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Sex Hormone Levels and Their Effects on body Function in Hypoxic Environments at High Altitude

Yanyan Wang[1], Yuan Xing[2]*, Yanxia Han[2]*, Pan Geng[1], Zhuanghao Feng[1]

[1]School of Public Health, Gansu University of Chinese Medicine, Lanzhou 730000, Gansu, China

[2]Department of Clinical Laboratory, the 940th Hospital of Joint Logistic Support Force, People's Liberation Army, Lanzhou 730050, Gansu, China

**Author to whom correspondence should be addressed.*

Abstract: The plateau environment is characterized by hypoxia, low air pressure, cold temperatures, and intense ultraviolet radiation. Hypoxia is a predominant factor affecting human physiological functions. Long and short-term exposure to high-altitude hypoxic environments indicate the triggering of adaptive adjustments across multiple systems of the body. The changes in the endocrine system, in sex hormones, provide evidence of associations with alterations in human functions. A review of the regulatory mechanisms of testosterone, estrogen, and progesterone secretion under hypoxic stress. An in-depth exploration of how these hormones influence the cardiovascular system, reproductive system, skeletal muscle metabolism, and neural functions has been made. A discussion of the dynamic changes in hormone levels during high-altitude adaptation and potential intervention strategies. The provision of theoretical reference is necessary for research in high-altitude medicine, exercise physiology, and reproductive health.

Keywords: High altitude; Hypoxia; Sex hormones; Cardiovascular system; Reproductive system; Metabolic system

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1. Introduction

High-altitude regions cover 25% of the Earth's surface, with more than 140 million people residing there. When the body is exposed to hypoxia, the decline in oxygen partial pressure (PO_2) is insufficient oxygen supply to tissues, triggering neuroendocrine and metabolic adaptive responses. Hypoxia can affect the hypothalamic–pituitary–gonadal (HPG) axis, altering the synthesis and secretion of sex hormones, exert wide-ranging effects on cardiovascular, reproductive, metabolic, and neural functions.

The human physiological response to high-altitude hypoxia involves a variety of adaptive mechanisms, evident in the endocrine system. Enhanced oxidative stress and disrupted metabolic pathways cause dysregulation of testosterone and estrogen secretion [1]. High-altitude environments disrupt gut microbial balance, altering in hormone levels and metabolic functions. Such imbalances exacerbate issues in appetite regulation and nutrient absorption, complicating the physiological adaptations necessary for survival under predominantly hypoxic conditions [2]. Prolonged exposure to hypoxia leads to

maladaptive responses and predisposes individuals to subsequent cardiovascular complications [3].

2. Regulatory mechanisms of high-altitude hypoxia on the hypothalamic–pituitary–gonadal (HPG) axis

The HPG axis is the central neuroendocrine system that regulates the synthesis and secretion of sex hormones. The hypothalamus secretes gonadotropin-releasing hormone (GnRH), stimulating the anterior pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This suppression decreased secretion of LH and FSH from the pituitary. Individuals exposed to high-altitude environments have lower serum testosterone and estrogen levels, which are associated with reduced LH and FSH secretion, their potential to complicate traditional interpretations of reproductive health in extreme conditions [4].

Hypoxia affects the testes and ovaries. Low-oxygen environments inhibit the activity of steroidogenic enzymes in Leydig and granulosa cells, decreasing testosterone and estrogen [5]. This dual mechanism impacts of hypoxia on sex hormone levels and contributes to reproductive dysfunction and impaired fertility.

2.1. Central nervous system regulation

The hypothalamus is a hypoxia-sensitive region. Hypoxia can activate the sympathetic nervous system via carotid body chemoreceptors, the stimulation of the paraventricular nucleus (PVN) of the hypothalamus releases corticotropin-releasing hormone (CRH), the regulatory factor of the hypothalamic–pituitary–adrenal (HPA) axis, inhibits the HPG axis through several mechanisms:

(1) Direct suppression of pulsatile release of GnRH neurons in the hypothalamus, reducing LH and FSH secretion;

(2) Promotion of pituitary β-endorphin release, which blocks GnRH signal transmission through opioid receptors;

(3) Elevation of glucocorticoid levels, which exert feedback inhibition on GnRH and LH secretion.

2.2. Oxidative stress and inflammatory responses

In hypoxic environments, mitochondrial electron transport chain dysfunction increases production of reactive oxygen species (ROS), resulting in oxidative stress. Oxidative stress activates the nuclear factor κB (NF-κB) signaling pathway, promotes the release of pro-inflammatory cytokines. Hypoxia at high altitudes may cause gonadal cell damage. Oxidative damage to the gonadal tissue under hypoxic conditions is a major factor of the decline in sex hormone levels [6]. Supplementation with antioxidants indicates a partial reversal of hypoxia-induced decreases in sex hormone levels, a protective role of antioxidants against oxidative stress [7].

