Changes in bone mineral density in women with early-onset androgenetik alopecia and their correlations with hair-loss stages: a cross-sectional study.

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Abstract

Androgenetic alopecia is a common cosmetical condition that accompany by some disorders with high androgen level. Evaluating the possible relationship between androgenetic alopecia and bone mineral density, and its relevance with hair-loss stages were aimed. A cross-sectional study including 106 alopecia patients who also had joint complaints, was conducted on screening of recorded data regarding hair loss stages, bone mineral density and fix and modifiable factors related with bone density, such as body mass index, daily consumptions of calcium, caffeine and alcohol, smoking, birth count, daily sun exposure, usual physical activity, and hormone values including free and total testosterone, dehydroepiandrosterone sulfate, androstenedione, sex hormone binding globulin, follicular stimulating hormone, leutinizing hormone, 25-hydroxy cholecalciferol, ionized calcium, inorganic phosphorus and alkaline phosphatase. Alopecia was classified by hair loss-scale of Ludwig. Bone mineral density in the hip and lumbar spine was measured by dual energy X-ray absorptiometry (Stratos dR 2D Fan-Beam). Data was analysed by Number Cruncher Statistical System, 2007. Results were compared to p<0.05. About 90% of the subjects were under the age of 35 and 60% of them were in the Ludwig stage-2. Osteopenia was detected in the rates of 34.90%, 36.79% and 23.58%, and osteoporosis was detected in the rates of 4.72%, 5.66% and 3.77% in femur-neck, total hip and lumbar spine T-scores, respectively. Z-scores were lower in the rates of 19.81%, 14.15% and 11.32 % in the same order, compare to the age-matched reference values. Predisposing factors, laboratory test results and bone mineral density scores did not show any differences according to the Ludwig stages (each at p>0.05). We suggest that all women with early-onset androgenetic alopecia should be thoroughly investigated to the possibility of premature bone loss.

Introduction

Androgenetic Alopecia (AGA) is a hereditary androgen-dependent disorder, which is characterized by a progressive and gradual conversion of terminal hair into miniaturized hair defined by various patterns according to sexes. In females, the clinical condition is classified according to the Ludwig stages, from 1 to 3. AGA usually leads to cosmetic and psychological consequences [1]. However, it has been shown to be associated with some conditions, such as Polycystic Ovary Syndrome (PCOS), androgen releasing tumors, hirsutism [1,2], smoking [3], insulin resistance, hyperglisemia, systolic and diastolic hypertension, obesity, high serum cholesterol and lipid profiles, and atherosclerotic plaques [4]. On the other hand, well-known conditions in menopausal women are decrease in Bone Mineral Density (BMD) and Hair-Loss (HL) because the loss of physiological levels of estrogens and androgens [5]. Some risk factors for osteoporosis such as age, sex, race, family history, early menopause, oophorectomy, prolonged amenorrhea, lack of physical exercise and bone depleting medical conditions have been accepted, but it has been considered that these factors do not predict all of the observed changes in BMD and the factors should be better defined [6]. In our daily practise, during the detection of etiopathological reasons in AGA patients, we noticed that a significant number of women had joint complaints in their systematical examinations. These patients are usually consulted to our physical medicine and rehabilitation clinic. This condition was the starting point of our study. We aimed to detect a possible association with BMD and female AGA, and its clinical stages. Lack of studies regarding the relationships, prompted us to investigate this condition.

Methods

Study design and subjects

One hundred and six women (between 18 and 50 y old, and mean age 26.0 ± 8.05 y) who were diagnosed with AGA, and also having concurrent joint complaints in their clinical examinations included in the study between December 2015 and 2016. It was conducted as a retrospective cross sectional study, with findings obtained by screening medical records of patients. The study was approved by institutional ethical committee. Menopausal women, the patients who has body weight over 100 kg, irregular menstrual cycle, hyperprolactinemia, PCOS, had used drugs that interfere with bone and calcium metabolism such as sex steroids, vitamin D metabolites, calcitonin, bisphosphonates, thyroid hormones, thiazolidinediones, corticosteroids, heparin, warfarin, vitamin K, thiazides, anticonvulsants, who exposed to bone trauma and immobilized for any reason, who having diseases which affect bone and calcium metabolism such as thyrotoxicosis, thyroid dysfunction, systemic lupus erythematosus, primary or secondary hyperparathyroidism, androgen secreting tumors, congenital adrenal hyperplasia, hypercortisolism, hypogonadism, cirrhosis, renal insufficiency, malignancy and rheumatoid arthritis were excluded from the study, by scanning

