

Bimodal influence of plasma estradiol on relation between insulin-like growth factor-I (IGF-I) and estradiol in women

Tomasz MILEWICZ¹, Józef KRZYSIEK¹, Iwona ROGATKO², Krystyna SZTEFKO², Ewa STOCHMAL³, Robert JACH⁴, Danuta GALICKA-LATAŁA⁵, Stanisław RADOWICKI⁴, Hubert HURAS⁴, Małgorzata RADOŃ-POKRACKA⁴

¹ Department of Gynecological Endocrinology, Jagiellonian University Medical College, Cracow, Poland

² Department of Clinical Biochemistry, University Children Hospital, Cracow, Poland

³ Department of Human Developmental Biology, Jagiellonian University Medical College, Cracow, Poland

⁴ Department of Gynecological Oncology Jagiellonian University Medical College, Cracow, Poland

⁵ Department of Metabolic Diseases Jagiellonian University Medical College, Cracow, Poland

⁶ Department of Gynecological Endocrinology, Medical University of Warsaw, Warsaw, Poland

Correspondence to: Tomasz Milewicz MD., PhD.
Department of Gynecological Endocrinology
Jagiellonian University Medical College
23 Kopernika St., 31-501 Cracow, Poland.
E-MAIL: milewicz@interia.eu

Submitted: 2011-08-17 *Accepted:* 2011-08-17 *Published online:* 2012-01-15

Key words: insulin-like growth factor-I; estradiol; hormones; plasma

Neuroendocrinol Lett 2011; **32**(6):857–864 PMID: 22286784 NEL320611A13 © 2011 Neuroendocrinology Letters • www.nel.edu

Abstract

OBJECTIVE: To compare the influence of low and normal endogenous estradiol concentration on circulating hGH, IGF-I and IGFBP-3 levels as well as on mutual correlations of these parameters. **PATIENTS:** 45 women (age 30.7 ± 9.0 years, BMI 25.7 ± 8.0) divided into group A – 15 hypoestrogenic women and group B – 30 normoestrogenic controls. Neither of the women was menopausal nor hyperprolactinemic. **METHODS:** Blood sample was taken at the standard conditions prior to the initiation of hormonal supplementation therapy in group A and at the day 3–5 of menstrual cycle in group B. Serum hGH, IGF-I, IGFBP-3, insulin, testosterone, sex hormone binding globulin (SHBG) dihydroepiandrosterone sulphate (DHEAS) and LH as well as prolactin (PRL), FSH and estradiol levels were measured by standard RIA kits. **RESULTS:** Mean IGF-1, LH, FSH, testosterone and estradiol and PRL plasma levels were lower in group A compared to group B. There were no significant differences in mean SHBG, insulin and DHEAS levels. There were also no differences in mean: age, body mass, BMI as well as percentage of each BMI range between groups. Regardless the estradiol level the IGF-I/age link was found in both groups. A IGF-I/IGFBP-3 relation was found in both groups. IGF-I/estradiol link was seen only in group A. In group B hGH/SHBG link was found, in group A this relation was indirect. A link between hGH and testosterone levels was found only in group B. SHBG was related in group B to IGFBP-3, testosterone and to DHEAS. Insulin/IGFBP-3 link was seen in group B. The stepwise multiple regression revealed DHEAS and LH as predictors of IGF-I level in group A, while in group B none of the parameters predicted IGF-I level. The results of the same analysis in case of hGH are as follows: in group A hGH level was predicted by estradiol and SHBG. In group B none of factors predicted hGH levels. **CONCLUSION:** Estradiol plasma level is correlated to circulating IGF-I, albeit the relation seems to be biphasic.

INTRODUCTION

The somatotropic axis is affected by hormonal milieu (Blake *et al.* 1997). A number of experiments indicate that sex steroids exert either stimulatory or inhibitory action on the somatotropic axis (Caufriez 1997). Evidence that estradiol is involved in the regulation of human Growth Hormone (hGH) – Insulin-like Growth Factor-I (IGF-I) – Insulin-like Growth Factor Binding Protein-3 (IGFBP-3) system is provided not only by the observation that mean hGH level is higher in women than men and that the fall in hGH as well as IGF-I levels with aging is correlated to estradiol level but also by the fact that estradiol has a direct effect on IGF-I synthesis and release independent of hGH. Estradiol plays also a permissive role in pituitary hGH release (Ho *et al.* 1996; Kirchengast *et al.* 1996; Wilson 1997). The latter role of estradiol is based on its influence on both pituitary increase in IGF-I mRNA as well as on regulation of pituitary somatostatin concentration (Hennessey *et al.* 1994; Michels *et al.* 1993).

Ovary in turn, is a site of hGH reception and action, where it can potentiate steroidogenesis and gametogenesis either directly or via endocrine action (Hesse *et al.* 1994). Growth hormone acts both by its receptors localized on granulosa cells as well as corpus luteum and indirectly by augmentation of hepatic IGF-I production (Sharara & Giudice 1997). IGF-I amplifies hGH induced estradiol production by granulosa cells, acting synergistically as gonadotropins (Xu *et al.* 1997; Yoshimura *et al.* 1996). IGF-I is also regarded as auto/paracrine mediator of estradiol action (Rajkumar *et al.* 1996). Ovarian function is even regarded a more contributing factor for circulating IGF-I levels than aging (Blake *et al.* 1997).

Estradiol exerts different effects on serum IGF-I levels depending on its origin, route of administration and dose (Blake *et al.* 1997). Therefore it seems interesting to compare the influence of low and normal endogenous estradiol concentration on circulating hGH, IGF-I and IGFBP-3 levels as well as on mutual correlations of these parameters.