2.3. Regulatory role of hypoxia-inducible factors (HIFs)

Hypoxia-inducible factors (HIFs), HIF-1α, play a substantial role in the response to low-oxygen environments. HIF-1α stabilization under hypoxia indicates the modulation of multiple steroidogenic enzymes [8]. The activation of HIF-1α is associated with alterations in the expression of genes, creating an interaction between hypoxia and hormonal regulation. HIF-2α influences sex hormone levels by regulating erythropoietin (EPO), and fluctuations in EPO have been linked to changes in reproductive hormone levels [9]. HIFs indicate the mediation of physiological adaptation to hypoxia and shape the hormonal landscape.

3. Effects of sex hormone changes on the cardiovascular system under hypoxic conditions

3.1. Relationship between reduced testosterone levels and cardiovascular function

In high-altitude hypoxic environments, the decline in testosterone levels has implications for cardiovascular health.

Hypoxia has a reduction in testosterone production, impairs endothelial function, and vascular reactivity. Low testosterone levels are associated with endothelial dysfunction, and endothelial health is critical for maintaining vascular integrity and regulating blood pressure.

Endothelial dysfunction associated with low testosterone arises from reduced nitric oxide bioavailability. Testosterone replacement therapy suggests that restoring testosterone levels helps mitigate the adverse cardiovascular effects of high-altitude exposure. Concerns persist regarding the potential cardiovascular risks of testosterone therapy reported [10–12].

3.2. Protective role of estrogen

Estrogen exhibits protective effects on cardiovascular health. This hormone indicates an enhancement of endothelial function by activating endothelial nitric oxide synthase (eNOS), and indicates an improvement in vasodilation. Estrogen supports the alleviation of hypoxia by supporting vasodilation and leads to a reduction in pulmonary arterial pressure, in overall cardiovascular function. The decline in estrogen levels is associated with reduced adaptability to high-altitude environments in women; estrogen's cardioprotective role is a crucial factor for maintaining vascular health. Understanding of estrogen's role in cardiovascular adaptation to hypoxia sheds light on sex differences in cardiovascular responses, and strategic insights for managing cardiovascular health in women exposed to high-altitude environments [11–14].

4. Effects of hormonal changes on the reproductive system under hypoxic conditions

4.1. Effects on male testosterone levels

Testosterone is the predominant male sex hormone. Acute hypoxia: short-term exposure to high altitude capable of causing a decline in male testosterone levels. The underlying mechanisms involve an acute activation of the HPA axis and accelerated hepatic testosterone metabolism [15].

4.1.1. Chronic hypoxia

Andean highlanders have testosterone levels of approximately 18% lower than those of lowland populations.

4.1.2. De-acclimatization phenomenon

Upon returning from high altitude to lowland areas, testosterone levels recover within 3 months. High-altitude exposure reduces testosterone levels, associated with decreased sperm count and motility, affecting fertility [4]. Oxidative stress exacerbates damage during spermatogenesis broadly, which leads to reduced sperm quality and an apparent increase in abnormal morphology [7]. Prolonged hypoxia increases the risk of male infertility, revealed through reduced testis and epididymis weight and an increase in germ cell apoptosis [4,7].

4.2. Effects on female estradiol and progesterone levels

The regulation of female sex hormone levels inherently complicates the discernible impact of high-altitude hypoxia. Initial observations concerning menstrual cycle disorders are that acute exposure to high altitude suggests a propensity for menstrual cycle irregularities.

Estradiol (E_2) is synthesized by ovarian granulosa cells under LH stimulation. These findings in a controlled acute hypoxia scenario are a decrease in follicular-phase E_2 levels by about 19%. This reduction was accompanied by an increased FSH/LH ratio and impaired follicular development. Regarding pregnancy, high-altitude hypoxia supports a causal link to placental insufficiency in pregnant women, accompanied by reduced secretion of human placental lactogen (hPL) and progesterone.

Hypoxia-induced hormonal changes also affect the timing of puberty and reproductive age, exacerbating the array of reproductive health challenges faced by women in high-altitude regions [1]. The pressing need to develop targeted strategies aimed at supporting female reproductive health under hypoxic conditions.

5. Effects of hormonal changes on the metabolic system under hypoxic conditions

The hypoxic environment of high altitudes causes alterations in sex hormone levels and affects metabolic functions. Hypoxic exposure disrupts hormonal balance, concerning testosterone and estrogen, the predominant regulators of metabolic processes. Hypoxia supports the exacerbation of insulin resistance, wherein the body's cells respond less effectively to insulin, reducing glucose uptake efficiency and typically elevating blood glucose levels.

