Serum Taurine as a Marker of Endometrial Cancer

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Abstract: Serum taurine levels were measured in fifty women selected from a wide number of patients presented with irregular uterine bleeding (IUB) to the outpatient clinic of the Obstetrics and Gynecology Hospital, Ain Shams University. No significant differences in age and menopausal status were found. The control group comprised ten healthy women that enrolled as volunteers. According to the findings observed after full clinical examination, ultrasonography, endometrial biopsy or fractional uterine curetting and tumor marker (CA-125) determination, 15 women were diagnosed with endometrial cancer (EC), 10 with cystic endometrial hyperplasia (CEH), 15 with fibromyoma, and 10 women were diagnosed as dysfunctional uterine bleeding (DUB). The results showed non significant ($P > 0.05$) changes in the levels of CA-125 in all patients except in the cancer group where it exhibited a value nearly double that of normal ($P < 0.01$). Serum taurine levels exhibited values lower than control with 8 %, 14 % , 32 % and 56 % in the serum of patients diagnosed as DUB ($P > 0.05$), fibromyoma ($P > 0.05$), CEH ($P < 0.01$) and EC ($P < 0.01$) respectively .

In conclusion, the data suggests that measurement of serum taurine in women with irregular uterine bleeding could help the early detection of malignant transformation of endometrial wall.

Keywords: Serum taurine, uterine bleeding, endometrial cancer, CA-125.

INTRODUCTION

Endometrial cancer (EC) is the most common presenting malignant tumor of the female genital organs comprising almost 50 % of all pelvic tumors [1,2]. In the last few years, the frequency of EC has surpassed that of cervical cancer [3,4]. Although the etiology of EC remains largely unresolved, it is known that the continued non cyclic estrogenic stimulation [5-7] of the endometrium associated with nulliparity and chronic an ovulation plays a major role in its pathogenesis [8-10].

As a women ends her reproductive years and ovulation tends to become less regular, endometrial hyperplasia may occur. So any abnormal bleeding in premenopausal or postmenopausal patients not on estrogen therapy should be evaluated by fractional uterine curetting to rule out the presence of endometrial or endocervical carcinoma [8].

Unlike the successful screening method for cervical cancer, there is no similar procedure for the early diagnosis of EC. Screening procedures currently being tested are too insensitive and non specific while diagnostics methods are either too complex or invasive [3,11].

Taurine is a sulfur containing β amino acid with a wide range of vital biological functions, ranging from neuromodulation, cell membrane stabilization to being an antioxidant and scavenging agent [12-16]. In the last decade it has been widely used in the field of oncology as a chemo protective agent against hepato carcinogenesis [17-21], and colon carcinogenesis [22-24]. Moreover, taurolidine (an anti-endotoxin) was found to reduce tumor necrosis factor toxicity [25,26] and induced suppression of vascular endothelial growth factor (VEGF) production on protein and messenger RNA level indicating an apoptotic and antiangiogenic effect for taurine [27]. Also, its concentration in the mucosal cells was found to be lower than normal in cancer colon [28,29]. While taurolidine heparin reduced intraperitoneal tumor growth when used as intra-operative lavage [30]. Concomitantly, taurine reduces vascular leak, enhances lymphocyte cytotoxicity and reduces tumor burden [31].

Moreover,the authors noticed in another work a marked diminution in the level of serum taurine in precancerous conditions (high risk patients) of breast and liver [32,33].

The aim of this study was to investigate the possibility of using the level of serum taurine as a bio marker in the early diagnosis of EC, especially in the early precancerous condition (high risk patients).

