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Influence of Vitamin D and Parathyroid Hormone on Bone and Metabolic Risk in Women with Previous Gestational Diabetes

Monica C. Serra* and Alice S. Ryan

Baltimore Maryland VA Medical Center & University of Maryland School of Medicine

Abstract

The purpose of this study was to compare plasma 25-hydroxy vitamin D (25(OH)D) and parathyroid hormone (PTH), VO₂max, bone (by DXA), and metabolic outcomes across age and race-matched postmenopausal women (54±1 years; mean±SEM): 1) with previous gestational diabetes (GDM) (32±1 kg/m²; N=17), 2) without previous GDM, but with a similar BMI to GDM (32±1 kg/m²; N=17), and 3) without previous GDM, but with a higher BMI than GDM (36±1 kg/m²; N=17; P<0.01). The prevalence of 25(OH)D insufficiency and deficiency was high (~80%), but not different across groups, while PTH tended to be ~30% lower in women with a history of GDM (P=0.09). Women with a history of GDM had lower HDL cholesterol and higher diastolic blood pressure and fasting and 2-hr glucose levels (by oral glucose tolerance test) (vs. groups 2 and 3; P's<0.05). Bone mineral density (BMD) tended to be slightly higher in women with prior GDM than the BMI matched women with no prior GDM (P=0.09). Overall, higher PTH was associated with lower femoral neck (r=-0.33) and (r=-0.38) (P's<0.05), while lower 25(OH)D was associated with lower VO₂max (r=0.25, P=0.05) and higher fasting glucose (r=-0.14) and insulin (r=-0.29 (P's<0.05). We observe that the poor metabolic profiles of postmenopausal women with a history of GDM are independent of 25(OH)D and PTH. However, due to associations between 25(OH)D and PTH with bone and metabolic outcomes, maintaining recommended 25(OH)D and PTH concentrations is important regardless of a previous history of GDM.

Keywords

Gestational Diabetes Mellitus; Vitamin D; Parathyroid Hormone; Metabolism; Bone Mineral Density

Vitamin D and parathyroid hormone (PTH) have a well-established role in calcium and bone metabolism, but recent evidence suggests that they also may influence metabolic outcomes. 25-hydroxy vitamin D (25(OH)D) concentrations are inversely associated with metabolic syndrome risk [1] and poor glycemic control and insulin resistance (by homeostasis model assessment-estimated insulin resistance index [HOMA-IR]) [2], while a direct relationship is observed between these metabolic abnormalities and PTH [3,4]. These risks are higher in postmenopausal women, as increasing age and fat mass are associated with lower 25(OH)D

*Corresponding Author, Baltimore VA Medical Center, 10 N. Greene St, GRECC (BT/18/GR), Baltimore, MD 21201, Phone: (410) 605 7000 x 4199, Fax: (410) 605 7913, mserra@grecc.umaryland.edu.

[5] and higher PTH [6,7] concentrations. Further, in older women, better cardiorespiratory fitness is associated with higher 25(OH)D concentrations [8], indicating that an age-associated decline in cardiorespiratory fitness may be related to concomitant decreases in 25(OH)D.

Approximately 18% of women will be diagnosed with gestational diabetes mellitus (GDM) during their pregnancy [9]. Women with a prior history of GDM are at elevated risk for developing several chronic diseases later in life, including type 2 diabetes mellitus (T2DM) and cardiovascular disease [10,11]. Previous studies show that women with a history of GDM have higher body mass index (BMI), blood pressure, and worse lipid profiles compared to women without a history [12,13]. These metabolic differences do not appear to result from differences in resting metabolic rate between women with and without a history of GDM [14]. Further, we have previously shown that women with and without a history of GDM do not differ with regard to cardiorespiratory fitness levels [15]. We also have shown that many of these risk factors are even higher in postmenopausal compared to premenopausal women with a previous history of GDM, even after controlling for age, adiposity, and cardiorespiratory fitness levels [15], indicating that postmenopausal women are especially vulnerable to metabolic disturbances.

