A randomized clinical trial of vitamin D₃ (cholecalciferol) in ulcerative colitis patients with hypovitaminosis D₃

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Aim: To prospectively evaluate the effects of vitamin D₃ on disease activity and quality of life in ulcerative colitis (UC) patients with hypovitaminosis D. **Methods:** The study was a prospective double-blinded, randomized trial conducted at Community Regional Medical Center, Fresno, CA from 2012 - 2013. Patients with UC and a serum 25(OH)D level <30ng/ml were eligible for the study. Enrolled subjects were randomized to receive either 2,000 IU or 4,000 IU of oral vitamin D₃ daily for a total of 90 days. The Short IBD Questionnaire (SIBDQ) for quality of life, the Partial Mayo Score for UC disease activity and serum lab tests were compared between the two treatment groups. Matched pair t-tests were computed to assess differences between the vitamin D levels, CRP, UC disease activity and SIBDQ scores before and after vitamin D₃ therapy using SPSS version 21. **Results:** Eight UC patients received 2,000 IU/daily and ten UC patients received 4,000 IU/ daily of vitamin D₃ for 90 days. Vitamin D levels increased after 90 days of oral vitamin D₃ in both dose groups. However, the increase in vitamin D levels after 90 days of oral vitamin D₃, in the 4,000 IU group was significantly higher 16.80 ± 9.15 (p<0.001) compared to the 2,000 IU group of vitamin D 5.00 ± 3.12 (p=0.008). Normal vitamin D levels (> 30 ng/dl) were achieved in four out of the ten UC patients (40%) in the 4,000 IU group and in one out of the eight UC patients (12%) in the 2,000 IU group. In the group receiving 4,000 IU/day of vitamin D₃ the increase in quality life scores (SIBDQ) was significant 1.0 ± 1.0 (p=0.017) but not in the 2,000 IU vitamin D₃ group 0.1 ± 1.0 (p=0.87). In the 2,000 IU of vitamin D₃ group the mean decrease in the Partial Mayo UC Score was -0.5 ± 1.5 (p= 0.38) compared to -1.3 ± 2.9 (p= 0.19) in the 4,000 IU vitamin D₃ group but this was not statistically significant. CRP levels decreased after 90 days of daily vitamin D₃ in both the 2,000 IU group and 4,000 IU group by -3.0 ± 9.4 (p=0.4) and -10.8 ± 35.0 (p=0.36) respectively. **Conclusion:** Vitamin D₃ may improve the quality of life and decrease disease activity in UC patients with hypovitaminosis D.

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49 **IRB statement:**

50 The Community Medical Centers Institutional Review Board granted approval to carry out this

51 study within its facilities. (IRB Number 2012043)

52

53 **Clinical trial registration statement:**

54 The study is registered at www.clinicaltrial.gov. The registration identification number is NCT

55 01877577.

56

57 **Informed consent:**

58 Before enrollment in the study, all study participants signed a written voluntary informed consent

59 document approved by the IRB.

60

61 **Conflict of Interest:**

62 All the authors of the study have no conflicts of interest to declare.

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Introduction:

Ulcerative colitis (UC) is an idiopathic, chronic, immune mediated disease that affects the gastrointestinal tract. It results from an exaggerated host immune response to luminal antigens or intestinal microflora in the gastrointestinal tract causing inflammation and has a relapsing and remitting course.[1, 2] What triggers this exaggerated immune response is not clearly understood and is thought to be due to a complex interplay of genetic, environmental, immune and microbial factors.[3] The concordance estimates of UC between twins is 20% or less, suggesting non-genetic factors also play a significant role in the pathogenesis of UC.[4] There is an increasing emphasis in identifying both the intestinal microbiome and external environment factors which may play a major role in the pathogenesis of inflammatory bowel disease (IBD). Some environmental factors that have been associated with IBD include cigarette smoking, oral contraceptive use, vitamin D levels, dietary factors, stress, non-steroidal anti-inflammatory drugs, physical activity and duration of sleep.[2] Vitamin D is increasingly being identified as an important environmental factor influencing many chronic disease including cancers, cardiovascular disease, and autoimmune diseases such as multiple sclerosis and IBD.[5]

