

## Male Infertility in Patients with Post-Traumatic Stress is Associated with Increased Serum Lipid Concentration

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<https://dx.doi.org/10.13005/bpj/2703>

(Received: 21 March 2023; accepted: 02 May 2023)

Post-traumatic stress disorder (PTSD) is a psychiatric disorder that can occur after experiencing or witnessing life-threatening events such as combat operations, terrorist attacks, accidents or violent physical attacks, rape, etc. Its prevalence is high and it very often occurs in comorbidity with other psychiatric and physical disorders. PTSD patients often exhibit dysregulated lipid metabolic profiles. The aim of the research was to determine the biochemical concentration of lipids (TC, TG, HDL, and LDL) in men with post-traumatic stress disorder, veterans of the war in Kosovo, who are being treated for infertility. Our study included 72 male patients with primary and secondary infertility. Patients with PTSD were permanent residents of the Dukagjin region (the cities of Pejë, Istog, Deçan, Klinë) in the Republic of Kosovo. Serum lipid concentrations were determined on the COBAS INTEGRA 400 plus apparatus. To determine male fertility, we analyzed the parameters of human ejaculation according to the latest manual (6th, WHO 2021). Criteria that must be met to confirm the diagnosis of PTSD. The following instruments were used in the research: ITQ (International Trauma Questionnaire). In patients with PTSD, the mean TC values were higher ( $6.38 \pm 1.20$ ) than the without PTSD group ( $5.28 \pm 0.37$ ) ( $p=0.018$ ), the concentration of bad cholesterol, LDL was higher in PTSD patients than without PTSD patients ( $4.16 \pm 0.31$  vs.  $3.65 \pm 0.49$ ) ( $p= 0.016$ ), TG also had higher concentrations ( $2.43 \pm 0.64$ ) than without PTSD patients ( $1.78 \pm 0.45$ ), ( $p = 0.036$ ). HDL in PTSD patients ( $1.17 \pm 0.40$ ) was significantly lower in without PTSD patients ( $2.47 \pm 0.50$ ) ( $p = 0.021$ ). BMI had no statistically significant differences between the two groups; with PTSD and non-PTSD ( $26.2$  vs  $25.6$ ) ( $p=0.430$ ). In conclusion, biochemical analyzes of the lipid profile of PTSD patients will help clinicians to reduce the possibility of vascular disease in this population during the treatment of male infertility.

**Keywords:** Infertility; HDL-C; LDL-C; lipids; PTSD.

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Post-traumatic stress disorder (PTSD) is a psychiatric disorder that can occur after experiencing or witnessing life-threatening events such as war, combat operations, terrorist attacks, accidents or violent physical attacks, rape, etc<sup>1</sup>. Its prevalence is high and it often

occurs in comorbidity with other psychiatric and physical disorders<sup>2</sup>. Numerous studies have examined the comorbidity of pain and PTSD in the general population or among war veterans and the impact of this on quality of life<sup>3,4</sup>. PTSD refers to the transmission of nightmares, intrusive

thoughts, flashbacks, and other symptoms typically experienced by traumatized individuals<sup>5</sup>. Elevated serum lipid concentrations have been found in studies of patients with post-traumatic stress disorder (PTSD). However, epidemiological as well as clinical studies have shown that PTSD often co-occurs with other psychiatric disorders<sup>6</sup>. Studies have shown that approximately 80% of individuals with PTSD meet the criteria for at least one additional psychiatric diagnosis. Major depressive disorder (MDD) is one of the most frequent comorbid conditions with PTSD, and the prevalence of MDD in PTSD patients is as high as 70%<sup>7</sup>. Previous studies have suggested that sexual dysfunction is associated with trauma-related mental illness, including PTSD<sup>8</sup>. Lipids play important roles in the brain, including neurogenesis, synaptogenesis, myelin formation, and impulse conduction<sup>9</sup>. Impaired lipid metabolism promotes infertility<sup>10</sup>. As a result of the war in Kosovo (1998-1999) PTSD, depression and emotional distress still remained high within the population<sup>11</sup>. As of 2013, PTSD prevalence rates were still as high as 17.9%. These findings suggest that PTSD constitutes a major public health issue in Kosovo<sup>12</sup>. Kosovo currently has the youngest population in Europe. However, in recent years, the rate of population growth in Kosovo has begun to slow, and the birth rate has decreased as a result of the increase in the rate of infertility with multiple causes among diagnosed male Kosovo war veterans. with PTSD<sup>13</sup>.

