The Effects of Gender-Affirming Hormone Treatment on Transgender Musculoskeletal Health: A Protocol for a Systematic Review and Meta-Analysis

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The Effects of Gender-Affirming Hormone Treatment on Transgender Musculoskeletal Health: A Protocol for a Systematic Review and Meta-Analysis

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Abstract

Gender-affirming hormone treatment (GAHT) is an intervention aimed at aligning transgender individuals' hormone levels with their gender identity, thereby alleviating gender dysphoria through modifications to secondary sex characteristics. However, to effectively promote skeletal health, it is crucial to consider the potential adverse effects of GAHT. A previous meta-analysis observed no significant effect of GAHT femoral neck (FN), lumbar spine (LS) or total hip (TH) bone mineral density (BMD) in transgender women. In transgender men, LS BMD showed a significant benefit (ES: 0.04 – 0.06 $g \cdot cm^{-2}$). However, since that analysis more data have been published and updated methods of meta-analysis have been developed; therefore, an updated systematic review and meta-analysis are warranted. Methods and analysis: Literature published in English up to 31/07/24 will be retrieved by searching 3 electronic databases, cross-referencing and expert review. The primary outcome measures will be changes in FN and LS BMD and lower limb BMD. The risk of bias for each study will be assessed using the Cochrane Risk of Bias instrument for non-randomised control trials (ROBINS-I), while the strength of evidence for each outcome will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) instrument. Standardised effect sizes will be calculated from each study and pooled using the inverse heterogeneity (IVhet) model. Prospero Trial Registration number: [CRD42024573102].

Introduction

Transgender individuals often experience psychological distress due to a mismatch between their assigned gender at birth and their experienced gender, a condition medically diagnosed as gender dysphoria [1, 2]. Approximately 3% of the global population, equating to around 241 million people [3] identify as transgender. Many of these individuals opt for medical interventions, including gender-affirming hormone treatment (GAHT) and gender-affirming surgery, to align their physical characteristics with their gender identity [4, 5]. The demand for transgender health services has notably increased in recent years across several European nations [6-8] reflecting a growing recognition and acceptance of gender diversity.

For transgender men (individuals assigned female at birth who identify as male), GAHT typically involves the administration of testosterone recommendation to maintain exogenous testosterone concentrations at cisgender male concentrations [9]. This therapy will produce masculinising effects such as increased muscle mass and redistribution of body fat which alleviate gender dysphoria [10] . For transgender women (individuals assigned male at birth who identify as female), GAHT usually involves a combination of oestrogen and anti-androgens being shown to reduce distress and increase the quality of life in transgender women [11-13]. Oestrogen promotes feminising effects such as breast development, softening of skin, reduction in muscle mass, and redistribution of body fat to hips and thighs [14]. Anti-androgens work by reducing the effects of testosterone, further facilitating the feminization process [4, 9, 14].

Androgens like Testosterone are essential for maintaining skeletal homeostasis [15-17] and oestrogen has a well-established positive effect on bone homeostasis [18-21]. This physiological context suggests that alterations of sex steroids can significantly alter bone health. Consequently, the implications of sex steroids on bone health must be carefully considered, especially in the context of GAHT. However, the effects of GAHT on muscle health are less understood.

A previous meta-analysis by Singh-Ospina [22] investigated the effects of GAHT on the Bone Health of Transgender Individuals. In transgender men, the authors observed no positive change caused by GAHT on femoral neck (FN) bone mineral density (BMD) (Effect size [ES] = 12 months 0.01 [-0.03, 0.03]), 24 months 0.02 [0.00, 0.05]) or LS BMD (ES = 12 months 0.00 [-0.01, 0.02]), 24 months 0.00 [-0.02, 0.03]). In transgender women, the authors found an increase in LS BMD at both 12 and 24 months (ES = 12 months 0.04 [-0.03, 0.06]), 24

months 0.06 [0.04, 0.08]), while finding no change in FN BMD (ES = 12 months 0.02 [0.00, 0.03]), 24 months 0.06 [0.00, 0.03]). The authors concluded that In transgender men, GAHT was not associated with significant changes in BMD, whereas in transgender women GAHT was associated with an increase in BMD at the lumbar spine

While the results reported by Singh-Ospina [22] are noteworthy, they were limited to only thirteen randomized trials, observational studies, and case series published up to April 2015 and lacked an assessment of BMD using quantitative computed tomography (QCT) [22]. However, since that time, additional studies have been published [23-25] and more robust methods for the undertaking and interpretation of meta-analytic results have been developed [26-29]. Furthermore, to the best of the authors' knowledge, no systematic review of previous systematic reviews with meta-analysis or original systematic review with meta-analysis has been conducted on the effects of GAHT on BMD in transgender populations since the original analysis. Finally, using previously developed guidelines for when to update a systematic review, it was decided that an updated review on this topic was needed [30]. Thus, given 1) updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [31], 2) the potential effects of GAHT on musculoskeletal health outside of BMD 3) the lack of recent meta-analytic work in this area, 4) the use of more robust methods for conducting meta-analytic research [26-29] and 5) decision tree analysis of when to update a systematic review [30] we aim to update and expand on the systematic review with a meta-analysis by Singh-Ospina [22], whereby we will examine the effects of GAHT on transgender musculoskeletal health.

