Region Nordjylland

Assessing body composition in trans gender males in hormonal therapy using bioimpedance analysis compared to dual x-ray absorptiometry

Ansøgning til Den Regionale Videnskabsetiske Komité

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2.1. Background

2.1.1. Standard care in trans gender persons

0,55% of the Danish population are gender incongruent and 0,10% defines themselves as trans gender. These are equally distributed as trans men and trans women. Some of these need gender affirming hormone therapy and gender affirming surgery (GAS). In Denmark, the requirements for surgery are a BMI<27 and BMI<35 for hormone therapy (Frisch et al., 2019). Endogenous sex steroids such as testosterone and estradiol play important roles in the accumulation and distribution of body fat and lean body mass and thus in the feminization and masculinization of body composition (Wells, 2007).

2.1.2. Methods for assessment of body composition

The golden standard for measuring body composition is using body imaging techniques as magnetic resonance imaging (MRI) and computed tomography (CT). They are considered very precise imaging systems. They can separate fat from other soft tissues in the body, making these methods the gold standard for estimating muscle mass in research. Alternatively, dual x-ray absorptiometry (DXA) is an attractive method for research and in the clinic to distinguish fat, lean tissue, and bone mineral. This whole-body scan exposes the patient to minimal radiation compared to CT. The main limitation with this method is that the equipment is not portable, which may hinder its use in large scale (Cruz-Jentoft et al., 2010).

Bioimpedance analysis (BIA) estimates the volume of fat and lean body mass. The test itself is easy to use, readily reproducible, suitable for outpatient clinic patients and inexpensive. BIA measurements under standard conditions have been found to correlate well with MRI. Predictions have been validated for multiethnic adults and reference values established for adult white men and women, including older subjects (Cruz-Jentoft et al., 2010). BIA equipment does not measure muscle mass directly, but instead derives an estimate of muscle mass based on whole-body electrical conductivity. BIA uses a conversion equation that is calibrated with a sex specific reference of DXA-measured lean mass in a specific population (Cruz-Jentoft et al., 2019). Therefore, BIA prediction models are most relevant to the population in which they have been derived – mainly healthy subjects and in patients with stable water and electrolyte balance with a validated BIA equation that is appropriate with regards to age, sex and race. The conversion

equations used may therefore algorithmically exclude certain minorities as trans gender persons (Albert & Delano, 2021; Kyle et al., 2004).

Palle et al. (2016) investigated the relationship between single cross-sectional MRI of the thighs, skeletal muscle mass as reference and multi-frequency BIA fat free mass (FFM) (using Tanita MC-780 MA) in 18 patients (10 males and 8 females) with colorectal cancer undergoing chemotherapy. They found that BIA overestimated FFM for all measurements with a mean of 12,4 kg (SD 6,2). BIA showed a constant (and therefore correctable) error compared to MRI single cross-sectional of the thighs. Part of this difference may be related to the software/equations for calculation of body composition used in the BIA (Palle et al., 2016).

2.1.3. Body composition in trans gender persons in hormonal therapy

Persons with gender incongruence are treated with exogenous steroids to obtain the physical phenotype of the identified gender, including a feminine or masculine body fat distribution, musculature, and body shape. Klaver et al. (2017) showed that, during the first year of cross-sex hormone therapy, total body fat increases and total lean body mass decreases in transwomen, while the opposite occurs in transmen (Klaver et al., 2017). In 2018, Klaver et al. found that cross-sex hormone therapy also causes a more feminine body fat distribution and a lower waist-to-hip ratio in transwomen and a more masculine body fat distribution with a lower hip circumference in transmen (Klaver et al., 2018). For both studies they used DXA-scans to assess body composition (Klaver et al., 2017, 2018).

