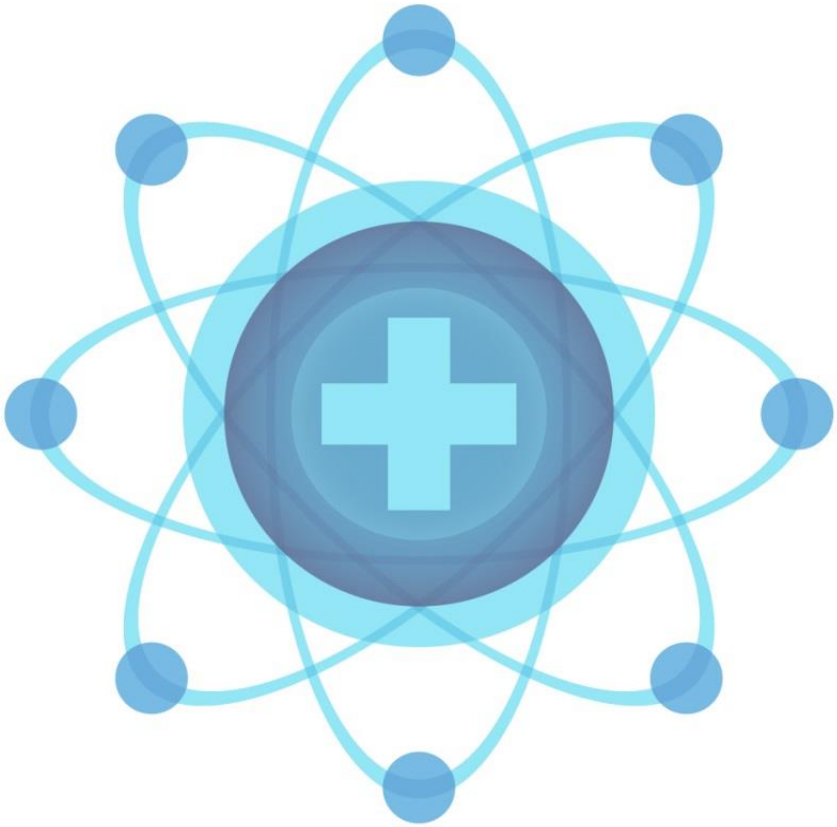

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Anthropometric, metabolic and bone changes in women with premature ovarian failure when using estradiol analogues

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Abstract. Goal. To compare changes in bone, metabolic and anthropometric parameters in young women with hypergonadotropic amenorrhea (premature ovarian failure [POF], complete androgen insensitivity syndrome [CAIS] with removed gonads), undergoing various HT (transdermal estradiol [TE], oral estradiol valerate [OEV], oral ethinyl estradiol [OEE] with or without progestin) or without therapy. Methods. A pilot cohort study based on prospectively collected data. Bone density, body composition and anthropometric parameters were assessed in 40 young women. Results. At time t0, only 5% of patients had normal bone mineral density (BMD) in all bone regions, while 75% and 20% had osteopenia or osteoporosis, respectively, in at least one bone region. Control densitometry (t1) was performed 22.1 ± 9.2 months later. Lumbar and femoral BMD increased over time in the treatment groups with a significant time-treatment interaction effect ($p = 0.004$ and $p = 0.025$, respectively). Conclusions. These preliminary data suggest that estradiol is administered both transdermally and orally in young women with hypergonadotropic amenorrhea.

Keywords: bones; hypergonadotropic hypogonadism; amenorrhea; estradiols; oral estradiol; transdermal estradiol.

Introduction. Premature ovarian failure (POF) is a clinical syndrome characterized by loss of ovarian activity before the age of 40; this is due to hypoestradiolism and oligo- or amenorrhea [1]. POF can have different etiopathogenic causes: it can be iatrogenic, as after chemotherapy, radiation therapy, or surgery, but it can also be associated with chromosomal / genetic defects (Turner syndrome or fragile X syndrome) and with autoimmune disorders, or it may be idiopathic [2].

