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Investigation of ovarian aging markers and hormonal regulation in menopausal transition

Samah Amer Hammood*, Noor Alamer, Mohammed Kareem S. ALquraish, Mohauman M. Majeed

Department of Laboratory Investigation, Science Faculty, University of Kufa, Najaf, Iraq

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Abstract

Menopause and ovarian dysfunction are consequences of ovarian aging, a continuous and natural process in women. Early symptoms of ovarian aging include inadequate response to ovarian stimulation, irregular menstruation, and loss of follicular function, which collectively contribute to a decline in fertility as women age. The effects of aging on the ovaries are more pronounced than on other organs, with deterioration in the follicular pool and oocyte quality influenced by endocrine, genetic, and metabolic factors. This study aimed to examine the correlation between menopausal symptoms and serum levels of vitamin D, anti-Müllerian hormone (AMH), and other fertility-related hormones, as well as their impact on the timing of menopause. Ninety-two female participants were recruited from the Fertility Center Laboratories and AL-Saader Medical City in Al-Najaf province. A structured questionnaire assessing age, weight, height, and the severity of eleven menopausal symptoms—rated on a scale from 0 (absent) to 4 (extremely severe)—was administered. Symptoms evaluated included hot flushes, heart discomfort, sleep disturbances, muscle and joint pain, psychological issues, and urogenital problems. Serum levels of follicle-stimulating hormone (FSH), 25-hydroxyvitamin D, AMH, and luteinizing hormone (LH) were measured using the ELISA method. The results showed a significant negative correlation between serum AMH and vitamin D levels with menopausal symptoms and advancing age in postmenopausal women. Vitamin D levels were also negatively correlated with age, depression scores, and body mass index (BMI). Women with vitamin D deficiency and decreased AMH experienced more severe menopausal symptoms such as hot flushes, heart discomfort, depression, irritability, bladder problems, and musculoskeletal pain. These findings suggest that low AMH and vitamin D levels during menopause, compared to younger control women aged 20–40 years, may exacerbate menopausal symptoms. Supplementation with vitamin D, AMH, and reproductive hormone regulators, alongside lifestyle management, may benefit menopausal women suffering from fertility decline and severe menopausal symptoms.

Keywords: Anti-mullerian hormone, Menopause, Postmenopausal, 25-OH vitamin D, Follicule stimulating hormone, Luteinizing hormone.

1. Introduction

As women become older, their ability to conceive naturally decreases; a growing number of women are putting off having children until later in life, thanks to advancements in education, more employment opportunities, and easier access to contraception [1]. The number of women diagnosed with infertility who are unable to conceive within a year and seek out assisted reproductive technology (ART) has grown due to the delay of maternal age, some are very fertile well into their forties, while others start to see a decline in fertility in their thirties, as women age chronologically, their ovaries experience changes in function, the most common of which are reproductive aging symptoms, so the effects of aging on the ovaries are greater than on any other part of the body cause of the decline in follicular pool and oocyte quality is still a mystery, is believed to be influenced by endocrine, paracrine, genetic, and metabolic variables [2].

Ovarian failure are consequences of ovarian aging, which is a continuous process so, insufficient response to ovarian stimulation, irregular menstruation, and loss of follicular functions are some of the early symptoms of ovarian age that Irrespective of one's chronological age at menopause, the 'fixed interval theory' states that there is a consistent, about 6-year delay between the onset of menstrual cycle abnormalities and menopause [3,4]. The process of physiological reproductive aging is thought to be caused by a decline in the quantity and quality of oocytes in the ovarian cortical follicles with a decrease in oocyte speed up as a person ages, particularly beyond the age of 38, subsequent a biphasic pattern[5,6]. Following the age of thirty, the monthly fecundity begins to drop about [7,8].

The word "menopausal " refers to the ovarian aging stage that begins around age 46. The menstrual cycle will shorten by two to three days, which is the first indicator of the reproductive aging process, although it is not immediately noticeable [9]. Menopause, the last menstrual cycle, is thought to be the physiological result of ovarian aging

* Corresponding author.
E-mail address: samahalobaid@uokufa.edu.iq (S. A. Hammood).
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and is anticipated to occur around the age of 51 (with a range of 40 to 60) [10,11]. Menopausal age has not changed much over the last century, despite increases in life expectancy and a decline in menarche age, so the natural menopause age is believed to be determined by environmental influences, with genetic control playing a significant role [12,13]. The objective of our study was to examine the correlation between menopausal symptoms and blood levels of vitamin D, anti-Müllerian hormone (AMH), and other fertility-related hormones, as well as to evaluate the impact of these parameters on the menopausal period in order to identify factors indicative of women's fertile age.