Materials and Methods

Study Eligibility Criteria

As this meta-analysis aims to update the Singh-Ospina [22] meta-analysis, the same *a priori* inclusion criteria will be employed (**Table 1**), with additional studies identified from 07/04/2015 forward. Studies that do not meet the criteria outlined in **Table 1** will be excluded from the analysis

Table 1. Study Eligibility Criteria

Criteria
1) Randomized trials, observational studies, and case series of transgender individuals who received GAHT
2) Published in English, with full text available.
3) Adolescents and adult transgender individuals (gender-affirming surgery is not an exclusion criterion)
4) Transgender women exposed to GAHT including oestrogen, antiandrogens (cyproterone acetate, spironolactone), or gonadotropin-releasing hormone (GnRH) agonists
5) Transgender men exposed to GAHT including testosterone
6) GAHT of at least > 3 months in duration
7) studies that compared baseline values of outcomes to post-therapy values in the same individuals or those that compared outcome values in the transgender group with a control or reference group
8) Outcomes related to Musculoskeletal health: Bone Mineral Density (BMD) at the Lumbar spine (LS), (FN), total hip (TH), fat mass (FM), fat-free mass (FFM) or Lean Mass (LM), Body mass (BM), Body Mass Index (BMI), muscle cross-sectional area (CSA), and muscular strength.
9) Included in Singh-Ospina [22] OR published since 7th April 2015

This meta-analysis will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [32]. The protocol was preregistered in PROSPERO (trial registration number: CRD42024573102 [33]).

Data Sources

Studies published up to 31st July 2024, will be retrieved from three electronic sources (PubMed, Embase, SportDiscus). Keywords relevant to all searches included “transgender”, “bone”, and “muscle”. Based on PRISMA guidelines [32], an example of the search strategy will be supplied in future Supplementary material [34]. The last author (BRH) will conduct all electronic database searches. In addition to electronic database searches, cross-referencing from retrieved studies was also conducted

Study Records and Selection

All studies were imported into EndNote (EndNote 20.6, Clarivate Analytics, USA) and duplicates will be removed electronically and manually by the last author (BRH). A copy of the reference database was then provided to the first author (AB) and Second (SMM) for dual screening. Both authors (AB and SMM) will select studies independently. Multiple studies will be handled by including only the most recently published articles. The screeners were not blinded to journal titles or the study authors/affiliations. Reasons for exclusion will be coded based on one or more of the following: 1) inappropriate population, 2) inappropriate intervention, 3) inappropriate comparison(s), 4) inappropriate outcome(s), 5) inappropriate

study design or 6) other. On completion, the screeners will meet to discuss their selections and reconcile any discrepancies by consensus. If an agreement cannot be achieved, the last author (BRH) will provide a recommendation. The agreement rate, before the reconciliation of any discrepancies, will be calculated using Cohen's κ statistic [35]. The precision of searches will also be calculated as the number of studies included divided by the number of studies screened (less duplicates) [36]. We will then calculate the number needed to screen (NNS) by taking the reciprocal of the precision [36].

Data Abstraction

Before data abstraction, an electronic codebook developed by the last author (BRH) will be provided to the first and second authors (AB/SMM). The extracted data will be coded based on the following major categories; 1) study characteristics (e.g., author, journal, year, etc.), 2) participant characteristics (e.g., age, height, mass, etc.), 3) intervention details (e.g., type, length, frequency, etc.), and 4) outcome characteristics (e.g., sample sizes, baseline/post-GAHT means and SDs, etc.).

The first (AB) and second (SMM) authors will extract all data independently of one another before meeting to resolve any discrepancies by consensus. If an agreement cannot be achieved, the last author (BRH) will provide a recommendation. Before this, the overall agreement rate will be assessed by Cohen's κ statistic [35].

Outcome Measures

A priori primary outcome measures will be changes in bone health parameters such as TH, FN and LS BMD measured by dual-energy x-ray absorptiometry (DXA), dual-photon absorptiometry (DPA), or quantitative computed tomography (QCT). Secondary, *a priori* outcomes included changes in body mass (BM), body mass index (BMI) in $kg \cdot m^2$, Lean body mass (LM) or fat-free mass (FFM), fat mass (FM), muscle cross-sectional area (CSA) and muscular strength. Obtaining missing data will be attempted for all primary and secondary outcome measures if assessed by a study but the data provided proves inadequate to calculate an effect size. The last author (BRH) will contact the study's corresponding author three times via email with one week between each communication. These communications will be tracked (e.g., dates, responses, success rates, etc.) to establish the success rate of this process.

