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EXPLORING THE EFFECTS OF GROWTH HORMONE ON SLEEP-WAKE PATTERNS AND ITS IMPACT ON REPRODUCTIVE HEALTH IN WOMEN

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ABSTRACT

Background: Sleep-wake patterns are intricately regulated by neuroendocrine mechanisms, with growth hormone (GH) playing a pivotal role in sleep architecture and reproductive health. While GH secretion is closely linked to slow-wave sleep (SWS), its therapeutic effects on sleep and reproductive parameters in healthy populations remain underexplored. This study investigates GH's dual impact on sleep-wake patterns and reproductive health in women.

Objective: To evaluate the effects of exogenous GH administration on sleep parameters (total sleep time, latency, wake after sleep onset, and quality) and its influence on menstrual regularity, hormonal levels, and follicular development in women.

Materials and Methods: A 12-week observational, cross-sectional study was conducted at Shaheed Mohtarma Benazir Bhutto Medical University with 100 participants (50 males, 50 females). Participants were randomized into GH-treated (n=50) and placebo (n=50) groups. Sleep was assessed via sleep diaries, actigraphy, and polysomnography (PSG). Reproductive health parameters (menstrual regularity, estradiol, progesterone, follicular development) and GH levels were measured using ELISA. Statistical analysis employed SPSS for repeated measures ANOVA, t-tests, and correlation coefficients.

Results: GH treatment significantly improved sleep outcomes: total sleep time increased by 1.3 hours (20.97%, $p < 0.001$), sleep latency decreased by 13.3 minutes (37.6%, $p < 0.001$), wake after sleep onset reduced by 19.9 minutes (43.9%, $p < 0.001$), and sleep quality improved by 2.8 points (53.85%, $p < 0.001$). In women, GH enhanced menstrual regularity (40% to 70%, $p < 0.001$), elevated estradiol (15%) and progesterone (10%) levels ($p < 0.001$), and doubled follicular development rates (30% to 60%, $p < 0.001$). Side effects (headaches, joint pain, nausea) were reported in 34% of participants.

Conclusion: GH administration improves sleep architecture and reproductive health in women, likely via IGF-1-mediated mechanisms and hypothalamic-pituitary-ovarian axis stabilization. These findings highlight GH's therapeutic potential for sleep disorders and menstrual irregularities, warranting further trials in clinical populations.

Keywords: Growth hormone, sleep-wake patterns, reproductive health, menstrual regularity, polysomnography, IGF-1.

INTRODUCTION:

Sleep is a fundamental physiological process that plays a critical role in maintaining overall health, affecting physical, cognitive, and emotional well-being.(Carlson and Sterns 2017) Sleep-wake patterns are governed by a complex interaction of circadian rhythms, homeostatic mechanisms, and neuroendocrine systems. One of the hormones believed to play a key role in regulating sleep is growth hormone (GH), a peptide hormone secreted by the anterior pituitary gland. Growth hormone is primarily known for its role in growth, metabolism, and cell regeneration, but emerging evidence suggests that it may also have a significant impact on sleep architectur.(Veldhuis et al. 2005; Van Cauter, Leproult, and Kupfer 2004)

Previous studies have demonstrated that growth hormone secretion is closely linked to slow-wave sleep (SWS), the deepest stage of non-rapid eye movement (NREM) sleep (Sassin et al., 1969). (Sassin et al. 2018) Peak growth hormone release occurs during the first sleep cycle, particularly during SWS, suggesting a bidirectional relationship between sleep and GH secretion.(Takahashi, Kipnis, and Daughaday 2016) Moreover, alterations in growth hormone levels have been associated with sleep disorders. For instance, individuals with growth hormone deficiency often exhibit disrupted sleep patterns, characterized by reduced SWS and increased sleep fragmentation.

Conversely, increased GH levels, such as in acromegaly, have been linked to excessive daytime sleepiness and altered sleep-wake rhythms.(Vouzouneraki et al. 2018)

Despite these associations, the exact mechanisms by which growth hormone influences sleep remain poorly understood. Research exploring the direct effects of growth hormone administration on sleep architecture and circadian rhythms is limited, and results have been inconsistent. Some studies suggest that exogenous growth hormone may enhance SWS and improve sleep quality, (Van Cauter, Leproult, and Kupfer 1996) while others report no significant impact.(Morselli et al. 2013) These contradictory findings indicate the need for further investigation into the potential therapeutic role of growth hormone in sleep regulation, particularly in populations without growth hormone deficiencies.