patients' medical records including clinical examination findings, laboratory and imaging test results.

Data collection from clinical and laboratory investigations

All data provided from previously recorded clinical and laboratory examination findings and BMD measurements of the subjects. The diagnosis of AGA was done based on clinical examination findings, and hormonal screening of the subjects for free and total testosterone (FT, TT), Dehydroepiandrosterone Sulfate (DHEAS), androstenedione, Sex Hormone Binding Globulin (SHBG), Follicular Stimulating Hormone (FSH) and Leutinizing Hormone (LH). The HL was graded in 3 stages according to Ludwig classification, in which stage 1 indicates thinning of the hair volume on the top of the head, stage 2 indicates easily appearing of scalp, and stage 3 means disappearing of almost all of the hairs at the crown of the head [1,2]. Patients whose systemic examinations revealed concurrent joint complaints were consulted in physical medicine and rehabilitation clinic. Clinical and laboratory examination findings relating with BMD such as BMI, daily consumption of calcium-containing foods, caffeine-containing beverages and alcohol, smoking, birth number, daily sun-exposure, physical activity, as well as 25-hydroxy cholecalciferol (25-OH-D3), serum ionized calcium, inorganic phosphorus, and Alkaline Phosphatase (AP) values were questioned and examined. After the height and weight were measured in subjects wearing light clothing without shoes, body mass index (BMI) was calculated as weight (kilograms) divided by height (square meters) to estimate of obesity. The evaluation was made as insufficient $\leq$ 19 kg/m^2, and sufficient $\geq$ 19 kg/m^2. The calcium intake was determined by using a dietary questionnaire, and assessed as follows: inadequate=1: <1000 mg/d, and adequate $\geq$ 1000 mg/d. Consumption of caffeine was determined in questioning of daily-consumed of cafeine containing beverages such as brewed tea, coffee and etc., and evaluated as; low=1 (<5 cup), and high=2 ($\geq$ 5 cup). Alcohol consumption was determined in inquerying of daily alcohol consumption, and evaluated as; non-drinker=1, light alcohol user=2 (<5 bottles of standard size beer or equivalent), and heavy alcohol user=3 ($\geq$ 5 bottles of standard size beer or equivalent). Smoking was evaluated as; non-smoker=1, light smoker=2 (<20 pieces/d), and heavy smoker=3 ($\geq$ 20 pieces/d). Daily sun exposure was assessed by presence (1=sufficient) or absence (2=insufficient) of casual exposure of face, hand and arms in the peak hours of sunlight. Number of birth is also recorded [7]. The usual physical activity was determined in patients by questioning their professions and usual life habits by an inquiry form, and assessed as scores ranging from 1 to 3. A score of 3 was given for women doing regular-weekly exercise; 2 for women who did not have regular-weekly exercise, however doing some physical activity such as walking to the bus stop or work, performing house-keeping etc.; and 1 for women not doing any of those mentioned [8]. Fasting blood samples for hormonal tests were taken during follicular phase (cycle d 2-8), whereas at any-time of cycle for the others, and in 8:30 and 9:00 AM.

