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Research Article

Role of Latent Genital Tuberculosis in the Relation between Levels of Vitamin D and Anti-müllerian Hormone among Female Patients with Infertility

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A B S T R A C T

Introduction: An association between low secretion level of anti-müllerian hormone (AMH) and low level of vitamin D in the study of female infertility has been established for a long time. This article sought to find out the quantification of the association of the level of anti-müllerian hormone with level of vitamin D and the role of latent genital tuberculosis (LGT), considered a leading cause of female infertility, in the association.

Materials and Methods: A total of 150 patients were recruited in this cross-sectional study who attended at reproductive medicine unit of Calcutta Fertility Mission, Kolkata. Patients were divided into two groups following the outcome of long time polymerase chain reaction (PCR) test to detect LGT. Levels of anti-müllerian hormone and vitamin D were measured for each patient.

Result: Medians of vitamin D and anti-müllerian hormone levels were significantly higher for patients from the PCR negative group (absence of LGT). The level of anti-müllerian hormone was significantly associated with the level of vitamin D (p-value < 0.01). More specifically, significant association was observed for lower levels of vitamin D and anti-müllerian hormone in the presence of LGT whereas elevated levels of anti-müllerian hormone and vitamin D were scattered most with the absence of LGT. Level of anti-müllerian hormone increased with vitamin D. Also, level of anti-müllerian hormone increased almost 3 ng/ml in the absence of LGT.

Conclusion: Association between anti-müllerian hormone and vitamin D levels was strongly affected by the presence of LGT. Low anti-müllerian hormone levels were strongly associated with vitamin D deficiency in the presence of LGT while in the absence of LGT, elevated levels of vitamin D and anti-müllerian hormone were more dispersed with an insignificant association. Vitamin D deficiency and low anti-müllerian hormone secretion could be an indicator of latent tuberculosis and female infertility.

Keywords: Anti-müllerian Hormone (AMH), Polymerase Chain Reaction, 25-Hydroxyvitamin D, Genital Tuberculosis, GLM Estimation

Introduction

Vitamin D has a potential role in infertility and the female reproduction system[1-4] where many female reproductive organs, including granulosa cells, contains vitamin D receptors (VDR).[5] Several studies on animals suggest that impaired folliculogenesis was observed among VDR null mutant mice with oestrogen levels was significantly lower.[6] A result from a study showed ovarian steroidogenesis was stimulated by vitamin D in ovarian cells.[7] One of the most important biomarkers to predict ovarian reserve is anti-müllerian hormone. The granulosa cells which produce anti-müllerian hormone, have a salient role in folliculogenesis and regulation in developing small antral follicles and early preantrals.

Several studies showed anti-müllerian hormone has an association with vitamin D in animal models[8] and through experiments in human granulosa cells,[9] which show that anti-müllerian hormone significantly affected by vitamin D. Though, the basic research finds a consistent relation between vitamin D and anti-müllerian hormone, some strongly contradictory results are found from different clinical studies. Some studies points on an affirmative association of ovarian reserve with vitamin D[10,11] whereas others negates any significant association of anti-müllerian hormone with vitamin D. Considering[12] this conflicting evidence from different studies on the association of vitamin D and anti-müllerian hormone in female reproduction, and increasing interest in the role of vitamin D in this regard, this prospective cross-sectional study was performed to evaluate the relationship between serum anti-müllerian hormone and vitamin D, two most important markers of ovarian reserve among infertile women. We have also observed low concentration of serum vitamin D has a direct correlation with a low anti-müllerian hormone concentration during an ovarian reserve test (ORT) in the presence of latent genital tuberculosis.

Materials and Methods

Study Design

This was a cross-sectional study, conducted in the reproductive medicine unit, Calcutta Fertility Mission, Kolkata. The patients were attendees of in vitro fertilization (IVF) programme at the clinic and prescribed for investigation of two biochemical hormone, anti-müllerian hormone and 25-OH vitamin D among others along with tubercular DNA PCR test. The study had 150 patients divided into two groups following the outcome of the tubercular DNA PCR test. Both groups of PCR positive (presence of LGT) and PCR negative (absence of LGT) had an equal number of patients. The patients were from the age group of 20-40 years on the basis of the criteria of primary or secondary infertility for more than 2 years since planning, and with normal menstrual cycle length of 26-34 days. The exclusion criteria includes if patients had polycystic ovaries or polycystic ovarian syndrome, endometriosis, any vaginal infection like chlamydia or gonorrhoea, suffered from pulmonary tuberculosis or extrapulmonary tuberculosis other than the genital organ, history of previous ATD treatment or had any genetic disorder.

