International Journal of Clinical Obstetrics and Gynaecology

ISSN (P): 2522-6614
ISSN (E): 2522-6622

www.gynaecologyjournal.com
2024; 8(2): 05-09
Received: 05-12-2023
Accepted: 09-01-2024

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The possible association of alpha tocopherol and uterine leiomyoma

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DOI: https://doi.org/10.33545/gynae.2024.v8.i2a.1426

Abstract
Background: Uterine leiomyomas are noncancerous growths of the reproductive tract that originate from uterine smooth muscle cells. Progesterone and steroid hormones, oestrogen, are regarded as the most crucial elements in the pathophysiology of UFs. Alpha-tocopherol represents the quantum peak of vitamin E's activity. ATs possessing structural determinants, which render them potential ligands for oestrogen receptors (ERs), is crucial with respect to UFs.
The purpose of this research was to determine whether serum alpha-tocopherol levels were associated with uterine fibroids.
Methods: A case-control investigation was conducted at the Babylon Teaching Hospital specialising in obstetrics and paediatrics from February to November 2019. The present investigation comprises a sample of 100 women. Fifty women diagnosed with uterine fibroids comprise Group A. As a control, fifty women without uterine fibroids comprised Group B. We determined the serum alpha-tocopherol levels of both groups in this investigation. The results were: The levels of serum alpha-tocopherol were compared using the Student's t-test between the two study groups. A statistically significant distinction was observed between the two groups, with cases exhibiting a mean difference of (7.53) µg/mL (11.83±4.50) µg/mL and controls (4.30±1.44) µg/mL (Students'-test = 11.27, d.f. = 98, P-value < 0.001).
Conclusion: A strong and statistically significant correlation was observed between elevated levels of AT in the serum and the presence of uterine fibroids. An analysis of serum AT levels revealed no significant correlation between age, BMI, and AT levels.

Keywords: The association, alpha, tocopherol, uterine, leiomyoma

Introduction
Uterine fibroids, also known as leiomyomas or myomas, represent the most common form of benign uterine tumors, with a significant impact on women's health worldwide. Originating from neoplastic transformation of single smooth muscle cells of the myometrium, these tumors are monoclonal in nature, indicating they stem from a single cell lineage within the uterine smooth muscle [1, 2]. Comprising large amounts of extracellular matrix (ECM), which includes collagen, fibronectin, and proteoglycans, fibroids present a complex biological structure [3, 4]. Their prevalence is notably high, affecting 20-40% of women during their reproductive years and up to 70% by the age of 50, contributing to significant morbidity in about 30% of these cases [5, 6]. Symptoms vary widely, ranging from heavy menstrual bleeding and anemia to pelvic pressure symptoms such as urinary discomfort and constipation [6]. Histologically, fibroids consist of spindled smooth muscle cells and fibroblasts, and their appearance can vary greatly in size and location. Most fibroids are found in the corpus of the uterus, although they can also develop in the cervix, uterine ligaments, and ovary [6]. The FIGO classification system is employed to categorize fibroids based on their location, which assists in clinical reporting and management [7]. The incidence and growth of fibroids are known to increase with age [5], and their development is influenced by various factors including racial differences, with Afro-Caribbean women at higher risk, and reproductive factors such as parity and use of oral contraceptives [8, 9]. Environmental factors and lifestyle choices also play roles in fibroid development [8, 9]. The etiology of fibroids is multifactorial, involving genetic, hormonal, and environmental components. Clonal studies have shown that fibroids arise from individual myometrial cells, with growth influenced by ovarian steroids acting through receptors present on fibroid and myometrial cells [5]. Cytogenetic abnormalities, including translocations and deletions in specific chromosomes, have been identified in a significant proportion of fibroids, contributing to their

