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Inflammatory, oxidative stress and anti-oxidative markers in patients with endometrial carcinoma and diabetes

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ABSTRACT

Background: The role of chronic inflammation and oxidative stress in the development of diabetes and cancer has been established. In this study, we aimed to investigate inflammatory and oxidative stress markers in patients with diabetes (DM) and endometrial carcinoma (EC) separately and in combination.

Methods: In a case-control study design, a total of 88 participants were enrolled including: 37 patients with EC (19 with DM and 18 without DM), 29 with type2 diabetes and 22 healthy controls. Cancer patients were sampled before treatment. Serum oxidative stress markers including: oxidized low density lipoprotein (ox-LDL,) nitric oxide (NO), advanced glycation end-products (AGEs) and advanced oxidation protein products (AOPP), malondialdehyde (MDA); ferric reducing ability of plasma (FRAP), as an antioxidant marker, and inflammatory markers including: Interleukin 6 (IL6), C reactive protein (CRP) and tumor necrosis factor alpha (TNFα) were measured.

Results: Ox-LDL, NO, MDA, AOPP and AGE were increased in all patients either with endometrial carcinoma and/or diabetes compared to healthy controls ($p < 0.05$). Patients with both EC and DM had higher oxidative markers including: OX-LDL (17.47 ± 0.84 vs. 12.36 ± 0.91), NO (82.27 ± 5.75 vs. 76.34 ± 5.36), MDA (3.3 ± 0.1 vs. 2.75 ± 0.48) and AGE (73.89 ± 5.71 vs. 69.02 ± 3.14) compared to those with EC alone ($\rho < 0.05$). Levels of FRAP was lower in patients with both diabetes and cancer, cancer alone and diabetes alone compared to healthy controls ($p < 0.05$). Inflammatory markers, TNFα, IL6 and hs-CRP, were also significantly increased in patients with EC with and without DM compared to controls ($\rho < 0.05$). However, there were no significant differences between two groups of EC regarding to inflammatory markers ($\rho > 0.05$). Patients with DM had significantly higher levels of inflammatory markers compared to control group (all $\rho < 0.05$). In addition, significant subadditive interaction effect between EC and DM regarding levels of oxLDL, NO, AGE, AOPP and FRAP) was observed ($p < 0.05$).

Conclusion: Increased levels of chronic inflammatory and oxidative stress markers were observed in both endometrial carcinoma and diabetes. Additional effect of diabetes in patients with cancer was mediated more significantly via increase in oxidative stress rather than inflammatory markers.

1. Introduction

According to clinical and epidemiological studies, diabetes (DM) is associated with increased risk of several types of cancers including endometrium, breast, liver, pancreas, colorectal, and bladder [1]. Endometrial carcinoma (EC) is the most frequently diagnosed gynecologic malignancy [2]. Diabetes is associated with poorer prognosis in EC [3]. DM and EC share potential risk factors such as obesity and age [4,5].

Increased inflammatory markers such as, interleukin 6 (IL6), C reactive protein (CRP) and tumor necrosis factor alpha (TNFα) have a potential role in diabetes development and its complications [6]. Previous studies proposed role of inflammation in EC [7,8]. Serum levels of

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IL6 [9], CRP [10,11] and TNFα [12] are associated with increased risk of EC. Oxidative stress markers also involved in diabetes complications [13,14]. There are few studies concerning level of oxidative stress in EC, which reported increased total oxidative stress and lipid peroxidation [15,16].

Several mechanisms such as hyperglycemia, hyperinsulinemia, chronic inflammation and oxidative stress are the possible biological links between DM and cancer [17]. Furthermore, effect of co-occurrence of the two diseases in the same individual on cellular pathways remains a great challenge. Whether the combined effect of the two diseases on inflammatory and oxidative markers levels may be beyond the separate effect of each disease has not been studied yet.

Here, we designed a case-control study to investigate markers of lipid peroxidation (ox-LDL and MDA), protein oxidation (AOPP and AGE), free radicals (nitric oxide), and anti-oxidant (FRAP) and also inflammatory markers including IL6, TNFα and hs-CRP in patients with endometrial cancer with and without diabetes and diabetes alone. We also address interaction between DM and EC on measured serum markers.