Vitamin D is a fat soluable vitamin and its role in maintaining and promoting bone health by increasing intestinal absorption of calcium is well known. However, the role of vitamin D as an immunomodulator is now being increasingly recognized. The first evidence of vitamin D as an immune regulator came in 1983[6,7] with the discovery of vitamin D receptors (VDR) on immune cells- peripheral monocytes, leukocytes and antigen presenting cells- macrophages, dendritic cells and CD_4 and CD_8 T cells.[8] Vitamin D can down regulate the inflammatory cascade by decreasing the proliferation of T cells (Th1), inhibiting cytokine production of IL-2 and INF-V and inducing proliferation of regulatory T cells.[9] 1,25 $(OH)_2D_3$ also inhibits differentiation of peripheral blood monocytes into dendritic cells.[1] The prevalence of vitamin D deficiency in UC patients ranges from 45-60%.[10] Animal experiments, epidemiologic and genetic studies have suggested that vitamin D levels may influence IBD. Murine experiments with IL-10 knockout mice that are genetically predisposed to IBD, who are either deficient in vitamin D receptors (VDR) or were fed diets low in vitamin D, developed a fulminant and lethal enterocolitis within 6-8 weeks.[8] VDR plays an important role in maintaining the integrity of the epithelial barrier which has been shown in animal experiments.[11] An arrest in IBD progression and symptom resolution in IL-10 knockout mice when supplemented with oral vitamin D suggest

101 that vitamin D may affect disease progression in IBD.[12] Furthermore, epidemiology studies also

102 suggest a link between vitamin D and IBD with observations of greater prevalence of IBD at

103 higher latitudes,[13] low vitamin D levels seen in newly diagnosed UC patients in winter,[14] and

104 peak UC flares occurring in December. These observations suggest that vitamin D may account

105 for the "north - south gradient" seen in the incidence of IBD.[1, 15, 16] Further genetic studies also

106 have also shown an association between single nucleotide polymorphisms in VDRs and the

107 development of IBD.[17-20]

108   Large population studies including the prospective Nurses Health Study have shown that

109 increased vitamin D intake was associated with a reduced incidence of IBD.[21] In a cross-

110 sectional study of UC patients, vitamin D deficiency was independently associated with higher

111 disease activity scores and increased steroid use than patients with sufficient vitamin D levels. [22]

112 Despite the evidence suggesting an association between vitamin D and IBD, there have been no

113 prospective human studies looking at the effects of vitamin D_3 in patients with ulcerative colitis.

114 The appropriate dose of vitamin D_3 in the management of IBD and hypovitaminosis D (vitamin

115 D levels <30 ng/ml) is also not well understood. The purpose of this pilot study was to examine

116 prospectively the effects of two different doses of vitamin D_3 on vitamin D levels, disease

117 activity, and quality of life in UC patients with hypovitaminosis D.

118

119 **Methods:**

120   The Community Medical Centers Institutional Review Board granted approval to carry

121 out this study within its facilities. (IRB number 2012043) The study was a prospective double-

122 blinded, randomized pilot trial conducted at Community Regional Medical Center (CRMC) in

123 Fresno, California from June 2012- July 2013. Patients with ulcerative colitis and serum 25(OH)

124 vitamin D levels less than 30 ng/ml within a year of enrollment, were eligible for participation in

125 the study. Exclusion criteria included age less than eighteen years, pregnant females and patients

126 on vitamin D supplementation > 2,000 IU/day. All study participants signed a written voluntary

127 informed consent document approved by the IRB prior to their enrollment in the study.

128   Ulcerative colitis patients at CRMC are routinely screened for vitamin D deficiency by

129 checking serum 25(OH) vitamin D levels. Interested and eligible patients were referred by their

130 providers to the research coordinator and co-investigators of the study for possible enrollment

131 and were confirmed to meet eligibility criteria. Participants were required to come for two study

132   visits - first at the time of enrollment and next at the end of the ninety-day study period. During

133   the initial visit each participant completed a data collection form including information

134   regarding: age, sex, medical history, duration and location of UC, smoking history, current

135   medications, sun exposure, and last corticosteroid use. At both study visits, participants

136   completed two questionnaires together with the investigators and had serum blood drawn for

137   laboratory studies. The two questionnaires included the Partial Mayo Score (PMS) to determine

138   UC disease activity and the short IBD quality of life questionnaire score (SIBDQ) to measure

139   quality of life in UC patients. The validated Partial Mayo Score for UC disease activity includes

140   sub-scores ranging from 0-3 in the following categories: stool frequency, rectal bleeding, and