Hypergonadotropic amenorrhea also occurs in women with complete androgen insensitivity syndrome (CAIS) who have undergone gonadectomy. CAIS is the most common sexual development disorder 46, XY, caused by mutations in the androgen receptor, causing complete resistance to the action of androgens [3].

Both POF and CAIS after gonadectomy are conditions associated with a high risk of bone health problems. POF is known to be associated with lower bone density than in healthy people [1,4–6] and with an increased risk of fractures at a later age [7]. In adolescents and adults with CAIS and remote gonads, there is a decrease in bone mineral density (BMD), mainly in the lumbar region; [8-13] however, adequate hormone therapy (HT) appears to be able to improve BMD, at least at the lumbar level [6,9,11].

HT is strongly recommended for women with POF and patients with CAIS gonadectomy because it plays an important role in bone protection, as well as in the

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prevention of cardiovascular disease and mortality [1]. There is still little data on the optimal dose, regimen and type of HT in young women with no ovarian estradiol production [6,14-17], and, in particular, there are still no data on oral administration of estradiol valerate.

The main objective of this retrospective pilot study was to assess the effect of various estradiolic molecules and routes of administration (oral estradiol valerate, transdermal estradiol, oral ethinyl estradiol) on bone health in young women with hypergonadotropic amenorrhea (idiopathic or iatrogenic POF, women with POF and Terner syndrome) and compare them with the results in untreated women. A secondary goal of our study was to evaluate the effect of these treatments on the biochemical and clinical characteristics of these patients.

Material and methods

Study design and population. In this retrospective pilot study, we evaluated young adults with secondary hypergonadotropic amenorrhea. The women were selected from among the patients who attended the Republican Specialized Scientific and Practical Medical Center of Endocrinology named after V.I. J.H. Turakulova. In this study, we included women with normal karyotype 46, XX with POF, gonadectomized women with SPNA, and women with Turner syndrome. All SPNA patients had a 46, XY karyotype with a confirmed androgen receptor mutation and previous bilateral gonadectomy, while Turner syndrome patients had a 45, X0 karyotype.

For all groups of patients, the following data were recorded: age of onset of amenorrhea, age of onset of estradiol intake, type and dose of estradiol, and route of administration (oral or transdermal). Age at gonadectomy was also recorded for CAIS subjects. Patients were divided into four study groups depending on treatment: transdermal estradiol in gel (TE), oral estradiol valerate (EV), oral ethinylestradiol (OE) with or without progestin or without treatment (Femur delta BMDs varied significantly between groups ($p = 0.004$), with a significant increase in both TE and EV groups compared to OE or E).

We compared BMD of the spine and hip in these four groups. All patients underwent clinical, laboratory and radiological examinations in accordance with clinical practice. Anthropometric measurements were carried out on all subjects: height was measured with a stadiometer as the distance from the top of the head to the floor, when the subject was asked to stand straight, barefoot, touching the walls with his shoulders. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg / m2).

Bone parameters were recorded in patient records. BMD was measured using dual x-ray absorptiometry. The BMD of the spine was obtained between the lumbar levels [1–4] (L1 - L4) and the total BMD of the femur in the femoral neck, trochanteric and intertrochanteric regions. The results of measuring the MIC were recorded in g / cm2. For BMD, the T-score indicates the extent to which BMD measured at a site of bone differs from BMD in a control sample of healthy subjects aged [25–30] years (age at which peak bone mass is achieved) ... The World Health Organization (WHO) criteria divide BMD T-scores as follows: normal: +2.5 to 1.0

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standard deviation compared to the mean maximum bone mass in a young person; osteopenia: –1 to –2.5 SD and osteoporosis: below –2.5 SD. BMD z-scores, on the other hand, refer to the number of standard deviations of values measured at sites of bone and how they deviate from values measured in a healthy control population of subjects of the same age and sex as the study patients. BMD changes were also expressed as deltas (the difference between the two BMD scans.