2. Materials and methods

2.1. Study design and participants

This was a case-control study of 88 participants, stratified into four groups including, 18 patients with endometrial carcinoma (EC) and type2diabetes (T2DM), 19 patients with EC alone, 29 patients with type2 DM alone and 22 healthy individuals.

Patients with suspicion of endometrial carcinoma who were schedule to undergo hysterectomy were recruited from the gynecology oncologic ward at Vali-Asr hospital, which is affiliated with Tehran University of Medical Sciences. Patient's serums were sampled before surgery and were enrolled in the study after pathologic confirmation of EC. Diabetes was diagnosed according to the criteria of the American diabetes association (ADA) 2016. Patients with history of current pregnancy, recurrent endometrial cancer, pre-surgical chemotherapy and radiation and the presence of other cancer were excluded. Demographic and anthropometric data including age, duration of diabetes, height, weight, blood pressure, menopausal status, number of abortion and age at menopause were recorded. Quetelet formula used to calculate BMI. The research was carried out according to the principles of the declaration of Helsinki. The local ethics review committee of Tehran University of Medical Science approved the study protocol.

2.2. Blood samples and laboratory evaluations

Morning, blood samples collected after almost 12 h fasting before surgery, centrifuged, and were kept at −70 °C until analysis. Measurement of IL6 was performed using a quantitative, sandwich, ELISA (human IL-6 immunoassay, Quantikine, USA) with intra-assay CV%: 2; inter-assay CV%: 3.8; sensitivity: 0.7 (pg/ml); ranged from 3.1 to 300 (pg/ml). Serum TNFα was performed using ELISA kit (Diaclone Besancon, France) with intra-assay CV%: 3.2; inter-assay CV%: 10.9; sensitivity: 8 (pg/ml); ranged from 25 to 800 (pg/ml). Serum Hs-CRP was assessed using a two-site, ELISA (Diagnostic Biochem, London, Ontario, Canada) with intra-assay CV%: 5; inter-assay CV%: 9.5; sensitivity: 10 (pg/ml); ranged from 34 to 63,680 (ng/ml). Measurement of oxLDL was performed using a commercially available sandwich ELISA method (Mercodia, Uppsala, Sweden) with intra-assay CV%: 4; inter-assay CV%: 7.3 (U/L); detection limit: 0.6 (mU/L); ranged from 1.4 to 22.5 (mU/L). Estradiol was measured using VIDAS, enzyme linked fluorescent assay, (bioMerieux SA, France) with intra-assay CV%: 2.4; inter-assay CV%: 6.4 (pg/ml); detection limit: 9 (pg/ml); ranged from 9 to 3000 (pg/ml). SHBG was measured, ELISA IBL kit with intra-assay CV%: 2.3; inter-assay CV%: 5.7; sensitivity: 0.23 (nmol/L); detection limit: 0.408 (nmol/L); ranged from 0.408 to 206 (nmol/L).serum *AOPP* was determined with spectrophotometric methods (FLUOstar OPTIMA, BMG, Germany) as described by Kalousova et al. (2002) [18]. In this method, 200 mL of serum is diluted by a factor of 5, in phosphate buffered saline (PBS). In addition, 200 mL of chloramin T (0–100 mmol/l) for calibration, and 200 mL of PBS as blank is also added to different micro plates. Finally, 10 mL of acetic acid, and 20 mL of 1.16 M potassium Iodide (KI) is added to preparations. Normal range was 82.3–232.7 (μmol/L). *FRAP* was measured with spectrophotometry as described by Benzie and Strain (1996) [19]. Based on this method, FRAP reagent is prepared with mixing 300 mmol/L of acetate buffer (pH: 3.6), 10 mmol/L of tripyridyl triazine (TPTZ) in 40 mmol/L HCL, and 20 mmol/L FeCl3·.6H2O Twenty five mL of serum is then added to 750 mL FRAP reagent and absorbance is recorded at 593 nm. Normal range was 612–1634 (μmol/L). *AGEs* were assessed by the spectrophotometric method of Kalousova et al. (2002)[18]. Patients' sera were diluted by a factor of 50 in PBS. Fluorescence intensity at 350 nm excitation and 440 nm emission was recorded and is expressed as percentage of fluorescent emission. Serum *MDA* was measured using a colorimetric method (Cayman, USA) with intra-assay CV%: 5.5; inter-assay CV%: 5.9; range of 1.83 to 3.94 (μmol/L). NO was measured using a calorimetric method (zellbio, germany) with assay range of 3.12 to 100 μmol. Glucose measurements were made using glucose oxidase method (intra-assay coefficient of variants (CV) = 2.1%, inter-assay CV = 2.6%). HbA1c was estimated by high-pressure liquid chromatography.

