

CORRELATION BETWEEN TBARS VALUE IN SERUM AND TISSUE AS OXIDATIVE STRESS MARKERS IN PREMALIGNANT AND MALIGNANT CERVICAL LESIONS

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Abstract: Introduction: Numerous risk factors affect the development of cervical intraepithelial neoplasia (CIN) and cervical cancer (CC), with high-risk subtypes of the human papillomavirus (HPV) being the most significant. Oxidative stress (OS) plays an important role in the pathogenesis of CC and CIN as a risk factor. A commonly used marker of OS, which measures lipid peroxidation products in cells, tissues, and body fluids, is thiobarbituric acid reactive substances (TBARS). This study aimed to determine the correlation between TBARS levels in tissue and serum and evaluate their diagnostic significance in patients with cervical lesions.

Patients and methods: The research was conducted at the Clinical Center of the University of Sarajevo. The experimental group consisted of 200 female patients with biopsy-confirmed changes consistent with CIN, carcinoma in situ (CIS), and CC. The control group (N = 40) had biopsy-confirmed non-pathological findings. The concentration of TBARS was determined for all subjects from biopsy samples and serum according to standard laboratory practice.

Results: We found a significant difference in serum/tissue TBARS levels between study groups. Serum/tissue levels of TBARS in patients with CIS were significantly higher compared to the control group, patients with CIN 1, CIN 2, CIN 3, and patients with CC ($p < 0.05$ for all). There was a significant positive correlation between TBARS levels in serum (μM) and TBARS levels in tissue (μM) (Pearson's $r = 0.494$, $p < 0.001$). Tissue and serum TBARS levels are major differentiation markers between CIS patients and the control group, as well as patients with CIN 1, CIN 2, CIN 3, and CC.

Conclusion: Patients with CIN and CC exhibit increased oxidative stress, indicated by higher levels of TBARS in their tissue and serum compared to healthy controls. TBARS levels in tissue are positively correlated with levels in serum. Tissue and serum TBARS levels are significant markers for differentiating the clinical stages of the disease.

Keywords: oxidative stress, cervical intraepithelial neoplasia, cervical cancer.

INTRODUCTION

Cervical cancer (CC) is one of the most common malignant diseases of the female reproductive system (1, 2). It represents a considerable health challenge worldwide, particularly in developing countries. CC develops through a series of pathological changes known as cervical intraepithelial neoplasia (CIN). Among the various risk factors for cervical cancer, the human papilloma virus (HPV), especially its high-risk subtypes, is the most significant (3). The therapeutic approach, prognosis, and survival depend on the clinical stage of the disease. Early diagnosis and treatment of CIN are crucial for the prevention of CC.

In the pathogenesis of CC and CIN, oxidative stress (OS) plays an important role as a risk factor (4-7). Oxidative stress and HPV infection primarily cause DNA damage. HPV and OS are closely associated because HPV proteins induce oxidative stress, which, in turn, promotes lipid peroxidation and cell damage (4).

Peroxidation of membrane lipids, as a result of oxidative stress, produces a broad range of oxidation products. The most frequent marker of this process is malondialdehyde (MDA), which binds to proteins and phospholipids of the membrane, exacerbating oxida-

tive cell damage (5). Another marker of oxidative stress that quickly and strongly binds to malondialdehyde is thiobarbituric acid reactive substances (TBARS). Lipid peroxidation products in cells, tissues, and body fluids are commonly evaluated by measuring TBARS.

AIM

The aim of this study was to determine the correlation between TBARS levels in tissue and serum and their diagnostic significance in patients with different severities of cervical lesions.

PATIENTS AND METHODS

The research was conducted at the Clinical Center of the University of Sarajevo. A total of 240 female respondents were included in the study, divided into two groups. The experimental group consisted of 200 patients, where the indication for biopsy was confirmed after a gynecological exam and Pap test. The biopsy indicated changes consistent with CIN, carcinoma in situ (CIS), and CC.

In the control group, which consisted of 40 subjects, the biopsy findings were confirmed to be non-pathological (excluding cervical carcinoma and any of the CIN stages).

The concentration of TBARS was determined for all subjects from simultaneously collected samples of biopsy material and serum using the spectrophotometric method according to standard laboratory practice.