PATIENTS AND METHODS

Patients

Patients were selected from fifty women presenting with irregular uterine bleeding were enrolled into the study. After full clinical examination, ultrasonography, hormonal assay, endometrial biopsy or fractional uterine curetting for a wide number of patients presented with IUB admitted to the outpatient clinic of the Obstetric and Gynecology Hospital, Faculty of Medicine, Ain Shams University. Only 15 women aged between 40-50 years diagnosed as premenopausal anovulatory DUB, and 15 women aged between 35-52 years

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Table 1. One Way Analysis of Variance (Anova) to Test the Effect of Using Serum Taurine of CA125 Markers in Difference Pathological Condition, Values are Expressed as Mean ± Standard Error

		Sum of Squares	df	Mean Square	F	Sig.
Taurine	Between Groups	5371.817	4	1342.954	82.798	0.000
	Within Groups	729.888	45	16.220		
	Total	6101.706	49			
CA125	Between Groups	36138.461	4	9034.615	74.820	0.000
	Within Groups	5433.824	45	120.752		
	Total	41572.285	49			

diagnosed with IUB due to fibromayoma, and 10 women diagnosed with a typical cystic endometrial hyperplasia aged between 38-53 years, and other ten women diagnosed with different stages of endometrial cancer aged between 40-61 years were enrolled in this study. In addition to the other investigations, serum CA 125 and serum taurine levels were only measured for the previous 50 selected patients. Ten normal healthy women, who needed general anesthesia for an intra uterine device (IUD) insertion, were enrolled as a control group.

Prior to participation in the study, all subjects had the procedure fully explained to them before signing the consent form.

METHODS

All subjects were subjected to a full clinical examination.

Ten cc of venous blood was collected from all women and allowed to stand for 2 hours at 4°C without shaking; clear sera were separated by centrifugation at 3500 r.p.m for 20 minutes. The separated sera were stored at -20°C until used for the assay of taurine and CA-125. Taurine was measured according to the method of Heinrikson and Meredith [34] using high performance liquid chromatography (HPLC). CA-125 was determined by the IMx CA-125 assay based on the microparticle enzyme immuno assay (MEIA) for the quantitative measurement of CA-125 values in human serum by fluorescent technique. The Abbott IMx CA-125 assay is based on the OC-125 monoclonal antibody which is available exclusively through Fujirebio Diagnostics. Inc. While IMx is a registered trademark of Abbott Laboratories, Abbott Park, USA (1999).

A biopsy of endometrial tissue was acquired by means of a minor surgical operation, dilatation and curettage (D & C) under general anesthesia. The endometrial tissues obtained by D & C were placed in 10 % phosphate buffered formalin (pH 7.2). Tissues were imbeded in paraffin wax. Sections (4mm) were stained with hematoxylin and eosin (H & E) stain.

Ultrasonography was done for all women in the Ultrasound Unit, Faculty of Medicine, Ain Shams University, using Medeson Machine (CED 123) Model Sa 600.

This work approved by ethical committee of Ain Shams University (approved by IRB).

RESULTS

One way analysis of variance (Anova test) to test the effect of using serum taurine of CA125 markers in difference Pathological condition are showed in Table **1**.

Serum taurine levels in 50 women suffering from irregular uterine bleeding are illustrated in Table **2**. The results

Table 2. Serum Levels of Taurine and CA-125 in Women Presented with Irregular Uterine Bleeding

Condition	Serum Level of	
	Taurine µ mol /L	CA-125 U/ml
1. Healthy control group (n=10) Aged between 25-35	50.78±5.25 (d)	8.55±6.35 (e)
2. Dysfunctional uterin bleeding (n =15) Aged between 40-50	47.20±5.55 (c)	10.80±8.66 (e)
3. Fibromyoma (n=15) Aged between 35-52	45.90±6.18 (c)	12.65±7.31 (e)
4. Cystic endometrial hyperplasia (n=10) Aged between 38-53	34.15±3.48 (b)	12.15±7.85 (e)
5. Ednometrial cancer (n= 10) Aged between 40-61	22.18 ± 3.16 (a)	78.50± 35.91 (f)

Average of the same letters are non significant (i.e. P> 0.05), where as others are significant (P< 0.05).

showed an inverse relation between its level and the severity of cases. Taurine levels in DEH (whether in proliferative phase or in secretory phase) and fibromyoma were similar ($P > 0.05$) lower (47.20 ± 5.55 and 45.90 ± 6.18 μmo1/L respectively), while they were markedly lower ($P < 0.01$) in CEH and EC (34.15 ± 3.48 and 22.18 ± 3.61 μmo1/L respectively) in comparison to that recorded in healthy control group (50.75 ± 5.25 μmo1/L). While CA-125 levels showed no change ($P > 0.05$) in all groups with the exception of EC group. The values were 10.80 ± 8.66, 12.65 ± 7.31 and 12.55 ± 7.85 U/m1 in DEH (in both conditions proliferative and secretory), fibromyoma, and CEH respectively, in comparison to 8.55 ± 6.35 U/m1 recorded in control group. But it significantly ($P < 0.01$) increased in EC when it exhibited a value of 78.50 ± 35.90 U/m1.

