

# Desquamative Inflammatory Vaginitis as a Manifestation of Vitamin D Deficiency Associated With Crohn Disease: Case Reports and Review of the Literature

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*Desquamative inflammatory vaginitis (DIV) is a chronic disorder associated with yellow vaginal discharge, vulvovaginal burning and pruritus, and dyspareunia. The cause of DIV is unknown; however, infectious, hormonal, and inflammatory etiologies have been proposed. In this series, we observe the association of DIV and vitamin D deficiency by reporting 4 cases of women with DIV and vitamin D deficiency associated with Crohn disease. We further show that the DIV symptoms resolve when the circulating concentrations of 25-hydroxyvitamin D (25-HD) returned to normal. These data provide further support for the notion that DIV can be associated with vitamin D deficiency and DIV symptoms reflect altered vaginal mucous membrane function.*

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**D**esquamative inflammatory vaginitis (DIV) is a chronic disorder associated with yellow vaginal discharge, vulvovaginal burning and pruritus, and dyspareunia.<sup>1-7</sup> Patients also describe a pungent odor associated with the discharge; however, the DIV odor appears to be distinct from the fishy odor of bacterial vaginosis. Physical examination of the vulva has subtle but distinctive

findings including marked erythema of both labia minora, extending from the introitus to the labia majora.<sup>1-7</sup> There can be copious amounts of yellow discharge draining from the vagina as well as a yellow secretion sticking to the external surface of the labia minora as they approximate the labia majora. Wet mount examination of the discharge is remarkable for vaginal epithelial cells and inflammatory cells.<sup>1-7</sup> Culture of the discharge frequently demonstrates the presence of group B streptococci, though DIV does not appear to be a transmissible disease. Treatments have included corticosteroids, antibiotics such as clindamycin phosphate and cephalexin, and estradiol,<sup>1-7</sup> though our experience has suggested that the response to these agents is limited and transient.

The cause of DIV is unknown.<sup>1-7</sup> It is thought that infectious, hormonal, and inflammatory processes play a role in producing the symptoms; however, it is unclear why these symptoms occur. We previously described a case of DIV associated with vitamin D deficiency; DIV symptoms resolved when the vitamin D level was within reference range. In this case, the cause of vitamin D deficiency appeared to be pregnancy and lactation.<sup>8</sup>

As we follow large numbers of women with recalcitrant vulvovaginal problems, we retrospectively reexamined our patients with DIV to determine if the common causes of vitamin D deficiency were represented in this referral population. We identified 4 premenopausal women with DIV, Crohn disease, and vitamin D problems. Of interest, the response of the vulvovaginal symptoms to vitamin D appeared to correlate with the severity of the underlying malabsorption. However, each patient's symptoms responded to

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vitamin D, which required that the circulating 25-hydroxyvitamin D (25-HD) level reach 50 ng/mL for a period of 12 weeks.<sup>9</sup>