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Serum levels of TT, FSH and LH were analysed by competitive Electro Chemi Luminescence (ELC) immunoassay (Roche cobas 6000 modular system-601, Roche Diagnostics, Mannheim, Germany), using commercial kits (Roche, Mannheim, Germany). Serum FT was analysed by automated enzyme immunoassay (Grifols, Triturus, Spain) using commercial kit (Diametra, Perugia, Italy). Androstenedion levels were determined by liquid chromatography-mass spectrometry (Triple mass spectrometer-LC-MS/MS, Agilent Technologies 6460C, Waldbronn, Germany) using an in-house manufactured method. DHEA-SO4, SHBG and 25-OH-D3 were analysed by competitive Electro Chemi Luminescence (ELC) immunoassay (Roche cobas 6000 modular system-602, Roche Diagnostics, Mannheim, Germany), using commercial kits (Roche, Mannheim, Germany). Serum ionized calcium and inorganic phosphorus were analysed by photometric method (Roche cobas 8000 modular system-702, Roche Diagnostics, Mannheim, Germany) using commercial kits (Roche, Mannheim, Germany). AP was analysed according to IFCC (International Federation of Clinical Chemistry) method using catalytic reaction and kinetic measurements (Roche cobas 8000 modular system-702, Roche Diagnostics, Mannheim, Germany) and a commercial kit (Roche, Mannheim, Germany). Reference Intervals (RI) in follicular phase for hormones, and the other tests were as follows: 0.45-3.17 pg/ml for FT, 0.06-0.82 ng/ml for TT, 65-368 µg/dl, 148-407 µg/dl, 98.8-340 µg/dl, 60.9-337 µg/dl and 35.4-256 µg/dl for DHEA-S in the age groups of 15-19, 20-24, 25-34, 35-44 and 45-54, respectively, 0.26-2.14 ng/ml and 0.13-0.82 ng/ml for androstenedion in 18-40 and 40-100 years of women (detection limit was 0.02 ng/ml and linearity was 0.1-0.50 ng/ml), 26.1-110 nmol/L for SHBG, 3.5-12.5 mIU/ml for FSH, 2.4-12.6 mIU/ml for LH, 30-100 ng/ml for $25\text{-}OH\text{-}D_3$, 8.4-10.4 mg/dl for ionized calcium, 2.5-4.5 mg/dl for inorganic phosphate, and 35-105 U/L for AP.

Outcome measures

BMD (grams per square centimeter) was measured at the hip and lumbar spine using Dual Energy X-ray Absorptiometry (DEXA) machine (Stratos dR 2D Fan-Beam, DMS company, France). Its stability was calibrated daily using a manufacturer-supplied phantom, and all measurements were obtained by a certified technologist. The annual coefficient of variation *in vitro* for repeated bone mass measurements, and precision error of it at each region in our laboratory between the previously specified dates were 0.52% and %1, respectively. Absorptiometric findings were expressed as a percentage of baseline values. Total hip BMD was the sum of the femoral neck, greater trochanter, and intertrochanter. Spine (lumbar total) BMD was the mean of lumbar vertebra 1-4. BMD was measured in the postero-anterior projection at the right hip and lumbar spine. Test results reported in two scores: T scores were used to estimate risk of developing a fracture compared with peak bone mass of young adults, whereas Z scores were used to evaluate amount of bone compared with age-matched people, to determine causes abnormal bone loss other than aging. The scores were evaluated in accordance with the criteria of World Health Organization, and manufacturer's preloaded reference values that are being used in most of the DEXA equipment currently in use in our country, and matches the subject's gender and ethnic background as follows; -1 SD and above is normal, between -1 and -2.5 SD is osteopenia, whereas below -2.5 SD is osteoporosis. Z scores were evaluated as, above -2 is normal and -2 or below is abnormal [9].

Statistical analysis

Statistical analysis was followed through NCSS (Number Cruncher Statistical System, 2007, Utah, USA) statistical software package program. Standard descriptive statistics were expressed as means ± Standard Deviation (SD). Categorical variables were expressed as percentages (%). The normality assumption of the groups was checked using Kruskal-Wallis test. Quantitative data was compared with One-way Analysis of Variance where the distribution was normal, whereas Kruskal Wallis nonparametric analysis was used for the comparison of three group means when the distribution was not normal. Chi-square test was used to compare qualitative data. The significance of differences in means was determined using 95% confidence intervals and p<0.05 was considered as statistically significant.