MATERIAL AND METHODS

Patients

45 women (mean: age 30.7 ± 9.0 years, body mass 68.9 ± 22.3 kg, BMI 25.7 ± 8.0) were divided into 2 groups according to their estradiol level. Group A embraces 15 hypoestrogenic women (plasma estradiol level below $50 \mu\text{g/l}$) whereas group B consisted of 30 normoestrogenic (plasma estradiol level over $50 \mu\text{g/l}$) controls. Neither of the women was menopausal nor hyperprolactinemic. The women in the study were not on any form of contraception. The hormonal contraception wash-out period was 6 months.

Methods

Each women underwent clinical and gynecological 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 supplementation therapy in group A and at the day 3–5 of menstrual cycle in group B. Plasma was frozen and kept at -70°C until hormonal evaluation. Plasma hGH, IGF-I, IGFBP-3, insulin, testosterone, sex hormone binding globulin (SHBG) dihydroepiandrosterone sulphate (DHEAS) and LH as well as prolactin (PRL), FSH and estradiol levels were measured by standard RIA kits.

Statistical analysis

Descriptive statistics was applied first. Median and interquartile (IQR) were calculated for all variables studied. For comparison between groups the Wilcoxon-rank test was used. The mutual relations between parameters were evaluated by means of Pearson linear correlation coefficients and stepwise multiple regression: *p*-values of 0.05 or less were considered as significant.

RESULTS

There were hardly any differences in means of age, body mass, BMI as well as percentages of each BMI range between groups (Table 1). Mean LH and FSH levels were significantly lower in hypoestrogenic group A than in controls (group B) (2.9 ± 5.1 vs 10.4 ± 8.4 IU/l; $p < 0.005$; 2.7 ± 2.3 vs 6.2 ± 1.9 IU/l $p < 0.001$ resp.). Mean plasma prolactin as well as estradiol levels were also lower in group A (6.1 ± 4.6 vs $15.3 \pm 7.0 \mu\text{g/l}$; 23.5 ± 15.2 vs 118.9 ± 68.7 g/l; $p < 0.001$; resp.) (Table 1).

Mean IGF-1 level was lower in hypoestrogenic women (group A) compared to group B (234.9 ± 156.2 vs $323.6 \pm 127.3 \mu\text{g/l}$). There were also no statistically significant differences either in mean SHBG, insulin, IGFBP-3, hGH or DHEAS levels (Table 2). Mean testosterone level was lower in group A compared to group B (0.42 ± 0.26 vs $0.56 \pm 0.18 \mu\text{g/l}$; $p < 0.05$) (Table 2).

Regardless the estradiol level the IGF-I/age correlation was found in both groups ($r_A = -0.57$; $p < 0.02$; $r_B = -0.53$; $p < 0.005$) (Figure 1). Age/DHEAS relation was observed also in both groups ($r_A = -0.74$; $p < 0.002$; $r_B = -0.38$; $p < 0.05$). Age dependent increase of the body mass and BMI could be observed only in group A (hypoestrogenic women) ($r_A = 0.6$; $p < 0.02$; $r_B = 0.13$; NS; $r_A = 0.60$; $p < 0.02$; $r_B = 0.21$; NS; resp.). Also in group A an indirect correlation between age and plasma SHBG ($r = -0.54$; $p < 0.05$) could be observed which was not found in group B ($r = -0.05$; NS), whereas in normoestrogenic controls (group B), there was an FSH/age link ($r = 0.42$; $p < 0.05$) which was not found in group A ($r = -0.20$; NS).

In normoestrogenic women (group B) the body mass correlated with plasma fasting levels of: insulin ($r = 0.76$; $p < 0.001$), SHBG ($r = -0.51$; $p < 0.005$), IGFBP-3 ($r = 0.51$;

$p < 0.005$) as well as testosterone ($r = 0.67$; $p < 0.001$). These correlations were either insignificant or hardly present in group A [$r = 0.44$; NS; $r = -0.15$; NS; $r = -0.05$; NS; $r = -0.05$; NS resp.). The above mentioned relations were in group B mimicked by BMI relations with insulin ($r = 0.73$; $p < 0.001$), IGFBP-3 ($r = 0.49$; $p < 0.01$) and testosterone ($r = 0.68$; $p < 0.001$) levels. The correlations were also either insignificant or hardly present in group A [$r = 0.51$; NS; $r = -0.09$; NS; $r = -0.07$; NS, resp.). The increase in serum insulin level followed the increase in BMI in both groups ($r_A = 0.52$; $p < 0.05$; $r_B = 0.73$; $p < 0.001$).

A relation between IGF-I and its main binding protein (IGFBP-3) was found in both groups (i.e. despite the estradiol level) ($r_A = 0.84$; $p < 0.001$; $r_B = 0.55$; $p < 0.002$) (Figure 2). IGF-I level was associated with plasma estradiol level only in hypoestrogenic women (group A) ($r = 0.54$; $p < 0.05$; vs $r_B = 0.03$; NS) (Figure 3).

In the normoestrogenic control group hGH was related to SHBG ($r = 0.38$; $p < 0.05$) but in hypoestrogenic group this relation was an indirect one ($r = -0.64$;

$p < 0.02$). Moreover in the controls (group B) there was also a correlation between plasma hGH and testosterone levels ($r = -0.56$; $p < 0.002$) which was not only indirect in group A but also became insignificant ($r = 0.25$; NS). The hGH/estradiol relation was not statistically significant in both groups, however the in group A it was indirect ($r = -0.44$; NS) and in group B it was direct ($r = 0.301$; NS).

