

Treatment of Late-onset Hypogonadism with Traditional Chinese and Western Medicine

Xin Kong¹, Hongxia Su^{2,*}

¹Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China

²Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712000, China

*Corresponding author

Abstract: Late-onset hypogonadism has also experienced changes in the names of "partial androgen deficiency syndrome in middle-aged and elderly men", "male climacteric syndrome" and "adult interstitial cell failure". With the acceleration of the aging process of the population in China, the incidence of late-onset hypogonadism in men is increasing year by year, which has become another major factor affecting the physical and mental health of middle-aged and elderly men, which is enough to attract the attention of the medical community and society. Both traditional Chinese medicine and Western medicine have their own views on this disease. We can understand the disease from different angles, so as to serve the clinical results. From the perspective of traditional Chinese medicine and Western medicine, this paper analyzes the related problems of late-onset hypogonadism from three aspects: the historical frontier of traditional Chinese medicine, the etiology and pathogenesis of traditional Chinese medicine and Western medicine, and the treatment of traditional Chinese medicine and Western medicine, so as to provide reference for clinical practice.

Keywords: Late-onset hypogonadism; dialectic; traditional Chinese and Western medicine treatment; testosterone

1. Introduction

Table 1: Clinical manifestations of LOH

1. vasomotor symptoms: hot flashes, paroxysmal sweating, palpitations, etc;
2. Mental and psychological symptoms: emotional distress, anxiety and depression, drowsiness or insomnia, lack of passion, emotional instability, memory loss, etc;
3. Physical symptoms: physical strength and energy decline, muscle strength decline, general weakness, centripetal obesity, waist knee and other bone joint pain, etc;
4. Sexual function symptoms: decreased libido, decreased quality of orgasm, inability to ejaculate, etc.

Table 2: Self test table for androgen deficiency (ADAM) in middle-aged and elderly men

1. Is there a decrease in sexual desire?
2. Is there a decrease in physical fitness?
3. Is there a decrease in physical strength and/or endurance?
4. Is there a decrease in height?
5. Is there a decrease in the enjoyment of life?
6. Do you have any sadness and/or bad temper?
7. Is there any weak erection?
8. Is there a decrease in athletic ability?
9. Do you like to doze off after meals?
10. Have you had any recent poor work performance?

Modern medicine believes that late-onset hypogonadism refers to a syndrome in which the serum testosterone levels in males gradually decrease with age, and a series of corresponding clinical symptoms and signs appear, which will affect the physical and mental health and quality of life of elderly men. The symptoms and signs of LOH vary from person to person, depending on the age of onset, the severity of androgen deficiency, and mental state, etc (Table 1). Elderly men can use ADAM tables for self testing, If they answer "yes" to questions 1,7, or any three other questions, it can be considered a positive answer sheet. Positive individuals should receive early diagnosis and treatment (Table 2). Although there is no

record of LOH in traditional Chinese medicine, the understanding of this disease is relatively early, which can be classified into the categories of "impotence", "depression", "consumption", "hysteria", "up-rushing gas syndrome", etc.

