

Skeletal Effects of Levothyroxine for Subclinical Hypothyroidism in Older Adults: A TRUST Randomized

Trial Nested Study

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ABSTRACT (maximum 250 words, actual 249)

Context: Both thyroid dysfunction and levothyroxine therapy (LT4) have been associated with bone loss, but studies on the effect of LT4 for subclinical hypothyroidism (SHypo) on bone yielded conflicting results.

Objective: To assess the effect of LT4 treatment on bone mineral density (BMD), Trabecular Bone Score (TBS), and bone turnover markers (BTMs) in older adults with SHypo.

Design and Intervention: Planned nested substudy of the double-blind placebo-controlled TRUST trial. Participants with SHypo were randomized to LT4 with dose titration vs. placebo with computerized mock titration.

Setting and Participants: 196 community-dwelling adults over 65 years enrolled at the Swiss TRUST sites had baseline and 1-year follow-up bone examinations; 4 participants withdrew due to adverse events not related to treatment.

Main Outcome Measures: One-year percent changes of BMD, TBS, and two serum BTMs (sCTX and P1NP). Student's t-test for unadjusted analyses, and linear regression adjusted for clinical center and sex, were performed.

Results: Mean age was $74.3y \pm 5.7$, 45.4% were women, and 19.6% were osteoporotic. The unadjusted 1-year change in lumbar spine BMD was similar between LT4 (+0.8%) and placebo-treated groups (-0.6%; between-groups difference +1.4%: 95%CI -0.1 to 2.9, $p=0.059$). Likewise, there were no between-group differences in 1-year change in TBS (-1.3%: 95%CI -3.1 to 0.6, $p=0.19$), total hip BMD (-0.2%: 95%CI -1.1 to 0.1, $p=0.61$), or BTMs levels (sCTX +24.1%: 95%CI -7.9 to 56.2, $p=0.14$), or after adjustment for clinical centers and sex.

Conclusions: Over one-year levothyroxine had no effect on bone health in older adults with SHypo.

Registration: ClinicalTrial.gov NCT01660126 and NCT02491008

Key words: Subclinical hypothyroidism, Levothyroxine, Bone mineral density, Trabecular Bone Score, Bone markers

Précis:

One year of levothyroxine for older adults with subclinical hypothyroidism does not affect bone health, as determined by bone mineral density, Trabecular Bone Score, or bone turnover markers.

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Introduction

The prevalence of subclinical hypothyroidism (SHypo), defined as an elevated thyrotropin (TSH) level with free thyroxine (FT4) within the reference range, increases with age, reaching >10% in men over 65 years and up to 21% in women ≥ 75 years [1, 2]. Increasing evidence suggests that treating SHypo with levothyroxine (LT4) does not confer clinical benefit [3, 4]. Although recent UK guidelines recommend against LT4 therapy except in very specific clinical conditions [5], others propose LT4 for adults with SHypo and a TSH > 10.0 mIU/L [6, 7] and up to nine out of ten women with SHypo and a TSH concentration between 5.5 and 10 mIU/L should be treated if some of these guidelines were followed [8].

The deleterious effect of high thyroid function on bone, even at high-normal levels [9, 10] is well established. On the contrary, studies have found no association between SHypo and bone mineral density (BMD) changes [11, 12]; a meta-analysis of individual participant data found no association between SHypo and fracture risk [10]. Concerns have been raised on the impact of LT4 on bone [13], but data on the effects of LT4 replacement on bone in SHypo are scarce and conflicting. Three small (n=17 to 66) randomized clinical trials (RCT) showed either no difference [14, 15], or a small yet not clinically significant bone loss in the LT4-treated group [16]. Only one RCT analyzed bone turnover markers (BTMs) which increased transiently at 24 weeks in the LT4-treated group (between 7.7% for alkaline phosphatase, and 29.9% for sCTX), during a 48 weeks treatment with LT4 [16]. No study has analyzed the effect of levothyroxine substitution on Trabecular Bone Score, a textural index that evaluates pixel gray-level variations in the lumbar spine DXA image and provides an indirect index of trabecular microarchitecture, independent of bone density [17].

