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ORIGINAL ARTICLE

Association between vitamin D status and hyperinsulinism

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ABSTRACT

Aims: Some studies have suggested that vitamin D deficiency is associated with an increased risk of first trimester miscarriages, others have suggested that it is associated with an increased risk of hyperinsulinism/insulin resistance and the development of gestational diabetes. Hyperinsulinism is also thought to increase miscarriages. We investigated the association between vitamin D levels and hyperinsulinism in a cohort of recurrent miscarriage patients.

Methods: Patients undergoing miscarriage investigations had insulin and vitamin D levels tested. Vitamin D levels were classified as: sufficient ($\geq$75 nmol/L), insufficient (50–74.9 nmol/L) or deficient ($<$50 nmol/L). Hyperinsulinism was assessed *via* a 75 g oral glucose tolerance test (OGTT) with insulin studies.

Results: One hundred and fifty-five patients underwent the testing. Hyperinsulinism was detected in 58.3% of the vitamin D deficient group, 38.7% of the insufficient group, and 33.3% of the sufficient group (chi-square $p = .034$). There were no significant associations between BMI and vitamin D levels, or BMI and hyperinsulinism. Caucasians comprised 82% of the clinic, and 67% of these women had vitamin D insufficiency/deficiency. Noncaucasians comprised 18% of the clinic but 89% of these patients had vitamin D insufficiency/deficiency.

Discussion: We found that insufficient or deficient vitamin D levels were significantly associated with hyperinsulinism in these patients. Vitamin D deficiency is also thought to contribute to an increased risk of adverse pregnancy outcomes including preeclampsia, preterm birth, small-for-gestational-age gestational diabetes mellitus, and miscarriages. Larger level one trials are needed to establish if increasing serum vitamin D levels prior to conception or in early pregnancy improves adverse pregnancy outcomes.

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Hyperinsulinism; insufficiency and deficiency; vitamin D sufficiency; recurrent miscarriages

Introduction

Vitamin D has been implicated as a modifiable risk factor for miscarriages, due to its function as an immune modulator and because it may modify maternal immune tolerance, without which the semiallogeneic human fetus cannot survive. Andersen et al., found the adjusted hazard of first-trimester miscarriage was lower with higher vitamin D concentrations [1–5]. Vitamin D is classically involved in the regulation of calcium homeostasis, directly *via* affecting intestinal calcium and bone absorption, and indirectly by suppression of parathyroid hormone (PTH) secretion. It also has several well established "nonclassical" roles in the immune system and in functional regulation of a wide variety of cell types [6]. Accumulating evidence has linked vitamin D deficiency with abnormal glucose metabolism, thought to mainly occur *via* direct effects of vitamin D, either on pancreatic β-cell function or on insulin sensitivity [7–9]. Studies have shown lower vitamin D levels in diabetic subjects compared to nondiabetics [10–14]. Lu et al. in a meta-analysis of observational studies involving 16,515 patients from 20 studies revealed that low vitamin D levels were associated with a 45% increased risk of the development of Gestational Diabetes Mellitus (GDM) [8]. Insulin resistance and the resultant hyperinsulinism is known to increase the risk of gestational diabetes and pregnancy loss, particularly in patients with polycystic ovarian syndrome.

Subjects

Patients referred to a Recurrent Miscarriage Clinic in a Tertiary Public Hospital. They were evaluated if they had had two or three clinically recognized, consecutive miscarriages, with the same partner.

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Materials and methods

Vitamin D testing was offered to all patients presenting to the recurrent miscarriage clinic, with the routine blood work up. Vitamin D (25-hydroxy vitamin D) assessment was performed using the Thermo Scientific™ LC-MS system by SA Pathology. 155 patients also had a 75 g Oral Glucose Tolerance test (OGTT) together with fasting and 2 h insulin levels measured as well. Insulin was measured using the Advia Centaur analytical system. This insulin assay detects recombinant insulin analogs in addition to endogenous insulin. The fasting insulin levels accepted as normal by our laboratory are 0–12 mU/L, we used the glucose: insulin ratio <4.5 and insulin levels ≥ 20 mU/L to diagnose fasting hyperinsulinism. Normal 2-h insulin concentrations in our laboratory are 10–40 mU/L. Using 10–40 mU/L gave a mean of 25.88 in our group of normal patients. We used three standard deviations from this mean as our cutoff for the diagnosis of 2-h hyperinsulinism, 52.6 mU/L, as there are no guidelines in the literature.

BMI was calculated as weight in kilograms divided by the height in meters squared, and 20–24.9 as normal BMI, 25–29.9 as overweight and ≥ 30 obese. Vitamin D levels were defined as deficient below 50 nmol/L, insufficient as 50–74.9 nmol/L and sufficient as ≥ 75 nmol/L [9].

Statistics

The association between hyperinsulinism, vitamin D levels, BMI categories, and ethnicity were examined using chi-squared test, or Fisher's exact test where appropriate. A Breslow-Day test was also performed to assess the homogeneity of odds ratios between hyperinsulinism and vitamin D levels across different BMI categories. Statistical analyses were performed in R 3.4.1 [15].

Results

The vitamin D results for 294 patients were available for assessment and 155 of these had 75 g OGTT's. Eighty-two% of the patients were Caucasian, and only 18% non-Caucasian, comprising Indian (5%), African (1.9%), Middle Eastern (6.5%), and Asian (4.6%).