### Case Reports

*Patient 1*—A 30-year-old premenopausal woman was referred in March 2002 for evaluation of vulvovaginal discharge, burning, itching, and dyspareunia of 5 years' duration. She had been diagnosed with Crohn disease in 1988 and her bowel disease had been complicated by diarrhea, abscess formation, and perianal fistulas. She had had 2 ileal resections; her last Crohn relapse was in 1995. At the time of evaluation, she reported diarrhea with 3 to 12 bowel movements daily. The mechanism of the diarrhea was thought to be malabsorption associated with the ileal resections, not active Crohn disease. At the initial visit, vulvovaginal examination was remarkable for marked erythema of the labia minora, extending from the introitus bilaterally to the inner surface of the haired area of the labia majora. A thick yellow mucus was adherent to the outer surface of the labia minora and there was a more watery yellow-green discharge flowing from the vaginal opening. Culture of this discharge demonstrated a few group B streptococci and the absence of pathogenic yeast (Table). Initial treatment included clindamycin phosphate vaginal ovules 100 mg daily for 21 days as well as oral fluconazole 100 mg daily to prevent yeast infection from the clindamycin. Follow-up demonstrated an improvement in the itching and discharge but continued reports of vaginal dryness, burning, and dyspareunia. Over the next 6 months, intermittent use of vaginal estradiol, clindamycin, and boric acid improved some but not all symptoms. Because of the history of Crohn disease, we wondered if there was a nutritional cause. Laboratory data revealed circulating concentrations of 25-HD to be deficient at 12 ng/mL and an intact parathyroid hormone (PTH) level was elevated at 88.4 pg/mL. By contrast, serum calcium and serum phosphorus levels were within reference range at 9.4 mg/dL and 3.3 mg/dL, respectively. (Reference ranges are provided in the Table.) We then treated her vitamin D deficiency with secondary hyperparathyroidism with calcium carbonate (1500 mg daily) and ergocalciferol (150,000 IU weekly) with a goal of increasing the circulating 25-HD levels to 50 ng/mL or greater, while keeping the levels of serum calcium and serum phosphorus within reference range.<sup>8</sup> Over 12 months, her vulvovaginal symptoms decreased to the point where sexual intercourse became possible and her vaginal cultures demonstrated an absence of group B

streptococci and an abundance of normal genital flora. In June 2005, the patient was seen for follow-up and reported having sexual intercourse 3 times weekly with no discomfort. Physical examination at this time revealed mild vulvar erythema with scanty vaginal discharge, showing no group B streptococci. Laboratory data revealed circulating 25-HD levels of 58 ng/mL, intact PTH of 52.4 pg/mL, serum calcium of 9.8 mg/dL, and serum phosphorus of 3.2 mg/dL. The long-term goal with this patient is to maintain her 25-HD levels within reference range but at a minimum concentration of 50 ng/mL. Because of her ileal resections and her tendency toward limited calcium and vitamin D absorption, her daily requirements for calcium carbonate and vitamin D are more than the average woman. At this time, she takes 2000 mg of calcium carbonate and 50,000 IU daily cholecalciferol to maintain the circulating levels of 25-HD described above. Of interest, during a recent pregnancy, the patient decreased her daily amounts of calcium carbonate and vitamin D at the request of her obstetrician. All vaginal symptoms returned when her circulating concentration of 25-HD reached 34 ng/mL. After delivery, the patient increased her daily intake of calcium carbonate and vitamin D to prior dosages and her symptoms resolved yet again. Her circulating level of 25-HD at this time was 58 ng/mL.

*Patient 2*—A 29-year-old premenopausal woman presented in December 2004 with vaginal discharge and vulvovaginal pruritus, burning, and dyspareunia of 5 months' duration. The discharge was yellow to green in color and had an odor. The patient had a 16-year history of Crohn disease, including 3 episodes of fistula formation with abscess requiring surgical intervention. She also reported an episode of erythema nodosum in response to 6-mercaptopurine. At the time of presentation, the Crohn disease was quiescent and she was not taking medications. Of interest, the patient gave a recent history of a normal pregnancy followed by 18 months of lactation. When the vaginal discharge developed, her gastroenterologist empirically placed her on oral levofloxacin and metronidazole; however, there was no change in the vaginal complaints. Abdominal computed tomography and colonoscopy failed to demonstrate any fistulous tracts, so the medication was stopped and she was referred for evaluation. Initial physical examination of the vulva revealed generalized erythema associated with greenish yellow vaginal discharge. Culture of this discharge demonstrated group B streptococci and the absence of pathogenic yeast (Table). The patient was empirically started