### Objective

Determination of the concentration of lipids; **TC**=Total Cholesterol, **TG** = Total triglyceride, **LDL-C** = Low-density lipoprotein cholesterol, **HDL-C**= high-density lipoprotein cholesterol in the serum of patients with post-traumatic stress disorder, veterans of the war in Kosovo. Fat concentrations of patients treated for male infertility and diagnosed with PTSD.

### MATERIALS AND METHODS

Our study included 72 patients with primary and secondary infertility, with permanent residence in the Dukagjin Region (Pej, Istok, Deçan, Klinë cities) in the Republic of Kosovo. This research was carried out at the Biolab Zafi Polyclinic in Klina and at the Biolab-Zafi-F

Medical Laboratory in Pej, Kosovo. Criteria that must be met to confirm the diagnosis of PTSD. During the patient encounter, a 15-20 minute interview was conducted by the Psychiatrist to meet the need for a short but accurate and structured psychiatric interview in multicenter clinical trials. The patients agreed to enter the study in a structured questionnaire on sociodemographic characteristics, health somatics and medication use. The following instruments were used in the research: ITQ (International Trauma Questionnaire)<sup>14</sup>. To determine male fertility, we analyzed human ejaculate (spermiogram), WHO (2021) lists the criteria for the analysis of human ejaculate<sup>15</sup>. Serum lipid concentrations were determined on the COBAS INTEGRA 400 plus, introduced in 2019 by Roche Diagnostics (Basel, Switzerland). Determination of lipidogram parameters was performed using the method: Enzymatic colorimetric test<sup>16</sup>.

### Statistical analysis

BMI and lipid data were analyzed using the t-test for independent samples, taking into account the fact that the lipid value follows a normal distribution curve. All data were saved in Excel and statistical analysis was performed using SPSS software (SPSS for Windows 11.0, Chicago, IL, USA). The obtained values of biochemical analyzes of serum lipids were presented as mean  $\pm$  standard deviation and compared with the test  $50C\ddot{U} < 0.05$  was considered a significant difference.

### RESULTS

All patients (72) were in infertility treatment with the male factor as an infertility factor divided into two groups. The first group of 34 patients was diagnosed with PTSD, and this group consisted of 11 patients who were included in our study in 2015 (13), and 23 patients diagnosed with PTSD from 2016-2022. The second group was the control of 38 patients without PTSD diagnosis but in the treatment of male infertility from 2016-2022. According to the type of infertility, there were 19 patients with primary infertility in the first group and 15 patients with secondary infertility. In the second control group, there were even more patients with primary infertility 22 patients, against 16 patients with secondary infertility. Patients

with PTSD were aged  $49.3 \pm 1.6$  years, mean age of patients without PTSD was  $47.8 \pm 1.5$ . The research subject was quite homogeneous in terms of nationality, all of them were Albanians, veterans of the last war in Kosova.

The obtained results showed that PTSD patients showed higher CT concentrations ( $6.38 \pm 1.20$ ) than the non-PTSD group ( $5.28 \pm 0.37$ ) ( $p=0.018$ ). Our results showed that HDL concentrations in the serum of patients with PTSD ( $1.17 \pm 0.40$ ) was significantly lower than in patients without -PTSD ( $2.47 \pm 0.50$ ) ( $p = 0.021$ ). In contrast, mean LDL concentrations were higher in the group of with-PTSD patients versus without-PTSD patients ( $4.16 \pm 0.31$  vs  $3.65 \pm 0.49$ ) ( $p= 0.016$ ). TG in with-PTSD patients had higher concentrations ( $2.43 \pm 0.64$ ) than without-PTSD patients ( $1.78 \pm 0.45$ ), this was statistically significant ( $p = 0.036$ ). BMI had no statistically significant differences between the two groups; ( $26.2$  vs  $25.6$ ) ( $p=0.430$ ).

The results of spermogram parameters divided into two groups with PTSD and without PTSD showed distinct percentages between the two groups and within the group itself when it comes

to the infertility status of the patients who were the subject of our study. Oligospermia (37.50% vs 26.47%) was greater in patients without PTSD (18 patients) versus those with PTSD (9 patients). Asthenozospermia (50% vs 29.18%) showed a greater presence in patients with PTSD (17 patients) than those without PTSD (14 patients). Oligoasthenozospermia (33.32% vs 20.58%) was greater in percentage in patients without PTSD (16 patients) than those with PTSD (7 patients). There was only one patient with teratozoospermia (2.95%) in the group of PTSD patients.