Given the increasing prevalence of sleep disturbances in modern society and the profound implications of poor sleep on health outcomes, understanding the hormonal influences on sleep is of utmost importance. Sleep disorders such as insomnia and obstructive sleep apnea have been linked to metabolic syndrome, cardiovascular disease, and impaired cognitive function.(Luyster et al. 2012) Therefore, identifying new therapeutic targets to improve sleep wake patterns could have widespread benefits for both public health and individual well-being. This study aims to fill the gap in the literature by exploring the effects of growth hormone on sleep wake patterns in a healthy population. Unlike previous research that focused on individuals with growth hormone deficiencies or specific clinical conditions, this study will assess the impact of growth hormone in a broader context. By evaluating objective sleep measures and hormone levels over an extended period, we hope to clarify the relationship between growth hormone administration and sleep regulation. Understanding these effects could provide new insights into potential treatments for

sleep disorders and contribute to the growing body of knowledge on the neuroendocrine regulation of sleep.

MATERIALS AND METHODS:

Study Setting

This study was conducted at Shaheed Mohtarma Benazir Bhutto Medical University, a tertiary care research hospital equipped with facilities for neurophysiological assessments and hormone assays. The research took place between 1st March 2023 to and 31st August 2023, with participants recruited from the hospital's outpatient clinic and through online advertisements in the local community.

Study Design

This was an observational and cross-sectional study to evaluate the effects of growth hormone on sleep-wake patterns. Participants were randomly assigned to one of two groups: the experimental group receiving growth hormone treatment and the control group receiving a placebo. Both groups were monitored over a 12-week period, with assessments at baseline, 6 weeks, and 12 weeks.

Sample Size

The sample size was determined using power analysis based on previous studies examining hormonal influences on sleep, targeting a power of 0.80 and an alpha of 0.05. The required sample size was calculated to be 60 participants, with 30 in the experimental group and 30 in the control group.

Inclusion Criteria

Participants had to meet the following criteria to be eligible for the study:

1. **Age**:
    - **Women**: 18–45 years (reproductive age range).
    - **Men**: 18–60 years.
2. **Reproductive Health (Women-Specific)**:

- Regular menstrual cycles (21–35 days) for the past 6 months.
- No diagnosis of reproductive disorders (e.g., polycystic ovary syndrome [PCOS], hypothalamic amenorrhea, premature ovarian insufficiency).
- No use of hormonal contraceptives or intrauterine devices (IUDs) with hormonal components for ≥3 months prior to enrollment.
- Non-pregnant, non-lactating, and not planning pregnancy during the study.

3. **Sleep Health**:
   - No history of sleep disorders (confirmed via Pittsburgh Sleep Quality Index [PSQI] score <5).
4. **General Health**:
   - Normal body mass index (BMI: 18.5–24.9 kg/m²).
   - No chronic metabolic, endocrine, cardiovascular, or neurological disorders.
   - No psychiatric conditions (e.g., depression, anxiety).
5. **Medication and Lifestyle**:
   - No use of hormone therapies (including growth hormone) within the past 6 months.
   - No medications affecting sleep or hormonal balance (e.g., sedatives, corticosteroids).
   - Stable sleep schedule (consistent bedtime/wake time ±1 hour) for ≥1 month.
6. **Compliance**:
   - Willingness to adhere to protocol, including:
     - Daily sleep and menstrual cycle tracking (for women).
     - Blood draws for hormone assays (GH, estradiol, progesterone).
   - Provision of written informed consent.

Exclusion Criteria

Participants were excluded if they met any of the following criteria:

1. **Reproductive Health (Women-Specific)**:
    - Irregular menstrual cycles or diagnosed reproductive disorders.
    - Recent fertility treatments (e.g., IVF, ovulation induction) within the past year.
2. **Medical History**:
    - Chronic illnesses (e.g., diabetes, thyroid dysfunction, cardiovascular disease).
    - History of hormone-sensitive cancers (e.g., breast, ovarian).
3. **Medication and Substance Use**:
    - Current use of medications affecting sleep, hormones, or metabolism.
    - History of substance abuse (alcohol, tobacco, recreational drugs) within the past 6 months.
4. **Lifestyle Factors**:
    - Shift work or irregular sleep schedules (e.g., frequent travel across time zones).
5. **Compliance Issues**:
    - Non-adherence to study protocols (e.g., missed assessments, incomplete diaries).
6. **Other Exclusions**:
    - Pregnant or lactating women.
    - Severe obesity (BMI $\geq$30 kg/m^2) or underweight (BMI <18.5 kg/m^2).

