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Wpływ estradiolu na aktywność osi hGH-IGF-I-IGFBP-3 i u kobiet z hipoestrogenizmem hipergonadotropowym

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Streszczenie

Cel. Porównanie poziomów ludzkiego hormonu wzrostu (hGH), insulinopodobnego czynnika wzrostu-I (IGF-I) oraz trzeciego białka wiążącego insulinopodobne czynniki wzrostu (IGFBP-3) u kobiet z przedwczesnym wygasaniem czynności hormonalnej jajników (POF) w porównaniu do kobiet zdrowych i kobiet po menopauzie.

Pacjentki. Grupa A – 15 kobiet z POF (wiek: 38,9±5,2 lat, FSH: 101,4±29,0 IU/l; 17β-estradiol 22,5±14,6 ng/l); Grupa B 15 kobiet po menopauzie (wiek: 54,7±2,7 lat, FSH: 81,9±32,1 IU/l; 17β-estradiol 17,1±8,0 ng/l); Grupa C 15 zdrowych kobiet o regularnym wzorcu miesiączkowania (wiek: 37,1±9,0 lat, FSH: 6,2±1,0 IU/l; 17β-estradiol 144,8±117,1 ng/l)

Metodyka. Wykonano pomiary podstawowych stężeń w surowicy hGH, IGF-I, IGFBP-3, FSH, prolaktyny, estradiolu, insuliny i testosteronu oraz takich parametrów klinicznych jak masa ciała i BMI.

Wyniki. Stężenie IGF-I w grupach A i B było porównywalne (NS) i niższe (p<0,005) niż w grupie C (208,3±66,5 ug/l w por. do 172,0±54,6 ug/l: w por do 273,6±109,0 ug/l). Analogicznie zależności obserwowano w odniesieniu do poziomów IGFBP-3 (3,1±1,0ug/l w por do 3,1±1,0ug/l w por. do 4,4±0,3 ug/l). Poziomy hGH nie różniły się pomiędzy grupami. W grupach A i B nie obserwowano zależności pomiędzy poziomami IGF-I a wiekiem oraz IGFBP-3 a wiekiem. Jedynie w grupie C obserwowano zależność poziomu estradiolu i hGH.

Wniosek. 17β-estradiol wydaje się być równie istotnym, jak wiek, czynnikiem regulującym aktywność osi hGH-IGF-I-IGFBP-3.

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Słowa kluczowe: *IGF-I, IGFBP-3, hGH, estadiol, POF*

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17β-estradiol regulation of human growth hormone (hGH), insulin-like growth factor-I (IGF-I) and insulin-like growth factor binding protein-3 (IGFBP-3) axis in hypoestrogenic, hypergonadotropic women

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Abstract

Objective. Ovarian hormonal function may be as important contributing factor to hGH-IGF-I-IGFBP-3 axis as age.

Aim. To examine plasma hGH, IGF-1 and IGFBP-3 levels in women with premature ovarian failure compared to healthy normal controls and postmenopausal ones.

Patients. Group A-15 women with premature ovarian failure (POF) (mean: age 38.9±5.2 years, FSH 101.4±29.0 IU/l; 17β-estradiol 22.5±14.6 ng/l). Group B consisted of 15 menopausal women (mean: age 54.7±2.7 years; FSH 81.9±32.1 IU/l; 17β-estradiol 17.1± 8.0 ng/l). Group C – controls – 15 normally menstruating women (mean: age 37.1±9.0 years; FSH 6.2±1.0 IU/l; 17β-estradiol 144.8±117.1 ng/l).

Methods. Body mass and BMI were measured. Basic fasting plasma hGH, IGF-I, IGFBP-3, insulin, testosterone and LH as well as prolactin (PRL), FSH and estradiol were assessed by RIA kits.

Statistical analysis. Shapiro-Wilk test, Mann-Whitney u-test, Spearman rang correlation coefficient, stepwise multiple regression.