pathophysiology [5]. Furthermore, the vasculature of fibroids and their response to angiogenic growth factors differentiate them from normal myometrial tissue [5]. Risk factors for developing fibroids include racial background, age, reproductive history, and lifestyle factors such as diet and substance use [9]. Hormonal influences, particularly the roles of estrogen and progesterone, are crucial in fibroid development and regression, underscoring the importance of the hormonal environment in fibroid pathophysiology [10]. Diagnosis of fibroids typically involves a combination of history taking, physical examination, and imaging techniques such as ultrasonography and magnetic resonance imaging (MRI), which provide detailed information on the number, size, and location of fibroids [11]. The management of fibroids is tailored to the individual, taking into account symptoms, fibroid characteristics, patient age, and fertility desires, and includes a range of medical and surgical options [12]. Recent research has explored the potential role of alpha-tocopherol (AT), a form of vitamin E, in fibroid biology due to its antioxidant properties and possible interactions with estrogen receptors [13]. AT's impact on fibroid risk and progression is under investigation, reflecting the ongoing effort to understand and manage this prevalent health issue [14].

Aim of the study: To assess the possible association between alpha - tocopherol level and uterine leiomyoma.

Methods

Between February and November 2019, a case-control study was carried out at the Babylon Maternity and Paediatric Teaching Hospital's Department of Obstetrics and Gynaecology. The research was authorised by the Iraqi board of medical specialisations and informed consent was obtained from all participants. The purpose of this study was to examine the correlation between uterine fibroids and alpha-tocopherol levels in a cohort of one hundred non-pregnant women aged twenty-four to fifty-six years. As cases, fifty women were chosen who had uterine fibroids confirmed by ultrasound and presented with symptoms including dysmenorrhea, abdominal distention, excessive menstrual haemorrhage.

In order to determine the number, size, and location of the fibroids, these women were subjected to comprehensive ultrasound examinations; some even underwent surgery to obtain additional histopathological confirmation. By means of ultrasound, fifty healthy, fibroid-free women comprised the control group. The selection of participants was conducted in accordance with predetermined inclusion and exclusion criteria. Pregnancy, endometriosis, adenomyosis, active or past neoplastic diseases, recent supplementation with vitamin E, and fibroid treatment were all excluded. In order to collect demographic data, patient complaints, gynaecological information, prior medical history, drug usage, and substance misuse details, comprehensive histories were obtained. In addition to measuring height, weight, and BMI, physical examinations inspected for abdominal and pelvic structures. The ultrasound assessments were performed utilising a Philips HD 11XE instrument. All participants' venous blood samples were collected, processed, and ELISA-analyzed for alpha-tocopherol levels. The data analysis was conducted utilising SPSS version 20. For categorical variables, frequencies and percentages were utilised in place of means ± standard deviation for continuous variables. The t-test for independent samples was utilised to compare the means of the two groups, while the correlation coefficient (r) was employed to determine the strength of the relationship between continuous variables. The p-value threshold for statistical significance was set at 0.05. The objective of this research endeavour was to shed light on the possible correlation between alpha-tocopherol levels and the likelihood or existence of uterine fibroids, thereby making a significant contribution to the understanding of fibroid aetiology and potential preventive measures.

Results

The participants' age was recorded as (39.85±8.11) on average, with a range of (24-56) years and a median of 42 years. Figure 1 depicted the distribution of age groups by study group. There was no statistically significant disparity in age between the control group and the cases (P-value = 0.816), as illustrated in Table 1.

