CIRCADIAN VARIATIONS OF ANDROSTENEDIONE, DEHYDROEPIANDROSTERONE SULFATE AND FREE TESTOSTERONE IN OBESE WOMEN WITH MENSTRUAL DISTURBANCES

Z. Ostrowska, K. Zwirska-Korczala, M. Pardela, M. Drozdz, Kos-Kudla B., B. Buntner

1st Department of Pathophysiology and Clinical Biochemistry, 2nd Department of General and Vascular Surgery, Silesian School of Medicine, 41-800 Zabrze

Objective. To assess the 24 h profile of androgenemia related to the androgens of both the ovarian and adrenal origin in obese women with menstrual disturbances.

Methods. The association of body mass and body fat distribution with circadian variations of selected androgens of ovarian and adrenal origin was examined in 16 obese women with menstrual disturbances (BMI between 38 and 51 kg/m^2; WHR between 0.80 and 0.99) and in 16 healthy volunteers with normal body weight (BMI between 21 and 24.6 kg/m^2; WHR between 0.73 and 0.76). The age range of all subjects was 29 to 40 (mean: 36.9±3.2 years).

Results. Both the patients and control subjects showed a significant 24 h rhythm of androstenedione (A) and free testosterone (FT), while the circadian oscillations of dehydroepiandrosterone sulphate (DHEAS) did not differ significantly. In all obese women mean 24 h A, DHEAS and FT levels were significantly higher than those in controls. Moreover, the disturbances of DHEAS and FT secretion in the form of acrophase shift (for DHEAS from 7.37 to 3.45 h and for FT from 6.04 to 3.31 h) and the elevation of their 24 h amplitude values were observed. All obese women showed higher values of FT/A and FT/DHEAS indexes in selected clock time of day/night cycle (except those at 8.00 h for FT/A and at 5.00 h for FT/DHEAS) when compared to control group. A positive correlation was noted in all women studied between the values of BMI index, WHR ratio and mean 24 h level of androgens studied as well as FT/A and FT/ DHEAS indexes. A weaker correlation was found between body mass and body fat distribution on the one hand and fasting level of hormones studied on the other. Higher correlation between the values of WHR ratio and mean 24 h FT levels as well as FT/DHEAS indexes were obtained in obese women when compared to those of healthy subjects.

Conclusions. Our findings suggest that, when assessing the androgen disturbances in obese patients, it is more useful to determine their circadian pattern than the basal level. The most reliable indicators of hyperandrogenism in obese women are: the 24 h concentration profile of FT and the value of FT/DHEAS index, not only during fasting but also after a meal at various time intervals. Circadian FT concentration and FT/DHEAS index values are essential indicators for visceral distribution of adipose tissue.

Key words: Obese Women - Androstenedione - Dehydroepiandrosterone Sulfate - Free Testosterone - Circadian Variations

Recent studies showed that in the course of android obesity in women the basic role is played by a well-defined group of disturbances concerning hormones of the hypothalamic-pituitary-peripheral gland axis. Among them the decisive changes appear to concern the sex steroids (Zumoff 1988; Glass 1989; Björntorp 1991, 1995; Vaque 1991; Luthold et al. 1993; De Pergola et al. 1994; Kissebah and Krakower 1994; Leenen et al. 1994; Clore 1995; Ostrowska et al. 1995a,b; Tschernof et al. 1996). In obesity, especially in that of android type, abnormalities are observed in the metabolism and secretion of androgens. Thus, together with hyperestrogenism, also hyperinsulinism and insulin resistance is a perquisite for overweight-related complications such as hirsutism, menstrual disturbances, late menopause, infertility and hormone-dependent neoplasms (Zumoff 1988; Glass 1989; Kitabchi et al. 1991; Buffington et al. 1994; Fendri et al. 1994; Crave et al. 1995; Milewicz 1995; Ostrowska et al. 1995a, b; Svacina et al. 1995; Bernasconi et al. 1996). Androgenemia does not always reflect the actual hormonal status of the patients. Concentration of circulating androgens result from the level of their biosynthesis, their forming process, active uptake by the tissues, bioavailability, readiness of adipose tissue (mainly visceral) to metabolize them and renal clearance as a compensatory mechanism (Zumoff 1988; Glass 1989; Vaque 1991; Björntorp 1995; Tschernof et al. 1996). A question may be asked which one among the circulating androgens appears the most characteristic for the hormonal status of the patient and whether it should be measured during 24 h or only in basal conditions.