Following the ethical guidelines of the Helsinki Declaration 1975, a written consent format was designed. Ethical clearance was taken from the Institutional Ethical Committee of Calcutta Fertility Mission, Kolkata, India. An informed consent form from each participant was collected prior to the collection of the sample. The details of the collecting methods of vitamin D and anti-müllerian hormone are discussed earlier.[13] The Calbiotech 25-OH vitamin D ELISA kit was used to estimate vitamin D of each participant. AMH Gen II Enzyme Linked Immuno Sorbent Assay (ELISA) was used to estimate anti-müllerian hormone concentration. The QIAamp DNA Mini Kit was used to extract DNA. The tuberculosis genome was identified by a multiplex PCR with three sets of primers.

Statistical analysis

Descriptive statistics were presented on the data including the median and interquartile range (IQR) for levels of anti-müllerian hormone and vitamin D, and age for both the groups of presence of LGT and absence of LGT. Box plot was used to visualise the differences of anti-müllerian hormone and vitamin D levels between the groups. The Mann-Whitney test was used to find significant differences between medians for continuous variables. The scatter plot was constructed to present the association between the levels of anti-müllerian hormone and vitamin D with and without presence of LGT. A generalised linear model (GLM) was fitted to anti-müllerian hormone level with vitamin D level, patient's age and presence of LGT as potential confounders for all patients. Gamma distribution is used for GLM of anti-müllerian hormone level as a good choice to model a positive continuous variable with an extended tail to the right of the distribution. We used R 3.2.4 software for data analysis. The p-value < 0.01 was considered as statistically significant.

Result

Out of 150 patients, 50% (75) the patients had presence of LGT while rest (50%) had the absence of LGT. The median age of the selected patients was 33 years. Levels of AMH and vitamin D were tabulated against two groups of PCR (Table 1), diagrammed by box plot (Fig.1). The median vitamin D level for patients with absence of LGT is nearly thrice the median value of patients with presence of LGT, and this difference is significant (p-value<0.01) (Fig.1 a,b). In a similar way, the median anti-müllerian hormone level for patients with the absence of LGT is more than twice compared to patients with the presence of LGT. The pres-

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ence of LGT also indicates more condensed lower values of both anti-müllerian hormone and vitamin D levels with a strong positive correlation (Fig. 2). However, age has no impact on median levels of vitamin D and anti-müllerian hormone (Table 1). The age of the patient and presence of LGT were considered as covariates along with vitamin D for anti-müllerian hormone level.

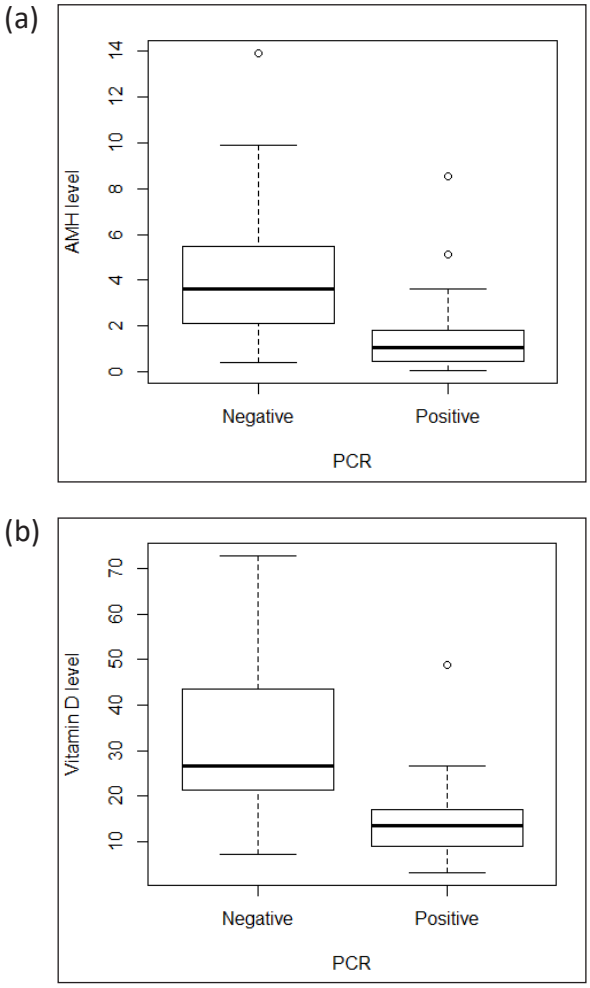

Figure 1(a,b).Box plot of Vitamin D level and anti-müllerian hormone level against PCR

