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Original article

Prevalence and Relation of Vitamin D and Obesity among Infertile Women

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ABSTRACT

Aims*. The current study aimed to assess the prevalence of vitamin D deficiency and obesity in infertile women.* ***Methods****. A cross sectional prospective study was conducted from Massa hospital, upon 153 infertile women between ages 21-44 years. All patients were assessed by taking a complete history, clinical examination, vitamin D investigation, and BMI measurement. Vitamin D categorize used were as the following; mild vitamin D deficiency - serum 25(OH)D levels 12-19 ng/mL (30-49 nmol/L), moderate vitamin D deficiency - serum 25 (OH)D 5-11 ng/mL (12.5-29 nmol/L), and severe vitamin D deficiency - serum 25(OH)D level < 5 ng/mL (< 12.5 nmol/L).* ***Results****. The present study did not detect a significant difference in the mean serum vitamin D of the infertile women (p value=0.605). The results also showed an indirect effect for factors resulting from interactions among them. The interactions of BMI and infertility (p value=0.040*), vitamin D and infertility (p value=0.047*), vitamin D and BMI (p value=0.044*) and age and infertility (p value=0.022*) were significant and illustrated pure effects on trial results and gynecological disease types. Otherwise, the study demonstrated a negative linear association between vitamin D levels and obesity in infertile women.* ***Conclusion****. Our findings suggested that a decreased vitamin D might correspond to a higher prevalence of obesity in infertile women, which reminded us to pay more attention to the supplement of vitamin D in obese infertile women.*

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INTRODUCTION

Vitamin D plays a crucial role in calcium and phosphate homeostasis, by increasing intestinal calcium absorption and renal calcium reabsorption [1]. It is found in two major forms, D_2 (ergocalciferol) and D_3 (cholecalciferol). The former is produced by ergosterol upon irradiation in plants and fungi. The latter is produced by 7-dehydrocholesterol upon irradiation in the epidermis [2]. After hydroxylation at carbon 25 [producing 25-hydroxyvitamin D, 25(OH)D, it is transported to the kidney, where it is hydroxylated by 1α-hydroxylase (CYP27B1) at the carbon 1 of the A ring, producing 1,25-dihydroxy-vitamin D [$1,25(OH)_2D$], the active form of vitamin D [3]. CYP27B1 is also present in extrarenal sites, such as macrophages, osteoblasts, epithelial, endocrine, placental and cancer cells [4].

The mechanism of $1,25(OH)_2D$ action involves its binding to vitamin D receptor (VDR), a transcription factor, member of the steroid hormone nuclear receptor family [2]. VDR and CYP27B1 are expressed in various cells, indicating that vitamin D is characterized by a plethora of extra-skeletal actions, such as those on the immune and cardiovascular system [5] Vitamin D deficiency is defined as 25(OH)D concentrations <20 ng/mL (50 nmol/L), whereas vitamin D insufficiency as 25(OH)D concentrations 20–30 ng/mL (50–75 nmol/L) [6].

The prevalence of vitamin D deficiency ranges from 8 to 90% in Europe (reaching >50% in Western European populations) and from 14 to 89% in North America [7]. Indeed, vitamin D deficiency has been associated with an increased risk of various autoimmune diseases (such as multiple sclerosis, rheumatoid arthritis and type 1 diabetes mellitus), susceptibility to infections [8], as well as type 2 diabetes mellitus (T2DM), metabolic syndrome and cardiovascular disease (CVD) [9].

A key role in human infertility has also emerged recently for vitamin D. This is mainly attributed to the presence of both VDR and CYP27B1 in various tissues of the reproductive system in both sexes [10]. On the other hand, obesity, defined as body mass index (BMI) > 30 kg/m^2 [11], is also associated with severe adverse health consequences, depending on the amount of adiposity and its distribution within the body [12]. Besides the well-recognized health concerns, such as T2DM, CVD and cancer, there is also a strong link between obesity and infertility [13,14]. Many pathogenetic mechanisms for this interplay have been proposed. With regard to male infertility, these include the aromatization of testosterone to estrogen in peripheral tissues, decreased sex hormone-binding globulin (SHBG) production in the liver [15,16], increased endorphin concentrations [leading to lower luteinizing hormone (LH) pulse and gonadotropin releasing hormone (GnRH) production] [17], increased oxidative stress, which promotes sperm DNA damage [18].

