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Relationship between bone density of paranasal sinuses and adrenal steroids pattern in women during menopausal transition

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ABSTRACT: The course of menopause transition (MT) is associated with peculiarities of alterations occurring in a woman's body, in particular, in the structure of bone tissue. Considering that bones of the paranasal sinuses (BPNSs) play a natural defense role against the spread of dental infection , their structure is important in dentistry. However, no information was found pertaining to changes of BPNSs during MT – a time when dental maladies increase in many women.
The aim of our study was to collate density of BPNSs with status of adrenal steroids in women during MT, since the pattern of their changes determines the course of MT.
Cross-sectional associations were examined between bone density of PNSs assessed by Spiral Computed Tomography and Serum content of testosterone (T), sex hormone binding globulin (SHBG), free androgen index (FAI), insulin, dehydroepiandrosterone sulfate (DHEAS), Adione, and Adiol in 113 women of perimenopausal age (age range from 45 to 55 years) who had already experienced premenopausal menstrual decline (amenorrhea less than 2 years).
Strong positive (r = 0.73) correlation between minimal bone density of maxillary sinus in women with level of DHEAS was detected. It is important to note, that the correlation between minimal density of the lower wall of frontal sinus is a weak positive (0.3). Therefore , it can be suggested that bone tissue of the maxillary sinus is more sensitive to changes in DHEAS.
The study showed that the level of male steroids, in particular DHEAS, affected the state of bone tissue in participants older than 50 years of age.

KEY WORDS: Bone density, male steroids, uncertainty of measurements, computed tomography

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Introduction

Menopause transition (MT) is the time during female lifespan when whole her body undergoes neurohormonal and metabolic changes that can impinge quality of life. The common idea that perimenopausal disorder is explicitly due to plummeting estrogen levels has been partially superseded by the recognition of a rise of adrenal androgens experienced by majority of women during MT, that leads to imminent future estradiol decline. The Study of Women's Health Across the Nation (SWAN) identified four adrenal androgens (dehydroepiandrosterone – DHEA, dehydroepiandrosterone sulfate – DHEAS; androstenedione – Adione; delta-5-androstenediol – Adiol) that rise during MT in at least 85% of women across the world (Bird et al. 1978). Also, SWAN recognized ethnic and individual differences in circulating adrenal steroids during MT that were much more substantial than in estradiol (E2) or testosterone profiles (Janssen et al. 2008). Perhaps, it could be suggested that the pattern of adrenal steroids predetermines alterations in female organism after menopause, that can either provide the potential for healthier aging or make women exposed to a awry hormonal profile and hostile metabolites. The latter is associated with a growing risk of adverse cardio-vascular events or neoplastic growth in susceptible tissues. Bone tissue is a well-known target for sex steroids, particularly, androgen and estrogen that improve bone density. However, progressive loss of bone density experienced by women during post-menopause shows substantial inter-female variation which is not consistent with the limited inter-female circulating E2 pattern type (Lasley et al. 2011). For example, bone density of the paranasal sinuses (BPNS), should be taken into consideration in the management of paranasal sinusitis as they can prevent inflammatory foci from spreading outside (or inside affected teeth roots). Despite the relative preponderance of androgen activity over estrogens throughout MT that triggers bone density loss, women with metabolic syndrome (MS) and android obesity appear to undergo this loss at a faster pace that makes their BPNS more compelling. Ongoing age-related insulin resistance may explain this controversy.

Decline of early follicular E2 level marks the final menstrual period (FMP) of MTwithin two years. However, even after the completion of FMP, E2 rate of decline varies between women until its ultimate cessation (Randolph et al. 2003). A responsive decrease of SHBG production triggers an overall increase in FAI which offset subsequent dwindling ovarian output of testosterone (T) throughout MT, but also contributes to mounting age-related insulin resistance (Crawford et al 2009). Reduction of T output lags behind the decrement of ovarian aromatase activity converting T to E2. Pre-existing obesity or substantial weight gain throughout MT instigates peripheral conversion of Adione via enhanced 17b-hydroxysteroid dehydrogenase (Lasley et al. 2002). Cumulative androgen preponderance over estrogens is considered as one of the drivers of MS.

