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A Review of Reproductive Hormone Levels in Male Smokers

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ABSTRACT

Introduction: Approximately thirty-seven percent of men smoke at reproductive age. Smoking negatively impacts men's reproductive health, due to the presence of over four thousand compounds in cigarettes. Nicotine and other chemicals can alter various hormones including sex steroid hormones, by affecting the hypothalamus - pituitary - gonad axis and hormone metabolism. These chemicals also cause oxidative stress producing free radicals that can damage cells and cell membranes, including Leydig cells, which are responsible for testosterone production. This damage affects spermatogenesis. Additionally, smoking can cause the narrowing of the blood vessels (atherosclerosis), including those supplying blood to the testicles. Therefore, this study aims to review male reproductive hormone levels in male smokers.

Method: The information was collated from various databases including PubMed, Wiley, Science Direct, Springer, Taylor and Francis, Scopus, Google, and Google Scholar using relevant keywords and Medical Subject Headings (MeSH) such as male smokers & follicle-stimulating hormone (FSH); male smokers & luteinizing hormone (LH); male smokers & testosterone.

Results: The literature review revealed contrasting reports on changes in FSH, LH and testosterone levels among male smokers. Some studies reported an increase while others observed a decrease in these hormone levels.

Conclusion: Exposure to cigarettes can harm reproductive health, leading to a decrease in testosterone levels and alterations in follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

Keywords: Male Smokers; Follicle-Stimulating Hormone; Luteinizing Hormone; Testosterone.

Introduction

Smoking has become one of the most common lifestyles in recent times, with approximately thirty-seven percent of men smoking during their reproductive years (Sharma *et al*., 2016). Smoking seriously impacts human health, including male reproductive health, due to the presence of over four thousand compounds in cigarettes. Cigarettes are produced from processed tobacco of the *Nicotiana tobacum* plant. When a cigarette is burned, combustion and pyrolysis reactions occur, releasing

various Products into the lungs, which then enter the bloodstream and affect the brain and other tissues (Maartens, 2013). Cigarette smoke contains numerous harmful elements, including nicotine, carbon monoxide, carbon dioxide, nitrogen oxide, polycyclic aromatic hydrocarbons, radioactive substances, benzo (a) pyrene, cadmium, and others (Dai *et al*., 2015).

Nicotine is a toxic component of cigarette smoke. Both nicotine and its metabolite (cotinine) have been found in the seminal plasma of smokers exposed to tobacco smoke (Oyeyipo et al., 2013). Nicotine can be absorbed into the bloodstream through the skin, lungs (the primary absorption site), and mucous membranes. Once absorbed, nicotine is transported through the blood to the brain and other tissues in the body (Maartens, 2013). Nicotine affects the central nervous system and can induce apoptosis in Leydig cells, inhibiting androgen biosynthesis. It also interferes with the male reproductive hormone system, causing changes in follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone levels (Oyeyipo et al., 2013).

Cadmium adversely affects Leydig cells by decreasing cell viability and testosterone secretion, while increasing levels of malondialdehyde (Maartens, 2013). The gases and particulates in cigarette smoke act as free radicals, leading to an increase in reactive oxygen species (ROS) in the body. Elevated ROS levels cause oxidative stress, resulting from an imbalance between oxidants and antioxidants(Ahmed et al., 2015; Ahmed et al., 2020; Ibrahim et al., 2018). Increased ROS is a key mediator of male infertility. While ROS plays a physiological role in sperm function, excessive levels are detrimental to sperm health. High ROS levels surpassing antioxidant defenses damage sperm membranes and impair Leydig cell function, disrupting spermatogenesis (Aldaddou et al., 2022; Aldaddou et al., 2023). Therefore, this study aims to review the impact of smoking on male reproductive hormone levels.

Methodology

The data was gathered from a comprehensive range of databases, including PubMed, Wiley, Science Direct, Springer, Taylor and Francis, Scopus, Google, and Google Scholar. The search utilized relevant keywords and Medical Subject Headings (MeSH) such as "male smokers & follicle-stimulating hormone (FSH)," "male smokers & luteinizing hormone (LH)," and "male smokers & testosterone." Articles published between 2011 and 2023 that met the inclusion criteria were selected for analysis.

Results

Smoking has been shown to significantly impact reproductive hormone levels in men. Below is a summary of the search results for the reviewed articles (Table 1).