2.3. Statistical analysis

Statistical analysis were performed using the SPSS software package, version 21 for windows (Chicago, IL, USA). The normality of distribution was assessed using Kolmogorov-Smirnov Test. Variables are presented as mean ± standard deviation (SD) or number (percent). One-way ANOVA, independent sample *t*-test and chi-squared tests were employed for group comparisons, as appropriate. Linear regression modeling was used to address interaction analysis and data modeling. A P value of < 0.05 was considered necessary to reject the null hypothesis.

3. Results

Baseline characteristics of study population are presented in Table 1. There were no significant differences between groups with respect to age, BMI, systolic and diastolic blood pressure, age at menopause, years after menopause, percent of abortion and serum SHBG level. Percentage of postmenopausal women was significantly higher in patients with EC with DM than three other groups ($\rho < 0.05$). Serum estradiol levels were higher in EC groups with (27.11 ± 15.65) and without (26.96 ± 11.45) DM compered to patients with DM (14.05 ± 4.33) and healthy controls (13.97 ± 4.57) ($\rho < 0.05$). Average duration of diabetes was higher in patients with DM without EC (6.6 ± 4.63) than with EC (2.58 ± 2.34) ($\rho < 0.05$), but serum FBS (171.67 ± 49.39 vs. 140.29 ± 41.97) and HbA1c (8.28 ± 1.68 vs. 7.24 ± 1.12) were not significantly different.

Markers of lipid peroxidation (oxLDL and MDA), protein oxidation (AOPP and AGEs), free radical (NO), antioxidant index (FRAP) and inflammation (TNFα, IL6 and hs-CRP) are presented in Table 2.

Ox-LDL, NO, MDA, AOPP and AGE were increased in all patients either with endometrial carcinoma and/or diabetes compared to healthy control ($p < 0.01$). There were also significant differences between patients with EC with and without DM in levels of oxidative markers including: OX-LDL (17.47 ± 0.84 vs. 12.36 ± 0.91), NO (82.27 ± 5.75 vs. 76.34 ± 5.36), MDA (3.3 ± 0.1 vs. 2.75 ± 0.48) and AGE (73.89 ± 5.71 vs. 69.02 ± 3.14) ($\rho < 0.05$), which were higher in patients with both diseases. Levels of oxidative stress markers were increased in patients with DM as much as increased in EC patients without DM ($\rho > 0.05$), except for oxLDL which is higher in patients

Table 1
Baseline characteristics of study population.

