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Deficiency of vitamin D leads to increased insulin-resistance and advanced glycation end-products (AGEs) accumulation and decreased DHEA-S level and oocyte maturation rate.

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Title: Deficiency of vitamin D leads to increased insulin-resistance and advanced glycation end-products (AGEs) accumulation and decreased DHEA-S level and oocyte maturation rate.

Study question: Is vitamin D deficiency associated with hormone levels, oxidative stress, insulin-resistance, advanced glycation end-products (AGEs), and outcome of IVF-ET in infertile patients?

Summary answer: Deficiency of vitamin D has been associated with increased insulin-resistance and AGEs accumulation and decreased DHEA-S level and oocyte maturation rate.

What is known already: Vitamin D is necessary for its function in maintaining calcium homeostasis and promoting bone metabolism. However, Vitamin D deficiency is still a common problem in the general population, and especially in women in reproductive age. Vitamin D receptors are expressed in a variety of tissues including skeleton and parathyroid glands as well as reproductive tissues. There is evidence that vitamin D exerts some effects on female reproduction.

Study design, size, duration: This study conducted 510 infertility women who received IVF treatment at HORAC Grand Front Osaka clinic between July 2016 until August 2017. Patients were divided into two groups according to their serum 25-hydroxyvitamin-D3 [25(OH)D] levels: Group A < 20 ng/ml, and Group B \geq 20 ng/ml and FF 25(OH)D levels: Group C < 20 ng/ml, and Group D \geq 20 ng/ml. This study was approved by the Local Ethics Committee.

Participants/materials, setting, methods: Vitamin D insufficiency and deficiency corresponded to levels of 25(OH)D < 30 and < 20 ng/ml, respectively. Serum 25(OH)D, AMH, basal FSH, testosterone, and DHEA-S were

measured at a commercially available laboratory. The reactive oxygen metabolite (d-ROM) and biological antioxidant potential (BAP) levels were measured as indicators of the degree of oxidative stress. AGEs were measured using the AGE Reader. The follicular fluid (FF) sample was obtained from preovulatory follicle sized \geq 18mm of diameter.

Main results and the role of chance: The number (%) of women with vitamin D deficiency was 337 (66.1%) and insufficiency was 141 (27.6%), respectively. No significant difference was observed in age (38.4 ± 4.7 vs. 38.1 ± 5.0 years), BMI (21.1 ± 4.1 vs. 21.0 ± 3.8 in kg/m^2) between the group A (n=337) and group B (n=173). DHEA-S in group A was lower than group B (165.9 ± 90.4 vs. 188.1 ± 115.4 $\mu\text{g}/\text{dL}$, $p < 0.05$). HOMA-R in group A was higher than group B (1.81 ± 1.5 vs. 1.28 ± 0.6 $\mu\text{g}/\text{dL}$, $p < 0.01$). AGEs in group A was higher than group B (213.6 ± 60.5 vs. 192.9 ± 29.4 AU, $p < 0.01$). However, no significant difference was observed in AMH, testosterone, basal-FSH, PRL, d-ROM, and BAP. Oral vitamin D supplementation has been increased FF 25(OH)D levels in deficiency and insufficiency cases (from 16.0 ng/mL to 29.7 ng/mL, $p < 0.01$). Oocyte maturation rate in group C was lower than group D (73.7 vs. 83.1%, $p < 0.05$). However, no significant difference was observed in rate of fertilization, good quality embryos, blastocyst, and good quality blastocysts.

Limitations, reasons for caution: Vitamin D status is fluctuating and can be influenced by several external factors such as sun exposure, seasonality, and diet. Therefore, the limitation of this study is that vitamin D levels may be varied. Small sample size, possible dispersion of the cause of their infertility or back ground of patients.

Wider implications of the findings: This study demonstrates that serum vitamin D are increased by oral vitamin D supplementation and this can have a significant impact on insulin resistance, DHEA-S levels, AGEs accumulation and oocyte maturation. Vitamin D deficiency might be involved in the pathogenesis of infertility.