Vitamin D levels in recurrent miscarriage patients were sufficient in 33% of Caucasians, and just 11% of non-Caucasians (Figure 1). Hyperinsulinism was significantly more common in recurrent miscarriage (RM) patients who had vitamin D deficiency or insufficiency ($p = .034$) (Figure 2) than in patients who had sufficient

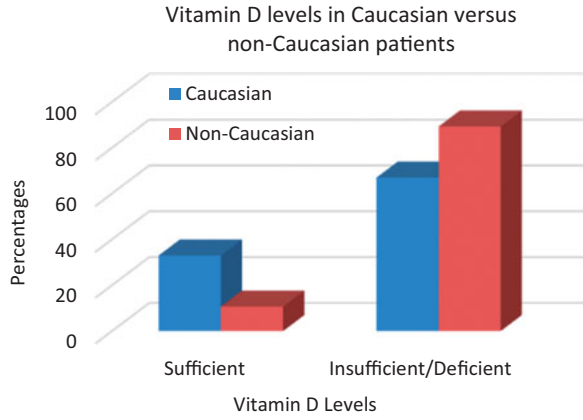

Figure 1. Vitamin D levels in Caucasian and non-Caucasian patients in the sufficient and insufficient/deficient groups.

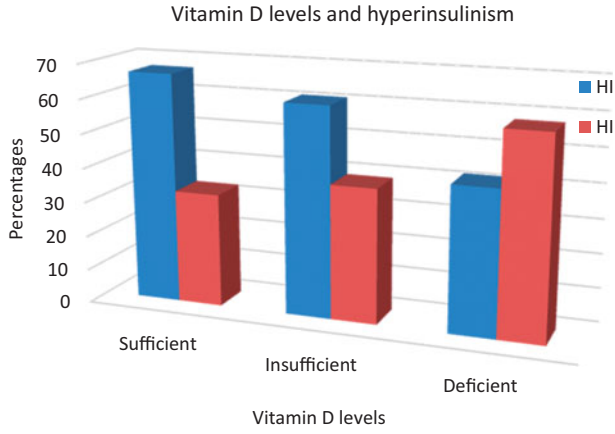

Figure 2. Vitamin D levels and hyperinsulinism. The risk of hyperinsulinism increased with decreasing vitamin D levels. S: sufficient; I: Insufficient; D: deficient vitamin D; HI: hyperinsulinism.

levels, and this was independent of BMI ($p = .41$). Vitamin D levels were also independent of BMI ($p = .09$).

Discussion

We have demonstrated that a low serum concentration of vitamin D is associated with hyperinsulinism. We have previously shown a significant increase in GDM in RM patients with prepregnancy raised fasting or 2-h insulin levels, in a subsequent pregnancy (submitted). The coexistence of vitamin D deficiency/insufficiency with hyperinsulinism in RM patients strengthens the link between insulin resistance and poor vitamin D status. Furthermore, it may indicate that improving vitamin D status and metabolic health could have important benefits for women planning pregnancy. Recurrent miscarriage (RM) affects from

1 to 4% of a population of reproductive age couples and is multifactorial in origin [16]. Women who suffer recurrent miscarriages are a heterogeneous group. Known causes include genetic and endocrine abnormalities, antiphospholipid syndrome, autoimmune disease and uterine structural abnormalities [16]. While genetic factors are an important cause of losses, lifestyle factors, many of which are modifiable, are significant. Increased maternal age and increased prepregnancy BMI are two such modifiable risk factors [15–17]. Vitamin D insufficiency and deficiency in pregnant women is common worldwide, particularly in the winter months, and vitamin D supplementation is thought to be a public health strategy that could improve both maternal and fetal outcomes [18].

Vitamin D is synthesized in the skin following sun exposure and to a lesser extent is present in the diet [18]. Dark skin pigmentation, cold climates with little sun exposure, clothing that limits sun exposure, sun screen, as well as inadequate diets, all lead to vitamin D deficiency. This is not necessarily predictable. People with darker skins are known to make less cutaneous vitamin D than those with little pigmentation [18]. However, in countries such as Australia, with extremely high incidence of malignant melanoma many people tend to limit sun exposure. Hence, hypovitaminosis D is increasing, and is suspected to be a public health problem in many parts of the world [18].

Vitamin D deficiency is associated with type 2 diabetes mellitus in adults [8] while in pregnancy it has been associated with an increased risk of preeclampsia, GDM, preterm birth, small for gestational age babies (SGA), as well as problems in infancy such as rickets [8]. Alternative actions for vitamin D in pregnancy loss have been reported. Ota et al. [19] showed that a high proportion of women with recurrent pregnancy loss had vitamin D deficiency citing its association with increased cellular and autoimmunity. They found that women with low vitamin D status had significantly increased antithyroid antibodies (ATA) antinuclear antibodies (ANA) and antiphospholipid antibodies (APA) [17,18]. APA's are known to cause pregnancy loss [19], whereas ANA's and ATA's are associated with losses [20].

We have demonstrated an association between decreased vitamin D levels and hyperinsulinism, which may suggest that vitamin D is a modifiable risk factor for adverse pregnancy outcomes. Large, well designed multicentre randomized controlled trials are required to actually determine whether vitamin D supplementation in women with low vitamin D status reduces the risk of adverse pregnancy outcomes.

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Disclosure statement

The authors declare that there are no conflicts of interest associated with this manuscript.

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