2. Materials and Methods

2.1. Patient group

This research was conducted on a group of 46 premenopausal women and 46 postmenopausal women who checkup at the fertility in center, with an age range of 20 to 65 years. The samples were obtained from the Fertility Center Laboratories and AL-Saader Medical City in AL-Najaf province, Iraq.

2.2. Questionnaire for exclusion criteria and symptom assessment

Menopausal symptoms of all participants were evaluated using a standardized questionnaire comprising eleven items. Each symptom was rated on a 5-point Likert scale ranging from 0 (absent) to 4 (extremely severe) to quantify symptom intensity. The questionnaire was organized into three distinct domains:

- **Somatic symptoms**, including hot flushes, heart discomfort, sleep disturbances, and muscle and joint pain;
- **Psychological symptoms**, including anxiety, irritability, depression, and physical and mental exhaustion;
- **Urogenital symptoms**, including bladder problems, sexual dysfunction, and vaginal dryness.

A detailed list of symptoms and rating criteria is provided in Table 1.

2.3. Patient group

The study groups included postmenopausal women aged between 20 and 65 years. After obtaining written informed consent from each participant, demographic data, medical histories, and results from physical and gynecological examinations were recorded, including weight, body mass index (BMI), and the duration since the onset of menopause. Menopause was defined as the absence of menstrual bleeding for more than one year. Five milliliters of blood were collected from each participant, then centrifuged to obtain serum, which was stored frozen until analysis. Enzyme-linked immunosorbent assay (ELISA) was used to measure serum levels of follicle-stimulating hormone (FSH), 25-hydroxy vitamin D, anti-Müllerian hormone (AMH), and luteinizing hormone (LH) in all participants.

The overall design and workflow of the analysis parameters used in this study are illustrated in Figure 1.

2.4. Statistical analysis

To compare the subdivided groups across the measured parameters, statistical analysis was performed using GraphPad Prism version 5. One-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test was applied to assess differences between groups. Data are presented as mean ± standard error of the mean (SEM). Correlation coefficients were calculated to evaluate the relationships between markers and parameters. Descriptive statistics and correlation analyses were conducted using MegaStat version 10.12, an add-in for Microsoft Excel 2007.

3. Results

3.1. Patient characteristics and symptom assessment

The average age of the patients was 55.8 years, with a range of 42 to 65 years. The average duration since menopause for patients was 6.1 years. Vitamin D insufficiency and other marker levels were seen in 46 control volunteers both before and during the menopausal phase in 46 patients, detected by choosing.

The patients' assessments for anxiety, physical and emotional exhaustion, sexual issues, and vaginal dryness were comparable between groups. Aside from that, the other questionnaire parameters showed significant differences between the groups Table 2.

3.2. Correlation between vitamin D levels and age in menopausal women

An analysis of the associations between independent demographic variables indicated a negative link between

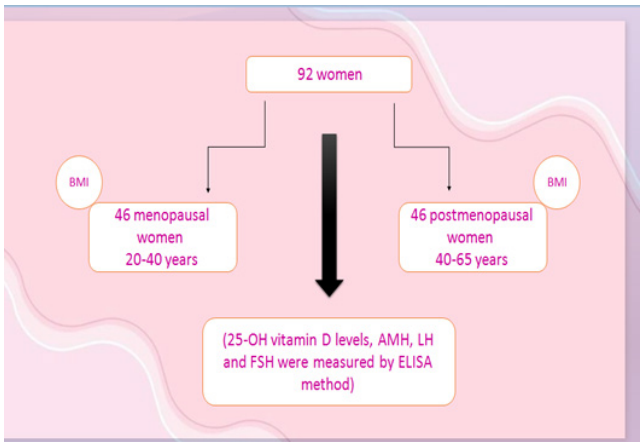

Fig. 1. Design of analysis parameter in this study.

Table 1. Questionnaire items and parameters used in this study to assess menopausal symptoms.

