Bone health in transgender people

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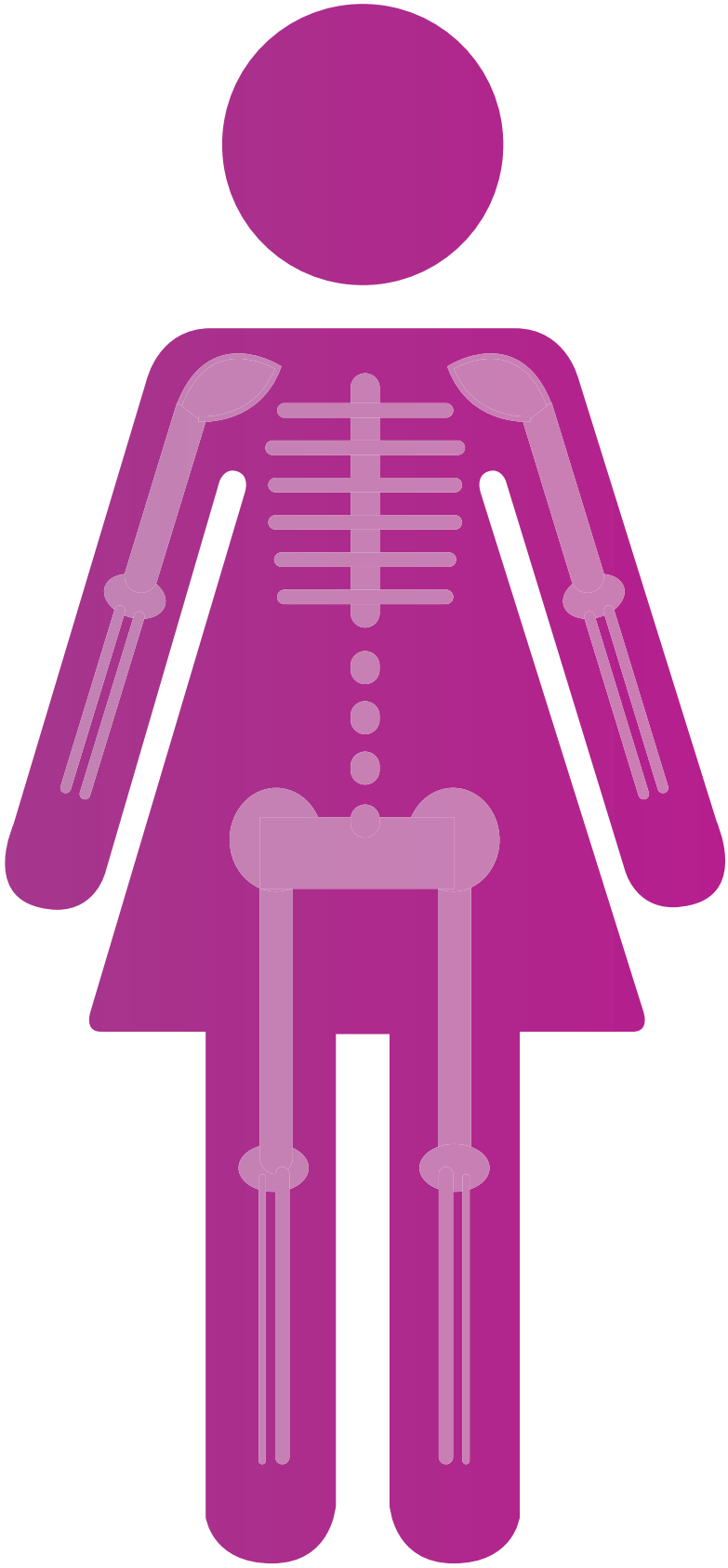

Chapter 10

General discussion

In this chapter, the main findings of the studies described in this thesis will be summarized (also described in Table 1 and Table 2) and will be discussed into the context of other studies, separately for trans women and trans men. A distinction will be made between short-term effects and long-term effects. Thereafter, the strengths and limitations of this thesis will be discussed and the implications for clinical practice will be given.