The aim of this study was to assess the 24 h profile of androgenemia related to the androgens of both the ovarian and adrenal origin in obese women with menstrual disturbances.

Subjects and Method

Circadian variations of A, DHEAS and FT level were evaluated in 16 obese women with menstrual disturbances (BMI between 38 and 51 kg/m^2; WHR between 0.80 and 0.99) aged 29 to 40 (mean: 36.2 ± 3.9 years). Obese subjects with polycystic ovary syndrome (PCO) were excluded. The control group consisted of 16 healthy age-matched volunteers with normal body weight (BMI between 21 and 24.6 kg/m^2; WHR between 0.73 and 0.76) and regular menstrual cycles.

All subjects were hospitalized during the study. Normal day-time activities and normal eating and sleeping patterns were permitted. The regularity of menstrual cycles was confirmed by progesterone (P) measurements on 22 nd day of cycle. In women with menstrual disturbances P levels were above 15 nmol/l. All menstruating women were studied between days 5 and 8 after the onset of menses. During the circadian study blood samples for the determination of A, DHEAS and FT were taken starting at 8.00 h and then every third hour until 5.00 h on the following day. Serum samples were obtained by centrifugation and stored at -70˚C until assayed.

The concentrations of A, DHEAS and FT were measured using DPC RIA kits (USA) and P by FARMOS RIA kits (Finland).

The sensitivities of assays were: A 0.14 nmol/l; DHEAS 0.03 μmol/l; FT 0.52 pmol/l and P 0.1 - 0.3 nmol/l. The intraassay coefficients of variation were: A 8 %; DHEAS 7.4 %; FT 3,8 % and P 7.9 %. The interassay coefficients of variation were: A 8.3 %; DHEAS 7.5 %; FT 4.2 % and P 8.1 %.

Data were expressed as mean±S.D. values. The statistical analysis of circadian rhythm was performed by cosinor test according to Halberg et al. (1967). Differences in the study mean values between groups were tested using Student t-test for unpaired data. The relation between results of hormonal determinations and body mass index (BMI) and waist to hip ratio (WHR) values was examined using simple regression analysis.

Results

All women studied showed a significant circadian rhythm of A and FT (Fig. 1 and 3) while the 24 h oscillations of DHEAS did not differ significantly (Fig. 2). The mesor level of A was significantly higher in all obese women as compared to healthy subjects, without acrophase rhythm shift. Mean serum concentrations of A were significantly elevated at 8.00, 20.00 and 23.00 h. Mean 24 h DHEAS concentration and the value of circadian amplitude were significantly higher in all obese women vs. control group. In addition, the acrophase shift from 7.37 to 3.54 h was observed. Mean levels of DHEAS value increased significantly at 2.00 and 5.00 h only as compared to healthy women.

A significant elevation of mean 24 h FT level, the stimulation of its circadian rhythmicity and acrophase rhythm shift from 6.04 to 3.31 h were found in obese women when compared to the values of controls. Mean serum levels of FT were significantly higher in selected clock time of day/night cycle (except those at 8.00 h).