The biochemical analyses were confirmed by the histopathological findings observed (Fig. **1A-F**).

Ultrasonography scanning for all patients showed:

- Proliferative endometrium showing trilaminar appearance with a thickness of about 9 mm, whereas in the control group it was about 4mm.
- Secretory endometrium (poor ovulatory phase) showing echogenic thickness of 9-11 mm, while in the control group it was 6mm.
- Myoma showing well circumscribed and defined capsule in different sizes and position (intramural or subserous).
- Cystic endometrial hyperplasia showing endometrial thickness more than 8mm in premenopausal and more than 4mm in postmenopausal women.
- Adenocarcinoma showing heterogenic malignant endometrium of more than 8mm thickness.

DISCUSSION

In the last decade, a new trend to investigate the possible correlation between antioxidants and the pathogenesis of cancer developed [35,36]. Taurine was used successfully as a chemotherapeutic agent against the powerful hepatocarcinogenic agent, diethy1 nitrosamine (DENA)-treated rats [17]. Also, successful results were recorded when used to treat cancer colon induced by azoxymenthan and hydrophobic bile acid [22-24].

Three main processes have been implicated in tumor growth: increased cell proliferation, inhibition of tumor cell apoptosis and enhanced angiogenesis [37,38].

Concomitantly, it was noticed that tauromustine is effective in treatment of disseminated malignant melanoma [39] and colonic tumor [40]. It was also used to potentiate the antitumor effect of 5 - flurouracil and hydralazine in the treatment of colon adenocarcinoma [41,42], nitrosourea in treatment of hepatoma [43] and lung cancer [44].

Moreover, taurine prevents the angiogenic factor VEGF in hepatocellular carcinoma patients [17] and it has modulatory effects on nephrotoxicity of tamoxifen, the antineoplastic drug used for the treatment of breast cancer [45].

In addition, taurine derivatives have also been used as chemo protective agent for several years, when taurocholic acid and taurolidine were reported to decrease the incidence of cholangio carcinoma in hamster, and reduce tumor necrosis factor (TNF) toxicity in mice respectively [25,46]. Taurolidine was also used to decrease the tumor cell growth of colon adenocarcinoma *in vitro* as well as intraperitoneal tumor growth *in vivo* [47,48]. Recently the serum level of taurine was used as a novel early biomarker in cancer breast and hepatocellular carcinoma [17-25]. Now there is no doubt that antioxidant deficiency enhances angiogenesis and stimulates tumor growth.

This assumption was reinforced when antioxidant components, such as glutathione, vitamin E, and selenium levels are reduced in the serum of women with cervical cancer [49]. The authors also observed a diminution in the level of some important antioxidant enzymes like erythrocyte superoxide dismutase; catalase; glutathione peroxidase; glutathione-s-transferase and glucose-6-phosphate dehydrogenase in the same cohort of patients (unpublished data). But the surprising point that drew the attention of the authors was the normalization of the biochemical parameters after a different mode of therapy.

Concomitantly, it was found that deficiency in Na-taurocholate co-transporting polypeptide (NTCP), which is a strong antioxidant substance, is considered as the main pathognomonic factor in human hepatocellular carcinoma [50]. Also it was used as adjuvant therapy to increase and facilitate the uptake and accumulation of the cytostatic drug, chlorambucil taurocholate, inside the hepatocyte in case of hepatocarcinoma [51,52]. Thus, it was postulated that there is a potential role of antioxidant deficiency in the pathogenesis of cervical intraepithelial neoplasia (CIN) and carcinoma of cervix [49,53].