Population

The number of people with gender identity issues who seek professional help increased enormously in the last decades, as described in Chapter 2.[1-3] Possible explanations for this increase can be sought in the increased media and society attention. This can lead to more awareness of the existence of gender dysphoria and the possibility for medical treatment, and to higher social acceptance. In addition, the change in treatment protocols, including the option for a 'partial' treatment such as hormones without surgery, or mastectomy without hormones [4], may lead to an increase in referrals. However, these possible explanations are only hypotheses, as we did not study the reasons for the increase in referrals.

While the ratio trans women : trans men remained stable in adults, in adolescents the population of trans boys increased relatively more than the population of trans girls, leading to that currently more trans boys than trans girls are seen. This finding is in line with another study reporting this phenomenon [5], but a clear explanation is not elucidated yet.

Only a very small percentage of people who underwent gonadectomy regretted their decision, expressed as start of hormonal treatment in line with their sex assigned at birth. The numbers reported in our study (0.5%) are in line with other studies investigating the regret rates, which are <1% in trans men and 1-1.5% in trans women in an older study [6], and 0% [7,8], 2% [9], and 6% [10] in more recent studies.

Bone health
Trans women

Before start of HT

In trans women, we found that the mean Z-score before the start of HT was lower than expected **(Chapter 7)**. Also, 20% had a Z-score below -2.0, which indicates a low BMD for age. We also observed that the mean vitamin D concentrations in trans women at baseline were low, which might be one of the explanations for this low BMD. This observation was earlier described by Haraldsen et al. in 2007.[11] They found that at baseline trans women had a lower lumbar spine BMD than cis men. They also found that trans women had a lower lean body mass and lower total body fat than cis men. Van

Caenegem et al. [12] also described this finding in 2013. They found that trans women had lower areal BMD at the total hip, femoral neck, and lumbar spine, a thinner radial cortex and lower cortical area. In addition, they had lower muscle mass and strength, and lower vitamin D concentrations than cis men, which might be contributing factors to the lower BMD. Possible explanations for these baseline differences could be found in lifestyle factors. It can be thought that trans women, before any medical intervention, don't go out much and therefore have low vitamin D concentrations and low muscle mass (and therefore lower mechanical loading), which negatively influences the achievement of bone mass.

Short-term effects of HT

During the first year of HT, we observed that BMD increased **(Chapter 3)** and the BTMs decreased **(Chapter 4)** in trans women. The largest increase in BMD was observed in the lumbar spine, which mainly consists of trabecular bone.[13] Trabecular bone is thought to be more metabolic active compared to cortical bone, which is particularly present in the hip.[13] We also observed that the changes in BTMs were mainly correlated to the change in LS BMD. This indicates that an increase in estradiol concentration inhibits osteoclast activity [14], shown by a decrease in bone resorption, which leads to an increase in BMD. The latter is supported by the relationship found between the change in estradiol concentration during HT and both BMD and BTMs. Mean estradiol concentrations during HT were positively associated with change in BMD. In addition, we found that the estradiol concentrations in the lowest quartile did not show a decrease, or showed even an increase in BTMs, indicating that these estradiol concentrations might be too low to result in a decrease in bone turnover.

Vitamin D deficiency (<50 nmol/L) is very common in trans women. In our study described in **Chapter 5**, we found that almost 70% of the trans women were vitamin D deficient at baseline. Trans women with vitamin D deficiency received treatment with vitamin D supplements, which also has positive effects on bone health.[15] We observed that the trans women who received both HT and vitamin D supplementation had a larger increase in BMD than trans women who only received HT (**Chapter 3**). However, we still observed an increase in BMD in trans women without vitamin D supplementation, indicating that the increase in BMD is not solely the result of the vitamin D supplementation. In addition, estrogens can influence vitamin D metabolism. Earlier studies found that cis women using oral anticonceptives [16] or during pregnancy [17,18] had a higher concentration of vitamin D binding protein (DBP). If more total vitamin D is bound to DBP, less free or bioavailable vitamin D is available for metabolic processes. This might indicate that hormonal treatment in trans women can influence vitamin D metabolism and might hamper diagnostics of vitamin D deficiency, with possible negative effects on bone health. In our study (**Chapter**

5), we found that DBP only increased mildly in trans women during HT, and free and bioavailable vitamin D decreased slightly. Total vitamin D concentrations did not change and were well correlated with free and bioavailable vitamin D concentrations. This indicates that hormonal treatment in trans women does not negatively influence vitamin D metabolism and diagnostics of vitamin D deficiency.

