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Original article

DEVELOPMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA AND INVASIVE CERVICAL CANCER DUE TO OXIDATIVE STRESS

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Abstract: **Background:** Cervical cancer (CC) ranks third among all malignant diseases of the female reproductive system. CC arises through a series of pathological changes called cervical intraepithelial neoplasia (CIN). Timely diagnosis and treatment of CIN are essential in the prevention of CC. Oxidative stress (OS) presents a major risk factor in the pathogenesis of both CC and CIN. This study aimed to determine the association between OS and the pathohistological severity of cervical lesions.

Materials and Methods: The research was conducted at the Clinical Center of the University of Sarajevo on 240 female respondents divided into two groups. The experimental group consisted of 200 women with changes consistent with CIN, carcinoma in situ (CIS), and CC determined by biopsy, divided into 5 subgroups (CIN 1, CIN 2, CIN 3, CIS, and CC) with 40 respondents per group. The control group (N = 40) had biopsy findings that were non-pathological. The concentration of acid thiobarbituric reactive substances (TBARS) was determined for all subjects from bioptic samples using the spectrophotometric method and according to standard laboratory practice.

Results: Our results showed a significant difference in age between patients with CIN 1, CIN 2, and CIN 3 and the control group as well as when compared to patients with CC. The oldest group comprised patients with CC. Tissue TBARS levels in the CIS group were significantly higher than that of the control group ($p < 0.001$), CIN 1 group ($p < 0.001$), CIN 2 group ($p < 0.001$), CIN 3 group ($p = 0.033$), as well as CC group ($p = 0.002$). Likewise, tissue TBARS levels in the CIN 3 group were significantly higher than those of the control group ($p = 0.023$), and CIN 1 group ($p = 0.024$).

Conclusion: Compared to healthy controls, patients with CIN and CC have increased oxidative stress. Tissue TBARS levels represent a significant differentiation marker of the clinical stage of the disease and can be a useful diagnostic tool influencing the selection of therapeutic procedures.

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

INTRODUCTION

Cervical cancer (CC) stands as the third most prevalent malignancy affecting the female reproductive system, accounting for approximately 12% of all malignant neoplasms in women (1, 2). Its precursor, cervical intraepithelial neoplasia (CIN), marks a spectrum of pathological changes that vary in severity, with higher-grade CIN posing an increased risk for the development of CC. The incidence of CC and CIN is influenced by a myriad of factors, including human papillomavirus (HPV) infection, early initiation of sexual activity, smoking, and socioeconomic status (3).

The successful implementation of screening programs significantly impacts the frequency of CC, emphasizing the importance of early detection and intervention (4). Diagnosis typically involves a combination of gynecological examinations, Pap smears, colposcopy, and biopsies to confirm CC. Treatment modalities vary based on disease stage, ranging from surgical interventions for early-stage disease to radiotherapy and chemotherapy for advanced cases. Prognosis hinges largely on disease stage and lymph node involvement (5, 6).

Early diagnosis and treatment of CIN are very important in the prevention of CC, and today, special attention is paid to screening examinations of women and HPV vaccination of the younger population of girls.

In the last decade, a series of discoveries indicate oxidative stress (OS) asanmayor risk factor in CC and

CIN pathogenesis (7). Oxidative stress induced peroxidation of membrane lipidscreates a broad range of oxidation products, among which the most common one is malondialdehyde (MDA), which binds to proteins and phospholipids of the membrane, thereby deepening oxidative cell damage (7). Today, MDA is used in many scientific studies as oxidative stress marker, more precisely for the assessment of lipid peroxidation. Another oxidative stress marker that quickly and strongly binds to malondialdehyde is Acid thiobarbituric reactive substances (TBARS). The involvement of lipid peroxidation in pathogenesis in female reproductive system malignant diseases has been proven (8).

AIM

The aim of this study was to determine the association between OS and pathohistological severity of cervical lesions.

MATERIAL AND METHODS

The study was conducted at the Clinical Center of the University of Sarajevo and received approval from the Ethics Committee (number: 0901-2-390/17) in accordance with the principles outlined in the Declaration of Helsinki.

Two hundred and forty female respondents were recruited and divided into two groups: an experimental group and a control group. The experimental group comprised 200 women with confirmed indications for biopsy based on colposcopy findings and Pap test results, showing changes consistent with cervical intraepithelial neoplasia (CIN), carcinoma in situ (CIS), or cervical cancer (CC). This group was further subdivided into five subgroups (CIN 1, CIN 2, CIN 3, CIS, and CC), each consisting of 40 respondents.

The control group comprised 40 women with non-pathological findings, excluding CC and CIN. Biopsy indication in this group was determined for other medical reasons.

