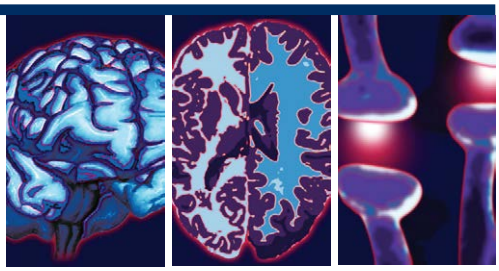

Insomnia in Peri- and Postmenopausal Women: Plasma Lipids, Lipid Peroxidation and Some Antioxidant System Parameters

N.V. Semenova†, I.M. Madaeva, S.I. Kolesnikov, E.I. Solodova, L.I. Kolesnikova

ABSTRACT

Purpose

According to the current data, most menopausal women have reduced quality of life and one of the main criteria is sleep. It is possible, that sleep loss may cause oxidative stress. This study determines sleep disorders characteristics, lipid profile, lipid peroxidation and antioxidant system parameters in peri- and postmenopausal women.

Methods

126 menopausal women divided into perimenopausal (n=56) and postmenopausal (n=70) groups were examined. Each group was divided into control (without sleep disorders) and main groups (insomnia and insomnia with obstructive sleep apnea syndrome (OSAS). Pittsburg Sleep Quality Index, Epworth Sleepiness Scale, Insomnia Severity Index, polysomnography were used for the assessment of sleep disorders. Lipid metabolism parameters by the enzymatic method were determined. Lipid peroxidation and antioxidant system parameters (conjugated dienes (CDs), malonyl dialdehyde (MDA), α-tocopherol, retinol, reduced and oxidized glutathione by spectrophotometric and fluorometric methods were determined.

Results

The increase of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels were observed in perimenopausal women with insomnia and OSAS. The increase of TC, triacylglycerol (TG), LDL-C, very-low-density lipoprotein cholesterol (VLDL-C) levels and decrease of high-density lipoprotein cholesterol (HDL-C) level were found in postmenopausal women with insomnia and OSAS as compared to control and group with insomnia. Accumulation of lipid peroxidation products was observed both in perimenopausal women with insomnia (CDs) and in postmenopausal women with insomnia (CDs, MDA) and insomnia with OSAS (MDA). There were no differences in antioxidant system parameters between main and control groups.

Conclusion

Both insomnia and insomnia with OSAS are associated with oxidative stress only in postmenopausal women. There are no differences in the accumulation of MDA between insomnia and insomnia with OSAS both in perimenopause and postmenopause.

Keywords

Insomnia, Sleep apnea, Lipid metabolism, Lipid peroxidation, Antioxidant system, Perimenopause, Postmenopause

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Introduction

Menopause is one of the critical periods in a woman's life and transition period from reproductive phase to its extinction and cessation of menstrual and genital function: follicular reserve of ovaries depletion, decreasing of its functional activity, changes in hormones relationship, estrogen level decreasing [1]. 60%-80% of menopausal women have vegetovascular, mental and metabolic disorders. Among the main signs of neuro-vegetative changes in menopausal women are sleep disorders. Some studies have shown that sleep problems are reported by 39%-47% of perimenopausal women and 35%-60% of postmenopausal ones [2]. According to the current data, most menopausal women have reduced life quality and one of the main criteria is sleep quality [3].

In recent years, it has been suggested that sleep has a regulating role in lipid homeostasis [4,5]. Moreover, it has been shown that the lipids concentration might depends on the circadian system [6]. Also, experimental investigations has shown, that sleep loss may cause oxidative stress [7-12], which is a result of imbalance between free radicals production and antioxidant system activity [13]. These can lead to development of different cardiovascular [14], endocrine [15], mental [16], oncology [17] and other pathologies. The consequences of lipid peroxidation products accumulation are changes in the metabolism of proteins, fats, carbohydrates, nucleic acids, water and electrolyte metabolism, which can cause severe tissue damages and organism adaptive capacity reduction [13]. The main investigations in human are devoted to oxidative stress and obstructive sleep apnea syndrome association (OSAS) [18-31]. There are few investigations on insomnia and lipid peroxidation relationship [32-34], but it is obvious that this data are of great importance for elaborating of preventive and therapeutic measures to improve life quality of menopausal women.

