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The impact of post-traumatic stress disorder on indicators of carbohydrate and lipid metabolism, metabolic age of civilian women during war

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Abstract. The consequences of post-traumatic stress associated with war are not only mental disorders, but also various unfavorable changes in physical functioning, in particular, metabolic disorders. Previous studies have shown an association between posttraumatic stress disorder (PTSD) and obesity, metabolic syndrome, and type 2 diabetes in military veterans. It has also been established that PTSD accelerates the rate of biological aging at the cellular level. However, the impact of PTSD on the frequency and manifestations of metabolic disorders in civilian women remains poorly understood. **Aim.** To determine the impact of PTSD on the state of carbohydrate and lipid metabolism, metabolic age (MA), and rate of metabolic aging (RMA) in women during the war. **Subjects and methods.** During the war, 120 civilian women aged 30-79 years without clinically significant diseases were examined, including 26 with PTSD and 94 without it. Data of 79 women of the same age examined before the war were used for comparison. The examination included analysis of PCL-5 questionnaire, enzyme immunoassay methods for determining cortisol and insulin in blood plasma, biochemical methods for determining glucose and lipids in blood, calculation of MA and RMA. **Results.** During the war, women without PTSD, compared with women examined before the war, had higher plasma insulin concentrations and an insulin resistance index, but plasma glucose levels were not yet changed. Women with PTSD, in addition to higher insulin concentrations and an insulin resistance index, had a statistically significantly higher fasting plasma glucose level during the war. In all age groups of women with PTSD during the war, the proportion of people with prediabetes was higher than before the war. Dyslipidemia was more common in young women with PTSD than before the war. In women with PTSD during the war, the RMA increases. **Conclusions.** During wartime in women with PTSD develop insulin resistance, which leads to prediabetes disorders of carbohydrate metabolism. In women with PTSD, the frequency of dyslipidemia is higher, the MA increases, and the RMA accelerates compared to the before the war level.

Keywords: posttraumatic stress disorder, civilian women, prediabetes, dyslipidemia, metabolic age.

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PTSD, which during war is a consequence of the impact on the body of strong or extreme stress factors, has not only a devastating effect on mental health, but can also provoke adverse changes in physical functioning. Among them are disorders of carbohydrate and lipid metabolism, metabolic syndrome, obesity [1-4], which are endogenous factors of cardiovascular risk. Pathological changes in metabolism accompanying PTSD lead first to the development of prediabetes, and then to DM2 [5, 6], which, in turn, significantly increase the risk of cardiovascular diseases and their complications [7].

Recently, considerable attention has been paid to the study of the impact of PTSD on aging processes [8, 9]. Studies on the determination of biological age of DNA methylation have shown a higher rate of aging in veterans with PTSD than in veterans without PTSD [10]. War veterans also experience shortening of telomere length compared to men without prior military experience [11, 12]. Thus, intense stress influences accelerate the processes of cellular aging. Accelerated aging, in turn, increases the risk of cardiometabolic diseases, which are the leading cause of death [7, 13].

Previous studies have shown that during wartime, civilian women have an increased MA compared to women examined before the war [14]. However, the impact of PTSD on MA and RMA during wartime has not been examined.

The aim of the work was to determine the impact of PTSD on the state of carbohydrate and lipid metabolism, MA, and RMA of civilian women during the Russian-Ukrainian war.

Material and methods

The study was conducted at the clinic of the State Institution «D.F. Chebotaryov Institute of Gerontology of the NAMS of Ukraine» in accordance with the laws of Ukraine and the principles of the Helsinki Declaration of Human Rights. The examination program, information for the patient, and the informed consent form were approved by the ethics committee of the clinical department of the State Institution «D.F. Chebotaryov Institute of Gerontology of the NAMS of Ukraine» (protocol No. 3 dated May 9, 2022). All subjects received detailed information about the study procedures.

For inclusion in the study the informed consent was signed before the start of the examination, the absence of a significant disease in the anamnesis and at the time of inclusion in the study. Patients with exacerbation or decompensated conditions of chronic diseases of the cardiovascular, digestive, respiratory systems, with type 1 and type 2 diabetes, and with oncological diseases were not included in the examination.

During the russian-ukrainian war, 122 civilian women aged 30-79 years without clinically significant diseases were examined, including the groups of 30-44 years (27 people), 45-59 years (48 people) and 60-79 years (47 people). During active hostilities in February and March 2022, they were in Kyiv or the Kyiv region. Some of those examined were under occupation for a long time. Others were strongly affected by such factors of war as rocket and artillery shelling, staying in bomb shelters or other shelters from May 2022 to July 2024. For comparison, data from 79 civilian women aged 30-79 were used, including 14 people in the age group of 30-44, 30 people aged 45-59, and 35 people aged 60-79, who were examined before the full-scale invasion of the russian federation into Ukraine (control group).