Hypoxia-induced alterations in lipid metabolism result in dyslipidemia. The interplay between hormone fluctuations and metabolic dysfunction under hypoxia involves intricate mechanisms to design targeted interventions that can mitigate the adverse health impacts of high-altitude exposure [7,16]. Testosterone replacement therapy has been investigated to counteract the adverse effects of high-altitude hypoxia on muscle mass and metabolic health.

Testosterone enhances insulin sensitivity and promotes fat oxidation, improving metabolic function in hypoxic environments. In clinical applications, testosterone replacement therapy supports the maintenance of lean body mass and enhances metabolic health, addressing the increased risks of insulin resistance and metabolic dysfunction. Optimizing testosterone levels improves metabolic function and reduces health complications among high-altitude populations [1,3]. Information can be seen in **Figure 1**.

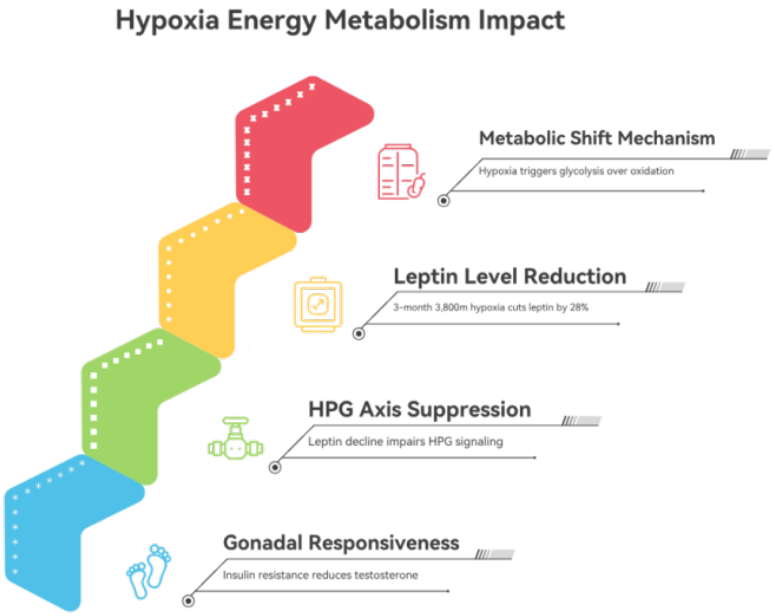

Figure 1. Hypoxia energy metabolism impact.

6. Hormonal changes in high-altitude hypoxia and their effects on other body functions

6.1. Changes in skeletal muscle function

There is a tendency to affect skeletal muscle function mainly by inhibiting the muscle protein synthesis of physiological adaptation. Testosterone promotes muscle growth and maintenance by activating anabolic processes. In high-altitude regions, the physiological stress on the body reduced testosterone levels.

Hypoxia interferes with the metabolic pathways necessary for muscle recovery and adaptation, impairing muscle function. Estrogen supports protective effects on skeletal muscle under hypoxic conditions. Estrogen enhances mitochondrial function, improving skeletal muscle tolerance to low oxygen. By optimizing energy production and reducing oxidative stress, estrogen helps mitigate the adverse effects of hypoxia on muscle function. Understanding these mechanisms is crucial for developing strategies to preserve muscle function [17,18].

6.2. Changes in the nervous system

High-altitude hypoxia has multidimensional effects on the nervous system. Prolonged exposure to low-oxygen environments indicates alterations in neurotransmitter levels and neural plasticity, affecting cognitive and emotional functions. In high-altitude settings, declining testosterone levels potentially lead to cognitive impairment and a greater susceptibility to mood disorders.

Hypoxia disrupts the balance of neurotransmitters that critical for mood regulation and cognitive performance. Further research needs to elucidate the specific mechanisms by which sex hormones influence nervous system function in high-altitude environments, which would lead to targeted interventions to support the psychological well-being of affected populations [1,10]. Related points are summarized in **Figure 2**.