Van Velzen et al. (2020) measured 323 transmen and 288 transwomen using BIA at consecutive visits to the outpatient clinic from the start of hormone therapy to a maximum of 24 months follow-up. This prospective cohort study is part of the European Network for the Investigation of Gender Incongruence (ENIGI). They used the Tanita MC-780 MA for the BIA-measurement. They defined absence of change as transmen with a decrease in lean body mass or transwomen with a decrease in fat percentage. They found a lack of change in body composition in 20,2% of transmen and 9,4% in transwomen. In conclusion, they found a large variation in body composition changes during hormone therapy (van Velzen et al., 2020). ENIGI also published another study investigating the effect of estrone in feminizing hormone treatment. They measured 212 transwomen using Tanita MC-780 MA at baseline, after 3 months, and after 12 months of hormone treatment (Tebbens et al., 2022). In these two studies ENIGI measures trans persons using BIA without considering that the conversion equation is calibrated with a binary reference population. As mentioned above, as the hormone treatment progresses the body composition of a trans gender person change towards the identified gender. Therefore, using BIA to estimate body composition may not give a feasible estimation of fat mass and lean body mass.

2.1.4. Using BIA in trans gender persons

Albert & Delano (2021) discuss the fact that BIA measurements are a product of proprietary regression equations that require a binary sex/gender as their input. Developing these regression equations Tanita, and other companies making BIA-measuring techniques, may not include a diverse background population which creates algorithmic exclusion. In practice, algorithmic exclusion means that the performance of these algorithms for individuals not in the original dataset are unknown, and that these algorithms likely work less well for those not included in the original dataset (Albert & Delano, 2021).

Generally, researchers suggest caution when using BIA working with populations that have altered body composition, such as patients with fluid overload, body shape abnormalities, altered fat/lean mass ratio etc (Kyle et al., 2004). In some of these cases, there are specific equations for a particular patient population, or alternative methods of body composition assessment that don't rely on regression (Keane et al., 2017).

2.1.5. Gender affirming surgery in trans gender males

Although the World Professional Association for Transgender Health (WPATH) guidelines for GAS doesn't specify a BMI requirement (Coleman et al., 2012), as mentioned, in Denmark a BMI<27 is required. Such criteria serve as barriers to essential surgeries and do not have an empirical basis (Brownstone et al., 2021; Martinson et al., 2020). BMI has been widely criticized as a marker of health or wellness due to its two-dimensional nature. Trans gender persons tend to exhibit higher BMI for a range of reasons, including engagement in gender-affirming hormone treatment, higher risk of binge eating and related disorders (Diemer et al., 2015). It is commonly recognized that for those who wish to pursue medical transition, GAS improves health and quality of life (Nobili et al., 2018).

Body fat percentage, measured by BIA, can accurately reflect body adiposity, and serves as a better indicator for obesity (Kyle et al., 2004). Obesity, measured by body fat percentage, is significantly associated with increased surgical complication rate and may be a better indicator for obesity and predictor for postoperative complications than traditionally used BMI (Chun et al., 2013).

Therefore, as fat percentage in trans gender males are relevant to their treatment and alternatively gender affirmation surgery, including mastectomy, the precision of the estimation of body fat percentage using BIA may have real world impact. As seen in the studies above, researchers rely more and more on these estimates in their research and in the clinic.

2.2. Objectives

Hypotheses:

- By optimizing the use of sex specific reference values, we can improve the precision of the estimation of body fat volume using BIA measurements in trans gender males.

Aim:

- To assess body composition of trans gender males in hormonal therapy using BIA compared to DXA.
- To investigate whether binary reference values using BIA measurements in trans gender males in hormonal therapy is reliable – and thereby if BIA maybe a useful tool for assessing whether a trans gender man is suitable for mastectomy.

3. Methods

3.1. Study design

This pilot study will be performed as a cross-sectional study. There are currently no plans of a larger scale follow-up study. In case of a follow-up study a second application will be sent.