The aim of this study is to determine lipid profile, lipid peroxidation and antioxidant system in peri- and postmenopausal women with insomnia.

Materials and Methods

■ Subjects

The present study was conducted in the Scientific Centre for Family Health and Human Reproduction Problems (Irkutsk, Russia) with ethical standards of Helsinki Declaration (World Medical Association Declaration of Helsinki, 2008). All participants provided written, informed consent. The program of the study included the following methods: clinical-anamnestic (questionnaire, general medical examination, gynecological examination, polysomnographic monitoring (PSG), laboratory (lipid profile, lipid peroxidation, antioxidant system parameters examination) and statistical. 126 menopausal women divided into 2 groups: perimenopause (n=56) and postmenopause (n=70) were examined.

Inclusion criteria for perimenopausal group: Age 45-55; oligomenorrhoea or amenorrhea during last 12 months; ultrasounds criteria: 1) endometrial dysfunction: mismatch of structure and thickness corresponding to the first and the second phases of the menstrual cycle; 2) ovaries follicular reserve depletion**.**

Inclusion criteria for postmenopausal group: Age 56-60; amenorrhea ≥ 12 months; follicle stimulating hormone level >20 iU/ml, index luteinizing hormone/follicle-stimulating hormone <1; ultrasounds criteria: 1) thin non-functional endometrium, endometrial echo thinner than 5 mm; 2) lack of ovaries follicular reserve.

Exclusion criteria: exacerbation of chronic diseases; hormone replacement therapy; surgical menopause; the presence of chronic sleep disorders before menopause (insomnia, parasomnia, hypersomnia, obstructive sleep apnea syndrome); the use of hypnotic pills in the previous two weeks; shift work.

After questioning and PSG, the each group was divided into 3 subgroups: 2 main (insomnia; insomnia with OSAS) and control (without sleep disorders). 33.9% perimenopausal and 37.1% postmenopausal women had no sleep problems and formed control groups. Basic characteristics of women are shown in **Table 1**.

■ Methods and elaborating on methods

Questionnaire: The Pittsburgh Sleep Quality Index, PSQI [35], Insomnia Severity Index (ISI) [36], Epworth Sleepiness Scale (ESS) [37] was employed.

The PSQI questionnaire consists of 19 items including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and

Table 1: Subject profiles.

Characteristics	Perimenopause			Postmenopause			p-value
	control	insomnia	insomnia and OSAS	control	insomnia	insomnia and OSAS	
	n=19	n=19	n=18	n=26	n=27	n=17	
	(1)	(2)	(3)	(4)	(5)	(6)	
	Mean ± SD						
age, years	49.08 ± 2.84	50.41 ± 3.43	50.61 ± 3.14	57.16 ± 1.12	58.02 ± 2.07	58.82 ± 2.21	P1-4* P2-5* P3-6*
BMI, kg/m^2	27.18 ± 4.58	29.11 ± 5.42	31.72 ± 5.59	27.96 ± 3.57	26.87 ± 3.28	33.81 ± 6.41	P1-3* P4-6* P5-6*
Duration of insomnia (years)	-	1.45 ± 1.02	2.03 ± 1.32	-	5.34 ± 1.22	6.41 ± 1.21	P2-5* P3-6*

*- p<0.05

daytime dysfunction. The total score of PSQI is 21 points.

The ISI questionnaire consists of 7 items. The answer each of the questions from 0 to 4 and a total score ranging from 0 (minimum) to 24 (maximum). The ISI results 0-7, 8-14, 15-21, 22-28 points were interpreted as norm, slight sleep disorders, moderate and expressed respectively.

The ESS consists of 8 items. The answer each of the questions from 0 (not at all likely to fall asleep) to 3 (very likely to fall asleep) and a total score ranging from 0 (minimum) to 24 (maximum). The ESS results 0-3, 3-9, 9-16, 16-24 points were interpreted as norm, insomnia, obstructive sleep apnea syndrome and narcolepsy respectively.

Polysomnographic monitoring: A full PSG was carried out with the using of GRASS-TELEFACTOR Twin PSG (Comet) system with As 40 amplifier with an integrated module for sleep SPM-1 (USA) by standard method [38].