Parameter Category	Items/Parameters
Demographic Parameters	Age, Weight, Height, Number of children, Residential address
Hormonal Parameters	Anti-Müllerian hormone (AMH), Vitamin D (25-OH vitamin D), Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH)
Somatic Symptoms	Hot flushes, Heart discomfort, Sleep disturbances, Joint and muscular discomfort
Psychological Symptoms	Depressive mood, Irritability, Anxiety, Physical and mental exhaustion
Urogenital Symptoms	Bladder problems, Vaginal dryness, and Sexual dysfunction

Table 2. Results of menopause rating parameters.

Parameters	Befor n=46	After n=46
Hot flushes	1, 15±1, 01	2, 20±1, 01*
Heart discomfort	0, 20±0, 56	1, 30±1, 10*
Sleep problems	1, 12±1, 16	1, 73±1, 15*
Depressive mood	1, 63±1, 12	3, 30±1, 27*
Irritability	1, 54±1, 14	2, 58±1, 146*
Anxiety	2, 43±1, 23	3, 33±3, 90(NS)
Physical and mental Exhaustion	2, 03±1, 31	1, 80±1, 07(NS)
Bladder problems	1, 12±1, 10	2, 07±1, 22*
Dryness of vagina	1, 25±1, 04	1, 79±1, 16(NS)
Joint and muscular Discomfort	1, 56±1, 10	3, 38±1, 26*

NS: non-significant; *Significant p <0.05.

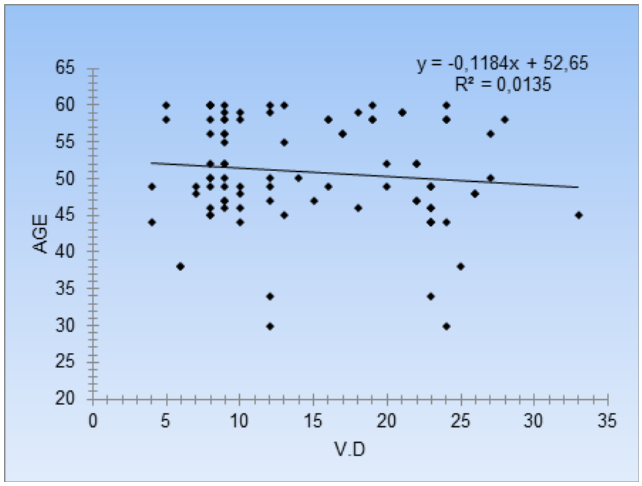

Fig. 2. The correlation between vitamin D and age.

vitamin D levels and the duration of age in years of the menopausal female (Figure 2).

3.3. Correlation between AMH levels and menopause timing

An analysis of the associations between independent variables indicated a negative link between AMH level and menopause time, which shows the decrease of AMH with increased age and the menopause (Figure 3).

3.4. Changes in vitamin D levels before and after menopause

The results of statistical analysis showed a significant increase ($p < 0.05$) in vitamin D levels before the menopausal phase compared to after women entered the menopausal stage (Figure 4).

This figure illustrates the significant decrease in vitamin D concentrations observed in women after entering menopause compared to the premenopausal phase ($p < 0.05$). The results suggest that menopausal transition is associated with a decline in vitamin D status, which may impact the severity of menopausal symptoms and overall health.

3.5. Significant increase in AMH levels before menopause compared to postmenopause

The results demonstrated a significant increase in AMH levels ($p < 0.05$) prior to menopause compared to the post-

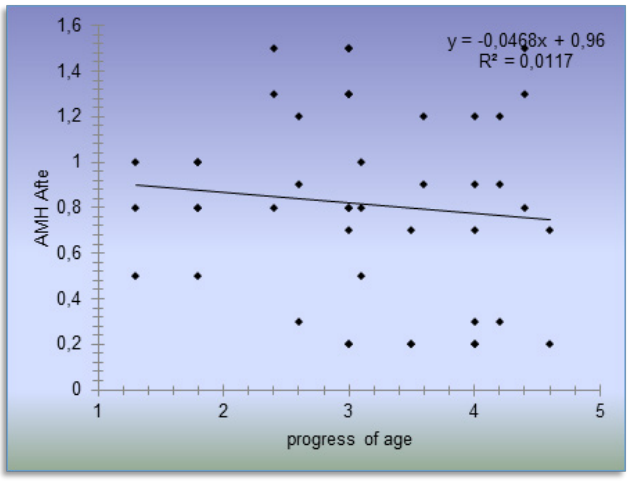

Fig. 3. The correlation between AMH and the progression of age in menopause period.