3.2. Study population

Inclusion criteria:

- Trans gender males in hormonal therapy
- Age ≥ 18 years
- Ability to provide informed consent

Exclusion criteria:

- Inability to comprehend written consent form or provide informed consent
- BMI > 35
- Pregnancy

3.3. Assessment of resources

The study will be conducted as a collaboration between the Department of Health Promotion, the Department of Endocrinology and the Center for Gender Identity, Aalborg University Hospital. Patients will be recruited at the Center for Gender Identity, BIA measurements will be performed at the Department of Health Promotion, and the DXA scans at the Department of Endocrinology by experienced personnel. The recruitment is directed by leading physician Astrid Højgaard at the Center for Gender Identity. She will be

responsible for instructing the nurses at the outpatient clinic which see patients for follow-up as a part of their treatment plan. Data collection is done by clinical manager and primary investigator Signe Graungaard from the Department of Health Promotion who will contact the patients if they are interested in participating, collect their written consent, and meet the patients at the hospital for the data collection regarding BIA-measurements and demographics. Jakob Dal from the Department of Endocrinology are responsible for the DXA-scans.

3.4. Study procedures

Patients are recruited at their consultation with the nurse at the Center for Gender Identity at Aalborg University Hospital. The consultation is part of the patient's treatment plan. Patients will be given information regarding the study, and if interested, they will be provided with a form to fill out with their contact information, so they can be contacted by the investigators. Should the patient agree to be contacted via telephone or e-mail, they will be given instruction regarding their rights as a participant in a scientific study ("*Dine rettigheder som forsøgsperson i et sundhedsvidenskabeligt forskningsprojekt*") as well as written material specifically pertaining to the study (*"Deltagerinformation"*). Should the subject be deemed fit for the study, based on the in- and exclusion criteria, contact will be made via phone or e-mail and they will receive further information regarding the study, and invited to a personal meeting the principal investigators office at the Department of Health Promotion. Here, the conversation can be undisturbedand details of the study procedures will be outlined. In advance, the subject will be informed of the opportunity to bring a relative or a representative to the meeting. At the meeting, the patient and any representative will be informed of the 24-hour deliberation period before providing informed consent, but if the patient agrees to participate, they will sign the informed consent form at the meeting and receive a copy of the signed form to take home. If they wish for time to deliberate, they can come by the principal investigators office another day to sign the form. No study procedures will be performed until the informed consent form has been signed by both the participant and the investigator. The signed consent form will give the principal investigator direct access to collect information from participants Electronic Patient Journal (EPJ) which are necessary to complete the study.

After providing informed consent, the participant will undergo the study procedures. Body composition will be analyzed by BIA-measurement and DXA scans. Data will be analyzed using relevant statistical analyses and presented as a cross-sectional study.

3.4.1. Whole body dual X-ray absorptiometry (DXA) scan

Through whole body DXA scans, we will obtain information regarding body composition. The effective radiation dose for one whole body DXA scan has been found to be between 0,001 and 0,01 mSv.

Estimated time: 30 min.

3.4.2. Bioelectrical impedance analysis (BIA)

In each patient body composition is measured using the “male” and “female” setting of the Tanita MC-780 MA, respectively. BIA-measurements take less than 1 minute, are without any side effects, and a part of standard care in this patient group when assigned for weight loss therapy at the Department of Health Promotion.

4. Data collection

Following the participants’ informed consent, data regarding age, sex, medication, onset of hormonal therapy, and blood samples (p-alanine transaminase, p-albumin, p-alkaline phosphatase, p-bilirubin, B-erythrocytes, B-hemoglobin, p-estradiol, p-follicle stimulating hormone, Hb(B)-hemoglobin A1c, p-cholesterol (LDL), B-leucocytes, B-erythrocyte volume (MCV), p-prolactin, p-sex hormone binding globulin, p-testosterone, p-free testosterone, p-thyroid screening, B-thrombocytes, p-lutropin will be collected from the participants’ EPJ. The information gathered is for use in the research project only.

The participants will be measured on the BIA scale twice and once with DXA and they will be asked questions about their habits concerning smoking and exercise. The center for Gender Identity regularly refers trans gender persons to the Department of Health Promotion for weight loss therapy. Patients at the Department of Health Promotion are routinely weighed on the Tanita MC-780 MA-scale. The blood samples collected in this study are routine samples and collected as a part of the participants treatment plan. DXA scans are not standard procedure in this patient group and is the only part of this project which is not part of the patient’s regular treatment plan.