The following laboratory test results have been reported: estradiol, LH, FSH, fasting glucose, total cholesterol (TC), high and low density lipoproteins (HDL and LDL), triglycerides (TG), aspartate and alanine aminotransferase, prothrombin time, and activated partial thromboplastin time. All patients were over 18 years of age at the time of enrollment.

Results

Clinical characteristics of the enrolled women, sixty-two women with amenorrhea were potentially eligible and screened. According to our inclusion-exclusion criteria, 22 women were excluded due to lack of densitometry data. Thus, 40 women were included in the data analysis. Their average age at the time of the first available densitometry assessment (t0) was 23.8 ± 5.5 years (range: 15–35 years). The etiopathogenetic factors of amenorrhea were distributed as follows: 22 women with POF, 10 women with Turner syndrome and eight with idiopathic (five patients) or iatrogenic POF (three patients after chemotherapy and / or radiation therapy for cancer treatment), the latter - 46, XX karyotype. The average duration of amenorrhea before the onset of HT was 13.2 ± 4.1 months.

The clinical characteristics of patients at the time of their first densitometry are presented in Tables 1 and 2. At t0 (first densitometry)), 30 patients (75%) did not receive hormones, while 10 patients (25%) underwent the first densitometry after starting treatment. Smoking rates did not differ between groups. Liver enzymes were within the normal range for all included subjects (data not shown). The groups were homogeneous, with no significant differences in assessed anthropometric and metabolic parameters, with the exception of LDL cholesterol, which showed significantly higher levels in EE compared with the EV group (133 ± 41 mg versus 88 ± 22 mg, p = 0.01) (table 1, 2).

Table 1

Baseline anthropometric and clinical parameters of patients included during their first DXA scan.

Parameters	**GT (n = 34)**	**BT (n = 6)**	**p**
Increase (years) in t0	24.2 ± 5.4	20.0 ± 6.2	0.093
GT in t0 (years) (for non-accepting GT, n)	2.6 ± 1.8 (10/34)	n.a.	
Height (cm)	58.6 ± 13.6	57.0 ± 13.5	0.792
Weight, kg)	1.64 ± 0.11	1.61 ± 0.12	0.547
BMI	21.5 ± 3.8	20.9 ± 3.0	0.719
Smoking	3 (8.8%)	0	0.999
Values are expressed as mean ± standard deviation, unless otherwise indicated. BMI, body mass index; HT, hormone therapy			

Table 2

Baseline anthropometric, clinical and bone parameters of the included patients undergoing various hormonal regimens.

Parameters	**TE (N = 12)**	**EV (N = 15)**	**EV (N = 7)**	**BT (N = 6)**	**R**
Age (years) in t0	24.3 ± 4.4	24.7 ± 5.3	23.0 ± 7.3	20.0 ± 6.2	0.247
Duration of GT in t0 (years) (for non-accepting GT, n)	2.3 ± 1.9 (5/12)	2.8 ± 1.4 (3/15)	3.4 ± 2.8 (2/7)	n.a.	0.248
Height (cm)	59.8 ± 15.6	57.9 ± 12.6	57.7 ± 12.5	57.0 ± 13.5	0.925
Weight, kg)	1.63 ± 0.11	1.66 ± 0.11	1.63 ± 0.13	1.61 ± 0.12	0.739
BMI	21.9 ± 4.0	21.3 ± 4.0	21.1 ± 2.7	20.9 ± 3.0	0.944
Smoking	3 (23%)	0	0	0	0.999
Δ BMD of the lower back (g / cm2) (T1-T0)	0.037 ± 0.041	0.064 ± 0.084 *	-0.003 ± 0.073	-0.078 ± 0.116	0.008
Δ BMD of the femur (g / cm2) (T1-T0)	0.026 ± 0.035 *	0.026 ± 0.034 * §	-0.06 ± 0.06	-0.048 ± 0.046	0.004
Values are expressed as mean ± standard deviation, unless otherwise indicated. BMI, body mass index; TE, transdermal estradiol; EV, oral estradiol; EE, oral ethinyl estradiol; NO, no hormonal treatment. * = p <0.01 compared with BT; § = p <0.01 compared to EE.					

