

EFFECTS OF HORMONAL THERAPY IN TRANSGENDERS

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(Received, 14th June 2024, Revised 20th July 2024, Published 31st July 2024)

Abstract: People who change their gender after birth are known as transgender people. They underwent surgical transformation along with hormonal therapy. Hormonal imbalance is the most common phenomenon in the transgender community due to hormonal therapy and other related issues. Hormonal therapy is essential for gender transformation, but this therapy poses several risks to the individual who is taking this therapy. Transgender people who are under hormonal therapy are more at risk of cardiovascular disorders as certain hormones like estrogen and testosterone, besides their intended function, also induce side effects, due to which individuals taking these hormones become more prone to cardiovascular disorder, irregular blood pressure, brain function, and structure start changing. The cross-sex hormone therapy is also associated with brain tumors, changes in body mass index, and several skin conditions. Such hormones also affect bone density in different individuals due to changes in the deposition pattern of calcium into the bone under hormonal control. Hormonal therapy causes certain metabolic disorders as well, and certain hormones interact with other hormones in a different way when they are not naturally produced in the body. The voice of such people undergoing gender transformation also changes due to the testosterone level. This review summarizes some aspects of hormonal therapy, but whether or not a person undergoes such transition is their choice.

Keywords: Bone Density, Cardiovascular Disorders, Hormonal Imbalance, Hormonal Therapy, Transgender Persons.

Introduction

Sex is the biological character that is controlled by genes and hormones (1), whereas gender is the social and psychological behavior of a person (2). The umbrella term 'transgender' means a person who exhibits variation between their gender identity and sex assigned at birth. The terms 'transsexual' and 'transgender' are used interchangeably (3–5). The term cisgender is used for the person who has the same gender as the assigned sex at the time of birth (6,7). The person who has a conversion from male to female (MtF) is known transwoman, and the person who has a conversion from female to male (FtM) gender is known as transmen (8).

For gender conversion purposes, hormonal replacement therapy or cross-sex hormone therapy is adopted. This treatment helps to reduce the development of the secondary sex character of the natal sex and promotes the development of secondary characteristics of the new desired sex (6,9,10). Transwomen undergo estrogen therapy, and transmen take testosterone for gender affirmation (11). This hormonal therapy not only changes the gender identity of the person undergoing hormonal therapy but also has many adverse effects, such as cardiovascular diseases, thromboembolism, and liver dysfunction (9,12). Estrogen has been found to cause granulomatous mastitis and venous thromboembolism in transwomen (13,14). Similarly, in transmen, testosterone may cause vaginal bleeding, which is a severe complication after initiation of cross-sex hormone therapy. Vaginal bleeding is known to be caused by a low level of serum testosterone and should be adjusted to a physiological male level of testosterone to stop bleeding (15). Amenorrhea for FtM person can be achieved through

testosterone hormone, time taken for complete cessation of menses is entirely dependent on the dose of hormone taken and varies from 1 month to more than six months (16)

Transgender hormonal therapy (THT) also affects brain size, i.e., in female-to-male transgender persons, the brain volume is noted to increase towards the cisgender male references, and total brain volume is observed to be decreased in male-to-female transgender people subjects (17,18). Meningiomas are two times more common in women than men (19). In MtF transgender people, exogenous hormone therapy is known to cause meningiomas. The tumor mass had been observed to increase after initial resection in MtF undergoing hormonal treatment, and these findings were also confirmed by immunohistochemistry, i.e., the presence of progesterone and estrogen receptors in the tissue section (20)

Voice is not only used to communicate our thoughts with others, but it is also a source of identification of gender. Transgender individuals more often encounter these types of issues (21). The quality of voice is directly related to hormone levels. Certain hormones such as androgens (testosterone) causes the voice to deepen irreversibly (22) These hormones are also used during gender affirmation to change voice. Female-to-male (FtM) individuals undergo testosterone therapy, and male-to-female (MtF) individuals have to go through surgical procedures along with hormonal and speech therapy to achieve a satisfactory voice (23). But in transgender persons, besides deepening of voice, testosterone also causes pathological complications such as vocal fatigue and hoarseness of voice (24).

Sex hormones highly influence bone development in pubertal age. Sex steroids shape the bone differently in males and females. Similar effects were also observed in transsexual persons. In male-to-female transsexual persons, the bone size is more comparable to the female reference range than to males. This may be due to the lack of physical activities and androgen deprivation (25–27)

Androgenetic alopecia is caused by testosterone hormone in males and is also known as male pattern baldness. This effect can also be reversed by using estradiol and spironolactone therapy in transwomen (28).

