Original Article

Serum antioxidant status in Iraqi women with endometrial cancer

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Abstract:

Background: Endometrial cancer is the most common gynecologic malignancy in the United States and the fourth most common cancer in women, comprising 6% of female cancers.

Objectives: The aim of this study is to investigate the antioxidant vitamins, Coenzyme Q_{10} and oxidative stress in patients with endometrial cancer.

Patients and methods: Fifty six endometrial cancer women patients with various clinical stages (stage 1A, stage1B, stage II, stage III, stage IV) mean aged 58.055 ± 10.561 years, and 30 healthy women volunteers mean aged 39.731 ± 13.504 years, were includes as control group.

Results: The results in this study revealed a highly significant decreased ($P<0.01$) in β- carotene, Vitamin E and significant increased ($P<0.01$) in (Uric acid and MDA). The results of (Coenzyme Q_{10} and Vitamins (A, C) showed a significant decreased ($P<0.05$), in the sera levels of patients with endometrial cancer as compared to control group.

Conclusions: This study suggest that high levels of oxidative stress and low levels of antioxidant defense system may be associated with increased the risks of endometrial cancer.

Keywords: Endometrial cancer, Vitamin A, Vitamin C, Vitamin E, β-carotene, Uric acid, MDA and Coenzyme Q_{10}.

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Introduction:

Endometrial cancer is very common gynecologic cancer and the fourth most repeatedly diagnosed cancer in women in the United States, (1). Early diagnosis of endometrial cancer can be through some symptoms as irregular menstruation or postmenopausal bleeding and this particularly worrisome, (2). More than 90% of women with endometrial cancer occur in women older than 50 years of age, with a median age of 63 years, (3). Term of "antioxidant systems" describes the diverse and responsible mechanisms for protection the cells from the actions of free radicals. This system includes: fat soluble antioxidants vitamins such as (vitamin A, E, carotenoids, and ubiquinones), water soluble antioxidants vitamins such as (ascorbic acid, uric acid, taurine and carnitine) and antioxidant enzymes such as GSH-Px, CAT and SOD; thiol redox system consisting of the glutathione system, (4). Vitamins are chemically unrelated organic compounds, cannot be synthesized in enough amount by humans so must be provided by the diet. Vitamin C is a water-soluble reducing agent (electron donor), vitamin C must be provided by fruits, vegetables and tablets, (5). The systematic name is (5R)-[(1S)-1,2-dihydroxyethyl]-3,4-dihydroxyfuran-2(5H)-one, (6). Vitamin E is a fat-soluble vitamin. The term of vitamin E include four tocopherols (α, β, γ and δ) and four tocotrienols (α, β, γ and δ). α-Tocopherol is the most active form of vitamin E in humans, is a part of the antioxidant defense system and is a peroxyl radical scavenger which protects polyunsaturated fatty acids within membrane phospholipids and plasma lipoproteins, (7). Vitamin A (retinol in mammals) is a fat-soluble vitamin. Two types of vitamin A Human can take in: provitamin A from plants and preformed vitamin A from animal source, (8), one of the earliest signs of vitamin A deficiency is night blindness. Vitamin A is related for growth, differentiation of cells and tissues, during pregnancy, during the breastfeeding time and has a significant role in the healthy development of the fetus and the newborn, (9). The important member in carotenoid family is the β-carotene is a red orange-colored pigment exist in plants and fruits and the major of carotenoid in human diet, (10). β-carotene is a precursor of vitamin A, it could yield two retinol molecules in existence of oxygen by the action of β-carotene 15, 15′-monooxygenase, (11, 12). β-carotene is an antioxidant vitamin because of the ability to preventing cellular damage and is a potent antioxidant, which capable to put out 1,000 free radicals per molecule, (13). Coenzyme Q_{10} (CoQ_{10}) also known as ubiquinone, (14), CoQ_{10} is a fat soluble substance found throughout the body and essentially in heart, liver, brain, kidney and human mitochondria. It is produced by the human body and is required for many organs function and chemical

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reactions in the body, (15). The end product of purine catabolism in humans is uric acid. It is a heterocyclic compound of carbon, nitrogen, oxygen, and hydrogen (16). Increase purine catabolism lead to overproduction of uric acid (hyperuricemia) and this lead to several diseases in human such as gout, (17). Uric acid is a water-soluble antioxidant. It creates ions and salts known as urates and acid urates such as ammonium acid urate, (18). Uric acids have antioxidant properties and in human serum play a role in 60% of free radical scavenging activity in its normal level, (19). MDA is one of α, β-unsaturated aldehydes, is a dicarbonyl compound and the second oxygen atom in its structure makes the double bond more reactive, (20). In lipid peroxidation hydroxyl radical damage the cell membranes and lipoproteins, the MDA and conjugated diene compounds will formation which consider cytotoxic and mutagenic, (21).

