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The features of the hormone homeostasis in women with coronary artery disease at various stages of physiological development according to clinical and epidemiological research

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Summary

Objective. *To assess and compare the features of hormone homeostasis in women with coronary artery disease (CAD) at various stages of physiological development according to clinical and epidemiological research.*

Materials and methods. *The study included 200 women with CAD, who were divided into 2 groups: I — epidemiological and II — clinical (99 and 101 patients, respectively). To verify CAD, patients underwent full range of epidemiological and clinical instrumental studies. Sex hormones — estradiol (E), testosterone (T), progesterone (P) and the adrenal cortex hormone — cortisol (K) were investigated in all participants in different age groups and were compared with the control group of healthy individuals.*

Results. *The study revealed heterogeneous changes in hormone homeostasis in women with CAD of reproductive age and at menopause, which also differed between groups of epidemiological and clinical examination. Thus, young women from group I showed significant decrease of E with a reciprocal increase of T, while women at menopause had statistically significant decrease of the P level in both groups. The decrease of K production was observed in both age groups. Young women of childbearing age mostly had the decrease of E: P ratio, and during menopause — of E: T ratio.*

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Conclusion. *Women with CAD have certain changes of hormone homeostasis according to epidemiological and clinical research, which differ between groups of reproductive and menopause age. The revealed changes confirm the hypothesis that hormonal changes in women can be considered as additional risk factors for CAD and can be used as predictors for its development.*

Keywords: *coronary artery disease, women, sex hormones, hormone homeostasis.*

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Coronary artery disease (CAD) is one of the most important issues in cardiology. It is still one of the leading causes of morbidity and mortality in young people (the working age population) [1]. For a long time, cardiovascular diseases (CVD) have been considered the leading cause of disability and mortality primarily in men. However, recently it has been shown that women are at 2–4 times higher risk of CV complications compared with men [2].

Previously it had been thought that early CAD in women were caused by the same risk factors (RF) as in men (mostly genetic conditions that result in metabolism problems), but now it has been reconsidered [3]. According to the recent studies, there are female-specific risk factors associated with women's reproductive health including the age of menopause, use of hormonal contraceptives and history of gynecological problems [2, 3].

CVD is the leading cause of mortality in women. According to the latest American Heart Association (AHA) studies, over 30 % of women have some form of CVD. Among women, annual CVD incidence rate is 35 per 1,000 persons aged 45–54 years [4]. According to the World Health Organization (WHO), the top causes of mortality in women over 45 are CVD, followed by lung disease, diabetes, and cancer [5]. In women aged 45–65 years, some form of CVD is present in 1 in every 9 women, in women over 65 years — in 1 in every 3 women. Premenopausal women are at twice the risk of CVD compared with postmenopausal women [6]. However, the incidence of CVD has recently increased both in young and older women including premenopausal women. That led to the introduction of the term "early CAD" meaning CAD in women younger than 55 years [6, 7]. Therefore, menopause provokes multiple problems including CVD [8].

Later manifestation of CAD in women is associated with protective effects of estrogens [1]. After menopause these effects wear off and leads to greater risk of CVD [9, 10]. The risk of CAD increases 7 times each decade after 40–45 years [11, 12].

Therefore, female sex hormones can be considered additional gender RF of CAD. The effects of menopausal hormone changes and other RF and predictors still need to be further investigated for more effective CVD prevention. CAD predictors include main or additional risk factors, that vary in different groups. Based on this information we divided all the participants into two groups: the epidemiologic group and clinical group.

Objective of this study was to assess and compare the features of endocrine homeostasis in women with coronary artery disease (CAD) at various stages of physiological development according to clinical and epidemiological research.

Materials and methods

The study was conducted in two separate phases. First, we carried out a cross-sectional epidemiologic study that included 952 women from the city of Sumgait; 228 (23,9 %) had CAD. Then, 99 women were randomly selected from all the participants with CAD and included into the final study.

The study group included 101 outpatient and inpatient females with CAD. CAD was verified with a thorough examination during hospital stay (40 women) or outpatient visit (61 women) in the M. A. Mirqasimov Clinical Hospital, Baku, Azerbaijan. Overall, 101 women were examined.

The final study included 200 women with CAD who were further divided into two groups..The first group included 99 participants with CAD that was identified epidemiologically. The second group included 101 participants with CAD verified with a thorough examination during hospital stay or outpatient visit.

We performed anthropometric measurements, laboratory evaluation that included biochemical parameters such as a lipid panel and other well-known

predictors of CAD. Sex hormones — estradiol (E), testosterone (T), progesterone (P) and the adrenal cortex hormone — cortisol (K) were investigated in all participants in different age groups and were compared with the control group of healthy individuals. Sex hormones were evaluated at the 6–8 days of the menstrual cycle (follicular phase).

The control group included 23 healthy women. Of those, there were 10 women of reproductive age (mean age 38± 2,5 years) and 13 women of postmenopausal age (mean age 53,4± 3,6 years).