Risk of Bias Assessment

The risk of bias for each study will be assessed using the recently revised Cochrane Risk of Bias instrument for Non-randomized Studies of Interventions (ROBINS-I) [37]. Using one or more signalling questions, the ROBINS-I instrument will assess the risk of bias in seven distinct domains: (1) bias arising from confounding, (2) bias in participant selection (3) bias in classification of interventions (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias in the measurement of outcomes and (7) bias in the selection of the reported result. Based on signalling questions, each domain will be assessed as either 'low risk', 'moderate risk', 'serious risk', or ''critical risk'. Based on responses to each domain, the overall risk of bias for each study will be assessed as either 'low risk', 'moderate risk', 'serious risk', or ''critical risk'. We choose to use this risk of bias instrument over the various study quality instruments, including those focused on intervention studies [38, 39] given the difficulty of the latter in differentiating between the quality of reporting and the quality of the conduct of a study [40].

No studies will be excluded from the analysis based on the risk of bias assessment [41]. The first (AB) and second (SMM) authors undertook the risk of bias assessment independently of one another, before meeting to resolve any discrepancies by consensus. Where this cannot be achieved, the second author (BRH) will provide a recommendation.

Statistical Analysis

Calculation of effect sizes

The *a priori* primary and secondary outcomes for this meta-analysis will be calculated using the Hedges standardised mean difference effect size (ES), *g*, adjusted for small sample sizes [42]. The *g* for each group will be calculated as the mean of the baseline measure or the control/reference group minus the mean of the GAHT intervention group, divided by the pooled and weighted standard deviation. If this information is unavailable, g will be calculated using procedures described by Follmann *et al*. [43]. For studies reporting multiple post-intervention time points, *g* was calculated based on the baseline and the final time point.

Effect size pooling

Results will be pooled using the inverse heterogeneity (IVhet) model [26], a model which is more robust than the Der Simonian–Laird random effects method employed by Singh-Ospina [22]. Two-tailed z-alpha values <0.05 and non-overlapping 95% confidence intervals will be considered statistically significant.

Heterogeneity and Inconsistency

For each pooled outcome, heterogeneity will be assessed using Q [44], with an alpha level of <0.10 representing statistically significant heterogeneity. Inconsistency will be assessed using I^2, an extension of Q. For this meta-analysis, inconsistency will be categorised as very low (<25%), low (25-50%), moderate (50-75%) or large (>75%) [44]. Absolute between-study heterogeneity will be assessed using tau squared (τ^2). In addition, influence analysis will be conducted by removing each study from our analysis once to examine the effect of that study on the overall findings. Given the expected small sample size, no subgroup or meta-regression analysis is planned a *priori*.

Meta-biases

Small-study effects (publication bias, etc.) will be assessed qualitatively using the Doi plot and quantitatively using the Luis Furuya-Kanamori index (LFK index) [29, 45]. The Doi plot has been suggested to be more intuitive than the funnel plot and the LFK index is more robust than the commonly used Egger's regression-intercept test [29, 45]. LFK values within ± 1, greater than ± 1 but within ± 2, and greater than ± 2 will be considered to represent no, minor, and major asymmetry [29].

Strength of evidence

The strength of findings for each outcome will be assessed using the most recent version of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) meta-analysis tool [46]. Quality of evidence will be assessed across the domains of risk of bias, consistency, directness, precision, and publication bias. Quality will be judged as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), or very low (very uncertain about the estimate of effect [46]

Software used for analysis

All data were analysed using Meta XL (version 5.3, Epigear International Pty Ltd). All data will be available as supplementary material [34].

Contributions

Conceptualisation, BRH; methodology, BRH; writing--original draft preparation, BRH; writing--review and editing, ALL.

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Abbreviations

The following abbreviations are used in this manuscript:

BMD: Bone Mineral Density
CSA: Cross-Sectional Area
LM: Lean Mass
FFM: Fat-Free Mass
BMI: Body Mass Index
DPA: Dual-energy Photon Absorptiometry
DXA: Dual-energy X-ray Absorptiometry
ES: effect size
FN: Femoral Neck
g: Hedges standardised mean difference effect size
GRADE: Grading of Recommendations Assessment, Development and Evaluation
IVhet: Inverse heterogeneity
LFK: Luis Furuya-Kanamori
LS: Lumbar Spine
NNS: Number-needed-to-screen
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses
pQCT: peripheral Quantified Computer Tomography
SD: Standard Deviation

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