In both groups there was an indirect relation between SHBG and insulin levels ($r_A = -0.57$; $p < 0.05$; $r_B = -0.47$; $p < 0.01$). SHBG was in group B also indirectly related to IGFBP-3 ($r = -0.47$; $p < 0.01$), testosterone ($r = -0.48$; $p < 0.02$) and to DHEAS ($r = -0.58$; $p < 0.001$).

Basic fasting insulin level in group B was in turn related to IGFBP-3 ($r = 0.48$; $p < 0.01$), to testosterone ($r = 0.4$; $p < 0.05$) and to DHEAS ($r = 0.58$; $p < 0.001$) whereas in group A indirectly to FSH ($r = -0.57$; $p < 0.05$). In group A DHEAS was related to sex steroids estradiol ($r = 0.52$; $p < 0.02$) and testosterone ($r = 0.59$; $p < 0.02$). The correlation coefficients in both group are given in Table 3 and Table 4.

Tab. 1. Clinical characteristics of hypoestrogenic women (group A) and normoestrogenic controls (group B).

Group Parameter	A (n=15)	B (n=30)	p-value
Age (years)	30.2 ± 9.4	31.1 ± 8.6	NS
Body mass (kg)	66.1 ± 21.1	71.6 ± 23.5	NS
BMI	24.9 ± 7.8	26.5 ± 8.2	NS
BMI < 20	20 %	16.7 %	NS
20 < BMI < 25	40 %	50 %	NS
BMI > 25	40 %	33.3 %	NS
LH (IU/l)	2.9 ± 5.1	10.4 ± 8.4	<0.005
FSH (IU/l)	2.7 ± 2.3	6.2 ± 1.9	<0.001
PRL (µg/l)	6.1 ± 4.6	15.3 ± 7.0	<0.001
Estradiol (ng/l)	23.5 ± 15.2	118.9 ± 68.7	<0.001

Tab. 2. Somatotrophic axis and other hormonal parameters in hypoestrogenic women (group A) and normoestrogenic controls (group B).

Group Parameter	A (n=15)	B (n=30)	p-value
IGF-I (µg/l)	234.9 ± 156.2	323.6 ± 127.3	<0.05
hGH (IU/l)	4.5 ± 4.9	6.4 ± 8.8	NS
IGFBP-3 (µg/l)	3.9 ± 1.3	4.3 ± 2.7	NS
SHBG (µg/l)	49.0 32.5	57.0 ± 39.6	NS
Insulin (IU/l)	24.8 ± 20.7	26.2 ± 24.1	NS
DHEAS (µg/l)	192.9 ± 126.7	218.3 88.9	NS
testosterone (µg/l)	0.42 0.26	0.56 ± 0.18	<0.05

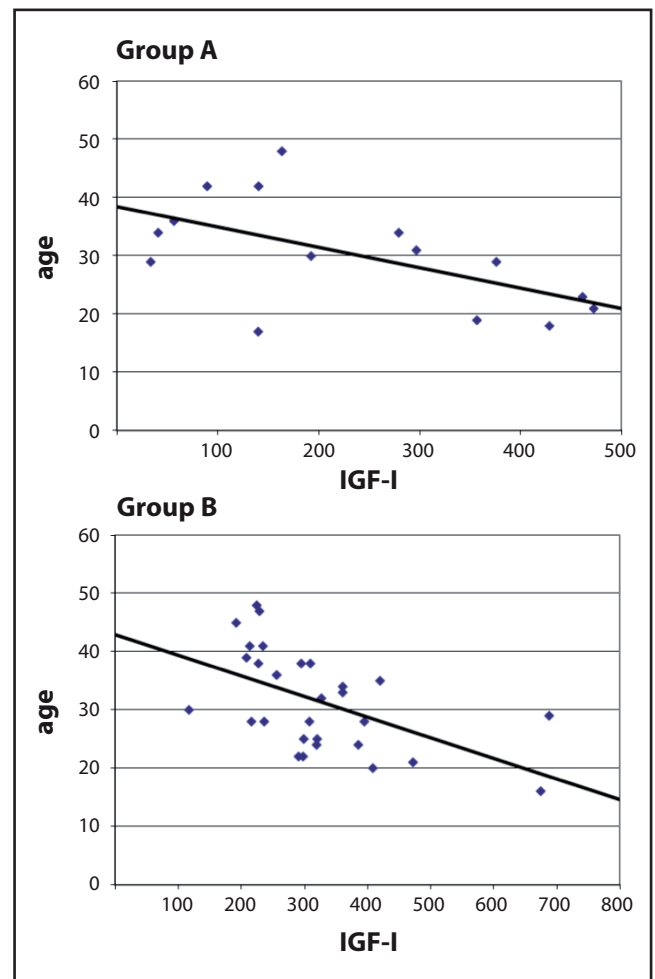


Fig. 1. The relation between IGF-I plasma concentration and age of patients with low estradiol group (group A) and in normoestrogenic group B.

Tab. 3. Correlation between clinical parameters, plasma levels of sex-steroids, gonadotropins, and the measured parameters of IGF-system in hypoestrogenic women (group A) (univariate analysis, R-values).

