Comorbidities in Transsexual Patients under Hormonal Treatment Compared to Age- And Gender-Matched Primary Care Comparison Groups

Maria Ángeles Bazarra-Castro1*, Caroline Sievers1, Stephany Fulda1, Jens Klotsche1, Lars Pieper2, Hans-Ulrich Wittchen2 and Günter Karl Stalla1

1Clinical Neuroendocrinology Group, Max Planck Institute of Psychiatry, Munich, Germany
2Clinical Sleep Research Group, Max Planck Institute of Psychiatry, Munich, Germany
3Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Dresden, Germany

Abstract

Background: There is limited data on safety aspects of hormonal treatment in transsexual patients and clinical trials are lacking. We aimed at evaluating the long-term hormonal treatment in transsexual patients.

Patients: 95 transsexuals (37 female-to-male (FMT) and 58 male-to-female transsexuals (MFT)) treated between 1996 and 2007 were compared to an age- and gender-matched primary care patient group from the DETECT- cohort (matching 1:3).

Results: Compared to age-matched control groups, we did not observe a higher prevalence of lifetime cardiovascular, endocrine or tumoural comorbidities. MFT showed a lower prevalence of endocrine diseases (FMT to females, p=0.008 and FMT to males, p=0.033). MFT showed a lower prevalence of cardiovascular diseases (MFT to females, p=0.005 and MFT to males, p<0.001) and endocrine diseases (MFT to females p<0.001 and MFT to males, p=0.001).

Conclusion: There is no indication of an increased risk associated with HT in transsexual patients in Germany.

Keywords: Transsexual; Comorbidities; Hormonal therapy; DETECT-Cohort

Abbreviations: HT: Hormonal treatment; FMT: Female-to-male transsexuals; MFT: Male-to-female transsexuals; DETECT: Diabetes cardiovascular risk-evaluation: targets and essential data for commitment of treatment

Introduction

Transsexualism is defined by “the desire to live and be accepted as a member of the opposite sex, accompanied by the wish to transform the body as congruent as possible to the preferred sex through surgery and hormone treatment (HT)” [1]. The prevalence is estimated to be 1:100000 females and 1:30000 males [2].

The etiology of transsexualism remains uncertain. While some authors hypothesise a biological cause, others favour a psycho-social etiology [3].

The proposed treatment for transsexual people encompasses five steps [3]. Firstly, the diagnosis must be confirmed and, in parallel, the patient undergoes psychotherapy. In the next phase, the patients “test” their new gender role and consolidate it. Cross-sex HT is initiated and sex-reassignment surgery follows. Long-term follow-up is recommended with regular medical visits.

The HT regimen for female-to-male transsexuals (FMT) consists of testosterone. In our clinic, testosterone esters, such as testosterone enanthate 250 mg intramuscular, are used every 2 weeks in the first months to induce amenorrhoea and, later, testosterone undecanoate 1000 mg every 12 weeks [4,5].

The treatment regimens for male-to-female transsexuals (MFT) include various forms of estrogens, progestins, and anti-androgens, depending on the preferences of the treating clinic [6]. In our clinic, the most common treatment regimen consists of transdermal estradiol 1.5-3 mg/d (2.5-5 g/d gel) and cyproterone acetate 100 mg/d until testosterone is lowered to female values with a consequent dose reduction [4,5]. These procedures are in accordance with the latest recommendations of endocrine societies [7].

HT in transsexuals is a lifelong treatment, although a reduction in estrogen dosages in older MFT patients should eventually take place in order to maintain estrogen levels with postmenopausal normal values. The use of HT in menopause, contraception or hypogonadism is comparatively well-studied, but, in all these examples, the hormones given are gender-consistent. An increased risk of diseases during the time-limited use of HT reported in postmenopausal women (e.g. stroke, breast cancer, coronary artery events) [8-10], has also been suspected to occur in MFT.

Studies on the unwanted effects of HT in FMT revealed indications of a decreased insulin sensitivity, acne, increased hematocrit and a poor lipid profile [5,11-13]. In MFT there were also reports of decreased insulin sensitivity, hyperprolactinemia, venous thrombosis and a decrease in haemoglobin [5,11,12]. In one long-term study, androgen deprivation plus an estrogen milieu in MFT had a more unfavourable effect on cardiovascular risk factors than the induced androgenic milieu in FMT [14]. However the patterns of long-term treatment risks have been poorly studied.

