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Normalization of Vitamin D Status is Associated with Reduced Risk of Surgery and Hospitalization in Inflammatory Bowel Disease: A Prospective Study

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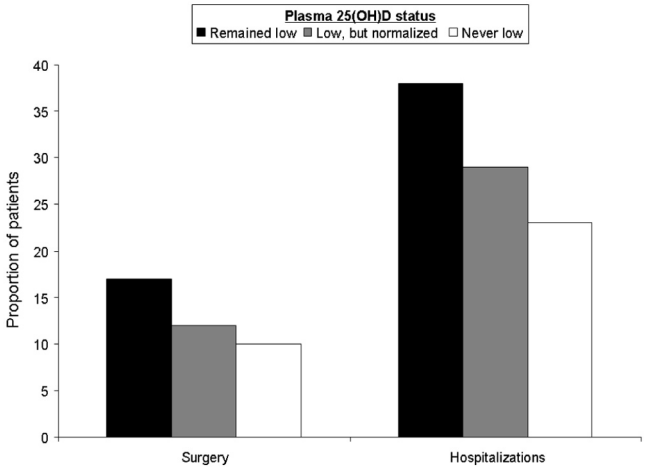
Introduction: Vitamin D may have an immunological role in Crohn's disease (CD) and ulcerative colitis (UC). Retrospective studies suggested a weak association between vitamin D status and disease activity but have been limited by inability to prospectively examine this hypothesis after excluding vitamin D values measured after outcomes of interest. Furthermore, no studies have examined whether normalization of vitamin D status is associated with improvement in patient outcomes. **Methods:** Using a multi-institution validated inflammatory bowel disease (IBD) cohort, we identified all CD and UC patients who had at least one measured plasma 25-hydroxy vitamin D [25(OH)D]. Our main outcomes were occurrence of first IBD-related surgery and IBD-related hospitalization. Secondary outcome included median C-reactive protein. We restricted our analysis to 25(OH)D measurements prior to the first surgery or IBD-related hospitalization. Logistic regression models adjusting for potential confounders were used. **Results:** Our study included 3,217 patients (55% CD, mean age 49 yrs). A majority were white (87%) and women (61%). One-third (39%) had ever used immunomodulators and 21% had used biologics. During a median follow-up of 8 years, 16% and 40% underwent an IBD-related surgery or hospitalization respectively. The median lowest plasma 25(OH)D was 26ng/ml (IQR 17–35ng/ml). One-third (32%) were deficient (plasma 25(OH)D < 20ng/ML), an additional 27% were insufficient. In CD patients on multivariate analysis, plasma 25(OH)D < 20ng/ml was associated with an increased risk of surgery (OR 1.76, 95% CI 1.24 – 2.51) and IBD-related hospitalization (OR 2.07, 95% CI 1.59 – 2.68) compared to those with 25(OH)D > 30ng/ml. Similar estimates were also seen for UC. Just under half of those with plasma 25(OH)D < 30ng/ml subsequently normalized their 25(OH)D (> 30ng/ml, 43%). Predictors of normalization were older age, use of anti-TNF biologics, and vitamin D supplementation while non-white race was inversely associated. Interestingly, CD patients who had initial levels < 30ng/ml but subsequently normalized their 25(OH)D had a reduced likelihood of surgery (OR 0.48, 95% CI 0.32 – 0.70) and hospitalization (OR 0.51, 95% CI 0.38 – 0.69) compared to those who remained deficient (Figure 1). Both CD and UC patients who were deficient but subsequently normalized their vitamin D status has lower median C-reactive protein levels (CD: –5 mg/L, p=0.002; UC: –7mg/L, p=0.03) than patients who remained deficient. **Conclusion:** To our knowledge, ours is the first study demonstrating prospectively that (1) low 25(OH)D is associated with greater C-reactive protein levels and increased risk of surgery and hospitalizations in both CD and UC; and (2) normalization of 25(OH)D status is associated with a reduction in the risk of surgery and IBD-related hospitalizations in CD.



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Predictors of recurrent Barrett's esophagus after successful radiofrequency ablation in a nationwide, multicenter cohort: Results from the U.S. RFA Registry.

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Background: Barrett's esophagus (BE) recurs in a minority of patients after successful treatment with radiofrequency ablation (RFA). Predictors of recurrence are poorly understood. We used data from a nationwide registry of patients treated with RFA to identify factors associated with recurrent BE after successful treatment with RFA. **Methods:** The U.S. RFA Registry is a prospective study of patients with BE treated with RFA at 148 institutions (113 community-based, 35 academic-affiliated). We included patients who achieved CEIM (complete eradication of intestinal metaplasia), were enrolled for at least 2 years, and had at least 2 biopsies performed after CEIM. Recurrence was defined as any biopsy from the tubular esophagus demonstrating BE. Patients with and without recurrence were compared using parametric statistics for demographic data, pre-treatment EGD findings (length of BE, presence of dysplasia, fundoplication) and number of treatments necessary to achieve CEIM. Characteristics associated with recurrence on bivariate analysis ($p < 0.20$) were included in a logistic regression model to identify independent predictors of recurrence. The model was reduced using the likelihood ratio test. **Results:** Among 5530 patients who received RFA for BE, 1128 (20%) were enrolled for 2 years, achieved CEIM, and had at least two post-CEIM biopsies performed. In this population, recurrence occurred in 28% (n=317) over a mean of 2.2 ± 1.1 yrs of surveillance. An additional 96 subjects (9%) had empiric retreatment with RFA for suspected recurrence without prior histological confirmation. Histology at recurrence was nondysplastic or indefinite for dysplasia in 87% (274/317). Compared to patients without recurrence, patients with recurrence were more likely in bivariate analysis to have: 1) more advanced age (63.3 vs. 60.5 yrs, p=0.0002); 2) longer BE segment (4.4 vs. 3.9 cm, p=0.01); 3) a pre-treatment fundoplication (8% vs. 5%, p=0.03); and 4) dysplastic BE (LGD or worse) prior to treatment (57% vs. 50%, p=0.047). In multivariate analysis, non-Caucasian race (OR 1.67, 95% CI 1.01 – 2.77), length of BE segment (1.09 per cm, 1.04 – 1.14), age (1.02 per yr, 1.01 – 1.03), and number of RFA sessions (0.85 per session, 0.77 – 0.94) were independent predictors of incomplete eradication (see table). Likelihood for recurrence was not influenced by sex, pre-treatment dysplasia, treatment with EMR, or treatment at an academic versus community-based practice in multivariable analysis. **Conclusions:** In the largest reported cohort treated with RFA for BE, likelihood for recurrence of BE after successful treatment with RFA was increased in those who are older, not Caucasian, had longer BE segments, and required fewer RFA treatment sessions to achieve CEIM. These findings should be considered in generating surveillance protocols and counseling patients after successful RFA treatment.