## Initial Laboratory Findings

Patient No.	Laboratory Values <sup>a</sup>				
	25-HD	PTH	Calcium	Phosphorus	Culture
1	pre, 12 ng/mL	88.4 pg/mL	9.4 mg/dL	3.3 mg/dL	Group B streptococci; negative for yeast
	post, 58 ng/mL				
2	pre, 38 ng/mL	51.8 pg/mL	9.0 mg/dL	3.6 mg/dL	Group B streptococci; negative for yeast
	post, 60 ng/mL				
3	pre, 33 ng/mL	50 pg/mL	9.2 mg/dL	3.8 mg/dL	Group B streptococci; negative for yeast
	post, 89 ng/mL				
4	pre, 16 ng/mL	43.1 pg/mL	9.0 mg/dL	3.1 mg/dL	Group B streptococci; negative for yeast
	post, 92 ng/mL				

Abbreviations: 25-HD, 25-hydroxyvitamin D; PTH, parathyroid hormone; pre, pretreatment levels of 25-hydroxyvitamin D, patient with symptoms; post, posttreatment levels of 25-hydroxyvitamin D, patient symptom free.

<sup>a</sup>Reference ranges: 25-HD, 32–100 ng/mL; PTH, 10–65 pg/mL; serum calcium, 8.5–10.4 mg/dL; serum phosphorus, 2.5–4.5 mg/dL.

on oral gatifloxacin 400 mg daily. Laboratory data revealed a circulating concentration of 25-HD of 38 ng/mL with an intact PTH level of 51.8 pg/mL. By contrast, serum calcium and serum phosphorus levels were within reference range at 9.0 mg/dL and 3.6 mg/dL, respectively. When the patient returned for follow-up, her symptoms had not improved on the second course of antibiotics and her culture still showed group B streptococci. We started her on clindamycin phosphate vaginal ovules 100 mg 3 times weekly, alternating with estradiol vaginal tablets 25 µg twice weekly. We also started vitamin D<sub>2</sub> (ergocalciferol) 50,000 IU once weekly and calcium citrate 630 mg daily. When the patient returned for follow-up 14 days later, the pruritus, burning, and discharge had significantly improved, but she reported cracks in the vulvar skin. Her vaginal culture demonstrated no group B streptococci. On physical examination, she had

fissures bilaterally between the labia minora and labia majora. We continued the treatment regimen, and when she returned 4 weeks later, she was symptom free. We then stopped the ergocalciferol and reexamined the circulating 25-HD levels. While awaiting the results of the blood tests, the patient called and stated that the symptoms had returned but were not as troublesome as when she was initially seen. Of interest, the 25-HD level was 40 ng/mL. We restarted the ergocalciferol at a dosage of 50,000 IU twice weekly for 10 weeks and she became symptom free. She is currently free of vaginal symptoms on calcium carbonate 1000 mg daily and cholecalciferol 4000 IU daily. Her most recent circulating 25-HD level was 60 ng/mL.

*Patient 3*—A 30-year-old premenopausal woman presented in November 2004 for evaluation of vaginal discharge associated with burning and dyspareunia of 2 months' duration. She had an