The Thyroid Hormone Replacement for Untreated Older Adults with Subclinical Hypothyroidism (TRUST) trial was a multicenter, international, double-blind parallel-group RCT of LT4 versus placebo [4, 18] and showed no apparent benefits of treatment on either primary objectives (Hypothyroid Symptoms or

Tiredness score) or secondary outcomes. Since there was scarce evidence on the effect of SHypo treatment by LT4 on bone health, we measured BMD, TBS and BTM in participants in Swiss centers, at baseline and follow-up of the TRUST trial to assess the effect of LT4 on bone.

Methods

Study population

This nested study focused on skeletal outcomes of participants in the Swiss centers (Bern and Lausanne) of the TRUST trial (clinicaltrials.gov NCT02491008, NCT01660126) [4, 18]. It included community-dwelling individuals aged ≥ 65 years with persistent SHypo. Briefly as previously described [4], persistent SHypo was diagnosed by elevated TSH levels (≥ 4.6 and ≤ 19.9 mIU/L) on at least two measurements at least three months apart, and FT4 levels within the assay reference range. Exclusion criteria included use of LT4, antithyroid, amiodarone or lithium treatment within 12 months, thyroid surgery or radio-iodine, severe acute comorbidities, dementia, terminal illness or galactose intolerance [4]. For this bone study, among the 217 participants of the TRUST trial in Switzerland, 21 participants lacked measurements at 1-year follow-up. Four participants withdrew due to adverse events not related to treatment: three on the treatment arm, and one on the placebo arm. This analysis focused on the 196 participants who had baseline and 1-year follow-up DXA and/or BTMs values. Of these, 79 had no DXA exam at baseline or 1-year, so there were 117 participants left with both DXA exams (**Figure 1**). Of the 196 participants, 6 had no BTMs measures at either baseline or 1-year follow-up for technical reasons, so 190 BTMs (sCTX and P1NP) were available for analysis.

The trial was approved by the local Institutional Review Boards, and written, informed consent was obtained from all participants. The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Intervention

Briefly as previously described [4], treatment started with LT4 50 micrograms daily (25 micrograms in individuals < 50 Kg body weight or with known coronary heart disease). Dose was titrated in the active treatment group according to target TSH levels ≥ 0.4 and < 4.6 mIU/L and a computerized mock titration in the placebo group.

Clinical data

We recorded baseline age, sex, current smoking and alcohol consumption, history of osteoporosis and diabetes mellitus, and all ongoing treatments. Bone-affecting treatments were classified in two categories. Beneficial treatments included anti-osteoporotics (raloxifene, bisphosphonates, denosumab or teriparatide), hormonal replacement therapy, and hydrochlorothiazide. Deleterious bone treatments included systemic or topical glucocorticoids, proton pump inhibitors, aromatase inhibitors, serotonin recapture inhibitors, and antiepileptic treatments. Incident fractures were prospectively recorded.

BMD and TBS measures

Participants had serial BMD and TBS measurements by dual energy X-ray absorptiometry (DXA) on a GEHC-Lunar Prodigy (GEHC, Madison, WI, USA) at the Bern study site, and on a GEHC-Lunar iDXA (GEHC, Madison, WI, USA) at the Lausanne site. The two machines were cross-calibrated at the beginning of the trial for both BMD and TBS using the appropriate phantom, and benefited of a daily on-site quality control with the dedicated phantom supplied by the manufacturer. No statistical differences were observed between the two DXA machines; no longitudinal changes were observed during the study period. BMD measures Least Significant Change (LSC) values are: (i) for the GEHC-Lunar Prodigy, 0.030 g/cm^2 at the lumbar spine (L1-L4) and 0.018 g/cm^2 at the total hip; (ii) for the GEHC-Lunar iDXA, 0.028 g/cm^2 at the lumbar spine (L1-L4) and 0.033 g/cm^2 at the total hip. Manufacturer recommendations were followed for DXA scans at

