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Original Research

Serum Vitamin D Concentrations in Baboons (*Papio* spp.) during Pregnancy and Obesity

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Obesity is associated with vitamin D deficiency, which can lead to serious problems during pregnancy. However, the mechanisms of the deficiency and guidelines for vitamin D supplementation during pregnancy are not established yet, and variations in environmental exposures combined with the difficulties of performing research in pregnant women are obstacles in the evaluation of vitamin D metabolism. Baboons (*Papio* spp.) are an excellent, well-established model for reproductive research and represent a unique opportunity to study vitamin D metabolism in a controlled environment. This study used secondary data and specimen analysis as well as a novel experimental design to evaluate pregnant and nonpregnant baboons that were or were not exposed to sunlight while they were obese and after weight reduction. Daily D_3 intake was 71% higher in nonpregnant obese baboons than in their nonobese counterparts, but serum vitamin D concentrations did not differ between these populations. In addition, serum 25-hydroxyvitamin D concentrations correlated negatively with the obesity index. This report is the first to show the effect of obesity and pregnancy on vitamin D concentrations in a NHP population. These data underline the importance of adequate vitamin D supplementation in obese animals.

Vitamin D deficiency during pregnancy is a major public health problem[30] that is associated with increased maternal and neonatal morbidity.[5,6,22,31] Even though vitamin D is actively involved in placental function and fetal growth,[5,11,43] the dosage of vitamin D supplementation during pregnancy has not been established.[30] Maternal serum concentrations of 25-hydroxyvitamin D are directly related to vitamin D intake and sunlight exposure in humans.[27] Obesity is an important risk factor for vitamin D deficiency for which the mechanisms remain unknown, and the effect of weight loss on vitamin D status is unclear.[14,15,33,34] In addition, obesity itself is a significant public health problem.[18,51] Several mechanisms linking obesity and vitamin D deficiency have suggested, including decreased exposure to sunlight, sequestration of vitamin D in the adipose tissue,[50] and other factors related to obesity.[34,49] In pregnancy an additional factor involved in vitamin D activation and metabolism is the placenta[46-48]—a temporary endocrine organ whose function is linked to the metabolism of the adipose tissue.[7]

An understanding of the relationship between vitamin D, obesity, and pregnancy is critical for reducing maternal and neonatal morbidity. Baboons (*Papio* spp.) have been used extensively in pregnancy-related research.[17,40] The advantages of this model include the similarity of its placentation to that in humans and the ability to create uniform exposures to environmental factors (for example, sunlight, dietary composition) and thus study underlying metabolic pathways, which are impossible to study in the heterogeneous human population. However, only a very few studies related to the vitamin D requirements in these NHP species are available,[35,39] and none of them addresses the effect of obesity and pregnancy on vitamin D metabolism. The objective of the current study was to evaluate the effects of obesity, weight reduction, and pregnancy on the systemic vitamin D status of baboons, by using data collected during prior studies as well as a novel study design.

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Materials and Methods

Animal housing and handling. All baboons were maintained in a social environment with partly controlled climate conditions. The baboons had unrestricted access to a commercial diet identical in composition to Purina 5038 (LEO 5, Purina, St Louis, MO) and water. The data from nonpregnant and near-term pregnant baboons (*Papio* spp.) were used in this study. The research complied with protocols approved by the Animal Care and Use Committee of the Texas Biomedical Research Institute (10/29/2007 no. 1129 and 12/21/2005 no. 1015). The research adhered to the regulations underlined in the AALAS position statements.