With respect to female infertility, the underlying mechanisms include functional alterations of the hypothalamic–pituitary–gonadal (HPG) axis due to insulin resistance and relative hyperandrogenaemia [14], disordered secretion of gonadotrophins and hyperleptinaemia, leading to impaired folliculogenesis and ovulatory dysfunction.[19-21]. The study aimed to assess the prevalence of vitamin D deficiency and obesity in infertile women.

METHODS

Study design and samples

This cross-sectional prospective study was conducted upon 153 patients from 18 October 2022 to 17 May 2023. The ethical approval to conduct the study was obtained. 153 patients whom visited dietitian and infertility outpatient clinic in Massa hospital

All patients were assessed by taking a complete history, clinical examination, vitamin D investigation, and BMI measurement. Vitamin D categorize used were as the following; mild vitamin D deficiency - serum 25(OH)D levels 12-19 ng/mL (30-49 nmol/L), moderate vitamin D deficiency - serum 25 (OH)D 5-11 ng/mL (12.5-29 nmol/L), and severe vitamin D deficiency - serum 25(OH)D level < 5 ng/mL (< 12.5 nmol/L).

Data collection and analysis

The dataset was structured in Excel csv file then; the Excel csv file was imported into R software to analyze it. R version 4.3.2 (Eye Holes) was used for analyzing dataset.

The univariate factors described as first step for descriptive analysis into quantitative and qualitative sections. Multivariate analysis of variance (MANOVA) was used as a model because dataset has two dependent variables which were trail results and gynecology disease types. This model was used to detect the effect of independent factors including body mass index (BMI), vitamin D, age, and infertility type (primary or secondary) on dependent factors. The model included the interactions effects of independents factors as well.

As a primary MANOVA model, all independent factors and their interactions were included to detect the significant factors. The insignificant factors and interactions were excluded. Model with significant factors was performed exclusively. As a primary MANOVA model, all independent factors and their interactions were included to detect the significant factors. The insignificant factors and interactions were excluded. Model with significant factors was performed exclusively. Additionally, the relationship among age, BMI and vitamin D was examined using correlation matrix. On other hand, logistic regression was performed to predict Infertility type utilizing BMI and Vitamin D.

RESULTS

Regarding the results that are illustrated in table 1; vitamin D (df=2, F=0.70, p value=0.605), infertility type (df=1, F=1.6, p value=2.55), and age (df=1, F=2.59, p value=0.144), were not significant and have no direct effects on dependent factors.

Table 1. MANOVA Table for trial result and response gynecological diseases type

Variables	Degree of freedom	F statistic	*P* value
Vitamin D	**2**	**0.70**	**0.605**
Infertility	**1**	**1.67**	**0.255**
Age	**1**	**2.59**	**0.144**
BMI	**4**	**2.84**	**0.036***
Vitamin D: BMI	**4**	**2.62**	**0.044***
Vitamin D: Infertility	**1**	**4.88**	**0.047***
BMI: Infertility	**3**	**2.30**	**0.040***
Age: Infertility	**1**	**6.86**	**0.022***

The results showed that the vitamin D (z= -1.52, p value= 0.129) was insignificant predictor in primary model used. Hence, vitamin D was excluded in final model which exhibited BMI as a significant predictor (z= -1.98, p value= 0.047)* for changes the log odds of infertility type by 0.06. Otherwise, BMI (df=4, F=2.84, p value=0.036*) significant and has direct effect on dependent factors as illustrated in figure1. In addition, the results were showing an indirect t- effect for factors resulting from interactions among them.