Collection of material: Venous blood sampled after 12-h of overnight fasting into tubes with EDTA between 8.00 and 9.00 a.m. Samples centrifuged for 10 min at 1.500 g at 4°C, and erythrocytes washed three times with 0.9% NaCl (wt/vol). Samples were used immediately (for total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triacylglycerol (TG) determination) or kept frozen at -40°C, but not more than one month (for determination lipid peroxidation and antioxidant defense system parameters).

Plasma lipids determination: TC, HDL-C and TG levels were measured photometrically by LIVA-Lachema kits on a BTS-330 automatic analyzer (Poland). The low-density lipoprotein cholesterol (LDL-C) and very-low-density lipoprotein cholesterol (VLDL-C) levels in serum was estimated mathematically with using the Friedewald formula [39]. The following lipid and lipoprotein levels were considered normal: TC <5.2 mmol/l, LDL-C <3.89 mmol/l, HDL-C <0.9 mmol/l, TG <1.7 mmol/l.

Lipid peroxidation products determination: Conjugated dienes (CDs) and end-product – malonyl dialdehyde (MDA) levels in blood plasma were evaluated with spectrofluorofotometer «Shimadzu RF-1501» (Japan). The CDs concentrations were detected by absorbance of plasma heptanes extracts at 232 nm [40]. Coefficient of molar absorption ($K=2.2\times10^5\ M^{-1}\ C^{-1}$) was used for absorption units to μmol/L conversion.

MDA levels were determined by reaction with thiobarbituric acid followed fluorescence intensity at 515 nm (excitation) and 554 nm (emission) measurement [41]. MDA concentration was expressed in μmol/L.

Antioxidant system parameters determination: Antioxidant system activity was detected by measurement of α-tocoferol, retinol levels in serum and reduced and oxidized glutathione (GSH, GSSG) levels in red cells using the spectrofluorofotometer «Shimadzu RF-1501» (Japan).

GSH and GSSG levels were detected in erythrocytes and performed at $\lambda=350$ nm (excitation) and $\lambda=420$ nm (absorption) [42]. Concentrations were expressed in mmol/L.

Alfa-tocopherol and retinol levels were detected in the plasma [43]. 0.2 mL of the plasma and 1 mL H_2O was added in the samples. After

shaking the samples 1 mL C_2H_5OH was added. After incubation for 15-20 min at 4°C, 5 mL C_6H_{14} was added in the samples and was shaken for 45 min. Then the samples stayed for 20 min and measurement was performed at λ=294 nm (maximum excitation) and λ=330 nm (maximum radiation) for α-tocopherol and at λ=335 nm (maximum excitation) and λ=460 nm (maximum radiation) for retinol. Concentrations were expressed in mcmol/L.

Statistical analysis

Statistical analysis was performed by STATISTICA 6.1 software (Stat-Soft Inc., USA) with parametric T-test (Student) and non-parametric U-test (Mann-Whitney) with significance level p<0,05. For descriptive analysis, results are presented as mean ± standard deviation (SD), median (inter-quartile range), 25th-75th percentile.

Results

Questionnaire and PSG results are shown in Table 2. PSQI, ISI and ESS points were higher in main groups as compared to controls. Moreover, ESS points were higher in groups with OSAS as compared to insomnia. The decrease of sleep

Table 2: Questionnaire and polysomnographic monitoring results in menopausal women.