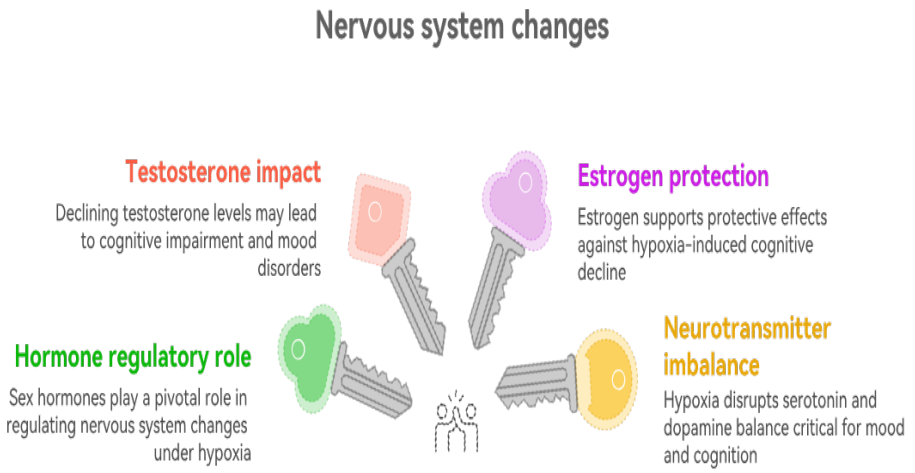

Figure 2. Nervous system changes.

7. Intervention strategies and future perspectives

To address sex hormone imbalances and functional decline purportedly caused by high-altitude hypoxia, intervention strategies can be considered. Pharmacological interventions suggest short-term use of GnRH agonists, stimulating LH secretion and increased testosterone levels. A complication of traditional interpretations is that long-term use suppresses the HPG axis via feedback inhibition.

Combining zinc, vitamin D, and omega-3 fatty acids improves sex hormone levels. Daily supplementation with 30 mg of zinc provides evidence that increases free testosterone levels in high-altitude men by 22%. For hypoxic pre-acclimatization training, stepwise altitude exposure shows a gradual activation of adaptive mechanisms in the body and a reduction in suppression of the HPG axis.

As for gene therapy, research on hypoxia adaptation genes such as EPAS1 lays a basis for future precision interventions. Sex hormones in short-term reductions may help lower energy expenditure and prioritize oxygen delivery to vital organs. In contrast, long-term disruptions can result in irreversible damage. Future research's key contents are outlined in **Figure 3**.

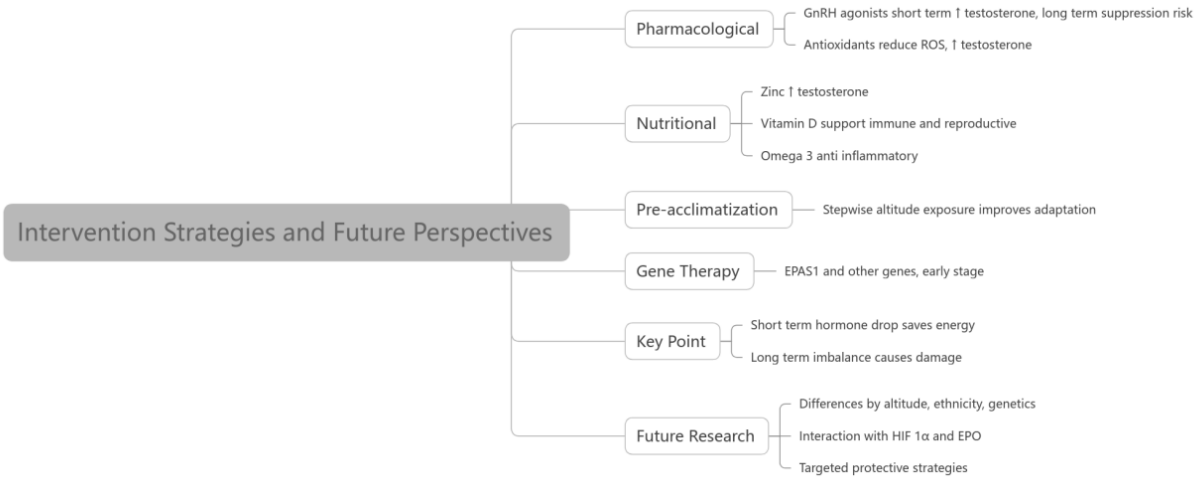

Figure 3. Key Contents of intervention strategies and future perspectives.

8. Conclusion

The relationship between high-altitude hypoxia and sex hormone levels involves multiple physiological and biochemical pathways, including HPG axis suppression, oxidative stress, HIF activation, and metabolic disturbances. Hormonal changes affect cardiovascular, reproductive, musculoskeletal, metabolic, and psychological health.

Hypoxia–hormone interactions are shaped by genetic background, acclimatization, and environmental factors, so multidisciplinary approaches integrating endocrinology, physiology, and environmental medicine are necessary. Deeper insights into the hypoxia–hormone physiology network will be crucial for developing effective interventions, enhancing resilience, and safeguarding health in high-altitude populations.

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Disclosure statement

The authors declare no conflict of interest.

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