In the present study, we investigated a large sample of transsexuals receiving HT, to determine whether they are at an increased risk of developing a wide range of diseases such as cardiovascular, endocrine or tumoural diseases. As gender had been reassigned for these patients, we contrasted our findings with female and male age-matched control samples.

Materials and Methods

Patients and comparison groups

From the total database (n=400) of patients aged 18 years or older...
with the diagnosis “transsexualism” (F64.0, ICD-10), treated in our clinic between 1996-2007, we enrolled 95 patients (37 FMT and 58 MFT). The response rate was 36.8%.

Age- and gender-matched comparison groups were sampled from the DETECT study (Diabetes Cardiovascular Risk Evaluation: Targets and Essential Data for Commitment of Treatment). Three controls were matched individually for each patient. The DETECT study is a large, multistage, prospective-longitudinal cohort study of an originally nationwide representative sample of 55518 primary care patients (59% women and 41% men; 18 years or older), sampled from 3188 nationally representative primary care settings in Germany. For a random subset of n=7519 patients (among these 3081 men), comprehensive laboratory assessment, and follow-up assessments over 5 years, were completed. For all patients, a comprehensive standardised clinical evaluation (patients’ self-report and physicians’ assessments) was conducted [15]. The response rate was 93.5%.

The transsexual study was approved by the local ethics committee of the LMU Munich (Nr. 132-08, date 07.07.2008). All transsexual patients and controls from the DETECT-cohort gave written informed consent.

Assessment

DETECT patients: The standardised assessment by the patient and clinician was designed to cover socio-economic factors, as well as frequency and severity of morbidities, such as cardiovascular, endocrine and cancerous diseases. Treatment modalities were also recorded (http://www.detect-studie.de for further information).

Transsexual patients: The questionnaire was based on the DETECT assessment. It covered the same domains, but incorporated more information about clinical history, treatment modalities, side effects and level of satisfaction with medical procedures. In addition, a comprehensive and standardised assessment of psychopathology, including sleep quality, was conducted. Assessment procedures were monitored by a Quality Circle in Munich, where experts regularly meet to discuss questions related to transsexualism.

The presence and absence of diseases and patterns of comorbidity were examined by using the lifetime occurrence of a total of 54 diseases. These were: cardiovascular diseases (e.g. myocardial infarction, high blood pressure, venous thrombosis), respiratory diseases (e.g. bronchial asthma, COPD, acute bronchitis), neurological diseases (e.g. neuropathy, transient ischemic attack, cerebral insult), endocrine diseases (e.g. obesity, diabetes mellitus, hyperuricemia), gastroenterological diseases (e.g. liver cirrhosis, abdominal pain), urinary diseases (e.g. nephropathies, renal colic), tumours and immune-mediated diseases.

Statistical analysis

Apart from the descriptive statistics, pair-wise group comparisons (biological women and FMT, biological women and MFT, biological men and FMT, biological men and MFT) were performed using the Wilcoxon Rank Sum test or Chi-square test.

Results

The average age in FMT at study time was 31.7 ± 8.9 years and in MFT 48.0 ± 11.5 years (p<0.001). The diagnosis of transsexualism was made during early adulthood in FMT (24.7±7.8 years) and significantly later in MFT (38.6±11.7 years, p<0.001).

The average duration of cross-gender HT was 4.9±4.6 years for FMT and 6.5±7.9 years for MFT (p=0.483). Treatment duration was less than 7 years in 26 FMT patients (70.3%) and in 38 MFT patients (65.5%). Treatment duration was more than 7 years in 11 FMT patients (29.7%) and in 20 MFT patients (34.5%). The majority of patients had undergone sex-reassignment surgery by the time of study (FMT: 67.6%; MFT: 70.7%).

FMT patients received transdermal testosterone (Testogel® 23.5%, Testin® 5.9%) or intramuscular testosterone (Testoviron® 61.8%, Nebido® 41.2%). MFT patients received either estrogens alone or in combination with cyproterone acetate (Androcour®). Estrogens were given in transdermal (Gynokadin® 37.5%), oral (Estrifam® 23.2%) and intramuscular preparations (Estradurin® 12.5%, Progynon® 8.9%). Combinations of estrogens with cyproterone acetate, Androcour® and Gynokadin® (32.1%), Androcour® and Estrifam® (5.3%) or Androcour® and Estradurin® (8.9%) were given.