Participants underwent physical, gynecological, and colposcopic examinations, as well as Pap tests, to establish the biopsy indication. TBARS concentration was determined from bioptic samples using a spectrophotometric method following standard laboratory protocols.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 16.0. Data were presented as mean ± standard deviation (SD) or as median and interquartile range (IQR). Analysis of variance (ANOVA) test was used for variables following a normal distribution, while non-parametric Kruskal-Wallis and Mann-Whitney U tests were applied as appropriate. A significance level of $p < 0.05$ was considered statistically significant.

RESULTS

The age statistics and tissue TBARS levels among the study groups are summarized in Table 1.

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

Group	N	Age (years)	TBARS-tissue (µM)
Controls	40	50.0 (42.0-57.0)	4.80 ± 0.22
CIN 1	40	44.0 (35.5-51.0)	4.78 ± 0.25
CIN 2	40	45.0 (36.0-51.67)	4.94 ± 0.24
CIN 3	40	41.0 (36.5-50.0)	5.94 ± 0.23
CIS	40	45.0 (40.0-61.5)	7.06 ± 0.31
CC	40	54.0 (38.5-62.25)	5.65 ± 0.24

A significant difference in age was found between the control group and patients with CIN 1 ($p = 0.042$), CIN 2 ($p = 0.036$) and CIN 3 ($p = 0.005$). Likewise, significant age differences were found between patients with CC and those with CIN 1 ($p = 0.015$), CIN 2 ($p = 0.022$) and CIN 3 ($p = 0.010$) (Figure 1).

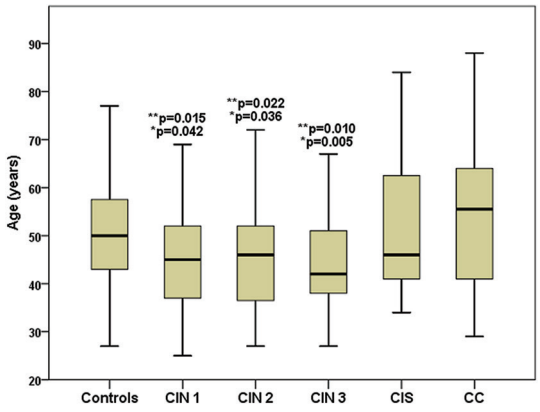

Figure 1. *Age of patients with CIN,CC and subjects of the control group*

(Results are shown as median and interquartile range /25-75 percentiles/; *compared to control group; **compared to group with CC).

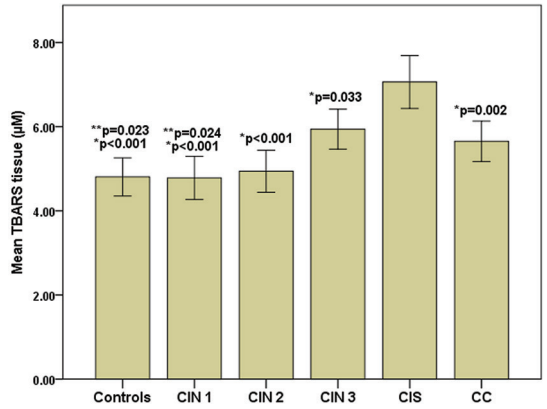

Figure 2. *Tissue TBARS levels in patients with CIN, CC and subjects of the control group*

(Results are shown as mean ± standard error of the mean (x ± SEM); *compared to CIS; **compared to CIN 3).

Tissue TBARS levels were significantly elevated in patients with CIS compared to the control group ($p < 0.001$), as well as compared to patients with CIN 1 ($p < 0.001$), CIN 2 ($p < 0.001$), CIN 3 ($p = 0.033$), and CC ($p = 0.002$). Additionally, tissue TBARS levels in patients with CIN 3 were significantly higher than those in the control group ($p = 0.023$) and in patients with CIN 1 ($p = 0.024$) (Figure 2).

DISCUSSION

Cervical carcinoma is often preceded by CIN. It can spontaneously regress or progress if not treated immediately. CIN stages 2 and 3 are associated with the risk of developing CC and are usually treated with rest. There is a certain chance that these lesions will resolve, and observation and follow-up may be chosen for certain patients. This is a particular option for women planning to give birth, as excisional procedures are followed by an increased risk of poor pregnancy outcomes.

Our results showed a significant difference in age between the control group and patients with CIN 1 ($p = 0.042$), CIN 2 ($p = 0.036$) and CIN 3 ($p = 0.005$). The same significant age difference has been noted between CC patients and patients CIN 1 ($p = 0.015$), CIN 2 ($p = 0.022$) and CIN 3 ($p = 0.010$). The oldest group were patients with CC.