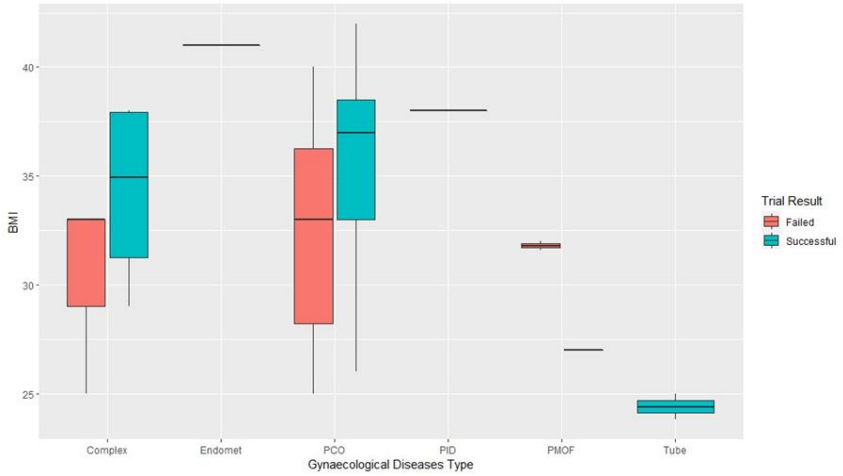

Figure 1. The direct effect of BMI in infertile women and gynecological diseases on the trial result of pregnancy

The interactions of BMI and infertility (df=3, F=2.30, p value=0.040*), Vitamin D and infertility (df=1, F=4.88, p value=0.047*), Vitamin D and BMI (df=4, F=2.62, p value=0.044*) as illustrated in figure 2, and age and infertility (df=1, F=6.86, p value=0.022*) were significant and illustrated pure effects on trial results and gynecological disease types.

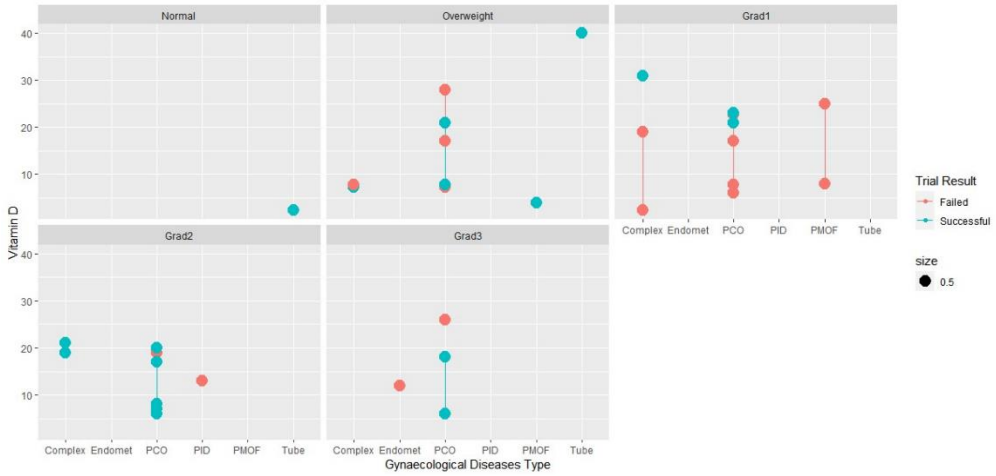

Figure 2. The interactions between BMI and infertility which has significant effect

Correlation matrix illustrates the strength and directions of relationship among age, BMI and vitamin D. The age significantly correlated to positively with BMI (r= 0.17, p value= 0.039*) which indicates that with age, the body mass index increases, and this can be explained by a decrease in the metabolism low rate, lack of movement, and consequences of pregnancy and childbirth as showed in figure3.
On other hand, the correlations among vitamin D and BMI (r= -0.018, p value= 0.82) and age (r= -0.039, p value= 0.64) were inverses and insignificant. However, the results indicate that as aging, vitamin D decreases in the body, and with a deficiency of vitamin D in the body, the body mass index increases. These results are logical, although weakness and insignificant as the results showed.