Patients and Methods:

This study was conducted in Oncology Teaching Hospital and Baghdad Hospital for the period from October 2015 to February 2016. The study included collection the blood samples from 56 endometrial cancer women patients before therapy mean aged (58.055 ± 10.561 year), a total of 30 healthy women volunteers mean aged (39.731 ± 13.504 year) served as control, also included some questionnaire regarding to age, menarche, menopause, infertility, HRT using, hypertension, personal and family history of cancer and/or diabetes mellitus, and smoking.

Analysis of Samples:

Specimen collection: Fasting blood samples (10 mL) were collected and placed into plane tubes. After centrifugation at 1500×g for 10 min, the sera were removed and retained directly for assay of the level of vitamin C and the remained sera were a liquates and stored at -80C^{o} until analysis for other parameters.

Laboratory assessments: The vitamin C concentration in serum was determined according to modified of method Washington and Toronto method, (22), based on the oxidation of ascorbic acid in serum by Cu^{2+} to form dehydroascorbic acid that react with the acidic 2,4-dinitrophenyl hydrazine to form a red bis-hydrazone which is measured at (λ_{ma} 520 nm). The concentration of vitamin E in serum was determined according to an antioxidant – reduction reaction is carried out according to Emmerie-Engle procedure in which tocopherol is oxidized to tocopherol quinone by addition the ferric chloride reagent, and the (Fe^{+2}) in the resultant $FeCl_2$ will be complex with α , α- dipyridyl to produce a red color which absorb at λ_{ma} 510 nm, (22). The concentration of vitamin A in serum was determined according to a modified method of Neeld and Pearson, (23).

Trifluoroacetic acid reacted with the conjugated double-bond system of the organic solvent-extracted compounds to produce a blue color complex, which absorbed at λ_{max} 620 nm, (24). β-Carotene is extracted into petroleum ether to remove it from interfering substance in serum. Because of its hydrophobic properties carotene usually binds to serum proteins. The resultant orange-yellow color is read at λ_{max} 450 nm. Uric acid was measured by enzymatic colorimetric assay using kit supplied by Human Gesellschaft, Germany. CoQ_{10} was measured by ELISA kit that supplied by SHANGHAI YEHUA Biological technology, China.

Statistical analysis:

All data were expressed as mean ± standard deviation. Statistical analysis was performed using LSD, considering $P<0.05$ as the lowest limit of significance. Statistical analysis was performed using a software program (SPSS 13 for Windows, USA). One-way analysis of variance (ANOVA) was used to compare means with least significant difference (LSD).

Results:

Table 1 displayed a highly significant increased ($P<0.01$) in age and a significant difference in systolic and diastolic blood pressure when compared between in endometrial cancer patient and control group. The results in Table 1 also showed that majority of cancer family history and married women (presenting %) estimated in endometrial cancer patients group, while the lowest recorded in control group. The presenting of physical activity and drinking coffee revealed in control group as compared to patients. Figure 1 illustrated graphically the distribution of age for all studied groups of endometrial cancer and control group.

Table 2 displayed a highly significant decreased ($P<0.01$) in β-carotene mg/dL and vitamin E mg/dL. A significant decreased ($P<0.05$) was observed in vitamins (A, C and CoQ_{10}) mg/dL, while a highly significant increased ($P<0.01$) was showed in serum (uric acid and MDA) mg/dL levels in women with endometrial cancer compared to control group.

Table 3 display a highly significant increased ($P<0.01$) in β-carotene mg/dL, MDA mg/dL and in uric acid mg/dL, while non-significant differences were observed in vitamins (A, C, E and CoQ_{10}) mg/dL between the stages of endometrial cancer patients and control groups.