etonogestrel–ethinyl estradiol vaginal ring. She also was taking mesalamine for Crohn disease, which was diagnosed in 1997. Although she was on medication, she described the Crohn disease as quiescent but did report frequent loose bowel movements. Moreover, colonoscopy and biopsy demonstrated inflammatory changes suggestive of cryptitis; she had numerous colonoscopies in the past. Physical examination of the vulva revealed marked erythema and edema with yellow discharge. Because of an irritant effect of the foreign body on the vaginal mucous membrane, we suggested that she remove the contraceptive ring. Culture of the discharge demonstrated group B streptococci and the absence of pathogenic yeast (Table). Because of her Crohn disease, she was reluctant to use any antibiotics, especially clindamycin. Laboratory data revealed a circulating 25-HD level of 33 ng/mL with an intact PTH of 50 pg/mL. By contrast, the serum calcium and serum phosphorus levels were within reference range at 9.2 mg/dL and 3.8 mg/dL, respectively. Despite the laboratory data, the patient was reluctant to use high doses of vitamin D; she started on calcium citrate 1230 mg daily and cholecalciferol 800 IU daily. There was no improvement in symptoms and the culture remained positive for group B streptococci. We then added ergocalciferol 50,000 IU weekly and estradiol vaginal tablets 25 µg 3 times weekly. Her symptoms worsened; we started the patient on clindamycin phosphate vaginal ovules 100 mg 3 times weekly, alternating with the estradiol vaginal tablets 25 µg. Again the symptoms worsened; we stopped all vaginal therapy but maintained the goal of increasing the circulating concentration of 25-HD to 50 ng/mL. After approximately 4 months of therapy with calcium citrate and vitamin D, the symptoms began to improve with a decrease in the discharge and burning; however, her vaginal culture remained positive for group B streptococci. Moreover, while the discharge improved, the dyspareunia did not improve. Laboratory data at this time revealed little change in the circulating 25-HD level (32 ng/mL) but a slight decrease in the intact PTH at 42.5 pg/mL. Serum calcium and serum phosphorus levels remained within reference range at 8.8 mg/dL and 2.8 mg/dL, respectively. Convinced that a more aggressive approach to the vitamin D status was needed, we started the patient on ergocalciferol 50,000 IU 3 times weekly in addition to calcium citrate 1260 mg daily. When seen 4 weeks later, the discharge was gone and the dyspareunia had significantly improved. We then discontinued the calcium citrate and placed the patient on calcium carbonate 1000 mg daily

with cholecalciferol 4000 IU. By August 2005, the patient was asymptomatic on this treatment regimen. Of interest, her culture remained positive for group B streptococci, while the circulating 25-HD level was 89 ng/mL.

*Patient 4*—A 30-year-old premenopausal woman presented for evaluation of vaginal discharge associated with odor and dyspareunia of 8 months' duration. She denied the use of any oral or vaginal contraceptives but did report a history of Crohn disease. While her bowel disease was asymptomatic at the initial visit (November 2004), she did give a history of treatment with infliximab and described 4 bowel movements daily. Physical examination of the vulva revealed erythema and yellow discharge. Cultures demonstrated group B streptococci and the absence of pathogenic yeast (Table). Laboratory data revealed a circulating concentration of 25-HD of 16 ng/mL with an intact PTH of 43.1 pg/mL. By contrast, her serum calcium and serum phosphorus levels were within reference range at 9.0 mg/dL and 3.1 mg/dL, respectively. We chose not to use antibiotics as an initial treatment; the patient was started on a vitamin D and calcium supplementation program of ergocalciferol 50,000 IU 3 times weekly and calcium citrate 1260 mg daily. She returned for follow-up 6 weeks later and reported that she was totally free of discharge. Repeat vaginal culture failed to demonstrate group B streptococci and sexual activity was free of discomfort. Repeat blood work demonstrated a circulating 25-HD level of 92 ng/mL. Ergocalciferol was stopped and she was maintained on calcium citrate 1260 mg daily and cholecalciferol 800 IU daily. She is currently free of symptoms.

### Comment

We describe 4 women with Crohn disease and DIV associated with vitamin D deficiency. Moreover, we demonstrate complete resolution of DIV symptoms when the vitamin D levels were within reference range. These data extend our prior observations<sup>8</sup> on the association of vitamin D deficiency with DIV by showing that DIV occurs in individuals with malabsorption and vitamin D deficiency, that is individuals with inflammatory bowel disease of the Crohn disease type. These data support the notion that vitamin D plays a role in the normal physiologic function of the vaginal mucous membrane and chronic vitamin D deficiency can lead to chronic vaginal symptoms. The protracted illnesses in the first 3 patients demonstrate that the management of DIV has been difficult, primarily because the cause was not known, which