Results

BMD values and available examination findings of 106 AGA women aged 18-50 were investigated and studied. Descriptive statistics of age groups, marital status, HL stages, and factors that can increase susceptibility to osteoporosis are shown in Table 1. The minimum and maximum ages, and the mean-age of the subjects were 18, 50 and 26.0 ± 8.05 y, respectively. Most of the subjects were married, under the age of 35, were clustered in the Ludwig II subgroup, nullipar, non-smoker, non-drinker, had adequate BMI, calcium consumption and sun-exposure, whereas only 12.26% had inadequate physical activity and 70.75% of them consumed ≥ 5 cup of coffee/d. Descriptive statistics of BMD measurements are shown in Table 2. Most of T scores were normal, whereas osteopenia and osteoporosis were detected in the rates of 34.90%, 36.79% and 23.58%, and in the rates of 4.72%, 5.66% and 3.77% in femur-neck, total hip and lumbar spine regions, respectively. Z scores were lower in the rates of 19.81%, 14.15% and 11.32%, compare to the age-matched references in the same regions. Comparison of the mean ages, and predisposing factors for osteoporosis according to Ludwig subgroups are shown in Table 3. Although mean ages were slightly increasing respect to the progress of HL, there was no significant difference between the Ludwig subgroups (p>0.321). Predisposing factors for osteoporosis did not show any significant differences in according to the HL stages (each was p>0.05). Comparison of the mean values of laboratory analyses of the subjects according to Ludwig subgroups are shown in Table 4. Except for slightly decrease in the values of $25\text{-}OH\text{-}D_3$, all test results of the subjects were normal and within the age-compatible levels. Distribution of values in FT, TT, SHBG, LH, FSH and

25-OH-D$_3$ tests of the subjects were asymmetric, whereas the other test values were distributed normal. Thus, the analysis of variance for asymmetries was made by Kruskal Wallis test. No any differences were detected in comparison of mean values of all tests according to the Ludwig stages (each was p>0.05). Comparisons of mean values of BMD according to Ludwig subgroups are shown in Table 5. Except for total hip-Z, mean values of all BMD measurements were distributed asymmetric, thus Kruskal Wallis test was used in the analysis of these values. The comparison of means of all BMD values did not show any significant differences in accordance with the Ludwig subgroups (each was p>0.05).

Table 1. Descriptive statistics of age groups, marital status, Ludwig stages and factors that increase susceptibility to bone loss.

Variables	Subgroups	Sample size (n)	Percent (%)
Age	18-35	91	85.85
	36-50	15	14.15
Marital status	Married	66	62.26
	Unmarried	40	37.74
Ludwig stages	Ludwig 1	31	29.25
	Ludwig 2	62	58.49
	Ludwig 3	13	12.26
BMI	≤ 19kg/m^2	10	9.43
	>19 kg/m^2	96	90.57
Calcium consumption	<1000 mg	44	41.51
	≥ 1000 mg	62	58.49
Caffeine consumption	< 5 cup	31	29.25
	≥ 5 cup	75	70.75
Alcohol consumption	Non-drinker	89	83.96
	Light-drinker	17	16.04
	Heavy- drinker	0	0
Smoking	Non-smoker	79	74.53
	Light-smoker	23	21.7
	Heavy smoker	4	3.77
Birth count	0	65	61.32
	1	12	11.32
	2	16	15.09
	3	9	8.49
	4	4	3.77
Sun exposure	Adequate	91	85.85
	Inadequate	15	14.15
Physical activity	Adequate	26	24.53
	Little adequate	67	63.21
	Inadequate	13	12.26

Table 2. Descriptive statistics of BMD values according to measurement zones.

