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Metabolic Impacts of Gender-Affirming Hormone Therapy (GAHT): A Comprehensive Review of Weight Gain, Fat Distribution, and Obesity Risk in Transgender Individuals

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Abstract

As gender-affirming hormone therapy (GAHT) becomes increasingly accessible, its physiological and metabolic consequences demand thorough understanding to ensure safe and individualised care for transgender individuals. This literature review critically examines the relationship between GAHT and changes in body composition, weight gain, and metabolic risk among transgender women (MTF) and transgender men (FTM). Oestrogen and anti-androgen therapy in MTF individuals are associated with increased subcutaneous fat, decreased lean muscle mass, and elevated risks of insulin resistance, dyslipidaemia, and cardiovascular disease. Conversely, testosterone therapy in FTM individuals enhances lean body mass and basal metabolic rate but may increase central adiposity and alter lipid profiles. Factors such as hormone dosage, administration route, genetics, and lifestyle influence these outcomes. This review also explores current clinical strategies for monitoring and mitigating metabolic risks, while highlighting significant research gaps, including limited long-term studies, the role of gut microbiota, and psychosocial influences on weight and eating behaviour. An integrated, patient-centred, and personalised approach to GAHT is essential to optimise physical and mental health outcomes in transgender populations.

Keywords: Gender-affirming hormone therapy (GAHT); transgender health; weight gain; fat distribution; metabolic syndrome; insulin resistance; cardiovascular risk.

Introduction

The use of gender-affirming hormone therapy (GAHT) has significantly increased over the past few decades as more transgender and gender-diverse individuals seek medical interventions to align their physical characteristics with their gender identity [1,2]. GAHT plays a crucial role in improving psychological well-being, reducing gender dysphoria, and enhancing overall quality of life [3,4]. However, alongside its benefits, GAHT presents several physiological and metabolic implications, particularly in relation to weight gain and obesity [5]. Weight changes among transgender individuals undergoing GAHT have become a topic of growing concern in medical and scientific research [6,7]. The interplay between exogenous hormones and metabolism leads to alterations in body composition, fat distribution, and muscle mass [8]. Several studies indicate that transgender women (MTF) and transgender men (FTM) experience distinct metabolic changes due to the hormonal differences between estrogen-based and testosterone-based treatments [9,10]. These changes may contribute to varying risks of obesity, cardiovascular disease, and metabolic syndrome in different transgender populations [11,12].

A crucial question in transgender healthcare is whether hormone therapy directly contributes to weight gain or obesity [13]. While some studies report increased body fat in transgender women due to estrogen therapy [14,15], others highlight increased muscle mass and redistribution of fat in transgender men undergoing testosterone therapy [16,17]. Additionally, the

metabolic effects of GAHT remain a subject of investigation, with some findings suggesting alterations in insulin sensitivity, lipid metabolism, and energy expenditure [18,19]. This literature review aims to explore the impact of GAHT on weight gain, fat distribution, and metabolism in transgender individuals. Specifically, it examines whether hormone therapy leads to obesity, how it affects metabolic processes, and whether there are differences in weight changes and metabolic health between transgender women (MTF) and transgender men (FTM).

2. Background on Hormone Therapy for Transgender Individuals

2.1 Types of Hormones Used For Gender-Affirming Hormone Therapy (GAHT) In MTF (Transgender Women) and FTM (Transgender Men)

The principal purposes of gender-affirming hormonal therapy are to suppress endogenous effects of sex hormones of an individual's assigned sex and to induce secondary sex characteristics with replacement of endogenous sex hormone levels under the individual's gender identity [20]. Estrogen therapy, often combined with anti-androgens, is central to feminizing regimens. Oral 17β-estradiol (2–6 mg/day) remains the most commonly prescribed form, though transdermal and injectable options are frequently used, especially in older individuals or those with thromboembolic risk factors [21]. Anti-androgens such as spironolactone (100–300 mg/day) are used to suppress endogenous testosterone production. Cyproterone acetate and gonadotropin-releasing hormone (GnRH) agonists are alternative agents, with the latter offering more complete suppression but at a higher cost [22,23]. Estrogen monotherapy may be sufficient in post-gonadectomy patients, as testosterone suppression is no longer required [24]. Outcomes from estrogen therapy include significant reductions in serum testosterone and changes in body composition [25]. Masculinizing hormone therapy primarily involves testosterone administration to achieve serum levels typical for cisgender men (300–1000 ng/dL). Intramuscular or subcutaneous injections of testosterone enanthate or cypionate (50–200 mg/week) are common, though transdermal gels and patches provide non-invasive alternatives [26,27]. Physical changes typically begin within months of therapy initiation, including cessation of menstruation, clitoral enlargement, increased body hair, and deepening of the voice. Voice deepening and facial hair growth tend to progress over 6 to 12 months, with continued masculinization over several years [21]. Studies indicate high satisfaction rates with testosterone therapy, though side effects such as acne, mood changes, and polycythemia necessitate careful monitoring. [28]

2.2 Physiological Effects of Gender-Affirming Hormone Therapy (GAHT)

Gender-Affirming Hormone Therapy (GAHT) induces major physiological changes in transgender individuals. These changes include shifts in body composition, metabolism, and cardiovascular risk profiles.