Identifying whether the prevalence of low 25(OH)D and elevated PTH differs in women with and without a history of GDM and predicts metabolic abnormalities may provide evidence that these modifiable markers are important risk factors to monitor in the prevention of chronic disease after the diagnosis of GDM. Thus, the purpose of this study was to determine whether low plasma 25(OH)D and elevated PTH may contribute to potential differences in bone and metabolic profiles of postmenopausal women with previous diagnosis of GDM compared to age and race-matched women without a previous diagnosis who had a similar body mass index (BMI) or significantly greater BMI. We hypothesized that lower 25(OH)D and higher PTH concentrations may contribute to worse bone and metabolic profiles in women with prior GDM compared to women without a history of GDM.

Materials and Methods

Overweight and obese ($\text{BMI} > 25 \text{ kg/m}^2$) sedentary women between the ages of 38-65 yrs were recruited for this study [15]. All women signed University of Maryland Institutional Review Board approved consent forms. Only Caucasian and African American postmenopausal (>one yr since previous menstruation [including surgical or medical menopause] and plasma FSH levels $> 30 \text{ mIU/ml}$) women, not on hormone replacement therapy, were used in the present analyses. Seventeen women with prior GDM (at least five years postpartum) were matched for age ($\pm 5 \text{ yrs}$) and race to two groups of women without a history of GDM ($N=17/\text{group}$). The “BMI matched” women without prior GDM had a BMI within one kg/m^2 of their GDM match, while the “more obese” women without prior had a BMI of at least three kg/m^2 greater than their GDM match. A physical examination, medical history, graded exercise stress test, and fasting blood profile were used as screening tools to exclude those with uncontrolled chronic disease.

Body Composition

Height and body weight were measured using a stadiometer and electric scale to calculate BMI (weight [kg]/height [m²]). A total body dual energy x-ray absorptiometry scan (Prodigy and DPX-IQ; LUNAR Radiation Corp., Madison, Wisconsin, USA) was performed to determine fat-free mass (FFM), fat mass, and % body fat, as well as regional scans to determine BMD (g/cm²) of the femoral neck, greater trochanter, lumbar spine (L1-L4), and total body.

Maximal Oxygen Uptake and Energy Expenditure

Cardiorespiratory fitness (VO₂max) was measured by indirect calorimetry during a graded exercise test on a treadmill as previously described [16]. After a minimum of a 12 hr fast, subjects underwent 30 minutes of indirect calorimetry to determine resting metabolic rate (RMR) using an open circuit dilution technique (SensorMedics DeltaTrac cart, Yorba Linda, CA). Continuous measures of carbon dioxide (CO₂) and oxygen (O₂) gases were averaged and recorded every 30 s during 30 min of testing. CO₂ and O₂ values were used to calculate the 24-h RMR using the Weir equation [17].

Metabolic Testing

Women also underwent a 2-hr 75 g oral glucose tolerance test (OGTT) for classification of impaired glucose tolerance and T2DM [18]. Plasma glucose and insulin were measured as previously described [15,19]. HOMA-IR was calculated as [(fasting insulin (μU/ml) × fasting glucose [mmol/l])/22.5] [20]. Serum calcium and creatinine were measured in the general chemistry laboratory of the Veterans Affairs Medical Center by sequential multiple analyzer (SMAC, Technicon Instruments, Tarrytown, NY, USA). Glomerular filtration rate (GFR) was calculated as $175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$, with a normal GFR considered 90 ml/min/1.73m² [21]. Additional bloods were collected for the analysis of plasma intact PTH by immunoradiometric assay (Quest Diagnostics, Madison, NJ) and plasma 25-hydroxy vitamin D (25(OH)D) by RIA (DiaSorin, Stillwater MN). High PTH was defined as >55 pg/ml [22]. Vitamin D insufficiency was defined as a 25(OH)D concentration between 20-30 ng/ml and deficiency as <20 ng/ml [23]. The presence of three or more of the following criteria was used to diagnose metabolic syndrome: central obesity (waist >88 cm), impaired glucose metabolism (fasting glucose >5.6 mmol/L), elevated blood pressure (>130/85 mmHg or antihypertensive treatment), and dyslipidemia (triglyceride (TG) >1.7 mmol/L, HDL-C <1.3 mmol/L, or hypolipidemic treatment) [24].