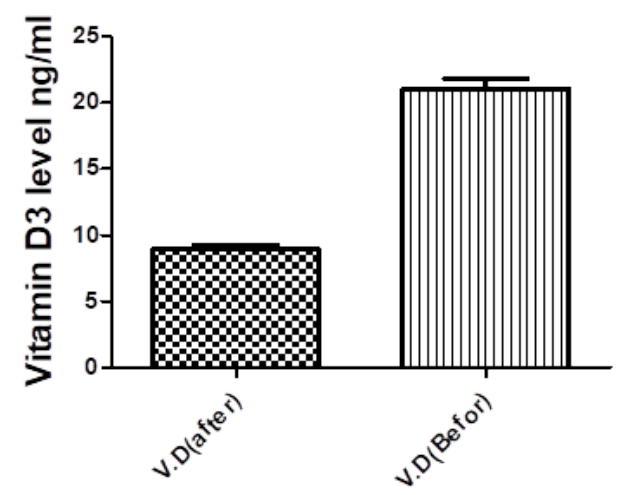

Fig. 4. Comparison of serum vitamin D levels before and after the menopausal period.

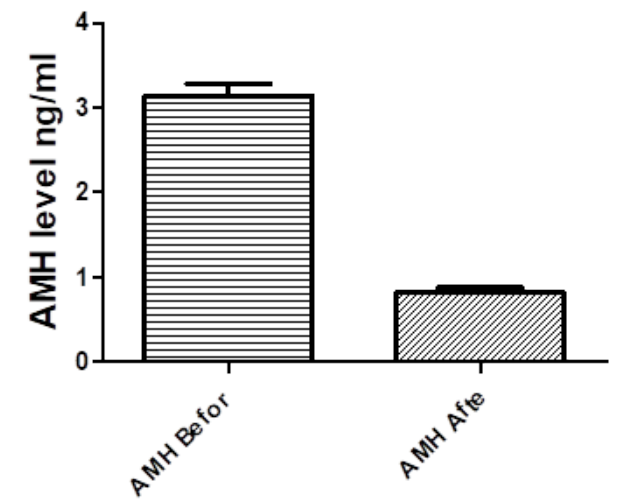

Fig. 5. Levels of AMH hormone before and after menopause period.

menopausal period, as shown in Figure 5.

3.6. Correlation between advancing age and vitamin D levels before and after menopause

Analysis of the correlation between advancing age and

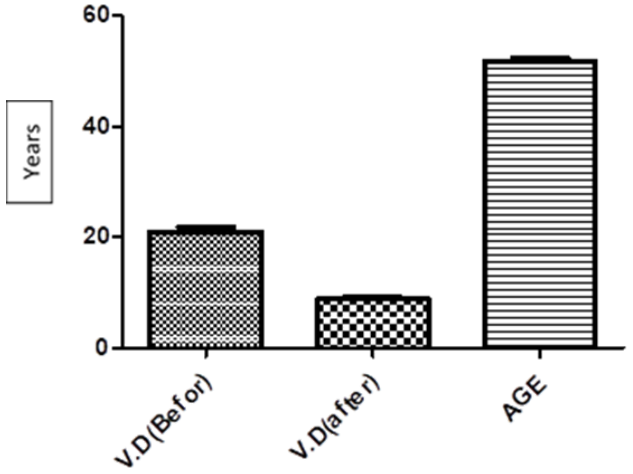

Fig. 6. The correlation between vitamin D and age before and after menopause period.

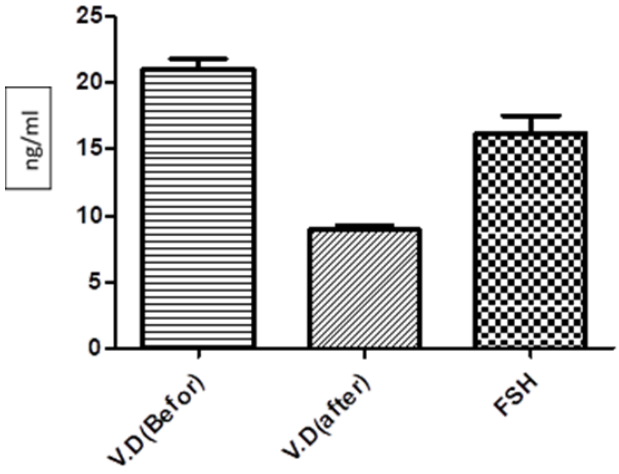

Fig. 7. The correlation between vitamin D and FSH levels before and after menopause period.

vitamin D levels revealed a significantly higher vitamin D concentration ($p < 0.05$) before the menopausal period compared to after menopause, with this increase being associated with age progression (Figure 6).