contrasts with patient 4 who experienced resolution that was more efficient as our understanding of how much vitamin D was necessary to reverse the symptoms became more clear. That said, it still takes an extended period of time for DIV symptoms to abate as the vitamin D levels return to within reference range. Although patient 2 (initial circulating 25-HD level, 38 ng/mL) and patient 3 (initial circulating 25-HD level, 33 ng/mL) may not classically be considered vitamin D deficient using a reference range of 32 to 100 ng/mL, it is important to note that this range primarily has been derived by the use of bone parameters.<sup>10</sup> It is not yet completely understood if vaginal mucous membrane requires higher circulating levels of vitamin D than bone to maintain normal function. When we began these clinical studies in 2003, the reference range used by many clinical laboratories was 9 to 54 ng/mL. Thus, what constitutes a reference circulating 25-HD level might be considered a work in progress, with the current range at 32 to 100 ng/mL.

Desquamative inflammatory vaginitis was first described in 1956<sup>1</sup> in a 50-year-old woman who reported copious amounts of vaginal discharge that on wet mount examination demonstrated many leukocytes and few epithelial cells. Gram stain also demonstrated leukocytes with gram-positive cocci and rods. Complete blood cell count showed eosinophilia and a vaginal biopsy showed loss of the vaginal surface epithelium with diffuse inflammation. Because of the inflammatory changes and the peripheral eosinophilia, an allergic etiology was suggested and the patient's symptoms slowly responded to topical hydrocortisone.<sup>1</sup> In 1968, Gardner<sup>3</sup> suggested that DIV shared many features with atrophic vaginitis in that the vaginal walls appeared thin and reddened, vaginal acidity was diminished, and normal lactobacilli were absent, yet these findings occurred in women during their menstrual life, suggesting that factors other than estradiol were necessary to maintain the normal functional integrity of the vaginal mucous membrane. He also suggested that DIV was not caused by a dietary deficiency, though he did report specific deficiencies that were examined. Of his therapies, topical hydrocortisone worked the best, with estrogens and antibiotics having limited results.<sup>3</sup>

A dermatologic perspective was provided for DIV in the 1980s<sup>11-15</sup> when it was shown that at least a subpopulation of individuals with DIV had oral lichen planus, leading to the suggestion that DIV and lichen planus were the same mucous membrane disorder. A single case of DIV in a 32-year-old woman appeared to be due to linear

IgA disease.<sup>16</sup> In our small series, none of our patients had oral mucous membrane symptoms; therefore, they are classic cases of DIV. Of interest, patient 3 had marked improvement in bowel function and dramatic resolution of her colonic cryptitis while taking vitamin D. While not described in detail here, we also have noted vitamin D deficiency associated with vulvar lichen planus, but it appears to manifest primarily in our menopausal population, similar to the report by Edwards and Freidrich<sup>14</sup> in which 3 of 5 patients were menopausal and 1 was perimenopausal. Moreover, we agree with the interpretation that DIV and mucous membrane lichen planus are related problems, but we now extend this hypothesis by suggesting that the underlying mucous membrane problem may reflect vitamin D deficiency. Moreover, we suggest that menopausal lichen planus is differentiated from premenopausal DIV by the presence of an estrogenic effect on the vaginal mucous membrane. In the presence of normal circulating levels of estradiol, there is a profound stimulus to regenerate and thicken the vaginal epithelium. In the absence of sufficient levels of vitamin D, the vaginal epithelial cells are shed, leading to the copious amounts of discharge that characterize DIV. By contrast, in the absence of the estradiol stimulus, as in menopause, there is much less discharge and more erosion, as seen in vulvovaginal lichen planus.