baseline and follow-up; quality assurance review was performed centrally at Lausanne for both the BMD and TBS parameters. BMD was measured at the lumbar spine (antero-posterior projection of L1 through L4) and the proximal femur (neck and trochanteric regions). Recorded images were reanalyzed for 5 individuals because there were inconsistencies within vertebral readings. Individual vertebrae were excluded if there were fractures or degenerative changes, in accordance with the ISCD rules for excluding individual vertebrae [19] and if considered outliers (T-score $\geq +3.0$ SD). The same vertebrae were excluded at different time points, and mean lumbar spine T-score was calculated as the mean of the included vertebra T-score values. Participants were excluded if only one vertebra remained for analysis. TBS of the spine was centrally assessed at Lausanne Center (blinded from clinical outcomes) with a modified version of TBS iNSight v3.0 which accounts for tissue thickness (Medimaps group, Geneva, CH) by Lausanne Center. Region of interest for TBS were (i) all vertebrae, because TBS is minimally affected by degenerative changes [20], and (ii) the same region used for spine BMD (e.g., the same included/excluded vertebrae). TBS LSC is 3.88%. Left femur measurements were used unless precluded by prosthetic material.

Bone turnover markers (BTMs) measurements

Venous blood was drawn at any time during the day and without regard to fasting status. The Bern University Hospital routine laboratory quantified serum concentration of bone biomarkers Procollagen type 1 N-terminal Polypeptide (P1NP), representing bone formation, and CrossLaps (sCTX), representing bone resorption, in blood samples at baseline and at 1-year follow-up using Roche Cobas© technology, from fresh samples (Bern participants) or from frozen samples (Lausanne participants).

Statistical analysis

We calculated we would need to include 375 participants to detect a difference in the change in total hip BMD as small as 1.3% over two years between groups, with power of 80% and two-sided alpha of 0.05, based on the annual bone loss observed in placebo treated individuals in several US trials [21].

Descriptive results (baseline data) are expressed as number of participants (percentage) or as mean \pm standard deviation (SD). Between-group comparisons on the difference between 1-year follow-up and baseline values were performed using Student's t-test for non-adjusted analyses, and linear regression adjusted for clinical site and sex to account for BMD differences resulting from DXA machines and gender, but unadjusted results were similar. Results are expressed as mean percent changes (95% confidence interval, 95%CI). Statistical significance was considered for p-values <0.05 . All analyses were performed using Stata version 15 (StataCorp, College Station, TX) for Windows.

Results

The mean age at inclusion was 74.3 ± 5.7 years, 45.4% were women, and participants presented with a mean BMI of 27.5 ± 5.0 kg/m² (**Table 1**). TSH was 6.4 ± 2.0 mIU/L and FT4 13.6 ± 1.9 pmol/L before randomization, corresponding to SHypo, which evolved to the euthyroid state at 1 year in the treatment arm but not in the placebo group (TSH 3.2 ± 1.5 vs. 5.6 ± 2.4 ; $p < 0.001$). The characteristics of the 117 participants with DXA exams are detailed by treatment group in **Supplementary Table 1 [22]**. At the baseline DXA exam, 19.6% of the participants were osteoporotic, and 20.5% were osteopenic according to the WHO definition based on the lowest T-score from lumbar spine, total hip or femoral neck [23]. Mean T-scores values were in the normal range at lumbar spine (-0.6 ± 1.5 SD) and total hip (-0.6 ± 1.2 SD), and in the osteopenic range at the femoral neck (-1.1 ± 1.1 SD). On the other hand, 26.5% had degraded TBS and 29.1% had partially degraded TBS, according to the thresholds defined in McCloskey et al [24]. The distribution of all parameters was balanced between groups (all p-values > 0.10) both in the whole study group and the DXA data subgroup, except for deleterious treatments (including systemic or topic glucocorticoids, proton pump inhibitors, aromatase inhibitors, serotonin recapture inhibitors, and antiepileptic treatments) in the DXA data subgroup, which were more frequent in LT4 treated participants (40.7%, vs. 22.4% of placebo treated participants, p -value=0.03).

Table 2 shows BMD and TBS values at baseline and 1-year follow-up by treatment group. One left femur value outlier due to femur anomalies was replaced by right femur readings; femur values were excluded for one participant as it was measured on different sides at each exam. Three participants had no hip image because of bilateral total hip prosthesis. At baseline, BMD in the placebo group was 1.122 ± 0.204 g/cm², 0.963 ± 0.166 g/cm² and 0.890 ± 0.131 g/cm² in lumbar spine, total hip and femoral neck respectively, and 1.133 ± 0.150 g/cm², 0.980 ± 0.167 g/cm², 0.908 ± 0.160 g/cm² in the same sites in the LT4 treated group. At baseline, lumbar spine TBS was 1.325 ± 0.113 in the placebo group vs. 1.307 ± 0.968 in the LT4 treated group.