Another event experienced in the majority of women throughout MT is the distinct rise in serum DHEAS due to adrenal activity, which has been also reported in women who underwent BSO at reproductive age (Janssen etal.2008). The extent of this DHEAS rise in middle-aged women varies significantly

between ethnicities. However, at least 85% of the female population in all five ethnicities reported to show spike of DHEAS as the harbinger of the incipient MT before other alterations in their hormonal profiles became evident (Lasley et al. 2002). Subsequently, increased circulating DHEAS level lasts for several years until it steadily declines towards the end of early post-menopause. Ethnic-specific peculiarities in the regulation of the delta-5 adrenal steroidogenic pathway in premenopausal women determine the pattern of DHEAS rise, which is found to be the most significant in the Chinese population (Yue et al. 2018). Despite between-ethnic differences in DHEAS trajectories, there is a common physiological mechanism of adrenal contribution to the realignment of sex-steroid balance throughout MT. Delta-4 steroidogenic pathway is responsible for Adione and T production. Meanwhile delta-5 pathway provides facilitates DHEA, DHEAS and Adiol (Randolph et al. 2003). Delta 4/5 isomerase converts delta-5 to delta-4 hormones. Perhaps a transient increase in adrenal delta-5 pathway experienced by a majority of women could be triggered by subtle ovarian changes (incremental attrition of high-quality primordial follicles, gradual loss of inhibin B and ensuing slight rise of FSH). However, this assumption does not explain a spike of serum DHEA experienced by ovaryectomized women at the time of natural MT.

In relation to the significance of anatomical peculiarities for BPNS in various medical fields (dentistry, otolaryngology, maxillofacial surgery and other) we decided to collate the density of BPNS controlling of adrenal steroids in women during MT that was the purpose of our work.

Material and Methods

Cross-sectional associations were examined between bone density of paranasal sinuses (PNSs) assessed by Spiral Computed Tomography (SCT) and serum content of T, sex hormone binding globulin (SHBG), free androgen index (FAI), insulin, DHEAS, Adione, and Adiol measured in 63 women of perimenopausal age who had already experienced premenopausal menstrual decline (amenorrhea less than 2 years). Accrual and all subsequent tests were carried out at Merefa Central District Hospital in 2018–2020 (Kharkov, Ukraine). Criteria of inclusion to this research were:

1. Natural menopausal transition.
2. Women age (older than 45 years and younger than 55 years).
3. Duration of amenorrhea more than 3 months and less than 2 years.

Any finding which indicated inflammatory or tumor lesions in PNSs, artificial menopause, women's age younger than 45 and older then 55, overt hypothyroidism, diabetes mellitus or other endocrine disorders were criteria of exclusion. All women were divided into two groups according to serum DHEA level. The first group (30 women) was constituted by women in the MT with upper median average DHEA values (second and upper quartiles) for this age, the second group consisted of 33women with DHEA levels that made up the lower limit of the physiological state (lower quartile). In order to get a benchmark for bone density of PNSs SCT, scans of 50 women without any previous ENT organ problems were taken as the control group. In their case, SCT was performed due to reasons non-related to their ENT organ pathology (an average age – 35.5 years). Overt hypothyroidism, diabetes

mellitus or other endocrine disorders, were also excluded from control group.

Our study complies with the requirements of the Declaration of Helsinki. All patients were informed of their participation in the study and written informed consent to participate in the study was obtained. The study was approved by the Bioethics Committee of Kharkiv National Medical University.