	Patients with endometrial carcinoma		Patients with diabetes (n = 29)	Healthy controls (n = 22)	*p*-value
	With diabetes (n = 19)	Without diabetes (n = 18)			
Age (years)	58.37 ± 8.77	52.17 ± 9.49	53.17 ± 8.37	52.19 ± 5.48	NS
BMI (kg/m^2)	30.41 ± 6.39	32.57 ± 6.32	28.68 ± 5.35	29.85 ± 4.71	NS
Duration of diabetes (year)	2.58 ± 2.34	–	6.60 ± 4.63	–	***p ≤ 0.001***
SBP (mmHg)	125.19 ± 13.04	120.14 ± 13.43	132.27 ± 19.17	126.47 ± 13.69	NS
DBP (mmHg)	76.63 ± 10.33	77.75 ± 8.05	80.00 ± 9.2	83.84 ± 7.77	NS
Age at menopause (year)	48.94 ± 3.54	46.56 ± 7.19	48.33(5.86	48.94 ± 4.88	NS
Years after menopause (year)	10.33(7.36)	8.33(7.03)	7.93(7.33)	5.68(4.82)	NS
Abortion+, (%)	31.6	33.3	48.1	33.3	NS
FBS (mg/dl)	140.29 ± 41.97*	112.43 ± 17.7#	171.67 ± 49.39*	92.5 ± 14.3	***p ≤ 0.001***
HbA1c (%)	7.24 ± 1.12*&	5.38 ± 0.78#	8.28 ± 1.68*	4.8 ± 0.61	***p ≤ 0.001***
SHBG (nmol/ml)	87.13 ± 33.32	94.75 ± 30.32	88.05 ± 40.53	73 ± 23.92	NS
Estradiol (pg/ml)	27.11 ± 15.65*#	26.96 ± 11.45*#	14.05 ± 4.33	13.97 ± 4.57	***p ≤ 0.001***

Data is presented as mean ± SD or percent.
* p ≤ 0.05, vs. *healthy control.*
# p ≤ 0.05, vs. patient with diabetes.
& p ≤ 0.05, vs. patient with endometrial cancer without diabetes.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; SHBG sex hormone-binding globulin.
Bold p-values indicate presence of overall statistically differences between all study groups. In order to define post hoc tests and pairwise comparisons symbols are used.

with DM (13.72 ± 1.38 vs. 12.36 ± 0.91, ρ < 0.05).

Level of FRAP, as an antioxidant marker, was decreased in EC patients with DM (1006 ± 203) and without DM (1124 ± 195) and also patients with DM alone (1126 ± 187) compared to normal controls (1463 ± 272) (p < 0.05) and there was no differences among patients groups with each other (p > 0.05).

Inflammatory markers, TNFα, IL6 and hs-CRP, were also significantly increased in patients with EC with and without DM than controls (ρ < 0.05). However, there were no significant differences between two groups of EC regarding to levels of TNFα (23.52 ± 9.64 vs. 22.1 ± 5.23, ρ > 0.05), il6 (22.6 ± 9.66 vs. 16.83 ± 9.19, ρ > 0.05) and hs-CRP (4.04 ± 2.56 vs. 4.26 ± 2.45, ρ > 0.05). In addition, levels of TNFα and hs-CRP, but not IL6, were higher in patients with EC alone compared to DM alone (ρ < 0.05). Patients with DM had significantly higher levels of inflammatory markers compared to control group, TNFα (15.13 ± 5.93 vs. 5.58 ± 2.1), IL6 (12.12 ± 6.15 vs. 3.24 ± 1.15) and hs-CRP (1.88 ± 1.91 vs. 0.43 ± 0.14) (all ρ < 0.05).

These results remained significant after adjusting for duration of diabetes, estradiol and HbA1c levels, using linear regression model.

We also performed interaction analysis between EC and DM on serum markers levels, Table 3. Three types of effects were obtained by regression analysis: the effect of diabetes alone, the effect of endometrial cancer alone and the joint effect of diabetes and cancer on measured marker levels. Our results showed significant interaction effect between EC and DM on levels of oxLDL, NO, AGE, AOPP and FRAP (p < 0.05), Fig. 1. Although, EC and DM had their own effects, a company effect of both diseases was lower than simple quantitative addition of each diseases effects that means the association between EC and DM represented subadditive interaction effect on levels of above

Table 2
Inflammatory and oxidative stress markers levels in studied groups.