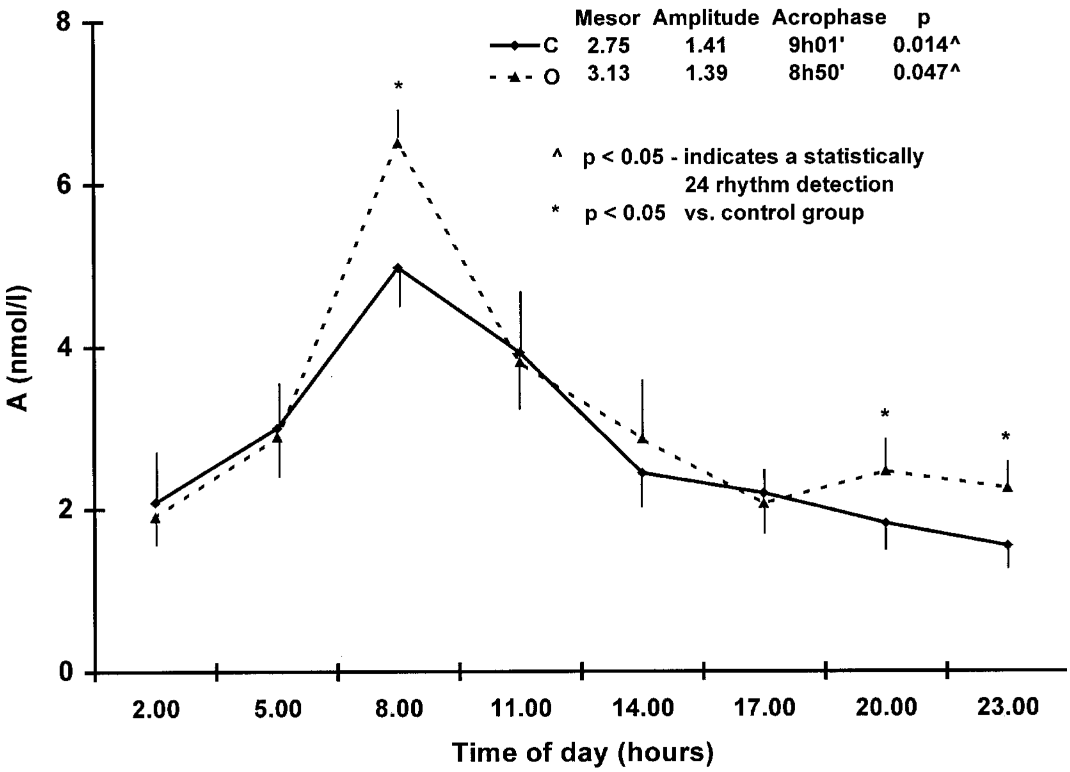

Fig. 1

Circadian variations of androstenedione (A), and the chronobiologic parameters of A circadian rhythm (mesor; amplitude and acrophase) in obese women with menstrual disturbances (O) and in healthy volunteers (C).