Results. Mean serum IGF-I level was the lowest ($p<0.005$) in group B (172.0±54.6 μg/l) and the highest in group C (273.6±109.0 μg/l). The mean plasma IGF-I level in group A was similar (NS) (208.3±66.5 μg/l) to that found in group B and lower ($p<0.02$) compared with that in group C. The lowest ($p<0.005$) serum IGFBP-3 level was found in group B (3.1±0.7 μg/l) compared to group C (4.4±0.3 μg/l). The mean plasma IGFBP-3 level (3.1±1.0 μg/l) in group A was lower than in group C ($p<0.005$) but identical as in group B. No statistically significant differences between groups were observed in mean hGH levels. Women in group A and C were younger ($p<0.001$) than those in group B. The lowest mean estradiol level was found in groups A and B. The highest was in group C ($p<0.001$). Mean plasma LH and FSH levels were higher ($p<0.001$) in groups A and B vs group C. In group C there were links between IGF-I and age ($r=-0.60$; $p=0.014$) The IGF-I/age relation disappeared in the groups A and B ($r_A=-0.26$; $r_B=0.10$; NS). The same regards IGFBP-3/ age link ($r_A=-0.44$, NS; $r_B=0,31$;NS). Estradiol level was related to hGH levels in group C ($r=-0.54$; $p<0.05$). In none of groups hGH/IGF-1 as well as IGFBP-3/hGH relations were found. Prolactin accounted for 69% of the variance in IGF-I level in the group B ($p=0.003$) and for 24% in group A (NS). Testosterone accounted for 88% ($p=0.004$) of the variance in IGF-I level in group B and IGFBP-3 was responsible for 86% ($p=0.038$) of the variance in IGF-I level in group C. Again IGFBP-3 was responsible for 47% ($p=0.023$) in group A and for 49% ($p=0.04$) in group B of the hGH variance.

Conclusions. 17β-estradiol may be as important contributor to insulin-like growth factor-I (IGF-I) plasma level as age in hypoestrogenic, hypogonadotropic women

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Key words: *IGF-I, IGFBP-3, hGH, estadiol, POF*

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Introduction

Having reached its peak activity during puberty, somatotropic axis function declines with ageing and therefore may be interpreted as a part of this process (27). Plasma levels of hGH, IGF-I and IGFBP-3 but not GHBP decrease with age until menopause (9,14,26-28,31). The pituitary pulsatile hGH secretion is influenced not only by circulating IGF-I levels through a negative feedback mechanism, but also by the hormonal milieu (sex steroids and corticosteroids) which participates in modulating hGH and IGF-I synthesis and secretion (5,11). The ovary is a site of hGH reception and action where it can potentiate steroidogenesis and gametogenesis by both increase in hepatic IGF-I synthesis and by acting directly on hGH receptors localised in the granulosa cells as well as in the corpus luteum (24). Growth hormone also amplifies IGF-I induced estradiol production by granulosa cells acting as a cogonadotropin (29,30).

A number of experiments indicate that sex steroids exert either stimulatory or inhibitory action on somatotropic axis (6). These effects are due to either amplifying action of estradiol on both neuroendocrinological regulation of pulsatile GH release and hepatic GH receptor expression or direct effect of estradiol on IGF-I plasma and tissue levels (7,13,16,17). Moreover the fall in hGH and IGF-I levels with ageing are correlated to estradiol levels, which increases also the GH response to provocative stimuli (15). IGF-I secretion appears positively affected by endogenous estrogens but negatively by exogenous oral formulations, presumably by inhibition of hepatic synthesis (2,17,28). IGF-I has also been implicated as autocrine/ paracrine modulator of estradiol action (22).

Blake, Adel and Santoro suggest that ovarian function may be even a more important contributing factor to IGF-I plasma levels than age (4). Women with premature ovarian failure present with as low sex steroids levels as postmenopausal ones have, but chronologically they are roughly 10-20 years younger. Therefore they seem to serve a good clinical model to evaluate either age and/ or estradiol level impact on somatotropic axis function

The purpose of our study was to examine plasma hGH, IGF-1 and IGFBP-3 levels in women with premature ovarian failure compared to healthy normal controls and postmenopausal ones.