Uterine cancer occurs in 1 to 2 cases per 1000 postmenopausal women per year in the general population and is one of the most common cancers in the female, exceeded in frequency only by carcinoma of the breast [54,55], thus the importance of their early detection and management is obvious because of the frequency with which they are encountered. Thereby, the measurement of the most powerful antioxidant β-amino acid, taurine, in serum of women presenting with different pictures of endometrial pathology including pre and cancerous changes is worthwhile.

In this study women with EC clearly had a lower serum level of taurine than those of the control group. The diagnosis was confirmed by pelvic ultrasonography, tumor marker CA-125 determination, and endometrial biopsy.

It is a well known fact that up to date, there is no highly specific marker for EC, but the ovarian cancer antigen, CA-125, is controversial in the diagnoses of it [56,57], although it was found that 98% of patients with clinical or surgical stage I or II had normal preoperative value [58,59].

Serum CA-125 measurement may be of value as prognostic indicator in EC and as a reflection of disease status in advanced endometriosis [58,60-62]. Also, it was found that serum CA-125 is expressed not only by epithelial ovarian tumors but also in various other pathological tissue of müllerian origin [63,64].

The usefulness of ultrasonography is unquestionable in the evaluation of adnexal areas, but its ability to accurately

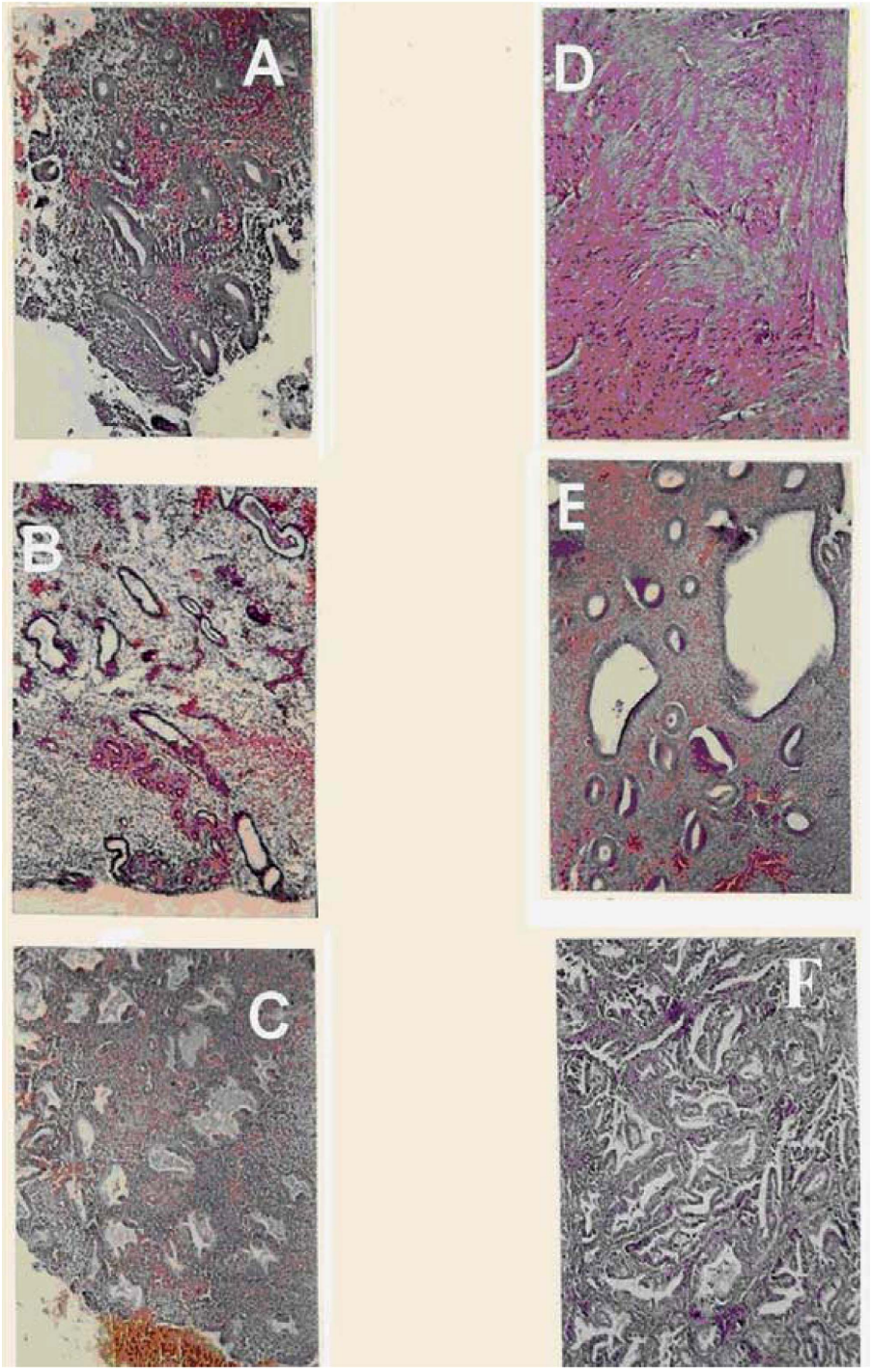

Fig. (1). The previous biochemical analyses were confirmed by the histopathological examination observed in Fig. (**1**).

(**A**): Proliferative endometrium showing small simple glands lined by columnar epithelium with nuclear pseudostratification . H&E x 40.

(**B**): Secretory endometrium day 22-23, showing tortuous glands lined by cuboidal epithelium. The stroma is oedematous with clustered spiral arterioles and early predicdual changes. H&E x 40.

(**C**): Secretory endometrium day 26 - 27, showing tortuous gland lined by cuboidal epithelium with saw-toothed appearance. The stroma shows diffuse predecidual changes with breakdown. H&E x 40.

(**D**): Leiomyoma (Fibromyoma), showing bundles of plain muscle cells and fibrous tissues which run in various direction, interlace and take various arrangements with intervening collagen. H&E x 40.

(**E**) Cystic endometrial hyperplasia, showing dilated glands of varying size and small proliferative glands in - between. There are patchy necrosis .H&E x 40.