	Age (yrs)	Body mass (kg)	BMI	IGF	hGH	Insul	Prol	LH	FSH	SHBG	E2	BP3	TST	DHEAS
Age (yrs)	1.000	0.599*	0.606*	-0.575*	0.156	-0.060	0.150	-0.409	-0.195	-0.536	-0.477	-0.450	-0.251	-0.737*
Body mass (kg)	0.599*	1.000	0.991*	-0.012	0.288	0.447	0.364	0.199	0.265	-0.153	0.009	-0.059	-0.051	0.297
BMI	0.606*	0.991	1.000	-0.027	0.250	0.517*	0.336	0.214	0.279	-0.170	0.044	-0.087	-0.073	0.232
IGF	-0.575*	-0.012	-0.027	1.000	-0.096	0.266	0.267	0.398	0.365	0.227	0.541*	0.840*	0.507	0.955*
hGH	0.156	0.288	0.250	-0.096	1.000	0.186	0.349	-0.013	-0.091	-0.641	-0.440	-0.448	0.250	-0.414
Insul	-0.060	0.447	0.517*	0.266	0.186	1.000	0.282	0.505	0.628*	-0.569	0.447	0.193	-0.113	0.222
Prol	0.150	0.364	0.336	0.267	0.349	0.282	1.000	0.049	-0.056	-0.370	0.064	0.631*	0.384	0.791*
LH	-0.409	0.199	0.214	0.398	-0.013	0.505	0.049	1.000	0.735	-0.665	0.413	-0.076	-0.285	0.120
FSH	-0.195	0.265	0.279	0.365	-0.091	0.628*	-0.056	0.735*	1.000	-0.626	0.295	0.147	-0.454	0.013
SHBG	-0.536*	-0.153	-0.170	0.227	-0.641*	-0.569*	-0.370	-0.665*	-0.626*	1.000	0.732*	0.029	-0.192	0.429
E2	-0.477	0.009	0.044	0.541*	-0.440	0.447	0.064	0.413	0.295	0.732	1.000	0.130	0.239	0.525*
BP3	-0.450	-0.059	-0.087	0.840*	-0.448	0.193	0.631*	-0.076	0.147	0.029	0.130	1.000	0.458	0.820*
TST	-0.251	-0.051	-0.073	0.507	0.250	-0.113	0.384	-0.285	-0.454	-0.192	0.239	0.458	1.000	0.587*
DHEAS	-0.737*	0.297	0.232	0.955*	-0.414	0.222	0.791*	0.120	0.013	0.429	0.525*	0.820*	0.587*	1.000

* $p < 0.05$ **Tab. 4.** Correlation between clinical parameters, plasma levels of sex-steroids, gonadotropins, and the measured parameters of IGF-system in normoestrogenic women (group B) (univariate analysis, R-values).

	Age (yrs)	Body mass (kg)	BMI	IGF	hGH	Insul	Prol	LH	FSH	SHBG	E2	BP3	TST	DHEAS
Age (yrs)	1.000													
Body mass (kg)	0.126	1.000												
BMI	0.215	0.982*	1.000											
IGF	-0.533*	0.252	0.201	1.000										
hGH	0.037	-0.169	-0.216	-0.096	1.000									
Insul	-0.008	0.764*	0.731*	0.044	-0.289	1.000								
Prol	0.151	-0.042	-0.081	-0.273	0.095	0.066	1.000							
LH	-0.098	-0.272	-0.336	-0.085	-0.068	-0.310	0.345	1.000						
FSH	0.420*	-0.253	-0.214	-0.266	0.218	-0.360	0.231	0.379*	1.000					
SHBG	-0.049	-0.513*	-0.419*	-0.173	0.382*	-0.467*	0.231	-0.144	0.005	1.000				
E2	-0.065	-0.144	-0.178	0.029	0.301	-0.099	0.245	0.028	-0.102	0.053	1.000			
BP3	-0.150	0.514*	0.488*	0.551*	0.084	0.481*	-0.390*	-0.302	-0.041	-0.469*	-0.131	1.000		
TST	0.085	0.672*	0.680*	0.220	-0.561*	0.397*	-0.272	0.103	-0.033	-0.484*	-0.311	0.197	1.000	
DHEAS	-0.377*	0.274	0.261	0.277	-0.325	0.576*	0.080	0.166	0.086	-0.582*	-0.265	0.337	0.534*	1

* $p < 0.05$

The stepwise multiple regression revealed DHEAS ($\beta=0.96$; $p < 0.02$) and LH ($\beta=0.30$; $p < 0.02$) as significant predictors of the circulating IGF-I level in group A, while in group B none of the evaluated parameters significantly predicted IGF-I level.

The same analysis was performed to determine correlations between hGH and other factors. The results showed that in group A hGH level was significantly predicted by estradiol ($\beta=-0.75$; $p < 0.05$) and SHBG

($\beta=-0.68$; $p < 0.05$). In group B none of assessed factors significantly predicted hGH circulating levels.

DISCUSSION

Our results suggest the presence of direct, statistically significant IGF-I/estradiol relation in women with low plasma estradiol level. Not only was the relation observed solely in hypoestrogenic women but also