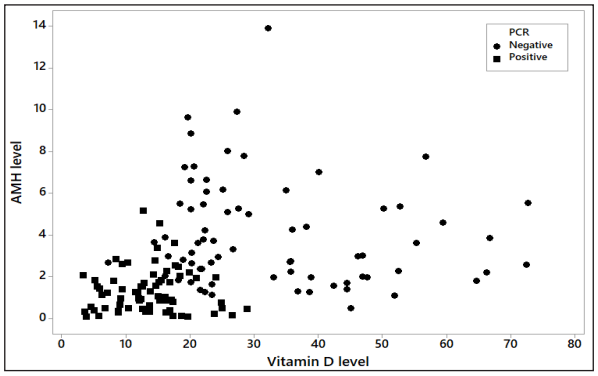

Figure 2.Scatter diagram of Vitamin D level and anti-müllerian hormone level

The GLM of anti-müllerian hormone level assuming a gamma distribution (Fig. 3) showed vitamin D level, the patient's age and the presence of LGT were significant predictors (p-value<0.01) of anti-müllerian hormone level. Table 2 presents the result of the model. We found that anti-müllerian hormone level increased with vitamin D level though the increment was quite low. Furthermore, anti-müllerian hormone level was almost 3 ng/ml higher with the absence of LGT. Moreover, age was significantly related to anti-müllerian hormone and lower anti-müllerian hormone level observed for older patients. Most significantly, the result found a moderate but significant (r = 0.289) positive association between the levels of vitamin D and anti-müllerian hormone (p-value<0.01). The association was attributed mainly to the presence of LGT with lower values of anti-müllerian hormone and vitamin D appearing more condensed and systematic way.

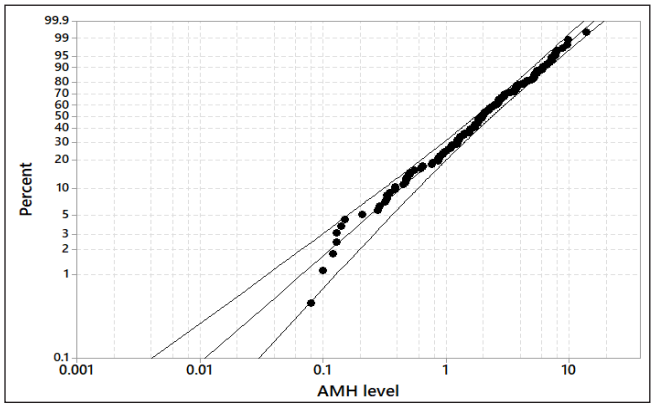

Figure 3.Probability plot of anti-müllerian hormone level

Table 1.Descriptive statistics of Vitamin D and Anti-Müllerian Hormone levels

	PCR status				
	Negative		Positive		p-value
	Median	IQR	Median	IQR	
Vitamin D level	26.761	23.253	13.693	8.000	0.000
AMH	3.610	3.442	1.044	1.364	0.000
Age	33	7	33	8	0.186

Table 2.Result for GLM assuming gamma distribution for anti-müllerian hormone level

Predictor	Coefficient	Std. Error	p-value
Intercept	2.679	0.996	0.007
Vitamin D level	0.022	0.007	0.002
Age	-0.184	0.028	0.000
Presence of LGT	-2.910	0.363	0.000

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Discussion

The basic research indicates that deficiency in vitamin D plays an important role in follicle development. A significant correlation of vitamin D with successful fertility treatments has been found among women with infertility who have undergone in vitro fertilisation.[10-14] Vitamin D showed a positive linear relationship with anti-müllerian hormone concentration in some studies.[15]

In a cross-sectional nested study, serum 25-OH vitamin D showed a weak significant positive correlation with anti-müllerian hormone among late reproductive-aged women.[11] Significantly this study found anti-müllerian hormone has no association with serum 25-OH vitamin D among younger patients. Dennis et al. found anti-müllerian hormone was correlated with magnitude change in vitamin D concentrations in a study with 33 premenopausal women.[10] However, 25-OH vitamin D and anti-müllerian hormone showed no correlation in a prospective cross-sectional study at University Hospital of Brussels by Drakopoulos et al.[16] Similarly, Pearce et al. reported no correlation observed for serum anti-müllerian hormone with vitamin D concentrations in polycystic ovary syndrome (PCOS) or ovulatory patients in a retrospective study of 340 women.[12]

Keeping in view these findings, the paper attempts to model and estimate the effect of vitamin D level and presence of LGT on anti-müllerian hormone level through GLM. No attention has been given to the nature and magnitude of the association of the level of anti-müllerian hormone with the level of vitamin D in previous studies as far as our knowledge. A significant positive association was observed in this study. Moreover, the association was found to be strong with lower levels of vitamin D and anti-müllerian hormone with the presence of LGT which had been considered as a leading cause of infertility.

Conclusion

Our finding is that the association of anti-müllerian hormone with vitamin D is quantified and the role of LGT is examined in relation to that association. The study found that low level of anti-müllerian hormone is strongly associated with vitamin D deficiency in the presence of LGT. Higher levels of vitamin D and anti-müllerian hormone are more dispersed in absence of LGT, suggesting an insignificant association. Anti-müllerian hormone and vitamin D levels were much higher in absence of LGT. The presence of LGT plays an important role in assessing the association between vitamin D and anti-müllerian hormone. Vitamin D deficiency with low anti-müllerian hormone secretion could be considered a biomarker of the presence of LGT and a cause of infertility.

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Declaration of Generative AI and AI-Assisted Technologies in the Writing Process: None

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