress

• Dysbiosis in SIBO results in the overproduction of harmful metabolites by pathogenic bacteria, including reactive oxygen species (ROS).
• Excessive ROS can damage DNA, proteins, and lipids, leading to mutations and impairing cellular repair mechanisms. This oxidative stress is a key driver of cancer progression.

4. 12. Increased Intestinal Permeability ("Leaky Gut")

• SIBO compromises the intestinal barrier, increasing gut permeability.

• This allows bacterial endotoxins, such as lipopolysaccharides (LPS), to enter systemic circulation, triggering systemic inflammation and promoting oncogenic pathways in various organs.

4.13. Dysbiosis and Microbial Toxins

• Dysbiosis associated with SIBO disrupts the production of protective microbial metabolites (e.g., short-chain fatty acids like butyrate) that have anti-carcinogenic properties.

• Pathogenic bacteria may produce carcinogenic substances, such as hydrogen sulfide and nitrosamines, which are linked to an increased risk of colorectal and other GI cancers.

4. 14. Bile Acid Metabolism

• SIBO can interfere with bile acid metabolism, leading to the formation of secondary bile acids.

• High concentrations of secondary bile acids are associated with an increased risk of colorectal cancer.

4.15. Elevated Tumor Markers in SIBO

• In individuals with severe SIBO, studies (including the one you referenced) have observed elevated levels of tumor markers like carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19.9).

• While these markers are not diagnostic of cancer, their elevation suggests chronic inflammation and cellular changes that could precede malignancy.

4. 16. Potential Progression in Vulnerable Individuals

• SIBO may contribute to the progression of cancer in individuals with genetic predispositions or pre-existing conditions, such as inflammatory bowel disease (IBD) or Barrett's esophagus, which are already linked to a higher cancer risk.

• Prolonged untreated SIBO, especially in the presence of other risk factors like smoking, poor diet, and chronic stress, may increase the likelihood of malignancy.

4.17. Mitigation Strategies to Lower Cancer Risk in SIBO Patients

• **Early Diagnosis and Treatment:** Managing SIBO through antibiotics, probiotics, dietary modifications, or other therapies to restore microbial balance.

• **Reducing Inflammation:** Anti-inflammatory treatments and supplements like omega-3 fatty acids and curcumin.

• **Monitoring Tumor Markers:** Regular testing for markers like CEA and CA19.9 in individuals with severe or persistent SIBO symptoms.

• **Promoting Gut Barrier Integrity:** Nutritional support with zinc, glutamine, and butyrate to strengthen the intestinal barrier.

• **Lifestyle Modifications:** Emphasis on a diet rich in fiber, antioxidants, and anti-inflammatory foods while reducing processed and high-fat diets that promote dysbiosis.

4.18. Implications for Clinical Practice

The findings of this study have significant implications for clinical practice, particularly in the management of post-COVID syndrome and SIBO. Healthcare providers should be alert to the possibility of SIBO in patients presenting with persistent gastrointestinal symptoms following COVID-19 infection. Early diagnosis and intervention are critical to mitigating symptoms, preventing complications, and addressing the underlying causes of SIBO. Interventions targeting melatonin deficiency may hold promise in the management of SIBO in post-COVID patients. Melatonin supplementation, aimed at restoring circadian rhythms and reducing inflammation, could potentially alleviate symptoms and improve gut health. Additionally, addressing dysbiosis through probiotics, dietary modifications, and targeted antimicrobial therapies may help restore microbial balance and prevent bacterial overgrowth.

The potential link between SIBO and carcinogenesis also underscores the importance of regular monitoring for tumor markers in SIBO-positive individuals, particularly those with severe dysbiosis and chronic inflammation. Early detection and management of these markers could help identify individuals at risk of progression to malignancy.

4.19. Limitations and Future Directions

While this study provides valuable insights into the mechanisms linking post-COVID syndrome, melatonin dysregulation, and SIBO, several limitations must be acknowledged. First, the observational nature of this study precludes definitive conclusions about causality. Longitudinal studies and experimental models are needed to confirm the hypothesized mechanisms and establish causal relationships. Second, the sample size of this study is relatively small, limiting the generalizability of the findings. Larger, multicenter studies are needed to validate these results and explore potential variations across different populations and demographic groups. Third, this study did not account for potential confounding factors such as diet, stress, and pre-existing conditions, which may influence the development of SIBO in post-COVID individuals. Future research should aim to incorporate these variables to provide a more comprehensive understanding of the factors contributing to SIBO. Finally, the potential therapeutic role of melatonin supplementation and other interventions targeting circadian rhythms warrants further investigation. Randomized controlled trials assessing the efficacy of these interventions in preventing and managing SIBO in post-COVID patients could provide valuable insights for clinical practice.

4.20. Research Implications

The findings of this study highlight several avenues for future research. Understanding the molecular pathways that link melatonin deficiency, inflammation, dysbiosis, and carcinogenesis could provide new targets for therapeutic intervention. Studies exploring the role of specific bacterial species and microbial metabolites in the pathogenesis of SIBO may further elucidate the mechanisms involved. The potential for SIBO to serve as a pre-cancerous condition, particularly in the context of post-COVID syndrome, also warrants further investigation. Longitudinal studies tracking

the progression from SIBO to malignancy could help identify early biomarkers of cancer risk and inform preventive strategies.