Patients

Group A consisted of 15 women with premature ovarian failure (mean: age 38.9±5.2 years, FSH 101.4 ± 29.0 IU/l; 17β-estradiol 22.5±14.6 ng/l). Group B and C were controls and consisted of 15 menopausal (B) women (mean: age 54.7±2.7 years; FSH 81.9±32.1 IU/l; 17β-estradiol 17.1± 8.0 ng/l) and finally group C embraces also 15 but normally menstruating women (mean: age 37.1±9.0 years; FSH 6.2±1.0 IU/l; 17β-estradiol 144.8±111.7 ng/l).

Methods

Each woman underwent clinical and gynaecological evaluation. Body mass as well as height was taken to calculate body mass index (BMI). Blood to obtain plasma was taken at the standard conditions prior to the initiation of hormonal replacement therapy in the group A and B and at the day 8-10 of menstrual cycle in the group C. Plasma was frozen and kept at -20^{o}C until hormonal evaluation. Serum hGH, IGF-I, IGFBP-3, insulin, testosterone and LH as well as prolactin (PRL), FSH and estradiol were assessed by RIA kits.

Statistical analysis

Due to lack of normal distribution of data (confirmed by W.Shapiro-Wilk test) nonparametric tests were used. To evaluate the significance of mean values differences Mann-Whitney U test was applied and mutual relations between parameters were estimated by means of Spearman rang correlation coefficient; p values of 0.05 or less were considered as significant. To elaborate the mathematical model of effects of independent variables the stepwise multiple regression was used.

Results

The mean age of women with premature ovarian failure (group A) (38.9±5.2 years) was significantly ($p<0.001$) lower than women after natural menopause (54.7±2.7 years) (group B). There were hardly any differences in mean age between group A and normally menstruating women (37.1±9.0 years) (group C). Obviously women in group C were younger ($p<0.001$) than postmenopausal women (group B) (table 1).

There were no significant differences in mean body mass but mean BMI was lower in women with premature ovarian failure (group A) compared to menopausal ones ($p=0.046$).

Mean plasma LH and FSH levels were higher ($p<0.001$) in both hypergonadotropic groups (A,B) compared to group C (63.4±19.2 IU/l; 49.3±19.8 IU/l vs 7.4±1.2 IU/l resp.) (101.4 ± 29.0 IU/l; 81.9 ± 32.1 IU/l vs 6.2±1.0 IU/l resp) Comparing gonadotropins' levels between groups A and B, LH and FSH were higher ($p<0.05$) in group A. No differences were found between groups in regard to mean prolactin plasma levels.

The lowest mean plasma estradiol level was found in postmenopausal women (17.1±8.0 ng/l) (group B) and the highest in normally menstru-

ating women (group C) (144.8±117.1 ng/l)(p<0.001) Hardly any difference (NS) in mean estradiol level was found between group A (22.5±14.6 ng/l) and B, although that was much (p<0.001) lower than in group C (table 1)

Mean serum IGF-I level was the lowest (p<0.001) in postmenopausal women (172.0±54.6 µg/l) and the highest in normally menstruating ones (273.6±109.0 µg/l). The mean plasma IGF-I level in women with premature ovarian failure (group A) was nearly similar (NS) (208.3±66.5 µg/l) to that found in postmenopausal group and much lower (p=0.039) compared to that found in the group C (table 2).

No statistically significant differences between groups were observed in regard to mean hGH levels although there was a tendency (NS) to decline hGH level with age and estradiol level (table 2).

The lowest (p<0.005) serum IGFBP-3 level was found in postmenopausal group B (3.1±0.7 µg/l) compared to group C (4.4±0.3 µg/l). The mean plasma IGFBP-3 level (3.1±1.0 µg/l) in group A was also lower than in group C (p<0.01) but showed no difference in regard to group B.

The highest (p<0.05) mean, basic fasting insulin level was observed in group C (normally menstruating women) (19.4±7.7 IU/l). There was hardly any difference in mean plasma insulin level between groups A and B (table 2).