3.7. Correlation between FSH and vitamin D levels before and after menopause

Evaluation of the correlation between FSH and vitamin D levels revealed that vitamin D concentrations were significantly higher before menopause compared to after menopause ($p < 0.05$), while FSH levels were significantly increased before menopause relative to the postmenopausal period, with these changes associated with advancing age in women, as shown in Figure 7.

3.8. Correlation between LH and vitamin D levels before and after menopause

Evaluation of the correlation between LH and vitamin D levels revealed that vitamin D concentrations were significantly higher before menopause compared to after menopause ($p < 0.05$). Additionally, LH levels were significantly increased before menopause relative to the postmenopausal period, with both changes associated with advancing age in women, as shown in Figure 8.

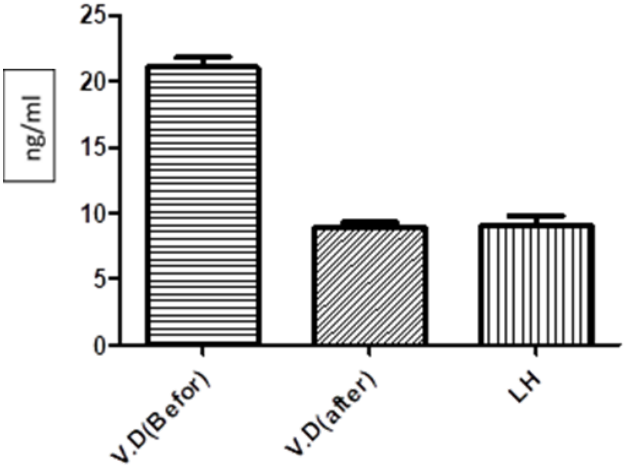

Fig. 8. The correlation between vitamin D and LH levels before and after menopause period.

3.9. Evaluation of the correlation between body mass index and vitamin D levels before and after menopause

Evaluation of the correlation between BMI and vitamin D levels indicated that vitamin D concentrations were significantly higher ($p < 0.05$) before the menopausal phase compared to after menopause, accompanied by an increase in body mass index (Figure 9).

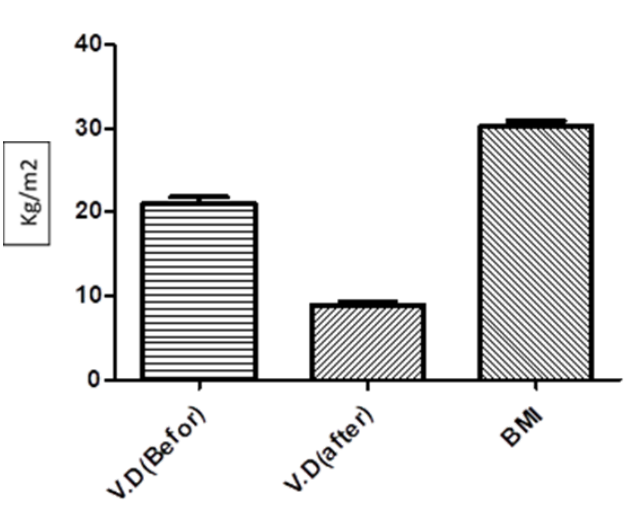

Fig. 9. The correlation between vitamin D and BMI before and after menopause period.

3.10. Analysis of AMH levels and BMI before and after menopause

The results of the statistical analysis indicated a significantly higher AMH level ($p < 0.05$) before menopause compared to after menopause, accompanied by an increase in BMI (Figure 10).

3.11. Analysis of changes in AMH and FSH levels before and after menopause

The analysis of relationships between variables showed a significant increase in AMH levels before menopause compared to after menopause, accompanied by a significant increase in FSH levels ($p < 0.05$), as shown in Figure 11.