2. The historical frontier of LOH

There is no specific name of "late-onset hypogonadism" in traditional Chinese medicine, but it has been discussed in ancient medical books, such as "Su Wen · Ancient Naivety Theory" said: "When a man is 40 years old, Kidney qi begins to fail, resulting in hair loss and withered teeth; At the age of 48, the yang energy on the head and face begins to weaken; At the age of 56, liver qi begins to decline, and the vitality of tendons decreases; At the age of 64, Tiangui is exhausted, with kidney essence decreases and the ability of the kidneys to store essence declines. The body often feels tired, and teeth and hair fall off... The functions of the five internal organs become exhausted, the ability to move muscles and bones is lacking, Tiangui is depleted. And the hair turns gray, the body always feels heavy with walking improperly, and it is impossible to have children". It can be seen that between the ages of 48 and 64, the male kidney qi gradually fails, the body function decreases, the Tiangui gradually dries up. And the qi, blood, yin and yang are imbalance, which is similar to the performance of LOH. "Su Wen·Yin Yang Ying Xiang Da Lun" clearly records that "if you can know seven losses and eight benefits, then the two can be adjusted, if you don't know how to use it, you will have a premature senility. At forty years old, the Yin Qi is half of itself, life is declining. At fifty years old, you will rise weight and your ears and eyes will not be smart. At sixty years old, Yin wilt, Qi declines greatly, the nine orifices are not functioning properly, the lower body is weak and the upper body is solid, and tears and tears all come out. " It emphasizes the importance of the laws of human growth and development, which goes against the laws of nature. It will lead to the failure of Qi, blood, Yin and Yang in the human body, resulting in the symptoms of premature aging ^[1]. "The experience prescription of Ruizhutang" also points out that "a private middle-aged person, one's energy is depleted and one's mind is weakened. It is often said that the heart is disheartened due to a lack of blood and fire, and the kidney qi is exhausted and water cannot rise, leading to isolation in the heart and disharmony between honor and defense. For those who suffer, the upper part of the heart is filled with fear, the middle part is congested and their diet is reduced, the lower part is empty and cold, and in some cases, the yin is weak and not rising, and the visceral qi is slippery." As well as the "Qian Jin Yao Fang: Elderly Care Examples": "When a person is over fifty years old, their yang qi gradually declines, causing damage day and day and affecting their mental strength, they forget the past and the future and be lazy in living, unsatisfactory in planning and teaching, unstable in visual and auditory perception, frequent retreat and lack of progress, varying between the sun and the moon, scattered in everything, feeling bored, forgetful and angry, changing in temperament, poor appetite, and restless sleep. " all of them clearly described the clinical symptoms similar to LOH ^[2], showing similar emotional and cognitive symptoms. It is not difficult to see that traditional Chinese medicine has a long history of understanding this disease. Although there is no clear disease name, but there are records of similar clinical symptoms in ancient books.

3. Etiology and pathogenesis of LOH

3.1. Etiology and pathogenesis of traditional Chinese Medicine

According to the discussion of the above ancient books, traditional Chinese medicine believes that the onset of late-onset hypogonadism is related to the deficiency and imbalance of the functions of the kidney, liver, heart and spleen, mostly around the kidney and liver, and also involves the rise and fall of Qi and blood.

Among them, the kidney is the water viscera, the origin of inborn, the origin of sealing. After men enter old age, the essence in the kidney gradually declines, the Yin and Yang in the kidney lose balance, and the functions of various viscera gradually become disordered, resulting in physical aging and functional failure. That is to say, the growth, development and aging of men are closely related to the decline of the essence of Qi in the kidney. Only when the kidney qi of the human body is filled to a certain extent, it will produce a subtle substance - "Tiangui", which can promote the maturation of the human reproductive organs and maintain the reproductive function. The "filling" and "decaying" of Tiangui is an important watershed for the turning point of physiological phenomena. If there is insufficient renal essence and insufficient transformation of Tiangui, symptoms such as decreased libido may occur; Kidney yang deficiency and decline, with the loss of warm yin organs, can lead to symptoms

of erectile dysfunction; If the kidney qi is not firm and the yang qi is weak and unable to lift, symptoms such as the penis being lifted but not firm, and being erect but not long will occur.

At the same time, the liver is the official organ of a general, the organ of strength, and the organ of wind and wood, it is mainly used to drain and store blood. It likes to regulate and dislikes depression, it can coordinate the functions of various viscera, and is the hub for maintaining normal life activities. The liver takes blood as its body, Qi as its use, Yin as its body, and Yang as its use, which integrates Yin and Yang, Qi and blood as a body. Therefore, the pathological changes of the liver can easily lead to the dysfunction of the viscera. Liver disease is often preceded by stagnation of liver qi, which will lead to many other pathological results. Stagnation of liver qi for a long time, failure to relieve, will turn into fire and injure Yin; Liver Yin is damaged and Yin does not contain Yang, leading to excessive rise of liver Yang and hyperactivity of liver Yang; The hyperactivity of liver Yang has no control, and wood fire generates wind, forming liver wind. Moreover, qi stagnation will lead to blood stasis, and the operation of blood depends on the promotion of Qi. The stagnation of Qi operation will lead to the disorder of blood operation, blood stasis, and phlegm dampness due to the disorder of body fluid operation. At the same time, the five elements generate and control each other. The liver is the son of the kidney and the mother of the heart. If the son steals the mother's Qi, it will hurt the kidney, and the mother's disease and the son will attack the heart; The liver belongs to the earth, and the spleen belongs to the wood. The wood invading the earth will hurt the spleen (Figure 1). Therefore, liver problems will lead to memory loss, irritability, drowsiness, mental decline and other symptoms.