2.2.1 Changes in Fat Distribution, Muscle Mass, and Metabolism

GAHT significantly alters body composition, primarily through the effects of sex steroids on adipose and lean tissue. In transgender women, estrogen therapy leads to increased subcutaneous fat and reduced muscle mass. Research observed a significant decrease in fat-free mass (−2.3 kg) and an increase in fat mass after 12 months of estrogen therapy [29]. Similarly, there is a decreased lean mass and increased fat mass in transgender women, aligning their body composition closer to cisgender females [30]. In transgender men, testosterone therapy increases muscle mass and reduces subcutaneous fat. There is a gain in fat-free mass (+3.1 kg) and a redistribution of fat towards a more male-typical pattern [29]. These effects are consistent with anabolic responses to testosterone reported across studies [30].

2.2.2 Insulin Sensitivity and Incretin Response

GAHT also influences glucose metabolism and insulin sensitivity. Shadid et al. reported that transgender women experienced a reduction in insulin sensitivity, evidenced by increased HOMA-IR scores [29]. Conversely, testosterone therapy in transgender men was associated with improved insulin sensitivity and lower fasting insulin levels [29]. These changes are partly mediated by body composition shifts and hormone-specific effects on glucose metabolism.

Incretin hormones such as GLP-1 and GIP were also altered. Shadid et al. found increased GLP-1 and GIP

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responses in transgender men, potentially supporting improved insulin response post-therapy [29]. These findings are novel and suggest further metabolic implications of GAHT beyond traditional markers.

2.2.3 Physical Performance and Strength

Testosterone increased muscle strength and hemoglobin levels in transgender men, contributing to enhanced endurance and power [31]. In contrast, transgender women undergoing estrogen therapy experienced reductions in strength and muscle mass, though these changes were modest over 12 months and did not fully negate prior male physiological advantages [31]. This is particularly relevant in athletic and occupational contexts, where physical performance is a factor.

2.2.4 Lipid Profiles and Cardiovascular Risk

Alterations in lipid profiles are a significant concern during gender-affirming hormone therapy (GAHT). Research indicates that estrogen therapy in transgender women is associated with increased triglyceride levels and reduced LDL cholesterol. In contrast, testosterone therapy in transgender men tends to raise both triglycerides and total cholesterol levels [32,33]. These shifts suggest that both feminizing and masculinizing hormone regimens may contribute to a more atherogenic lipid profile, potentially increasing long-term cardiovascular risk. Additionally, both systolic blood pressure and body mass index (BMI) have risen significantly following the initiation of GAHT in both populations, further emphasizing the importance of regular cardiovascular monitoring throughout treatment [32,33].

2.2.5 Sociopsychological Effects and Satisfaction

Beyond physiological metrics, GAHT profoundly impacts psychological well-being and satisfaction. Transgender individuals experienced improved body image, emotional stability, and overall satisfaction with therapy [34]. These benefits, while not strictly physiological, contribute to adherence and quality of life, which indirectly affect physical health outcomes.

3. Hormonal Effects on Weight Gain and Obesity

3.1 Transgender Women (MTF) – Estrogen & Anti-Androgens Changes in Fat & Muscle Composition

Estrogen therapy in transgender women leads to increased subcutaneous fat deposition, particularly in the hips, thighs, and buttocks, contributing to a more traditionally feminine body shape [35,36]. However, this shift in fat distribution is accompanied by a decrease in lean muscle mass [35,37] and a reduction in basal metabolic rate (BMR) [36,38]. These changes may predispose transgender women to gradual weight gain, particularly if dietary and exercise habits remain unchanged [35,38]. The impact of estrogen on adipose tissue distribution is influenced by genetic factors, lifestyle, and the duration of therapy [38,41].