As basic therapy, patients in both groups could take ACE inhibitors, statins, and a prophylactic dose of acetylsalicylic acid, provided that they were used in a constant dose for at least a month before inclusion in the study and throughout the study.

Screening of the subjects for PTSD symptoms was performed using the PCL-5 questionnaire, which consists of 20 questions, each of which is scored from 0 to 4 points depending on the severity of the manifestation [15]. The total score was calculated by adding up the number of points for each answer. The minimum score is 0, the maximum is 80. For the diagnosis of PTSD, it was mandatory exposure to a traumatic event, and the total score on the PCL-5 questionnaire must be 33 or higher.

The subjects were measured for fasting plasma glucose concentration and after a 2-hour standard glucose tolerance test (GTT), serum lipid concentration, blood plasma cortisol and insulin, and the insulin resistance index (HOMA-IR), MA, and metabolic aging rate as the difference between metabolic and chronological age (CA) were calculated.

Glucose in blood plasma was determined by the glucose oxidase method on a semi-automatic biochemical analyzer BTS-330 («BioSystems», Spain), using the «Glucose» reagents of the «BIO-LA-TEST» («Erba Diagnostics», Germany). To detect prediabetic disorders of carbohydrate metabo-

lism, a standard oral GTT was performed [16]. At a fasting plasma glucose level of 6.1 to 6.9 mmol/L, impaired fasting glycemia was diagnosed. At a plasma glucose level after 2-hours standard GTT of 7.8 to 11.0 mmol/L, impaired glucose tolerance was diagnosed. Both disorders or their combination were designated as «prediabetes».

To assess the state of lipid metabolism, the levels of cholesterol (C), high-density lipoprotein C (HDL-C) and low-density lipoprotein C (LDL-C), and triglycerides (TG) in blood serum were determined using standard biochemical methods by an biochemical analyzer «BM Autolab PM 4000/3» («Boehringer Mannheim», Germany). The levels of C and TG were investigated by the enzymatic colorimetric method, and HDL-C – by the precipitation method with phosphoric-tungstic acid using BIO SYSTEMS reagents. The LDL-C level was calculated using accepted mathematical formulas. Dyslipidemia was diagnosed if two of the following criteria were present: C >6.2 mmol/L, LDL-C >4.1 mmol/L, HDL-C <1.3 mmol/L, and TG >1.7 mmol/L [17].

The concentration of insulin and cortisol in blood plasma was determined by enzyme-linked immunosorbent assay using DRG Insulin ELISA and DRG Cortisol ELISA kits (DRG Instruments GmbH, Germany). Insulin resistance index (Homeostasis Model Assessment for Insulin Resistance, HOMA-IR) was calculated using the formula [18]:

HOMA-IR = fasting plasma glucose × fasting plasma insulin / 22.5

MA was determined by the formula that we obtained from the data of 180 healthy people aged 20 to 80 examined before the war:

$$MA = 0.588 \times X1 + 2.838 \times X2 + 5.946 \times X3 + 1.53 \times X4 + 0.60 \times X5 - 49.2$$

where:

X1 – ratio of waist circumference to height squared, $cm \times m^2$;

X2 – blood plasma glucose concentration after 2 hours of GTT, mmol/L;

X3 – fasting blood plasma glucose concentration, mmol/L;

X4 – urea concentration in blood serum, mmol×L,

X5 – CA.

The RMA of the body is the difference between the determined MA and CA.

Statistical data processing was performed using the Statistica 7 program (Statistica 7, USA). The significance of differences in mean values of indicators in groups was determined by the Student's t-test. Differences were considered significant at $p<0.05$.

Results and discussion

Stress in general is an adaptive reaction of the body, which helps it adapt to new conditions of functioning. At the same time, prolonged stress leads to disruption of adaptive reactions and a decrease in the functional capabilities of the body. The consequence of the long-term effect of strong or extreme stress factors during war is PTSD. At the same time, as studies show, PTSD did not develop in all people who have been exposed to the stress factors of war. That is, most people are resistant to the development of PTSD. Only 20% of those who have experienced post-traumatic stress subsequently have serious psychological problems, while the majority use their self-control abilities, which allow them to successfully adapt and readapt after a traumatic experience**.** In regions where civilians have been exposed to prolonged and intense stress, the incidence of PTSD may be higher than in the military. For example, according to [19], the incidence of PTSD among displaced persons who were in a combat zone was 23.5%.