Acute Cardiovascular Events:

Trans women are more prone to developing cardiovascular diseases as compared to trans men (29). Exogenous hormonal therapy in transgender increases the risk of cardiovascular events such as stroke, myocardial infarction, and venous thromboembolic events (30). An observational study with 20 transgenders undergoing gender-affirming hormonal therapy was conducted in 2015; findings declared impairment in lipid profile, that is, homocysteine and leucocytes count, total lean mass, and changes in body composition were increased and decreased total fat mass; all changes in above parameters increases cardiovascular diseases risks (31). In a study with an average of 10 years of hormonal therapy in transgender, transsexual men have fewer cardiovascular diseases than transwomen, like thromboembolism (32). A two-year follow-up study with 309 transgenders (165 transmen and 144 transwomen) undergoing gender-affirming hormonal therapy, by observing the changes in cholesterol (decrease), triglycerides (decrease), and lipids (unfavorable changes), results declared an increased risk of cardiovascular diseases in transmen as compared to transwomen because of no significant changes in above parameters (33,34). A multivariable study conducted between 2014-17 in transgender people who were subjected to hormonal therapy shown that transgender population is at more risk of developing cardiovascular diseases as compared with cisgender population but less risks were observed in transgender women (35).

Testosterone Effect on Cardiovascular System (CVS):

Exposure to testosterone in female males does not affect cardiovascular (CV) events but already presents CVS diseases and age factors effects (36). Androgen and estrogen receptors are present in the body's endothelial cells; testosterone and estrogen bind to these receptors, increasing the transcription of athero-protective and pro-atherogenic genes and decreasing CVS disease risk (37). Testosterone hormonal therapy in male trans is safe in the short and the medium term of CVS health in them (38)

Use of Estrogen:

The use of estrogen for the long term in transfeminine develops the risks of venous thromboembolism, myocardial infarction, and ischemic stroke due to long-term follow-up of estrogen (36,39). Long-term use of estrogen is linked with cardiovascular diseases, leading to mortality (40,41).

In a study conducted with 247 transsexual participants, estrogenic compounds increased the cardiovascular risks in male-to-female transsexuals. (42,43). Research having 676 transgender participants undergone oral estradiol therapy produced low levels of venous thromboembolism.44 Route of administration of estrogen has adverse effects on transgender and causes CV diseases and venous thrombosis; in its oral, estradiol shows a rise in agglutination and also thick blood but no effect if we use it transdermally.45 Transdermal use of estrogen decreases the risks of cardiovascular diseases (46–48). The use of androgen and estrogen has adverse effects on the cardiovascular system if used male to female but no significant results if used female to male in transgender people (49). A research study conducted on cisgender women who were going to be treated with progesterone combined with estrogen to increase breast development showed increased risks of cardiovascular diseases (50). Increased cardiovascular risks (mainly thromboembolism) were observed in cisgender women population who were going hormonal therapy with oral contraceptives, estrogen with or without progesterone (51).

Hormonal Therapy (HT) Effect on Blood Pressure:

The use of testosterone slightly increases blood pressure, while estradiol and cyproterone acetate are associated with thromboembolic risk in transgender (52). Gonadotropin-releasing hormone analogs (GnRH_a) are used in hormonal therapy 19 transgender were included in a study and treated with GnRH_a, and 15 were treated with estrogen; both of these hormones did not increase blood pressure (53). Four hundred seventy transgender participants were taken in a retrospective study having two groups, trans feminine and transmasculine, to check hormonal therapy effect on blood pressure; findings declared that HT decreased systolic blood pressure (SBP) in the trans feminine group and increased SBP in the transmasculine group while no changes in diastolic blood pressure were seen (54-57). transgender participants (a study completed by 23 transgender women and 34 transgender men) were included in a survey to check the effect of hormonal therapy on blood pressure; decreased blood pressure was observed in transgender women (55).

Effects on Adolescents Regarding CVS diseases:

Endocrinological treatment of hormones in transgender in a study by observing the changes in systolic and diastolic blood pressure, body mass index glucose level, results denoted that regarding CVS diseases risks, adolescents' treatment is safe (56,57)

Cardiovascular diseases and hypertension:

In a study comprising 200 transgender women (100 in the control group and 100 undergoing hormonal therapy), increased CVS risk factors were observed (58). Cardiovascular diseases are linked with hypertension, decreased life period, and cause cardiovascular diseases. (59,60).