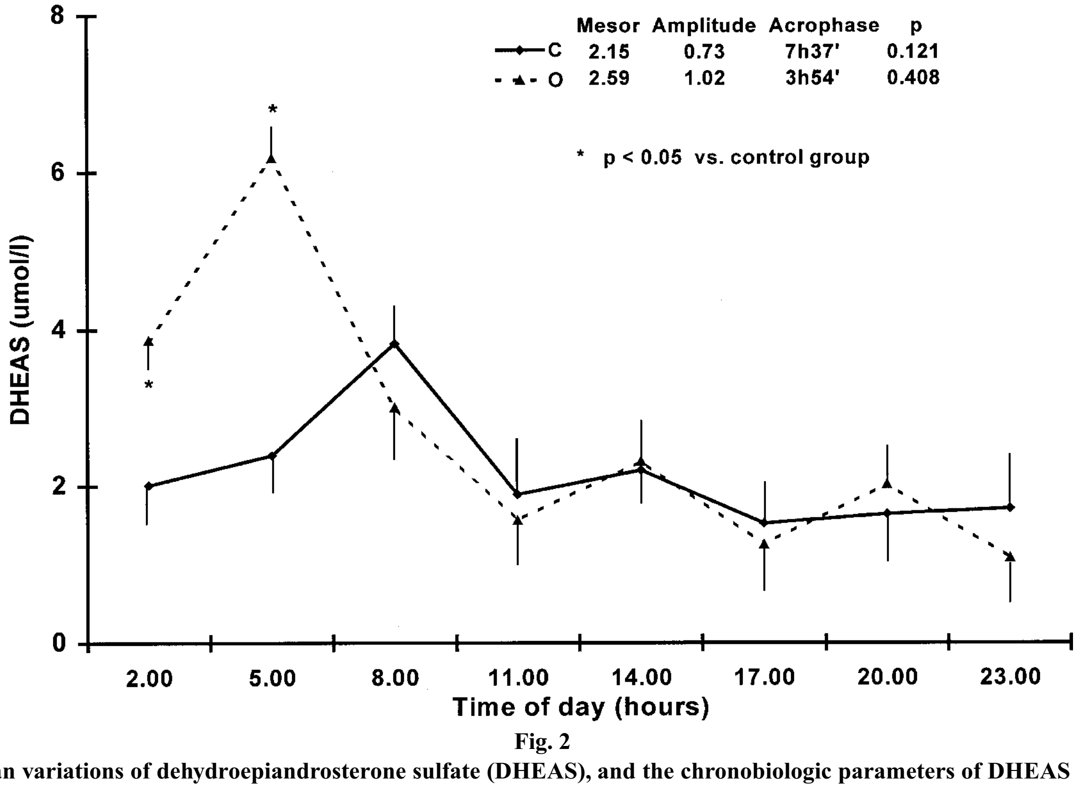

Fig. 2

Circadian variations of dehydroepiandrosterone sulfate (DHEAS), and the chronobiologic parameters of DHEAS circadian rhythm (mesor; amplitude and acrophase) in obese women with menstrual disturbances (O) and in healthy volunteers (C).

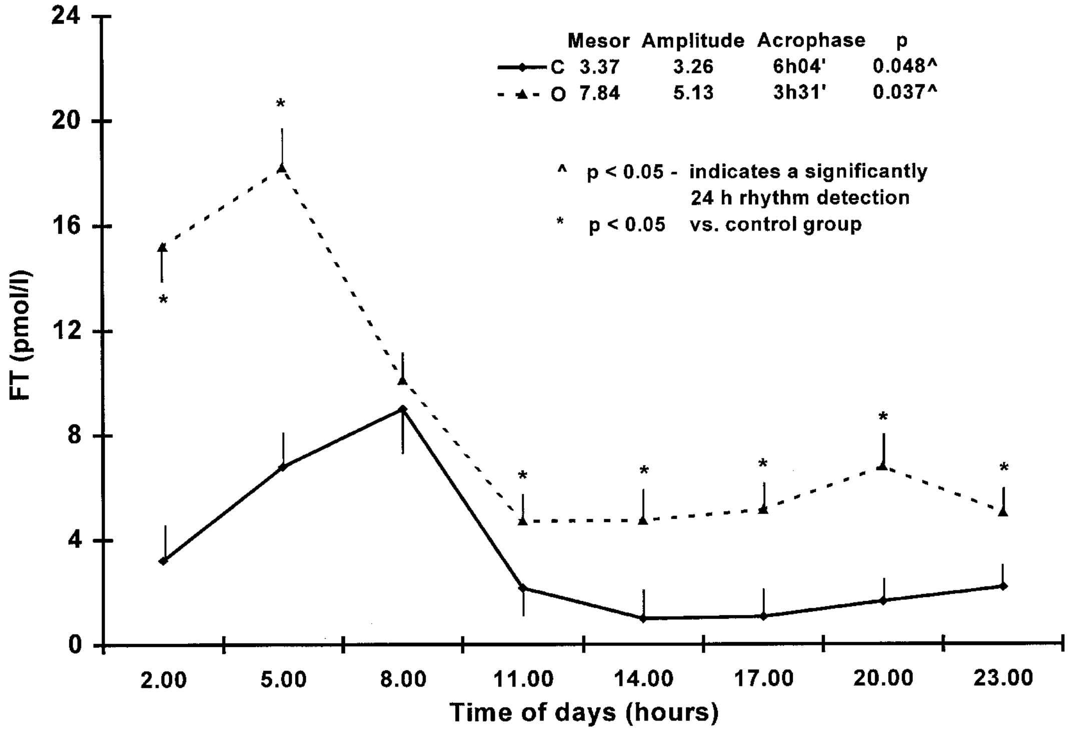

Fig. 3
Circadian variations of free testosterone (FT), and the chronobiologic parameters of FT circadian rhythm (mesor; amplitude and acrophase) in obese women with menstrual disturbances (O) and in healthy volunteers (C)

All obese women showed significantly increased values of FT/A and FT/DHEAS index in selected clock time of day/night cycle (except those at 8.00 h for FT/A and at 5.00 for FT/ DHEAS).