Hormonal Analysis

DHEAS level was detected with chemiluminescent immunoassay method on microparticles. Adione – was detected using enzyme immunoassay method, whereas testosteron, SHBG, insulin – with electrochemiluminescence immunoassay method. FAI was calculated as ratio between molar concentration of total testosterone and molar concentration of SHBG, Adiol – serum samples were analysed by gas chromatography. In order to have benchmark for stratification of tested women according to the density of PNB, another 50 healthy women of reproductive age (under 35 years) were selected as control group (an average age in this group was 35,5 years). Bone density of lower walls of sinuses was detected for all groups of patients (see Fig.1). Attention was drawn to the maxillary sinus, given the fact that maxillary sinusitis is the most common form of rhinosinusitis. At the same time, inflammatory processes in the frontal sinus are often associated with the development of complications.

SCT scans

The SCT scans were obtained from a 64-slice Toshiba Aquilion-4 device. It is a multi-slice CT scanner with the possibility of simultaneous data collection of 4 slices 0.5 mm thick and featuring high performance with a full revolution time of up to 0.4 s. The high-speed rotation mechanism and the fast system reconstruction unit provides accelerated data collection, which increases the scanner throughout. Bone density was detected with Hounsfield scale and then uncertainty of its measurements was calculated. Bone density of the lower walls of sinuses was detected for all groups of patients (see Fig. 1). Attention was drawn to the maxillary sinus, given the fact that maxillary sinusitis is the most common form of rhinosinusitis. At the same time,

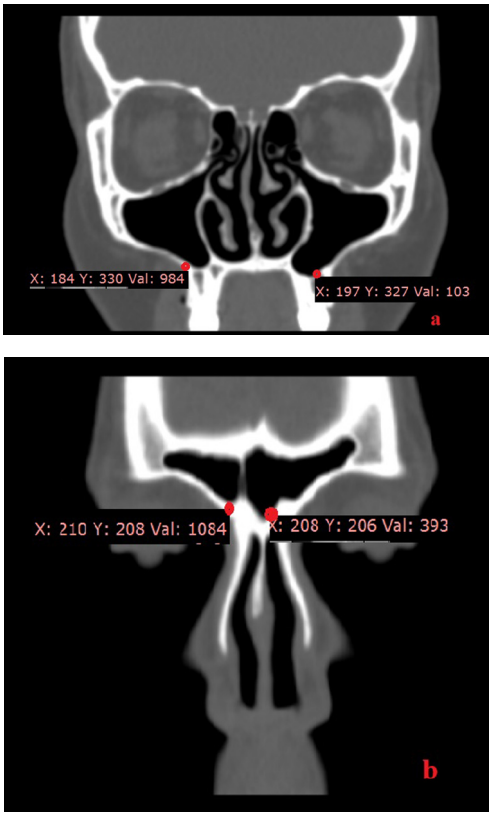

Fig. 1. Study of the density of the lower wall of the maxillary (a) and frontal (b) sinuses in physiological conditions. SCT. Coronary sections

inflammatory processes in the frontal sinus are often associated with the development of complications.

The study concerned the lower wall of the maxillary sinus, as being potentially dangerous for the development of odontogenic maxillary sinusitis. The lower wall of the maxillary sinus is a common cause of pathogenic spread into the orbit. Noninvasive detection of internal intravital peculiarities is important for human organism morphology and function (Krivenko et al. 2020), with nonobligatory linear-feedback connection (Krivenko and Krivenko 2014). Adherence to the principle of non-invasive investigation is so important that often the study of processes in the human body is replaced by modeling or setting up an experiment (Lyndin M et al. 2019).

Statistics

Correlation analysis was performed using Spearman rank correlation coefficient. To improve the accuracy of our measurements, we used a method that we have repeatedly used in our previous studies (Nechyporenko et al. 2020).

Uncertainty can be defined as the entire range of values that are valid for a particular value. The uncertainty of the result of a measurement reflects the lack of exact knowledge of the value of the measured (Vogt et al. 2018).

Any report regarding uncertainty should consist of a complete list of components specifying each method used to obtain its numerical value. The purpose of using Type A and Type B classifications were to indicate the two different ways of evaluating uncertainty components. Thus, a Type A standard uncertainty is obtained from a probability density function derived from an observed frequency distribution, while a Type B standard uncertainty is obtained from an assumed probability density function based on the degree of belief that an event will occur (Nechiporenko 2015). The standard uncertainty of the result of a measurement, is when that result is obtained from the values of a number of other quantities (combined standard uncertainty). It is the estimated standard deviation associated with the result that is equal to the positive square root of the combined variance obtained from all variance and covariance components. Calculations were conducted in accordance with the algorithm described from our previous studies (Nechyporenko 2019a, Nechyporenko 2019b).