The study was approved by the Ethics Committee of the Clinical Center of the University of Sarajevo (number: 0901-2-390/17). It was conducted in accordance with the ethical principles of the Declaration of Helsinki. The results were processed and analyzed using the Statistical Package for Social Sciences (SPSS), version 21.0. Results are expressed as mean (X) and standard deviation (SD). Differences in TBARS values be-

tween groups were tested using ANOVA with post-hoc analysis. Correlation between tissue and serum TBARS levels was analyzed by Pearson's correlation. A value of $p < 0.05$ was considered statistically significant.

RESULTS

The age statistics of the test subjects and the values of tissue and serum TBARS according to study groups are shown in Table 1.

ANOVA test (Table 2) showed a significant difference in TBARS levels in serum and tissue between the study groups. Post-hoc tests revealed that CIS patients had significantly higher levels of TBARS in both tissue and serum compared to the control group, patients with CIN 1, patients with CIN 2, patients with CIN 3, as well as patients with CC ($p < 0.05$ for all).

There is a significant positive correlation between levels of TBARS in serum (μM) and levels of TBARS in tissue (μM), Pearson's $r = 0.494$, $p < 0.001$ (Figure 1).

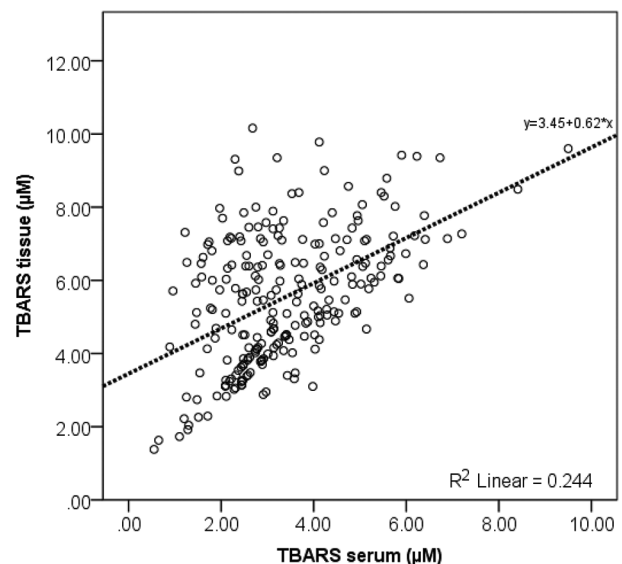


Figure 1. Correlation between serum and tissue TBARS values (μM)

Table 1. Descriptive statistics for age and TBARS according to study groups

Group	N	Age (years)	TBARS-tissue (μM)	TBARS-serum (μM)
Controls	40	50.28 \pm 10.56	4.80 \pm 0.22	2.81 \pm 1.15
CIN 1	40	45.10 \pm 11.32	4.78 \pm 0.25	2.80 \pm 1.18
CIN 2	40	45.53 \pm 11.73	4.94 \pm 0.24	3.23 \pm 1.29
CIN 3	40	45.08 \pm 11.63	5.94 \pm 0.23	3.68 \pm 1.27
CIS	40	49.78 \pm 13.73	7.06 \pm 0.31	4.59 \pm 1.72
CC	40	54.08 \pm 15.59	5.65 \pm 0.24	3.07 \pm 1.11

Table 2. Difference in Age and TBARS Levels Between Study Groups

Parameter	Sum of Squares	df	Mean Square	F	Sig.
TBARS serum (μM)	93.022	5	18.604	10.894	< 0.001
TBARS tissue (μM)	158.386	5	31.677	12.082	< 0.001

Table 3. Sensitivity and specificity of TBARS in tissue as a marker of differentiation

TBARS tissue	CIS/controls	CIS/CIN1	CIS/CIN2	CIS/CIN3	CIS/CC
Cut off	5.82	6.58	7.32	7.24	7.26
Sensitivity	78.95%	89.29%	95.24%	76.92%	76.92%
Specificity	76.19%	71.15%	66.10%	62.96%	62.96%
AUC	0.808	0,801	0.788	0.710	0.710
95%CI	0.712-0.903	0.705-0.897	0.688-0.887	0.561-0.799	0.595-0.824
p-value	< 0.001	< 0.001	< 0.001	0.006	0.001

Sensitivity and specificity of TBARS in tissue as a marker of differentiation between patients with CIS and: controls (CIS/controls), patients with CIN 1 (CIS/CIN1), patients with CIN 2 (CIS/CIN2), patients with CIN 3 (CIS/CIN3), patients with cervical carcinoma (CIS/CC). AUC - area under curve.