		Patients with endometrial carcinoma		Patients with diabetes (n = 29)	Healthy controls (n = 22)	*p*-value
		With diabetes (n = 19)	Without diabetes (n = 18)			
Oxidative stress markers						
Free radical	**NO**(U/mL)	82.27 ± 5.75*#&	76.34 ± 5.36*	77.55 ± 5.09*	40.6 ± 5.56	*p ≤ 0.001*
Lipid peroxidation	**ox-LDL**(mU/L)	17.47 ± 0.84*#&	12.36 ± 0.91*#	13.72 ± 1.38*	7.5 ± 1.55	*p ≤ 0.001*
	MDA(μmol/L)	3.3 ± 0.1*#&	2.75 ± 0.48*	2.82 ± 0.63*	2.01 ± 0.15	*p ≤ 0.001*
Protein oxidation	**AOPP**(μmol/L)	132.79 ± 11.59*	128.65 ± 6.37*	129.64 ± 16.1*	107.90 ± 26.54	*p ≤ 0.001*
	AGES %	73.89 ± 5.71*&	69.02 ± 3.14*	70.42 ± 7.46*	49.76 ± 3.02	*p ≤ 0.001*
Anti-oxidant						
FRAP (μmol/L)		1006 ± 203*	1124 ± 95*	1126 ± 187*	1463 ± 272	*p ≤ 0.001*
Inflammatory markers						
TNF-α (pg/ml)		23.52 ± 9.64*#	22.1 ± 5.23*#	15.13 ± 5.93*	5.58 ± 2.1	*p ≤ 0.001*
Interleukin-6 (pg/ml)		22.6 ± 9.66*#	16.83 ± 9.19*	12.12 ± 6.15*	3.24 ± 1.15	*p ≤ 0.001*
hs-CRP (mg/L)		4.04 ± 2.56*#	4.26 ± 2.45*#	1.84 ± 1.71*	0.43 ± 0.14	*p ≤ 0.001*

Data is presented as mean ± SD.
* *p ≤ 0.05,* vs. *healthy control.*
# p ≤ 0.05, vs. patient with diabetes.
& p ≤ 0.05, vs. patient with endometrial cancer without diabetes.
NO, nitric oxide; ox-LDL, oxidized low density lipoprotein; MDA, malondialdehyde; AOPP, advanced oxidation protein products; AGE, advanced glycation end products; FRAP, ferric reducing ability of plasma; TNFα, tumor necrosis factor α; IL6, interlukine6; hs-CRP, highly sensitive- C reactive protein.

Table 3
Regression modeling was obtained to study single and joint effects of EC and DM on serum measured markers. Data is presented as coefficient.

	Simple model			Interaction model
	Main effect of EC and DM	Main effect of EC	Main effect of DM	Interaction effect between EC and DM
NO	41.67*	35.74*	33.22*	**−27.28***
OX-LDL	9.97*	5.08*	6.22*	**−1.32***
MDA	1.29*	0.73*	0.81*	−0.25
AOPP	27.92*	23.78*	22.53*	**−18.39***
AGEs	25.83*	19.89*	20.74*	**−14.80***
FRAP	−456.49*	−328.33*	−336.95*	**208.79***
TNF-α	34.87*	29.64*	16.07*	−7.84
IL-6	38.28*	20.92*	6.91	10.14
Hs-CRP	3.36*	3.67*	1.30*	−1.61

* $p \leq 0.05$.
EC, endometrial carcinoma; DM, diabetes; NO, nitric oxide; ox-LDL, oxidized low density lipoprotein; MDA, malondialdehyde; AOPP, advanced oxidation protein products; AGE, advanced glycation end products; FRAP, ferric reducing ability of plasma; TNFα, tumor necrosis factorα; IL6, interlukine6; hs-CRP, highly sensitive- C reactive protein.
If joint effect of DM and EC compared to single disease effects was significant, the coefficient presented in bold numbers.