Subjects collected a 24 hour urine sample. Samples were analyzed for daily urinary calcium excretion by potentiometry utilizing a calcium ion selective electrode in conjunction with a sodium reference electrode and daily creatinine excretion by Jaffe rate method (Synchron Clinical System, Beckman Coulter, Inc., Brea, CA).

Statistical Analyses

Comparisons of the three groups were performed using one-way ANOVAs with post-hoc analyses, and χ^2 tests. Cohen's d were calculated as standardized effect size measures of the main outcome measures: 25(OH)D (0.36), PTH (0.66), greater trochanter BMD (0.72),

femoral neck BMD (0.24), lumbar spine BMD (0.47), fasting glucose (0.84), 2-hr glucose (0.77) glucose, HDL-cholesterol (0.88), and triglycerides (0.84) between subjects with and without GDM. Linear regression predicting bone and metabolic outcomes from a model including hormone concentrations of 25(OH)D or PTH, an indicator variable for GDM, and a hormone concentrations*indicator variable interaction was used to determine if the slope or intercept differed between the two groups (with vs. without prior GDM). Analyses with 25(OH)D were controlled for the season of the blood draw. Statistical significance was set at a two-tailed $P < 0.05$. Data were analyzed using SPSS (PAWS Statistics, Version 18, Chicago, IL). Results are expressed as mean $\pm$ SEM.

Results

Subject Characteristics (Table 1)

Women were approximately 55 $\pm$ 1 yrs old and 82% Caucasian. Fat mass and body fat percentage was similar between women with prior GDM and the BMI matched women with no prior GDM, but, as expected, both of these groups had a significantly lower BMI, fat mass, and body fat percentage than the more obese women with no prior GDM ($P < 0.01$). By ACSM criteria [25], women had “very poor” fitness (overall mean $\text{VO}_{2\text{max}}$: 20 $\pm$ 0.6 ml/kg/min), which was comparable between groups. Resting metabolic rate also was similar between groups (overall mean: 1532 $\pm$ 31 kcal/d).

Bone and Metabolic Profiles (Table 1)

Suboptimal 25(OH)D concentrations were highly prevalent (~47% were insufficient and ~33% were deficient). The prevalence of insufficiency and deficiency did not differ across groups, nor did mean concentrations. PTH tended to be ~30% lower in women with a history of GDM than both groups of women without prior GDM ($P = 0.09$). The prevalence of high PTH was 41% in each of the no prior GDM groups and only 29% in the prior GDM group, but this difference did not reach statistical significance. Greater trochanter and lumbar BMD tended to be slightly higher ($P = 0.09$) in women with a history of GDM than the BMI matched women with no prior GDM. Both serum and urinary calcium were similar across groups, as was urinary creatinine, but GFR was 39% and 14% higher in women with GDM than in women without prior GDM that were matched for BMI or more obese, respectively. Further, only 47% of women with prior GDM had GFRs < 90 ml/min/1.73m² compared to 82% in both of the non-GDM groups ($P < 0.05$), suggesting that women with prior GDM had better kidney function than those without prior GDM.