Parameters	Perimenopause			Postmenopause			p-value
	control	insomnia	insomnia and OSAS	control	insomnia	insomnia and OSAS	
	n=19	n=19	n=18	n=26	n=27	n=17	
	(1)	(2)	(3)	(4)	(5)	(6)	
	Mean ± SD						
PSQI (points)	2.11 ± 0.53	16.21 ± 3.11	15.87 ± 2.63	3.08 ± 1.36	14.99 ± 1.98	16.12 ± 1.85	P1-2* P1-3* P4-5* P4-6*
ISI (points)	3.13 ± 0.97	22.8 ± 0.69	22.46+1.03	4.05 ± 2.11	25.2 ± 0.72	24.22 ± 2.90	P1-2* P1-3* P4-5* P4-6*
ESS (points)	1.64 ± 0.33	6.63 ± 0.54	12.39 ± 2.44	2.08 ± 1.02	7.42 ± 1.88	15.31 ± 0.83	P1-2* P1-3* P2-3* P4-5* P4-6* P5-6*
Sleep efficiency (%)	96.21 ± 2.20	75.14 ± 3.32	71.74 ± 8.43	92.51 ± 5.93	70.32 ± 3.42	68.41 ± 5.43	P1-2* P1-3* P4-5* P4-6*
Sleep latency (min)	19.28 ± 6.15	49.53 ± 2.11	38.10 ± 5.38	22.33 ± 18.16	36.69 ± 9.76	46.44 ± 6.12	P1-2* P1-3* P4-5* P4-6*
N1 (%)	5.52 ± 1.61	7.90 ± 3.15	51.15 ± 3.71	7.61 ± 4.17	10.10 ± 5.69	6.92 ± 2.82	-
N2 (%)	58.25 ± 15.90	53.51 ± 18.41	61.51 ± 15.94	53.95 ± 7.02	58.19 ± 19.24	64.24 ± 18.77	-
N3 (%)	23.20 ± 5.85	18.64 ± 5.78	11.10 ± 4.99	19.42 ± 3.85	15.94 ± 7.46	10.20 ± 6.10	P1-3* P4-6*
REM (%)	20.17 ± 5.65	21.72 ± 10.41	22.81 ± 12.14	25.89 ± 4.33	21.76 ± 14.15	20.65 ± 9.80	-
AHI (event/hour)	3.21 ± 0.53	4.82 ± 1.50	13.27 ± 2.42	4.11 ± 0.15	5.51 ± 0.28	15.22 ± 3.48	P1-3* P2-3* P4-6* P5-6*
SaO_2 (%)	96.45 ± 3.59	95.61 ± 0.28	90.11 ± 3.10	96.27 ± 2.12	93.36 ± 0.58	90.15 ± 4.58	-

PSQI: Pittsburgh Sleep Quality Index; ISI: Insomnia Severity Index; ESS: Epworth Sleepiness Scale; N1: Non-rapid eye movement sleep stage 1; N2: Non-rapid eye movement sleep stage 2; N3: Non-rapid eye movement sleep stage 3; REM: Rapid Eye Movement; AHI: Apnea-h=Hypopnea Index; SaO_2: Oxygen Saturation.
*- p<0.05

efficiency and the increase of sleep latency were found in main groups as compared to controls. The time of non-rapid eye movement sleep stage 3 was less in group with OSAS as compared to control.

Table 3 summarized lipid profile in women with sleep disorders and control. TC and LDL-C levels were significant higher in perimenopausal women with insomnia and OSAS as compared to control and group with insomnia ($p<0.05$). Also, the increase of TC, TG, LDL-C, VLDL-C levels and decrease of HDL-C level were found in postmenopausal women with insomnia and OSAS as compared to control and group with insomnia ($p<0.05$).

Table 4 summarized lipid peroxidation and antioxidant system parameters in peri- and postmenopausal women. CDs levels were significant higher in group with insomnia as compared to control and group with insomnia and OSAS in perimenopause ($p<0.05$). CDs and MDA levels in insomnia group and MDA levels in group with insomnia and OSAS were significant higher as compared to control in postmenopause ($p<0.05$). No differences in α-tocopherol, retinol, GSH, GSSG between main groups and controls both perimenopause and postmenopause registered.

Discussion

It has been proposed that cerebral free radicals accumulating during wakefulness and are removing during sleep. Removal of excess free radicals during sleep is accomplished by decreased rate of free radicals and increased efficiency of endogenous antioxidant mechanism [44]. So sleep disorders may lead to the accumulation of free radicals in the body.

The results of the experimental studies insomnia and oxidative stress association are ambiguous. Thus, sleep loss may be oxidative damage cause of the brain, because it is sensitive to oxidative stress due to polyunsaturated fatty acids high content in the brain cells membranes and low antioxidant capacity [10]. But other study have not shown any changes in rats brain, liver, skeletal muscle proteins free radical oxidation and lipids parameters at 1-2 week of sleep deprivation [9]. Moreover, lipid peroxidation parameters association with sleep deprivation time has been found. Thus, it has been shown an increase of MDA blood plasma level at 48 h and 72 h, while minimal change at 24 h and 96 h of sleep deprivation period [11]. Also, there are differences in antioxidant defense system parameters depending on the sleep deprivation period. Thus, at short-term total sleep deprivation (6 h) there is increase GSH level in the cortex,

Table 3: Lipid profile parameters in menopausal women with sleep disorders and control.