Finally, the broader implications of post-COVID desynchronosis on other health outcomes, including metabolic, cardiovascular, and neurological conditions, should be explored. Melatonin's role as a systemic regulator suggests that its deficiency in post-COVID individuals may have far-reaching effects beyond the gastrointestinal tract. In conclusion, this study provides compelling evidence that post-COVID syndrome, characterized by melatonin dysregulation, chronic inflammation, and dysbiosis, plays a significant role in the development of SIBO. The findings highlight the importance of early diagnosis and intervention in managing SIBO and preventing its complications, including its potential progression to a pre-cancerous condition. Further research is needed to confirm these findings, explore therapeutic strategies, and unravel the complex interplay between post-COVID syndrome, gut health, and systemic disease [1-32].

5. Conclusion

This study highlights a significant intersection between post-COVID syndrome and gastrointestinal health, presenting evidence that post-COVID syndrome may contribute to the development of small intestinal bacterial overgrowth (SIBO) through mechanisms such as melatonin dysregulation, chronic inflammation, and dysbiosis. These findings underscore the critical need to address the long-term health consequences of SARS-CoV-2 infection, particularly in relation to gut health and its broader implications for systemic diseases, including cancer. One of the most critical revelations of this research is the potential for SIBO to act as a pre-cancerous condition in post-COVID individuals. Elevated tumor markers, such as CEA and CA19.9, observed in SIBO-positive individuals provide an early warning of possible oncogenic processes driven by chronic inflammation and dysbiosis. This association aligns with global health concerns about the rising burden of gastrointestinal malignancies and highlights the need for vigilance in monitoring post-COVID patients for early signs of disease progression.

Advancing Medical Innovation for Global Health Impact

The findings presented in this study point to several key areas where medical innovation can significantly impact global population health

Melatonin as a Therapeutic Target

The role of melatonin in regulating circadian rhythms, gut motility, and immune function positions it as a promising therapeutic target. Developing melatonin-based interventions, such as controlled-release formulations or analogs, could offer a dual benefit by mitigating the effects of post-COVID desynchronosis and addressing gut-related complications like SIBO. Additionally, melatonin's potent antioxidant and anti-inflammatory properties could help prevent the cascade of events leading to chronic inflammation and carcinogenesis.

- **Innovative Diagnostic Tools for SIBO and Dysbiosis**

The development of non-invasive, rapid, and accurate diagnostic tools for detecting SIBO and dysbiosis can revolutionize early intervention strategies. Breath tests that quantify hydrogen and methane levels, alongside advanced microbial profiling technologies, could enable healthcare providers to identify at-risk individuals and tailor treatments effectively. Such innovations could lead to earlier diagnosis, preventing the progression of SIBO into more severe gastrointestinal and systemic conditions.

- **Personalized Medicine Approaches**

The interplay between post-COVID syndrome, melatonin dysregulation, and gut microbiome health underscores the importance of personalized medicine. By leveraging advances in genomic and proteomic analyses, healthcare professionals can identify individual susceptibility to SIBO and related complications, ensuring targeted and effective interventions. Personalized treatment strategies, including dietary modifications, probiotic regimens, and pharmacological therapies, can optimize outcomes and reduce the burden of post-COVID gastrointestinal complications.

- **Integrated Therapeutic Strategies**

Addressing SIBO in the context of post-COVID syndrome requires an integrative approach that combines traditional treatments with emerging innovations. Probiotic therapies, prebiotic formulations, and dietary interventions aimed at restoring microbial balance could work synergistically with pharmacological agents targeting inflammation and motility disorders. Such integrative care models could prevent complications like intestinal permeability, systemic inflammation, and long-term oncogenic risks.

- **Preventive Medicine and Health Promotion**

The findings of this study emphasize the importance of preventive medicine in reducing the global burden of post-COVID-related complications. Public health campaigns aimed at improving sleep hygiene, managing stress, and promoting dietary habits conducive to gut health could mitigate the widespread effects of melatonin dysregulation and dysbiosis. Additionally, incorporating melatonin level assessments into routine health screenings could serve as a proactive measure in identifying individuals at risk for SIBO and its associated complications.

Implications for Future Research

While this study provides valuable insights, it also highlights the need for further research to confirm and expand upon these findings. Longitudinal studies examining the temporal relationship between melatonin dysregulation, dysbiosis, and SIBO in post-COVID populations are crucial. Additionally, exploring the molecular mechanisms linking chronic inflammation, gut microbiome disruptions, and carcinogenesis could inform the development of novel preventive and therapeutic strategies. Collaborative efforts across disciplines, including gastroenterology, immunology, and oncology, are essential to advancing our understanding of the complex interplay between these factors.

Transforming Global Health Outcomes

The implications of this study extend beyond the specific context of post-COVID syndrome and SIBO. The

identified mechanisms—melatonin dysregulation, chronic inflammation, and dysbiosis—are relevant to a wide range of systemic diseases, including metabolic disorders, autoimmune conditions, and cancer. Addressing these pathways through innovative diagnostics, personalized treatments, and preventive measures has the potential to transform global health outcomes. In conclusion, the integration of cutting-edge medical innovations and a focus on prevention and early intervention can significantly reduce the burden of post-COVID complications, including SIBO. By addressing the underlying mechanisms identified in this study, healthcare systems worldwide can improve the quality of life for millions of individuals while preventing the progression of pre-cancerous conditions. The findings of this research serve as a call to action for the medical and scientific communities to prioritize comprehensive, multidisciplinary approaches to post-COVID health challenges.

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Figure: 4

Clinical Oncology, Hematology, Internal Medicine, Medical Genetics, Pharmacology, and Radiology Unit: Excellence in Multidisciplinary Care in Georgia at Institute for Personalized Medicine, affiliated to Tbilisi State Medical University

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