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Literature Review: Hypogonadism in Men

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Abstract: Male hypogonadism is a medical condition characterized by reduced testosterone production due to disorders of the testes or the hypothalamic–pituitary axis. This study employs a quantitative approach to systematically review the literature on the prevalence, risk factors, and physiological and psychological impacts of hypogonadism in men. Data were drawn from clinical and observational studies published over the past four years that analyzed associations among testosterone levels, age, body mass index, and symptoms such as erectile dysfunction and decreased libido. The review indicates that hypogonadism is more common in men over 40 years of age, particularly those with obesity or metabolic disease. Beyond sexual function, the condition also affects muscle mass, bone density, and emotional balance. In conclusion, early detection and appropriate testosterone replacement therapy play an important role in improving quality of life and preventing long-term complications in men with hypogonadism.

Keywords: Hypogonadism, Testosterone, Men, Quantitative Methods, Erectile Dysfunction, Hormones, Reproductive Health.

INTRODUCTION

Hypogonadism is defined as a clinical and biochemical syndrome characterized by insufficient production of sex hormones, particularly testosterone in men and estrogen in women. Hypogonadism is divided into two categories: primary hypogonadism and secondary hypogonadism. Primary hypogonadism is caused by the failure of the testes to produce testosterone, resulting in increased gonadotropins accompanied by low testosterone levels. Secondary hypogonadism, on the other hand, is caused by insufficient secretion of gonadotropin-releasing hormone (GnRH) in the hypothalamus or failure of the pituitary gland to secrete gonadotropins, which can lead to low levels of gonadotropins and testosterone in the blood (Rosario, 2019).

In Indonesia, hypogonadism shows a worrying prevalence. The incidence of hypogonadism increases with age, particularly among the elderly, affecting approximately 40.6% of men aged 40 and over. This highlights the importance of age as a risk factor. Furthermore, gender

differences are also significant, as men are more frequently diagnosed with hypogonadism than women. Other risk factors contributing to hypogonadism include obesity, chronic diseases such as diabetes and cardiovascular disease, certain medications, and lifestyle choices such as smoking and excessive alcohol consumption (Yeo S, 2021).

Clinically, hypogonadism has significant implications for the quality of life of sufferers. This disorder can cause symptoms such as decreased libido, erectile dysfunction, fatigue, and mood disorders. These symptoms not only affect physical health but also significantly impair social interactions and emotional control. Furthermore, untreated hypogonadism is associated with an increased risk of comorbidities such as osteoporosis and metabolic syndrome, creating a vicious cycle that further worsens the sufferer's health. Therefore, recognizing and treating hypogonadism is crucial to improving the quality of life and overall health status of affected individuals, especially in Indonesia (Bruno, 2015).

RESEARCH METHOD

Quantitative methods in the literature review on male hypogonadism were used to objectively and measurably analyze the relationship between variables, such as testosterone levels, age, body mass index (BMI), and clinical symptoms experienced by patients. This approach involved collecting numerical data from various previous studies, including observational studies, clinical surveys, and laboratory analyses, which were then processed using descriptive and inferential statistical techniques. The goal was to identify patterns, trends, and risk factors contributing to the development of both primary and secondary hypogonadism. Using quantitative methods, the literature review results can provide an empirical picture of prevalence, correlations between testosterone levels and reproductive and metabolic function, and the effectiveness of hormone replacement therapy. This approach also allows researchers to draw more valid conclusions and robust generalizations based on objective and measurable data.

RESULT AND DISCUSSION

Anatomy and Physiology

Testis

The testes are a pair of organs that produce sperm and secrete the hormone testosterone, which stimulates sperm production, regulates the development of male secondary sex characteristics, and stimulates sex drive. The testes are controlled by*Luteinizing Hormone (LH)*

And *Follicle-Stimulating Hormone (FSH)* which is a gonadotropic hormone released by the anterior pituitary. LH and FSH are produced by the same type of cell, namely the gonadotropes (Sherwood, 2018).

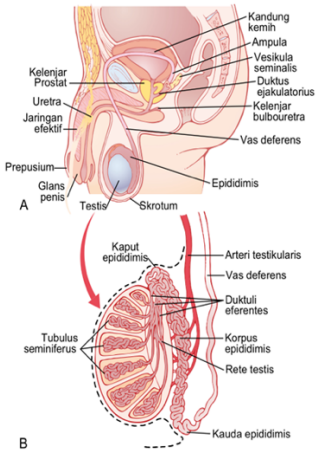

Figure 1. Male Reproductive Anatomy Structure (Sherwood, 2018)

Regulation of LH and FSH hormones by the hypothalamic-pituitary-gonadal axis

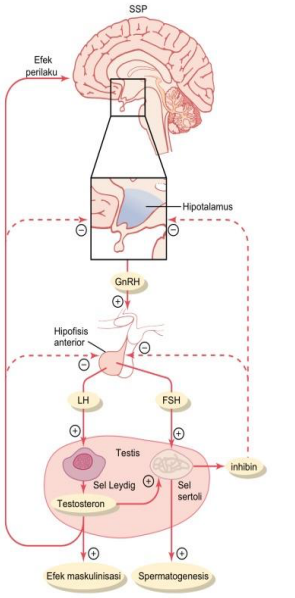

Figure 2. Regulation of FSH and LH in men (Guyton, 2019).