Table 1: The demographic characteristics of study women in endometrial cancer and control groups

Parameters	Controls, N=30 (mean ± SD)	Patients, N=56 (mean ± SD)	P- value
Age (years)	39.731 ± 13.504	58.055 ± 10.561	0.0001**
Diastolic BP (mmHg)	7.360 ± 1.114	7.982 ± 1.027	0.02*
Systolic BP (mmHg)	11.840 ± 1.841	12.927 ± 1.259	0.0031**
Coffee (Yes, No)%	(36%, 64%)	(4%, 96%)	-
Physical activity	(50%, 50%)	(0%, 100%)	-
Cancer family history Yes, No)%	(43%, 57%)	(63%, 37%)	-

* The mean difference is a significant at p≤ 0.05 ** the mean difference is a highly significant at the p< 0.01 level

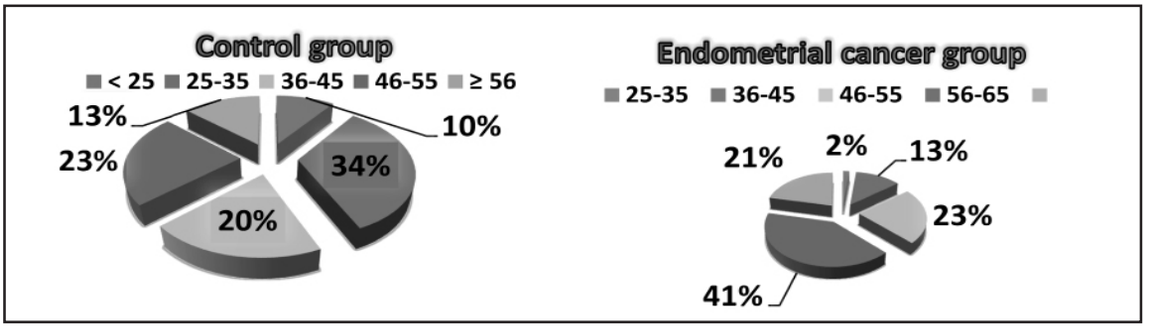

Figure 1: Pie charts for the distribution of endometrial cancer patients and control according to age group.

Table 2: Means ± SD of antioxidants components for endometrial cancer and control groups

Parameters	Controls, N=30 (mean ± SD)	Patients, N=56 (mean ± SD)	P- value
Vitamin C (mg/dL)	2.136 ± 0.559	1.865 ± 0.454	0.02*
Vitamin E (mg/dL)	2.221 ± 0.626	1.773 ± 0.754	0.007**
Vitamin A (mg/dL)	0.385 ± 0.102	0.348 ± 0.018	0.03*
β- carotene (mg/dL)	1.507 ± 0.363	0.860 ± 0.389	0.0001**
CoQ_{10} (mg/dL)	0.113 ± 0.061	0.088 ± 0.029	0.02*
Uric acid (mg/dL)	4.457 ± 0.595	5.289 ± 1.449	0.004**
MDA (mg/dL)	0.799 ± 0.705	2.243 ± 1.254	0.0001**

* The mean difference is a significant at p≤ 0.05 ** the mean difference is a highly significant at the p< 0.01 level.

Table 3: Statistics of antioxidants and oxidative stress parameters distributed in endometrial cancer patients & control group according to stages

Parameters		Control group N=30	Endometrial Cancer Patients				
			Stage1A N=14	Stage1B N=20	Stage II N=4	Stage III N=10	Stage IV N=8
Vit A (mg/dL)	mean	0.385	0.346	0.355	0.352	0.341	0.356
	SD	0.102	0.056	0.052	0.080	0.058	0.048
	P value	NS					
β-carotene (mg/dL)	mean	1.507	0.921	0.804	0.876	0.887	0.758
	SD	0.363	0.379	0.386	0.485	0.341	0.549
	P value	0.0001**					
Vit C (mg/dL)	mean	2.136	2.004	1.921	2.267	1.970	1.984
	SD	0.559	0.432	0.710	0.590	0.779	0.659
	P value	NS					
Vit E (mg/dL)	mean	2.221	1.958	2.019	1.512	1.727	2.248
	SD	0.626	0.912	0.895	0.825	0.788	0.988
	P value	NS					
CoQ_{10} (mg/mL)	mean	0.108	0.096	0.104	0.079	0.083	0.099
	SD	0.062	0.049	0.051	0.010	0.032	0.039
	P value	NS					
UA (mg/dL)	mean	4.457	4.734	5.535	4.829	6.034	4.697
	SD	0.595	0.689	1.143	1.598	2.574	0.646
	P value	0.004*					
MDA (mg/dL)	mean	0.799	1.989	2.487	2.457	2.046	2.315
	SD	0.705	1.560	1.031	1.324	1.233	1.612
	P value	0.0001**					