Risk of Weight Gain & Metabolic Syndrome

Studies have linked estrogen therapy to increased fat accumulation, which may elevate the risk of obesity and metabolic syndrome [36,40]. Anti-androgens, which are often used to suppress testosterone levels, can further influence weight gain [39]. Spironolactone, a common anti-androgen, has been associated with water retention and appetite changes, potentially leading to additional weight fluctuations [39,42]. Research suggests that transgender women on long-term GAHT have a higher prevalence of metabolic complications, including insulin resistance and dyslipidemia [40,43]. A higher percentage of body fat coupled with reduced muscle mass may contribute to long-term weight regulation challenges [35,36,38].

Insulin Sensitivity & Cardiovascular Risks

GAHT affects glucose metabolism, potentially increasing the risk of insulin resistance and type 2 diabetes [42,44]. The combination of estrogen and anti-androgens has been shown to alter lipid profiles, raising concerns about cardiovascular health [40,43]. Transgender women undergoing long-term hormone therapy may experience elevated triglyceride levels, reduced HDL cholesterol, and increased blood pressure, all of which contribute to a heightened risk of cardiovascular disease [40,42,43]. Lifestyle interventions, including dietary adjustments and regular exercise, are recommended to mitigate these risks [38,41].

3.2 Transgender Men (FTM) – Testosterone Therapy Changes in Body Composition

Testosterone therapy induces significant increases in lean muscle mass while reducing overall fat mass [37,39]. However, fat redistribution tends to favor central adiposity, leading to increased abdominal fat accumulation, similar to the pattern observed in cisgender men [37,39]. This shift may have

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implications for metabolic health and long-term weight regulation [39,44].

Metabolic Risks

While testosterone enhances muscle mass and overall energy expenditure, it may also contribute to metabolic syndrome by increasing insulin resistance [39,44]. Some studies suggest that transgender men on long-term testosterone therapy have a higher risk of developing type 2 diabetes and lipid abnormalities [42,43], including elevated LDL cholesterol and reduced HDL cholesterol [40,43].

Effect on Appetite & Energy Expenditure

Testosterone therapy has been associated with increased appetite and caloric intake, which, if not managed, can lead to unintended weight gain [37,39]. However, testosterone also increases basal metabolic rate (BMR) [37], which may offset some of the weight gain risks. The balance between increased energy intake and expenditure varies among individuals, highlighting the importance of dietary monitoring and physical activity [38,41].

4. Factors Influencing Weight Changes During Hormone Therapy

Understanding the multifactorial influences on weight during hormone therapy (HT) is essential for optimising treatment outcomes and guiding clinical management. Several key variables, including the duration, type, and dosage of HT, baseline body mass index (BMI), genetic predisposition, lifestyle habits, and underlying medical conditions, significantly affect weight trajectories in patients undergoing hormone-related treatments.

Duration of Hormone Use

The length of HT plays a critical role in its impact on body composition. Short-term HT (e.g., <6 months) may cause temporary weight fluctuations due to fluid retention or appetite changes, whereas long-term HT has more sustained effects on fat distribution and lean body mass. For instance, studies have shown that oestrogen-based HT in postmenopausal women is associated with a redistribution of fat rather than significant weight gain, while long-term testosterone therapy in transgender men tends to increase lean muscle mass and reduce fat mass [44]. However, inconsistencies in study designs and populations highlight the need for longitudinal studies with standardised protocols [45].

Dosage and Type of Hormone Therapy

The formulation and administration route—oral, transdermal, or injectable—also influence metabolic outcomes. Oral oestrogens undergo first-pass hepatic metabolism, potentially increasing triglyceride levels and affecting appetite-regulating hormones such as leptin and ghrelin [46]. Transdermal preparations, in contrast, bypass the liver and may have fewer metabolic side effects [47]. Injectable formulations, particularly in gender-affirming HT, often lead to more rapid and pronounced changes in body composition [48]. The dosage further modulates these effects; supraphysiologic doses may exacerbate weight gain or loss depending on the hormone type and patient physiology [49].

Baseline BMI and Genetics

An individual's baseline BMI and genetic background significantly mediate the effects of HT. Patients with pre-existing obesity or insulin resistance may exhibit exaggerated metabolic responses, including increased fat accumulation or impaired glucose tolerance [50]. Genome-wide association studies (GWAS) have identified several loci associated with hormone metabolism and fat distribution, suggesting that genetic polymorphisms could alter responsiveness to HT [51]. This genetic variability underscores the importance of personalised HT regimens [52].