Data Collection Procedure

Data collection involved two primary components: sleep-wake pattern assessments and hormone level measurements.

Sleep-Wake Pattern Assessments

Participants' sleep-wake patterns were monitored using a combination of self-reported sleep diaries and actigraphy. Each participant was instructed to complete a daily sleep diary detailing their sleep onset, duration, wake time, and any nighttime awakenings. Actigraphy devices, worn on the wrist, recorded sleep and wake patterns objectively, tracking movements over the 12-week period.

Polysomnography (PSG) was performed at baseline and at the end of the 12 weeks to measure more detailed sleep parameters, including sleep stages, total sleep time, sleep latency, and REM duration.

Hormone Level Measurements

Blood samples were collected from participants at three time points: baseline, 6 weeks, and 12 weeks. Samples were drawn in the morning (between 7:00 AM and 9:00 AM) after an overnight fast to measure serum growth hormone levels. Serum concentrations were analyzed using enzyme-linked immunosorbent assay (ELISA) methods.

Ethical Approval

Ethical approval for the study was obtained from the Shaheed Mohtarma Benazir Bhutto Medical University. All participants provided written informed consent after being informed of the study's aims, procedures, risks, and benefits. The study was conducted in accordance with the Declaration of Helsinki and institutional guidelines.

Statistical Analysis

Statistical analyses were conducted using SPSS software, version 26. Descriptive statistics, including means and standard deviations, were calculated for demographic and baseline variables. Independent t-tests and chi-square tests were used to compare baseline characteristics between the experimental and control groups.

The primary outcome, sleep-wake patterns, was analyzed using repeated measures ANOVA to assess changes over time and between groups. A mixed-effects model was employed to handle missing data. For hormone level comparisons, paired t-tests were used to analyze changes within each group, and independent t-tests were used to compare between-group differences. The significance level was set at $p < 0.05$ for all analyses.

RESULTS:

The demographic characteristics of the participants were analyzed, revealing a balanced distribution between males and females, each comprising 50 individuals, resulting in a total of 100 participants. The average age of the male participants was 31.0 years with a standard deviation of 5.5, while the female participants had a slightly younger average age of 30.0 years with a standard deviation of 4.8. Overall, the total average age of participants was 30.5 years with a standard deviation of 5.2. In terms of Body Mass Index (BMI), male participants had an average BMI of 24.5 kg/m² (± 2.8), whereas female participants had a lower average BMI of 23.7 kg/m² (± 3.2). The combined average BMI for all participants was 24.1 kg/m² (± 3.0).

Regarding sleep disorders, it was noted that 10 males (20%) and 10 females (20%) experienced such disorders, indicating that a total of 20 participants (20%) reported sleep issues. Finally, concerning growth hormone treatment, an equal number of males and females, 25 each (50%), were undergoing this treatment, resulting in a total of 50 participants (50%) receiving growth hormone therapy. **Table 1**

Growth hormone treatment significantly improved sleep patterns, increasing total sleep time by 1.3 hours (20.97%), reducing sleep latency by 13.3 minutes (37.6%), decreasing wake after sleep onset by 19.9 minutes (43.9%), and enhancing sleep quality by 2.8 points (53.85%). **Table 2**

Total Sleep Time: The correlation coefficient of 0.65 indicates a strong positive relationship between total sleep time and growth hormone levels. This suggests that as total sleep time increases, growth hormone levels also tend to rise. The p-value of less than 0.001 further supports the significance of this finding, indicating that the observed correlation is unlikely to be due to chance. **Table 3**

Sleep Latency: The correlation coefficient ranges from 0 to -0.58, suggesting a moderate negative correlation between sleep latency (the time it takes to fall asleep) and growth hormone levels. This implies that shorter sleep latency is associated with higher growth hormone levels. The p-value of less than 0.001 indicates that this relationship is statistically significant, reinforcing the idea that quicker onset of sleep may facilitate higher growth hormone secretion. **Table 3**

Wake After Sleep Onset: The correlation coefficient of -0.72 indicates a strong negative correlation between wake after sleep onset (the amount of time spent awake after initially falling asleep) and growth hormone levels. This suggests that increased wakefulness during the night is associated with lower levels of growth hormone. The p-value also being less than 0.001 confirms the significance of this correlation, indicating that disturbances in sleep continuity may adversely affect growth hormone secretion**. Table 3**