No difference in mean plasma testosterone level was found between groups (table 2).

In 15 normally menstruating women (group C) there was age related IGF-I level decrease (r=-0.60; p=0.014). A similar but non-significant (p=0.074) tendency was observed in regard to IGFBP-3. The IGF-I/age relation disappeared in both hypoestrogenic groups (A, B) (r_A=-0.23; r_B=0.17; NS). IGF-I serum level relations to IGFBP-3 level did not reach the level of significance in any of the groups. Neither in group C nor in the groups A or B statisti-

Table 1. *The clinical characteristics of premature ovarian failure (group A) and postmenopausal (group B) patients as well as normally menstruating women (group C).*

Tabela 1. *Charakterystyka kliniczna pacjentek z przedwczesnym wygasaniem czynności hormonalnej gonad (grupa A), pacjentek pomenopauzalnych (grupa B) oraz grupy kontrolnej prawidłowo miesiączkujących kobiet (grupa C)*

Group Parameter	A n=15	B n=15	C n=15	p.
Age (years) Range	38.9 ± 5.2 (27 - 46)	54.7 ± 2.7 (49 - 59)	37.1 ± 9.0 (18 – 49)	A/C<0.001; B/C<0.001; A/C=NS
Body mass (kg) (range)	63.8 ± 12.5 (46 – 91)	65.9 ± 10.3 (44 – 91)	68.9 ± 13.7 (48 – 95)	NS
BMI (range)	23.8 ± 4.8 (17.6 - 36.4)	25.7 ± 3.2 (17.6 - 31.6)	25.8 ± 4.3 (19.5 - 34.1)	A/B<0.05; B/C; A/C=NS
LH (IU/l) (range)	63.4 ± 19.2 (43 - 112.5)	49.3 ± 19.8 (24.6 – 89.9)	7.4 ± 1.2 (5.3 - 9.6)	A/C<0.001; B/C<0.001; A/B=0.025
FSH (IU/l) (range)	101.4 ± 29.0 (64.9 - 150)	81.9 ± 32.1 (46.1 – 143.5)	6.2 ± 1.0 (5 - 8)	A/C<0.001; B/C<0.001; A/B=0.04
PRL (µg/l) (range)	9.7 ± 5.1 (4.4 - 22.1)	9.5 ± 5.2 (2.8 – 21.3)	13.6 ± 7.2 (4.6 - 27)	NS
Estradiol (ng/l) (range)	22.5 ± 15.8 (3.3 - 43.7)	17.1 ± 8.0 (3.6 – 31.1)	144.8 ± 111.7 (55-400)	A/C<0.001; B/C<0.001; A/B=NS

Table 2. *The somatotropic axis characteristics and mean insulin as well as testosterone levels in premature ovarian failure (group A) and postmenopausal (group B) patients as well as normally menstruating women (control group C).*

Tabela 2. *Stężenia w surowicy hormonów osi somatotropowej oraz insuliny i testosteronu u pacjentek z przedwczesnym wygasaniem czynności hormonalnej gonad (grupa A), u pacjentek pomenopauzalnych (grupa B) oraz w grupie kontrolnej prawidłowo miesiączkujących kobiet (grupa C)*

Group parameter	A n=15	B n=15	C n=15	p.
IGF-I (µg/l) (range)	208.3 ± 66.5 (125.8 – 367.3)	172.0 ± 54.6 (83.8 - 282.9)	273.6 ± 109.0 (142.8 – 505.8)	A/C=0.033; B/C<0.001; A/B=NS
hGH (µg/l) (range)	3.1 ± 3.9 (0.2 - 11.6)	1.7 ± 1.6 (0.3 - 6.2)	5.0 ± 5.9 (0.6 - 19.0)	NS
IGFBP-3 (µg/l) (range)	3.1 ± 1.0 (1.4- 4.4)	3.1 ± 0.7 (2.3 - 4.5)	4.4 ± 0.3 (1.4- 5.7)	A/C<0.01; B/C<0.02; A/B=NS
insulin (IU/l) (range)	12.9 ± 9.9 (3.6 – 37.8)	11.3 ± 5.5 (4.8 - 25.6)	19.4 ± 7.7 (6.5 – 29.7)	A/C=0.026; B/C<0.005; A/B=NS
testosterone (µg/l) (range)	0.4 ± 0.24 (0.2 - 0.8)	0.47 ± 0.18 (0.2 - 0.7)	0.41 ± 0.22 (0.2 - 0.6)	NS