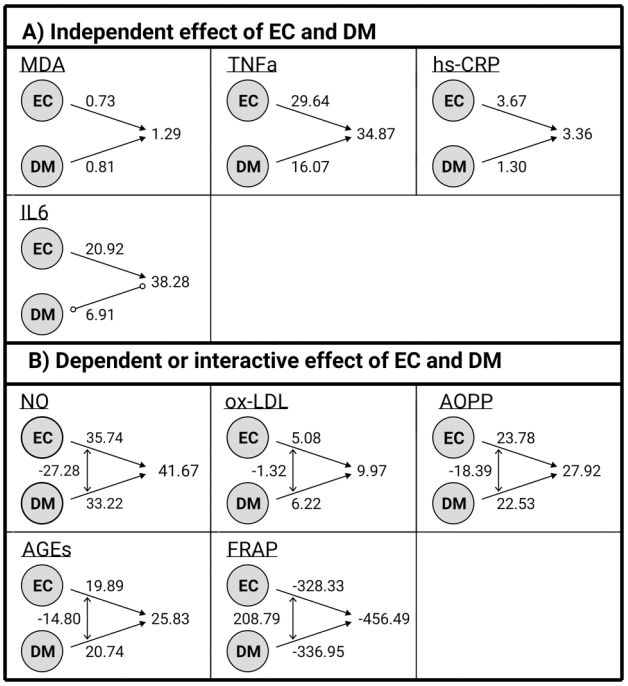

Fig. 1. Interaction between endometrial cancer and diabetes on measured markers levels. Main effect of individual diseases is indicated next to the arrows and the observed effect in patients with both diseases is showed by the number at the right of each pair. Interactive effect of DM and EC is indicated next to the Two-way arrows. Data was presented as coefficient. (A) The effects of EC and DM on serum level of MDA, TNFα, hs-CRP and IL6 were independent and interaction analysis was not significant. (B) Endometrial cancer and diabetes interacted significantly on serum levels of NO, oxLDL, AOPP, AGEs and FRAP ($\rho < 0.05$). Although, EC and DM had their own effects, a company effect of both diseases was lower than simple quantitative addition of each diseases effect. This pattern of interaction is called subadditivity with interference.

markers. There were no significant interaction between EC and DM on serum levels of hs-CRP, IL6, TNFα and MDA ($p > 0.05$). However, the observed levels in patients with both diseases represent subadditive levels.

4. Discussion

Our data showed higher serum levels of oxidative stress markers in patients with endometrial carcinoma and diabetes. Patients with both diseases represented significantly higher levels of NO, oxLDL, MDA and AGEs compared to patients having EC or DM alone and also healthy controls. Serum levels of AOPP and FRAP had no significant difference among patients with both diabetes and cancer, diabetes and cancer alone. But AOPP was significantly higher and FRAP was lower in all groups compared to healthy controls.

We also questioned whether presence of DM and EC together had a joint effect beyond the separate effect of each, single disease on oxidative stress marker levels. The net effect of DM and EC in combination on NO, oxLDL, AOPP, AGEs and FRAP levels was interactive and subadditive. Presence of DM and EC together interfered with expression of mentioned markers. Therefore, as presented in Fig. 1 observed coefficient of EC and DM together was less than quantitative sum of coefficients of each diseases. When two diseases underling mechanisms overlap, disturbance leading to one disease will likely interfere in pathways involved in the other diseases [20]. In this study, levels of NO, oxLDL, AOPP, AGEs and FRAP were affected by presence of both EC and DM. This suggests interaction in molecular roots, despite different mechanisms involved in diseases process [21]. It could be hypothesized that the subadditive interaction may be due to adverse effect of excessive oxidative stress beyond the cellular tolerance that leads to cytotoxicity and apoptosis of tumor cells, which is observed in high concentration of NO [22].

Hyperglycemia, oxidative stress and complications of diabetes are closely linked together [23]. In consistent with our results, increased level of oxidative stress markers such as oxLDL [14], MDA [13], AOPP and AGEs [24] were reported in diabetes. Previous research has identified increased levels of AGEs in cancer [25]. A study of AGE receptor (RAGE) in endometrial cancer indicated association of RAGE and microvascular formation and proliferation [26]. NO is also over expressed in diabetes and many tumors [27], which could induced DNA damage and is correlated with endometrial carcinoma angiogenesis [28].

Our results also showed significantly increased levels of IL6, hs-CRP and TNFα in patients with EC. However, presence of DM in patients with EC did not lead to a significant increase in inflammatory marker levels. The achieved net effect of EC and DM in combination on IL6, hs-CRP and TNFα was independent and subadditive and interaction effect was not significant. This may be because of limitation in tissue responsiveness. Patients with EC alone had significantly higher hs-CRP and TNFα levels compared to patients with DM alone.