NS: non-significant at p>0.05 * Significant at p≤ 0.05 ** Significant at p≤ 0.01

Discussion:

Age is an important risk factor for endometrial cancer. Most women are diagnosed after menopause. The women after 40 years are the most exposure to endometrial hyperplasia it is an abnormal increase in the number of uterus cells, is not a cancer but may be develops into cancer, (25). Coffee compounds prevent the initiation phase of the carcinogenic process, decrease damage of DNA and protect cells against reactive oxygen species (ROS) by inducing production of detoxifying enzymes through some mechanisms, (26). The risk of endometrial cancer increased with a family history of endometrial cancer because of genetic factors, (27). Bjorge et al., described that abnormal blood pressure associated with significantly increased risks of all endometrial cancer subtypes except the serous and 'other' tumors, (28). Physical activity is a modifiable risk factor related to obesity which regulates hormonal and metabolic pathways and helps control body weight, and thus may protect against endometrial cancer, (29). The role of vitamin C as antioxidant may help to protect the endometrium tissue from oxidative stress, (30). vitamin C when combined to other antioxidant vitamins such as vitamin E be able to modulate upregulation estrogen receptor thereby inhibit endometrial toxicity, estrogen receptor act at proliferative and secretion in endometrial and this increased the risk of endometrial cancer. Among antioxidants vitamins E regulate cell differentiation and proliferation, low tocopherol level in women diagnosed with endometrial cancer may be due to their increased utilization in scavenging lipid peroxides as well as sequestration by tumor cells, (31). Vitamin A may be involved in the prevention and treatment of cancer and there is correlation between low dietary vitamin A intake and development of certain cancers, serum level of vitamin A in cancer patients was lower than of controls this suggested the association between vitamin A and the development of cancer through involved in regulating the growth, differentiation and apoptosis of normal and malignant cells, also its effect on immune function which is one of the most important defense mechanisms for protection against cancer, (32). β-carotene have Anti-estrogenic properties, (33). In endometrial cancer cells β-carotene inhibits cancer cell proliferation induced by estrogen and attenuating the DNA damage, (34). The results were in the same line with Maggio et al., which observed significant decline in β-carotenoid concentrations with aging and aging consider one of the risk factors of endometrial cancer (35). CoQ_{10} acts endogenous as well as exogenous antioxidant scavenges carcinogens because its albites to neutralizes free radicals which may causes the carcinogenesis, which consider complex and multistage process activated and stimulated through free radicals, (36). Study by Keri, showed that CoQ_{10} levels were significantly lower in patients of cervical cancer when compared to controls and these low levels may also reflect increased utilization of antioxidants to avoid the oxidative stress (37). Due to antioxidant properties uric acid play a protective role in carcinogenesis. High serum uric acid levels are related to an increased risk of cancer as well as the large lysis of malignant cells in patients with tumor lysis syndrome can result in hyperuricemia which can predispose patients to renal failure, coronary heart disease, and gout, (38). Levels of uric acid associated with higher cancer stage and the reasons maybe as a result of increased purine metabolism by xanthine oxidase because of tumors cell breakdown or the antioxidant property of uric acid become better (elevated concentrations) due to its role in protecting against free radical, oxidative damage that play a major role in cancer disease by initiation and increasing the mutation rate in cells and this lead to tumor stages development, (39). ROS increased able to stimulate cell progression and promote cell cancer proliferation. Women with gynecological disorders as endometrial cancer women patients which have impaired antioxidant defense system this lead to elevated levels of lipid peroxidation like MDA as markers of oxidative stress in endometrial tissue and this might be used in clinical evaluation for cancer stages, (40).

Conclusion:

In conclusion, results from this study suggest that Iraqi women patients with endometrial cancer in different stages have higher levels of oxidative stress and this lead to decreased the antioxidant defense system.

Authors Contributions:

Rana K. Jasim: Collecting samples, analysis of data and writing the manuscript.

Salwa H. N. Al- Ruba'ei: Designer research, analysis of data and performed statistical analysis.

Khudhair J. S. Al-Rawaq: Facilitate the task and supervision of collecting blood samples in the hospital.

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