Lifetime diseases and comorbid patterns in FMT compared to age- and gender-matched primary care patients

FMT patients did not significantly differ from female or male age-matched comparison groups with regard to lifetime rates of cardiovascular, respiratory, gastroenterological, urinary, tumoural or immune-mediated diseases. FMT subjects even showed a lower prevalence of endocrine diseases than in the comparison groups. There was no statistical significant difference in BMI between FMT and both comparison groups (Table 1). Furthermore, the prevalence of lifetime diseases in FMT treated with sexual hormones for less than 7 years, and in FMT treated longer than 7 years was not higher compared to controls.

Discussion

We found that MFT and FMT under HT do not reveal indications of an increased prevalence of lifetime comorbidities, in relation to the primary care comparison groups.

It is particularly noteworthy that the prevalence of cardiovascular conditions and obesity in FMT was not statistically different from controls, while MFT showed an even lower rate of cardiovascular morbidity and were leaner than the comparison groups. Nevertheless, transsexual patients reported a significant weight gain during HT (10.8±6.6 kg FMT, 8.7±9.8 kg MFT; Bazarra-Castro et al., data not published), a fact also reported by other authors [16]. This appears to be due to the sexual hormonal effects leading to muscular mass increase in FMT and a feminine fat distribution in MFT.

Additionally we found differences in age between MFT and FMT. The average age of FMT at study time was 31.7 ± 8.9 years and in MFT 48.0 ± 11.5 years (p<0.001). The diagnosis of transsexualism was made during early adulthood in FMT (24.7±7.8 years) and significantly later in MFT (38.6±11.7 years, p<0.001).

The average duration of cross-gender HT was 4.9±4.6 years for FMT and 6.5±7.9 years for MFT (p=0.483). Treatment duration was less than 7 years in 26 FMT patients (70.3%) and in 38 MFT patients (65.5%). Treatment duration was more than 7 years in 11 FMT patients (29.7%) and in 20 MFT patients (34.5%). The majority of patients had undergone sex-reassignment surgery by the time of study (FMT: 67.6%; MFT: 70.7%).

FMT patients received transdermal testosterone (Testogel® 23.5%, Testin® 5.9%) or intramuscular testosterone (Testoviron® 61.8%, Nebido® 41.2%). MFT patients received either estrogens alone or in combination with cyproterone acetate (Androcour®). Estrogens were given in transdermal (Gynokadin® 37.5%), oral (Estrifam® 23.2%) and intramuscular preparations (Estradurin® 12.5%, Progynon® 8.9%). Combinations of estrogens with cyproterone acetate, Androcour® and Gynokadin® (32.1%), Androcour® and Estrifam® (5.3%) or Androcour® and Estradurin® (8.9%) were given.

Lifetime diseases and comorbid patterns in MFT compared to age- and gender-matched primary care patients

The rates of gastrointestinal, urinary, tumoural or immune-mediated diseases did not significantly differ between MFT and age-matched comparison patients. MFT, compared to controls, showed a lower prevalence of endocrine diseases and, notably, also cardiovascular diseases. Furthermore, MFT had a lower BMI than the comparison population (Table 2). The prevalence of diseases in MFT under hormonal treatment for less than 7 years, and in MFT treated for more than 7 years, was not higher compared to comparison groups.
We are of the opinion that our findings provide some evidence for the position of long-term HT as the only available actual treatment option for transsexuals based on various considerations:

Firstly, our study is the first to compare FMT and MFT patients with large age- and gender-matched comparison groups. Secondly, Hembree and co-workers recently reported an evidence-based guideline of endocrine societies for clinical practice in the endocrine treatment of transsexual persons [7]. Our patient selection for HT, diagnosis procedures and treatment follows their recommendations. Thirdly, we ascertained that there was no increase in risk contingent on the length of treatment.

The potential differences to other studies could be due to different sample size or study methodology, as well as a different selection criteria for treating transsexual patients in different countries.

Finally, the limitations of this study should be mentioned. Firstly, the number of transsexual subjects is limited and the low response rate may have resulted in a selection bias. Secondly, as we studied the morbidity pattern in middle and not in old age, with a substantial yet not exceedingly high HT exposure duration, we cannot entirely exclude the possibility that there might be an increase in morbidity later in life. Third, despite the fact that middle-aged primary care patients are typically regarded as being representative of the community, these subjects are more morbid than subjects in the community not seeing their primary care doctor. Nevertheless an overlap is previsible and may allow a generalization. Other limitations might be the danger of understating their disease status.