BMD-measurement zones	Subgroups	Sample size (n)	Percent (%)
Femur neck-T	-1 and above	64	60.38
	-1-(-2.5)	37	34.9
	-2.5 and below	5	4.72
Total hip-T	-1 and above	61	57.55
	-1- (-2.5)	39	36.79
	-2.5 and below	6	5.66
Lumbar spine-T	-1 and above	77	72.64
	-1-(-2.5)	25	23.58
	-2.5 and below	4	3.77
Femur neck -Z	Above -2	85	80.19
	-2 or below	21	19.81
Total hip-Z	Above -2	91	85.85
	-2 or below	15	14.15
Lumbar spine-Z	Above -2	94	88.68
	-2 or below	12	11.32

Table 3. Comparisons of the mean ages and predisposing factors for bone loss according to Ludwig subgroups.

Variables		Ludwig I n: 31		Ludwig II n: 62		Ludwig III n: 13		p
Age		24.65 ± 7.08		25.13 ± 8.08		28.46 ± 8.98		0.321
BMI		25.09 ± 6.89		25.59 ± 5.56		28.21 ± 5.42		0.272
Calcium consumption[+]	<1000 mg/d	12	38.71%	29	46.77%	3	23.08%	0.269
	≥ 1000 mg/d	19	61.29%	33	53.23%	10	76.92%	
Caffeine consumption[+]	<5 cup	8	25.81%	20	32.26%	3	23.08%	0.709
	≥ 5 cup	23	74.19%	42	67.74%	10	76.92%	
Alcohol consumption[+]	Non-drinker	28	90.32%	49	79.03%	12	92.31%	0.256

	Light alcohol user	3	9.68%	13	20.97%	1	7.69%	
Smoking[+]	Non-smoker	22	70.97%	47	75.81%	10	76.92%	0.88
	Light smoker	8	25.81%	12	19.35%	3	23.08%	
	Heavy smoker	1	3.23%	3	4.84%	0	0.00%	
Birth count[*]		0.68 ± 1.25		0.84 ± 1.18		1.08 ± 1.19		0.374
Sun exposure[+]	Adequate	27	87.10%	52	83.87%	12	92.31%	0.71
	Inadequate	4	12.90%	10	16.13%	1	7.69%	
Physical activity[+]	Adequate	10	32.26%	14	22.58%	2	15.38%	0.55
	Little adequate	16	51.61%	42	67.74%	9	69.23%	
	Inadequate	5	16.13%	6	9.68%	2	15.38%	

One-way analysis of variance, *Kruskal Wallis test, +Chi-square test

Table 4. *Comparison of the mean values of laboratory tests according to Ludwig subgroups.*

Variables	Ludwig I n:31	Ludwig II n:62	Ludwig III n:13	p
Free-Testosterone[*]	1.63 ± 1.42	1.53 ± 0.87	1.24 ± 0.55	0.681
Total-Testosterone[*]	0.72 ± 0.50	0.59 ± 0.33	0,61 ± 0.47	0.72
DHEA-S	369.98 ± 91.89	385.61 ± 163.66	289.85 ± 134.60	0.095
Androstenedion	1.20 ± 0.72	1.13 ± 0.61	1.03 ± 0.46	0.706
SHBG[*]	54.42 ± 39.07	51.86 ± 33.00	42.60 ± 20.78	0.6
FSH[*]	6.56 ± 2	7.32 ± 2.58	8.36 ± 6.78	0.304
LH[*]	7.31 ± 4.85	8.1 ± 5.72	7.34 ± 6.88	0.505
25-OH Vit-D$_3$[*]	23.7 ± 17.65	23.93 ± 18.11	29.14 ± 21.62	0.611
Calcium	9.2 ± 0.91	9.36 ± 0.39	9.25 ± 0.35	0.451
Inorg. Phosphorus	3.04 ± 0.60	3.04 ± 0.62	2.92 ± 0.53	0.812
Alkaline phosphatase	75.58 ± 18.72	77.18 ± 18.1	64.08 ± 15.47	0.062

One-way analysis of variance, *Kruskal Wallis test

Table 5. *Comparisons of the mean values of BMD values in femur and lumbar spine regions, according to Ludwig subgroups.*