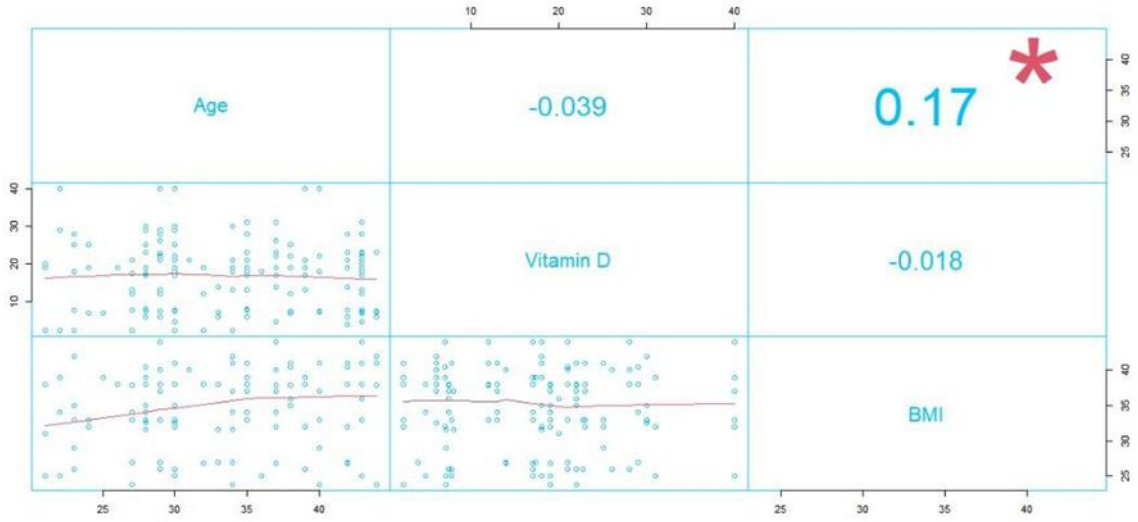

Figure 3. The relationship between BMI, Age and Vitamin D among infertile women

DISCUSSION

Our cross-sectional study aimed to investigate the prevalence and association between vitamin D and obesity in infertile women of childbearing age, as obesity and vitamin D have important effects on human fertility.
The present study did not detect a significant difference in the mean serum 25(OH)D concentrations of the infertile women. Furthermore, we found that the prevalence of vitamin D deficiency (20-30ng/dl) was 35.0% among the infertile women of reproductive age in this study. These results are consistent with the prevalence of 36% that has been reported in the American general population [22] Furthermore, vitamin D deficiency may be related to lifestyle changes that reduce exposure to sunlight and/or the use of sunscreen [23]. Our data were extracted from infertile women aged 21–44 years; we found that serum vitamin D levels were inversely associated with BMI.
We observed that the prevalence of obesity/abdominal obesity was significantly higher in those with the lowest quartile serum vitamin D compared to those with the highest quartile of serum vitamin D in all models. To test whether this relationship was linear, we used multivariate-adjusted spline regression and found a negative linear relationship between vitamin D levels and obesity. Our study had similar findings to previous studies. Indeed, data from a bi-directional Mendelian randomization analysis of large cohorts support that obesity may contribute to vitamin D deficiency and vice versa. Specifically, a one-unit increase in BMI (1 kg/m^2) was associated with a 1.15% reduction in 25(OH)D, after adjusting for age, sex, season, and other confounding factors [24]. And the negative correlation was stronger in the North American study. However, this relationship has not been proven in infertile women. A prospective study aimed to evaluate the relationship between follicular 25-hydroxyvitamin D levels and body weight in 199 infertility patients who received intracytoplasmic sperm injections (ICSI). Their results showed that patients with lower follicular 25(OH)D3 levels had a greater average weight than those with higher 25(OH)D3 levels [25].
Infertility is a widespread problem that has major implications for individuals, families, and society [26,27]. Modifiable lifestyle factors, such as overconsumption of food and vitamin deficiency can affect pregnancy. It has been well-established that obesity and vitamin D deficiency are two major pandemics undermining global public health [28, 29]. Several studies have shown great interest in exploring the association between obesity and vitamin D deficiency and their underlying pathophysiological mechanisms [30,31].
Our study demonstrated a negative linear association between vitamin D levels and obesity in infertile women. The possible mechanisms for the inverse relationship between vitamin D and obesity were as follows. On the one hand, when obesity is considered to be the cause of vitamin D deficiency, one possible explanation includes lower sunlight

exposure due to a sedentary lifestyle, and decreased participation in outdoor activities [32]. Another hypothesis is that vitamin D is a fat-soluble vitamin that is stored in large quantities in various body fat compartments of obesity, which leads to decreased serum vitamin D levels [33]. Recent evidence suggests that obesity is associated with reduced expression of genes encoding the synthesis of important enzymes involved in vitamin D metabolism [34]. On the other hand, when obesity is considered to be a consequence of vitamin D deficiency, one possible explanation includes vitamin D deficiency or vitamin D receptor (VDR) over expression can inhibit preadipocyte differentiation, which is implicated in adipose tissue expansion and ultimately leads to obesity [35]. Another hypothesis is that low vitamin D status may increase parathyroid hormone and calcium leading to weight gain and excess fat accumulation [36].