Table 4. Sensitivity and specificity of TBARS in serum as a marker of differentiation

TBARS serum	CIS/controls	CIS/CIN1	CIS/CIN2	CIS/CIN3	CIS/CC
Cut off	4.18	3.12	4.79	4.73	4.61
Sensitivity	88.0%	72.73%	76.72%	77.78%	84.0%
Specificity	67.27%	77.78%	62.96%	64.15%	65.45%
AUC	0.809	0.812	0.734	0.662	0.770
95%CI	0.713-0.904	0.705-0.897	0.622-0.847	0.542-0.783	0.667-0.873
p-value	< 0.001	< 0.001	< 0.001	0.013	0.001

Sensitivity and specificity of TBARS in serum as a marker of differentiation between patients with CIS and: controls (CIS/controls), patients with CIN 1 (CIS/CIN1), patients with CIN 2 (CIS/CIN2), patients with CIN 3 (CIS/CIN3), patients with cervical carcinoma (CIS/CC). AUC - area under curve.

Furthermore, we analyzed ROC curves to identify the sensitivity and specificity of the best cutoff points of TBARS in serum and tissue as a discriminator of the probability of significant cervical lesions (Tables 3 and 4).

DISCUSSION

In addition to the well-established association between the risk of developing CC and age (3, 6), as well as its correlation with HPV infection, other risk factors such as oxidative stress (OS) are also associated with CIN and uterine cancer (7, 8). As the organism ages, DNA damage accumulates, and during the division of such cells, this damage becomes permanent, leading to the development of mutations and malignant diseases (7, 8).

Oxidative stress (OS) holds an important place in the pathogenesis of a multitude of malignant diseases, including lung cancer, colorectal cancer, renal cancer, etc. (9).

The oxidized form of DNA, resulting from interactions with reactive oxygen species, leads to mutations and the development of carcinogenesis. This process is further enhanced by environmental factors such as radiation, pollution, and UV radiation (10). Cancer cells are often more exposed to OS compared to normal cells, although they can also develop resistance to OS through mechanisms that are not fully elucidated (11,

12). At the local level, OS within malignant tissue itself may have a beneficial effect on the apoptosis of carcinomatous cells and prevent their proliferation (12).

HPV infection is strongly associated with the initiation, promotion, and progression of cancer due to the expression of viral oncoproteins. While HPV oncoproteins are necessary for the progression of cervical cancer (CC), other conditions and factors are also required for the complete transformation of cells (13). OS, among commonly proposed factors, is often understudied but ultimately plays a role in CC. It acts synergistically or independently on HPV infection, contributing to the disease process.

In addition to DNA oxidation, lipid oxidation, or so-called lipid peroxidation, is a risk factor for carcinogenesis and its progression. Damaged lipid hydroperoxides yield a wide range of end products, including MDA. Lipid peroxidation plays a significant role in malignant transformation (14). Altered levels of lipid peroxidation have also been reported in many precancerous lesions (15). It has been confirmed that oxidative stress (OS) and its consequence, lipid peroxidation, occur in the early stages of carcinogenesis, including in relation to cervical intraepithelial neoplasia (CIN) (16).

Another cancer promoter arising as the end product of lipid peroxidation is highly cytotoxic MDA. Patients with CC have significantly increased levels of MDA,

which is also observed in patients with various cancer types compared to healthy controls (17, 18). Plasma MDA levels have been identified as an independent prognostic parameter of survival in these patients (19).

The pathogenesis of malignant diseases of the female reproductive system involves lipid peroxidation.

MDA is commonly used as a marker of oxidative stress, particularly for assessing lipid peroxidation. Acid thiobarbituric reactive substances (TBARS) are another marker of oxidative stress that quickly and strongly binds to malondialdehyde. Lipid peroxidation products in cells, tissues, and body fluids are commonly evaluated by measuring TBARS.

Our study results demonstrated that tissue levels of TBARS in CIS patients were significantly higher compared to other groups (controls, CIN 1, CIN 2, CIN 3, CC). Tissue TBARS levels reflected changes in cellular conditions, with significantly higher levels observed in the CIN 3 group compared to the control group and patients with CIN 1.