BMD percentage changes after one year were not statistically different in placebo and LT4-treated participants in non-adjusted analyses (**Table 2, Figure 2**) at lumbar spine BMD (-0.6% vs.+0.8%; between group difference +1.4%: 95%CI -0.1 to 2.9, p=0.059). Likewise, there were no between-group differences in 1-year change in total hip BMD (-0.2%: 95%CI -1.1 to 0.1, p=0.61) or femoral neck BMD (-0.2%: 95%CI -1.8 to 1.4, p=0.82). Further adjustment for center and sex did not change the results (**Supplementary Table 2 [22]**). Unadjusted lumbar spine TBS percentage changes after one year were not statistically different between the two groups either (-1.3%: 95%CI -3.1 to 0.6, p=0.19). We found similar results for TBS both in adjusted analyses, and independently of the included vertebrae (all vertebrae, or only those included in BMD analysis after application of ISCD guidelines). Results were similar after excluding participants receiving bone-affecting treatments.

We assessed the effect of LT4 treatment vs placebo on BTMs: There was no statistically significant difference between groups, either in unadjusted (**Table 3**), or adjusted analyses (**Supplementary Table 2 [22]**). The results were similar in sensitivity analyses by clinical site, or after excluding participants who were receiving bone affecting treatments (data not shown).

In each group, 3 fractures were observed during follow-up, with no significant difference between groups.

Discussion

Our study did not show any harmful effect of LT4 replacement for one year on bone health, which we assessed by measuring BMD, TBS and BTMs in community-dwelling adults aged ≥ 65 with SHypo. Our study is the largest randomized controlled trial for SHypo treatment to date, and no other study has analyzed SHypo treatment effect on bone microarchitecture as assessed by lumbar spine TBS.

Three earlier RCTs analyzed the effect of LT4 treatment of SHypo in bone with conflicting results. Similar to our study, a double-blinded ($n=31$, 75% women, mean age: 68 years, follow-up 10 months) [14], and an unblinded ($n=17$ post-menopausal women, follow-up 14 months) [15] RCT did not find a significant difference in BMD change between LT4 and placebo treated individuals. Meta-analyses on the association of SHypo with fracture risk [10, 12] or BMD [11, 12] showed no difference in observed results when they included or excluded LT4-treated individuals, but did not analyze outcomes specifically in this group. Only the double-blinded RCT by Meier et al. reported a statistically but not clinically significant BMD loss [16] at the lumbar spine when it compared treatment to placebo (-1.15%) in 66 women (56.1 years, follow-up 48 weeks). In this study TSH at follow-up (3.1 ± 0.3 mU/L) was similar to that of our study (3.2 ± 1.5 mU/L) but was higher at baseline (12.8 ± 1.4 mU/L, as compared to 6.3 ± 1.9); a stronger change in TSH could explain the observed results. Of note, 74% were postmenopausal; 37% of these women were on hormone replacement therapy (HRT), but interaction with estrogens was not analyzed. The transient increase in BTMs in the study by Meier et al. [16] may indicate that LT4 treatment restored bone turnover to the usual early menopause values in these almost two decades younger participants. Pines et al. reported that the beneficial effects of estrogen replacement on BMD were reduced when it was combined with LT4 replacement therapy [25]. In our study, participants were older than in the Jaeschke et al. RCT [14], under half were women, and very few participants were on HRT (less than 6.9%) so we could not conduct a separate analysis. Adjustment by sex did not change the magnitude or the statistical significance of the

effect. Our results thus accord with those of two studies with a similar population [14, 15], suggesting LT4 treatment for SHypo does not harm bone health after one year of treatment in individuals over 65; the current study results may however not apply to a younger population.

Only three studies analyzed the effect of thyroid function on TBS. In two prospective cohorts of participants with thyroid cancer undergoing TSH suppressive therapy for 5 to 10 years [26, 27], excess LT4 treatment had a deleterious effect on TBS only in women transitioning from pre- to post-menopause [26], and no effect in post-menopausal women at treatment initiation [26, 27]. But in a euthyroid cohort [28] high-normal free T4 levels, but not TSH values, were associated with low TBS only in post-menopausal women. In our study, as published, TBS changes are not associated to TSH values changes; the link to free T4 cannot be analyzed in detail, as it was not measured at follow-up.