cally significant correlation between hGH and IGF-I was found (r_A=-0.05; NS; r_B=-0,11; NS, r_C=0.12;NS).

In the control group C a statistically significant, reverse relation between hGH and estradiol levels was found (r=-0.68; p=0.008). The statistical significance of this relation disappeared in the groups A and B (r_A=-0.05; NS; r_B=0,04; NS). The IGF-I/estradiol correlation, in turn was observed in none of groups. (r_A=0.04; NS; r_B=0,03; NS, r_C=-0.11;NS).

The correlation between hGH and FSH was statistically significant in group A (r=0.54; p=0.037) and practically vanished in other groups (r_A=-0.14; NS; r_B=0,19; NS).

The well known relations between serum basic fasting insulin levels and both body mass and BMI were statistically significant only in control group (r=0.62; p<0.02, r=0.76; p<0.002, resp.). Neither in postmenopausal nor in POF groups both mentioned correlations were significant (r coefficient ranging from 0.12 to 0.2; NS, resp.).

In postmenopausal women there was statistically significant reverse relation between body mass and LH (r=-0.54; p=0.021) as well as between FSH and BMI (r=-0.55; p=0.018). In POF group these relations were still inverse yet insignificant (r=-0,1; NS, r=-0.43; NS, resp.). The relations in control group kept being insignificant but became positive ones (r=0.22; NS, r=0.42;NS, resp.).

In the group A plasma testosterone level was linked inversely to both FSH and estradiol levels (r=-0.60 and r=-0.73; p<0.05 resp.) and directly to prolactin plasma level r=0.70; p=0.024). None of such relations were found in other investigated groups.

The stepwise multiple regression revealed that prolactin accounted for 69% of the variance in IGF-I level in the group B (p=0.003) and for 24% in group A (NS). Testosterone accounted for 88% (p=0.004) of the variance in IGF-I level in group B and IGFBP-3 was responsible for 86% (p=0.038) of the variance in IGF-I level in group C. Again IGFBP-3 was responsible for 47% (p=0.023) in group A and for 49% (p=0.04) in group B of the hGH variance. In the group C none of the evaluated parameters significantly accounted for hGH variance.

Discussion

Our results showed that mean plasma IGF-I level in hypoestrogenic, hypergonadotropic women (groups A and B) is lower than in normoestrogenic controls and nearly equal between groups with low plasma estradiol, despite the 16 year difference in their mean age. The similar tendency regarded mean plasma hGH levels although due to wide standard deviations the differences were insignificant. These wide deviations could have resulted from method of blood collecting. Plasma basic hGH level was assessed in single, morning blood sample. The same explanation regards the lack of significant correlation between hGH and IGF-I plasma levels. Mean plasma IGFBP-3 level was again the lowest in postmenopausal women. However there were significant differences in mean IGFBP-3 levels between groups of younger women (POF and control ones). Well known, statistically significant relations between plasma IGF-I, hGH, IGFBP-3 levels and age followed the above mentioned findings and also vanished in women with low estradiol level. Human growth hormone level link to plasma estradiol also disappeared in hypoestrogenic, hypergonadotropic women. The findings imply that not only age but also hormonal ovarian activity influences the circulating levels of IGF-I. Blake, Adel and Santoro suggest that ovarian function may be even a more important contributing factor to IGF-I plasma levels than age (4). In 20 women studied by them, the elevated in the older group (age range 42-47 years) estradiol level exerted a stimulatory influence on somatotropic axis preventing the expected age related decline (4). Apparently this study does not go along with numerous reports on age related decline in mean serum hGH and IGF-I. The difference is based on methodology of these studies. They not only compare women in their 20's with those in their 60-80's but also disregard the estradiol level. Moreover the serum IGF-I level in postmenopausal women remains low, stable and with no relation to estradiol level (1). In our groups the inverse IGF-I/age relation was statistically significant only in women with normal estradiol level.