The results showed that the higher values of lipid status in significant degree of all groups of patients with PTSD compared to the values of lipid status of patients without PTSD ( $p < 0.05$ ). However, the results obtained within the groups of patients divided according to lipid parameters and spermogram parameters did not show significant changes ( $p>0.50$ ).

**DISCUSSION**

PTSD is unique among psychiatric disorders because of the great importance given to

**Table 1.** BMI parameters, CT, LDL, HDL, and TG concentration in patients with PTSD, control group without PTSD, Kosovar veterans in infertility treatment procedure

Parameters	With Post-traumatic stress disorder (34)	Without Post-traumatic stress disorder (38)	p-value
TC (mmol/L)	$6.38 \pm 1.20$	$5.28 \pm 0.37$	0.018
TG (mmol/L)	$2.43 \pm 0.64$	$1.78 \pm 0.45$	0.036
HDL (mmol/L)	$1.17 \pm 0.40$	$2.47 \pm 0.50$	0.021
LDL (mmol/L)	$4.16 \pm 0.31$	$3.65 \pm 0.49$	0.016
BMI (kg/m <sup>2</sup> )	26.2	25.6	0.430

TC=Total Cholesterol, TG = Total triglyceride, LDL-C = Low density lipoprotein cholesterol, HDL-C= high density lipoprotein cholesterol

**Table 2.** The distribution of PTSD and non-PTSD patients according to spermogram parameters

Group	Nr	Abstinence (day)	Volume (ml)	*OS	**AS	***OAS	****TS
Patients with PTSD% (n)	34	9-13(10)	3.8-7.5(6.5)	26.47 %(9)	50 %(17)	20.58 % (7)	2.95 %(1)
Patient without PTSD % (n)	38	2-6(4)	2.3-6.0(4.3)	37.50 %(18)	29.18 %(14)	33.32 %(16)	0.00 %(0)

\*Oligoasthenozospermia. \*\*Asthenozospermia. \*\*\*Oligoasthenozospermia. \*\*\*\*Teratozoospermia

**Table 3.** Lipid profile in patients with PTSD and without PTSD according to spermogram parameters

Lipids	Patients with PTSD			Patients-without PTSD			p		
	*OS	**AS	***OAS	****TS	*OS	**AS		***OAS	****TS
TC	6.38±0.37	6.47±0.35	6.39±0.43	6.31±0.67	5.17±0.26	5.28±0.42	5.26±0.37	5.24±0.57	0.018
TG	2.39±0.34	2.58±0.49	2.41±0.64	2.24±0.54	1.67±0.47	1.91±0.45	1.81±0.45	1.76±0.45	0.036
HDL	1.19±0.45	1.14±0.75	1.18±0.55	1.20±0.35	1.53±0.50	1.48±0.50	1.47±0.50	1.37±0.50	0.021
LDL	4.11±0.41	4.19±0.31	4.16±0.48	4.18±0.67	3.55±0.59	3.85±0.59	3.45±0.59	3.58±0.59	0.016

\*Oligoasthenozoospermia, \*\*Asthenozoospermia, \*\*\*Oligoasthenozoospermia, \*\*\*\*Teratozoospermia

TC=Total Cholesterol, TG = Total triglyceride, LDL-C = Low density lipoprotein cholesterol, HDL-C= high density lipoprotein cholesterol

the etiological factor, i.e., the traumatic stressor<sup>17</sup>. The problem of post-traumatic stress disorder (PTSD) caused by war trauma is present in the Republic of Kosovo in the last twenty-three years after the post-war period. Our results cannot be generalized to patients who developed PTSD in a non-military setting. Our sample consisted only of male patients, veterans of the last war in Kosovo, who were being treated for infertility with primary or secondary male factors such as Oligospermia (reduction in the number of spermatozoa in the human ejaculate), Asthenospermia (decreased sperm motility), Teratozoospermia (decreased normal sperm morphology in human ejaculate) or their combination and this condition was associated with sexual dysfunction (disordered impotence) in PTSD patients. Eliahu Levitas, M.D. et al., (2005) concluded that erectile dysfunction is the most common symptom in PTSD patients. Erection is a hormonally and psychologically controlled neurovascular phenomenon<sup>18</sup>. Male factor infertility is reported to account for 30-40% of couple infertility cases. Infertility is defined as the inability to achieve a successful pregnancy after 12 months of unprotected intercourse or therapeutic donor insemination<sup>19</sup>. Our study is the first study conducted in Kosovo on the relationship between serum lipids; CT, HDL, LDL, and TG in men with infertility and post-traumatic stress disorder (PTSD). It is important to note that our study sample consists of 72 patients, which can be considered small, but our explanation is based on the criteria that the patients of the first group had to fulfill. Limitations were related to the first group (PTSD + male infertility). In terms of control, we could increase it several times more, but they thought it would be a numerical issue. In our study, the mean age of all PTSD and non-PTSD patients was (49.3 ± 1.6 vs 47.8 ± 1.5). Other authors (Iwasaki A, et al. 1992) have concluded that the proportion of men who were 45 years or older with PTSD had a high TC/HDL ratio<sup>20</sup>. Our patients of both groups had slightly overweight BMI values (26.2 vs 25.6), but the values were not statistically significant between the two groups of patients (p=0.430). In 2017, our group was the author of a study that addressed the role of obesity in male infertility in Kosovar men from the Dugagjin Region. The results of this study show that obesity in our country, the Republic of Kosovo, is a growing problem in the development