Although the cause-and-effect relationship between vitamin D deficiency and obesity is controversial, evidence from meta-analyses has consistently shown a negative association between vitamin D and obesity [30,37]

Although the cause-and-effect relationship between vitamin D deficiency and obesity is controversial, evidence from meta-analyses has consistently shown a negative association between vitamin D and obesity [30,37]. Our study in an infertile population also demonstrated this point and further showed that the negative correlation between vitamin D levels and obesity was linear, namely the lower vitamin D levels, the greater the chance of obesity, which also suggests that when to treat such patients, doctors should pay special attention to emphasize the importance of weight loss as well as the vitamin D supplements. Certainly, larger sample of clinical and interventional studies are needed to focus on infertility patients either vitamin D supplementation in obese or weight loss in vitamin D-deficient. Considering the results of our study, it is crucial to develop public health education strategies for couples to raise public awareness of the impact of obesity and vitamin D deficiency. In addition, when treating infertility, it is equally important to establish guidelines for clinicians to effectively manage these issues.

CONCLUSION

Our findings suggested that a decreased vitamin D might correspond to a higher prevalence of obesity in infertile women, which reminded us to pay more attention to the supplement of vitamin D in obese infertile women.

Obesity and abdominal obesity are associated with low vitamin D status and are inversely linear. The causal relationship between vitamin D and obesity/abdominal obesity is controversial. Future large-scale prospective observational or interventional studies are needed**.**

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انتشار وعلاقة فيتامين د والسمنة بين النساء المصابات بالعقم

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المستخلص

الأهداف. تهدف الدراسة الحالية إلى تقييم مدى انتشار نقص فيتامين د والسمنة لدى النساء المصابات بالعقم. **طُرق الدراسة.** أجريت دراسة استطلاعية مقطعية من مستشفى ماسا على 153 امرأة مصابة بالعقم تتراوح أعمارهن بين 21-44 سنة. تم تقييم جميع المرضى من خلال أخذ التاريخ الكامل والفحص السريري وفحص فيتامين د وقياس مؤشر كتلة الجسم. تصنيف فيتامين د المستخدم كان على النحو التالي: نقص فيتامين د خفيف - مستويات المصل 25-12 D(OH) 19نانوجرام/مل (30-49 نانومول/لتر)، نقص معتدل فيتامين د - المصل 25 11-5 D(OH) نانوجرام/مل (12.5-29 نانومول/لتر)(L ، ونقص حاد في فيتامين د - مستوى المصل 25 5> D(OH)نانوغرام/مل (<12.5 نانومول/لتر). **النتائج**. لم تكشف الدراسة الحالية وجود اختلاف كبير في متوسط فيتامين د في مصل الدم لدى النساء المصابات بالعقم (قيمة .(p = 0.605 كما أظهرت النتائج وجود تأثير غير مباشر للعوامل الناتجة عن التفاعلات فيما بينها. كانت التفاعلات بين مؤشر كتلة الجسم والعقم (قيمة(* p = 0.040 ، وفيتامين د والعقم (قيمة(* p = 0.047 ، وفيتامين د ومؤشر كتلة الجسم (قيمة (* p = 0.044 والعمر والعقم (قيمة (* p = 0.022 كانت كبيرة. والتأثيرات النقية الموضحة على نتائج التجارب وأنواع الأمراض النسائية. بخلاف ذلك، أظهرت الدراسة وجود علاقة خطية سلبية بين مستويات فيتامين د والسمنة لدى النساء المصابات بالعقم. **الخاتمة**. تشير النتائج التي توصلنا إليها إلى أن انخفاض فيتامين د قد يتوافق مع ارتفاع معدل انتشار السمنة لدى النساء المصابات بالعقم، مما يذكرنا بإيلاء المزيد من الاهتمام لمكملات فيتامين د لدى النساء المصابات بالعقم البدينات.

الكلمات الدالة. فيتامين د، السمنة، العقم، مؤشر كتلة الجسم.