Group composition and procedures. The data were collected from the following nonpregnant animals: obese baboons (n = 3; weight [mean ± SEM], 18.8 ± 0.7 kg), the obese animals after weight reduction (n = 3; weight, 17.94±1.02), and nonobese baboons (n = 4; weight, 13.5 ± 0.7 kg; Table 1). Obesity in nonpregnant

Table 1. Description of study baboons

	Nonpregnant			Pregnant		
	Obese (n = 3)	Nonobese (n = 4)	P	Obese (n = 4)	Nonobese (n = 3)	P
Age (y)	11.7 ± 2.7	13.4 ± 1.2	0.480	11.5 ± 3.0[a]	8.9 ± 0.6[a]	0.480
Weight (kg)	18.8 ± 1.5	13.5 ± 1.5	0.034	16.7 ± 1[a]	15.2 ± 1[a]	0.480
Waist circumference (cm)	52.9 ± 5.9	43.5 ± 5.1	0.034	not done	not done	–
Abdominal skinfold thickness (mm)	6.0 ± 1.0	4.2 ± 0.8	0.077	not done	not done	–
Obesity index (Rh) (kg/m^2)[b]	not shown	not shown	–	48.7 ± 2.1[a]	41.9 ± 4.0[a]	0.034
Serum 25-hydroxyvitamin D (ng/mL)	61.4 ± 15.3	83.0 ± 40.8	0.480	49.2 ± 7.6	84.0 ± 30.2	0.077
Daily vitamin D intake (IU)[c]	2836.9 ± 10.3	1661.9 ± 218.6	0.034	not done	not done	–

P values are derived from Wilcoxon–Mann–Whitney analyses of differences between nonobese and obese baboons of the same pregnancy status.
[a]Data obtained from reference 17.
[b]The reproductive health index was documented in 4 baboons but was not included in this table.
[c]Vitamin D intake was estimated according to the number of biscuits eaten.

baboons was defined according to weight, waist circumference, and skinfold thickness; the cut off for baboons to be characterized as obese was a waist circumference of 50 cm.[12] Weight loss was achieved by using individualized reduction of total daily food consumption by 30% over 3 mo, as detailed previously for pregnant baboons.[40] Venous blood was collected as previously described.[41]

In nonpregnant baboons, the number of biscuits eaten during individual feeding sessions was recorded daily and the total weight consumed was calculated.[40] Supplemental vitamin D_3 was added to the diet at 6.6 IU/g, according to the diet manufacturer's recommendation.

Secondary analysis was performed for 6pregnant baboons which were housed in outdoor cages.[20] Three of these animals had direct exposure to sunlight (3585 Lux), whereas the other 3 did not (85.5 Lux).[20] The calculation of the UV light exposure in both groups during pregnancy (duration of pregnancy 175 d of gestation) was performed based on the information provided by the National Oceanic and Atmospheric Administration for daily UV light exposure in the baboons' geographic area. For sunlight-exposed baboons, the average daily erythemally weighted dosage rate during pregnancy was 213.2 ± 33.7 mW_t/m^2 on sunny days and 174.5 ± 28.8 mW_t/m^2 on cloudy days. Sunlight-unexposed baboons received 180.9 ± 27 mW_t/m^2 daily on sunny days and 148.0 ± 22.8 mW_t/m^2 on cloudy days. All 6 of these baboons underwent cesarean sections at 175 d gestational age (0.97 gestation); maternal and umbilical cord plasma were collected, flash frozen in liquid nitrogen, and stored at –80 °C until evaluated for 1,25-dihidroxyvitamin D_3.[20]

Secondary analysis was performed for the data from 4 pregnant, nonobese and 3 pregnant, obese animals, which underwent cesarean section at 165 d of gestation (0.92 gestation);[17] one sample from the published set was unavailable for analysis in the current study. The animals were naturally obese,[8,10,24-26] with obesity defined by using the Obesity index (Rh) (the NHP equivalent of the BMI) as described previously.[17] Ma-ternal serum was collected at the time of cesarean section, flash frozen in liquid nitrogen, and stored at –80 °C until further evaluation.