Parameters	Perimenopause			Postmenopause			p-value
	control	insomnia	insomnia and OSAS	control	insomnia	insomnia and OSAS	
	n=19	n=19	n=18	n=26	n=27	n=17	
	(1)	(2)	(3)	(4)	(5)	(6)	
	Mean ± SD Median 25th–75th percentile						
TC, (mmol/L)	4.38 ± 0.85 4.24 3.80-5.18	4.51 ± 1.05 4.05 3.82-5.09	5.23 ± 1.18 5.43 4.46-6.01	5.36 ± 1.20 5.08 4.53-6.04	5.06 ± 1.25 4.94 4.21-5.73	6.37 ± 1.21 6.19 5.21-7.38	P1-3* P2-3* P1-4* P4-6* P5-6*
TG, (mmol/L)	0.93 ± 0.56 0.80 0.49-1.19	0.92 ± 0.52 0.88 0.45-1.18	0.98 ± 0.39 0.95 0.79-1.08	1.12 ± 0.53 1.03 0.69-1.30	1.07 ± 0.58 0.97 0.63-1.37	1.63 ± 0.22 1.59 1.51-1.78	P4-6* P5-6*
HDL-C, (mmol/L)	1.26 ± 0.28 1.33 0.99-1.50	1.25 ± 0.34 1.23 1.00-1.48	1.18 ± 0.26 1.23 0.93-1.33	1.16 ± 0.23 1.10 0.98-1.37	1.23 ± 0.33 1.16 1.04-1.37	0.91 ± 0.19 0.88 0.80-1.02	P4-6* P5-6*
LDL-C, (mmol/L)	2.64 ± 0.84 2.40 2.07-3.19	2.85 ± 0.88 2.62 2.25-3.51	3.61 ± 1.21 4.02 2.81-4.30	3.69 ± 1.11 3.58 2.84-4.35	3.36 ± 1.12 3.35 2.55-3.69	4.78 ± 0.79 4.55 4.26-5.42	P1-3* P2-3* P1-4* P4-6* P5-6*
VLDL-C, (mmol/L)	0.42 ± 0.26 0.33 0.22-0.54	0.42 ± 0.24 0.40 0.20-0.54	0.45 ± 0.18 0.43 0.36-0.49	0.51 ± 0.24 0.47 0.31-0.59	0.49 ± 0.26 0.44 0.29-0.62	0.69 ± 0.20 0.68 0.54-0.78	P4-6* P5-6*
p<0.05							

Table 4: Lipid peroxidation–antioxidant system parameters in women with sleep disorders and control.

Parameters	Perimenopause			Postmenopause			p-value
	control	insomnia	insomnia and OSA	control	insomnia	insomnia and OSA	
	n=19	n=19	n=18	n=26	n=27	n=17	
	(1)	(2)	(3)	(4)	(5)	(6)	
	Mean ± SD Median 25th–75th percentile						
CDs, (μmol/L)	1.10 ± 0.35 1.14 0.92-1.40	1.38 ± 0.89 1.26 0.70-1.62	0.95 ± 0.60 0.88 0.46-1.44	1.23 ± 0.70 1.10 0.66-1.88	1.75 ± 0.69 1.80 1.06-2.18	1.39 ± 0.81 1.34 0.66-1.74	P1-2* P2-3* P4-5*
MDA (μmol/L)	1.14 ± 0.52 1.00 0.67-1.48	1.34 ± 0.52 1.25 1.03-1.67	1.12 ± 0.32 1.11 0.83-1.33	0.89 ± 0.27 0.87 0.67-1.12	1.08 ± 0.33 0.95 0.87-1.28	1.13 ± 0.45 0.92 0.77-1.61	P4-5* P4-6* P1-4*
GSH (mmol/L)	2.67 ± 0.53 2.61 2.36-3.16	2.52 ± 0.48 2.59 2.21-2.81	2.68 ± 0.37 2.68 2.49-2.89	2.46 ± 0.45 2.36 2.22-2.56	2.50 ± 0.54 2.40 2.17-2.95	2.51 ± 0.48 2.54 2.09-2.72	-
GSSG (mmol/L)	2.17 ± 0.60 2.11 1.64-2.62	1.84 ± 0.41 1.81 1.56-2.14	1.85 ± 0.53 1.77 1.32-2.36	1.87 ± 0.35 1.84 1.64-2.02	1.95 ± 0.48 1.86 1.52-2.21	1.90 ± 0.50 1.74 1.60-2.14	P1-4*
α-tocopherol (mkmol/L)	8.71 ± 2.56 9.01 6.46-9.95	8.51 ± 4.00 7.51 5.70-9.43	8.14 ± 2.43 8.26 5.87-10.63	6.35 ± 1.42 5.93 5.32-7.33	6.89 ± 3.00 5.82 5.07-7.70	6.68 ± 1.55 6.81 5.51-7.04	P1-4*
retinol (mkmol/l)	0.73 ± 0.19 0.67 0.61-0.86	0.79 ± 0.31 0.81 0.53-0.93	0.66 ± 0.23 0.59 0.52-0.78	0.64 ± 0.18 0.63 0.49-0.77	0.65 ± 0.19 0.59 0.47-0.89	0.68 ± 0.19 0.73 0.55-0.79	P1-4*
p<0.05							