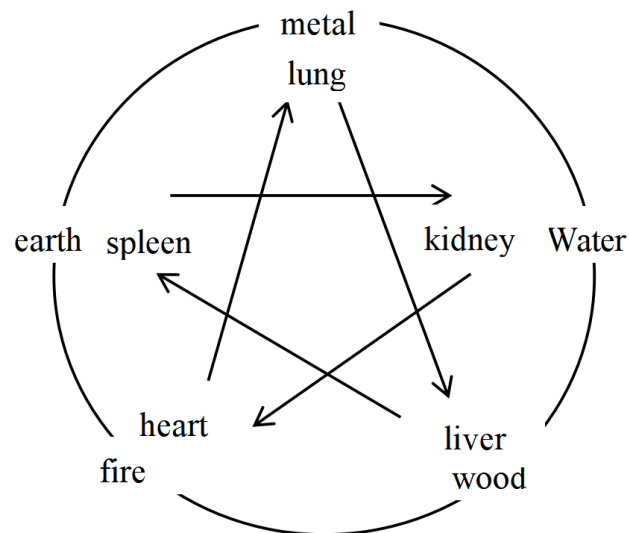


Figure 1: The Diagram of Five Elements Generating and Suppressing Each Other

Finally, the spleen and stomach are the earth and the acquired foundation, and they jointly undertake the important task of transforming Qi and blood. Therefore, they are also known as "the official of the barn", "the sea of water and valley", "the biochemical source of Qi and blood". All the substances that maintain the life activities of the human body are transformed from the food transported by the spleen and stomach; The heart is a fire viscera, which governs the blood vessels and hides the spirit. The heart qi promotes and regulates the blood circulation in the veins, playing the role of nutrition and moistening the whole body, therefore, the viscera function of the human body is closely related to the heart and spleen. In middle-aged and elderly people, the function of spleen and stomach transportation decreases, unable to regenerate Qi and blood, Qi deficiency and blood deficiency, heart and pulse loss, and unable to nourish the whole body, which will lead to the decline of physical strength and energy, muscle strength, waist and knee pain and other symptoms manifested as shown by LOH.

It can be seen that the interaction between the viscera organs has a significant impact on the occurrence of LOH. In addition, zhangdengke^[3] believes that the main pathogenesis of this disease is kidney deficiency and liver depression, and the secondary pathogenesis is Yin and blood deficiency and heart and spleen deficiency. Yuanshuyan et al^[4] believes that kidney deficiency and liver depression are the basic pathogenesis of the disease. Professor Wang Qi^[5] also proposes the pathogenesis of "kidney deficiency and liver depression" and believes that it should be treated by "tonifying the kidney and soothing the liver". Wangyanping et al^[6] believe that it is related to kidney qi deficiency and yin-yang imbalance. The root cause of the disease is in the kidney, the target is in the liver, and it is closely related to the heart and spleen. Daidongxi et al^[7] take 55 patients as samples and conclude that the disease is the

result of failure and imbalance of kidney, liver, heart and other organs. The dialectical classification is mainly Yin deficiency. Professor Zhoufusheng^[8] points out that kidney deficiency and imbalance of yin and yang are the pathogenesis basis of the disease, liver depression, phlegm and blood stasis are the pivot of the disease, and tonifying the kidney, soothing the liver and calming nerves are the key to treatment. Huhaixiang^[9] believes that this disease is due to kidney deficiency, which can also involve other internal organs. The kidney is "the root of yin and Yang in the five zang organs". The kidney essence generates kidney qi, which is divided into yin and Yang. Kidney yin and kidney yang can mutually support, promote and coordinate the balance of yin and Yang in the organs of the whole body. Therefore, "the gradual loss of kidney essence and the decline of tiangui" is the fundamental cause of male climacteric syndrome. The imbalance of Qi and blood in the Zang Fu organs and the imbalance of yin and yang are the basic pathogenesis of this disease.