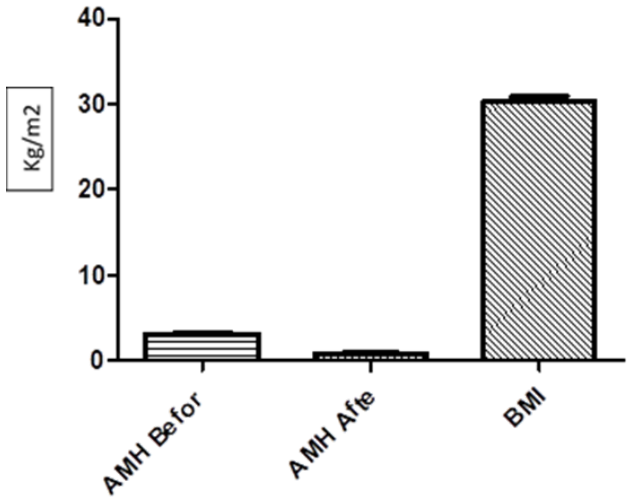

Fig. 10. The correlation between AMH levels and BMI before and after menopause period.

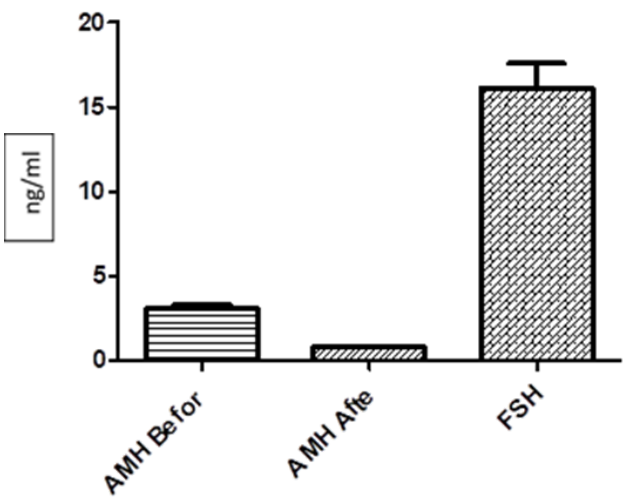

Fig. 11. The correlation between AMH and FSH before and after menopause period.

3.12. Analysis of changes in AMH and LH levels before and after menopause

The analysis of relationships between variables showed an increase in AMH levels before menopause compared to after menopause, accompanied by an increase in LH levels, as shown in Figure 12.

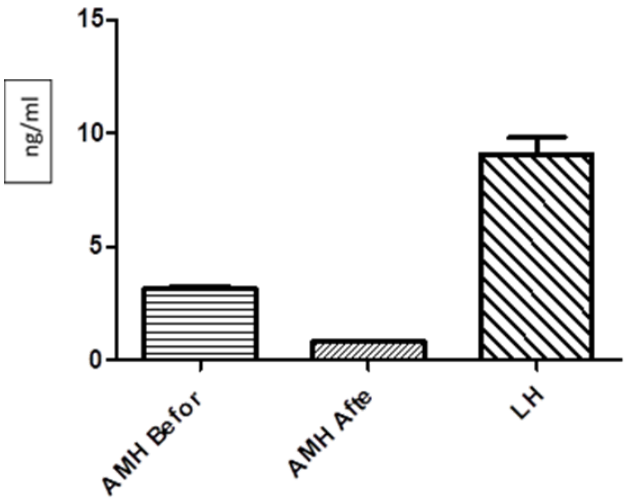

Fig. 12. The correlation between AMH and LH before and after menopause period.

4. Discussion

We established a significant relationship between blood vitamin D levels, AMH, and menopausal symptoms in women recently transitioned into menopause. Our findings revealed a clear and statistically significant negative correlation between vitamin D levels and both advancing age and the postmenopausal period. Furthermore, women with deficiencies in vitamin D and AMH experienced notably more severe symptoms during postmenopause, including hot flushes, chest discomfort, irritability, bladder problems, and joint and muscle pain. Additionally, we determined a threshold level of 25-hydroxyvitamin D for women who reported menopausal symptoms despite having what would generally be considered adequate vitamin D levels. This threshold was determined for women who satisfied the criteria. The results of a study that was conducted came to the conclusion that they were unable to establish any kind of connection between menopausal symptoms and blood vitamin D levels [14].