In both obese and control women significant and positive associations were found between the values of BMI index, WHR ratio and mean 24 h levels of A, DHEAS, FT as well as FT/A (for BMI: from 11.00 to 5.00 h; from WHR: for 14.00 to 8.00 h) and FT/DHEAS indexes (Tab. 2). A significant but generally weaker correlation was shown between BMI index, WHR ratio and fast-

Table 1
The values of FT/A and FT/DHEAS indexes during day/night cycle in obese women with menstrual disturbances (O) and in healthy volunteers (C)

Time of day (hours)	FT/A		FT/DHEAS	
	C	O	C	O
2.00	1.54±0.31	8.01±1.27*	1.92±0.27	3.94±0.55*
5.00	2.25±0.48	6.68±1.01*	2.84±0.42	3.22±0.64
8.00	1.81±0.30	1.62±0.29	2.35±0.38	3.36±0.71*
11.00	0.71±0.08	1.23±0.17*	1.13±0.29	3.82±0.68*
14.00	0.40±0.05	2.20±0.29*	0.45±0.06	3.30±0.77*
17.00	0.48±0.08	2.49±0.30*	0.69±0.11	4.10±0.68*
20.00	0.90±0.11	2.75±0.39*	1.00±0.14	4.39±0.73*
23.00	1.41±0.17	2.22±0.28*	1.27±0.22	4.62±0.791*

FT - free testosterone
A - androstenedione
DHEAS - dehydroepiandrosterone sulfate
* P≤0.05 vs. control group

Table 2

Correlation between the values of body mass index (BMI), waist to hip ratio (WHR) and serum concentrations of androstenedione (A),dehydroepiandrosterone sulfate (DHEAS) and free testosterone (FT)in obese women with menstrual disturbances (C) and in healthy volunteers (O). The values are correlation coefficients (r).

Hormones		Groups	BMI	WHR
A (nmol/l)	m	C	**0.502**	**0.621**
	f		**0.512**	**0.490**
	m	O	**0.595**	**0.629**
	f		**0.521**	**0.501**
DHEAS (μmol/l)	m	C	**0.580**	**0.593**
	f		**0.487**	**0.502**
	m	O	**0.589**	**0.565**
	f		**0.490**	**0.480**
FT (pmol/l)	m	C	**0.641**	**0.629**
	f		**0.513**	**0.529**
	m	O	**0.626**	**0.857***
	f		**0.542**	**0.600**

m - mean 24 h values
f - fasting values
* $P \leq 0.05$ (significantly higher values of correlation coefficient vs. control group)

Table 3

Correlation between the values of body mass index (BMI), waist to hop ratio (WHR) and FT/A and FT/DHEAS indexes during day/night cycle in obese women with menstrual disturbances (O) and in healthy volunteers (C). The values are correlation coefficients (r).

Indexes	Time of day	Groups (hours)	FT/A	FT/DHEAS
BMI	2.00	C	**0.507**	**0.645**
		O	**0.489**	**0.687**
	5.00	C	**0.490**	**0.589**
		O	**0.492**	**0.602**
	8.00	C	0.351	**0.702**
		O	0.374	**0.689**
	11.00	C	**0.539**	**0.542**
		O	**0.595**	**0.499**
	14.00	C	**0.550**	**0.695**
		O	**0.542**	**0.714**
	17.00	C	**0.502**	**0.557**
		O	**0.495**	**0.504**
	20.00	C	**0.569**	**0.625**
		O	**0.551**	**0.698**
	23.00	C	**0.492**	**0.711**
		O	**0.550**	**0.677**
WHR	2.00	C	**0.497**	**0.611**
		O	**0.502**	**0.869***
	5.00	C	**0.590**	**0.612**
		O	**0.581**	**0.855***
	8.00	C	0.360	**0.671**
		O	0.351	**0.894***
	11.00	C	0.398	**0.568**
		O	0.402	**0.799***
	14.00	C	**0.496**	**0.520**
		O	**0.513**	**0.800***
	17.00	C	**0.512**	**0.601**
		O	**0.501**	**0.795***
	20.00	C	**0.511**	**0.589**
		O	**0.525**	**0.817***
	23.00	C	**0.492**	**0.521**
		O	**0.500**	**0.631***