141   physician's global assessment of well-being.[23] The Partial Mayo Score is the sum of these three

142   sub-scores and ranges from zero which is normal and up to nine for severe disease. The validated

143   ten item SIBDQ includes questions based on bowel, systemic, emotional and social domains

144   with each question score ranging from 1-7. The total SIBDQ score is calculated by adding the

145   total points of the ten items and then dividing it by ten with one being the lowest quality of life

146   and seven being the highest quality of life. [24] Serum blood draws for laboratory studies were

147   completed at both study visits and included: a complete blood count (CBC) with differential,

148   liver function tests, renal function test, serum phosphorous, serum calcium, serum parathyroid

149   hormone (PTH), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and 25(OH)

150   vitamin D.

151   Each study participant was randomized to receive 2,000 IU/daily or 4,000 IU/daily of

152   vitamin D_3 for ninety days. (Figure 1) The ninety day supply of vitamin D_3 for each subject was

153   relabeled and packaged so that both the subjects and the investigators were blinded throughout

154   the study. The packages were distributed by block-randomization among the study participants

155   as they enrolled into the study and a record was kept by a randomization list. The sealed

156   envelope with the randomization list was never opened by the investigators to unmask blinding

157   until study completion. Medication compliance was evaluated through patient interview and by

158   counting the number of pills left at the final visit. Adverse events of vitamin D were monitored

159   for and participants were asked about any possible side effects associated with vitamin D toxicity

160   during the study visits and with a follow up phone call at day forty-five.

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163   Statistical Methods:

164   Funding limited the sample size and enrollment of this pilot study to twenty subjects.

165   Partial Mayo Score for UC disease activity, SIBDQ score and serum lab values for 25(OH)

166   vitamin D and CRP before and after ninety days of vitamin D_3 treatment were compared and

167   analyzed between the 2,000 IU and 4,000 IU groups at the end of the study. The correlation

168   between change in 25(OH) vitamin D levels and change in disease activity and quality of life

169   scores were also compared across all study subjects using Pearson correlation coefficient. All

170   tests were two-sided with a p value of $p < 0.05$ considered as statistically significant. Continuous

171   variables were compared using student T-test and categorical variables were compared using

172   Fisher's exact test. The data was analyzed using SPSS.

173

174   **Results:**

175   Twenty patients with ulcerative colitis and hypovitaminosis D were enrolled during the

176   study period.   Two patients were excluded from the study: one patient had normal vitamin D

177   levels at the time of randomization, and one patient left the study without taking their vitamin D_3

178   treatment. Thus, a total of eighteen patients completed the study and were included in the

179   analysis of results.   Eight patients received 2,000 IU of vitamin D_3 and ten patients received

180   4,000 IU of vitamin D_3 for ninety days and were followed prospectively.

181   At study enrollment and baseline there were no significant differences in sex, age,

182   smoking status, BMI, UC duration history, daily sun exposure and use of anti-TNF and

183   immunomodulator therapies between the two treatment groups. Baseline serum levels of

184   25(OH) vitamin D, ESR, CRP, PTH, calcium, albumin, and phosphorus and SIBDQ quality of

185   life scores were also similar between the two groups. The baseline Partial Mayo Score for UC

186   disease activity was significantly higher in the 4,000 IU vitamin D_3 group compared to the 2,000

187   IU vitamin D_3 group, with a mean score of 4.0 versus 1.4 respectively. (Table 1) None of the

188   patients enrolled in the study had a colectomy.

189   Vitamin D levels increased after ninety days of oral vitamin D_3 in both treatment groups.

190   However, the increase in vitamin D level in the 4,000 IU group of 16.80 ± 9.15 ($p < 0.001$) was

191   significantly higher compared to the increase in the 2,000 IU group of 5.00 ± 3.82 ($p = 0.008$).