In our study, screening for PTSD in civilian women was conducted according to generally accepted recommendations [15]. The number of detected cases of PTSD was different in the three age groups – in 11 of 27 people at the 30-44 age group, in 10 of 48 people at the 45-59 age group, and in only 5 of 47 people at the 60-79 age group. That is, the frequency of detection of PTSD during war is the highest in young women and lowest in older women (respectively, 40.7% and 10.6%, $p<0.05$).

According to the results of the analysis of the PCL-5 questionnaire, PTSD manifestations were detected mainly in young and middle-aged women. That is why the effect of PTSD on carbohydrate and lipid metabolism, MA and metabolic aging rate was studied in women aged 30-59 years.

Women with PTSD, compared with women without PTSD, had a significantly higher total score of the PCL-5 questionnaire, 40.3±1.8 and 16.5±1.2 points ($p<0.01$), respectively.

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The results of the study showed that the plasma cortisol concentration was statistically significantly ($p<0.05$) higher in the group of women with PTSD (536±82 mmol/L) than in women examined before the war (345±20 mmol/L). This indicates a more pronounced stress strain of the pituitary-adrenal system in women with PTSD during the war.

Women without PTSD during the war, compared to women before the war, have significantly higher insulin concentrations and insulin resistance index, but their blood plasma glucose levels are the same as those of women before the war **(Table 1)**.

Table 1. Indicators of carbohydrate and lipid metabolism in group of women aged 30-59 before and during the war (M±m)

Indicators	Before the war (n =44)	During the war, without PTSD (n =55)	During the war, with PTSD (n =20)
Fasting plasma glucose, mmol/L	5.23±0.08	5.32±0.09	5.58±0.12*
Plasma glucose after 120 min of GTT, mmol/L	5.86±0.21	6.48±0.24	6.25±0.39
Fasting plasma insulin, μUm/L	9.1±1.0	15.4±1.1*	14.6±1.2*
HOMA-IR insulin resistance index	1.99±0.25	3.58±0.27*	3.61±0.29*
C, mmol/L	5.59±0.17	5.96±0.15	5.59±0.28
HDL-C, mmol/L	1.63±0.03	1.64±0.05	1.57±0.05
LDL-C, mmol/L	3.45±0.16	3.80±0.16	3.46±0.26
TG, mmol/L	1.14±0.08	1.18±0.08	1.25±0.19
Atherogenic index, conv.un.	2.44±0.10	2.77±0.15	2.59±0.18

*Note. * p<0.05 compared to the before the war.*

Women with PTSD, along with higher insulin concentrations and a higher insulin resistance index, also had higher blood plasma glucose level. In addition, during the war, all age groups of women with PTSD had a higher proportion of individuals with prediabetes disorders than in the corresponding age groups of women examined before the war **(Table 2)**.

Dyslipidemia was more frequently detected in young women with PTSD during the war than in those examined before the war.

Women examined before the war did not show a significant excess of MA over CA **(Table 3)**. That is, they did not have accelerated metabolic aging. Women who were not diagnosed with PTSD during the war had a slight increase in the RMA by one year compared to those examined before the war.

Table 2. Frequency of detection of prediabetes disorders and dyslipidemias in civilian women of different ages before and during the war, %

Age groups, years	Before the war (n=44)	During the war, without PTSD (n=55)	During the war, with PTSD (n=20)
Prediabetes disorders			
30-44	0	12.5	18.2 *
45-59	10.3	30.8	44.4 *
60-74	30.3	42.9	60.0 *
Dyslipidemias			
30-44	14. 3	25 .0	54.5 *
45-59	37. 9	51. 3	55. 6
60-74	33. 3	64. 1	60.0

*Note. * p<0.05 compared to the before the war.*

Table 3. MA and RMA in civilian women before and during the war (M±m)

Indicators	Before the war (n =44)	During the war, without PTSD (n =55)	During the war, with PTSD (n =20)
CA, years	47.3±1.2	49.0±1.0	45.9±1.6
MA, years	51.8±1.2	54.5±1.3	54.4±2.2
RMA, years	4.5±0.6	5.5±0.9	8.5±1.8*

*Note. * p<0.05 compared to the before the war.*

Women with PTSD have a slightly lower CA than women before the war. At the same time, women with PTSD had a higher MA compared to the group of women before the war. In women with PTSD, the RMA is statistically significantly higher than in women examined before the war. Moreover, the RMA (8.5±1.8 years) indicates an accelerated development of age-related changes in women with PTSD manifestations.