Bone parameters

Bone parameters during baseline densitometry (t0)

In the entire cohort, the BMD of the lumbar spine at the first densitometry was 0.913 ± 0.131 with a T-score of -1.92 ± 1.04 and a Z-score of -1.81 ± 0.98. Femur mineral density was 0.865 ± 0.125 with a T-score of -1.06 ± 0.99 and a Z-score of -1.02 ± 0.90. Taking the entire cohort into account, 30/40 patients (75%) had osteopenia and 8/40 (20%) osteoporosis in at least one site of the bone. No osteoporotic fractures were found in the study groups. At time t0, the BMD of the lower back and hip did not differ significantly between the four groups. In addition, most of 10 women already using HT during their first densitometry had BMD abnormalities, three patients had osteoporosis (two in the TE group and one in the EV group) and six had osteopenia (three in the TE group, one in the EV and one in the EE group) in at least one site of the bone. Two had normal BMD in all areas of the bone.

Variations in bone tissue parameters in women receiving different hormonal regimens. The time interval between the two estimates of bone mineral density (t1 - t0) was 22.1 ± 9.2 months, with no significant differences between the four groups (the time interval of densitometry was 20.6 ± 8.9 months for TE, 22.9 ± 9 , 3 months for EV, 20.3 ± 8.8 months for EE and 25.0 ± 9.5 months for BT). All HT patients reported correct and consistent use of their treatment between the two BMD scores. Lumbar BMD showed a significant interaction of time and treatment (p = 0.004]. The changes in BMD from t0 to t1 (delta) varied significantly between treatment groups (p = 0.008) .A posteriori analysis revealed a significant increase in lumbar BMD in the EV group compared to the BT group (p = 0.006) and in the TE group compared to

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BT (p = 0.036). In addition, the BMD of the femur showed a significant effect of time interaction and treatment (p = 0.025). Changes in BMD from t0 to t1 (delta) significantly differed between groups (p = 0.004), with a significant change (increase) in BMD of the femur both in the TE and EV groups compared to BT or with EE.

Anthropometric and metabolic parameters

BMI at baseline was within normal limits and the same in all groups. BMI and metabolic parameters (glucose, total cholesterol, HDL and LDL cholesterol, triglycerides and liver enzymes) did not show significant changes in patients receiving and not receiving therapy. Blood pressure was within normal limits and did not change during the study period.

Discussion. In this pilot study, we compared changes in bone, metabolic, and anthropometric parameters in very young women with hypergonadotropic hypogonadism, POF, and CAIS receiving different hormonal regimens (oral estradiol valerate, transdermal estradiol, oral ethinyl estradiol, or no hormonal therapy). Although our results should be validated in a larger sample, both transdermal and oral estradiol appeared to be associated with large short-term improvements in bone BMD compared with ethinyl estradiol or no therapy.

During their first densitometry, the entire cohort presented T-scores indicative of osteopenia, in particular for the lumbar region, but also for the femur, with only five percent of patients having normal BMD in all areas of the bone. The second BMD study was performed 22.1 ± 9.2 months after the first. Both oral estradiol valerate and transdermal estradiol were associated with significant increases in lumbar BMD and changes in femur BMD, significantly different from those obtained with oral ethinyl estradiol or no treatment. In women who received oral ethinylestradiol or did not receive treatment, there was a slight decrease or no significant changes in BMD.

No significant changes in anthropometric and metabolic parameters were observed during the treatment period, even though the small sample size may have limited the detection of differences.