In general, this article believes that this disease is rooted in the kidney and targeted at the liver, which is closely related to the heart and spleen. Clinical dialectical treatment should be based on kidney deficiency, liver depression as the standard, taking into account other organs and treating with symptoms^[10].

3.2. Etiology and pathogenesis of Western Medicine

Modern medicine believes that age, obesity, bad living habits, harmful environmental factors, systemic diseases, drugs and other factors are the important causes of the disease.

The pathogenesis of late-onset hypogonadism is complex and not yet fully understood. At present, it is considered that the main pathogenesis of late-onset hypogonadism is the reduction of androgen levels and the sensitivity of target organs to androgens. It may be related to the increase of age. The impulse secretion of GnRH in the hypothalamus becomes slow, the pituitary response to GnRH becomes slow, and the production of LH decreases, resulting in the decline of hypothalamus-pituitary-gonadal axis function and testicular function (Figure 2). Or with the increase of age, the decrease in androgen receptor (AR) levels and sensitivity leads to a partial lack of androgen effect, which makes the clinical symptoms of LOH more obvious. Or with the increase of age, sex hormone binding globulin (SHBG) increases. SHBG is a multifunctional protein that transports androgens, which can prevent androgens from being degraded by blood vessels. The combination of SHBG and androgens will lead to the significant decrease of plasma bioactive testosterone level, resulting in the decline of testicular function^[11]. Moreover, the change of testosterone level is also related to the increase of body weight and some metabolic and chronic diseases, such as abnormal glucose metabolism, hypertension, dyslipidemia, liver or renal failure^[12].

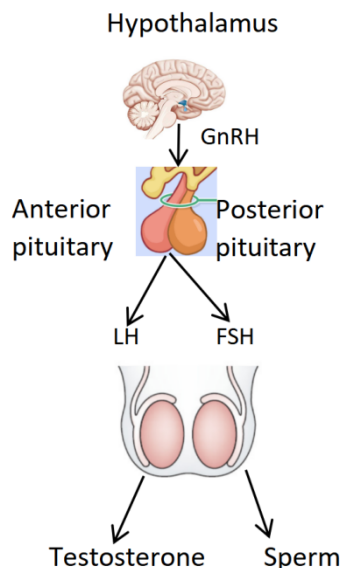


Figure 2: Hypothalamic-pituitary-gonadal axis

In addition, the occurrence of LOH is also related to the testis itself. Studies have shown that with the increase of age, the volume of male testis decreases, the texture becomes soft, the number of Leydig cells (LCs) decreases, the response to gonadotropins decreases, and the activity of enzymes related to testosterone synthesis decreases, resulting in the decline of the function of LCs in the synthesis and

secretion of testosterone ^[13]. (Figure 3)