Inflammatory markers such as IL6, TNFα and CRP are considered as a predictor of diabetes [29]. Moreover, laboratory studies have demonstrated direct carcinogenic effects of IL6 and TNFα [11]. Previous studies supported the role of inflammation in endometrial carcinogenesis [7,30].

In the current study, patients with DM or EC alone had similar increase in oxidative stress markers including NO, MDA, AOPP and AGEs, except oxLDL which was higher in diabetes. However, a different level of inflammatory markers was observed and was higher in patients with cancer alone. It may be concluded that intensity of inflammation was higher in carcinoma.

Initial experiments on the role of ROS in tumor initiation have assumed that direct DNA damaging agents leading to carcinogenesis [31]. However, recent evidence has revealed that ROS are involved in the link between chronic inflammation and cancer by activating certain signaling pathways [32]. Indeed, an important step in the onset and progression of cancer is recruitment of inflammatory cells and ROS generation stimulation. In the course of carcinogenesis key molecular player is inflammation and the main chemical effectors are free radical species [32,33]. Oxidative stress and chronic inflammation network is interconnected and setting up a vicious cycle that maintains tumor development. Diabetes by interacting in oxidative state maybe

associated with poorer survival and increased risk of all-cause death and death from EC [3].

The principal limitation of the present study is limited sample size. Despite the collection of patients within two years, the number of patients with endometrial carcinoma was limited. This may affect by our exclusion criteria, which some patients had a history of chemotherapy or surgery and were excluded.

In conclusion, levels of chronic inflammatory and oxidative stress markers were increased in both endometrial cancer and diabetes. Effect of EC and DM together on levels of oxLDL, NO, AGE, AOPP and FRAP) was interactive and subadditive. It seems that Additional effect of diabetes in patients with cancer was mediated more significantly via increase in oxidative stress rather than inflammatory markers.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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References