The largest and most comprehensive analysis of women with DIV appeared in 1994<sup>5</sup> and offered an infectious disease perspective on the problem. In a retrospective manner, Sobel<sup>5</sup> reviewed his experience with 51 cases of DIV seen in a referral university vaginitis clinic and noted that the majority of these women were similar to those reported by Scheffey et al<sup>1</sup> and Gardner,<sup>3</sup> with the major DIV symptom being discharge associated with burning, itching, and dyspareunia. The microscopic and microbiologic findings also were similar to the classic DIV findings, with many leukocytes and parabasal cells in the discharge and vaginal cultures demonstrating many gram-positive cocci, usually group B streptococci. He further demonstrated that his patients responded to clindamycin phosphate vaginal cream 2%, providing support for the notion that DIV possibly represented an infectious process. Finally, he argued against the contention that DIV represented lichen planus because in his patient population the individuals did not have oral or cutaneous lesions.<sup>5</sup> Further studies from this group nicely demonstrated an association of DIV with fertility surgeries, hormone usage, and other genitourinary conditions.<sup>7</sup> Neither an organism that causes DIV nor an

underlying cause of the vaginitis have been identified. While our 4 patients are similar to those reported by Sobel,<sup>5</sup> we could not demonstrate a consistent response to antibiotics, including vaginal clindamycin, even when used for weeks at a time. Thus, it was particularly satisfying to demonstrate a vitamin D–deficient state in patient 4, in association with DIV and vaginal group B streptococci, and reverse the process with vitamin D, without the use of antibiotics.

Based on these cases of DIV as well as the prior case report,<sup>8</sup> we suggest that vitamin D is necessary to maintain the normal integrity and barrier function of the vaginal mucous membrane. Circulating 25-HD levels less than 50 ng/mL, as shown in these women, lead to loss of the barrier function of the wall with subsequent secondary inflammation and infection. As demonstrated in our patients, the barrier function returns to normal when circulating 25-HD levels return to within reference range, which leads to resolution of the DIV symptoms. Therefore, by identifying the cause of DIV in these 5 patients, we developed a treatment plan that reversed the underlying problem—the vitamin D deficiency—which is not a new concept. In 1951,<sup>17</sup> vitamin D was shown to influence the cellular constituents of vaginal epithelium in 27 women at the time of menopause in a manner similar to estradiol, even in the absence of functioning ovaries.

Reversing the DIV symptoms in our series required much trial and error, particularly with our initial 3 patients, and contrasts with the observations of Sobel<sup>5</sup> who suggested that clindamycin and hormone replacement are sufficient for symptom resolution. The management of patients with DIV can be extremely difficult. However, we believe that some of the difficulty occurred as we sought to answer a fundamentally important question: What is the circulating 25-HD level necessary to normalize vaginal epithelium and therefore reverse the DIV symptoms?<sup>10</sup> In patient 1, symptoms improved when her levels reached the current lower limit of the reference range (25-HD, 32 ng/mL), but she still reported dyspareunia. We then sought a higher target vitamin D level that ultimately was shown in patient 1 and subsequently in the other patients to be approximately 50 ng/mL. We cannot determine if our clinical observations reflect the idea that a higher than normal level of vitamin D is necessary to maintain normal vaginal barrier function or if this disease requires pharmacologic doses of vitamin D to reverse the process. However, the vitamin D–deficient status of patient 1 suggested to us that vitamin D deficiency may be the origin of DIV.