Measurements of vitamin D metabolites. Serum 1,25-dihydroxyvitamin D_3 levels were measured in duplicate by using a radioimmunoassay kit (catalog no. 026-AA-54F2, ALPCO Diagnostics, Windham, NH). The intraassay coefficient of variation was 0.3% to 3.4%. Serum concentrations of 25-hydroxyvitamin D were measured in duplicate by using an ELISA kit (Immunodiagnostic Systems, Fountain Hills, AZ) according to the manufacturer's instructions; the intra-assay coefficient of variation was less than 7%.

Statistical analyses. Data were analyzed by using the nonparametric Wilcoxon signed-rank test. The association between 2 continuous variables of interest was assessed according to Spearman rank correlation. Data are presented as means ± SEM. Significance was set at P value of less than 0.05; the P values reported were not adjusted for multiplicity. All analyses were conducted using SAS software (version 9.4, Cary, NC).

Results

Nonpregnant baboons. Among nonpregnant baboons, the daily food consumption (and thus calculated vitamin D intake) were lower in nonobese baboons (42.7 ± 5.6 biscuits) than in obese animals (72.9 ± 0.3 biscuits; $P < 0.05$). Serum vitamin D concentration did not differ between obese and nonobese nonpregnant baboons. Food restriction in the obese animals resulted in weight losses of 0.28, 0.96, and 1.36 kg, leading to postrestriction differences in serum vitamin D levels of –9.38, 8.52, and –9.99 ng/mL, respectively, relative to the level before food restriction. Vitamin D concentrations before and after food restriction did not differ statistically.

Pregnant baboons. Plasma concentrations of 1,25-dihydroxyvitamin D_3 did not differ between sunlight-exposed and -unexposed pregnant baboons (325.24 ± 58.57 ng/L compared with 229.82 ± 33.33 ng/L, respectively) or their fetuses (102.35 ± 11.54 ng/L compared with 93.40 ± 3.68 ng/L). In addition, the maternal:fetal ratio of 1,25-dihydroxyvitamin D_3 plasma concentrations did not differ between the 2 groups (sunlight-exposed, 2.2 ± 0.2; sunlight-unexposed, 3.5 ± 0.6).

Serum concentrations of 25-hydroxyvitamin D concentrations were higher (P = 0.077) in pregnant, nonobese baboons than in their obese counterparts. The group sample sizes (pregnant obese, n = 4; pregnant nonobese, n = 3) achieved 80.0% power to reject the null hypothesis of equal means for vitamin D serum concentration when the population mean difference is $\mu1 - \mu2 = 142.4 - 93.2$ ng/mL, with standard deviations of 7.6 ng/mL for pregnant

obese baboons and 30.2 ng/mL for pregnant nonobese animals and a significance (α) level of 0.050 by using a 2-sided 2-sample unequal-variance *t* test. In the pooled data set (combining pregnant and nonpregnant baboons), vitamin D concentrations were significantly negatively rank-correlated with the reproductive health index ($P = 0.01$) and showed a trend toward positive rank-correlation with kidney weight in pregnant animals ($P = 0.11$; Table 2).

Table 2. Association of serum 25-hydroxyvitamin D concentrations with parameters of maternal morphometry

	n	Spearman's ρ	*P*
Reproductive Health index[a]	11	−0.74	0.01
Age[a]	14	−0.35	0.22
Kidney weight[b]	6	0.71	0.11
Fat gain during pregnancy[b]	7	−0.36	0.43
Weight gain during pregnancy[b]	7	−0.21	0.64
Placental weight[b]	7	−0.11	0.82
Weight loss in nonpregnant obese animals[c]	3	−0.50	0.67

[a]Includes both pregnant and nonpregnant baboons with available data
[b]Data obtained from reference 17.
[c]Nonpregnant obese baboons underwent 30% food reduction over 3 mo.