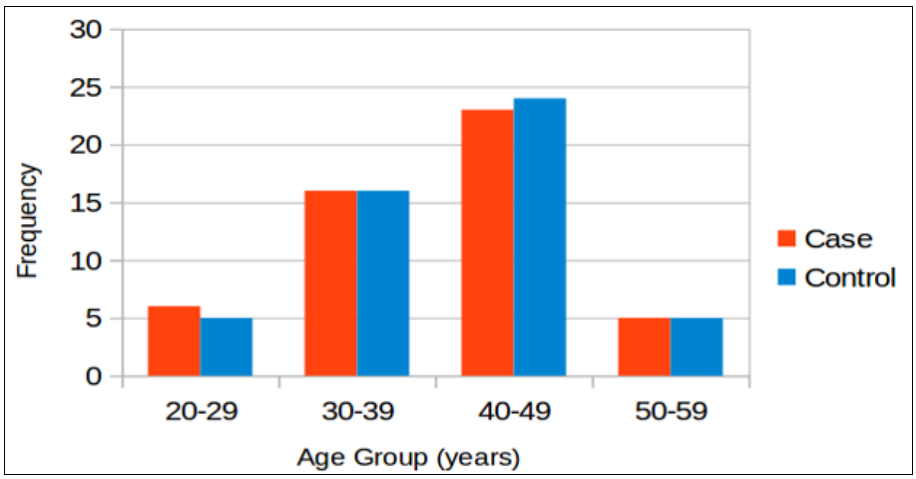

Fig 1: Age group distribution of study participants by study group

Table 1: Age characteristics of the study groups

Group	Age			P-value
	Mean	SD	Range	
Case (n=50)	39.66	8.27	24-56	0.816
Control (n=50)	40.04	8.03	24-56	
Total (n=100)	39.85	8.11	24-56	

The body mass index (BMI) of the participants in the study varied between 25 and 38 kg/m^2, with an average BMI of 29.89±3.27. The t-test for students was applied to compare the BMI of the study groups. A lack of substantial variation was detected in the mean value of cases (30.10±3.44) versus controls (29.68±3.10) (P-value = 0.523). The BMI of the patients and the

control group in the study was compared in Table 2.

Table 2: BMI classification of patients by study groups

BMI class	BMI range (kg/m^2)	Study group		Total
		Case	Control	
Overweight	25.0-29.9	26 (48.15%)	28 (51.85%)	54 (100%)
Obese class I	30.0-34.9	17 (48.57%)	18 (51.43%)	35 (100%)
Obese class II	35.0-39.9	7 (63.64%)	4 (36.36%)	11 (100%)
Total		50 (50.00%)	50 (50.00%)	100 (100%)

The levels of serum alpha-tocopherol were compared using the Student's t-test between the two study groups. A statistically significant distinction was observed between the two groups, with cases exhibiting a mean difference of (7.53) µg/mL (11.83±4.50) and controls (4.30±1.44) µg/mL (Students'-test = 11.27, d.f. = 98, P-value < 0.001). The observations are represented using a Whisker boxplot in Figure 2.

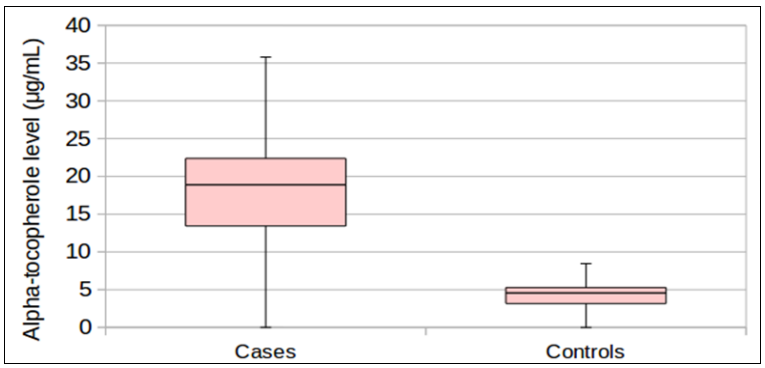

Fig 2: A whisker boxplot illustrating the relationship between the levels of alpha-tocopherol in the cases and controls

The Pearson's product-moment correlation coefficient was utilised to evaluate the correlations between age and BMI and serum alpha-tocopherol level. The aforementioned comparisons were conducted for both study groups. The analysis revealed no statistically significant correlation (R = -0.13, P = 0.375) between age and serum alpha-tocopherol levels in the cases group (Figure 3). In a similar fashion, the correlation between serum Alpha-tocopherol level and BMI was not found to be statistically significant (P = 0.617, correlation coefficient (R) = 0.07; Figure 4).