Our conclusions are reinforced by the absence of a significant difference in BTMs changes between both groups at one year. Meier et al. [16] obtained similar results by measuring different BTMs, including sCTX, finding no changes at 48 weeks. They did observe a transient increase (at 24 weeks) in treated adults, which they interpreted as restoration of normal remodeling levels that had been decreased in SHypo. We did not have earlier BTMs measures to evaluate this hypothesis.

The greatest strengths of our trial were its double-blind RCT design and that it was the biggest RCT on SHypo and bone (past ones n=17 to 66). Among limitations, it may still be underpowered because we were able to include only 196 individuals. However, the point estimates in the current results went in the opposite direction to published ones, with a non-significant BMD increase under LT4 and a slight decrease under placebo, which makes it unlikely that we would have found different results with a larger sample. This trend for an eventual benefit of LT4 treatment on lumbar spine ($p=0.06$ for the difference in adjusted analysis) is most probably due to chance. Also the largest change included in the 95% confidence intervals is a gain of 2.9% spine BMD, or a loss of 4.0% for TBS, which makes it very unlikely that we have missed a

clinically important difference. We might have been limited by the short follow-up period, although it was the longest blinded trial. Our study cannot address with appropriate power the effect in participants with more pronounced subclinical hypothyroidism, due to the low number of participants with TSH > 10 mIU/L, although this is also the case in the general population [1]. In our study TSH target values were < 4.6 mIU/L as proposed for older persons [29], with some different expert opinions [7], and we cannot exclude that attaining lower TSH values might have a deleterious effect on bone health. Lumbar spine BMD baseline values were quite high in our participants, suggesting underlying degenerative changes that may interfere with the measures. However, degenerative changes do not affect femoral measures, neither lumbar spine TBS, which give similar results. Finally, sCTX pre-analytical conditions were not standardized (not done fasting in the morning) explaining the large range, but P1NP, which does not depend on these pre-analytical conditions, did not change neither over time nor depending on treatment, confirming the absence of LT4 effect on remodeling at 1-year follow-up.

Our results are reassuring in the context of the large number of individuals with SHypo treated with LT4, although this trend may change in the view of latest evidence and guidelines [5]. Only a large long-term, placebo-controlled trial will definitively determine if treatment of SHypo adversely affects bone health, and to the best of our knowledge such a trial is not ongoing or planned in the near future. Until long-term safety is ascertained, we suggest that physicians who wish to treat SHypo in their older patients prescribe the lowest thyroxine dose to achieve a clinical response and keep TSH within the normal range.

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Figure 1: Flowchart of the nested TRUST bone study

(Footnotes):

FU: follow-up. AE: adverse events. DXA: Dual-X-ray-Absorptiometry. ISCD: International Society for Clinical Densitometry. BTMs: Bone Turnover Markers.

Figure 2: One year change in BMD (bone mineral density, left) at LS (lumbar spine, continuous line), TH (total hip, dotted line) and FN (femoral neck, broken line), in placebo (diamonds) and LT4 (cross) treated patients.

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Table 1: Characteristics of included participants, by treatment group

	Placebo	LT4 treated
Sample size	96	100
Bern study site	71 (74)	74 (74)
Female	44 (45.8)	45 (45)
Age (years)	74.2 ± 6.1	74.3 ± 5.3
Weight (kg)	75.0 ± 14.8	78.2 ± 17.4
Height (cm)	166.5 ± 8.9	167.1 ± 8.6
BMI (kg/m ²)	27.0 ± 4.5	27.9 ± 5.3
Current smoking	8 (8.3)	8 (8.0)
Excess alcohol consumption	11 (11.5)	8 (8.0)
TSH (mUI/L)		
Baseline	6.5 ± 2.2	6.3 ± 1.9
Median (IQR)	5.7 (5.2 – 7.1)	5.8 (5.1 – 6.8)
Range	4.6 – 17.0	4.6 – 16.8
Free T4 (pmol/L)	13.7 ± 1.8	13.5 ± 2.0
GFR < 30 ml/min	3 (3.1)	3 (3.0)
Osteoporosis history	13 (13.5)	13 (13.3)
Diabetes history	10 (10.4)	16 (16.0)
Ca supplemented	24 (25.0)	18 (18.0)
Vitamin D supplemented	23 (24.0)	32 (32.0)
Bone affecting treatments		
Anti-osteoporotic or HRT	11 (11.5)	5 (5.0)
HTZC	12 (12.5)	11 (11.0)
Systemic GC	3 (3.1)	2 (2.0)
Deleterious	28 (29.2)	40 (40.0)