(**F**) Endometrial adenocarcinoma Grade I, showing irregular malignant acini with varying size. They are lined by one or more layers of haphazardly arranged columnar malignant cells with no basement membrane some acini are dilated and forming cystic space. They are separated by fibrous stroma.

detect and define myometrial invasion has yet to be proven [54]. In the present study the values of CA-125 measured in different types of endometrial pathology including DEH, fibromyoma, and CEH which is considered as precancerous lesion [59,65] were non significantly changed from that recorded in control group, all of them below 35 U/ml. Despite the marked increase recorded in typical cancer patients, some of them exhibited values nearly similar to the upper normal range of CA-125.

Contrarily, serum taurine levels were mild lower in patients presented with DUB & fibromyoma, and marked lower were observed in patients with CEH, while it exhibited a value sever lower than normal in EC.

Therefore one might suspect malignant transformation in the uterine wall when the serum level of taurine exhibits a value lower than 30 U mole/L. The advantage is the correlation found between the severity in endometrial pathology and the decrease in taurine level.

These observations are supported where a marked diminution in serum taurine levels were recorded in leukemia patients [66,67] and in tissue biopsies from cancer mucosal cells in the colon [28,68]. In confirmation, it was found that hypotaurine might be a useful marker for astrocytoma (brain cancer) and that it plays a role in cell differentiation and cell division [69].

The latter observations strongly support the hypothesis which considers antioxidant deficiency a powerful pathognomonic factor in cancer.

In conclusion, the encouraging results of this study suggest that decreasing serum low serum taurine levels in women suffering from irregular uterine bleeding can be used as an early indicator for existing EC and may qualify as a promising screening marker for EC, especially in high risk patients such as in CEH, which is considered as a precancerous condition. But more investigations are needed on a larger sample of patients to correlate between the different pathological stages of EC and the percent decrease in serum taurine level, by other mean to ensure the specificity of taurine as a screening marker in EC.

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