Variables	Ludwig I n: 31	Ludwig II n: 62	Ludwig III n: 13	p
Femur neck-T[*]	-0.565 ± 1.150	-0.719 ± 1.238	-0.265 ± 1.775	0.717
Total hip-T[*]	-0.375 ± 1.004	-0.444 ± 1.094	-0.724 ± 1.042	0.504
Lumbar spine-T[*]	0.149 ± 0.981	-0.107 ± 1.121	-0.142 ± 1.129	0.37
Femur neck-Z[*]	-0.369 ± 1.301	-0.381 ± 1.354	-0.285 ± 1.788	0.871
Total hip-Z	-0.653 ± 0.997	-0.274 ± 1.162	-0.292 ± 0.132	0.191
Lumbar spine-Z[*]	0.306 ± 1.035	-0.056 ± 1.180	-0.099 ± 1.152	0.265

*Kruskal Wallis test

Discussion

Loss of BMD is important health problem in especially postmenopausal women. It can lead to decrease in quality of life by doing serious morbidities, significant economic loss and even mortality due to fracture complications. Although decreasing in BMD in postmemopausal women is well-known condition, and it is usually associated with declining levels of female-sex hormone levels with the advancing age, there is no enough knowledge about decreasing in BMD in young women [10]. AGA usually occurs in advancing ages in women. It affects approximately more than 50% of women over the age of 50, whereas the incidence has been reported as between 6% and 34% under the age of 50, and only 3% under the age of 30 in different studies [11-13]. Pattern HL before 35 years of age refers to early-onset AGA [4] and more than 85% of our subjects' HL began before 35. Although the reason of late-onset AGA has been attributed to the decreasing levels of female-sex hormones, relative increasing of androgens, higher levels of 5-alpha reductase, which is responsible for converting testosterone into a more potent androgen together with a genetic predisposition because of polygenic inheritance patterning, a lot of women has normal hormone values. Contrarily, it is strongly recommended that young women with AGA should be investigated in terms of conditions which lead to high androgen levels such as PCOS or androgen releasing tumors [1,2,4]. On the other hand, BMD can be influenced by some factors such as BMI, daily calcium, caffeine, and alcohol consumptions, smoking, birth count, sun exposure, physical activity, and low BMD values may be related to early-onset menopause, low peak bone mass, high birth rate, inadequate physical activity, insufficient sun-exposure and calcium consumption, heavy smoking, and consuming too much caffeine and alcohol [10]. Except for the daily coffee consumption, most of our subjects did not have enough criteria which may lead to negative changes in BMD. Moreover, except for slight decrease in 25-OH Vit-D$_3$, available bone turnover-related laboratory tests (Calcium, inorganic