The biological inactivity of vitamin D, which is produced by the skin or consumed via food, must be converted by enzymes into active metabolites. Research has shown the involvement of hormones in the elevation of the vitamin D-activating enzyme [15]. Thus, it is plausible to consider that the decline in some hormone levels during the postmenopausal period might exacerbate the symptoms of subclinical vitamin D insufficiency, namely, neuropsychiatric problems. There is little research available to assess the neuroprotective effects of vitamin D. A study investigating the impact of menopause on behavioral health found that menopause may be associated with a decline in memory function [16]. In vivo research conducted that the hippocampus cytoskeletal alterations brought about by ovariectomy may be reversed by taking vitamin D supplements. Increasing the levels of calcidiol in ovariectomized rats by the use of vitamin D supplementation was shown to diminish the levels of inflammatory mediators associated with the hippocampi, including nuclear factor-kappa B and interleukin-6, according to another set of animal tests [17].

In case of ovaries removed, cholecalciferol was shown to have anxiolytic effects in addition to its effects on the hippocampus [18]. These findings provide evidence for the psychological outcome in our investigation. The deficient group had considerably higher ratings in depressive mood and irritation compared to the other participants. In addition, the group also exhibited a greater anxiety level, but this difference did not reach statistical significance. A significant disparity in the overall psychiatric score had previously been seen in the deficient group throughout the evaluation. In study including a large number of patients, it was shown that throughout the postmenopausal era, there was a correlation between low levels of 25-OH vitamin D and high depression ratings [19]

Some studies found that a BMI of more than 30 kg/m2 was significantly correlated with a greater depressed mood score in a cross-sectional research conducted in Turkey using MRS [20]. The elevated urogenital subscale

ratings in the deficit and insufficiency groups were another result in our investigation. The score on the bladder issues part of this subscale was found to be noticeably high.

Based on the aforementioned outcome, it was observed that there may be a correlation between low urinary tract symptoms and blood vitamin D levels. Low amounts of vitamin D may have an impact on the strength of the pelvic floor muscles. A research was conducted to assess the pelvic floor muscle strength in both pre- and postmenopausal individuals. The results showed that postmenopausal patients with vitamin D levels below 20 ng/mL had reduced pelvic floor muscular strength. The research found that women with vitamin D insufficiency had a higher urine incontinence score; however, no statistically significant difference was seen [21]. In contrast to that particular investigation, our findings regarding the correlation between vitamin D levels and urinary system symptoms exhibited statistical significance. Similarly, another study found that the prevalence of lower urinary tract symptoms was significantly higher in women with low vitamin D levels compared to those with normal levels [22]. Furthermore, a randomized controlled by reported a significant improvement in lower urinary symptoms in postmenopausal individuals treated with high-dose vitamin D for a year [23].

Somatic symptoms, such as hot flashes, can be problematic for menopausal women; regardless of their vitamin D levels, the majority of women report experiencing these symptoms [24].

Elevated vitamin D levels may help protect against somatic symptoms, especially hot flashes, during menopause. Moreover, research has shown that women with sufficient vitamin D levels experience fewer menopausal symptoms compared to those with a deficiency [25]. The purpose of this research was to determine if certain menopause-related symptoms may be caused by a vitamin D deficiency. In order to reduce external factors that can alter scale rates, we attempted to exclude individuals with any additional comorbidities and employed a standardized questionnaire, the MRS. In terms of demographics and hormones, our patient groups were comparable. In addition, we provided a cutoff 25-OH vitamin D level for women with adequate vitamin D levels who have menopause-related symptoms.

Low levels of AMH and vitamin D during the menopausal stage may exacerbate symptoms associated with menopause. Women's clinical diagnosis of menopause is mostly predicated on a 12-month amenorrhea period; as such, it is established retrospectively [26]. Moreover, amenorrheic women might have difficult diagnoses, especially after a hysterectomy or endometrial ablation, while using a hormonal intrauterine device, or when undergoing systemic hormonal ovarian suppression. Remarkably, only two studies were found that assessed AMH as a menopausal diagnostic marker [27]. Neither of them carried out a comprehensive analysis of the function of AMH as a formal diagnostic criterion, and both were quite small. An extremely low or undetectable AMH concentration in women of late reproductive age was shown to be predictive of approaching menopause, according to the findings of the SWAN trial. However, the accuracy of this prediction was much lower in women up to the age of 48 years compared to those beyond the age of 51 years. On the other hand, the scientists from SWAN observed that a low but detectable AMH was a significantly more reliable predictor of the fact that menopause was not immediately approaching [28].