Besides direct effects of estrogens on bone, also indirect effects might occur, for example effects on muscle mass. During hormonal treatment, the testosterone concentrations decrease. Testosterone concentrations are positively associated with muscle mass [19-21], and higher muscle mass and therefore higher mechanical loading, is associated with a higher BMD.[22] We observed in **Chapter 6** that in trans women, grip strength and muscle muss decreased during HT. However, BMD increased in these individuals. These findings indicates that, even though muscle mass decreases in trans women, one year of HT does not have deleterious effects on bone health.

Long-term effects of HT

As described in **Chapter 7**, we studied the change in BMD during the first ten years of HT. We found that BMD initially increased during the first two years of HT and decreased thereafter, to the same BMD after ten years of HT than at baseline. However, as the majority of the included trans women were after the age of peak bone mass, the natural course of BMD is to decrease over time. As we did not follow a cis control group for ten years, we also analyzed the change in Z-score during the first ten years of HT. This Z-score is the BMD of the study population compared with the BMD of someone of the same ethnicity, age, and birth-sex. We observed that Z-score increased initially and stabilized thereafter. This indicates that the decrease in BMD is due to the aging of the population and not due to HT. In line with the short-term study as described in **Chapter 3**, we found that change in BMD was associated with the mean estradiol concentrations during HT. Trans women who were in the highest estradiol tertile showed an increase in BMD. Trans women who were in the middle estradiol tertile showed no change in BMD, while trans women who were in the lowest estradiol tertile showed a decrease in BMD. This shows that estradiol concentrations are associated with change in BMD and that adequate hormone substitution and therapy compliance should be stimulated.

Differences in bone geometry exist between cis men and cis women. Cis men have a larger bone size than cis women, with a larger periosteal circumference.[23] In cis women, the endosteal circumference is smaller than in cis men [24], indicating that the bone of cis women growths towards the inside of the bone. Cortical thickness is however similar between cis men and cis women.[25] In the study described in **Chapter 8**, we studied whether bone geometry changed during HT. We found that subperiosteal width, endocortical diameter, cortical thickness, and section modulus were not different between hormone-naïve trans women at baseline, and trans women using HT for 5, 15,

or 25 years of HT. As these measurements of the hip are mainly of cortical origin, we also studied whether trabecular bone changes by investigating the change in trabecular bone score (TBS). We found that trans women who were using HT for either 5, 15, or 25 years, had a higher (or tended to be higher) TBS than trans women at baseline. This indicates that treatment with anti-androgens and estrogens does not influence cortical bone size, as measured by hip structure analysis, but it affects trabecular bone, as shown by the higher TBS values. As low TBS is associated with an increased fracture risk [26], the higher TBS in trans women using HT indicates that HT does not have detrimental effects on bone health, but may even be beneficial.

In the general population, cis men have a higher fracture risk than cis women at younger ages.[27,28] This is because cis men are probably more involved in accidents, for example sporting accidents, leading to an increased fracture risk.[27,28] At older ages, cis women have a higher fracture risk than cis men. This is the result of the lower BMD in cis women because of menopause [27], whereas this is not the case in cis men. In the last study described in **Chapter 9**, we investigated the fracture risk in trans women using HT. Trans women using long-term HT were divided into two groups: <50 years and ≥50 years. They were compared both with cis men and cis women. In trans women <50 years, we found that fracture risk was in between the risk of cis men and cis women: it was lower than the fracture risk of cis men, but tended to be higher than the fracture risk of cis women. The lower fracture risk of trans women than cis men can be thought to be the result of a less active life style than cis men, with also less sporting activities, leading to a decreased fracture risk. In trans women ≥50 years, we found that fracture risk was increased compared with cis men, but similar to cis women. Also the type of fractures differed: trans women experienced more often a hip, spine, forearm, or humerus fracture (as an approximation of osteoporotic fractures) than cis men, but similar to cis women. This indicates that fracture risk in trans women at older ages resembles the risk of cis women, while at younger ages the risk is in between the risk of cis men and cis women.