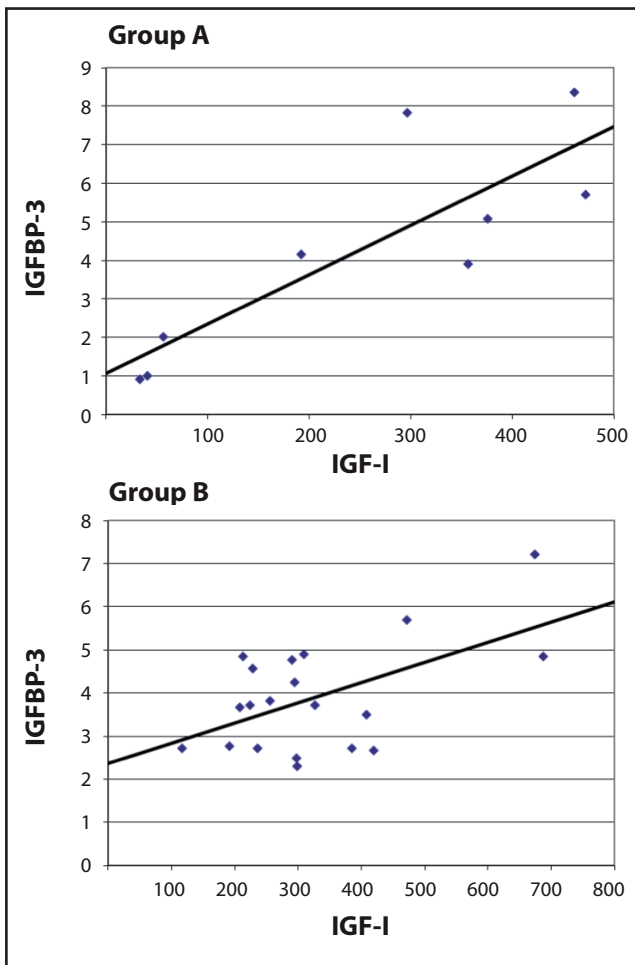


Fig. 2. The relation between IGF-I and IGFBP-3 plasma concentrations in patients with low estradiol serum level (group A) and with normal estradiol level (group B).

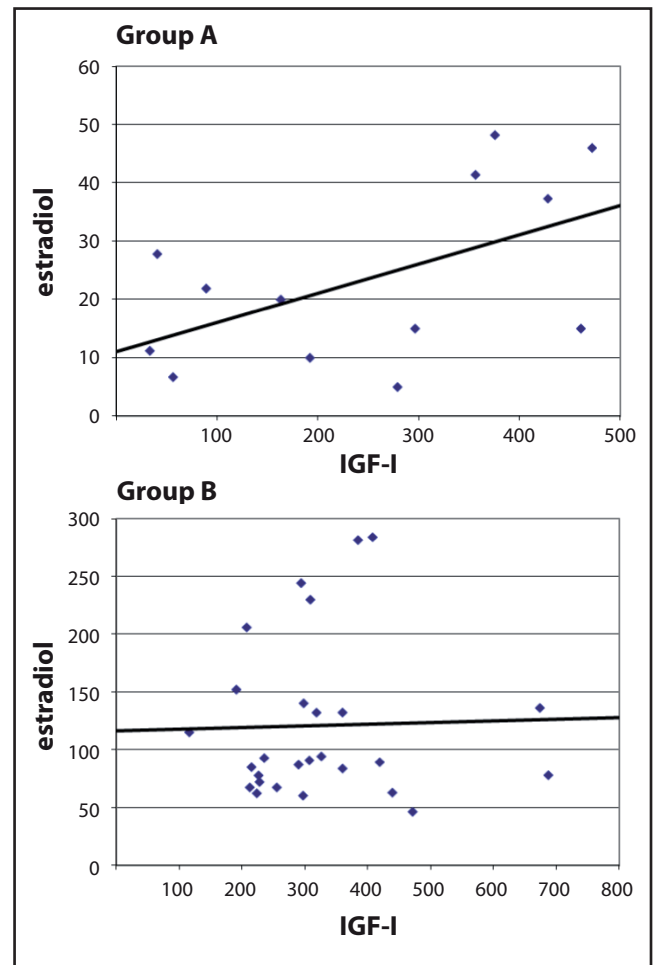


Fig. 3. The relation between IGF-I and estradiol plasma concentrations in low serum estradiol patients (group A) and normal estradiol level patients (group B).

plasma IGF-I and hGH levels were lower in this group despite the similar mean age and BMI of both normo- and hypoestrogenic women. Moreover multiple stepwise regression analysis revealed, that in women with plasma estradiol level below $50\mu\text{g/l}$, the hGH plasma level could have been significantly predicted by serum estradiol level and sex hormone binding globulin. Our findings are in accordance with results of Blake *et al.* (1997) who suggest that ovarian hormonal function is a factor contributing even more to the plasma level of IGF-I than chronological ageing (Blake *et al.* 1997). Massa *et al.* (1993) observed a direct correlation between the levels of estradiol and IGF-I ($r=0.69$; $p<0.01$) in spontaneously menstruating women and this coefficient was similar to that obtained in our study ($r=0.54$; $p<0.05$) (Massa *et al.* 1993). Helle *et al.* (1998) observed small but significant difference in plasma levels of IGF-I ($p<0.01$) measured by RIA between the three phases of the menstrual cycle. The highest plasma levels of IGF-I were seen during the follicular phase. They also found a correlation between plasma levels of IGF-I and estradiol but not progesterone at different times during the men-

strual cycle (Helle *et al.* 1998). Hesse *et al.* (1998) also found a direct IGF-I/estradiol correlation in pubertal girls (Hesse *et al.* 1994). The same investigators suggested a direct stimulatory effect of DHEAS on IGF-I production as well as indirect augmentation of IGF-I synthesis by DHEAS stimulation of sex steroids production. Brick *et al.* attributed 49% of hGH and IGF-I variability to free testosterone and 7% to estradiol in a study done on 32 women whose BMI varied from anorectic to obese (Brick *et al.* 2010). Lapauw *et al.* (2009) observed a decrease in IGF-I concentration in men whose estradiol and testosterone levels were reduced by aromatase inhibition. On the contrary postmenopausal women over 55 years of age lacked both the IGF-I/estradiol as well as IGF-I/age relationships (Wuster *et al.* 1993). However the plasma estradiol level in such postmenopausal women without hormone replacement therapy is even lower than found in pubertal girls. In our earlier report we observed no correlation between IGF-I and estradiol in severely hypoestrogenic women with plasma estradiol level below $25\mu\text{g/l}$ (Milewicz *et al.* 2005). The levels of growth hormone and of course