During the war, civilians are constantly exposed to many stress factors, which limits the body's adaptive capabilities. This leads to various stress-associated disorders, mental and somatic diseases, disability, and premature death [7, 13, 20].

One of the mechanisms through which the negative impact of post-traumatic stress realizes on human health is considered to be the accelerated development of age-related changes in the body [8]. The hypothesis of accelerated aging in people with post-traumatic stress disorder [9], has been supported in recent years by the results of studies on the determination of biological age by DNA methylation [10, 13, 21]. In war veterans with PTSD, DNA methylation changes characteristic of accelerated aging have been found, which are amplified with an increase in the number and severity of stress disorder symptoms [10]. Other studies

have shown that war veterans have a shortening of telomere length compared to men without previous military experience [11, 12]. The relationship between PTSD and accelerated aging has also been found in civilian populations [22]. Thus, studies have shown that patients with PTSD have accelerated cellular aging. However, the question of the rate of metabolic aging in individuals with PTSD has not been answered.

Our study is the first to show that civilian women with PTSD during wartime had a higher RMA compared to a group of women examined before the war. In women without PTSD during wartime, the RMA was almost the same as before the war. The results of the study complement the concept of accelerated aging in people with PTSD.

Conclusions

1. The frequency of detection of PTSD according to the PCL-5 questionnaire during the war is significantly higher in young women, and it decreases almost 4 times in women over 60 years of age.
2. During wartime, women with PTSD develop insulin resistance, which leads to prediabetes disorders of carbohydrate metabolism. Young women with PTSD are more often diagnosed with lipid metabolism disorders than before the war.
3. During the war, women with PTSD have an increased MA and an accelerated rate of metabolic aging compared to the pre-war level.

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Оригінальні дослідження

Abbreviations

C – cholesterol
CA– chronological age
GTT – glucose tolerance test
HDL-C – high-density lipoprotein cholesterol
LDL-C – low-density lipoprotein cholesterol
MA – metabolic age
PTSD – posttraumatic stress disorder
RMA – rate of metabolic aging
TG – triglycerides

Вплив посттравматичного стресового розладу на показники вуглеводного та ліпідного обміну, метаболічний вік цивільних жінок під час війни

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Резюме. Наслідками посттравматичного стресу, пов'язаного з війною, є не тільки розлади психічного здоров'я, а й різноманітні несприятливі зміни фізичного функціонування, зокрема, метаболічні порушення. Попередні дослідження показали зв'язок між посттравматичним стресовим розладом (ПТСР) і ожирінням, метаболічним синдромом і діабетом 2-го типу у ветеранів війни. Також встановлено, що ПТСР пришвидшує біологічне старіння на клітинному рівні. Проте вплив ПТСР на частоту та прояви метаболічних розладів у цивільних жінок залишається недостатньо дослідженим. **Мета.** З'ясувати вплив ПТСР на стан вуглеводного та ліпідного обміну, метаболічний вік і темп метаболічного старіння жінок під час війни. **Матеріал і методи.** Під час війни обстежено 120 цивільних жінок вікової групи 30-79 років без клінічно значущих захворювань, серед яких було 94 особи без ПТСР та 26 із ПТСР. Для порівняння використано дані 79 жінок такого ж віку, обстежених до війни. Обстеження включало аналіз опитувальників PCL-5, імуноферментні методи визначення в плазмі крові кортизолу та інсуліну, біохімічні методи визначення глюкози в плазмі та ліпідів у сироватці крові, розрахунок метаболічного віку і темпу метаболічного старіння. **Результати.** Під час війни жінки без ПТСР, порівняно з обстеженими до війни, мали вищу концентрацію інсуліну в плазмі та індекс інсулінорезистентності, проте рівень глюкози в крові ще не змінився. Жінки із ПТСР, окрім вищих показників концентрації інсуліну та індексу інсулінорезистентності, під час війни мали статистично значимо вищий рівень глікемії натще. У всіх вікових групах жінок із ПТСР частка осіб із прediабетом вища, ніж до війни. У молодих жінок із ПТСР дисліпідемії виявлялись частіше, ніж до війни. У жінок із ПТСР збільшується темп метаболічного старіння. **Висновок.** Під час війни у жінок із ПТСР виникає інсулінорезистентність, яка призводить до розвитку прediабетичних порушень вуглеводного обміну. У жінок із ПТСР, порівняно із довоєнним рівнем, збільшується частота виявлення дисліпідемій, зростає метаболічний вік та пришвидшується темп метаболічного старіння.

Ключові слова: посттравматичний стресовий розлад, цивільні жінки, прediабет, дисліпідемія, метаболічний вік.

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