Table 1. Summarizing table of the main outcomes of the described studies in this thesis in trans women

	Number of trans women	Measurement	Time points	Outcome
Before start of hormonal treatment				
- Bone mineral density	711	DXA	0 year	↓
Short-term effects				
- Bone mineral density	231	DXA	0 and 1 year	↑
- Bone turnover markers	121	Blood samples	0 and 1 year	↓
- Vitamin D concentrations	29	Blood samples	0 and 3 months	=
- Grip strength/lean body mass	249	Dynamometer/DXA	0, 3, 6, 9, 12 months	↓
Long-term effects				
- Bone mineral density	711	DXA	0, 2, 5, 10 years	↑ / =
- Bone geometry				
• Trabecular bone score	535	DXA	0, 5, 15, 25 years	↑
• Hip structure analysis	535	DXA	0, 5, 15, 25 years	=
- Fractures				
• <50 years	1,089	National registry	8 years	↑ vs cis women ↓ vs cis men
• ≥50 years	934	National registry	19 years	= vs cis women ↑ vs cis men

Trans men

Before start of HT

Before the start of hormonal treatment, we found that trans men had a normal lumbar spine BMD, expressed as a Z-score of zero (**Chapter 7).** This is in agreement with earlier baseline studies in trans men. Haraldsen et al. [11] described in 2007 that trans men had a similar lumbar spine BMD than cis women, but a higher femoral neck BMD. Van Caenegem et al. [29,30] reported in 2012 and in 2015 that trans men at baseline had similar bone and body composition than cis women. This indicates that prior to HT, no decreased bone health is present in trans men.

Short-term effects of HT

During the first year of HT (**Chapter 3**), we observed small increases in BMD of the lumbar spine and total hip, and no change in femoral neck. However, the BTMs increased as well (**Chapter 4**). The changes in BMD and BTMs were not associated with the mean testosterone concentrations during HT. Interestingly, we found an age difference in change in BMD and BTMs. In people over 50 years, who were thought to be postmenopausal and therefore estrogen deficient at baseline, BMD increased

more compared to the younger trans men. BTMs decreased in this group, while it increased in the younger trans men. Because testosterone is aromatized into estradiol, supplementation with testosterone will not only increase the testosterone concentrations in this older group but also the estradiol concentrations. As the younger trans men had higher estradiol concentrations at baseline than older trans men, only an increase in testosterone concentrations was observed and no change in estradiol concentrations was seen. This indicates that, in trans men, estrogen is mainly responsible for the increase in BMD and the decrease in BTMs, because in trans men with no change in estrogen concentrations but only in testosterone concentrations, only a small increase in BMD was found, and BTMs increased. These findings are in line with the study performed by Finkelstein et al. [31] who included a large population of cis men and treated them with gonadotropin-releasing hormone agonists. Half of the group was treated with testosterone only, in different dosages, while the other half of the group also received an aromatase inhibitor to inhibit the aromatization of testosterone into estradiol. Therefore, the first group had normal testosterone and normal estradiol concentrations, while the other group had normal testosterone but low estradiol concentrations. They observed that BMD of the lumbar spine decreased in the group using an aromatase inhibitor, with low estradiol concentrations, and remained stable in the group without an aromatase inhibitor and normal estradiol concentrations. This also shows that the effect of testosterone on BMD maintenance mainly occurs through the indirect effects of aromatization of testosterone into estradiol, instead of direct effects of testosterone.

Also in trans men, vitamin D deficiency occurs frequently. In our study described in **Chapter 5**, we found a prevalence of almost 70% at baseline. Testosterone might influence vitamin D metabolism, as a study in hypogonadal cis men treated with testosterone demonstrated that DBP concentrations decreased.[32] However, we observed that DBP only tended to decrease minimally, and also free and bioavailable 25(OH)D concentrations tended to increase minimally. Total 25(OH)D concentrations did not change because of HT and were well correlated with free 25(OH)D concentrations. This indicates that hormonal treatment in trans men does not have negative effects on vitamin D metabolism.