LT4: Levothyroxine. BMI: body mass index. Excess alcohol consumption: more than 2 units per day. Ca: calcium. Anti-osteoporotic treatments: raloxifen, bisphosphonates, denosumab or teriparatide. HRT: hormonal replacement therapy. HTZC: hydrochlorothiazide. GC: glucocorticoids. Deleterious: proton

pump inhibitors, systemic or topic glucocorticoids, aromatase inhibitors, serotonin recapture inhibitors, antiepileptic treatments. Results are expressed as mean \pm standard deviation for continuous variables and as number of participants (percentage) for categorical variables.

Table 2: BMD (g/cm²) and TBS values, and percentage changes after one year of treatment, by treatment group.

	Placebo	LT4 treated	LT4 treated vs. Placebo	p-value
Lumbar spine , sample size	53	52		
BMD				
Baseline (g/cm ²)	1.122 ± 0.204	1.133 ± 0.150		
1-year follow-up (g/cm ²)	1.115 ± 0.206	1.140 ± 0.145		
Changes after one year treatment, non-adjusted (%)	-0.6 (-1.8 to 0.6)	0.8 (-0.1 to 1.7)	1.4 (-0.1 to 2.9)	0.059
TBS				
Baseline (unitless)	1.325 ± 0.113	1.307 ± 0.968		
1-year follow-up (unitless)	1.331 ± 0.098	1.299 ± 0.108		
Changes after one year treatment, non-adjusted (%)	0.7 (-0.6 to 2.1)	-0.5 (-1.9 to 0.8)	-1.3 (-3.1 to 0.6)	0.19
Femur , sample size	57	56		
Total hip				
Baseline (g/cm ²)	0.963 ± 0.166	0.980 ± 0.167		
1-year follow-up (g/cm ²)	0.960 ± 0.166	0.975 ± 0.173		
Changes after one year treatment, non-adjusted (%)	-0.4 (-1 to 0.3)	-0.6 (-1.2 to 0.1)	-0.2 (-1.1 to 0.7)	0.61
Femoral neck				
Baseline (g/cm ²)	0.890 ± 0.131	0.908 ± 0.160		
1-year follow-up (g/cm ²)	0.885 ± 0.131	0.901 ± 0.161		
Changes after one year treatment, non-adjusted (%)	-0.5 (-1.3 to 0.2)	-0.7 (-2.2 to 0.7)	-0.2 (-1.8 to 1.4)	0.82

LT4: Levothyroxine. Pl: placebo. n: sample size. BMD: bone mineral density. TBS: trabecular bone score. Results are expressed as mean BMD/TBS ± SD, or as mean percentage BMD/TBS change in one year (95% CI). Between-group comparisons performed using Student's *t*-test.

Table 3: BTMs values, and non-adjusted percentage changes after one year of treatment, by treatment group.

	Placebo	LT4 treated	LT4 treated vs. Placebo	p-value
Sample size	94	96		
sCTX				
Baseline (ng/L)	247.9 ± 148.9	244.7 ± 156.1		
1-year follow-up (ng/L)	252.0 ± 166.8	259.3 ± 149.9		
Changes after one year treatment (%)	9.1 (-1.7 to 19.9)	33.2 (3.1 to 63.3)	24.1 (-7.9 to 56.2)	0.14
P1NP				
Baseline (µg/L)	39.5 ± 15.9	40.0 ± 25.1		
1-year follow-up (µg/L)	39.1 ± 17.9	41.8 ± 22.8		
Changes after one year treatment (%)	2.3 (-4.1 to 8.8)	10.7 (3 to 18.3)	8.3 (-1.6 to 18.3)	0.10

BTMs: bone turnover markers. LT4: Levothyroxine. Pl: placebo. sCTX: serum C-terminal Crosslinked Telopeptides. P1NP: Procollagen Type 1 N-terminal Propeptide. Results are expressed as mean sCTX/P1NP ± SD, or as mean percentage sCTX/P1NP change in one year (95% CI). Between-group comparisons performed using Student's *t*-test.