To begin with we obtained the combined standard uncertainty using the following expression:

$$u_c(S_P) = \sqrt{u_A^2(S_{Pi}) + u_B^2(S_{Pi})} \qquad (1)$$

where: $u_A(S_{Pi})$ – Type A standard uncertainty, $u_B(S_{Pi})$ – Type B standard uncertainty.

In order to obtain the Type A standard uncertainty we used the expression:

$$u_A(S_{Pi}) = \sqrt{\frac{1}{n(n-1)} \sum_{i=1}^{n} (S_{Pi} - S_P)^2} \qquad (2)$$

where: S_{Pi} – i-e value of measurement in dataset, S_P – mathematical expectation, n – number of measurements in a dataset.

For calculation of Type B standard uncertainty we used the expression:

$$u(S_P) = S_P \frac{\delta_s}{\sqrt{3 \times 100}} \qquad (3)$$

where: δ_S – an error of software that has been used for measurement; where it does not exceed 0,0001%.

Finally, it makes sense to calculate the additional measure of uncertainty, as it meets the requirement of providing an interval assessment. The expanded uncertainty U is obtained by multiplying the combined standard uncertainty $u_C(S_P)$ by a coverage factor k:

$$U = ku_c \quad (4)$$

where: k – coverage factor.

The choice of the value of the factor k, which is usually in the range 2 to 3, is based on the coverage probability or level of confidence required of the interval (ISO/IEC GUIDE 2008:98). In this case, the hypothesis of normal distribution law has been accepted. As a result, the factor k for probability 0.95 is equal to 2.

Results

It turned out that women who fell into the two different subsets according to the density of their BPNS (either low density – 1st group, or the density matching control group – 2nd group) depicted androgen profiles that were distinctive to each group (Table 1).

During the study, at each section, the maximum and minimum indicators of this parameter were determined as superficially to the sinus cavity as possible.

At the next stage, the density of bone tissue of the lower wall of the maxillary sinus was determined in women from

Table 1. Levels of hormones in different groups of patients

Hormone (serum)	1st group Low density of BPNS (n = 30)	2nd group Density of BPNS matching control group (n = 33)
Testosterone (T), nmol/l	12.7±0.0002	9.5±0.0014
Sex hormone binding globulin (SHBG), nmol/l	34.8±0.003	50.05±0.034
Free androgen index (FAI),	0.51	0.18
Insulin fasting, mlU/L	6.1±0.0023	4.01±0.2
Dehydroepiandrosteronesulfate(DHEAS),mg/dL	130.6±34.4	280±0.33
Androstenedione (Adione), ng/dL	94.2±0.033	58.4±0.1
Delta-5-androstenediol (Adiol),nmol/l	0.8±0.021	5.3±0.01

Table 2. Density (Hu) of bone tissue of the maxillary and frontal sinuses in women with an average level of DHEAS

Name of the sinus, the studied wall		Density indicators			
		U a	U b	U s	U expanded
Maximum density of maxillary sinuses (lower wall)	right	241.72	0.00048	241.73	483.46
	left	263.97	0.00054	263.971	527.943
Minimum density of maxillary sinuses (lower wall)	left	197.46	3.358	197.464	394.927
	right	159.15	2.7596	159.146	318.291
Density of the right frontal sinus (lower wall)	minimum	231.12	4.9991	231.117	462.233
	maximum	301.86	0.00054	301.861	603.723
Density of the right frontal sinus (lower wall)	minimum	190.2	3.089	190.204	380.407
	maximum	393.90	0.00057	393.901	787.802

each presented group and control group. The results are presented in Tables 2–4.