brain stem and basal forebrain, and glutathione peroxidase activity in the hippocampus and cerebellum [8], and decrease Cu/Zn-superoxide dismutase activity in the hippocampus and brain stem at 5-10 days sleep deprivation [7].

Some studies have reduced glutathione peroxidase activity and increased MDA levels have shown in human insomnia, whereas myeloperoxidase and superoxide dismutase activity and glutathione level not changed [33]. Patients with insomnia have reduced total antioxidant status and increased systemic oxidative stress. Authors suggested that decreased of paraoksanase activity may play role in the development of oxidative stress in these patients [34]. However, main groups of these studies include both men and women, and gender influence was not considered, although gender differences in lipid peroxidation – antioxidant defense system are evident [45]. Zhao et al. study have demonstrated lower serum uric acid levels in patients with chronic insomnia that can lead to oxidative stress because uric acid is considered as a major antioxidant. Moreover, among chronic insomnia patients, decreased serum uric acid levels were associated with poor sleep quality [46].

In our investigation both insomnia and insomnia with OSAS with the development of oxidative stress and accumulation of lipid peroxidation products was found only in postmenopausal women that can be connected with duration of sleep disorders and mild OSAS in perimenopausal women. However, changes in antioxidant defense system parameters were not found. Our findings are consistent with Hachul et al. who also demonstrated an increased thiobarbituric acid reactants level and similar with control catalase and superoxide dismutase activities in postmenopausal women with insomnia [32].

It is possible that sleep has a regulating role in lipid homeostasis [4,5]. The results of study in Chinese population have shown the decrease in choline plasmalogen levels demonstrating that these lipids are susceptible to degradation by oxidative stress and the increase in phosphatidylcholines and triacylglycerides in men with sleep deprivation [6]. Another study has not shown a lipid metabolism changes and insomnia association in men. However, dyslipidemia and insomnia association with the increase in total cholesterol levels has been found in menopausal women with frequent insomnia. One of the mechanisms proposed to explain the insomnia and dyslipidemia link might be the increase activity of hypothalamicpituitary-adrenal-axis and excessively cortisol secretion [47]. Increased midnight cortisol levels in menopausal women with primary chronic insomnia have been

demonstrated in Seeling et al. study. However, it was not associated with impaired metabolism of lipids [48], which agrees with our data.

It is known that hypoxia during OSAS is a stress factor which may change free radical homeostasis, manifested in reactive oxygen products deficiency and activation of lipid peroxidation [49,50]. Thus, an increasing of free radicals level in leukocytes [18], plasma, urine and condensate of exhaled air [25], intensification of lipid peroxidation processes [19,25,26], oxidation of DNA [20] have been demonstrated in patients with OSAS. However, some studies have not shown assosiation of oxidative stress with OSAS [21-23]. This leaves the question of its association with this pathology. The results of our study demonstrated no differences in lipid peroxidation and GSH, GSSG, retinol, α - tocopherol levels in women with insomnia and OSAS as compared to women only with insomnia. Simiakakis et al. in their study has found that obesity and smoking have a greater impact on the development of oxidative stress than hypoxia, whose role is to enhance the already existing oxidative stress [29].