[1] K.K. Tsilidis, et al., Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies, Bmj 350 (2015) g7607.
[2] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2016, CA Cancer J Clin 66 (1) (2016) 7–30.
[3] K. Lindemann, M. Cvancarova, A. Eskild, Body mass index, diabetes and survival after diagnosis of endometrial cancer: a report from the HUNT-survey, Gynecol Oncol 139 (3) (2015) 476–480.
[4] B.S. Saltzman, et al., Diabetes and endometrial cancer: an evaluation of the modifying effects of other known risk factors, American J. Epidemiol. 167 (5) (2008) 607–614.
[5] A.T. Ali, Risk factors for endometrial cancer, Ceska Gynekol 78 (5) (2013) 448–459.
[6] C. Phosat, et al., Elevated C-reactive protein, interleukin 6, tumor necrosis factor alpha and glycemic load associated with type 2 diabetes mellitus in rural Thais: a cross-sectional study, BMC Endocr Disord 17 (1) (2017) 44.
[7] L. Dossus, et al., Hormonal, metabolic, and inflammatory profiles and endometrial cancer risk within the EPIC cohort–a factor analysis, Am. J. Epidemiol. 177 (8) (2013) 787–799.
[8] F. Modugno, et al., Inflammation and endometrial cancer: a hypothesis, Cancer Epidemiol. Biomarkers Prev. 14 (12) (2005) 2840–2847.
[9] S. Bellone, et al., High serum levels of interleukin-6 in endometrial carcinoma are associated with uterine serous papillary histology, a highly aggressive and chemotherapy-resistant variant of endometrial cancer, Gynecol Oncol 98 (1) (2005) 92–98.
[10] C.M. Friedenreich, et al., Case-control study of inflammatory markers and the risk of endometrial cancer, Eur. J. Cancer Prev. 22 (4) (2013) 374–379.
[11] T. Wang, et al., A prospective study of inflammation markers and endometrial cancer risk in postmenopausal hormone nonusers, Cancer Epidemiol. Biomarkers Prev. 20 (5) (2011) 971–977.
[12] L. Dossus, et al., Tumor necrosis factor (TNF)-alpha, soluble TNF receptors and endometrial cancer risk: the EPIC study, Int. J. Cancer 129 (8) (2011) 2032–2037.
[13] A. Rashidi, et al., Association between oxidant/antioxidant markers and proteinuria in type 2 diabetes: results in 142 patients, J. Nephrol. 22 (6) (2009) 733–738.
[14] M. Nakhjavani, et al., Serum oxidized-LDL is associated with diabetes duration independent of maintaining optimized levels of LDL-cholesterol, Lipids 45 (4) (2010) 321–327.
[15] S. Pejic, et al., Lipid peroxidation and antioxidant status in blood of patients with uterine myoma, endometrial polypus, hyperplastic and malignant endometrium, Biol. Res. 39 (4) (2006) 619–629.
[16] M. Rossi, et al., Dietary total antioxidant capacity in relation to endometrial cancer risk: a case-control study in Italy, Cancer Causes Control 27 (3) (2016) 425–431.
[17] C.-X. Xu, H.-H. Zhu, Y.-M. Zhu, Diabetes and cancer: Associations, mechanisms, and implications for medical practice, World J. Diabetes. 5 (3) (2014) 372–380.
[18] M. Kalousova, J. Skrha, T. Zima, Advanced glycation end-products and advanced oxidation protein products in patients with diabetes mellitus, Physiol. Res. 51 (6) (2002) 597–604.
[19] I.F. Benzie, J.J. Strain, The ferric reducing ability of plasma (FRAP) as a measure of "antioxidant power": the FRAP assay, Anal. Biochem. 239 (1) (1996) 70–76.
[20] H. Paik, et al., Unraveling human protein interaction networks underlying co-occurrences of diseases and pathological conditions, J. Transl. Med. 12 (2014) 99.
[21] J. Menche, et al., Disease networks. Uncovering disease-disease relationships through the incomplete interactome, Science 347 (6224) (2015) 1257601.
[22] K. Harada, et al., Overexpression of iNOS gene suppresses the tumorigenicity and metastasis of oral cancer cells, Vivo 18 (4) (2004) 449–455.
[23] K. Nowotny, et al., Advanced glycation end products and oxidative stress in type 2 diabetes mellitus, Biomolecules 5 (1) (2015) 194–222.
[24] A. Esteghamati, et al., Effects of metformin on markers of oxidative stress and antioxidant reserve in patients with newly diagnosed type 2 diabetes: a randomized clinical trial, Clin. Nutr. 32 (2) (2013) 179–185.
[25] D.P. Turner, Advanced glycation end-products: a biological consequence of lifestyle contributing to cancer disparity, Cancer Res. 75 (10) (2015) 1925–1929.
[26] L. Zheng, et al., Effects of receptor for advanced glycation endproducts on microvessel formation in endometrial cancer, BMC Cancer 16 (2016) 93.
[27] B. Salimian Rizi, et al., Nitric oxide mediates metabolic coupling of omentum-derived adipose stroma to ovarian and endometrial cancer cells, Cancer Res. 75 (2) (2015) 456–471.
[28] W. Li, et al., Expression of cyclooxygenase-2 and inducible nitric oxide synthase correlates with tumor angiogenesis in endometrial carcinoma, Med. Oncol. 22 (1) (2005) 63–70.
[29] C. Liu, et al., Adiponectin, TNF-alpha and inflammatory cytokines and risk of type 2 diabetes: a systematic review and meta-analysis, Cytokine 86 (2016) 100–109.
[30] M. Slater, M. Cooper, C.R. Murphy, Human growth hormone and interleukin-6 are upregulated in endometriosis and endometrioid adenocarcinoma, Acta Histochem 108 (1) (2006) 13–18.
[31] A.L. Jackson, L.A. Loeb, The contribution of endogenous sources of DNA damage to the multiple mutations in cancer, Mutat. Res. 477 (1–2) (2001) 7–21.
[32] S. Reuter, et al., Oxidative stress, inflammation, and cancer: how are they linked? Free Radic. Biol. Med. 49 (11) (2010) 1603–1616.
[33] A. Federico, et al., Chronic inflammation and oxidative stress in human carcinogenesis, Int. J. Cancer 121 (11) (2007) 2381–2386.