Lifestyle and Behavioural Factors

Dietary habits, physical activity, smoking status, alcohol use, and socioeconomic conditions can either buffer or exacerbate weight changes during HT [53]. For example, sedentary behaviour and high caloric intake have been shown to worsen HT-related weight gain, whereas lifestyle modifications involving structured exercise and nutritional counselling can mitigate adverse effects [54]. Socioeconomic factors may influence access to healthcare resources, adherence to HT, and the ability to maintain healthy behaviours, thereby indirectly affecting weight outcomes [55].

Pre-existing Medical Conditions

Co-morbidities such as type 2 diabetes mellitus, polycystic ovary syndrome (PCOS), and thyroid disorders further complicate weight management

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during HT [56]. In women with PCOS, who already exhibit hyperandrogenism and insulin resistance, oestrogen therapy may improve metabolic profiles but could also lead to weight gain in the absence of lifestyle interventions [57]. Similarly, in individuals with hypothyroidism, the slowed basal metabolic rate may magnify HT-induced weight gain [58], while poorly controlled diabetes can affect both the safety and efficacy of HT [59].

5. Clinical Implications and Management Strategies

5.1 Importance of Monitoring Weight and Metabolic Changes

The initiation and maintenance of gender-affirming hormone therapy (GAHT) have profound effects on metabolic health, making regular monitoring essential. Changes in body composition, particularly increases in total fat mass and visceral adiposity, have been observed among trans women receiving oestrogen therapy and trans men on testosterone [60,61]. In addition, oestrogen administration can lead to elevations in triglycerides and reductions in insulin sensitivity, while testosterone therapy has been associated with increases in low-density lipoprotein cholesterol (LDL-C) and reductions in high-density lipoprotein cholesterol (HDL-C) [62]. These alterations collectively elevate the risk of cardiovascular disease, type 2 diabetes mellitus, and non-alcoholic fatty liver disease. Therefore, systematic monitoring of BMI, lipid profile, fasting glucose, haemoglobin A1c, and insulin sensitivity should be integrated into routine care at baseline and at regular intervals thereafter. Current guidelines recommend at least annual evaluations, although higher-risk patients may require more frequent assessments [63]. Regular monitoring not only identifies emerging abnormalities but also allows for the adjustment of treatment strategies to mitigate long-term health consequences, contributing to safer and more sustainable hormone therapy.

5.2 Nutritional and Exercise Recommendations

Lifestyle interventions, particularly targeted nutritional and exercise programmes, are crucial adjuncts to GAHT to address metabolic alterations. Weight gain during GAHT is not merely a cosmetic concern but represents a shift towards a more metabolically unfavourable profile, necessitating proactive management [64]. Aerobic exercise has been shown to improve lipid profiles and insulin sensitivity, while resistance training is particularly effective in preserving or increasing lean muscle mass, which can be reduced during oestrogen therapy [65]. Dietary strategies should emphasise caloric balance, macronutrient distribution favouring lean proteins and complex carbohydrates, and minimisation of saturated fats and added sugars. Micronutrient monitoring, including calcium, vitamin D, and iron, may be especially important given hormonal effects on bone density and haematological parameters. Programmes should also be adapted to the psychological needs of transgender individuals, who may experience body dysphoria, impacting their motivation and relationship with diet and exercise. Importantly, interventions that integrate culturally sensitive counselling and peer support have demonstrated greater success in promoting sustainable behaviour change [66]. Thus, lifestyle management must be positioned not as optional, but as a critical component of comprehensive GAHT care.

5.3 Pharmacological Considerations

Optimising the pharmacological regimen of GAHT is another critical factor in mitigating metabolic risks. Oestradiol administered via oral routes has been associated with a higher risk of thromboembolic events and more adverse impacts on lipid metabolism compared to transdermal administration, likely due to first-pass hepatic metabolism [67]. Consequently, transdermal oestradiol is often preferred in patients at elevated cardiovascular risk. Similarly, while intramuscular testosterone injections provide effective masculinisation, they can cause supra-physiological peaks that may exacerbate erythrocytosis and lipid abnormalities; thus, dose titration and, if necessary, switching to transdermal formulations can reduce these risks [68]. The importance of using the lowest effective dose to achieve desired clinical outcomes cannot be overstated. In addition, adjunct pharmacological agents, such as statins for dyslipidaemia or antihypertensive medications, may be required as part of a holistic approach. Importantly, pharmacovigilance must extend beyond the hormones themselves to encompass drug interactions, particularly as many transgender individuals may also be receiving psychotropic medications that influence weight and metabolism [69]. Therefore, pharmacological management must be dynamic and

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responsive to evolving metabolic profiles and patient-specific factors.