192   (Figure 2) Normal vitamin D levels (> 30 ng/dl) were achieved in four of ten (40%) of UC

193   patients in the 4,000 IU group and in one of eight (12%) of UC patients in the 2,000 IU group

194   after ninety days of vitamin D_3 treatment. Quality of life scores as measured by SIBDQ

195   increased among all the UC patients after ninety days of vitamin D_3. This increase in SIBDQ

196   scores was statistically significant in the 4,000 IU vitamin D_3 group 1.00 ± 1.00 (p=0.017) but

197   not in the 2,000 IU vitamin D_3 group 0.10 ± 1.00 (p=0.87). (Figure 3)

198   Overall UC disease activity scores decreased in both treatment dose groups after ninety

199   days of vitamin D_3 however this change was not statistically significant. In the group receiving

200   2,000 IU of vitamin D_3 daily, the mean decrease in the Partial Mayo Score was -0.5 ± 1.5 (p=

201   0.38) compared to -1.3 ± 2.9 (p= 0.19) in the 4,000 IU group. (Figure 4) Similarly CRP levels

202   overall decreased in both treatment dose groups after ninety days of vitamin D_3 however this

203   change was not statistically significant. CRP level decreased by 3.0 ± 9.4 (p=0.40) in the group

204   receiving 2,000 IU of vitamin D_3 and decreased by 10.0 ± 35.0 (p=0.36) in the 4,000 IU group.

205   (Figure 5)

206   Across all eighteen UC patients in the study, the increase in vitamin D levels after ninety

207   days correlated with an increase in SIBDQ quality of life scores with a Pearson correlation

208   coefficient of 0.52, p = 0.028, and this increase in vitamin D level also correlated with a decrease

209   in Partial Mayo UC activity scores at -0.58, p = 0.012.

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211   **Discussion:**

212   This is the first prospective randomized pilot study to our knowledge evaluating the

213   effects of vitamin D_3 on the disease activity and quality of life in patients with UC. The

214   prevalence of vitamin D deficiency in adults with ulcerative colitis has been reported to be as

215   high as about 45-50% and has been attributed to various factors including decreased sunlight

216   exposure, low oral vitamin D intake, disturbed enterohepatic circulation and increased loss of

217   vitamin D as the result of protein-losing enteropathy.[25] However, it is unclear if vitamin D

218   deficiency is an environmental trigger for autoimmunity in IBD or if IBD directly causes vitamin

219   D deficiency. Factors that have been associated with lower QOL in IBD patients include: early

220   age of onset, increased number of hospitalizations for flares, female gender, and low vitamin D

221   levels. [25] This study evaluated the effects of oral vitamin D_3 on QOL after ninety days in patients

222   with UC and hypovitaminosis D. The results show that UC subjects receiving 4,000 IU/day of

223   vitamin D_3 had significantly higher quality of life scores after ninety days as compared to the

224   2,000 IU/day group. This suggests that higher doses of oral vitamin D_3 may be needed to achieve

225   beneficial vitamin D levels and higher QOL in UC patients.

226   Vitamin D deficiency in IBD patients has also been shown to be an independent risk

227   factor for higher disease activity scores and increased frequency of corticosteroid use.[22, 25]

228   Vitamin D affects both the innate and adaptive immune systems and leads to immune-tolerance

229   of self-structures. [26] Vitamin D has been used in other autoimmune diseases such as multiple

230   sclerosis, rheumatoid arthritis, and systemic lupus erythematosus and found to have a beneficial

231   effect in reducing disease severity. Vitamin D through its receptors influences the maturation

232   and differentiation of antigen presenting cells, dendritic cells and macrophages, resulting in the

233   decreased activation of T cells and suppression of inflammatory cytokines[1] and may thereby

234   reduce disease activity in IBD.

235   In this study oral vitamin D_3 for ninety days in UC patients decreased UC disease

236   activity scores, but this failed to reach statistical significance. An explanation for this could be

237   because only 40% of UC patients (4 of 10) in the 4,000 IU/day group and 12% (1 of 8) in the

238   2,000 IU/day group achieved sufficient vitamin D levels of >30 ng/ml after ninety days. This

239   suggests that a longer duration or higher doses of vitamin D are required to achieve sufficient

240   vitamin D levels >30 ng/ml to affect UC disease activity. It has been suggested that there may

241   be two levels of vitamin D that could be relevant to the management of IBD: vitamin D levels

242   less than <20 ng/ml that are associated with higher risk for developing osteoporosis,

243   osteomalacia, or rickets and vitamin D levels >30 ng/ml which may ensure normal immune

244   system regulation. [1] Oral vitamin D_3 was well-tolerated by all the study participants with no

245   adverse events reported throughout the study. Serum calcium and parathyroid hormone levels

246   were checked during the study and were normal. There were no signs or symptoms of vitamin D

247   toxicity observed in either dose groups.