The anterior pituitary produces hormones that are released into the blood. One of them is *Gonadotropin-Releasing Hormone* (GnRH) which will secrete FSH and LH which will act on the gonads. GnRH is released in 2-3 hours in large amounts, and no secretion occurs in between (Guyton, 2019). The kiss 1 neuron in the arcuate nucleus will release kisspeptin, which is a neurotransmitter that stimulates GnRH secretion and targets the anterior pituitary to release

FSH and LH which will circulate in the testes to regulate testicular secretion. LH will stimulate interstitial cells to produce testosterone and will encourage spermatogenesis and maintain secondary sex characteristics then FSH stimulates the seminiferous tubules to release a*ndrogen binding protein* which helps increase the ability to bind to testosterone and maintain testosterone in the lumen because it is fat-soluble and can easily diffuse through the plasma membrane and leave the lumen. Production of a*ndrogen binding protein* stimulated by testosterone (Sherwood, 2018).

Testosterone Production Mechanism

Testosterone

Kiss 1 neurons in the arcuate nucleus release kisspeptin, a neurotransmitter that stimulates GnRH secretion and targets the anterior pituitary to release FSH and LH, which circulate in the testes to regulate testicular secretion. LH stimulates interstitial cells to produce testosterone and promotes spermatogenesis (Sherwood, 2018).

Classification of Hypogonadism

Hypogonadism in men is usually classified based on the degree of dysfunction:

1. Primary hypogonadism

   Primary hypogonadism or hypergonadotropic hypogonadism is caused by disorders in Leydig cells which cause decreased testosterone production, disruption of spermatogenesis mechanisms, and increased gonadotropin levels which can result in erectile dysfunction and infertility.

2. Secondary hypogonadism

   Secondary hypogonadism, or hypogonadotropic hypogonadism, is caused by defects in the central hypothalamus and pituitary gland. This condition causes decreased testosterone levels, impaired spermatogenesis, and low gonadotropins, which can impair male fertility, lead to loss of muscle mass, loss of libido, and even impotence.

3. Functional hypogonadotropic hypogonadism

   Functional hypogonadotropin-dependent hypogonadism (FHH) is a decrease in testosterone levels and spermatogenesis due to certain etiologies such as obesity, hypertension, dyslipidemia, etc. (Gloria Kang GJ, Ewing-Nelson SR, Mackey L, Schlitt JT, Marathe A, Abbas KM 2018).

Etiology and Risk Factors

The causes of hypogonadism are divided into primary, secondary, and combined primary and secondary. Inadequate hormone synthesis can cause primary hypogonadism, while secondary hypogonadism occurs when signals from the hypothalamus or pituitary gland to the testes/ovaries fail to stimulate sufficient hormone production. Causes of primary hypogonadism in men include Klinefelter syndrome, undescended testes, radiation therapy, and *orchid hemochromatosis.* Secondary hypogonadism in men is caused by Kallmann syndrome, *syndrome prader-willi*, pituitary disorders, head trauma, and radiation therapy. Other causes of hypogonadism, which are a combination of primary and secondary, include alcoholism, aging, HIV, corticosteroid therapy, and systemic diseases (liver damage, uremia, and sickle cell disease). Obesity, traumatic brain injury, and stress can also trigger hypogonadism. Hypogonadism in men is most often caused by Klinefelter syndrome, undescended testis, and *hemochromatosis*, pituitary disorders (pituitary tumors, granulomas, and abscesses), and Kallmann syndrome. Several factors that can increase the risk of developing hypogonadism include autoimmune diseases, a poor lifestyle, and environmental influences. These include excessive alcohol consumption, smoking, frequent consumption of foods and drinks high in sugar, fat, and calories, and stress. Environmental influences can include excessive radiation exposure or chemotherapy (Batmomolin, Agnes., 2023; Marcdante, K. J., 2021; Rahayu, Sri*and all*., 2020).