Effect of Hormone Therapy on Brain in Transgenders

The study of hormone therapy (HT) in transgender people described that testosterone and other hormones in HT affect the structure and functions of the brain. The brain will not work correctly, and also mental health will be disturbed. Hormone therapy can affect the heart, liver, lipids, bones, brain, skin, and reproductive organs; likewise, behaviors and gender-affirming procedures may alter the risks, prevalence, and screening techniques of sexually transmitted infections (62). By hormone therapy, the brain started to change in its culture and connectivity as brain structure and function were disturbed (63).

Brain Function and Structural Changes Due to Hormonal Treatment

Different neuroscientists researched hormonal effects by using various neuroimaging techniques to check the brain structure changing when cross-sex treatment was given. The hormone treatment with an extra dosage of testosterone will change the human brain morphology, which changes the functions by affecting neurotransmitters, mainly affecting men more than females (64). When transgender men get testosterone treatment to transition from female to male, changes in the brain structure are detected by the technique of quantitative magnetic resonance imaging due to the anabolic effect of changes in cortical volume thickness and subcortical volume. Sex steroid treatments in young adults affect the brain as eight transsexual persons, male to female, treated with anti-androgen hormone decreased the brain volume. When six transsexual female male persons were treated with estrogen, the resulting brain and hypothalamus volume increased (65). Differences in hemispheric connectivity reactions (HCR) are driven by increased interhemispheric lobar connectivity in Males to females but decreased intrahemispheric lobar connectivity in females to Males (66). Treatment with testosterone majorly effected on the brain of transmen. It changes the brain by modulating its body perception (67).

Subcortical Gray Matter and Microstructure of White Matter changes due to Hormonal Treatment.

Testosterone hormone therapy mainly affects cortical thickness due to changes in hormonal levels when the hormonal treatment effect is seen on the 15 females to males and 14 males to females in transsexual treatment (68). Cross-sex hormone therapy for a long time with a high dose of testosterone and estradiol hormone changes the progesterone level, which correlates with gray matter and also with subcortical. This affected the subcortical gray matter detected with the help of Magnetic resonance imaging MRI (69). In various neuropsychiatric conditions, gray matter (GM) and microstructure of white matter (WM) are due to hormonal therapy, which is done by weighing the volume of GM and WM (70).

Brain Tumors Due to Cross-Sex Hormonal Treatment

Benign brain tumors occurred due to cross-sex hormonal therapy. Different researchers have diagnosed clinically and

radiologically that meningiomas, prolactinomas, pituitary adenomas, and vestibular schwannoma are tumors that arise due to hormonal treatment—cross-sex hormones like testosterone, progesterone, and estrogen (71). Transsexual patients, male to female, were treated with estrogen and cyproterone acetate for four years; as a result of hormone therapy, meningioma was detected by magnetic resonance imaging (72). A report of prolactinomas in a transwoman associated with spironolactone and the alternate progestin medroxyprogesterone acetate and documentation of the transient changes in prolactin from baseline (before feminizing hormones) in two transwomen demonstrate that marked hyperprolactinemia develops early in the course of Gender Affirming Hormone Therapy (GAHT) (73). Long-term hormonal therapy of transgender people may produce prolactinomas (74).

Effect of Hormonal Therapy on Skin in Transgender:

Those individuals who are going to transition from male to female with hormone therapy have reduced hair growth in certain parts of the body, like skin, and they also have reduced acne. The transition from female to male has increased the chance of hair growth on the face and axillary regions and acne (75).

Testosterone is a hormone that is used in masculinizing hormonal therapy, responsible for secondary sexual characteristics, and stimulates male pattern hair growth and body contour. It is given intramuscularly, orally, buccal, or via subcutaneous implants. Testosterone has a role in the pathogenesis of acne, and its mechanism has not yet been fully discovered. Testosterone is converted into dihydrotestosterone, binding cytoplasmic androgen receptors, which is more abundant in sebocytes, dermal papilla, and endocrine sweat glands. Increased sebum will result in acne vulgaris in sebocytes. In different studies on transgender individuals, the prevalence of acne growth on the face is higher than on the other parts of the body, like the chest or back. Lesion type depends on hormonal therapy, age, and sebum production (76).