The understanding of normal vitamin D levels primarily has been driven by the needs of the skeleton. Using a variety of nonskeletal biomarkers, vitamin D deficiency has been defined as circulating 25-HD levels less than 32 ng/mL.<sup>10</sup> In our DIV group, however, sustained improvement occurred only when levels of 50 ng/mL were achieved and maintained for a minimum of 12 weeks. This time frame is in agreement with studies demonstrating that a steady state level of vitamin D and calcium can be achieved in 90 days, independent of the daily dose of vitamin D.<sup>9</sup> As with any tendency to a deficient state and to avoid the development of vitamin D toxicity, the patients are closely monitored with serial measurements of 25-HD, intact PTH, serum calcium, serum phosphorus, and 24-hour urine calcium collections. When there is an alteration of the normal absorbing surfaces of the small bowel, as shown in patient 1, the daily requirement for vitamin D increases to as much as 5 times the daily recommended amount of vitamin D. The overall goal in each patient is to maintain circulating 25-HD levels of 50 to 100 ng/mL, which is known to be safe,<sup>10</sup> using cholecalciferol and calcium carbonate. In our patients, we have not noted hypercalcemia, kidney stone formation, or vitamin D toxicity to date. While we initially used ergocalciferol (vitamin D<sub>2</sub>) in these patients, we currently believe that cholecalciferol (vitamin D<sub>3</sub>) should be the agent of choice, as vitamin D<sub>2</sub> substantially upregulates the catabolism of both forms of the vitamin, decreasing the effective potency of coadministered vitamin D<sub>3</sub>.<sup>18,19</sup> Our current initial treatment plan for our patients with DIV, depending on the underlying cause of the vitamin D deficiency, is vitamin D<sub>3</sub> 50,000 IU 3 times weekly for 4 weeks with calcium carbonate 1200 mg daily. At this time, we repeat the blood work to determine a maintenance dose that keeps the circulating 25-HD level at 50 ng/mL or higher.

What role might vitamin D play in the normal vaginal mucous membrane? Vitamin D is a hormone capable of activating transcription events by binding to a nuclear receptor, the vitamin D receptor (VDR), and regulating the expression of downstream target genes.<sup>20</sup> To date, most of our knowledge about vitamin D relates to its role in bone disease, as vitamin D deficiency manifests as rickets in children and osteomalacia in adults. A study of rat vaginal epithelium, however, demonstrated positive staining for the VDR protein in the basal and suprabasal layers of the vaginal epithelium after treatment with estrogen.<sup>21</sup>

By contrast, ovariectomized rats failed to exhibit positive VDR staining. These authors interpreted their data to suggest that vitamin D and its receptor play a role in the proliferation and differentiation of vaginal squamous epithelium, similar to estrogen.<sup>21</sup> Our observations provide a clinical frame of reference for their observations. Furthermore, we would suggest both estradiol and vitamin D are necessary to maintain the structural integrity of the vaginal mucous membrane, and decreased circulating levels of either hormone can lead to disease states that are similar but not identical. Estrogen deficiency leads to the symptoms of atrophic vaginitis, while vitamin D deficiency leads to DIV, which, as described by Gardner,<sup>3</sup> mimics certain aspects of atrophic vaginitis but is found in menstruating women with normal cyclic levels of estradiol.

As vitamin D and its receptor activate transcription, it will ultimately be important to determine what genes are regulated by vitamin D in the vaginal epithelium whose loss of function could lead to the altered barrier function of the vagina, as seen in DIV. Altered barrier function is seen in individuals with certain blistering diseases associated with mutant keratin genes. Thus, the vaginal keratins are reasonable vitamin D transcription targets. The vaginal epithelium expresses a variety of keratins (K5 and K14, K4 and K13, K1 and K10) as well as unique pairings of keratins depending on the hormonal status of the individual.<sup>22-25</sup> It remains to be determined if any of these keratins are regulated by vitamin D in vaginal epithelium and if it is an area of active research.

## Conclusion

We describe in detail the association of DIV and vitamin D deficiency associated with Crohn disease and further demonstrate resolution of the symptoms when vitamin D deficiency is reversed; however, the vitamin D level must be maintained at levels greater than 50 ng/mL for a minimum of 12 weeks. This response has been consistently demonstrated in the absence of any symptoms or signs of vitamin D toxicity. We suggest that vitamin D, a known transcription regulator, alters the expression of structural proteins that are necessary for normal vaginal mucous membrane function, and when vitamin D levels decrease, the barrier function of the vagina is altered. These data support the contention that DIV represents a disorder of altered vaginal mucous membrane function and that infection and inflammation are secondary processes.

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