Tissue TBARS levels served as a significant differentiation marker between patients with CIS and various other groups, including CC.

Similarly, serum TBARS levels in our subjects showed significant differences between patients with CIS and the control group, as well as patients with different stages of CIN. Serum TBARS levels also differentiated between patients with CIS and CC.

These findings align with previous studies by Jelić et al. (20), which reported higher levels of lipid peroxidation in precancerous and uterine carcinoma tissues compared to controls. Elevated TBARS levels, indicative of oxidative stress, were observed in all examined groups and were significantly higher in women with advanced CC.

The production of oxygen radicals, which increase lipid peroxidation, is associated with disease progression, indicating greater cell membrane degeneration in advanced CC patients compared to those with lower stages.

Lipid peroxidation-induced tissue degeneration can spread through circulation, causing damage to other tissues (21).

Studies by Zahra et al. (17) and Carneiro et al. (21) further support the involvement of oxidative stress in cervical cancer pathogenesis, manifested by increased lipid peroxidation

Additionally, Visalli et al. found higher oxidative stress levels in patients with severe cervical intraepithelial lesions (SIL) compared to controls, even among patients with low-grade SIL (22).

Gonçalves et al. (23) demonstrated significantly higher TBARS levels in erythrocytes of women with malignant and premalignant lesions compared to con-

trols. This study also identified a positive association between lipid peroxidation and lesion severity, suggesting that TBARS levels in erythrocytes can serve as early markers of oxidative stress, evident even in premalignant conditions.

Following the level of lipid peroxidation through TBARS concentration, Manju et al. (24) observed significantly higher levels in the plasma of patients with CC compared to healthy women. Furthermore, the researchers noted significantly lower levels of enzymatic antioxidants in CC patients compared to healthy subjects. They concluded that the increased consumption of enzymatic antioxidants was due to the removal of lipid peroxides and their sequestration by cancer cells.

Sahah et al. (25) demonstrated that the mean concentration of MDA in the serum of patients with CC was lower compared to the control group. Additionally, they found that the mean concentration of total antioxidant capacity (TAC) was significantly lower in the group of patients with CC compared to healthy subjects.

Naidu et al. (18) observed significantly higher levels of serum lipid peroxide in the form of MDA and NO in patients with CC compared to healthy controls. The maximum increase of MDA and NO was recorded in phase IV compared to healthy controls.

The association between oxidative stress (OS) and CC progression was described by Borges et al. (26), who detected a two to threefold increase in TBARS levels in the erythrocytes of patients with squamous intraepithelial lesions (SIL) or CC. Additionally, MDA levels in healthy women were almost three times lower than in women with SIL. Higher levels of MDA were recorded in women positive for HPV. These findings suggest that higher concentrations of MDA and TBARS reflect an increase in OS. Conflicting evidence indicates that malignant neoplasias are capable of releasing free radicals into the bloodstream, suggesting that the presence of cancer may cause increased OS, rather than being its consequence.

After forming at primary sites, lipid peroxidation or oxidative damage is transferred through the circulation. Therefore, we investigated whether there is a correlation between TBARS levels in tissue and serum (27).

Our research showed a significant positive correlation between TBARS levels in tissue and serum, with Pearson's $r = 0.494$, $p < 0.001$, indicating a relationship between tissue and serum oxidative stress markers.

We were unable to find existing literature on the correlation between tissue and blood levels of TBARS, not only in cervical cancer pathology but also in other cancers. Consequently, we are unable to offer a comprehensive explanation of our results. However, we speculate that the elevated TBARS serum levels may reflect heightened levels in tissue.

Biomarkers for lipid peroxidation hold promise as diagnostic tools in screening, predicting cancer recurrence, disease progression, or therapy effects in cancer patients. However, further comprehensive research is necessary to draw definitive conclusions.

Bearing in mind that the results of our research showed that both tissue and serum concentrations of TBARS were the highest in the group of subjects with CIS, and were significantly higher than the TBARS values in the control group, significantly higher than the TBARS values of patients with premalignant lesions, as well as significantly higher from the TBARS values of patients with uterine cancer, we are of the opinion that the increase in lipid peroxidation in this stage of the disease can serve as a potential biomarker for differentiating the transition of the disease from premalignant to malignant form. A possible increase in the level of TBARS in this stage may be a consequence of the progression of the disease, but the possibility that the organism at this stage responds to pronounced lipid peroxidation at the local and systemic level as a potential defense is not excluded, because oxide radicals can be harmful to cancer cells.