FT - free testosterone; A - androstenedione; DHEAS - dehydroepiandrosterone sulfate; * - $P \leq 0.05$ (significantly higher values of correlation coefficients vs. control group)

ing levels of adrenal and ovarian androgens studied. Higher correlation between the values of WHR ratio and mean 24 h FT levels as well as FT/DHEAS indexes were found in obese women when compared to controls.

Discussion

Many authors point out the occurrence of clinical and hormonal features of hyperandrogenism in women with android type obesity (ZUMOFF 1988; GLASS 1989; FENDRI et al. 1994; GUZIK et al. 1994; LEENEN et al. 1994; BJÖRNTORP 1995; CRAVE et al. 1995; OSTROWSKA et al. 1995a,b; TSCHERNHOF et al. 1996). Obese women with menstrual disturbances were shown to have abnormalities in adrenal androgen production corroborated by a significant increase in DHEA and DHEAS concentrations and normal or moderately changed values of A (which, as opposed to adrenal androgen DHEA and its sulfate, is formed not only in adrenals but also in the ovaries) (GLASS 1989; CLORE 1995; MILEWICZ 1995). We found a distinct increase in the mean 24 h concentrations of DHEAS and A in obese women examined as well as increase of circadian DHEAS oscillations and its acrophase shift from 7.37 to 3.45 h. It is interesting that fasting levels of DHEAS were slightly lower compared to control group and thus reflected the clinical status of the appropriate patients to much lesser degree, while the fasting concentrations of A were markedly elevated. The in-

Table 1
Correlation coefficient between the values of body mass index (BMI), waist to hip ratio (WHR), and the mean 24 h concentrations of serum androstendione (A), dehydroepiandrosterone sulfate (DHEAS) and free testosterone (FT) in obese women with menstrual disturbances (C) and in healthy volunteers with normal body weight (O).

Hormones	Groups	BMI	WHR
A	C (n = 12)	0.502	0.621
(nmol/l)	O (n = 16)	0.595	0.629
DHEAS	C (n = 12)	0.580	0.593
(µmol/l)	O (n = 16)	0.589	0.565
FT	C (n = 12)	0.641	0.629
(pmol/l)	O (n = 16)	0.626	0.857*

* significantly higher values of correlation coefficient vs control group

crease in the level of adrenal androgens in women with clinical manifestations of hyperandrogenism may be explained by hyperreactivity of hypothalamic-pituitary adrenal axis in response to stress or (and) temporary hypoglycemia caused by hyperinsulinism (GLASS 1989; BJÖRNTORP 1991, 1995; KITABCHI et al. 1991; NESTLER and STRAUSS 1991; KISSEBAH and KRAKOWER 1994; CRAVE et al. 1995; SVACINA et al. 1995). 24 h concentrations of DHEAS and A correlated positively with BMI and WHR indicators of obese women examined and the correlation was similar to that in women with proper body mass. Similar interrelations were found in the fasting levels of DHEAS and A, but in these cases the values of correlation coefficients were generally lower. The results obtained suggest that, when assessing hyperandrogenism in obese women, it is more useful to measure the concentration of adrenal androgens in their 24 h profile than in basal conditions.