Strong positive (r = 0.73) correlation between minimal bone density of maxillary sinus in women with level of DHEAS was detected (see Fig. 2). It is important to note, that the correlation between minimal density of the lower wall of frontal sinus is weak positive (0.3). Therefore, it can be suggested that bone tissue of the maxillary sinus is more sensitive to changes in DHEAS.

Discussion

Hormones play an essential role in womens' lives (Jusiakowska-Piputa and Kaczmarek 2018).

Adiol and Adione show that sex steroid activity is significant after the loss of essential ovarian hormones during and after MT. It has been shown that higher serum DHEA, as the precursor of Adiol and Adione during perimenopause, is associated with almost unaffected cognitive

Table 3. Density (Hu) of bone tissue of the maxillary and frontal sinuses in women with low DHEAS

Name of the sinus, the studied wall		Density indicators			
		U a	U b	U s	U expanded
Maximum density of maxillary sinuses (lower wall)	right	240.72	0.0004	240.722	481.444
	left	195.67	0.00036	195.672	391.343
Minimum density of maxillary sinuses (lower wall)	left	146.01	−4.51325	146.011	292.021
	right	211.91	2.16361	211.913	423.827
Density of the right frontal sinus (lower wall)	minimum	153.57	−7.01596	153.565	307.130
	maximum	228.47	0.00035	228.468	456.936
Density of the right frontal sinus (lower wall)	minimum	120.04	−6.173	120.038	240.076
	maximum	401.05	0.00043	401.052	802.104

Table 4. Values of the density (Hu) of bone tissue of the maxillary and frontal sinuses in the control group of women

Name of the sinus, the studied wall		Density indicators	
		Ua	U expanded
Maximum density of maxillary sinuses (lower wall)	right	310.2026	395.0
	left	306.7441	613.4882
Minimum density of maxillary sinuses (lower wall)	left	220.178	440.356
	right	197.617	395.0
Density of the right frontal sinus (lower wall)	minimum	155.282	276.43
	maximum	374.24	732.274
Density of the right frontal sinus (lower wall)	minimum	138.217	310.56
	maximum	366.1371	748.48

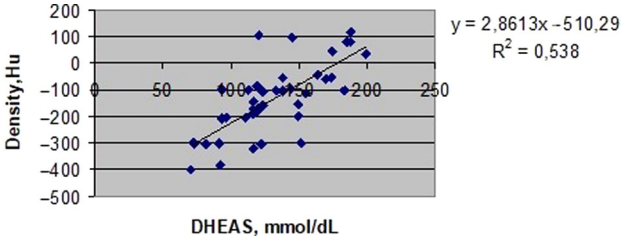

Fig. 2. Correlation between density of the lower wall of Maxillary sinus and DHEAS

and executive function, which usually undergoes deterioration during MT (Yoldemir et al. 2020). Howerver, attempts to use DHEA supplements proved to be of no benefit in deterring cognitive loss. This could be due to conversion of DHEA to less favorable final products (Willi and Ehlert 2019). We may speculate here that that is was not DHEA itself, but rather its downstream products that were explicitly or implicitly responsible for sustainable estrogen-dependent integrity of estrogen-sensitive tissues. Individual vacillations of circulating E2 during early MT, as well as E2 pattern among female population of perimenopausal age are not consistent with the impending changes MS, such as android obesity and cardiovascular disease (Lasley et al 2011). Scientific dictum maintains that adrenal androgen pattern during MT predetermines postmenopausal metabolic regulation, and thus, the capacity for healthy ageing (Janssen et al. 2008).