We analyzed hormonal profile in healthy women of reproductive and postmenopausal age without CAD and compared them with each other and with populational data. According to our results, the levels of all hormones except for estrogen were similar in different age groups and in the two groups in general. Therefore, based on these findings, we further used hormonal profile of healthy women. Age and estrogen levels were excluded from the final analysis (Table 1).

Table 1. **Hormonal profile in healthy women of different ages**

Hormones	Control group of healthy women (n=20)	Fertile (n=10)	Post-menopausal (n=13)	p
Estrogen (pg/ml) M±m	45,6± 3,8	49,8± 2,1	36,7± 1,2	p1< 0,05 p2< 0,01 p3< 0,001
Progesterone (ng/ml) M±m	0,46± 0,11	0,64± 0,06	0,38± 0,09	NA
Testosterone (ng/ml) M±m	0,34± 0,05	0,46± 0,05	0,38± 0,05	NA
Cortisol (ng/ml) M±m	138± 9,9	136,5± 7,8	135,0± 6,5	NA

Note. P1 — difference between healthy women and women of reproductive age with CAD, p2 — difference between healthy women and women of postmenopausal age with CAD; p3- difference between fertile and postmenopausal women with CAD.

Sex hormone levels were measured in the morning after overnight fasting using the «BioScreen-500» reader system (USA) with HUMAN's system reagents. 10–15 ml of blood were drawn from the cubital vein. Reference hormone ranges according to HUMAN are the following: estrogen in healthy women — 30–120 pg/ml during follicular phase; 15–60 pg/ml; after menopause; progesterone 0,2–1,4 ng/ml during follicular phase, 0,1–1 ng/ml after menopause; testosterone In healthy women <0,6 ng/ml during follicular phase, <0,8 ng/ml after menopause; cortisol in adults 50–250 ng/ml.

Statistical analysis was performed using the SAS statistical software and Statistic for Windows. The groups were compared using Student's t-test. The mean (M), standard error of mean (m), minimal (min) and maximal (max) values were calculated. P<0,05 was considered statistically significant.

Results

Of 200 participants, 79 were of reproductive age and 121 in postmenopausal age; in group I, 55 patients were of reproductive age and 44 of menopausal age, in group 2–24 were o reproductive age and 77 were in postmenopausal age.

We compared the levels of hormones in various physiological phases in women of reproductive and postmenopausal age with CAD (Table 2).

As shown in Table 2, both patients of reproductive and postmenopausal age in group I have lower levels of estrogen, but these differences aren't statistically significant. However, estrogen levels were lower in women of reproductive age from this group compared with healthy females of the same age group (p<0,05). Patients in group II had higher levels of estrogen but the differences between fertile and postmenopausal women and women in group II and I weren't statis-

Table 2. **Mean hormone levels in women of reproductive and postmenopausal age**

Groups		Estradiol (pg/ml)	Progesterone (ng/ml)	E:P	Testosterone (ng/ml)	E:T	Cortisol (ng/ml)
Group I (n=99)	Fertile (n=55)	40,5±3,9^	0,7±0,1	57,85	0,76±0,1^^	53,3	139,1±4,6
	Postmenopausal (n=44)	40,9±5,0	0,29±0,05**	141,0	0,66±0,8	61,9	154,3±6,5*^
Group II (n=101)	Fertile (n=24)	48,9±7,8	0,65±0,17	75,23	0,34±0,06^^^	143,8	121,4±7,6
	Postmenopausal (n=77)	45,3±4,3^	0,24±0,02**^	188,7	0,47±0,04^	96,4	140,3±5,2*
Здоровые лица (n=23)	Fertile (n=10)	49,8±2,1	0,64± 0,06	77,8	0,46± 0,05	108,3	136,5±7,8
	Postmenopausal (n=13)	36,7±1,2	0,38± 0,09	96,6	0,38± 0,05	96,6	135,0±6,5

Note. P — difference between I and II groups in women of reproductive and postmenopausal age (*— p< 0,05; **— p< 0,01; ***— p< 0,001); ^ — difference between women with CAD and healthy women.

tically significant. Climacteric women from group II had statistically higher levels of estrogen compared with control group (45,3±4,3 vs 36,7±1,2, p<0,05).

Of note is that progesterone levels were lower only in postmenopausal women compared with women of reproductive age (p<0,001 in group I и p<0,001 — in group II). Levels of testosterone were higher in patients in group I compated both with women of postmenopausal age (0,76±0,1 vs 0,66±0,8, p<0,001), and with healthy fertile wonen (0,76±0,1 vs 0,46±0,05, p<0,001). However, fertile women in group II had lower levels of testosterone compared with healthy individuals (0,34±0,06 vs 0,46±0,05, p<0,001). There was no statistically significant difference between the levels of testosterone in women of reproductive and postmenopausal age.

At the same time, E:P and E:T ratios in group I are significantly lower in fertile women with CAD compared with those of postmenopausal age (57,85 и 53,3 vs 141,0 and 61,9 respectively).