Lipid (~15%) and blood pressure (~30%) medication usage was similar across groups. In general, lipid profiles were slightly above recommended values, but homogeneous between groups, except that women with a history of GDM had ~25% lower HDL cholesterol than both groups of women without prior GDM ($P < 0.01$), which was ~10% lower than recommendations for older women. All three groups had similar systolic blood pressure, but women with a history of GDM had ~10% higher diastolic blood pressure than both groups without prior GDM ($P < 0.05$). Although fasting insulin and HOMA-IR were ~18% and 24% higher, respectively, in women with prior GDM than women without, the difference

was not significant. Fasting and 2-hr glucoses were higher in women with a history of GDM than in women without a history of GDM (P 's<0.05).

Although not statistically different, 81% of women with prior GDM had metabolic syndrome, compared to 67% of BMI matched women without prior GDM and 53% of more obese women without prior GDM. The combined prevalence of impaired glucose tolerance and T2DM was significantly greater in women with prior GDM (59%) than either group without prior GDM (BMI matched, no prior GDM: 29% and more obese, no prior GDM: 24%) (P 's<0.05).

Associations with 25(OH)D and PTH

Body fat percentage ($r=-0.37$, $P<0.01$) and fat mass ($r=-0.40$, $P<0.01$) were inversely associated with 25(OH)D, with a trend for a positive association with PTH (body fat percentage: $r=0.24$; fat mass: $r=0.23$, P 's=0.08). VO_2 max was associated with 25(OH)D ($r=0.26$, $P=0.05$), but not PTH. 25(OH)D was positively associated with urinary calcium excretion ($r=0.32$, $P<0.05$), while PTH was negatively associated with urinary creatinine ($r=-0.44$, $P<0.01$). Overall, we observed that 25(OH)D was inversely associated with fasting glucose ($r=-0.18$), fasting insulin ($r=-0.30$), and HOMA-IR ($r=-0.36$, Figure 1) (P 's<0.05). Additionally, we observed that PTH was inversely associated with lumbar spine ($r=-0.38$, Figure 2A) and femoral neck ($r=-0.33$, Figure 2B) BMD in all women (P 's<0.05). The slopes and intercepts of these relationships did not differ across groups.

Discussion and Conclusions

While lower 25(OH)D and higher PTH concentrations are observed in pregnant women with an active diagnosis of GDM than those without GDM [26] and lower 25(OH)D and higher PTH is associated with greater metabolic risk in women with current GDM (during gestation) [27], this is the first study to examine whether these hormones are associated with greater metabolic abnormalities later in life. We find that women with previous GDM are at greater metabolic risk (higher diastolic blood pressure and fasting and 2-hr glucoses and lower HDL cholesterol). Although our effect sizes for differences in 25(OH)D and PTH across groups were small, indicating the need for a larger sample size to determine a definitive role of these hormones on metabolism, our observation that PTH was higher and 25(OH)D comparable across groups, suggests that this elevated metabolic risk appears independent of 25(OH)D and PTH concentrations. This is further supported by our observation that the inverse relationship observed between 25(OH)D and HOMA-IR is not different between women with and without a history of GDM. However, due to the significant associations with fasting glucose and insulin and HOMA-IR, 25(OH)D is an important plasma marker to monitor in older women.

The current study also adds to our previous findings that women with GDM are at risk for poor cardiorespiratory fitness [15], by suggesting that 25(OH)D may influence fitness levels. However, while low 25(OH)D concentrations may be detrimental to fitness in older women, the concentrations do not affect it differently in women with versus without a prior history of GDM. Further, our results do not suggest a relationship between PTH and fitness levels, despite identified potential mechanisms of action on cardiorespiratory fitness (discussed

below). We were unable to identify studies that have examined the role of PTH on fitness previously. This has been mentioned as a limitation in many studies [28,29] and should be examined in future trials.