Adiol is able to elicit response from both androgen and estrogen receptors. This can tip the balance to one or another favor depending on the distribution of specific steroid hormone receptors in target tissues and availability other higher-affinity ligands such as T or E2. Thus, Adiol exerts its influence on available receptors in targeted tissues providing that its serum level is much higher than more active confounds (in the case of latter deficiency). Despite structural resemblance to androgens Adiol mainly acts as a weak estrogen with a potency of 0.01 to 0.1% that of E2. Throughout the reproductive years Adiol's concentration (<1 nmol/l)is insufficient to deliver tangible impact on estrogen receptors. However, DHEAS spike confined to the timeframe from early perimenopause to early postmenopause makes serum Adiol attain values (3–4 nmol/l) outweighing E2 by approximately one hundred times that enables Adiol to elicit estrogenic response. However, approximately 15% of women fail to experience perimenopausal rise in DHEAS leaving them with low Adiol. In the other 85% of perimenopausal-aged female population, diverse DHEAS downstream pattern results in wide range of circulating Adiol (<1to 4 nmol/l). the considerable variation of phenotypes emerging across MT does not correspond to a relatively minimal range of circulating E2 levels during this time. Therefore, other contributors can play an influential role in establishing a new androgen/estrogen balance, as well as in hormonal-driven alterations of phenotypes while a woman undergoes MT (Randolph et al. 2003).

Recent data have recognized adrenals as the main source of androgen cascade across MT with evident of increase of both T and Adione concomitant with DHEAS perimenopausal spike. Mounting FAI due to abating SHBG production that is down-regulated by opposing T rise and E2 decline, is considered as the best predictor of adverse outcomes (MS and cardiovascular diseases) in postmenopause. There was interesting assumption that also rising Adione and Adiol, as SHBG ligands with affinity lower than T, nevertheless were capable to occupy some binding sites for T, if their output by adrenal-derived androgen cascade reached abundant values, leaving the latter free and correspondingly more active (Yoldemir et al. 2020).

While DHEAS at the time of MT proved to be strongly associated with better self-reported well-being, cognitive and physical functioning, fewer thrombotic events due to lower PAI-1, tPA and fibrinogen, and lower rate of MS (inverse

relation with BMI and waist-hip ratio), (Williams MSet al. 2016) DHEAS spike itself cannot explain all these favorable signs, as it has failed to protect 85% of women from adverse outcomes . The combination of DHEAS products such as Adiol or, for example, conversion delta-5 hormones to delta-4 ones driven by delta 4/5 isomerase might be considered as a plausible model of various postmenopausal phenotypes. Adiol dual weak estrogen/androgen capacity might contribute to favorable phenotypes associated with perimenopausal DHEAS increase, whereas Adione contribution to the total androgenicity and its link with metabolic disorders should not be neglected. Amajority of women show doubling of T and Adione and possibly a five-fold increase in Adiol during menopause (Lasley et al. 2011). However, there exist several subtypes and variations in Adiol/Adione-perimenopausal secretion that might underline multifarious elements of ageing. Of course, the role of devastating stressful factors should be taken into account, since overproduction of cortisol drains substrate resource for DHEAS rise.

Obtained data are important for detection of anthropometric peculiarities. Although, the present study was connected with our previous studies, here we used a fundamentally new method of calculating – uncertainty of measurements (Gargin et al. 2019).

Since the rise of MS rate in perimenopause coincides with imminent FSH growth during early MT, the latter increment (as well as, the rate of E2 decline) cannot predict ensuing adrenal response from a woman's postmenopausal phenotype. Differences in DHEAS and Adiol levels are the most profound of any hormone during postmenpause (Yue et al2018), narrowing range of E2 decline. Adiol spike can reach five-fold increment in some women as it has much lower estrogenic bioactivity compared to E2. Yet this capacity to respond of all adrenal best to MT varies among women being geared to hereditary predisposition (ethnical and individual), pre-existent disease and impact stress experienced during this timeframe.

Regarding DHEAS obtained by our study in both groups, we hypothesized that lower DHEAS in the subset with low density of BPNS a did not explain why women who had failed to experience DHEAS spike at all or the extent of its rise had been negligible. The most plausible explanation involves genetic predisposition, but also the impact of chronic stress that had triggered overt cortisol production at the expense of DHEAS, thereby reducing the latter's influence. Since the mean level of DHEAS remained within normal range, this may have converted to other bioactive compounds .