Cortisol levels in fertile women with CAD were lower in both groups compared with climacteric patients (p<0,05) and were also lower in patients from group II compared with women of all age groups with CAD from group I (p<0,01). Compared with healthy individuals, only postmenopausal patients from group I had higher levels of cortisol that were statistically significant (154,3±6,5 in women with CAD vs 135,0±6,5 in menopausal women from control group, p<0,05). The changes in hormonal levels such as rise in cortisol and decrease in progesterone in postmenopausal women with CAD can be due to increased activity of steroidogenesis in adrenal glands and reduced function of corpus luteum [13]. These findings are similar to epidemiologic populational data but nevertheless there were some differences in postmenopausal women: compared with populational data and women of reproductive age they had lower levels of progesterone, higher cortisol and lower E:P ratio. These changes in postmenopausal women with CAD are most likely associated with lower cardioprotective effects of estrogen and progesterone [14].

Postmenopausal women had higher estrogen levels and lower progesterone levels compared with the general group data (p<0,05 and p<0,01, respectively). However, E:P ratio was significantly higher in these patients compared with healthy individuals. E:T ratio was similar in both groups. Progesterone levels in women of reproductive age were similar to those in the control group (0,65±0,17 vs 0,64±0,06 in healthy women), but higher than in women of postmenopausal age (0,65±0,17 vs 0,24±0,02, p<0,01). At the same time cortisol levels were higher in postmenopausal women than in young women of reproductive age (140,3±5,2 vs 121,4±7,6, p<0,05). Lower levels of progesterone together with higher levels of estrogen and testosterone as well as higher levels of cortisol in women with CAD from group II can be a sign of adrenal hyperfunction [13]. E:P ratio is lower in women of reproductive age and E:T ratio in women if postmenopausal age. E:P is one of the negative predictors of CAD and hormonal imbalance is an important risk factor in young women of reproductive age [13, 15].

Discussion

In this study we demonstrated the changes in endocrine homeostasis in women of different age and from different epidemiologic and clinical groups. These changes of hormonal levels in both groups can be explained by the fact that patients from group II had atherosclerosis and active forms of CAD. According to the existing studies estrogen effects depend on the length of estrogen deficiency and can change from antiatherosclerotic to proatherosclerotic [16]. These affects were first described in WISE, HERS and WHI studies in which hormonal replacement therapy (HRT) didn't lead to reduction of CVD risk. These studies included older patients in late menopause with worse atherosclerosis and therefore exogenous estrogens didn't have any cardioprotective effects [17]. Lower levels of progesterone can be associated with poor cardioprotective effects of estrogens. At the same time, protective effects of female hormones can also be alleviated by their imbalance. Many authors note that the main CAD predictor in both women and men is the reduced E:P [15]. Progesterone, as well as estrogen, binds to specific myocardial and coronary vessel progesterone receptors. The number of progesterone receptors is modulated by estrogen. Progesterone reduces endothelial estrogen-mediated vasodilation [17]. Therefore, it is likely that in fertile women from group I with CAD but without severe atherosclerosis hormonal imbalance is associated with low levels of estrogen, increased levels of progesterone and testosterone that lead to androgenization and the loss of cardioprotective effects of estrogens [17]. Increased levels of progesterone inhibit endothelial vasodilation caused by estrogen [13]. Therefore, decrease in estrogen and rise in progesterone lead to vasoconstriction, worse coronary blood flow and endothelial dysfunction that causes CAD in young fertile women [18]. In postmenopausal women, higher levels of estrogen

lead to atherosclerotic effects. Reduction in progesterone leads to vasoconstriction and fluid retention due to higher aldosterone activity and Na reabsorption [19].

Women with CAD have different endocrine profiles. These differences were noted in women in different physiologic phases and also in epidemiologic and clinical study groups. According to the epidemiological study results, fertile women with CAD have lower levels of estrogen, higher levels of testosterone and reduced production of cortisol. On the contrary, clinical study results women had higher levels of estrogen and lower levels of testosterone compared with healthy control group. Changes in cortisol production were similar in both groups: cortisol production was lower in fertile women, especially in group II, compared with menopausal women. Postmenopausal women had higher levels of estrogen compared with healthy individuals according to clinical examination, as well as lower progesterone and higher cortisol in both groups.

In our study we have demonstrated the different hormonal changes in women with CAD in different physiologic phases, with different stage and length of atherosclerosis and also in epidemiologic and clinical study groups. These changes between groups I and II can become the foundation for CAD predictor research. The results of this study should be considered during the development of national CAD prevention program in women.

Conclusion

Estrogen levels were lower in women of reproductive age compared with healthy females of the same age group ($p<0,05$) according to epidemiological study and higher in climacteric women compared with control group according to clinical study ($p<0,05$).

Progesterone levels were lower in postmenopausal women according to both clinical and epidemiological investigations.

Changes in testosterone production were noted only in women of reproductive age: testosterone levels were higher in patients from group I compared with group II and with healthy individuals and lower in group II compared with control group.

Cortisol production was reduced in women of reproductive age according both to epidemiological and clinical investigations. Cortisol levels in group II were lower compared with group I both in fertile and postmenopausal women.

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