An increase in TBARS in the CIS compared to other stages may indicate the risk of disease progression. These results open up new perspectives in the diagnosis and therapy of the disease, in such a way that lipid peroxidation can serve as a possible biomarker of the stage of the disease, and as such can be a useful diagnostic tool.

CONCLUSION

Patients with CIN and CC have increased oxidative stress, indicated by higher levels of TBARS

in their tissue and serum compared to healthy controls. The positive correlation between TBARS levels in tissue and serum underscores the significance of these markers in disease evaluation. Tissue and serum TBARS levels are a significant marker of differentiation of the clinical stage of the disease and can be a useful diagnostic tool influencing the selection of therapeutic procedures, but its application in screening is also possible.

Abbreviations

CC - Cervical Cancer
CIN - Cervical Intraepithelial Neoplasia
CIS - Carcinoma in Situ
DNA - Deoxyribonucleic acid
HPV - Human papillomavirus
MDA - Malondialdehyde
OS - Oxidative stress
TBARS - Acid tiobarbituric reactive substances

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Note: Artificial intelligence was not used as a tool in this study.

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Sažetak

KORELACIJA IZMEĐU VREDNOSTI TBARS-a U SERUMU I TKIVU KAO MARKERA OKSIDATIVNOG STRESA U PREMALIGNIM I MALIGNIM LEZIJAMA GRLIĆA MATERICE

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Uvod: Brojni faktori rizika utiču na razvoj intraepitelne neoplazije grlića materice (CIN) i cervikalnog karcinoma (CC), pri čemu su visoko rizični podtipovi humanog papiloma virusa (HPV) najznačajniji. Oksidativni stres (OS) igra važnu ulogu u patogenezi CC i CIN kao faktor rizika. Često korišćeni marker OS-a, koji meri produkte lipidne peroksidacije u ćelijama,

tkivima i telesnim tečnostima, je reaktivna supstanca tiobarbituricne kiseline (TBARS). Ova studija ima za cilj da utvrdi korelaciju između nivoa TBARS-a u tkivu i serumu i proceni njihov dijagnostički značaj kod pacijenata sa lezijama grlića materice.

Pacijenti i metode: Istraživanje je sprovedeno u Kliničkom centru Univerziteta u Sarajevu. Ekspe-

rimentalnu grupu činilo je 200 pacijentkinja sa biopsijski potvrđenim promenama koje su konsistentne sa CIN, karcinomom in situ (CIS) i CC. Kontrolnu grupu (N = 40) činile su pacijentkinje sa biopsijski potvrđenim neoplasmičkim nalazima. Koncentracija TBARS-a određena je za sve subjekte iz uzoraka biopsije i seruma prema standardnoj laboratorijskoj praksi.

Rezultati: Utvrdili smo značajnu razliku u nivoima TBARS-a u serumu i tkivu između studijskih grupa. Nivoi TBARS-a u serumu i tkivu kod pacijenata sa CIS bili su značajno viši u poređenju sa kontrolnom grupom, pacijentima sa CIN 1, CIN 2, CIN 3 i pacijentima sa CC ($p < 0,05$ za sve). Postojala je značajna pozitivna korelacija između nivoa TBARS-a u serumu

(μM) i nivoa TBARS-a u tkivu (μM) (Pearson-ov $r = 0,494$, $p < 0,001$). Nivoi TBARS-a u tkivu i serumu predstavljaju glavni marker diferencijacije između pacijenata sa CIS i kontrolnom grupom, kao i pacijenata sa CIN 1, CIN 2, CIN 3 i CC.

Zaključak: Pacijenti sa CIN-om i CC-om pokazuju povećani oksidativni stres, što ukazuju viši nivoi TBARS-a u njihovom tkivu i serumu u poređenju sa zdravim osobama. Nivoi TBARS-a u tkivu pozitivno su povezani sa nivoima u serumu. Nivoi TBARS-a u tkivu i serumu su značajni markeri za diferencijaciju kliničkih stadijuma bolesti.

Cljučne reči: oksidativni stres, cervikalna intraepitelna neoplazija, karcinom grlića materice.

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