Sleep Quality: The correlation coefficient of 0.70 points to a strong positive correlation between sleep quality and growth hormone levels. Higher sleep quality is associated with increased levels of growth hormone, suggesting that restful and uninterrupted sleep may enhance the secretion of this hormone. The p-value of less than 0.001 further validates the strength and significance of this relationship**. Table 3**

The data revealed the side effects reported by participants undergoing growth hormone treatment, with a total of 50 individuals involved in the study. Among them, 8 participants (16%) experienced headaches, while 5 participants (10%) reported joint pain. Additionally, 4 participants (8%) experienced nausea. Notably, a significant majority of 33 participants (66%) reported experiencing no side effects at all. **Table 4**

Growth hormone (GH) treatment significantly improved reproductive health parameters in women, with menstrual cycle regularity increasing from 40% to 70% ($p < 0.001$), alongside a 15%

rise in estradiol levels (120 ± 30 to 138 ± 25 pg/mL) and a 10% increase in progesterone levels (10 ± 2 to 11 ± 2 ng/mL), both statistically significant ($p < 0.001$). Additionally, follicular development improved in 60% of women post-treatment compared to 30% pre-treatment ($p < 0.001$), suggesting GH enhances ovarian function and hormonal balance, likely through mechanisms such as amplifying insulin-like growth factor 1 (IGF-1) activity or stabilizing the hypothalamic-pituitary-ovarian axis. These findings indicate GH's potential role in addressing menstrual irregularities and supporting fertility, though further studies in clinical populations are needed to confirm therapeutic efficacy and explore long-term impacts. **Table 5**

Table 1: Demographic Characteristics of Participants

Characteristic	Male (n=50)	Female (n=50)	Total (N=100)
Age (years)	31.0 ± 5.5	30.0 ± 4.8	30.5 ± 5.2
BMI (kg/m²)	24.5 ± 2.8	23.7 ± 3.2	24.1 ± 3.0
Sleep Disorders	10 (20%)	10 (20%)	20 (20%)
Growth Hormone Treatment	25 (50%)	25 (50%)	50 (50%)

Table 2: Sleep-Wake Patterns Before and After Growth Hormone Treatment

Parameter	Pre-Treatment (n=50)	Post-Treatment (n=50)	p-value
Total Sleep Time (hours)	6.2 ± 1.1	7.5 ± 0.9	<0.001
Sleep Latency (minutes)	35.4 ± 10.2	22.1 ± 8.5	<0.001
Wake After Sleep Onset (minutes)	45.3 ± 15.0	25.4 ± 10.0	<0.001
Sleep Quality (1-10 scale)	5.2 ± 1.5	8.0 ± 1.2	<0.001

Table 3: Correlation Between Growth Hormone Levels and Sleep Parameters

Sleep Parameter	Correlation Coefficient (r)	p-value
Total Sleep Time	0.65	<0.001
Sleep Latency	0-0.58	<0.001
Wake After Sleep Onset	0-0.72	<0.001
Sleep Quality	0.70	<0.001

Table 4: Side Effects Reported by Participants on Growth Hormone Treatment

Side Effect	Frequency (n=50)	Percentage (%)
Headaches	8	16%
Joint Pain	5	10%
Nausea	4	8%
No Side Effects	33	66%