estradiol vary across menstrual cycle (Faria *et al.* 1992). The presence of previously mentioned correlation between IGF-I/estradiol can explain IGF-I fluctuations during menstrual cycle (Helle *et al.* 1998; Van Dessel *et al.* 1996). Transdermal estradiol induction of increases in total and free IGF-I during hormone replacement therapy in perimenopausal women was reported by other investigators (Milewicz *et al.* 1999; Slowinska *et al.* 1992). Lebenthal *et al.* (2006) measured plasma IGF-I in 34 short peripubertal children (17 boys and 17 girls) aged 8–12.5 yr before and after sex hormone priming for GH stimulation testing. In girls, priming with estrogen led to a supraphysiological increase in estradiol levels (1313.8 ± 438.0 pmol/l) but had no effect on IGF-I (Lebenthal *et al.* 2006). Such a high estradiol level could have destroyed the link between estradiol and IGF-I or lasted too short and did not induce the IGF-I increase. The effect of estradiol supplementation on somatotrophic axis depends on route of administration and dose (Blake *et al.* 1997; Sonnet *et al.* 2007; Stefano *et al.* 2003). Oral estrogens increase basal and GH-RH stimulated GH secretion, but depress IGF-I, whereas transdermal estradiol administration is either irrelevant in this regard or even increases the IGF-I level (Slowinska *et al.* 1992; Kelly *et al.* 1993; Weissberger *et al.* 1991; Wolinska-Witord *et al.* 2000). Sex steroids exert priming effect on both hGH and IGF-I leading to augmentation of the IGF-I action by 45 to 80% (Itagane *et al.* 1991). In ovariectomized animals high dose estradiol supplementation caused the decline in plasma IGF-I level, whereas low dose one did not influence the somatotrophic axis or increase the IGF-I level (Kalu *et al.* 1994). Kanbur-Oksüz *et al.* (2004) conducted a cross-sectional study to investigate the relationships among IGF-1 axis and sex steroids during pubertal development in 205 healthy adolescents aged 9–17 years. In their study, estradiol levels of girls and testosterone levels of boys differed significantly between stages, and in both sexes, plasma IGF-1 levels and IGF-1/IGFBP-3 ratios were significantly correlated with sex steroid levels. Sex steroids which levels increased with pubertal development, caused a rise in IGF-I levels and IGF-1/IGFBP-3 ratios (Kanbur-Oksuz *et al.* 2004). Rosenfeld *et al.* (1998) suggests a biphasic effect of estradiol influence on growth, stimulatory in low doses, but inhibitory in high ones. Helle *et al.* (2002) studied the relation of IGF-I to sex steroids in 39 premenopausal and 114 postmenopausal women. These investigators found no correlation between estradiol and IGF-I in both pre- and postmenopausal women but they observed a link between estradiol and IGF-II in low estradiol postmenopausal group. However they were unable to show a statistically significant age/IGF-I correlation in any group, neither did they find any link between body mass and IGFBP-3, BMI, or IGFBP-3 in either of groups, whereas we were able to show an association in normoestrogenic controls. Helle *et al.* (2002) showed the IGF-I/IGFBP-3 link which was also showed in our study. They also

observed an indirect link link between IGFBP-3 and SHBG in the hypoestrogenic women. In our study there was no relationship in between IGFBP-3 and SHBG in the hypoestrogenic group but a significant indirect link in normoestrogenic controls could be seen. The reason for the discrepancies between our results and the data of Helle *et al.* (2002) can be explained by the differences in the age of examined women: our patients were at least 20 years younger. Furthermore, our hypoestrogenic group had also higher plasma testosterone level than the normoestrogenic controls. Helle *et al.* (2002) did not report the mean testosterone level in for either of their study groups.

Sex hormone binding globulin (SHBG) is of hepatic origin. Its synthesis is enhanced by estradiol and thyroid hormones and reduced by insulin and IGF-I (Nestler *et al.* 1991; Singh *et al.* 1990). As a result of body mass increase, SHBG level declines and the ratio of free estradiol to testosterone becomes higher. The diminished SHBG level is an independent risk factor for noninsulin-dependent diabetes mellitus (Haffner *et al.* 1993). In our study we observed an increase in body mass with ageing in hypoestrogenic women and a correlated decrease in SHBG level. In the same group of patients with low estradiol (group A) the mean SHBG plasma level tended to be lower. In our earlier studies we also observed the BMI/age relation in women with low estradiol level as well as the correlation between leptin and age and leptin and DHEAS (Krzysiek *et al.* 1998; Milewicz *et al.* 1999). Furthermore, our present results indicate the insulin induced decline of SHBG in groups examined ($rA = -0.57$; $p < 0.05$; $rB = -0.47$; $p < 0.01$). Taking into account the direct link between IGF-I and IGFBP-3 observed also in our study, the indirect relation between IGFBP-3 and SHBG that we observed indicates the involvement of IGF-I in regulation of hepatic SHBG synthesis.