In spite of an overall greater loss of BMD observed in women with active GDM (during pregnancy) [30], our results suggest that a prior diagnosis of GDM does not negatively impact BMD, as women with a history of GDM tended to have higher BMD than women without a history. Similarly, a higher BMD in non-pregnant women with T2DM is observed previously [31]. Although the mechanism for this reduced risk is unknown, there are several pathways that have been suggested, including changes in insulin levels, lower insulin-like growth factor-I, inflammation, and hypercalciuria [32]. Our results also suggest that women with prior GDM may have higher kidney function. Declines in kidney function are associated with a progressive rise in osteocyte-derived fibroblast growth factor 23 (FGF-23) and, later, a progressive rise in endogenous PTH [33,34]. Further, higher fat accumulation is associated with less BMD loss during pregnancy [30], which may influence BMD in later life. Since we did not collect the weight history of these women and obesity is a risk factor for the development of GDM [35], it is possible that a higher weight throughout life may have contributed to a higher BMD, as well as worse metabolic profiles, in women with previous GDM. However, congruent with our results, previous literature in postmenopausal women shows inverse associations between hip and lumbar BMD with PTH, but not 25(OH)D [36]. Our data highlight the importance of preventing elevations in PTH to maintain bone health in postmenopausal women, regardless of obesity status.

Vitamin D and PTH have the potential to influence bone and metabolic risk and cardiorespiratory fitness through their effects on intracellular calcium, which when elevated impairs the activation of osteoblasts [37], insulin action [38,39], and vascular smooth muscle contraction and vascular calcification [40]. In vitamin D receptor knockout mice, the absence of receptor activation leads to alterations in amino acid, carbohydrate, and fatty acid synthesis and metabolism [41], as well as upregulation of the renin-angiotensin system, with the development of hypertension and left ventricular hypertrophy [42]. While an elevation in PTH is common when serum 25(OH)D levels are below 30 ng/ml [43,44], our results do not support elevated risk for hyperparathyroidism in women with previous GDM. The mean PTH concentrations tend to be lower in women with a history of GDM and the prevalence of elevated PTH, in approximately a third of women, is similar between our groups and other reports of postmenopausal women [45]. Although inadequate 25(OH)D is highly prevalent (~80% are insufficient and deficient) in our sample of women, the rates do not differ significantly across previous GDM groups, indicating that the elevated risk for bone and metabolic health and poor cardiorespiratory fitness in women with prior GDM does not appear to be driven by differences in 25(OH)D concentrations. Further, this high prevalence of inadequate 25(OH)D is common among postmenopausal women [46]. Thus, independent of previous GDM diagnosis, promoting clinical management of hypovitaminosis D and hyperparathyroidism appears warranted among older women.

The treatment of low 25(OH)D is less complex than elevations in PTH, as primary hyperparathyroidism (enlargement of one or more of the parathyroid glands causes overproduction of the hormone) is most commonly treated with surgery, while secondary

hyperparathyroidism (occurring as a result of another disease that initially causes low levels of calcium in the body and over time, increases parathyroid hormone levels), requires identification and treatment of the underlying cause of the hypocalcemia (often chronic renal failure). Oral supplementation with vitamin D leads to significant improvements in 25(OH)D concentrations [47]. While there is some evidence that 25(OH)D repletion may improve metabolic outcomes (e.g. blood pressure, lipids, and inflammation [48]), the majority of studies in older, obese adults show no or only marginal metabolic improvements with regard to insulin sensitivity [49,50], cardiovascular health [48], or physical fitness [51]. Variations in the subject population, degree of deficiency, duration of treatment, and sample size make comparisons across studies difficult. A review of supplementation trials shows no improvements in cardiovascular disease events following long term vitamin D supplementation [52]. However, vitamin D supplementation improves low BMD in the presence of 25(OH)D insufficiency and primary hyperparathyroidism [53]. Together, these data indicate the need for chronic monitoring of these markers to prevent changes in 25(OH)D and PTH concentrations to help maintain metabolic and bone health in older adults.

In summary, we are the first to provide evidence that the poor metabolic profiles of postmenopausal women with a history of GDM do not appear dependent upon 25(OH)D and PTH. Nonetheless, due to observed associations between 25(OH)D and PTH with cardiorespiratory fitness and bone and metabolic outcomes, maintaining recommended 25(OH)D and PTH concentrations is important to preserve overall health in postmenopausal women regardless of a previous history of GDM.