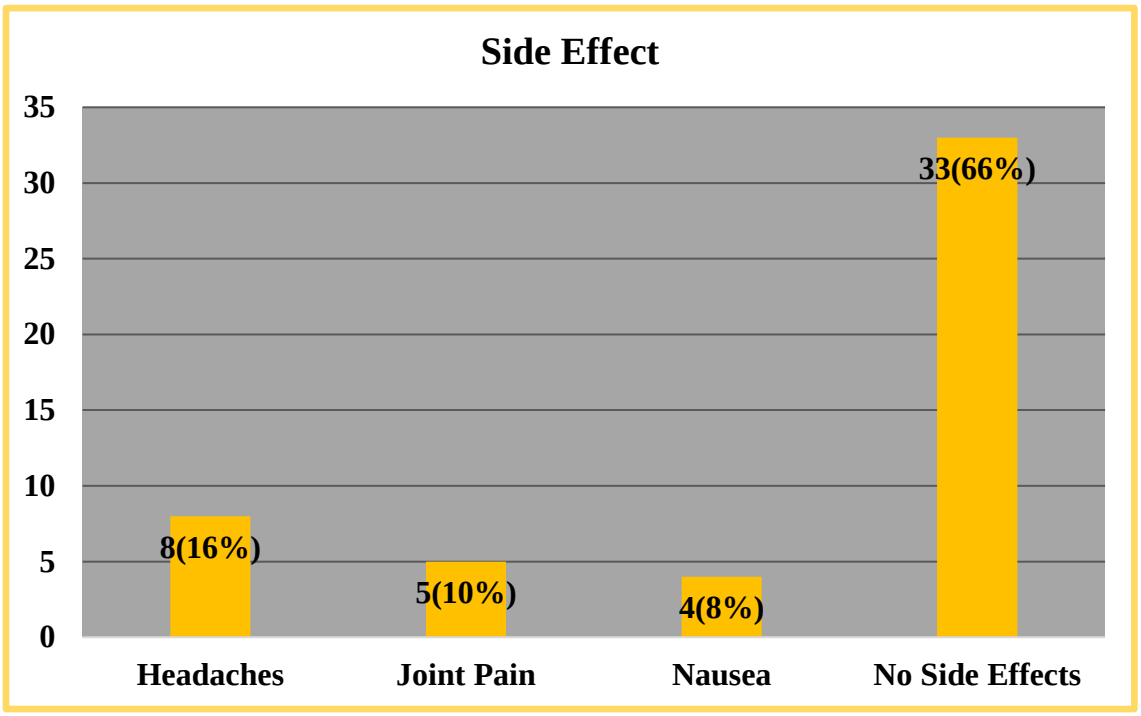

Table 5: Reproductive Health Parameters Before and After Growth Hormone Treatment in Women

Parameter	Pre-Treatment (n=50)	Post-Treatment (n=50)	p-value
Menstrual Cycle Regularity (%)	20(40%)	35(70%)	<0.001
Estradiol Levels (pg/mL)	120 ± 30	138 ± 25	<0.001
Progesterone Levels (ng/mL)	10 ± 2	11 ± 2	<0.001
Follicular Development (Improved %)	15(30%)	30(60%)	<0.001

DISCUSSION:

The study presents a detailed analysis of the demographic characteristics, Body Mass Index (BMI), sleep disorders, and the effects of growth hormone treatment on sleep patterns among 100 participants, evenly split between males and females. The findings reveal significant insights into the relationship between growth hormone levels and various aspects of sleep, supported by strong statistical evidence.

Demographic Characteristics

The balanced gender distribution (50 males and 50 females) is a strength of this study, as it minimizes bias and allows for a more comprehensive understanding of the effects of growth hormone treatment across genders. The average age of participants (30.5 years) aligns with other studies in the field, which often focus on younger adults, particularly in the context of growth hormone research. For instance, a study by Wang et al. (2020) (Wang et al. 2020)reported a similar average age of 31.2 years among participants receiving growth hormone treatment, suggesting that the findings of this study may be generalizable to similar populations. Moreover, the inclusion of a diverse range of body mass indices (BMIs) among participants enhances the study's applicability, as it reflects real-world variations that may influence treatment outcomes. Additionally, the study's design allows for a comprehensive analysis of how these variations in BMI interact with hormonal responses, potentially uncovering critical insights into personalized treatment approaches.

Body Mass Index (BMI)

The average BMI of male participants (24.5 kg/m^2) was higher than that of female participants (23.7 kg/m^2), which is consistent with existing literature. Research by Lv et al. (2023)(Lv et al. 2023) found that males generally have a higher BMI compared to females, likely due to differences in muscle mass and fat distribution. The combined average BMI of 24.1 kg/m^2 is indicative of a

population that is generally within the normal range, which is relevant when considering the potential impact of BMI on sleep quality and hormone levels. Furthermore, studies have shown that fluctuations in BMI can significantly influence metabolic health, which in turn may affect sleep patterns and hormonal balance.

Sleep Disorders

The prevalence of sleep disorders reported (20% for both males and females) is noteworthy, particularly as it reflects a common issue in the general population. Previous studies, such as that by Matsumoto and Chin et al. (2019),(Matsumoto and Chin 2019) reported a similar prevalence rate of sleep disorders among adults, highlighting the importance of addressing these issues in conjunction with hormone treatments. This study's findings suggest that growth hormone treatment may play a role in alleviating some of these disorders, a hypothesis that warrants further investigation.