Testosterone also influences muscle mass, as demonstrated in studies in hypogonadal cis men with testosterone replacement therapy.[19] Testosterone affects myoblast proliferation and myoblast differentiation, and testosterone increases the number of satellite cells, which promotes protein synthesis of muscle mass.[21] We observed that grip strength increased during the first year of HT in trans men and that this increase in grip strength was associated with an increase in lean body mass (as an approximation of muscle mass). Change in grip strength was not associated with change in BMD, while change in muscle mass was mildly associated with change in femoral neck BMD. This might indicate that the preserving effects of testosterone on bone health in trans men is, besides the estrogen-mediated effects after aromatization, also

partially mediated by an increase in muscle mass and therefore an increase in mechanical loading. The latter was earlier described by van Caenegem et al. [30], who also found a correlation between BMD and muscle mass in trans men.

Long-term effects of HT

The first ten-year effects of HT on BMD in trans men are described in **Chapter 7**. We found that BMD remained stable during the first ten years of HT. However, because of aging we would expect BMD to decrease. Therefore Z-score was also analyzed, which revealed a continued increase in Z-score during the first ten years of HT, indicating no negative effects of testosterone treatment on BMD. As observed in the short-term study, also in this study the oldest age group experienced a larger increase in BMD than the younger age groups, which is thought to be a result of the baseline postmenopausal status as explained above. Testosterone and estradiol concentrations were not associated with change in BMD, but LH concentrations showed a relationship with BMD. Trans men with suppressed LH concentrations (<2 U/L) had an increase in BMD during the first ten years of HT, while in trans men with not suppressed or elevated LH concentrations (>2 U/L) no change in BMD was found. This indicates that adequate hormone substitution and therapy compliance should be stimulated for bone health.

The differences in bone geometry in trans men with and without testosterone treatment were studied in **Chapter 8**. We found that overall, no differences in subperiosteal width, endocortical diameter, cortical thickness, and section modulus were found between hormone-naïve trans men at baseline and trans men who were using HT for 5, 15, or 25 years, except again for the postmenopausal baseline group. Changes in trabecular bone score were found in all age groups. Trans men at baseline had a higher TBS than trans men using testosterone. Estrogens are known to positively influence trabecular bone.[33,34] Decreasing concentrations of estrogen can therefore negatively influence trabecular bone. Although we found that TBS was lower in trans men using testosterone than trans men at baseline, we did not find a linear relationship with duration of HT. This indicates that trabecular bone score decreases because of HT, but does not continue to decrease.

As last step, we investigated the fracture risk in trans men using long-term HT (**Chapter 9**). Overall, we found that trans men had a similar fracture risk than cis women and a lower fracture risk than cis men. This might be explained by that trans men are more careful or participate less in (sporting) activities than cis men, leading to less fractures. As the total number of fractures in trans men was already low, we could not stratify the analysis for age groups or type of fracture.

To conclude, in the past, it was thought that testosterone treatment in trans men would be detrimental for bone health because of the decreasing estradiol concentrations. Loss of estrogen at menopause leads to an increased osteoclastic activity and therefore accelerated bone loss.[14] However, we found in trans men that, because of the aromatization of testosterone into estradiol, no large changes in estradiol concentrations were observed. Also, no changes or even increases in BMD were observed. Even larger increases in BMD and decreases in BTMs were found in trans men with larger changes in estradiol concentrations. This indicates that HT does not have deleterious effects on bone health in trans men, which might to be caused by the adequate estradiol concentrations after the aromatization of testosterone into estradiol.

Table 2. Summarizing table of the main outcomes of the described studies in this thesis in trans men

	Number of trans men	Measurement	Time points	Outcome
Before start of hormonal treatment				
- Bone mineral density	543	DXA	0 year	=
Short-term effects				
- Bone mineral density	199	DXA	0 and 1 year	↑ / = <50 years ↑↑ ≥50 years
- Bone turnover markers	132	Blood samples	0 and 1 year	↑ <50 years ↓ ≥50 years
- Vitamin D concentrations	30	Blood samples	0 and 3 months	=
- Grip strength/lean body mass	278	Dynamometer/DXA	0, 3, 6, 9, 12 months	↑
Long-term effects				
- Bone mineral density	543	DXA	0, 2, 5, 10 years	↑ / =
- Bone geometry				
• Trabecular bone score	473	DXA	0, 5, 15, 25 years	↓
• Hip structure analysis	473	DXA	0, 5, 15, 25 years	=
- Fractures	1,036	National registry	9 years	= vs cis women ↓ vs cis men