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Nortriptyline for Idiopathic Gastroparesis: A Multicenter, Randomized, Double-Masked, Placebo-Controlled Trial (NORIG).

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In clinical practice, tricyclic antidepressants (TCAs) are often used as neuromodulators for treatment of nausea, vomiting, and abdominal pain in patients with gastroparesis. There is little evidence for this based on well-designed studies. The primary **aim** of this trial was to determine whether treatment with nortriptyline, a TCA with reduced anticholinergic side effects, results in symptomatic improvement in patients with idiopathic gastroparesis. **Methods:** This 15 week multicenter, randomized, placebo-controlled, double-masked, parallel groups, dose-escalated clinical trial compared nortriptyline to placebo for symptomatic relief in patients with idiopathic gastroparesis. Inclusion criteria included delayed gastric emptying by scintigraphy and symptom scores > 21 on the 0-45 point 9-symptom Gastroparesis Cardinal Symptom Index (GCSI). Nortriptyline was escalated at 3-week intervals (10, 25, 50, 75 mg). The primary outcome measure was a decrease from the baseline GCSI score of at least 50% on two consecutive 3 week visits over 15 weeks of follow-up. The study was powered at 90% to detect a two-fold increase in symptomatic improvement rate, based on intention to treat. **Results:** Overall symptomatic improvement (primary outcome) did not differ between 65 patients randomized to nortriptyline and 65 patients randomized to placebo: 23% (n=15) in the nortriptyline group vs 21% (n=14) in the placebo group (relative improvement rate: 1.06 [95% CI 0.56, 2.00]; p=0.86). The nortriptyline group had greater decrease in nausea (p=0.04) and abdominal pain (p=0.004) at 3 weeks, but not after. At 15 weeks, the nortriptyline group had greater improvement in appetite (p=0.03) and tended toward greater improvement in ability to finish a meal (p=0.08) together with greater increase in body mass index (BMI) (0.5 vs. -0.2 kg/m2 (p=0.03)). Subgroup analysis of baseline physiologic characteristics showed among patients with impaired meal consumption on satiety testing (<250 mL Ensure consumption), nortriptyline tended toward greater symptomatic improvement (p=0.06) in comparison to placebo. Treatment was stopped more often with nortriptyline than placebo (n=19 vs 6, respectively; p=0.007) with the primary reason being side effects (n=10 vs 3, respectively). Conclusions: In this first adequately powered randomized clinical trial of a neuromodulator in idiopathic gastroparesis, nortriptyline did not improve overall symptoms in idiopathic gastroparesis over a 15 week period, although improvements in appetite, satiety and BMI were noted. An early improvement in nausea was seen at low doses (10 mg), but this was not sustained as dosing was increased. Nortriptyline was associated with early treatment discontinuation in 29% of patients. Further studies are needed to determine the role for TCAs and other neuromodulators in patients with idiopathic and other forms of gastroparesis.

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Prevalence and Predictors of Missed or Interval Colorectal Cancer: A Population-based Study in Utah

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Introduction: Colonoscopy has now become the preferred option for colorectal cancer (CRC) screening in the USA. It is estimated that most CRCs diagnosed within a few years after an index colonoscopy are due to missed lesions or new interval cancer development. Most reports on the rates and predictors of missed CRCs are from countries with healthcare systems different from those in the US. Studies completed solely in the Veterans or Medicare populations may also not reflect the US population. Aim: In this study we aim to assess the rate, characteristics and predictors of missed-interval CRC occurring within 6 to 60 months of colonoscopy in a large population-based study from Utah, reflecting usual clinical care in the United States. Methods: We performed a population-based retrospective cohort study of residents of the state of Utah, between 50 and 80 years of age, who underwent colonoscopy between February 15, 1995 and January 31, 2009 at Intermountain Healthcare or University of Utah Health System which together provide care to >85% of state residents. De-identified medical information on patients undergoing colonoscopy was merged with cancer histories from the Utah Cancer Registry. CRCs diagnosed within 6 months of a colonoscopy were categorized as detected CRCs and those 6-36 months or 6-60 months after a colonoscopy as alternative measures of missed-interval CRCs. Logistic regression analysis was performed to identify risk factors in the 6-60 month cohort of missed-interval CRCs. We performed a manual chart review validation of 42 missed cancers, confirming 41 (98% accuracy). Results: There were 126,936 unique patients who underwent colonoscopy. We identified a diagnosis of CRC in 2659 patients. The rate of missed-interval cancers was 3.5% (n=91)