In a study by Chang et al. (9), it was shown that CIN 3 and CC incidence rates decrease with time, while CIN 1 and CIN 2 increase significantly ($p < 0.001$). The peak age of incidence was 25–29 and 30–34 years for CIN 1 and 2, respectively, and 70–74 years for CIN 3 and CC. The frequency of CIN 1 and 2 showed an increasing trend in all age groups. CC was significantly reduced in all age groups, except for the 35-39 age group.

The study by Wang et al. (3), where the researchers monitored age, spouse occupation, hygiene after intercourse, and average daily folate intake as predictors of CIN, yielded interesting data. The 56-65year-old group was at the highest risk for developing CIN, while the risk of CIN in the group aged 36-45 was determined to be 61.4% of the risk in the older group.

CIN and uterine cancer can also be associated with other risk factors, such as marked OS. Oxidative damage in the human body is a daily occurrence, but most oxidative lesions can be significantly repaired by specific DNA glycosylases. The repair of damage, however, is never complete, so it accumulates with age. As the organism ages, during the division of such cells, damage becomes permanent, along with the development of mutations and malignant diseases. (10, 11).

OS holds an important place in the pathogenesis of many malignant diseases such as cancer of the kidney, bladder, lung, colon, etc (12).

A number of researchers believe that selective OS, i.e. free radicals at the local level (in the malignant tissue itself) could have a beneficial effect on the apoptosis of carcinomatous cells and prevent their proliferation (13).

OS is an understudied factor when it comes to its role in CC, where the main questions are whether it acts synergistically or independently of HR-α-HPV infection. HPV-positive cervical lesions show higher levels of oxidative DNA damage when compared to control HPV-negative samples. The extent of damage is closely related to high-risk HPV types (14).

OS and lipid peroxidation already appear in the early stages of carcinogenesis when it comes to CIN. MDA, as lipid peroxidation product, is highly cytotoxic and acts as a cancer promoter. Patients with CC were shown to have significantly higher levels of MDA (15).

Previous studies have shown inconsistent results when examining the levels of OS markers in patients with CIN and CC.

Srivastava et al. (16) showed that the level of lipid peroxidation was increased in patients with CC compared to the control group, but in relation to different stages of carcinoma, lipid peroxidation levels in these patients did not differ.

Carrero et al. (17) showed a positive correlation between the increase in the cellular level of superoxide anions and the progression of CIN. According to this research, the increased production of superoxide anions in CIN lesions can lead to oxidative DNA damage, which can lead to CC. According to this study, measuring the level of cellular superoxide anions can have a predictive role in monitoring the progression of premalignant changes on the cervix. Lipid peroxidation levels and OS monitored in other malignant diseases showed mostly their higher levels compared to the healthy population.

Our results showed significantly higher tissue TBARS levels in patients with CIS compared to levels of other groups (controls, CIN 1, CIN 2, CIN 3, CC). The level of TBARS in the tissue of patients followed the level of changes in the cells. TissueTBARS levels in CIN 3 group were significantly higher than those in controls and patients with CIN 1.

These results are similar to the results of Jelić et al. (15), who showed that the lipid peroxidationlevel is higher in cervical precancers, as well as in uterine cancer compared to the control group. Their research concluded that TBARS as an OS marker was higher in all study groups compared to controls, especially in women with advanced CC.

The same authors also showed that the activity of other markers such as superoxide dismutase, catalase, glutathione-S-transferase were significantly higher in cervical pre-cancers, as well as in uterine cancer compared to the control group.

It is believed that disease progression followed by production of oxygen radicals and increase in lipid peroxidation causegreater degree ofcell membrane degeneration in patients with advanced CC when compared to patients with lower stages, indicating that lipid peroxidation can cause CC progression. Tissue degeneration can be caused by increased lipid peroxidation and this process can spread from primary sites through the circulation.OS is probably involved in the pathogenesis of CC due to increased lipid peroxidation and changes in the antioxidant defense system (18).

The data obtained in the study by Zahra et al. (7) also show OS involvement in CC pathogenesis, demonstrated by increased lipid peroxidation, higher of 8-OhdG levels and alteration in the antioxidant defense system. The authors believe that OS can be considered a dominant risk factor even in the initial stage of carcinogenesis. Cancer cells produce oxidants, deplete antioxidants and establish a vicious stress multiplication cycle. This cycle is characteristic in advanced stages because of increase in cancer burden. The disruption of oxidant-antioxidant levels leading to oxidative lipid damage and promotion of cancer initiation and progression is hypothesised by Zahra et al.