Strengths, limitations, and recommendations for further research

Strengths

In this thesis, we analyzed the short-term effects of HT on BMD, BTMs, vitamin D metabolism, and grip strength, and the long-term effects of HT on BMD, bone geometry, and fracture risk. These studies had several strengths. In the majority of our studies, we included a large population, considering the rarity of the diagnosis. This allowed us not only to answer our main research questions, but also to perform subgroup analyses, such as analyzing the effects of different hormone concentrations. We also included people with a wide age range, therefore we were able to stratify the analyses for different age groups. Some studies were part of a multicenter prospective study, in which measurements were performed before and during HT. All trans people were treated according to a defined treatment protocol, and standardized measurements were used for physical examination, laboratory measurements, and DXA. Also in the long-term studies, the same DXA scanner was used for all analysis and most measurements were performed before and during HT. Fracture data was obtained using a nationwide registry.

Limitations

However, there are also some limitations. First, we did not include control groups in the analyses, except for fractures. Trans people may change their life style during HT, such as becoming more physical active, developing healthier eating habits, and stop smoking cigarettes. It can therefore not be proven that the change in, for example BMD and BTMs, are solely the result of HT. However, it is ethically not possible to perform a randomized controlled trial where some trans people would be withhold to use HT to investigate whether the change in BMD and BTMs are solely the effect of HT. A possible, but not optimal, solution would be to include a cis control population during the same follow-up period.

Second, only the effect of the first ten years of HT on BMD are investigated. Although it is not likely that the effects of HT on BMD for longer terms, for example 30 or 40 years, would be different than the first ten years, it is interesting to investigate this, particularly in regard to therapy compliance. One may assume that therapy compliance becomes lower after longer use of HT.

Third, bone health was only assessed using DXA. Although in regular patient care BMD is also assessed using DXA, this does not give insight into whether changes occur in BMD, bone geometry, or other characteristics such as cortical porosity. We tried to overcome this limitation by using additional software such as HSA and TBS. However, the DXA was not developed to analyze these changes. Another possibility could be to use peripheral qCT. Some short-term studies already studied this issue, but no long-term longitudinal changes have been studied yet.

Fourth, we only investigated fracture risk after long-term HT. Most ideally, fracture risk would be studied before the start of HT, in order to investigate what the baseline fracture risk is in trans people, and to follow the trans people from the moment they start with HT, to investigate whether fracture risk changes because of HT. In addition, fracture risk was only studied using clinical fractures, but no vertebral fracture assessment (VFA) was performed. As not all fractures become clinical, using VFA would provide more information.

Future research perspectives

In this thesis, only people who used the standard protocol of hormonal treatment were included. However, the last years more gender variant people who experience all kinds of identity issues may wish to receive different treatments. Examples of these different treatments include gonadectomy without the use of sex hormones, low dosages of sex hormones, or only suppression of the endogenous hormone production. These treatments may result in different effects on bone health. It would be worthwhile to investigate what the minimal amount of sex hormones is that should be used, in order to maintain adequate bone health, but what is also in line with the wishes of the treated individual.

Also in this thesis, only people who started treatment during adulthood (≥18 years of age) were included. Just as the increase in referrals in transgender adults, also a large increase in referrals in transgender adolescents is observed. These adolescents receive a different kind of treatment than adults. Their treatment first starts with gonadotropin-releasing hormone agonists to suppress the development of secondary sex characteristics of the sex assigned at birth. After several months or years of treatment, depending on the age of start with this treatment, sex hormones are added to this treatment. This different treatment approach may have different effects on maintaining adequate bone health, but also on bone development and accrual during puberty. Given the increase in referrals in transgender adolescents, it is necessary to investigate this population as well.

Implications for clinical practice

Trans women

Trans women often experience low bone mass at baseline, but it increases during HT. Therefore, regularly performing DXA scans to measure BMD during HT is not necessary. However, we observed that BMD decreased in those with lower estradiol concentrations (mean 118 pmol/L, range 20-182 pmol/L) and remained stable or increased in those with higher (mean 238 pmol/L and 443 pmol/L, respectively) estradiol concentrations. This indicates that concentrations of 118 pmol/L are too low for bone health in trans women and higher concentrations, at least 180 pmol/L, should be aimed for.