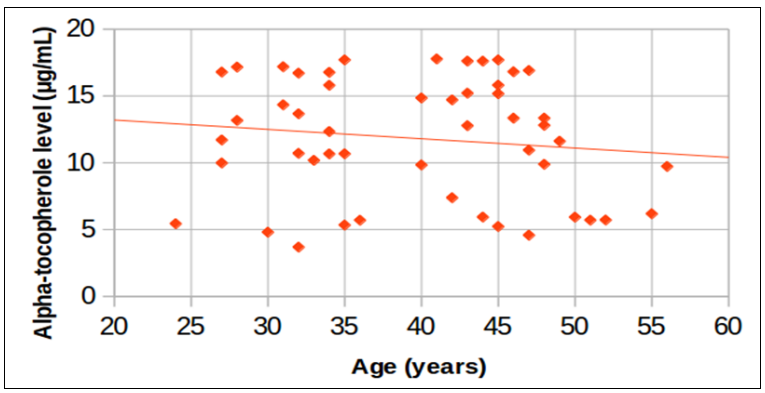

Fig 3: Correlation between serum Alpha-tocopherol and age among the cases

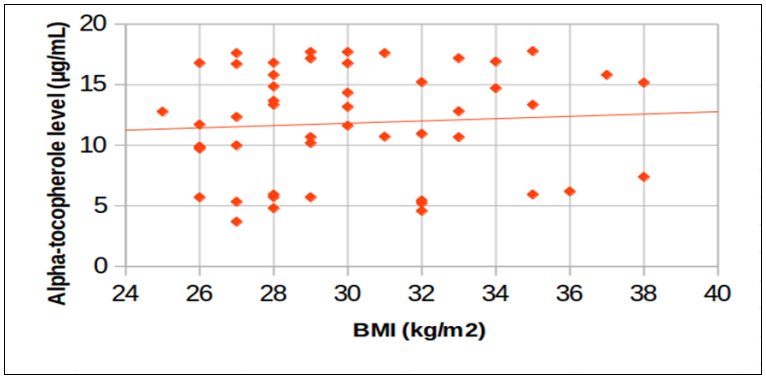

Fig 4: Within the case group, correlation between BMI and serum alpha-tocopherol

Likewise, a non-significant correlation was observed between age and serum Alpha-tocopherol level in the control group (Figure 5), as indicated by the correlation coefficient (R) of 0.19 and P-value of 0.183. Furthermore, there was no significant correlation observed between BMI and serum Alpha-tocopherol levels (Figure 6; correlation coefficient (R) = 0.06; P-value = 0.682). The correlations between serum alpha-tocopherol levels and age and BMI for both study groups were summarised in Table 3.

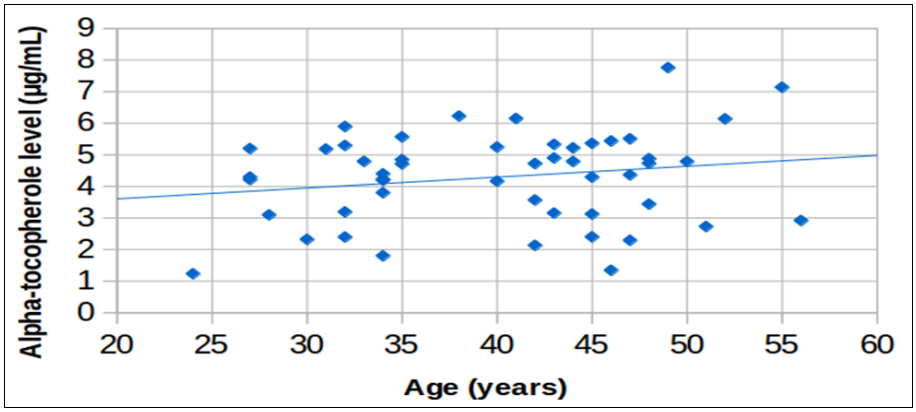

Fig 5: Age and serum alpha-tocopherol levels were correlated in the control group