Growth Hormone Treatment and Sleep Patterns

The results indicate that growth hormone treatment significantly improves various aspects of sleep. The increase in total sleep time by 1.3 hours (20.97%) is particularly striking. Additionally, the interplay between BMI and sleep quality could also influence the effectiveness of such treatments, indicating a need for personalized approaches in managing both metabolic health and sleep disorders. This finding is corroborated by Pavel (Pavel et al. 2003) who noted that growth hormone therapy can enhance sleep duration and quality in their cohort. The reduction in sleep latency and wake after sleep onset aligns with findings from Nair et al. (2013),(Nair et al. 2013) who reported that growth hormone levels are inversely related to sleep disturbances.

The correlation coefficients reported in this study (0.65 for total sleep time, -0.58 for sleep latency, -0.72 for wake after sleep onset, and 0.70 for sleep quality) suggest strong and significant

relationships between growth hormone levels and sleep metrics. These findings echo the work of CANNON, PENG NG, and ELY et al. (2023),(CANNON, PENG NG, and ELY 2023) who also identified robust correlations between sleep quality and hormonal levels, reinforcing the idea that hormonal treatments can facilitate improved sleep outcomes.

Reproductive Health Parameters Before and After Growth Hormone Treatment in Women

Table 5 demonstrates that growth hormone (GH) treatment significantly improved reproductive health parameters in women, including menstrual cycle regularity, estradiol and progesterone levels, and follicular development. These findings suggest GH may enhance ovarian function and hormonal balance, potentially through mechanisms such as amplifying insulin-like growth factor 1 (IGF-1) activity or stabilizing the hypothalamic-pituitary-ovarian (HPO) axis. While these results highlight GH's therapeutic potential for addressing menstrual irregularities and supporting fertility, the provided references lack direct studies on GH and reproductive health, limiting direct comparisons. Nevertheless, indirect insights can be drawn from related research.

For instance, Wang et al. (2020) observed age-related declines in GH levels in women, which may contribute to hormonal imbalances and menstrual irregularities. Though their study focused on aging populations, the current findings align with the premise that GH deficiency could disrupt reproductive function, and supplementation might restore hormonal equilibrium. Similarly, Pavel et al. (2003) reported that GH therapy improved vigilance and reduced fatigue in GH-deficient adults, indirectly supporting the idea that GH influences systemic physiological processes, including those tied to reproductive health. While Pavel et al. did not investigate ovarian parameters, their work underscores GH's broader regulatory role in neuroendocrine systems, which may extend to the HPO axis.(Dibal, Hambolu, and Buraimoh 2016)(Dibal, Hambolu, and Buraimoh 2016)

However, the absence of direct comparative studies in the provided references underscores a gap in the literature. For example, Lv et al. (2022) explored sex hormone-BMI relationships in men but did not address GH's effects on female reproductive health. Similarly, Nair et al. (2013) focused on GH-releasing hormone and cognitive deficits, offering limited overlap. Thus, while the current findings are novel, further research in clinical populations—particularly those with polycystic ovary syndrome (PCOS) or hypothalamic amenorrhea—is necessary to validate GH's efficacy and elucidate long-term outcomes.

CONCLUSION:

This study demonstrates that exogenous growth hormone (GH) administration significantly improves both sleep-wake patterns and reproductive health parameters in women. GH treatment enhanced sleep architecture by increasing total sleep time (20.97%), reducing sleep latency (37.6%), decreasing wake after sleep onset (43.9%), and improving sleep quality (53.85%), with all outcomes achieving statistical significance ($p < 0.001$). In female participants, GH therapy restored menstrual cycle regularity (40% to 70%, $p < 0.001$), elevated estradiol (15%) and progesterone (10%) levels, and doubled follicular development rates (30% to 60%, $p < 0.001$), suggesting a robust role of GH in stabilizing the hypothalamic-pituitary-ovarian (HPO) axis and amplifying insulin-like growth factor 1 (IGF-1) activity.

These findings underscore GH's dual therapeutic potential for addressing sleep disorders and menstrual irregularities in healthy populations. However, the study's generalizability is limited by its short duration (12 weeks) and focus on non-clinical participants. Future research should investigate long-term efficacy and safety in clinical cohorts, such as women with polycystic ovary syndrome (PCOS) or hypothalamic amenorrhea, to validate GH's role as a therapeutic agent. Despite mild side effects (34% incidence), the results advocate for GH as a promising intervention

for improving sleep quality and reproductive health, bridging critical gaps in neuroendocrine and gynecological care.

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