Pathophysiology

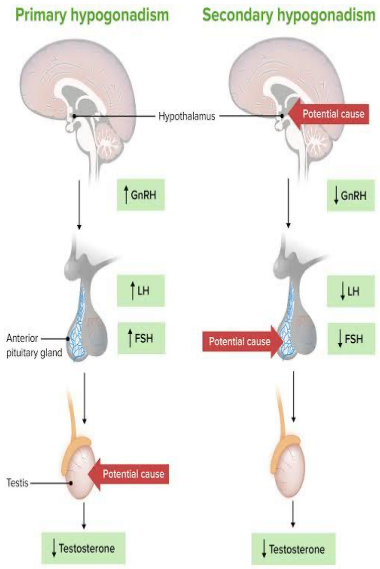

Figure 3. Pathophysiology of Primary and Secondary Hypogonadism in Men (Oiseth*and all*., 2022)

Hypogonadism occurs when the HPG axis is disrupted at any level. There are two types of hypogonadism: primary and secondary. Primary hypogonadism occurs when testicular steroidogenesis is insufficient to synthesize adequate levels of testosterone, while secondary hypogonadism occurs when signals to the testes (either from the pituitary gland via LH or from the hypothalamus via GnRH) fail to stimulate sufficient Leydig cell testosterone production (Oiseth*and all.,* 2022).

1. **Primary Hypogonadism**

   Primary hypogonadism, or hypergonadotropic hypogonadism, occurs when there is primary gonadal failure, specifically in the ovaries or testes. Because there is no negative feedback from testicular testosterone, estradiol, or inhibin B, gonadotropin levels increase sufficiently. Spermatogenesis is inhibited if the body does not produce enough androgens (Sizar & Schwartz, 2022).

2. **Secondary Hypogonadism**

   Secondary hypogonadism, or hypogonadotropic hypogonadism, occurs when there is a permanent delay in the maturation of the HPG axis. Partial or complete GnRH deficiency results in decreased LH and FSH release, ultimately leading to decreased testosterone production (Sizar & Schwartz, 2022).

Clinical Manifestations

Hypogonadism in men can cause different clinical manifestations depending on gender and the type of hypogonadism suffered. In primary hypogonadism, elevated levels of FSH and LH are generally found. This is related to the negative feedback effect on the anterior pituitary gland due to decreased testicular function. Meanwhile, in secondary (central) hypogonadism, FSH and LH levels decrease due to impaired production by the anterior pituitary gland. Individuals with both primary and secondary hypogonadism will have low testosterone levels (Sizar*et al.*, 2024). This will cause several clinical manifestations such as, late onset of puberty and failure of secondary sex characteristics development if it occurs before puberty (Ali & Donohoue, 2020). In addition, there are very typical symptoms that occur due to hypogonadism, namely decreased libido or sexual desire, fatigue and lethargy, reduced hair growth in the facial, armpit, and pubic areas, decreased muscle mass, breast enlargement (gynecomastia), decreased or small testicular volume (<20 cc), erectile dysfunction, and potentially causing infertility. Sufferers of secondary hypogonadism often experience additional symptoms in the form of visual disturbances in the outer half of the visual field

(bitemporal hemianopsia) and often complain of headaches (Sizar*et al.*, 2024). Some other less specific symptoms that can be experienced by someone suffering from hypogonadism include depressed mood, irritability, decreased physical performance, and weight loss and appetite loss (Mulhall*et al.*, 2018).

Establishing a Diagnosis

Anamnesis

Anamnesis can be done by asking about the presence of late puberty, marked by no signs of puberty until the age of 14 years. Evaluation is necessary, because most cases are caused by...*Constitutional Delay of Growth and Puberty (CDGP)*(Saloniа*et al.*., 2019). Genetic diseases in the family (e.g., Turner or Klinefelter syndrome, obesity, chronic comorbidities, use of certain medications (such as opioids or glucocorticoids), and lifestyle patterns (malnutrition or excessive physical activity) are important to ask about as risk factors for hypogonadism (IAUI 2023; Saloniа*et al.*., 2019). In addition, several specific and less specific symptoms related to hypogonadism are listed in the following table.

Table 1. Symptoms of Male Hypogonadism (IAUI, 2023)

Category	Sexual symptoms	Physical symptoms	Psychological symptoms
More specific	- Decreased libido- Erectile dysfunction- Reduced spontaneous/morning erections	- Reduced capacity for strenuous physical activity- Difficulty walking >1 km- Stiffness	- Mood and affect disturbances- Decreased motivation- Fatigue
Less specific	- Decreased frequency of intercourse- Decreased frequency of masturbation- Delayed ejaculation	- Hot flushes- Weakness and tiredness- Decreased physical ability, activity, and function	- Impaired concentration and memory- Sleep disturbances

Physical Examination

BMI and waist circumference measurements are recommended to detect obesity associated with functional hypogonadism. Virilization abnormalities and ambiguous genitalia (micropenis, hypospadias, and cryptorchidism) can provide useful information about overall androgen status. *Eunuch* (scant body hair, high-pitched voice, small penis and testicles) are common in prepubertal hypogonadism or delayed puberty. Nonspecific clinical features, such as weakness, fatigue, lethargy, and sexual dysfunction, may be present. A digital rectal

examination is necessary to rule out prostatic abnormalities before testosterone therapy or to support the suspicion of hypogonadism (in cases of volume reduction) (IAUI, 2023).