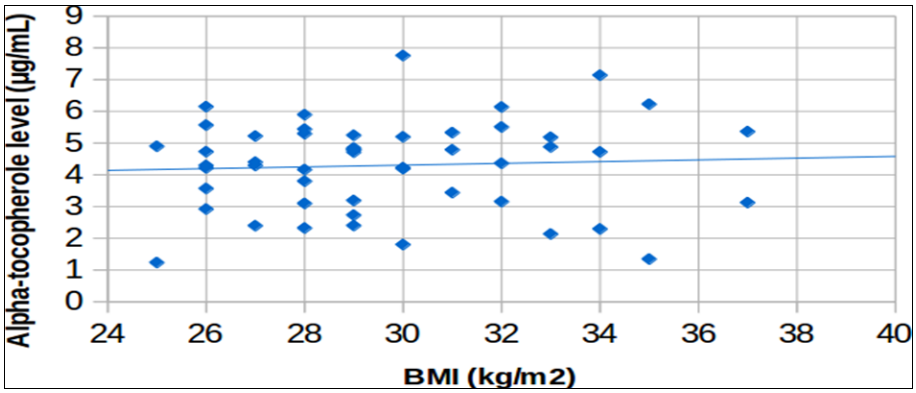

Fig 6: In the control group, correlation between BMI and serum alpha-tocopherol levels

Table 3: Correlations between specific variables and the level of alpha-tocopherol in the serum

Variables	Correlation with serum alpha-tocopherol level			
	Case group		Control group	
	Correlation coefficient (R)	P-value	Correlation coefficient (R)	P-value
Age	-0.13	0.375	0.19	0.183
BMI	0.07	0.617	0.06	0.682

Discussion

In the study examining the relationship between uterine leiomyomas (UFs) and serum levels of alpha-tocopherol (AT), no significant correlations were found with age and BMI, aligning with the findings of Whited *et al*. (2001) [15], which also reported no association between these variables and AT serum levels but identified a strong correlation with total serum cholesterol and triglycerides. Contrarily, Ciebiera *et al*. (2018) [16] observed elevated AT serum levels in Caucasian women with uterine fibroids, suggesting a racial disparity in AT levels among women with UFs, albeit with only a slight significant correlation with BMI, diverging from the current study's findings. Further exploration by Young *et al*. (2004) [17] into the effects of various agents, including vitamin E succinate, on UF cell growth revealed that while thiazolidinediones inhibited proliferation, vitamin E succinate notably reduced UF cell numbers, suggesting a potential for inducing cell death in UF cultures. Despite these promising *in vitro* results, broader research has yet to establish a definitive preventive role for vitamin E against tumor development [18]. The estrogen-like properties of ATs, which may act as ligands for estrogen receptors (ERs), present an intriguing aspect of their potential impact on UFs [18]. Khallouki *et al*. (2016) [19] demonstrated that ATs are agonists for ER subtypes, affecting estrogen-mediated gene regulation, a finding supported by earlier observations of AT's estrogen-like effects [20]. Peralta *et al*. (2009) [20] further elucidated the influence of vitamin E on estrogenic markers in breast biopsies, showing increased expression in women supplementing with vitamin E during tamoxifen therapy, thereby suggesting a potential interaction that could affect tamoxifen efficacy [21]. This interaction raises concerns about AT intake during tamoxifen treatment, potentially compromising treatment outcomes [22]. Additionally, vitamin E's utility in managing menopause symptoms [23] and its beneficial effects on endometrial thickness in IVF patients with implantation failure underscore its therapeutic potential [24]. The antioxidant and anticoagulant properties of vitamin E are proposed mechanisms for these effects, highlighting its significance in reproductive health and disease management [25].

Conclusion

An extremely significant correlation was observed between elevated levels of AT in the serum and the presence of uterine fibroids. An analysis of serum AT levels revealed no significant correlation between age, BMI, and AT levels.

Conflict of interest

Not available.

Financial support

Not available.

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How to Cite This Article
Salman GD, Rubayae BJA. The possible association of alpha tocopherol and uterine leiomyoma. International Journal of Clinical Obstetrics and Gynaecology. 2024;8(2):05-09.