of public health and is an important risk factor for the occurrence of male infertility. The increase in BMI values contributes to the deterioration of sperm parameters in the human ejaculate; decrease in number, decrease in movement, and normal morphology<sup>21</sup>. Even other authors such as Sharain Suliman *et al.*, reported their findings in a systematic review and meta-analysis, suggesting that there is a relationship between PTSD and BMI<sup>22</sup>.

Our results (Tab 1.) show that patients with PTSD, regardless of type, have an increase in total cholesterol ( $6.38 \pm 1.20$  versus  $5.28 \pm 0.37$ ) of the control group ( $p=0.018$ ). LDL values in patients with PTSD were higher ( $4.16 \pm 0.31$  vs  $3.65 \pm 0.49$ ) than in patients without PTSD ( $p=0.016$ ). HDL values were lower in patients with PTSD compared to patients without PTSD and ( $1.17 \pm 0.40$  vs  $2.47 \pm 0.50$ ) ( $p=0.021$ ), TG also had higher values in patients with PTSD ( $2.43 \pm 0.64$  vs  $1.78 \pm 0.45$ ).  $p=0.036$ ). Our results showed that PTSD has a negative relationship with serum HDL concentration and a positive relationship with CT, LDL and TG. Our results corresponded to the results published in the 2022 meta-analysis study by Veni Bharti *et al.*, the authors concluded that their results show that patients with PTSD show an increase in total cholesterol, LDL and TG, and a decrease in HDL levels<sup>23</sup>. A year ago, the same authors Beharti Vet *al.*, (2021) in the publication; model of lipid profiles of patients with major depressive disorder (MDD) found that patients with MDD showed a decrease in TC levels, an increase in TG and VLDL levels, and no change in LDL and HDL levels<sup>24</sup>. Maia *et al.*, (2008) also reported that people with PTSD showed higher levels of serum total cholesterol, LDL, and TG than those without PTSD<sup>25</sup>. Even the other author Hua Jin *et al.*, (2009) has concluded that posttraumatic stress disorder can be associated with deterioration of the metabolic profile<sup>26</sup>.

During the treatment of patients with PTSD, depending on the clinical picture, the psychiatrist has prescribed antipsychotic therapy. Patients have stated that they have received these medications, but we have not had a convincing response to receive antipsychotic therapy continuously. Regarding the impact of antipsychotic therapy on the concentration of lipids in the serum, groups of different authors give different results. No large-

scale trials have quantified the effects of atypical antipsychotic drugs on lipid metabolism several studies suggest that changes are concordant with weight changes and that clozapine and olanzapine tend to be associated with adverse changes in serum concentrations of triglyceride and cholesterol<sup>27</sup>. The largest increases in triglycerides appear to occur with clozapine, olanzapine and quetiapine<sup>28</sup>. Bruce L Kagan *et al.*, (1999) concluded that no evidence of elevated cholesterol levels has been reported in PTSD, but elevated cholesterol levels have been reported in panic disorder and anger attacks, but not in depression big. Lipid levels may result from activation of the noradrenergic system<sup>29</sup>. Another study by Lewis GF., *et al* (2005) reported that antipsychotic medications increase lipid levels by stimulating sterol regulatory element binding protein, which increases the expression of genes related to lipid biosynthesis<sup>30</sup>. The group of Croatian authors Ana Kovak-Mufiæ *et al.*, in their study published in 2007 concluded that some atypical antipsychotics are associated with weight gain, the occurrence of diabetes and high concentrations of cholesterol and triglycerides<sup>31</sup>.