248   In this study, increases in vitamin D levels correlated with higher QOL scores and

249   decreased UC disease activity scores in UC patients after ninety days of oral vitamin D_3. Other

250   studies have shown normal vitamin D levels can predict a decreased incidence risk of IBD.[21]

251   Similarly lower vitamin D levels have been reported in newly diagnosed children with IBD. [27]

252   To date there is no consensus on the appropriate dosage of vitamin D needed in patients with UC

253   with vitamin D deficiency. This pilot study compared the effects of two different doses of

254   vitamin D_3 with 2,000 IU/daily versus 4,000 IU/day in UC patients. Patients with UC who

255   received 4,000 IU/day of vitamin D_3 for ninety days had significantly higher vitamin D levels

256   and increased quality of life scores compared to the 2,000 IU/day group. The UC group with

257   4,000 IU/day of vitamin D_3 also tended to have decreased UC disease activity scores and lower

258   CRP levels compared to the 2,000 IU/day group after ninety days but these differences did not

259   reach statistical significance and was most likely limited by the small sample size as a pilot

260   study. Another limitation of the study was the lack of a placebo control group which was not

261   feasible with the study investigators and IRB both agreeing that appropriate care would be to

262   treat all UC patients with hypovitaminosis D with vitamin D replacement therapy. This study

263   also does not include endoscopic evaluation for mucosal healing, and potential dietary sources of

264   vitamin D may be a confounding variable.

265   This is the first prospective human study evaluating the effects of vitamin D_3 in UC

266   patients with hypovitaminosis D. We conclude from this study that oral vitamin D_3 is effective

267   in improving quality of life in UC patients with hypovitaminosis D and may decrease UC disease

268   activity. Vitamin D_3 at a higher dose of 4,000 IU/day is more effective than a lower dose of

269   2,000 IU/day in increasing vitamin D to sufficient levels in UC patients with hypovitaminosis D,

270   however higher doses or treatment beyond ninety days is likely needed. Further larger and

271   longer-term studies are needed to investigate the effects of vitamin D in ulcerative colitis.

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369 **Figure 1: Study overview**
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371 IBD patients seen for clinical encounter get screened for vitamin D deficiency
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376 Patients with UC and vitamin D deficiency are identified
377 and enrolled after providing informed consent (n = 20)
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383 Enrollment Visit - Day 0: (n = 20)
384 - Baseline medical history questionnaire
385 - Partial Mayo Score for UC disease activity
386 - SIBDQ quality of life score
387 - Serum labs drawn
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393 2 patients excluded   Randomization (n = 18)
394 - 1 normal 25(OH) vitamin D level
395 - 1 left study without taking vitamin D_3
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399 Vitamin D_3 2,000 IU/day x 90 days   Vitamin D_3 4,000 IU/day x 90 days
400 (n = 8)   (n = 10)
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406 Completion Visit – Day 90 (n = 18):
407 - Partial Mayo Score for UC disease activity
408 - SIBDQ quality of life score
409 - Serum labs drawn
410 - Pill count for compliance
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414 Analysis (n = 18)