Exogenous hormones affect hair development and sebum production, resulting in xerosis from estrogen or acne. Condyloma and HPV-associated skin cancer have been reported in women who have undergone gender confirmation surgery. Estrogen effectively removes body hair but does not obliterate facial hair; it only decreases its size and density (77).

Hormone therapy may cause undesirable cutaneous effects like xerosis, pruritus, and eczematous changes, and it also affects the overall body fat. If one has no human papillomavirus vaccine and has a high prevalence of human papillomavirus infection, dermatological conditions like squamous cell carcinoma and lichen sclerosis may occur internally and externally in neovagina (78)

Understanding medical and surgical care goals is important because it is essential in adapting dermatologic therapy safely and affirmatively. The use of GAH may impact the development and treatment of acne. GnRH is used as a puberty blocker in the treatment of acne, and a study was conducted involving six women aged 20-32 years who were treated with GnRH agonists, and there was an improvement in acne sores. When dermatologists treat transgender

[Citation: Arshad, A., Atif, M., Huzaifa, M., Tayyab, M.M., Rafiq, B., Khan, M.L.A., Shahid, M.N., (2024). Effects of hormonal therapy in transgenders. *Biol. Clin. Sci. Res. J.*, 2024: 948. doi: <https://doi.org/10.54112/bcsrj.v2024i1.948>]

patients with acne, the environment should be supportive, and they should discuss their long-term goals and also discuss how their skin influences their mode and feelings (79).

Effect of Hormonal Therapy on Bones in Transgenders

In boys, estrogen plays the main role during the physiological limits; in men and women, during puberty, testosterone stimulates periosteal and has a common role in bone metabolism and remodeling (80).

In transwomen, surgery was based on the reassignment drug and administration of testosterone, and transmen were less than transwomen (81).

In women, during menopause, less estrogen enhances the one resorption and less bone mineral density (BMD). More androgen was found in the trabecular (BMD) in women. After orchiectomy in men, testosterone deficiency was found to be associated with accelerated bone loss.⁸² A study shows that in the first ten years of HT, there is no negative effect on bone mineral density (BMD) and indicates that it is not necessary to check BMD during HT regularly (82). Sex steroids are crucial in Hormonal Therapy for transgenders. When estrogen treatment is done, then it has a positive effect on the trabecular bone score, which is increased in transmen and decreased in transwomen. However, there was no effect on cortical bone geometrical parameters during the hormone therapy (83).

One year of treatment of transgender people with different formulations of sex hormones such as testosterone is very safe with no significant effect on bone (84).

We treat the transmen with transdermal or intramuscular testosterone. The cross-hormone treatment (CHT) increases the (BMD) after the treatment of one year (85).

Cross-sex hormonal therapy, for a long time, was affecting the metabolites and bones of transgenders. Hormone therapy with benefits has many serious bad effects on the body (86).

Hormonal therapy with a sufficient dose of estrogen in female transgenders produces feminizing changes and suppresses the developed masculinization when estrogen is used as antiandrogen (87).

Effects on Metabolism

Lipid Metabolism

THT normally causes changes in blood lipids among transgender individuals (88). In a cohort study of transgender patients taking spironolactone and estrogen, MtF showed an increase in high-density lipid-protein (HDL) and no change in triglycerides. FtM taking testosterone showed no significant changes in HDL, triglycerides, and low-density lipid protein (LDL) (89). Testosterone therapy in transgender individuals has the effect of increased fat production in the abdominal area with an increase in muscle mass strength (90). TW using estradiol hormone therapy had no change in lipid measurements, while TM carrying testosterone hormone therapy had increased triglycerides and decreased high-density lipid-protein (91). In a 5-year retrospective study, TM following testosterone therapy showed a relative

increase in LDL in the 3rd and 4th to 5th years and a decrease in HDL in the early two years. However, TW, following estrogen therapy, had a rise in HDL at three months, but no significant change in the absolute value of LDL and total cholesterol was observed.⁹² In a recent study, hormone therapy by the use of estradiol in TW shows a decrease in total cholesterol LDL-cholesterol and HDL-cholesterol with no change in triglycerides and non-significant changes in total cholesterol and low-density lipoprotein cholesterol (LDL-C), and TM having testosterone administration gives a significant increase in triglycerides and reduction in HDL-C by follow up of 12 months (88).