POF and CAIS are known risk factors for bone health. Several studies have shown that women with POF have lower BMD and a significantly increased risk of fractures [7,18,19]. Long-term HT can reduce the increased risk of fractures [4,17,20-22]. In particular, a major health concern for very young women with POF is that potentially long-term estradiol deficiency at a young age can lead to a decrease in peak bone accumulation in the event of delayed or inadequate HT [4]. Likewise, it is known that women living with CAIS have low BMD both before and after gonadectomy due to a combination of estradiol deficiency and bone resistance to androgens, and in some cases due to inadequate HT after gonadectomy [9,11, 12]. The lumbar spine is more prone to BMD deficiency, as it is characterized by a predominance of trabecular bone. Recently, it was confirmed that HT-containing estradiols are able to increase BMD in this area, but not on the femoral neck [6, 20]

Research on optimal hormonal treatment for women with POF and CAIS is still limited. In our cohort, the transdermal route was confirmed to be superior to oral ethinyl estradiol in improving BMD in the lumbar and femoral regions. Transdermal

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estradiol administration has already been associated with better BMD in women with POF compared to both conjugated oral estradiols and oral ethinylestradiol [15,21]. In the CAIS population, the transdermal route of estradiol administration appears to be superior to oral administration in terms of increasing total body mineral density [6].

Although the sample size is limited, our study appears to show that oral estradiol valerate is superior to oral ethinyl estradiol in increasing BMD in the lumbar and femoral regions. This is the first study to show the ability of oral administration of 2 mg estradiol valerate with or without progestin to increase BMD more than oral administration of ethinyl estradiol plus progestin: the increase in BMD in the lumbar spine was the same as with transdermal estradiol. and even more than that obtained transdermally in the femoral neck.

There are limited but consistent data on estradiol in this population: Cartwright et al. In a two-year, open-label, randomized trial reported the superiority of estradiol 2 mg (plus 5 mcg levonorgestrel for 12 days per month) over 30 mcg ethinyl estradiol (plus levonorgestrel). 150 mcg taken daily for 21 days a month) to increase BMD of the lumbar spine in women with spontaneous POF [17].

Some limitations of this study should be noted. First of all, POF at this young age and CAIS are rare conditions; for this reason, a small cohort was analyzed in this pilot study, and this could lead to a statistical error of type II. In addition, various etiologies of amenorrhea were included in the analysis. In addition, some statistically significant associations should be interpreted with caution given the small number of subjects in each group. Another limitation is the retrospective nature of the study. The two BMD evaluations were performed on the same machine for each patient, but the cohort as a whole used different machines.

In conclusion, these preliminary data suggest a superiority of oral estradiol valerate over oral ethinyl estradiol in improving lumbar and femoral BMD in young women with hypergonadotropic hypogonadism. In accordance with previous literature, our cohort of women with POF and CAIS was characterized by some violation of the BMD, in particular, at the level of the lower back. After 22.1 ± 9.2 months, treatment with oral estradiol valerate or transdermal estradiol showed the ability to induce positive changes in the lumbar and femoral regions, while women who received oral ethinyl estradiol or did not receive any treatment showed little or no significant changes in BMD. Further research in larger cohorts is imperative to understand which hormone treatment is best for bone health in young women with POF or CAIS, as there is little data available on optimal molecules, regimen, and dosages.