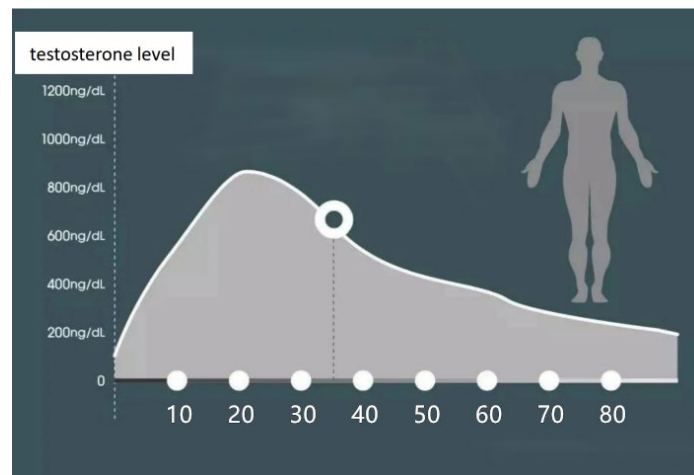


Figure 3: The trend of changes in male hormones with age

4. Treatment of LOH with traditional Chinese and Western Medicine

4.1. Western medicine treatment of LOH

First, studies have shown that obesity and hypogonadism promote and cause each other. Weight loss caused by moderate aerobic exercise, diet control, weight loss surgery and other healthy methods in obese patients can increase serum testosterone levels. Therefore, the European Society of Urology guidelines regard weight loss and changing habits as "strong recommendations" for treatment, and weight loss is a "required course" before hormone therapy.

Secondly, for modern medicine, the basic principle of LOH treatment is to supplement exogenous testosterone, improve serum testosterone level, and maintain normal body function. The treatment based on testosterone replacement therapy is becoming more and more mature, and is regarded as the gold standard for LOH treatment. Currently, there are oral preparations, injection preparations, skin patches, etc. in clinical practice. Oral testosterone undecanoate capsules are the most widely used. After oral administration, testosterone undecanoate is absorbed into the blood through the chylous duct in the lymphatic vessels of the small intestine, avoiding the first pass effect and hepatotoxicity of the liver. It is safe, effective and easy to carry. At the same time, the most common symptom of LOH patients is accompanied by erectile dysfunction. It is often effective to supplement androgen with phosphodiesterase 5 inhibitors such as tadalafil.

However, long-term androgen therapy will not only increase the risk of benign prostatic hyperplasia and prostate cancer, but also increase the risk of male breast cancer, resulting in fluid retention, hematocrit rise and other adverse reactions. At this time, finasteride can be used in combination 5 α reductase inhibitors can reduce the production of androgen in the prostate, promote the apoptosis of prostate cells, reduce the volume of the prostate, and effectively alleviate the side effects of androgen therapy on the prostate. And the effect of TST in improving the mental and psychological status of patients is not ideal, so it needs to be treated with traditional Chinese medicine.

In addition, human recombinant insulin-like growth factor-1 (rhIGF-1), testicular stromal cell transplantation, testicular transplantation and stem cell transplantation are all under development, which plays a good role in enriching the treatment of LOH in the future.

4.2. TCM treatment of LOH

Si Hongmei ^[14] and others screened out 9 literatures and 739 patients by searching the database, and carried out systematic evaluation and meta-analysis research on the treatment of LOH with traditional Chinese medicine. The research showed that the curative effect of traditional Chinese medicine in the treatment of LOH was equivalent to that of testosterone replacement therapy, with less toxic and side effects and stable curative effect, and traditional Chinese medicine was superior to western medicine in improving cardiovascular symptoms and mental state of patients. Traditional Chinese medicine can be

used to treat LOH in many ways, such as dialectical treatment of prescription and medicine, acupuncture and moxibustion, diet therapy, exercise therapy and so on.

4.2.1. Dialectical treatment of prescription and medicine

So far, the dialectical understanding of LOH in the field of traditional Chinese medicine is a hundred schools of thought, and a unified basic syndrome type and treatment principle have not been established yet. Its dialectical standard is affected by patient samples, regional differences and personal experience of doctors. Although LOH is dialectically diverse, the essence of its pathological changes is still mainly deficiency with excess. The viscera involved are mainly liver and kidney, involving heart, spleen and Qi and blood. Deficiency is mainly manifested by deficiency of Yin, Yang, Qi and blood, while excess is mainly manifested by phlegm, fire and blood stasis. Many classic formulas can be used for treatment such as Qiju Dihuang Pill, Huanglian Wendan decoction, Zishen-jieyu formula, ect.

In addition to the classical prescriptions, many physicians treat with self-made prescriptions, such as self-made Zishui Qinggan Decoction by Huang Ling^[15], self-made Yishen Tianjing Decoction by Wang Yanping^[16], self-made KangLong capsule by Li Guangbin^[17], and self-made Bushen Yijing Decoction by Li Zengbang^[18], all of which have achieved good curative effects.