Other investigations suggested the ovarian origin of hyperandrogenism in women with android type obesity. A steady rise in estrogen concentration may increase androgen synthesis in the ovaries by stimulating the pituitary to produce LH (BRINGER et al. 1988; GLASS 1989). The rise in ovarian androgen production may also be linked with hyperinsulinism (KITABCHI et al. 1991; NESTLER and STRAUSS 1991; MARCELLI et al. 1993; BUFFINGTON et al. 1994). Insulin excess together with coexistent hepatic and muscular insulin resistance may stimulate ovarian thecal cells to produce androgens via IGF-I receptors and also may directly inhibit SHBG synthesis in the liver, increasing thus the free testosterone pool. Many authors have demonstrated a considerable increase of testosterone fasting levels in obese women with menstrual disturbances, accompanied by a marked decrease in SHBG values (GLASS 1989; WEAVER et al. 1991; GIAGULLI et al. 1992; LUDHOLD et al. 1993; FENDRI et al. 1994; GUZIK et al. 1994; CRAVE et al. 1995; OSTROWSKA et al. 1995a,b; BERNASCONI et al. 1996). In our previous studies we showed considerable abnormalities in circadian oscillations of total testosterone (TT) and SHBG in women with coexisting menstrual disturbances and android type obesity (OSTROWSKA et al. 1995a,b). On the other hand we noted only slight changes of TT and SHBG concentrations in obese women with normal menstrual cycles as compared to healthy women. Similarly, other authors showed only a slight change in the level of androgenic hormones in obese women with no menstrual disturbances which most likely resulted from the augmentation of renal clearance accompanying increased production of androgens (SAMOJLIK et al. 1984; KURTZ et al. 1987; DE PERGOLA et al. 1994).

In examined women with coexisting menstrual disturbances and android type obesity we found a significant elevation of mean 24 h FT level, the stimulation of its circadian rhythmicity and acrophase rhythm shift from 6.04 to 3.31 h as compared to controls. The differences in FT fasting levels between obese and healthy women were less distinct. The results obtained show that the assessment of circadian FT concentration profile is the more reliable indicator of hyperandrogenism in obese women than the values of fasting FT levels. Mean 24 h levels of FT as well as its fasting concentrations correlated significantly and positively with both BMI index and WHR ratio values in all subjects studied. Computed values of correlation coefficients were generally lower compared to fasting FT levels. However, much better correlation in obese patients was found for the mean 24 h levels of FT and WHR ratio values. It has been known that sex steroids, including androgens, take part in the regulation of adipose tissue distribution (KIRSCHNER et al. 1990; DE PERGOLA et al. 1994; KISSEBAH and KRAKOWER 1994; LEENEN et al. 1994). A crucial relationship was shown between their blood concentration and that of lipoprotein lipase - an enzyme responsible for the formation and accumulation of adipose tissue. On the other hand, adipose tissue is capable of storing sex steroid and it is an important site of their metabolism (BJÖRNTORP 1991; CLORE 1995; MILEWICZ 1995). Since the androgenemia of adrenal and ovarian origin (especially under fasting conditions) does not always reflect clinical and hormonal status of obese women examined, the FT/A and FT/DHEAS indicators were calculated and their usefulness was examined. According to ZUMOFF (1988) and DE PERGOLA et al. (1994) the FT/DHEA and FT/DHEAS indicators are essential markers for the android distribution of adipose tissue. All obese women studied showed significantly increased values of FT/A and FT/ DHEAS in selected clock time of the day/night cycles (except those at 8.00 h for FT/A and at 5.00 h for FT/DHEAS). The values of FT/A and FT/DHEAS indexes in all subjects studied correlated positively with body mass index and body fat distribution at all time points and the values of correlation coefficients were significantly higher in obese women compared to healthy women only in the case of FT/DHEAS index and WHR ratio values. The results obtained suggest that FT/DHEAS index which may be determined not only during fast but also after a meal at various times of day and night represent as important marker of androidal distribution of fat tissue in obese women.

In summary, the assessment of circadian FT concentration profile and values of FT/DHEAS index determined not only during the fast, but also after a meal at various times of day and night appear to be the most reliable exponents of hyperandrogenism in obese women. Mean 24 level of FT and the value of FT/DHEAS index are essential markers of android type distribution of adipose tissue.

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Corresponding author: Dr. Z. Ostrowska
Silesian Academy of Sciences
pl. Traugutta 2
41-800 Zabrze, Poland

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