416 **Figure 2: Change in vitamin D levels after ninety days**

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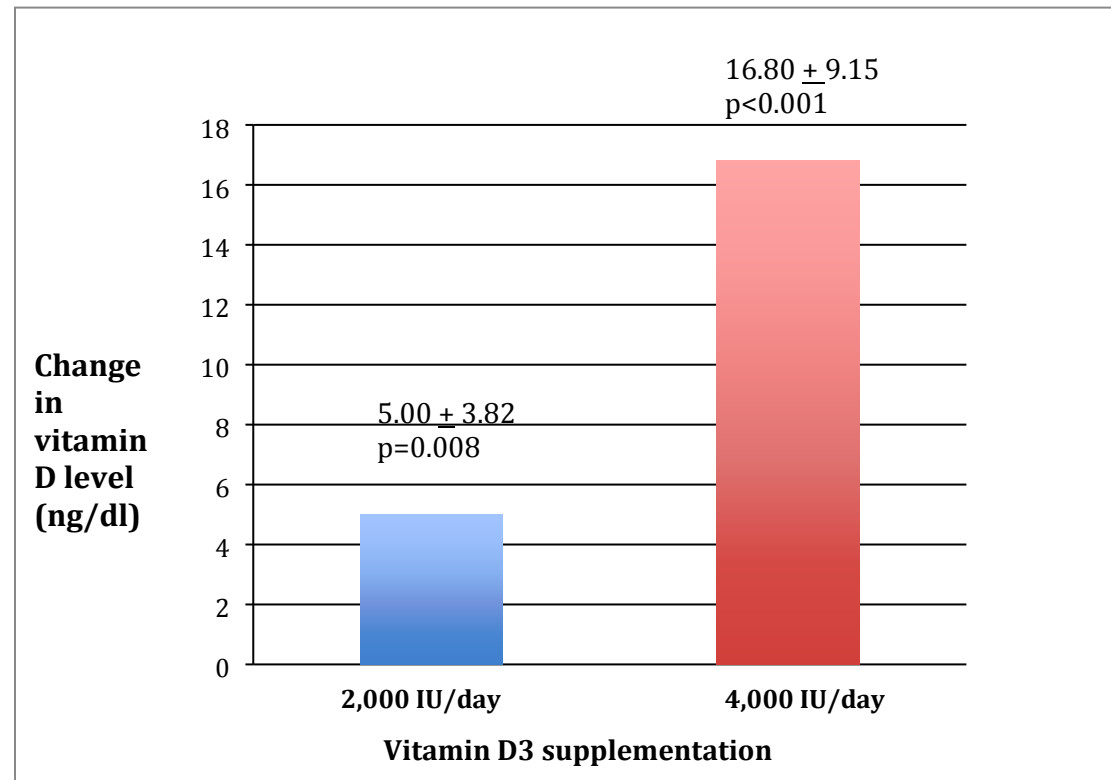
420 **Figure 3: Change in quality of life after ninety days**