4.2.2. Acupuncture and moxibustion treatment

Acupuncture and moxibustion treatment has the characteristics of no side effects and definite curative effect. Acupuncture and moxibustion originated more than 2000 years ago. As early as in the Yellow Emperor's Canon of internal medicine, there were records about acupuncture and moxibustion used to strengthen the body and anti-aging. At the same time, a consensus was reached at the acupuncture and moxibustion hearing held by the National Institutes of Health (NIH) in 1997, which believed that acupuncture and moxibustion not only had significant effect on analgesia, but also affirmed the impact of acupuncture and moxibustion on the endocrine system, respiratory system and digestive system^[19].

Acupuncture and moxibustion can restore the balance of Yin and Yang of the Zang Fu organs, regulate the endocrine of the human body, adjust the relationship between the Zang Fu organs of elderly men, so as to improve the functions of the brain, pituitary, adrenal gland and gonad^[20]. According to the etiology and pathogenesis of this disease, it can be seen that the disease is mostly located in the liver and kidney, and the pathological nature is mainly deficiency. Deficiency can be divided into two different properties of "Yin" and "Yang" in traditional Chinese medicine. Therefore, acupuncture and moxibustion treatment should "tonify the liver and kidney, balance Yin and Yang", just as "When Yin is calm and Yang is secret, and the spirit is the cure" recorded in "Su Wen · Sheng Qi Tong Tian Lun". Clinical acupoints should be selected dialectically according to different symptoms.

4.2.3. Other adjuvant therapy

For the treatment of LOH in traditional Chinese medicine, in addition to the traditional dialectical treatment and acupuncture treatment, it can also be combined with other adjuvant treatments to enhance the curative effect, such as massage, ear acupoint pressing beans, Taijiquan, Baduanjin, Wuqinxi and other sports health preserving methods and emotional nursing to reduce the clinical symptoms, so as to enhance the clinical curative effect. Professor Wang Qi^[21] also stressed that diet therapy can protect the spleen and stomach, replenish qi and blood, enhance body quality, so as to prevent and reduce symptoms.

5. Summary

Elderly men and women are different. Their sperm formation, Leydig cell function and adrenal function are a gradual decline process. There is no clear dividing line for women to "menopause". Therefore, LOH is occult, and it is difficult to have a clear diagnostic standard, which is often ignored, which makes the research progress of LOH in China slow.

However, with the accelerating process of aging in China and the increasing work pressure and mental pressure of people, more and more middle-aged and elderly men will experience LOH in the future, and the physical and mental health problems of middle-aged and elderly men will become increasingly obvious and receive much attention. It is not difficult to find that simple western medicine treatment can achieve good results on some symptoms of LOH patients, but when insomnia, amnesia and other psychological and mental symptoms occur, simple androgen replacement therapy has no obvious effect. At this time, the intervention of traditional Chinese medicine is needed. The unique treatment advantages of traditional Chinese medicine can make up for the shortcomings of Western medicine treatment and expand the treatment of this disease. Therefore, from the perspective of traditional Chinese medicine,

actively explore the idea and method of traditional Chinese medicine for LOH diagnosis and treatment, which is conducive to better serve the clinic, and is worthy of in-depth study.