Supporting Examination

Table 2. Laboratory Examination

		Leaf Hormone			
Category	**Location of Dysfunction**	**Testosterone**	**LH**	**FSH**	**GnRH**
Primary Hypogonadism	Testis	⬇ or low N	⬆	⬆	⬆
Secondary Hypogonadism	Anterior Pituitary	⬇ or low N	⬇ or N	⬇ or N	⬆
	Hypothalamus	⬇	⬇	⬇	⬇
Isolated defect in spermatogenesis	Testis	N	N	⬆ or N	N
Andropause	Testes and Hypothalamus	⬇ or low N	⬆ or N	⬆ or N	⬇ and abnormal secretions

AMH (Anti-Müllerian Hormone) and inhibin B are the primary markers of childhood hypogonadism, as gonadotropin and testosterone levels decline after 6 months of age. Secondary hypogonadism is characterized by low AMH and inhibin B with no increase in gonadotropins (Saloni*a et al.*., 2019). Pituitary MRI, as well as evaluation of other pituitary hormones, is necessary in the presence of specific symptoms such as visual disturbances, headaches, or when hyperprolactinemia is present. In addition, pituitary MRI is also performed in cases of severe hypogonadism (<6 nmol/L, 1.75 ng/mL) with low gonadotropin levels (IAUI 2023; Saloni*a et al.*., 2019).

Management

The goal of therapy for hypogonadism sufferers is to restore sexual health and function, as well as stimulate or maintain secondary sex characteristics, restore fertility, and increase bone mineral density and muscle mass (Richard-Eaglin, 2018).

Hypogonadism therapy in men

The primary treatment for hypogonadism in men is testosterone replacement. The goal of testosterone therapy is to stimulate serum testosterone levels to normal levels in healthy young men.

1. Testosterone enanthate or cypionate injection

   The injection is given intramuscularly at a dose of 50-75 mg/month and is slowly increased every 6 months to 100-150 mg/month as puberty induction, while in adult males it is given at a dose of 75-100 mg per week.
2. Testosteron intradermal

   Intradermal testosterone is available in 1% gel and patches. A 5-10g gel containing 50-100 mg of testosterone and a 5-10 mg patch are applied daily to the skin in areas of the upper arm, back, or thigh that receive minimal pressure or friction.
3. Testosteron tablet

   Testosterone tablets with a 30 mg dosage are consumed twice a day or every 12 hours.

Therapy for hypogonadism due to pituitary tumors

In cases of hypogonadism caused by tumors in the pituitary gland, the main treatment is surgery or radiation therapy to treat the tumor (Russ*et al.,*2024)

Prognosis and Complications

Complications of Hypogonadism

1. **Erectile Dysfunction**: In men, hypogonadism can cause difficulty in achieving or maintaining an erection.
2. **Gynecomastia**: Breast enlargement in men due to hormonal imbalance
3. **Infertility**: The inability to have children, which can occur in both men and women
4. **Osteoporosis**: Decreased bone density which can lead to fractures,
5. **Mood Disorders**: Patients may experience depression or anxiety due to hormonal changes (Indirli*et al.*, 2023).

With treatment:

If hypogonadism is discovered and treated early, the prognosis is positive. Testosterone replacement therapy can help reduce symptoms and improve sexual function, bone density, and muscle mass (Duarsa*et al.*, 2023).

Without treatment:

If hypogonadism is not treated, this condition can lead to long-term problems such as infertility, decreased sexual desire, and mood changes (Ida*et al.*, 2023).

CONCLUSION

Hypogonadism is an endocrine disorder characterized by inadequate sex hormone production in both men and women. It can be classified as primary, secondary, or functional, each with diverse etiologies, including gonadal, hypothalamic, or pituitary disorders, and risk factors such as age, obesity, and an unhealthy lifestyle. This condition can cause various clinical manifestations, including decreased libido, infertility, erectile dysfunction, fatigue, and complications such as osteoporosis and mood disorders. Diagnosis is made through anamnesis, physical examination, and supporting tests such as hormone levels and radiology. Therapy focuses on hormone replacement, treatment of the specific cause, and restoration of sexual function and quality of life. With appropriate treatment, the prognosis is generally good, although if left untreated, it can lead to serious complications that impact the physical and mental health of sufferers.

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