Discussion

In general, data regarding the vitamin D status in baboons are sparse. One of the limitations of the current study, the small population size, is associated with the study design, secondary data analyses. Taking into consideration the uniform social and physical environments, dietary composition, and animals' ages, these data provide information that would require larger numbers in human population studies. In addition, despite the few baboons studied, our dataset represents the largest one in adult *Papio* baboons and the only data set that describes consumed (not provided) vitamin D amounts and corresponding vitamin D serum concentrations[19,35,39,13,52] (Table 3).

For every 100 IU vitamin D ingested daily, the blood level of 25-hydroxyvitamin D increases approximately 1 ng/mL in nonobese humans, whereas the intake needed to achieve this level in obese persons is 2 to 3 times higher.[28,29] Even the almost 2-fold increased D_3 intake by the obese compared with nonobese nonpregnant baboons in our study did not increase serum 25-hydroxyvitamin D concentrations. Therefore, the vitamin D supplementation dosage for obese baboons might need to be increased to 3 times that of their nonobese counterparts, as has been described for humans.[16] In addition, pathophysiologic effects associated with obesity, specifically diabetes and insulin resistance, are highly similar between baboon and humans.[8-10,24-26]

A nearly 5% reduction in the weight of obese nonpregnant baboons did not change their serum vitamin D levels. In humans, data regarding vitamin D concentrations after weight reduction are inconclusive.[3,37] In postmenopausal women, a weight reduction of 5% to 9.9% over 12 mo increased serum 25-hydroxyvitamin D levels by 2.7 ng/mL, but this increase was nonsignificant when compared with the control group.[34] The loss of almost 40 kg of body fat after gastric bypass surgery was associated with an increase of 10 ± 2 ng/mL[2] or no changes in the serum 25-hydroxyvitamin D concentration.[37] The reason for these discrepancies might be related to the degree of obesity, magnitude or duration of the weight loss, diet, D_2 compared with D_3 intake, and sunlight exposure. The level of 25(OH)D depended on dietary D3 compared with D_2 consumption in crab-eating macaques (*Macaca fascicularis*), rhesus monkeys (*M. mulatta*), squirrel monkeys (*Saimiri sciureus*), and owl monkeys (*Aotus vociferans*).[32] Sunlight exposure is the most important factor determining the 25-hydroxyvitamin D levels in humans[1,4,38] and NHP.[21,53] In our study, all baboons, except for sun-light deprived group, were maintained in the same group environment with similar sunlight exposure. Interestingly differences in exposure to sunlight did not influence the concentration of the active form of the vitamin D in our pregnant baboons. This result can be attributed to the role of the placenta in the production of different active forms of vitamin D_3,[46-48] or perhaps even the lower level of sunlight exposure was sufficient to maximize skin D3 production in the baboons. In addition, the differences between D_3 intake and serum concentrations might reflect sequestration in adipose tissue and not the different environmental conditions. Moreover, obesity might blunt UV-dependent vitamin D synthesis in skin. Given the critical role of the vitamin D in the functions of various organs and systems, vitamin D supplementation in baboons should be adjusted according to their BMI (that is, their Obesity index (Rh)), as is recommended by the Endocrine Society for humans.[29]

The finding that serum concentrations of 25-hydroxyvitamin D were lower in pregnant obese than pregnant nonobese baboons agrees with data published for humans, in whom pregnancy itself and high prepregnancy BMI puts women at high risk of vitamin D deficiency.[5,23] Similar to its effect in human pregnancy, obesity is a risk factor for fetal loss in baboons.[42] Obesity profoundly influences fetal and maternal vitamin D metabolism.[5] In addition, the placenta has an active role in the D3 metabolism, which includes both the classic pathway (D3→25-hydroxyvitamin D_3→1,25-dihydroxyvitamin D_3) and a CYP11A1-activated pathway (D_3→20S-hydroxyvitamin D_3→$(OH)_n$-D_3).[45-48] The differences in the vitamin D3 metabolism between obese and nonobese baboons should be considered when interpreting the data from experimental studies involving pregnant animals and determining their dietary supplementation.