Glucose and Insulin Metabolism

A cohort research study –undergoing gender affirming hormone therapy (GAHT) for 12 months shows increase in fasting insulin level in transwomen, and decrease in transmen. However, both had particularly no change in fasting glucose, glucose, and insulin levels during the oral glucose tolerance test (OGTT) (93). Corresponding to the previous one, another cohort study shows no effect of GAHT on fasting plasma glucose and an insignificant decrease in fasting insulin levels, homeostatic model assessment for insulin resistance (HOMA-IR) in TM. While TW showed no change in fasting plasma glucose, it was followed by higher fasting insulin levels and HOMA-IR, respectively (94). A GAHT cross-sectional control study shows that in TM, a significantly low level of HbA1C and high levels of fasting insulin and HOMA-IR occurred. There was no difference in the metabolism of glucose levels among TW compared to the control group of cisgender males and females (95).

Body Mass Index (BMI)

The effect of hormone therapy on BMI has been studied in various studies. A retrospective study gives no significant impact of hormone therapy in both TM or TW (92). The GAHT in an observational study of the sizeable transgender group with a follow-up of 12 months report a slight increase in BMI irrespective of administration routes (96). A two-year follow-up prospective study of cross-sex hormone treatment shows a significant increase in BMI as compared to the baseline in both TW and TM (97). However, a recent longitudinal study of a large population size of 470 transgender following GAHT showed a significant increase in the mean BMI after 22 months among TW having estradiol administration. The TM had an increase in mean BMI and body weight within the 3-4 months of testosterone hormone therapy (98).

Effects of Hormonal Therapy on Voice in Transgender Youth

Significant hormonal changes have an impact on voice power and range. Vocal folds of transgender men and transgender women have a minor effect on voice after puberty in response to hormonal treatment. Orofacial motricity is the area of speech therapy that maintains oral functions. Speech therapy is essential for transgender

people's vocal confirmation, significantly increasing vocal tract awareness. This treatment is even for those who weren't using testosterone.⁹⁶ The vocal changes in a sizeable group of trans boys undergoing testosterone (T) therapy are the subject of the first longitudinal study. After a year of treatment, F0 values were congruent with significant interindividual variants (99). Endocrine Society's recommendation for transgender males is testosterone therapy to increase voice and testosterone treatment to decrease pitch. Estrogen and anti-androgen treatment do not affect the voice of transgender women who take estrogens in addition to androgen-reduction drugs (100). Only desire partial virilization that is deepening, testosterone therapy combined with 5 α -reductase inhibitors or from treatment with nandrolone (androgen compound) may be used (101).

Speech Therapy

The personality, well-being, and physical security of transgender people may suffer significantly if their voices do not meet their sexual identity (102). Speech therapy, which combined exercise with a large tube and low laser intensity, increased the voice tone. Results checked before and after treatment—vast range for pitch and loudness, low amplitude fluctuation, and minimal pitch variation before the therapy. In the time following treatment, the sizzling voice is no longer audible (103). The content is heard, created in collaboration with speech therapy professors at Northwestern's University Center for Audiology, speech, and Language, and focuses on enhancing verbal communication, such as pitch and tone (104). According to Trans Women Voice Questionnaire, voice identity related to taking voice lessons from a speech expert (105).

Testosterone Therapy

GnRHA is a type of medication that affects voice quality. In research, researchers observed that voice frequency decreased by 30 Hertz after one year of GnRHA therapy. Sex hormones influence voice quality, and testosterone may cause vocal fold changes (106). Voice deepening is a significant side effect of transgender-affirming testosterone medication (107). The frequency response of migrating female to male transsexuals diminishes, but early treatment vocal alterations are irreversible. Treatment with testosterone was sufficient to produce pitch (108). Thyroplasty type III is a method used to reduce FO in transgender men who are dissatisfied with their voice after lengthy gender-affirming hormone treatment. This is accomplished by doing bilateral vertical strip excisions, one centimeter from the midline, to reduce an anteroposterior thyroid alae distance (109).

Declarations

Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate.

It is approved by the department concerned.

Consent for publication

Approved

Funding

Not applicable

Conflict of interest

The authors declared an absence of conflict of interest.

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[Citation: Arshad, A., Atif, M., Huzaifa, M., Tayyab, M.M., Rafiq, B., Khan, M.L.A., Shahid, M.N., (2024). Effects of hormonal therapy in transgenders. *Biol. Clin. Sci. Res. J.*, 2024: 948. doi: <https://doi.org/10.54112/bcsrj.v2024i1.948>]

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