A study by Visalli et al. (19) that included 202 samples from colpo-cytopathology examinations found much higher OS levels in patients with more severe squamous intraepithelial lesions (SIL)compared to the control group. Higher OS levels were also found among patients with intraespithelial lesions of lower grade.

This is also backed by Carneiro et al. study (20), where it was shown that women with SIL had higher levels of MDA compared to women with normal histopathological findings.

Lipid peroxidation products could indeed be one of the possible causes of uterine cancer progression. Sahah et al. (21) showed that the mean concentration of total antioxidant capacity (TAC) was significantly lower in the group of patients with CC compared to healthy subjects.

Taking into account that the results of our research showed the highest TBARS concentrations in the CIS group, compared to the control group, patients with premalignant lesions, and patients with uterine cancer, we are of the opinion that the increase in lipid peroxidation in this stage of the disease can be used as a potential differentiation biomarker indicating transition of the disease from premalignant to malignant form. A possible increase in TBARS levels at this stage may be a consequence of disease progression, but it is not excluded that the organism at this very stage responds with pronounced lipid peroxidation at the local and systemic level as a potential defense, because it is known that oxygen radicals can be harmful to cancer cells.

The fact is that most studies classify OS as a risk factor for the pathogenesis and progression of the disease,meaning that the increase in TBARS in the CIS stage may indicate the risk of disease progression. In any case, the results of this study open new perspectives in the diagnosis and therapy of the disease. Lipid peroxidation can serve as a possible biomarker of disease staging, and as such can be a useful diagnostic tool (22).

CONCLUSION

Patients with CIN and CC have increased levels of oxidative stress.Tissue TBARS levels in patients with the CIS stage were significantly higher compared to subjects with CC and subjects with any of the lower CIN stages. TBARS level is 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 Intaepithelial Neoplasia
CIS - Carcinoma in Situ
DNA - Deoxyribonuceic 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.

Sažetak

RAZVOJ INTRAEPITELNIH NEOPLAZIJA I INVAZIVNOG KARCINOMA GRLIĆA MATERICE ZBOG OKSIDATIVNOG STRESA

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Uvod: Karcinom grlića materice (CC) zauzima treće mesto među svim zloćudnim bolestima ženskog reproduktivnog sistema. CC nastaje kroz seriju patoloških promena nazvanih intraepitelne neoplazije grlića materice (CIN). Pravovremena dijagnoza i lečenje CIN su ključni u prevenciji CC. Oksidativni stres (OS) predstavlja glavni faktor rizika u patogenezi kako CC,tako i CIN. Cilj ovog istraživanja bio je utvrditi povezanost između OS-a i patohistološke ozbiljnosti cervikalnih lezija.

Materijali i metode: Istraživanje je sprovedeno na Kliničkom centru Univerziteta u Sarajevu na 240 ženskih ispitanica podeljenih u dve grupe. Eksperimentalnu grupu činilo je 200 žena s promenama koje su bile u skladu s CIN-om, karcinomom in situ (CIS) i CC-om utvrđenim biopsijom, podeljenim u 5 podgrupa (CIN 1, CIN 2, CIN 3, CIS i CC) sa po 40 ispitanica u svakoj grupi. Kontrolnu grupu (N = 40) činile su biopsije koje nisu bile patološke. Koncentracija reaktivnih supstanci tiobarbituratne kiseline (TBARS) određena je za sve ispitanice iz bioptičkih uzoraka koristeći spektrofotometrijsku metodu i prema standardnoj laboratorijskoj praksi.

Rezultati: Naši rezultati pokazuju značajnu razliku u uzrastu između pacijentkinja s CIN 1, CIN 2 i CIN 3 i kontrolne grupe, kao i u poređenju s pacijentkinjama s CC. Najstariju grupu činile su pacijentkinje s CC. Nivoi TBARS-a u tkivu u CIS grupi bili su značajno viši nego u kontrolnoj grupi ($p < 0,001$), CIN 1 grupi ($p < 0,001$), CIN 2 grupi ($p < 0,001$), CIN 3 grupi ($p = 0,033$), kao i u CC grupi ($p = 0,002$). Isto tako, nivoi TBARS-a u tkivu u CIN 3 grupi bili su značajno viši nego u kontrolnoj grupi ($p = 0,023$), i CIN 1 grupi ($p = 0,024$).

Zaključak: U poređenju s zdravim kontrolama, pacijentkinje s CIN i CC imaju povećani oksidativni stres. Nivoi TBARS-a u tkivu predstavljaju značajan diferencijalni marker kliničkog stadijuma bolesti i mogu biti korisno dijagnostičko sredstvo koje utiče na izbor terapijskih postupaka.

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

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