5.4 Personalised Approach to GAHT

Personalisation of GAHT is increasingly regarded as the gold standard for safe and effective therapy. Evidence suggests substantial interindividual variability in the metabolic responses to hormone therapy, influenced by factors such as age, genetic background, ethnicity, baseline cardiovascular health, and concurrent medications [70,71]. For example, older transgender individuals or those with pre-existing metabolic syndrome may require lower hormone doses and closer monitoring compared to younger, metabolically healthy patients. Furthermore, emerging evidence highlights the potential role of genetic polymorphisms, such as in oestrogen receptor or androgen receptor genes, in modulating hormonal effects, suggesting future possibilities for genomics-driven GAHT tailoring [72]. A patient-centred approach that involves shared decision-making, transparent communication about risks and benefits, and respect for patient autonomy is critical to achieving optimal outcomes. This personalized model not only enhances medical safety but also supports mental health and overall quality of life, as patients feel empowered and respected in their treatment journey [73,70]. Thus, a "one-size-fits-all" paradigm is no longer acceptable in GAHT; nuanced, individualised care represents the future of transgender medicine.

6. Research Gaps and Future Directions

Despite the growing body of evidence examining the metabolic and behavioural impacts of hormone therapy, several important gaps remain unaddressed in the literature. Notably, there is a paucity of longitudinal studies that evaluate weight fluctuations and body composition changes in transgender individuals over extended periods [74,75]. Most existing research adopts cross-sectional or short-term prospective designs, which limits the ability to discern long-term patterns and causal relationships between hormone therapy and sustained weight gain, redistribution of adipose tissue, or changes in lean mass [76]. Future investigations employing long-term follow-up and standardised outcome measures are essential to elucidate the temporal trajectory of these effects [77].

Another emerging area requiring further exploration is the interaction between gut microbiota and appetite regulation in the context of gender-affirming hormone therapy [78,79]. Preliminary studies in cisgender populations suggest that hormones such as oestrogen and testosterone can influence the gut microbiome, which in turn affects satiety and hunger-related hormones like leptin and ghrelin [80,81]. However, it remains unclear how these mechanisms operate in transgender individuals undergoing hormone therapy [82]. Investigating microbiota composition and its metabolic signalling during gender transition may offer novel insights into appetite control and energy balance within this population [83]. Furthermore, current research is predominantly based on Western, predominantly White cohorts, limiting generalisability [84]. There is a critical need for studies examining ethnic and genetic variability in response to hormone therapy [85,86]. Differential metabolic, endocrine, and psychosocial responses across racial and ethnic groups may exist, shaped by both biological predispositions and sociocultural contexts [87]. Inclusion of more diverse samples in future studies will be vital to ensure equity in clinical guidance and to understand whether current recommendations apply universally [88]. Finally, the intersection between mental health, body image, and eating behaviours in transgender individuals remains underexplored [89,90]. While some studies have addressed the psychological benefits of gender-affirming treatment, few have delved into how hormone therapy may influence emotional eating patterns, disordered eating risk, or perceptions of body satisfaction [91]. Given the high prevalence of body dysphoria and eating disorders in transgender populations, future research should incorporate validated psychometric tools to assess these variables longitudinally, alongside physiological measures [92,93]. Understanding these relationships will be crucial for developing holistic, patient-centred care models that address both the physical and emotional dimensions of gender-affirming therapy [94].

Conclusion

This literature review highlights the important effects of gender-affirming hormone therapy (GAHT) on body weight, fat distribution, and metabolic health in transgender individuals. Estrogen and anti-androgen therapy for transgender women (MTF) often results in more subcutaneous fat, less lean muscle mass, and a

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higher risk of insulin resistance and lipid disorders. On the other hand, testosterone therapy for transgender men (FTM) usually increases muscle mass and metabolic rate but may also lead to more belly fat and increase the risk of metabolic syndrome and heart problems. The physiological responses to GAHT differ notably between MTF and FTM populations, reflecting the differing hormonal pathways involved. These disparities highlight the necessity for personalized approaches to hormone regimens and lifestyle interventions, tailored to individual risk profiles, genetic predispositions, and baseline metabolic health. Ongoing clinical monitoring including assessments of BMI, lipid panels, insulin sensitivity, and cardiovascular markers is essential to mitigate potential long-term health consequences. Despite a growing body of research, critical gaps remain, particularly regarding long-term outcomes, the role of gut microbiota, and the intersection of mental health and eating behaviors. Future studies should prioritize diverse populations and employ longitudinal designs to improve the generalizability and depth of findings. Integrating psychosocial, physiological, and behavioral insights into transgender healthcare will be vital for advancing evidence-based, inclusive, and holistic care for individuals undergoing GAHT.

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