The plasma levels of insulin and IGFBP-1 are correlated indirectly whereas direct correlations were found for insulin and IGF-I and for insulin and IGFBP-3 concentrations (Conover *et al.* 1992). A similar correlation (insulin/IGFBP-3) was observed in our study. Group A consisted of women with hypothalamo-hypophyseal insufficiency and that resulted in low gonadotropin, estradiol and testosterone levels. Insulin and IGF-I potentate the LH action on ovarian theca cell androgen production (Bergh *et al.* 1993). In polycystic ovary syndrome patients, the high IGF-I plasma level correlated with both plasma insulin and androgenism (Milewicz *et al.* 1998), which can explain the insulin/testosterone correlation observed in our study as well as LH influence on IGF-I level.

Concluding, low circulating levels of hGH, IGF-I can be observed in women with plasma estradiol level below $50 \mu\text{g/l}$. In women with both low estradiol level and low hGH/IGF-I axis activity, a link between plasma concentrations of estradiol and IGF-I was found, whereas in normoestrogenic women of similar age, with high

somatotropic activity such link could not be observed. Therefore estradiol influence on hGH/IGF-I axis seems biphasic.

Author Disclosure Statement

The authors stated that no competing financial interests exist. The authors have no conflict of interest to report.

REFERENCES

- Bergh C, Carlsson B, Olsson JH, Selleskog U, Hillensjö RA (1993). Regulation of androgen production in cultured human thecal cells by insulin-like growth factor I and insulin. *Fertil.Steril.* **59**: 323–331.
- Blake EJ, Adel T, Santoro N (1997). Relationships between insulin-like growth hormone factor-1 and estradiol in reproductive aging. *Fertil Steril.* **67**: 697–701.
- Brick DJ, Gerweck AV, Meenaghan E, Lawson EA, Misra M, Fazeli P, et al (2010). Determinants of IGF1 and GH across the weight spectrum: from anorexia nervosa to obesity. *Eur J Endocrinol.* **163**: 185–191.
- Caufriez A (1997). The pubertal spurt: effects of sex steroids on growth hormone and insulin-like growth factor I. *Eur J Obstet Gynecol Reprod Biol.* **71**: 215–217.
- Conover CA, Lee PDK, Kanaley JA, Clarkson JT, Jensen MD (1992). Insulin regulation of insulin-like growth factor binding protein-1 in obese and nonobese humans. *J Clin Endocrinol Metab.* **74**: 1355–1361.
- Faria ACS, Bekenstein LW, Booth RA Jr, Vaccaro VA, Asplin CM, Veldhuis JD, et al (1992). Pulsatile growth hormone release in normal women during the menstrual cycle. *Clin Endocrinol.* **36**: 591–596.
- Haffner SM, Valdez RA, Morales PA, Hazuda HP, Stern MP (1993). Decreased sex hormone binding globulin predicts noninsulin-dependent diabetes mellitus in women but men. *J Clin Endocrinol Metab.* **77**: 56–60.
- Helle SI, Ekse D, Holly JM, Lønning PE (2002). The IGF-system in healthy pre- and postmenopausal women: relations to demographic variables and sex-steroids. *J Steroid Biochem Mol Biol.* **81**: 95–102.
- Helle SI, Anker GB, Meadows KA, Holly JM, Lønning PE (1998). Alterations in the insulin-like growth factor system during the menstrual cycle in normal women. *Maturitas.* **28**: 259–65.
- Hennessey AC, Wilson ME, Albers HE (1994). Somatostatin mRNA levels within the periventricular nucleus are regulated by estradiol and insulin-like growth factor-I in immature female rats. *Mol Cell Neuroscience.* **5**: 540–548.
- Hesse V, Jahreis G, Schambach H (1994). Insulin-like growth factor I correlations to changes of the hormonal status in puberty and age. *Experiment Clin Endocrinol.* **102**: 289–298.
- Ho KK, O'Sullivan AJ, Weissberger AJ (1996). Sex steroid regulation of growth hormone secretion and action. *Hormone Res.* **45**: 67–73.
- Itagane Y, Inada H, Fujita K, Isshiki G (1991). Interactions between steroid hormones and insulin-like growth factor-I in rabbit chondrocytes. *Endocrinology.* **128**: 1419–1424.
- Kalu DN, Arjmandi BH, Liu CC, Salih MA, Birnbaum RS (1994). Effects of ovariectomy and estrogen on the serum levels of insulin-like growth factor-I and insulin-like growth factor binding protein-3. *Bone & Mineral.* **25**: 135–148.
- Kanbur-Oksüz N, Derman O, Kinik E (2004). Correlation of sex steroids with IGF-1 and IGFBP-3 during different pubertal stages. *Turk J Pediatr.* **46**: 315–321.
- Kelly JJ, Rajkovic IA, O'Sullivan AJ (1993). Effects of different oral oestrogen formulations on insulin-like growth factor-1, growth hormone and growth hormone binding protein in post-menopausal women. *Clin Endocrinol.* **39**: 561–567.
- Kirchengast S, Hartmann B, Huber J (1996). Serum levels of sex hormones, thyroid hormones, growth hormone, IGF I, and cortisol and their relations to body fat distribution in healthy women dependent on their menopausal status. *Zeitschrift für Morphologie und Anthropologie.* **81**: 223–234.
- Krzysiek J, Milewicz T, Opiła J (1998). Surowicze poziomu hormonu wzrostu i insulinopodobnego czynnika wzrostu u kobiet z nieprawidłowym obrazem tomograficznym przestrzeni wewnątrzrodowej. *Przeg Lek.* **55**: 51–56.
- Lapauw B, T'Sjoen G, Mahmoud A, Kaufman JM, Ruige JB (2009). Short-term aromatase inhibition: effects on glucose metabolism and serum leptin levels in young and elderly men. *Eur J Endocrinol.* **160**: 397–402.
- Lebenthal Y, Gat-Yablonski G, Shtaf B, Padoa A, Phillip M, Lazar L (2006). Effect of sex hormone administration on circulating ghrelin levels in peripubertal children. *J Clin Endocrinol Metab.* **91**: 328–331.
- Massa G, Igout A, Rombauts L, Frankenne F, Vanderschueren-Lodeweyckx M (1993). Effect of oestrogen status on serum levels of growth hormone-binding protein and insulin-like growth factor-I in non-pregnant and pregnant women. *Clin Endocrinol.* **39**: 569–575.
- Michels KM, Lee WH, Seltzer A (1993). Up-regulation of pituitary [125I]insulin-like growth factor-I (IGF-I) binding and IGF binding protein-2 and IGF-I gene expression by estrogen. *Endocrinology.* **132**: 23–29.
- Milewicz T, Krzysiek J, Sztéfko K, Radowicki S, Krzyczkowska-Sendrakowska M (2005). 17-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. *Endokrynol Pol.* **56**: 876–882.
- Milewicz T, Krzysiek J, Sztéfko K (1999). Transdermal 17β-estradiol replacement therapy increases serum free IGF-I in postmenopausal women. *Eur J Obstet Gynecol Reprod Biol.* **86**: 516.
- Milewicz T, Krzysiek J, Sztéfko K (1999). Serum leptin level in hypogonadal women may depend on age and serum DHEAS level. *Climacteric.* **2**: suppl.1: 255.
- Milewicz T, Krzysiek J, Sztéfko K, Radowicki S, et al (1998). The high serum IGF-I level in polycystic ovary syndrome correlated both with serum insulin and androgenism. 4th Eur Congr Endocrinol, May 9–13, 1998, Sevilla, Spain.
- Nestler JE, Powers LP, Matt DW, Steingold KA, Plymate SR, Ritmaster JN, et al (1991). A direct effect of hyperinsulinemia on serum sex hormone binding globulin levels in obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* **172**: 83–89.
- Rajkumar K, Dheen T, Krsek M, Murphy JL (1996). Impaired estrogen action in the uterus of insulin-like growth factor binding protein-1 transgenic mice. *Endocrinology.* **137**: 1258–1264.
- Rosenfield RL, Perovic N, Devine N (1998). Optimizing estrogen replacement treatment in Turner syndrome. *Pediatrics.* **102**: 486–488.
- Sharara FI, Giudice LC (1997). Role of growth hormone in ovarian physiology and onset of puberty. *J Soc Gynecol Invest.* **4**: 2–7.
- Singh A, Hamilton-Fairley D, Koistinen R (1990). Effect of insulin-like growth factor-I (IGF-I) and insulin on the secretion of sex hormone binding globulin and IGF-binding protein (IGFBP-1) by human hepatoma cells. *J Endocrinol.* **124**: R1.
- Słowinska-Srzednicka J, Zgliczynski S, Jeske W (1992). Transdermal 17 beta-estradiol combined with oral progestogen increases plasma levels of insulin-like growth factor-I in postmenopausal women. *J Endocrinol Invest.* **15**: 533–538.
- Sonnet E, Lacut K, Roudaut N, Mottier D, Kerlan V, Oger E (2007). Effects of the route of oestrogen administration on IGF-1 and IGFBP-3 in healthy postmenopausal women: results from a randomized placebo-controlled study. *Clin Endocrinol (Oxf).* **66**: 626–631.
- Stefano GB, Zhu W, Mantione K, Jones D, Salamon E, Cho JJ, et al (2003). 17-beta estradiol down regulates ganglionic microglial cells via nitric oxide release: presence of an estrogen receptor beta transcript. *Neuro Endocrinol Lett.* **24**(3–4): 130–6.