Table 1: Article Search

Author	Results	Study
(Al-Turki, 2015) Saudi Arabia	The study found that smokers had significantly lower total serum testosterone levels (383.8 ± 239.5 ng/dL) compared to nonsmokers (422.5 ± 139.2 ng/dL) (p = 0.009)	Retrospective study

(Lotti et al., 2015) Italy	Significantly higher androgen (total testosterone, p =0.001; calculated free testosterone, p= 0.005) and lower FSH (p= 0.05) levels were observed in CS	Retrospective cross-sectional analysis
(Osadchuk et al., 2023) Russia	No significant differences were found in serum levels of LH, FSH, and testosterone between smokers and non-smokers.	Based Study
(Eze et al., 2015) Nigeria	Testosterone was significantly lower in both active ($p<0.05$) and passive smokers ($p<0.05$) when compared to non-smokers. The FSH of the active smokers was significantly higher ($p = 0.034$) than that of the controls while the passive smokers had the highest LH values ($p = 0.0001$)	Case-control study
(W. Zhao et al., 2020) China	Higher concentrations of LH were also associated with lower sperm progressive motility (P for trend = 0.04).	Cohort
(El Salam et al., 2021) Cairo	Significant statistical difference between smoker and non-smoker groups concerning serum total testosterone (T), with P values of 0.002.	Cross-sectional study
(Devita, 2019) Indonesia	The results showed levels of FSH in heavy smokers and non-smokers were 3.857 ± 1.493 mIU / ml and 4.977 ± 2.083 mIU / ml with p-value = 0.034. LH levels showed 4.984 ± 2.237 mIU/ml and 5.500 ± 2.623 mIU with p-value = 0.458. While testosterone levels showed results of 15.393 ± 2.782 nmol / l and 20.836 ± 6.360 nmol /l with p value = 0.000.	Analytical with Crosssectional design
(Wang et al., 2013) China	(a) smokers had significantly higher TT and FT levels compared to nonsmokers.	Cross-sectional study
(J. Zhao et al., 2016) Hongkong	Smokers had higher mean testosterone than non-smokers (1.53 nmol/L, 95% confidence interval (CI) 1.11 to 1.96)	Observational study systematic review and meta-analysis
(Asare-Anane et al., 2016) Ghana	Free testosterone and follicle-stimulating hormone ($p <0.05$ respectively), compared with non-smokers.	Cross-sectional study with matched controls
(Oyeyipo et al., 2013) Nigeria	Results showed that nicotine administration significantly decreased ($P < 0.05$) testosterone in the low and high-treated groups and FSH in the high-dose treated group when compared	Experiment

	with the control group. There was a significant increase (P < 0.05) in mean LH when compared with the control	
(Bannison Bani et al., 2022) Ghana	testosterone level, which is significantly higher in smokers compared to non-smokers.	Cross-sectional
(Bassey et al., 2018) Nigeria	The mean testosterone level was significantly lower (P<.0001) in the smokers compared to the controls while LH and FSH values were significantly higher (P<.0001) in the smokers compared to controls.	Cross-sectional
(Khalifa et al., 2014) Sudan	There is significant lower levels in testosterone [M±SD =3.0±1.9ng/ml] compared with control group (M±SD = 6.1±2.8ng/ml), P = 0.03. The study concluded that there was a significantly lower level of testosterone in smokers compared to nonsmokers, while there were no significant differences in serum levels of Luteinizing Hormone	Descriptive cross-sectional laboratory-based study.
(Liu et al., 2021) China	Total testosterone was positively associated with number of cigarettes consumed in smokers aged 40-49 and 50-59 years	Cross-sectional study

Research conducted by (Devita, 2019) reported a decrease in FSH levels. (Asare-Anane et al., 2016), similarly found much lower FSH levels in smokers, while (Lotti et al., 2015) also reported a decrease in FSH levels. On the contrary, other studies reported increased FSH levels in active smokers compared to non-smokers (Eze et al., 2015); (El Salam et al., 2021); (Oyeyipo et al., 2013); (Bassey et al., 2018). (Osadchuk et al., 2023), found that there was no significant difference in serum FSH levels between smokers and non-smokers in the study population.

The review of articles shows there is no significant difference in luteinizing hormone (LH) levels between smokers and non-smokers (Devita, 2019), (Bannison Bani et al., 2022), (Osadchuk et al., 2023). However, several studies, including those conducted by (El Salam et al., 2021), (Khalifa et al., 2014) reported increased LH levels among passive smokers. Additionally,(Oyeyipo et al., 2013) found a significant increase in LH levels in smokers compared to controls. (W. Zhao et al., 2020), (Bassey et al., 2018), higher LH concentration.)

Several studies (Oyeyipo et al., 2013); (Al-Turki, 2015); (Asare-Anane et al., 2016); (Bassey et al., 2018); (Devita, 2019); (El Salam et al., 2021);(Khalifa et al., 2014), consistently shows that serum total testosterone levels are lower in smokers compared to non-smokers. On the contrary, (Lotti et al., 2015), (J. Zhao et al., 2016); and (Bannison Bani et al., 2022), reported increased testosterone levels among smokers. (Liu et al., 2021), total testosterone is positively related to the number of cigarettes consumed by smokers. No significant differences were found in serum

testosterone levels between smokers and non-smokers in the study population (Osadchuk et al., 2023).

The review results above show a significant decrease, increase, and increase in FSH, LH, and Testosterone levels in smokers. Testosterone, as an important androgen, plays an important role in several aspects of sexual maturation, behavior, spermatogenesis, differentiation, and maintenance of accessory sex organs. The synthesis and release of androgens depend on pituitary gonadotropins, namely FSH and LH. FSH and LH are important for testicular function and spermatogenesis. LH is the main trophic regulator of Leydig cell function without which androgen production is impossible.