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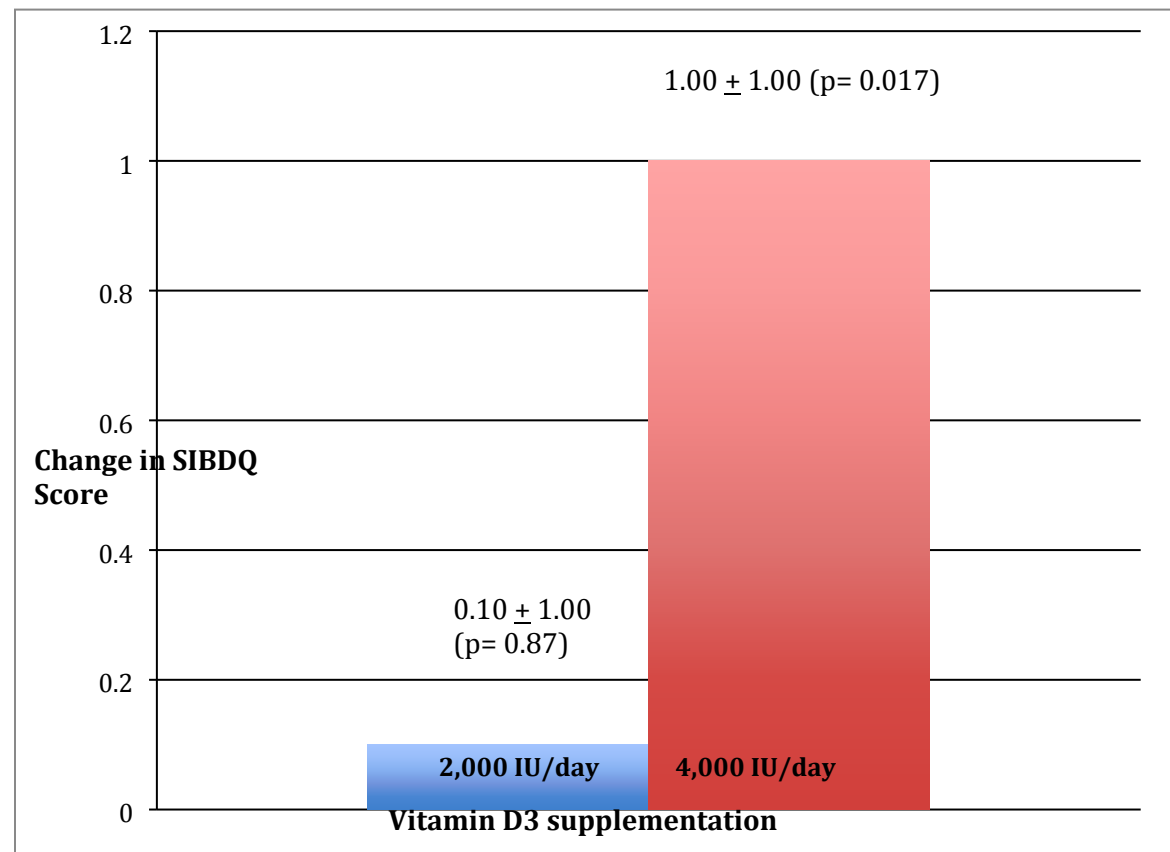
424 **Figure 4: Change in UC disease activity after ninety days**
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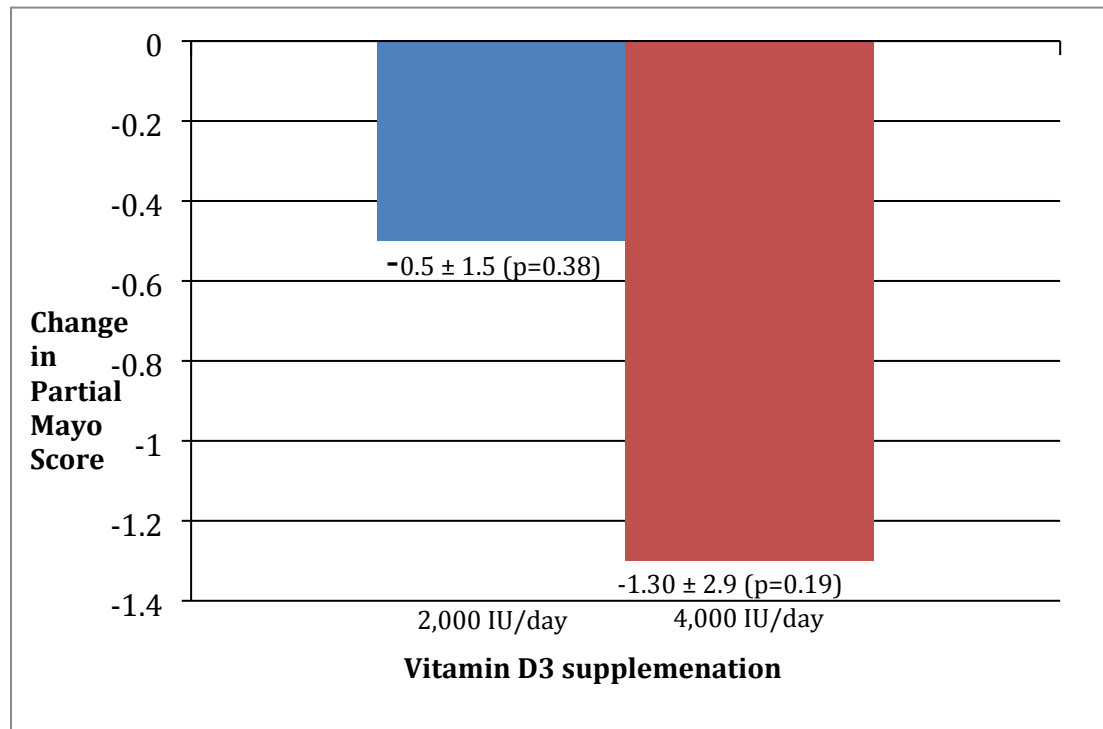
428 **Figure 5: Change in CRP levels after ninety days**