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Figure 1.
The relationship between plasma 25(OH)D concentrations and HOMA-IR was examined with linear regression ($r=-0.36$, $P<0.05$; $N=51$).

Figure 2.

A linear relationship between plasma parathyroid hormone and lumbar spine was identified with regression analyses ($r = -0.38$, Figure 2A) and femoral neck ($r = -0.33$, Figure 2B) bone mineral density (P 's < 0.05) ($N = 51$).

Table 1

Subject Characteristics

	Prior GDM (N=17)	BMI matched, no prior GDM (N=17)	More obese, no prior GDM (N=17)
Age (yrs)	53 ± 2	56 ± 1	55 ± 2
BMI (kg/m ²)	32 ± 1	32 ± 1	36 ± 1 **
Fat Mass (kg)	38 ± 2	39 ± 2	49 ± 3 **
FFM (kg)	47 ± 1	48 ± 1	46 ± 1
Body Fat (%)	45 ± 1	44 ± 1	52 ± 1 **
RMR (kcal/d)	1583 ± 47	1570 ± 58	1447 ± 50
VO ₂ max (ml/kg/min)	20 ± 1	21 ± 1	20 ± 1
Plasma 25(OH)D (ng/ml)	25 ± 3	24 ± 2	22 ± 2
Plasma PTH (pg/ml)	36 ± 7	54 ± 7 ‡	54 ± 8 ‡
Serum Calcium (mg/dl)	9.15 ± 0.13	9.26 ± 0.07	9.25 ± 0.08
Serum Creatinine (mg/dl)	0.68 ± 0.02	0.94 ± 0.07 **	0.76 ± 0.02
GFR (ml/min/1.73m ²)	96 ± 4	69 ± 5 **	84 ± 4 *
Urinary Calcium (mg/24 hrs)	162 ± 22	145 ± 17	137 ± 14
Urinary Creatinine (g/24 hrs)	1.28 ± 0.07	1.34 ± 0.06	1.18 ± 0.08
Lumbar Spine BMD (g/cm ²)	1.23 ± 0.04	1.11 ± 0.04 ‡	1.20 ± 0.03
Femoral Neck BMD (g/cm ²)	0.99 ± 0.04	0.96 ± 0.03	0.97 ± 0.03
Greater Trochanter BMD (g/cm ²)	0.87 ± 0.03	0.78 ± 0.03 ‡	0.78 ± 0.03
Triglycerides (mmol/l)	1.8 ± 0.3	1.4 ± 0.2	1.7 ± 0.2
Total Cholesterol (mmol/l)	5.2 ± 0.3	5.4 ± 0.1	5.5 ± 0.3
HDL Cholesterol (mmol/l)	1.16 ± 0.05	1.63 ± 0.05 **	1.53 ± 0.08 **
LDL Cholesterol (mmol/l)	3.3 ± 0.3	3.1 ± 0.1	3.2 ± 0.3
Fasting Glucose (mmol/l)	6.0 ± 0.3	5.2 ± 0.1 *	5.3 ± 0.2 *
2-hr Glucose (mmol/l)	8.7 ± 0.8	6.6 ± 0.4 *	7.2 ± 0.5 *
Fasting Insulin (pmol/l)	92 ± 13	78 ± 12	78 ± 11
HOMA-IR	4.1 ± 0.7	3.4 ± 0.5	3.1 ± 0.44
Systolic BP (mmHg)	125 ± 5	123 ± 4	123 ± 4
Diastolic BP (mmHg)	78 ± 2	71 ± 3 *	68 ± 2 *

Values are means±SEM. FFM= fat-free mass, GFR= estimated glomerular filtration rate. Significantly different than women with a GDM history:

* P<0.05,

** P<0.01,

‡ P=0.09.