Figure 1

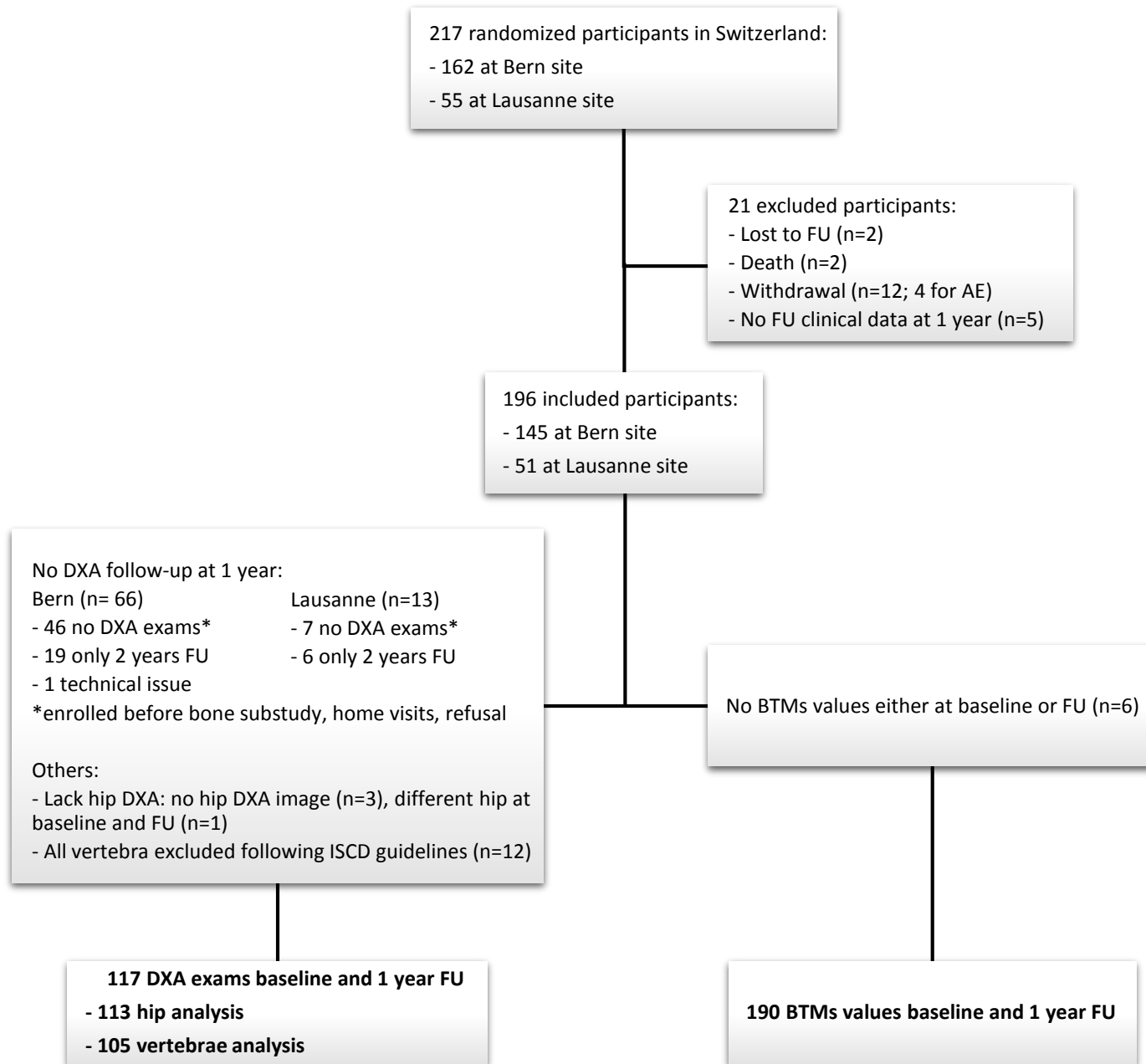


Figure 2