Discussion

Smoking has been shown to exert contrasting effects on male reproductive hormones, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone levels. Chronic smoking leads to the accumulation of nicotine and other harmful constituents in the bloodstream, which disseminate throughout the body, including the reproductive organs. This exposure contributes to significant hormonal changes, which may adversely affect male fertility, given the crucial role of testosterone in sperm production (Lotti et al., 2015). Furthermore, smoking is recognized for its detrimental impact on the endocrine system, potentially leading to pituitary dysfunction (El Salam et al., 2021). During puberty, the hypothalamus releases Gonadotropin Releasing Hormone (GnRH), stimulating the anterior pituitary to secrete gonadotropins—FSH and LH. LH stimulates Leydig cells to produce testosterone, essential for the development of secondary sexual characteristics, while FSH stimulates Sertoli cells to initiate spermatogenesis (Maartens, 2013). The complex interplay between smoking and male fertility underscores the need for further research to elucidate the mechanisms underlying these hormonal alterations. Understanding these mechanisms is crucial for developing effective interventions to mitigate the adverse effects of smoking on reproductive health. From this mechanism, it is necessary to develop an intervention that can repair Leydig cells. Due to cigarette exposure, when the Leydig cells are in good condition, testosterone secretion also becomes normal, so that negative feedback will occur. In the end, the regulation of the hormonal system in male reproduction runs normally.

Despite the contrasting reports in the literature, it is evident that the constituents of cigarettes can significantly impact the central nervous system, Nicotine, in particular, can reduce the stimulation of the hypothalamus within the central nervous system, subsequently decreasing the secretion of Gonadotropin Releasing Hormone (GnRH) This reduction in GnRH leads to decreased stimulation of the anterior pituitary gland, resulting in lowered production of luteinizing hormone (LH).. LH is crucial for stimulating Leydig cells in the testes to produce testosterone. Testosterone secretion by the interstitial Leydig cells is directly proportional to the amount of LH available. According to the hypothalamus-pituitary-gonadal system, an increase in LH typically leads to a corresponding rise in testosterone levels. This increase in testosterone provides negative feedback to the hypothalamus and pituitary, subsequently decreasing LH levels. However, heavy smokers often exhibit lower testosterone levels compared to non-smokers. Nicotine's interference with GnRH secretion leads to decreased levels of both FSH and LH, thereby disrupting the normal

function of the hypothalamus-pituitary-gonadal system. Previous research has indicated that cigarette smoke can significantly disrupt this delicate hormonal balance, impairing reproductive health and fertility. Understanding these mechanisms highlights the importance of addressing smoking's adverse effects on the endocrine system and reproductive health. Further research is necessary to explore the full extent of these disruptions and to develop strategies for mitigating the negative impacts of smoking on male fertility.

Prolonged smoking has been shown to cause testicular damage characterized by Leydig cell degeneration, a phenomenon supported by animal studies. Histological examination of the testicles of mice exposed to cigarette smoke had significantly smaller seminiferous sizes tubule diameter and epithelial height, decreasing the number of Leydig cells and increasing the percentage tubules with loss of germ cells (Mohamed et al., 2011). Additionally, tobacco users, both smokers and chewers, exhibit elevated levels of reactive oxygen species (ROS)(Kumar et al., 2015). Oxidative stress is believed to be the main factor contributing to sperm quality and quantity being affected by excessive free radical production. Excessive reactive oxygen species (ROS) impact male fertility.(Hussain et al., 2023). While ROS plays a crucial physiological role in sperm function at normal levels, excessive ROS levels can be detrimental. High ROS levels, exceeding the body's antioxidant defenses, can damage sperm membranes and impair Leydig cell function, thereby disrupting the spermatogenesis process. This oxidative damage to Leydig cells, crucial for testosterone production, further exacerbates the negative impact of smoking on male fertility. The combination of Leydig cell degeneration and oxidative stress underscores the importance of mitigating smoking's harmful effects on reproductive health. Future research should focus on elucidating the mechanisms of ROS-induced damage and developing effective strategies to protect against oxidative stress in smokers.

Conclusions

Exposure to cigarette smoke has detrimental effects on reproductive health, which are characterized by a decrease in testosterone levels and alterations in both follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels in male smokers. Chronic smoking disrupts the hypothalamus-pituitary-gonadal axis, leading to hormonal imbalances that impair the production and regulation of essential reproductive hormones. These changes can result in reduced spermatogenesis and overall fertility. The oxidative stress induced by smoking further exacerbates these issues, damaging Leydig cells and sperm membranes, thereby compounding the negative impact on male reproductive health. Given the significant implications for fertility, it is crucial to address and mitigate the harmful effects of smoking through targeted interventions and public health strategies. In addition, further research is needed to increase reproductive hormone levels in male smokers.

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