- 35 Van Dessel HJHMT, Chandrasekher Y, Yap OWS (1996). Serum and follicular fluid levels of insulin-like growth factor I (IGF-I), IGF-II and IGF-binding protein-1 and -3 during the normal menstrual cycle. *J Clin Endocrinol Metab.* **81**: 1224–1231.
- 36 Weissberger AJ, Ho KKY, Lazarus L (1991). Contrasting effects of oral and transdermal routes of estrogen replacement therapy on 24-hour growth hormone (GH) secretion, insulin-like growth factor I and GH-binding protein in postmenopausal women. *J Clin Endocrinol Metab.* **72**: 374–381.
- 37 Wilson ME (1997). Administration of IGF-I affects the GH axis and adolescent growth in normal monkeys. *J Endocrinol.* **153**: 327–335.
- 38 Wolinska-Witort E, Snochowski M, Gajewska A, Lerrant Y, Counis R, Baranowska B (2000). Effect of estradiol 17-beta on LH subunits and prolactin mRNAs expression in the pituitary of old female rats. *Neuro Endocrinol Lett.* **21**(6): 431–436.
- 39 Wuster C, Blum WF, Schlemlich S, Ranke MB, Ziegler R (1993). Decreased serum levels of insulin-like growth factors and IGF binding protein 3 in osteoporosis. *J Intern Med.* **234**: 249–259.
- 40 Xu YP, Chedrese PJ, Thacker PA (1997). Growth hormone as an amplifier of insulin-like growth factor-I action: potentiated oestradiol accumulation. *J Endocrinol.* **152**: 201–209.
- 41 Yoshimura Y, Ando M, Nagamatsu S, Iwashita M, Adachi T, Sueoka K, et al (1996). Effects of insulin-like growth factor-I on follicle growth, oocyte maturation, and ovarian steroidogenesis and plasminogen activator activity in the rabbit. *Biol Reprod.* **55**: 152–160.