References

- [1] Zhou Minquan, Zhang Yingjuan, Zhou Qilin. *Traditional Chinese Medicine treatment of male menopausal syndrome*[C]. Beijing: Chinese Society of Traditional Chinese Medicine, 2008.
- [2] Xia Zhibo. *Review of Traditional Chinese Medicine Research on Male Menopausal Syndrome* [J]. *Guangming Traditional Chinese Medicine*, 2009, 24 (11): 2229-2230.
- [3] Zhang Dengke. *Progress in Traditional Chinese Medicine Treatment of Male Menopausal Syndrome* [J]. *New Traditional Chinese Medicine*, 2010, 42 (9): 100-102.
- [4] Yuan Shuyan, Xiong Yan. *Treatment of male menopausal syndrome based on liver theory* [J]. *Journal of Clinical Chinese Medicine*, 2020, 32 (3): 453-455.
- [5] Chen Wushan. *Professor Wang Qi's experience in distinguishing and treating male menopause* [J]. *Hebei Journal of Traditional Chinese Medicine*, 2000, 15 (1): 39-40.
- [6] Wang Yanping. *Yi Shen Gu Jing Tang for the treatment of 76 cases of male menopausal syndrome* [J]. *Chinese Journal of Traditional Chinese Medicine Information*, 2001, 8 (9): 66.
- [7] Dai Dongxi, Xie Yi, Zhao Rongshun. *Analysis of Traditional Chinese Medicine Syndrome Types for Partial Androgen Deficiency in Middle and Elderly Men* [J]. *Chinese Journal of Traditional Chinese Medicine Information*, 2003, 10 (6): 49-51.
- [8] Ji Xingshu, Xu Shijie, Liang Xuefen. *Professor Zhou Fusheng's Experience in Treating Male Menopausal Syndrome* [J]. *New Traditional Chinese Medicine*, 2008, 40 (6): 10-11.
- [9] Li Changcheng, Hu Haixiang. *Hu Haixiang's Experience in Treating Male Menopausal Syndrome* [J]. *Henan Traditional Chinese Medicine*, 2013, 33 (9): 1413-1415.
- [10] Zhang Bin. *Observation on the therapeutic effect of modified decoction on 78 cases of male menopausal syndrome* [J]. *Yunnan Journal of Traditional Chinese Medicine*, 2006, 27 (4): 18.
- [11] Li Xingchen, Peng Cheng, Liu Wei, et al. *Research progress on delayed hypogonadism* [J]. *Chinese Journal of Andrology*, 2016, 30 (8): 65-66.
- [12] G. Corona, G. Rastrelli, M. Maggi. *Diagnosis and treatment of late-onset hypogonadism: Systematic review and meta-analysis of TRT outcomes* [J]. *Best Practice & Research Clinical Endocrinology & Metabolism*, 2013, 27(4):557-579.
- [13] Gao Yong, Xiang Peng, Deng Chunhua. *Basic research progress on male delayed hypogonadism* [J]. *International Journal of Reproductive Health/Family Planning*, 2011, 30 (1): 34.
- [14] Si Hongmei, Yu Xudong, Shang Jianwei, et al. *A systematic evaluation and meta-analysis of traditional Chinese medicine in the treatment of delayed hypogonadism* [J]. *Chinese Journal of Experimental Formula*, 2021, 27 (3): 191-197.
- [15] Huang Ling. *Modified Zishui Qinggan Yin for the treatment of 56 cases of male menopausal syndrome* [J]. *Fujian Traditional Chinese Medicine*, 2006, 37 (1): 41.
- [16] Wang Yanping. *Treatment of 76 cases of male menopausal syndrome with Yishen Filling Essence Decoction* [J]. *Chinese Journal of Traditional Chinese Medicine Information*, 2001, 8 (9): 66.
- [17] Li Guangbin, Zhao Hongbo, Zhao Fengxia, et al. *Clinical observation of Kanglong capsules in the treatment of 50 cases of male menopausal syndrome* [J]. *Hebei Traditional Chinese Medicine*, 2002, 24 (9): 700.
- [18] Li Zengbang, Li Yanwen. *Treatment of 62 cases of male menopausal syndrome with integrated traditional Chinese and Western medicine* [J]. *Jiangsu Traditional Chinese Medicine*, 1998, 19 (12): 24.
- [19] Han Jisheng. *Acupuncture and moxibustion Hearing Held by the National Institutes of Health* [J]. *Acupuncture Research*, 1997 (4): 311-313.
- [20] Zhou Shaohu, Chen Jiwen. *Research progress on traditional Chinese medicine treatment of male menopausal syndrome* [J]. *Chinese Journal of Sexual Science*, 2007, 16 (7): 9-10.
- [21] Wang Qi. *Wang Qi Andrology* [M]. Henan: Henan Science and Technology Press, 2007:806.