Moreover, reduced antioxidant activity in patients with OSAS without influence obesity and smoking has been shown. It may be due to the genes disregulation involved in the modulation of reactive oxygen species or enzymatic antioxidants. A decrease of total antioxidant activity in patients with OSAS has been also demonstrated in some studies [25,51], however, there were no changes in the superoxide dismutase [22] and glutathione peroxidase activity [51]. Moreover, it has been shown that oxidative stress intensity correlates with the degree of OSAS severity [24,28,30]. High frequency of hypoxia episodes leads to more pronounced oxidative stress and oxidation of DNA involving anti-aging genes. Down regulation of anti-aging genes reduces hepatic xenobiotic metabolism that lead to involvement toxic compounds in nuclear receptor dysfunction such as the nuclear receptor Sirtuin 1 [52]. Sirtuin 1 involves in epigenetic processes and its defects lead to defective xenobiotic metabolism with effects on mitophagy and corruption of the nuclear-mitochondria interaction. It has been shown Sirtuin 1 regulates the suprachiasmatic nucleus in the hypothalamus with effects on melatonin secretion [53].

Melatonin plays an important role in activation of antioxidant system enzymes, such as superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and glucose-6-phosphate dehydrogenase [54]. So, melatonin deficiency might contribute to the development of oxidative stress. It is well known that melatonin hormone is one of the key regulators of circadian biorhythms and violation of its secretion in menopausal women might lead to changes in metabolism and the formation of various diseases, including sleep disturbances. Studies carried out to date have been shown that people with insomnia have a lower melatonin level [55]; moreover, the peak of the hormone secretion is shifted, which have been demonstrated in the study on the association of melatonin, menopausal depression and sleep time. A delay in the peak of hormone secretion before morning have been revealed in women with menopausal depression, which, according to researchers, may be caused by longer sleep duration as a compensation for insomnia in these women [56]. Similar results have been obtained in our study in which the shift in the peak of melatonin secretion in the early morning hours in women with insomnia in perimenopause was shown. In postmenopause, the morning melatonin peak has been also noted, regardless of the presence of insomnia [57]. The present study further have revealed the association of melatonin secretion circadian rhythms with *Clock 3111T/C* gene polymorphism in Caucasian patients with insomnia, consisting of an increased hormone level in early morning hours in carriers of the *TT*-genotype, which allows considering *3111T* allele as risky in the formation of melatonin circadian rhythm disturbances in these patients [58]. Moreover, differences in the circadian rhythms of melatonin in the Asian women depending on the genotype of the *Clock 3111T/C* polymorphism have not been found. Is there circadian rhythm melatonin and oxidative stress relationship in women of different ethnic groups with insomnia is unclear. The results of some studies have demonstrated links between the circadian clock and Sirtuin 1 function. It is possible that Sirtuin 1 defects lead to suprachiasmatic nucleus in the hypothalamus defects are related to the peripheral circadian clock dyssynchrony [52,59]. Probably, oxidative stress severity in Asian women with insomnia will differed from Caucasian ones. However, to proof this hypothesis, further researches are required.

It has been shown that insomnia leads to memory impairment and memory depends on the subtype insomnia [60]. Also, close relationship of insomnia and mental diseases [61], obesity

[62], cardiovascular diseases [63], diabetes [64], oncology [65] in whose pathogenesis there is role of oxidative stress has been significant proved. So, lipid peroxidation investigations in patients with sleep disorders deserve special attention for development of preventive and curative measures to improve health and quality of life.

Conclusions

It is well known that xenobiotic biotransformation is reduced with aging. Xenobiotics induce epigenetic changes that involve chromatin remodelling by alterations in transcriptional regulators with modification of histones that lead to metabolic disorders with neurodegeneration. Sirtuin 1 defects lead to suprachiasmatic nucleus in the hypothalamus defects and changes of melatonin level [66]. Firstly, melatonin is one of the key regulators of circadian biorhythms and violation of its secretion might lead to the formation of insomnia with cerebral free radicals accumulation [55]. Secondly, melatonin plays an important role in antioxidant system and its deficiency might contribute to the development of oxidative stress [54].

Our data proved that both insomnia and insomnia comorbidity with OSAS are associated with oxidative stress only in postmenopausal women. It is possible that the duration of sleep disorders influences the accumulation lipid peroxidation products. There are no differences in the accumulation of MDA between insomnia and insomnia with OSAS that can be connected with mild OSAS in perimenopausal women and moderate OSAS in postmenopausal ones.

Conflict of Interest

The authors state no conflict of interest.

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