References

1. European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI, Webber L, Davies M, Anderson R, et al. ESHRE Guideline: management of women with premature ovarian insufficiency. Hum Reprod. 2016;31:926-37.
2. Maclaran K, Panay N. Current concepts in premature ovarian insufficiency. Womens Health (Lond). 2015;11:169-82.
3. Berglund A, Johannsen TH, Stochholm K, et al. Incidence, prevalence, diagnostic delay, and clinical presentation of female 46, XY disorders of sex development. J Clin Endocrinol Metab. 2016;101: 4532-40.
4. Popat VB, Calis KA, Vanderhoof VH, et al. Bone mineral density in estradiol-deficient young women. J Clin Endocrinol Metab. 2009;94:2277-83.
5. Uygur D, Sengül O, Bayar D, Erdinç S, Batioğlu S, Mollamahmutoglu L. Bone loss in young women with premature ovarian failure. Arch Gynecol Obstet. 2005;273:17-9.
6. Gava G, Mancini I, Orsili I, et al. Bone mineral density, body composition and metabolic profiles in adult women with complete androgen insensitivity syndrome and removed gonads using oral or transdermal estradiols. Eur J Endocrinol. 2019;181:711-8.
7. van Der Voort DJ, van Der Weijer PH, Barentsen R. Early menopause: increased fracture risk at older age. Osteoporos Int. 2003;14:525-30.
8. Bertelloni S, Baroncelli GI, Federico G, Cappa M, Lala R, Saggese G. Altered bone mineral density in patients with complete androgen insensitivity syndrome. Horm Res. 1998;50:309-14.
9. Danilovic DL, Correa PH, Costa EM, Melo KF, Mendonca BB, Arnhold IJ. Height and bone mineral density in androgen insensitivity syndrome with mutations in the androgen receptor gene. Osteoporos Int. 2007;18:369-74.
10. Sobel V, Schwartz B, Zhu Y-S, Cordero JJ, Imperato-McGinley J. Bone mineral density in the complete androgen insensitivity and 5alpha-reductase-2 deficiency syndromes. J Clin Endocrinol Metab. 2006;91:3017-23.
11. Han TS, Goswami D, Trikudanathan S, Creighton SM, Conway GS. Comparison of bone mineral density and body proportions between women with complete androgen insensitivity syndrome and women with gonadal dysgenesis. Eur J Endocrinol. 2008;159:179-85.
12. Soule SG, Conway G, Prelevic GM, Prentice M, Ginsburg J, Jacobs HS. Osteopenia as a feature of the androgen insensitivity syndrome. Clin Endocrinol (Oxf). 1995;43:671-5.
13. Marcus R, Leary D, Schneider DL, Shane E, Favus M, Quigley CA. The contribution of testosterone to skeletal development and maintenance: lessons from the androgen insensitivity syndrome. J Clin Endocrinol Metab. 2000;85:1032-7.
14. Webber L, Anderson RA, Davies M, Janse F, Vermeulen N. HRT for women with premature ovarian insufficiency: a comprehensive review. Hum Reprod Open. 2017;2017:hox007.

10.5281/zenodo.5772964
15. Guttmann H, Weiner Z, Nikolski E, et al. Choosing an oestradiol replacement therapy in young adult women with Turner syndrome. Clin Endocrinol (Oxf). 2001;54:159-64.
16. Sullivan SD, Sarrel PM, Nelson LM. Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. Fertil Steril. 2016;106:1588-99.
17. Cartwright B, Robinson J, Seed PT, Fogelman I, Rymer J. Hormone replacement therapy versus the combined oral contraceptive pill in premature ovarian failure: a randomized controlled trial of the effects on bone mineral density. J Clin Endocrinol Metab. 2016;101:3497-505.
18. Abdullaeva U.K. Predicting the risk of atrophic transformation in chronic gastritis using serum pepsinogen // World journal of pharmaceutical research, Faculty of Pharmacy Medical University, Bulgaria, Vol. 8, Iss. 13, 2019, P. 219-228.
19. Abdullaeva U.K., Sobirova G.N., Karimov M.M., Aslonova I.J. The prevalence and possibilities of prevention of noncardial gastric cancer in the Bukhara region // American journal of medicine and medical sciences, 2020, 10(9), P. 679-681.
20. Abdullaeva U.K., Shadjanova N.S. Using the OLGA system in chronic atrophic gastritis // New day in medicine, 2020, №2, P. 9-12.
21. Abdullaeva U.K. The value of interactive teaching methods in improving the level of clinical knowledge of students // Medical education and professional development. 2019, №1 (33), P. 29-32. [in Russian]
22. Abdullaeva U.K. Predicting the risk of atrophic transformation in gastritis associated with chronic Helicobacter pylori // abstract of PhD dissertation on medical sciences. Tashkent. 2021. 46-p.