In summary, and despite these limitations and remaining reservations, we found no indication for an increased risk associated with HT of up to 10 years duration in transsexual patients in Germany. However, clinical trials, evaluating even longer periods of treatment to determine safety and the use of completely healthy controls, are required.

Acknowledgements

Diabetes cardiovascular risk-evaluation: targets and essential data for commitment of treatment (DETECT) is a cross-sectional and prospective-longitudinal, nationwide clinical epidemiological study. DETECT is supported by an unrestricted educational grant from Pfizer GmbH, Karlsruhe, Germany.
Principal investigator: Prof. Dr. H.-U. Wittchen; Staff members: Dipl.-Psych. L. Pieper, Dipl.-Math. J. Klotsche, Dr. T. Eichler, Dr. H. Glaesmer, E. Katze. Steering Committee: Prof. Dr. H. Lehert (Lübeck, Coventry), Prof. Dr. G.K. Stalla (Munich), Prof. Dr. A.M. Zeiher (Frankfurt); Advisory Board: Prof. Dr. W. März (Graz/Heidelberg), Prof. Dr. S. Silber (Munich), Prof. Dr. U. Koch (Hamburg), PD Dr. D. Pittrow (Munich, Dresden), Professor Dr. M. Wehling (Mannheim), Dr. D. Leistner (Frankfurt), Dr. H.J. Schneider (Munich), Dr. C. Sievers (Munich).

The DETECT study received the approval of the Ethics Committee of the Carl Gustav Carus Medical faculty at the Technical University of Dresden (AZ: EK149092003; Date: 16.09.2003), and all patients gave written informed consent.

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

References

1. World Health Organization (WHO) (1993) International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).
2. Diagnostic and Statistical Manual of Mental Disorders, (1996) American Psychiatric Association, edn IV, Washington DC.
3. Michel A, Mormont C, Legros JJ (2001) A psycho-endocrinological overview of transsexualism. Eur J Endocrinol 145: 365-376.
4. Schlattener K, von Werder K, Stalla GK (1996) Multistep treatment concept of transsexual patients. Exp Clin Endocrinol Diabetes 104: 413-419.
5. Schlattener K, Yassouridis A, von Werder K, Poland D, Kemper J, et al. (1998) A follow-up study for estimating the effectiveness of a cross-gender hormone substitution therapy on transsexual patients. Arch Sex Behav 27: 475-492.
6. Moore E, Wisniewski A, Dobs A (2003) Endocrine treatment of transsexual people: a review of treatment regimens, outcomes, and adverse effects. J Clin Endocrinol Metab 88: 3467-3473.
7. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ, et al. (2009) Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 94: 3132-3154.
8. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, et al. (2004) Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women’s Health Initiative randomized controlled trial. Jama 291: 1701-1712.
9. Chlebowski RT, Kuller LH, Prentice RL, Stefanick ML, Manson JE, et al. (2009) Breast cancer after use of estrogen plus progestin in postmenopausal women. N Engl J Med 360: 573-587.
10. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, et al. (2003) Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 349: 523-534.
11. Polderman KH, Gooren LJ, Asscheman H, Bakker A, Heine RJ (1994) Induction of insulin resistance by androgens and estrogens. J Clin Endocrinol Metab 79: 265-271.
12. van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ (1997) Mortality and morbidity in transsexual subjects treated with cross-sex hormones. Clin Endocrinol (Oxf) 47: 337-342.
13. Goh HH, Loke DF, Ratnam SS (1995) The impact of long-term testosterone replacement therapy on lipid and lipoprotein profiles in women. Maturitas 21: 65-70.
14. Gooren LJ, Giltay EJ, Bunck MC (2008) Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. J Clin Endocrinol Metab 93: 19-25.
15. Wittchen HU, Glaesmer H, Marz W, Stalla G, Lehner H, et al. (2005) Cardiovascular risk factors in primary care: methods and baseline prevalence rates—the DETECT program. Curr Med Res Opin 21: 619-630.
16. Asscheman H, Gooren LJ, Eklund PL (1989) Mortality and morbidity in transsexual patients with cross-gender hormone treatment. Metabolism 38: 869-873.
17. Gomez-Gil E, Trilla A, Salamero M, Godas T, Valdes M (2009) Sociodemographic, clinical, and psychiatric characteristics of transsexuals from Spain. Arch Sex Behav 38: 378-392.