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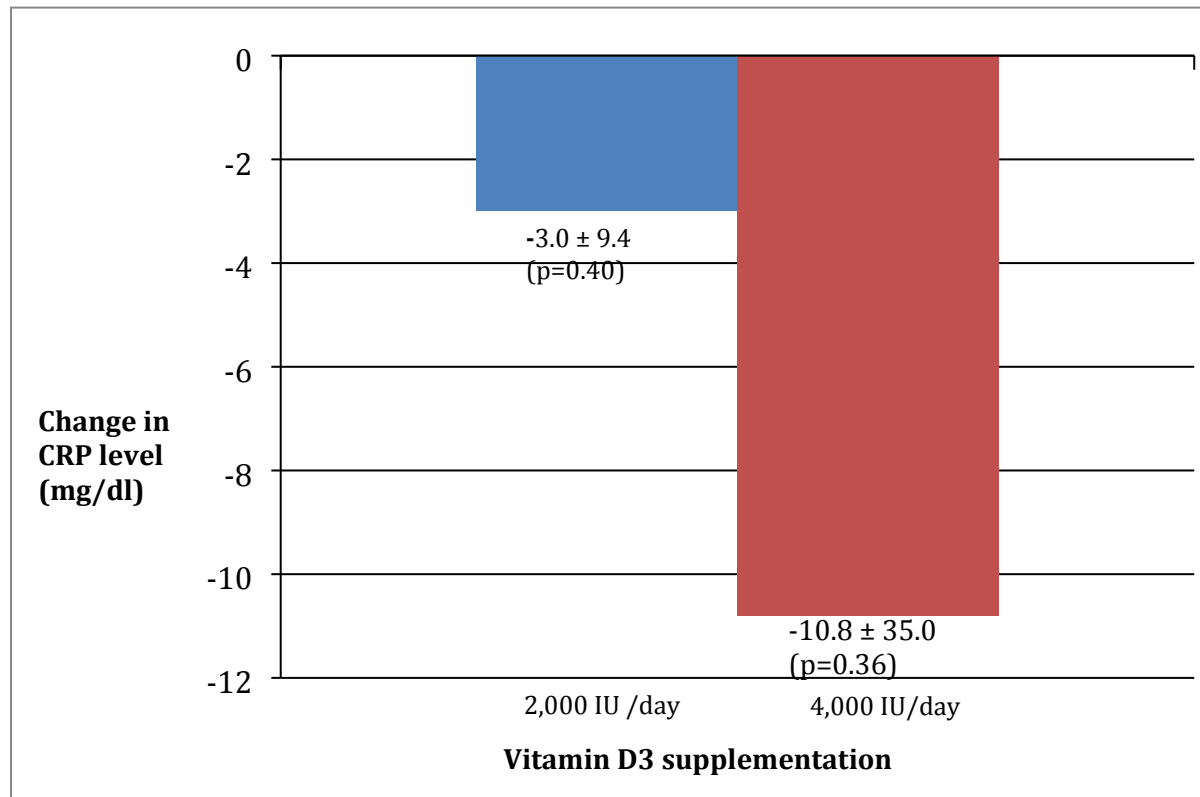
432 **Table 1: Baseline characteristics**

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Characteristic	Vitamin D₃ 2,000 IU group (n = 8)	Vitamin D₃ 4,000 IU group (n = 10)	p value
Sex: n (%)			
a) Male	7(88)	6(60)	0.20
b) Female	1(13)	4(40)	
Age in years at enrollment (mean, SD)	41.1 (13.7)	40.2 (16.2)	0.90
Ethnicity: n (%)			0.64
a) White	4 (50)	5 (50)	
b) Hispanic	3 (38)	3 (30)	
c) African American	1 (13)	0 (0)	
d) Asian	0 (0)	2 (20)	
Current smoker: n (%)			0.44
a) Yes	1(13)	0 (0)	
b) No	7 (88)	10 (100)	
BMI mean (SD)	27.78 (4)	25.7(5.4)	0.32
UC duration in years mean (SD)	3.7 (2.9)	5.2 (4.7)	0.57
Daily hours of sun mean (SD)	3.6 (2.4)	2.4 (2.5)	0.22
Baseline vitamin D level (ng/ml) mean (SD)	17 (5.24)	14.3 (4.24)	0.243
Partial Mayo UC disease activity score mean (SD)	1.4 (1.2)	4.0 (2.3)	0.03
SIBDQ score mean (SD)	5.6 (0.6)	4.8 (1.4)	0.21
ESR (mm/hr) (normal: 0-10) mean (SD)	10.5 (8.4)	27.0 (26.7)	0.20

CRP (mg/dl) (normal: 0-3) mean (SD)	6.9(8.8)	20.8 (34.8)	0.21
PTH (pg/ml) (normal: 14-72) mean (SD)	42.7(12.7)	46.4 (15.8)	1.0
Calcium (mEq/L) (normal: 8.5-10.5) mean (SD)	9.5(0.5)	9.3 (0.5)	0.6
Albumin (g/dl) (normal: 3.4- 4.8) mean (SD)	4.5 (0.3)	4.2 (0.6)	0.66
Phosphorous (mg/dl) (normal: 2.7-4.5) mean (SD)	3.2 (0.7)	3.7 (0.9)	0.38

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