5. Data analysis

5.1. Statistical methods

5.1.1. Sample size

In this study we aim to include 10 participants. It was not possible to conduct a sample size calculation based on the reference data on the Tanita MC-780 MA-scale, as Tanita will not share their data or information about their population. We have a vast experience with DXA scans in the clinic, and from this

experience we know that 10 persons will be enough to detect a difference in body composition in a pilot study.

5.1.2. Statistical methods

Student's unpaired t tests will be used to compare variables between groups. Correlation analyses will be performed using Pearson's correlation coefficient. Wilcoxon rank-sum test will be used to compare nonparametric data between groups. Fischer's exact test will be used to test differences in cross tables.

5.1.3. Statistical significance

We use a statistical significance level of $\alpha<0,05$.

6. Data safety

The project will be registered with the North Denmark Region and all sensitive data will be stored on the secure servers of Aalborg University Hospital and in accordance with the Data Protection Agency (*databeskyttelsesloven*) and the data protection regulation is complied with. All stored data will be anonymized after termination of the project. No data will be given over to a third party.

7. Study limitations

In this study we use a small cohort, and therefore we do not have the statistical foundation to be able to improve the sex specific reference values of BIA measurements, but we can use the data to assess body composition of trans gender males in hormonal therapy using BIA compared to DXA, and thereby assess whether BIA is a useful tool for assessing body composition in trans gender males. Furthermore, we aim to use these data for further hypothesis generation.

8. Ethical considerations

8.1. Informed consent

The initial inquiry about participation of trans gender persons will be made by the specialist at the Center for Gender Identity. Potential participants will receive both oral and written information

("*Deltagerinformation*"). Further information will later be given, by the principal investigator, and will include details about the tests involved.

The information will include:

- This is a scientific project designed to investigate the feasibility of assessing body composition in trans gender persons in hormonal therapy using BIA
- Information regarding the included examinations, including the risk of the minimal exposure to ionizing radiation associated with DXA scans
- That withdrawal of consent, and as such withdrawal from participation, is possible at any time and with no given notice or explanation
- That collected data will be published in anonymized form with no possibility of being raced to the participant
- That collected data will be stored in accordance with the rules in place
- That at least 24 hours are given to deliberate before providing informed consent
- That potential participants have the right to bring a relative or other representative to the informational meeting

Potential participants are given at least 24 hours to deliberate before any consent form is signed.

The project will be performed in compliance with the ICH GCP and the Helsinki Declaration for biomedical research involving human test subjects.

The project will be prospectively registered with www.clinicaltrials.gov.

8.2. Risks and side effects

All methods used have been tested in previous studies with no side effects being reported. The risks associated with the above-mentioned procedures are limited as only low-dose ionizing radiation (0,001-0,01 mSv) is used, and all measures are taken to ensure sterility when relevant.

No changes in the participants' regular medication will be made and no new medication will be administered.

8.3. Benefits to subjects

The participants will not benefit directly from participation in this study. However, as we aim to investigate which method for assessing body composition in trans gender persons is feasible, our findings may contribute to the treatment protocol of trans gender persons regarding weight loss and reference to gender affirmation surgery.

8.4. Costs to subjects

Apart from transportation to the hospital to participate, no other costs will be incurred to participants.

8.5. Compensation to subjects.

No economical compensation will be paid to participants and participants are responsible for the financial costs associated with their transportation to the hospital in connection with their participation in the study.

In case of unforeseen side effects or other adverse events related to the examination, affected participants will be covered by the Danish Health Act and "*patienterstatningsordningen".*

8.6. Plan for dissemination of findings

The results of the project are planned to take the form of a research article to be published in an internationally acknowledged scientific journal such as the International Journal of Transgender Health. All data will be published in anonymized form. Results will be published regardless of submission acceptance or denial, and both positive, negative and inconclusive results will be published.

8.7. Economy

The initiative of the project is planned by the project's clinical manager Signe Graungaard (MSc Clinical Nutrition) and supervisors Astrid Højgaard (MD) and Jakob Dal (MD).

The study is internally financed and hasn't received any funding.

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