Decreased of AMH and other reproductive hormone in period increased age and postmenopausal, results emphasize how challenging it is to identify the tiny and fluctuating number of follicles in the ovary that are actively developing in the late stages of reproduction, when the number of preantral and small antral follicles, which generate AMH, is less strongly correlated [29], The need for a single dominant follicle to develop and provide enough oestrogen to induce menstruation or alleviate menopausal symptoms [30]. Improving the sensitivity of the test may enhance the accuracy of AMH in measuring significant ovarian activity throughout the latter stages of reproductive life. The first improvements in the use of AMH for menopause prediction included analyzing AMH in relation to age. This was done either by including age into the model [31] or by using age-specific centiles [32]. These metrics provide additional information, especially considering the alignment of AMH trajectories as age increases and the decline of the ovarian reserve [33]. A number of studies also looked into whether a person's rate of change or decline in AMH, as opposed to a single value, offered a more accurate picture of the trajectory towards menopause and decreased within-subject variation by providing an overall summary as opposed to a single snapshot in time [34].

Transition to undetectable levels of Anti-Mullerian Hormone (AMH) or a further decrease in AMH levels, particularly in the presence of already low AMH levels, provides the most accurate prognosis and indicates a decrease in ovarian follicles and the onset of menopause, both of which are linked to advancing age. Additional prospective investigations are necessary to see whether this conclusion derived from modeling can be used in a clinical setting. Aside from the decrease in the number of follicles, the aging ovary experiences alterations in stromal function, such as an increase in fibrosis. These changes are linked to variations in collagen and hyaluronan levels, as seen in the study by [35].

Various internal and external variables might affect the amounts of AMH, Vitamin D and progress of development and accelerate the period of menopause, AMH levels shouldn't be utilized as a fertility test since the predictive usefulness of AMH for a successful clinical pregnancy (in both natural and assisted reproduction) is less hopeful. Assessing AMH, vitamin D, and hormone levels using manual enzyme-linked immunosorbent assay (ELISA) has limitations owing to variations within and across assays for assay the fertility age in women**.** AMH assay systems exhibit superior accuracy, quicker turnaround time, heightened sensitivity, and wider availability in detected the fertility and menopause with age, also, AMH is the ideal ovarian reserve marker because to the exact findings, simplicity of a serum-based test, independence from particular time in the cycle serum, independence from hypothalamic pituitary function, and very low inter-observer variability. The appropriate interpretation of AMH findings in a clinical situation may be limited by the absence of an international guideline for age-specific AMH diagnostic thresholds for assessing functional ovarian reserves or predicting age of menopause. The identification and analysis of biomarkers measuring implications for how AMH is interpreted other immunity and physiological markers.

This study highlights the significant negative correla-

tion between serum levels of vitamin D and anti-Müllerian hormone (AMH) with menopausal symptoms and advancing age in women undergoing menopausal transition. Vitamin D deficiency and decreased AMH levels are associated with an exacerbation of common menopausal symptoms, including hot flushes, cardiovascular discomfort, psychological disturbances, urinary problems, and musculoskeletal pain. Our findings suggest that maintaining sufficient vitamin D and AMH levels may help alleviate the severity of menopausal symptoms. Furthermore, vitamin D supplementation alongside hormonal and lifestyle interventions could offer therapeutic benefits for women in the menopausal period. Future research should aim to establish standardized diagnostic thresholds and explore the clinical utility of these biomarkers in predicting menopausal onset and improving symptom management.

Author contributions

Samah Amer Hammood, Noor Alamer, and Mohammed Kareem. S. ALquraish worked on the study conception and data acquisition, analysis, and interpretation. Samah Amer Hammood and Mohauman M. Majeed contributed to the study conception and data acquisition, secured the resources, supervised the study and contributed to the manuscript drafting. All authors have read and agreed to the published version of the manuscript.

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Ethical approval

Approval for the use of archival material for research purposes was obtained from the local Human Ethics Committee.

Informed consent

Not applicable.

Data availability

The supplementary data will be available to the readers when they send the request.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

Anti-Müllerian hormone (AMH**),** Assisted reproductive technology (ART), Follicle stimulating hormone (FSH), Luteinizing hormone (LH)**,** Body mass index (BMI), Manual enzyme-linked immunosorbent assay (ELISA).

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