In regards to DHEAS increase during MT,our study concluded that the peri- and postmenopausal timespan might be informed via delta-5 steroidogenic pathway activation and delta 4/5 isomerase activity which converts delta-5 to delta-4 hormones, thereby tipping the scale of Adione/Adiol balance from one to another. Excessive androgen activity (Adione, T, low SHBG) may precipitate MS with inherent insulin resistance that might affect beneficial androgen impact on bone density. Our study results found an association between low density BPNS in women with relative androgen preponderance but with low level of Adiol, also between density of BPNS, matching to this value in females under 35 years, in those women of perimenopausal age who showed higher Adiol and less substantial Adione, are consistent with this

point of view. However, this conclusion is not consistent with some reports that claimed highlighted the protective role of insulin resistance on bone density (radius and tibia) in postmenopausal nondiabetic women (Lasley et al. 2011). We argue that throughout MT every bioactive compound is significant since they facilitate sustainable regulation in targeted tissues including bones when ovarian source of T and E2 declines. The androgen/estrogen balance matters as each hormone has to attenuate the negative consequences of the other while reinforcing its positive effects. Thus, Adione without the appropriate concentration of Adiol can adversely affect tissue to which androgens are otherwise favorable.

We posit that the major changes in level of these hormones correlates with the severity of the pathological process in the sinus and oral cavity (Kuzenko et al. 2014, Avetikov et al. 2018). Under physiological conditions, the lowest density of bone tissue was determined in participants who had a minimum level of DHEAS in the >50 years age groupnI contrast, maximum densitometric indices were detected in younger participants. Possibly, these indicators show variation in sports people (Romanenko et al. 2018).

The bone density in women over 55 years of age with a high level of androgens was almost equal to that in the control group. Consequently, the level of male sex hormones, being a marker of changes associated with menopause in women, was found to have a significant effecton bone density. This inevitably entails a change in its microarchitectonics, thereby, a decrease in bone density, precipitating the the development of intracranial and intraorbital complications of rhinosinusitis. Moreover, a decrease in bone tissue density of the lower wall can lead to complications (Alekseeva et al. 2019) during dental implantation due to improper load dosing during this procedure. The study showed that each patient required an individual approach to the diagnosis and treatment of rhinosinusitis. However, it should be noted that such a personal approach does not always elicit the desired diagnostic effect or treatment. Our study found that by determining a woman's hormonal background(i.e. the level of androgens in women) made it possible to choose the right therapy, and prevent the development of odontogenic maxillary sinusitis.

The correlation between the density of long tubular bones (femur, radius, ulna, etc.) and estrogen decline during perimenopausal age is well-known. In our study, for the first time, the relationship between bone density of the facial skulland adrenal steroid patterning during the menopausal transition, as well as early traits of PNS bone density loss in the case of unfavorable adrenal steroid patterning were recognized. This parameter is a biomarker of the severity of bone destruction. its decrease often leads to the development of inflammatory processes of the paranasal sinuses which increases risk of traumatization (Ignasiak et al. 2015). In addition, since density is a rather variable indicator, we used a new method for detecting it– calculating of the uncertainty, which is well-known in medicine (Chumachenko et al. 2019). Furthermore, this new method has not been previously applied for detecting the structure of paranasal sinuses.

Conclusion

The study showed that adrenal steroid levels, in particular DHEAS, arebeneficial

for maintaining PNSs bone density and structure in females (45–55 years) during the menopausal transition. Lower serum DHEAS levels are associated with rapid loss of targeted bone density, therefore, increasing female risk to odontogenic infection to PNSs. . Thus, it isevident that a favorable pattern of adrenal steroids can deter bone density loss during perimenopausal in BPNS, as well as long tubular bones. thereby reducing inflammatory complications related to dental issues.

The Authors' contribution

VG, OV – laboratory practices; IM, VA – concept of the study; VB, AN – design of the study; AN, NS – data collection or processing; NS, IM, VA – data analysis or interpretation; VB, OV – search; VG, IM, VA, AN – writing.

Conflict of interest

The authors declare that there is no conflict of interest.

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