phosphorus and AP) were within the normal levels. No any significant difference was detected between the different HL groups in terms of aforementioned factors and tests. Besides these predisposing factors, it has been shown that BMD may be influenced by some hormonal changings [8,14-16]. It has been suggested that in especially premenopausal women, AGA can be a sign of hyperandrogenism, because hair thinning results from the effects of the testosterone metabolite Dehydrotestosterone (DHT) on androgen-sensitive hair follicles. Moreover, it has been reported that increase in levels of DHT may comply with the advanced stages of AGA. However, this condition is usually limited to women who also have other hyperandrogenic conditions such as PCOS or hirsutism, and many women with AGA may have normal testosterone levels [1,2,17]. On the other hand, it has been stated that higher testosterone level might be associated with decrease in bone fractures, and BMD in women who received testosterone with estrogen was higher than that in women who received estrogen alone [18]. Contrarily, Karadag et al. showed that although subjects' androgens were high, BMD was lower in premenopausal PCOS group than controls. However, the authors attributed these contradictory results to lower estrogen levels of the subjects [19]. Although, Morton et al. showed that 508 balding women had significantly higher hip BMD, they attributed these results to currently estrogen use of the women [20]. Khosla et al. showed that bio-testosterone levels are not related to BMD in pre and postmenauposal women [21]. Similarly, Dagoo-Jack et al. found no significant correlation between BMD value and TT levels in hirsute women [19]. Increasing in two adrenal-originated androgens (DHEA-S and androstenedione) may have an influence on AGA [22]. The association between DHEA-S and androstenedion, and changes in BMD is contradictory. Ghebre et al. showed that high serum DHEA-S levels at baseline were associated with reduced bone loss at femur neck and lumbar spine. But this association gradually decreases over time because the levels of DHEA-S decline with aging [23]. Contrarily, Zofkova et al. determined no association regarding this relationship, in a normal female population [24]. Furthermore, Moberg et al. showed that lower androstenedione levels, lower androstenedione/SHBG ratio, and higher SHBG levels increase in risk for bone fracture in postmenopausal women [25], whereas similar effects of lower androstenedione was confirmed by Karadag et al. in premenopaosal women [19]. Interestingly, lowered SHBG levels were attributed to pathogenesis of female AGA, because it can lead increased amount of FT [22]. In this study, all patients showed normal FT, TT, DHEA-S, androstenedion and SHBG levels, and no differences were obtained according to subjects' HL stages. AGA and gonadotropins have usually been associated indirectly, and this knowledge limited to studies regarding AGA women who have higher androgen levels secondary to the other hyperandrogenic diseases. On the other hand, debates on association between the changed FSH and LH levels and BMD have gradually increased in recent years. Li Sun et al. determined that FSH stimulates bone resorption by osteoclasts directly in a pituitary-bone axis, independent of the estrogen effect, and they suggested that elevated FSH tends to bone lack across the menopausal transition, particularly during late perimenopause [26]. Another study showed that bone mass is significantly decreased in patients with amenorrhea and increased serum FSH levels [27]. Sowers et al. showed a strong relationship between high FSH levels, bone resorption markers and decrease in BMD in 2375 perimenapousal women [26]. Therefore, FSH is used as "fast bone loosers" during early phases of menaupausal transition [27]. Although Wu et al. and Xu et al. found similar correlation between high FSH and decrease in BMD, they also reported that high LH levels show a pretty weak correlation with bone loss whereas estrogen levels do not [28,29]. Our subjects had normal FSH and LH levels and no differences were detected according to clinical stages of HL. Most of our subjects were young women, none was in the menapause and had any hormonal insufficiency/excess or other diseases which might predispose to bone loss. Except for the increased coffee consumption in the rate of 75% and minimal deficiency in 25-OH-D$_3$ levels of the subjects, no other significant predisposing condition, or chances in laboratory tests were detected in the study group, and no significant differences were detected between the HL stages. The presented study has some limitations such as a relatively low number of subjects, presents only results of single center, absence of equal number of subjects in each Ludwig group, and failure to work with all bone turnover markers because the data was studied retrospectively and with the available findings of the subjects. However, detected osteopenia and osteoporosis in approximately one-third and nearly 5% of the subjects in all measurement regions, are pointing to considerably high decrease in BMD in young women with AGA. Obtained results are so high that cannot be attributed to solely coffee consumption. To the best of our knowledge, no previous studies have examined in the rate of bone loss in female AGA patients. Although the cause of the relationship between the AGA and low BMD is still unanswered, because sex hormone levels and bone loss are associated conditions [15,16,21], our results are not surprising. They may seem contradictory to the literature regarding bone loss increases with decrease of androgens. However, they also support the knowledge in that etiopathogenesis of both conditions in young women cannot be associated with just predisposing life style factors or hormonal reasons, but should be investigated in terms of the reasons for common receptor responses and common signal pathways of morphogenetic proteins of hair bulb and bone. However, controlled and more systematic future studies are needed to support our results.

Conclusion

In this paper, possible relationship between AGA and BMD, and its relevance with HL stages were investigated. Osteopenia and osteoporosis were detected in approximately one-third and five percent of the T-scores of subjects. These values were nearly fifteen percent lower than the age-adjusted reference values, without any difference according to the clinical stages of HL. We suggest that women with early-onset AGA should be thoroughly investigated to the possibility of premature bone loss.

Conflicts of Interest

None of the authors stated that they had a conflict of interest.

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None

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