The authors Lydia A. Chwastiak, *et al.*, (2011) concluded that there are three predisposing conditions for PTSD, physical activity, obesity, and smoking<sup>32</sup>. Smoking among PTSD patients in our study was in a high percentage (85%), according to our hypothesis, this may be a consequence of the feeling of guilt from not being able to have children. The authors of a Systematic Review publication (Amaury C *et al.* 2022) emphasized the need for more research regarding the mechanisms underlying the combination of PTSD symptoms and alcohol consumption, especially prospective longitudinal studies, as the literature on this topic is scarce<sup>33</sup>. The reason why we did not reflect data on alcohol consumption among our patients lies precisely in the "truths" of the answer we would receive (the religious faith of our patients, most of whom are Albanian Muslims). Alcohol can significantly increase triglyceride levels<sup>34</sup>.

The diagnosis of male infertility relies on sperm analysis, based on the reference limits proposed by the World Health Organization (WHO, 6th edition, 2021) (11). In the laboratory of our Polyclinic (Biolab-Zafi), we performed the analysis of human ejaculate. The normal status of male fertility is called Normospermia; the

sperm count in 1.0 ml must be equal to or greater than 15 million/ml. Oligospermia; decrease in sperm count in human ejaculate <15 mil/ml. Asthenozoospermia; Total sperm motility <42% (category a+b =32%), Teratozoospermia; normal morphology <4%. Oligoasthenozoospermia; number and reduced mobility<sup>15</sup>. According to the results of the ejaculate analysis, each patient was placed into the group of patients with PTSD and patients without PTSD (Table 2). The highest percentage within the group of patients with PTSD were with Asthenozoospermia, the difference between the groups was 50% patients with PTSD versus 29.18% patients without PTSD, in our opinion this is related to erectile dysfunction in these patients because they had a longer time abstinence time >10 days and larger ejaculate volume (6.5 ml vs. 4.3 ml). According to current guidelines, semen samples for analysis should be collected after a minimum of 2 days and a maximum of 7 days of sexual abstinence<sup>15</sup>.

Eliahu Levitas, et al (2004) have discovered a significant deterioration of sperm parameters with a prolonged period of sexual abstinence, expressed by a decrease in the percentage of motility and normal morphology<sup>18</sup>. In our group of authors in 2015, a publication related to this topic (Shkëlzen E., Zafer G., etc.) concluded that these pathologies can explain the prolonged stay of spermatozoa in the genital tract of patients with infertility, especially in patients with varicocele<sup>13</sup>. Reduced sperm motility in the ejaculate (asthenozoospermia) can also occur after sperm damage as a result of DNA fragmentation, infection, and leukocyte infiltration as a source of ROS presentation resulting in reduced sperm motility<sup>35-36</sup>. Atypical sperm morphology (Teratozoospermia) is very rarely found in normospermic men, usually found in Asthenozoospermia and Oligoasthenozoospermia, severe degree of male infertility. In our study, there was only one patient with teratozoospermia (2.95%) in the group of patients with PTSD. In 2021, our group of authors for the first time in Kosovo discovered an 11-year-old infertile man who had severe Globospermia (genetic defect such as acrosomal malformation of sperm) that is actually classified as Teratozoospermia<sup>37</sup>. Globozoospermia is a rare condition estimated to affect 1 in 65,000 men. It is most common in North Africa, where it accounts for approximately 1 in 100

cases of male infertility. Globozoospermia is most commonly caused by mutations in the DPY19L2 gene, which are found in about 70 percent of men with the condition. Mutations in other genes are also likely to cause globozoospermia<sup>38</sup>. The results in Table 3 present the lipid profile in PTSD and non-PTSD patients according to ejaculatory parameters. The results obtained within the groups of patients divided according to lipid parameters and spermogram parameters did not show significant differences ( $p>0.50$ ).

## CONCLUSIONS

At the end of our study, we conclude that the treatment of male infertility in men with PTSD is more complex than in patients without PTSD. The psychiatric specialist treats PTSD patients with adequate therapy, the Urologist or Endocrinologist prescribes the appropriate therapy for the treatment of infertility, and the increased lipid status in these patients appears as an additional condition that requires attention and training. To complete the male infertility treatment regimen, hyperlipidemia should be treated simultaneously where it occurs, as well as erectile dysfunction in men with primary or secondary infertility diagnosed with PTSD.

## Recommendations

Biochemical analyzes of the lipid profile of PTSD patients will help clinicians to reduce the possibility of vascular disease in this population during the treatment of male infertility. In further studies, it will be necessary to include larger samples of research subjects.

## ACKNOWLEDGMENT

We thank all study participants.

## Conflict of Interest

All authors declare no conflict of interest

## Funding Source

No sources of funding for this research.

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