This should be weighed against the possible increased risk for side effects of hormonal treatment, for example cardiovascular events (CVE) or breast cancer. However, a recent study analyzing the CVE risk found that trans women with a CVE used similar dosages of estradiol compared to trans women without a CVE [35], although they do not give any information regarding estradiol concentrations or compliance. A recent study that reported on breast cancer risk in trans women found that trans women who experienced breast cancer had similar mean estradiol concentrations during HT than trans women without breast cancer.[36] These studies indicate that the concentrations of estradiol are not linear related to the increased CVE and breast cancer risk, and therefore increasing the lower limit of estradiol concentrations would not be detrimental regarding these side effects. This is also more in line with the aimed estradiol concentrations as described in the Endocrine Society Guidelines [37], which are between 367 and 734 pmol/L. In addition to this, it should be considered to perform a DXA in trans women with potential therapy incompliance after gonadectomy, as they will have low estradiol concentrations and therefore may experience a decrease in BMD.

We also observed that trans women often are vitamin D deficient at baseline (around 70%). Supplementation with vitamin D supplements increased BMD more than in trans women without supplementation of vitamin D. Therefore, all trans women should be treated with vitamin D supplementation daily to increase or maintain the vitamin D concentrations and to increase BMD. Also giving them life style advises for optimizing bone health, such as quitting smoking and becoming more physically active, seems relevant, as earlier studies found that trans women had lower muscle mass and smoked more often than their control cis peers, which has negative effects on bone health.[38]

Cis women experience decreases in estradiol concentrations because of menopause. No guidelines exist about whether estradiol dosing should be lowered or stopped in trans women using HT. Based on the low initial BMD in trans women, the decrease in BMD in trans women with low estradiol concentrations, and the increased fracture risk of trans women compared with cis men, it may be thought that lowering or stopping estradiol dosing should not be standard in trans women based on their bone health. However, what concentrations should be aimed for is not known yet and should be a topic for further research.

Trans men

We found that at baseline trans men had a BMD as expected for age. BMD did not change during the first ten years of HT. After long-term use of HT, fracture risk was not increased in trans men compared with the control population. Therefore, it does not seem necessary to check BMD in trans men before or during HT. However, if a DXA scan is performed in trans men and low bone mass is found, one might aim for suppressed LH concentrations (<2 U/L) during HT, as we observed an increase in

BMD in trans men with suppressed LH concentrations. This however should be done on a case-by-case base, also taking the possible increased risk for side effects taking into account, such as polycythemia.[39]

Reference values

Different reference values exist for cis men and cis women to calculate T-scores and Z-scores. However, some studies found that fracture risk was similar in cis men and cis women with the same absolute BMD.[40] Therefore, there is discussion about whether sex-specific reference values should be used for both cis men and cis women, or that female reference values should be used for everybody. It is not known what reference values should be used for trans people if sex-specific reference values are used. Most trans people already achieved their peak bone mass before they started with HT, therefore the reference values of the sex-assigned at birth are most commonly used. In the ideal situation to determine what reference values should be used, BMD of the trans population should be compared with the BMD of cis men and cis women with a similar fracture risk. Unfortunately, such study has not been performed yet. Based on the results of this thesis that bone geometry of the hip in trans women are more related to male reference values, and in trans men are more related to female reference values or in between female and male reference values, and did not change during HT, the reference values of the birth-assigned sex should be used. However, the change in TBS in both trans women and trans men might indicate that the reference values of the identified sex should be used in trans people using HT. Furthermore, both trans women and trans men had a mean BMD at baseline that was more closely related to female reference values than male reference values.[41] This might indicate that female reference values should be used for all trans people. Therefore, data about which reference values should be used is not clear yet and more research is needed.

Conclusion

In conclusion, we found in this thesis that bone mineral density did not decrease after short term and long-term hormonal treatment in both trans women and trans men. Fracture risk in trans people did not exceed the fracture risk of cis people. This indicates that hormonal treatment does not have detrimental effects on bone health. However, bone health should be an important health topic in trans people, given that trans women often had low bone mineral density before the start of hormonal treatment, and the high prevalence of vitamin D deficiency. Taken all these results into account, we consider the results of this thesis as reassuring with regard to the safety of hormonal treatment in trans people.

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