Fonseca et al. found a direct link between hGH and both IGF-I (r=0.9) and estradiol (r=0.74) (11). Helle et al. and Massa et al. also reported a direct positive relation between plasma IGF-I and estradiol levels (r=0.69; p<0.002) (12,18). On the contrary Elias et al. found no relation between IGF-I and estradiol plasma levels in POF women even during treatment with conjugated estrogens (8). In our study the hGH/estradiol link was found only in normally menstruating women. Although the IGF-I/estradiol correlation was not significant in any of our groups but the highest correlation coefficient was observed again in normally menstruating controls. Long term treatment with GnRH analogues leading to hypoestrogenism causes a relative deficiency in circulating IGF-I level (10). The similar effect of diminished IGF-I liver synthesis is exerted by tamoxifen receptor blockade (21).

Oral and transdermal estrogens exert differing effects on somatotropic axis but neither form completely reverses the known age related reduction in spontaneous or GHRH induced increase in both hGH and IGF-I (3). Oral administration of estrogenes to postmenopausal women increases secretion of hGH, exercise and GHRH induced hGH response, but these effects are secondary to IGF-I decrease. The dissociation of hGH/IGF-I axis

is likely to arise from oral estrogen first passage, hepatocellular effect on IGF-I (15). Transdermal 17β-estradiol administration do not affect liver IGF-I production to such extend and appear to decrease hGH (4). There are reports suggesting even an increase in both total and free IGF-I during transdermal 17β-estradiol application (19,25).

However Hartmann et al. found no difference in mean plasma IGF-I level between women with premature ovarian failure and normally menstruating controls. Mean IGF-I was lower in postmenopausal women compared to both mentioned above groups. This discrepancy with our results could be explained by younger age of their patients (age range 19-35 years) compared to our POF group (age range 27-44 years) (32).

A stepwise multiple regression analysis, applied in our study, showed that IGFBP-3 accounted for nearly 50% of the variance in hGH level in hypoestrogenic, hypergonadotropic groups. Prolactin, testosterone and again IGFBP-3 accounted for 24 to 88% of variance in the IGF-I plasma level in investigated groups.

Similar results of multiple regression analysis were obtained by Fisker et al. in growth hormone deficient females and males. In their study of 59 patients and 69 controls IGFBP-3 was the significant predictor of IGF-I level both in patients and controls, while prolactin and gender predicted the IGF-I levels only in patients (33). In our earlier studies we showed a prolactin-induced increase in IGF-I local secretion by progesterone receptor expressing non-malignant mammary tissue (35). High mean plasma IGF-I level was related to plasma fasting insulin and androgenism in women with polycystic ovary syndrome, what may suggest the link between IGF-I and testosterone (36).

A well known insulin resistance in postmenopausal women may explain the disappearance of significant BMI/insulin relation in group B and the highest mean basic plasma insulin level in group C is a result of the highest body mass and BMI in the group. In young hypoestrogenic women with functional hypothalamic amenorrhoea the serum IGFBP-1 level was increased that led to decrease in biologically active IGF-I level (34).

Santoro et al. found a higher mean LH and FSH level in women with premature ovarian failure compared to menopausal ones although according to Petraglia, mean inhibin A and B levels did not differ between POF women and menopausal ones (20,23). In our group A (POF) mean gonadotropin levels were also higher than those in menopausal women. This phenomenon could be explained by age related decrease in gonatropin secretion which may be of hypothalamo-hypophyseal origin (23).

Conclusion

17β-estradiol may be as important contributor to insulin-like growth factor-I (IGF-I) plasma level as age in hypoestrogenic, hypogonadotropic women

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