The serum 25-hydroxyvitamin D concentration of the nonpregnant baboons in our study is higher to that obtained in D_3-sufficient human subjects (40 to 60 ng/mL)[28] and is within the range reported for *M. mulatta* (from 50 ± 4 ng/mL to 154.8 ± 5.5 ng/mL).[44,55] The D_3 levels among New World primates reportedly are much higher than those of Old World Primates and humans due to organ resistance to D_3 and that this resistant state could be compensated by maintenance of high 1,25-dihydroxyvitamin D levels, for example, 478 ± 108 ng/mL in common marmosets (*Callithrix jacchus*),[44] 48 to 236 ng/mL in cottontop tamarins (*Saguinus oedipus*),[36,54] and 104.8 to 137.1 ng/mL in black-faced marmosets (*C. penicillata*)[53]

In summary, to our knowledge, the current study is the first to address the effect of obesity and pregnancy on vitamin D concentrations in any NHP species. These data underline the importance of adequate vitamin D supplementation in obese animals.

Table 3. Published studies regarding vitamin D status in baboons (*Papio* spp.) and values from selected human studies

	25-hydroxy-vitamin D (g/mL)	1,25-dihydroxy-vitamin D_3 (pg/mL)	*n*	Sex	Age (y)	Daily dietary vitamin D (IU/d)[a]	Feeding mode	Housing characteristics	Location	Reference
Baboons (*P. anubis*)	NR	NR	7	3 male, 4 female	NR	400	Unrestricted	Outdoor, uncontrolled conditions	Trust Research Laboratories, Nairobi, Kenya	19
Baboons (*Papio* spp.)	NR	NR	2	male	3.5	1000	Individual unrestricted	Indoor year-round	Regional Primate Research Center	39
Baboons (*P. ursinus*)	14.07 ± 4.05	NR	28	20 male, 8 female	0.5–1	100 IU/ 100 g diet	NR	Indoor during reported time period	University of the Witwatersrand, Johannesburg, South Africa	35
Baboons (*P. cynocephalus*)	48.1 (36.6–59.6)	66 (55–77)	2	NR	7–21	NR	Group	Indoor year-round	Brookfield Zoo	13
Humans[b]	15–40	15–80	NR	NR	NR	NR	NA	NA	NA	13
Baboons (*Papio* spp.)	35.0 ± 5.127	82.2 ± 14.0	6	male, female	NR	34.9	Group	Some exposure to natural light as well as to indoor lighting	Brookfield Zoo, Fort Worth Zoo, Lincoln Park Zoological Gardens, and North Carolina Zoological Park	52
Humans[b]	24.3 ± 16.9	34.3 ± 18.0	20	male, female	56.6 ± 5.1	NR	NA	NA	Turkey	1
Baboons (*Papio* spp.)	72.2 ± 28.1	NA	7	female, nonpregnant	12.6 ± 1.1	2249.4	Individual unrestricted	Outdoor, partially controlled	Southwest Primate Research Center, San Antonio, Texas	Present study
Baboons (*Papio* spp.)	66.6 ± 18.9	NA	7	female, pregnant	10.2 ± 1.3	NR	Individual unrestricted	Outdoor, partially controlled	Southwest Primate Research Center, San Antonio, Texas	Present study
Baboons (*Papio* spp.)	NA	277 ± 0.04	6	female, pregnant	9.5 ± 1.0	NR	Group unrestricted	Outdoor, partially controlled[c]	Southwest Primate Research Center, San Antonio, Texas	Present study

NA, not applicable; NR, not reported.
[a]The amount provided but not necessarily consumed.
[b]Data from a human study performed during the same time period as the NHP studies in the preceding row(s).
[c]Combined average daily erythemally weighted dosage rate during pregnancy for baboons exposed to and deprived of sunlight: 179.15 ± 28.25 mW_t/m^2.

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