Vitamin D concentration and disease risk: the concerns

Dear Sir:

In their interesting retrospective cohort study, Quraishi et al (1) highlight the increased risk of hospital-acquired bloodstream infection (HABSI) in 2135 adult patients from 2 Boston teaching hospitals with lower serum 25-hydroxyvitamin [25(OH)D] concentrations. The study analysis in adult patients shows that 25(OH)D concentrations <10 ng/mL before hospitalization were associated with significantly increased odds of developing HABSI. Current research on vitamin D has highlighted its important role as a key regulator of innate and adaptive immune systems that may influence host susceptibility to infections. The study by Quraishi et al has also necessitated the initiation of randomized trials to test the role of vitamin D supplementation to reduce the burden of HABSI. In this regard, several interesting facets of 25(OH)D functions warrant attention. First, the requirement of optimal 25(OH)D concentrations for the induction of antimicrobial host-defense mechanisms via Toll-like receptor (TLR2, TLR1) stimulation provides a crucial basis for clinical observations in infections (2). This is discussed by Quraishi et al in addition to discussion of depressed macrophage phagocytosis, chemotaxis, and proinflammatory cytokine production as a result of low 25(OH)D concentrations (1). Reports also show that activation of TLRs results in secretion of antimicrobial peptides by tracheobronchial epithelial cells that facilitate the development of adaptive immune responses at the site of infection (3). Therefore, the presence of vitamin D metabolites is important for the proper induction of host-defense mechanisms and suggests that vitamin D supplementation should be carefully examined. Second, substantial seasonal variation in concentrations of 25(OH)D at the population level is an important aspect that needs attention (4). Quraishi et al (1) analyzed the 25(OH)D concentrations in patients before hospitalization between 1993 and 2010. Their observational findings depend on multivariable analyses and suggest that vitamin D supplementation may provide a novel approach to lowering HABSI risk. However, the seasonal variation in vitamin D concentrations adds to the complexities in vitamin D epidemiology and requires much consideration before widespread supplementation is implemented (5). Third, it was importantly noted that vitamin D metabolism and concentrations vary widely according to race-ethnicity (6). Interestingly, baseline 25(OH)D concentrations are lower in blacks, and their response to supplementation with respect to clinical outcomes may differ from that in whites (7), suggesting caution for supplementation with an emphasis on racial information. Fourth, 25(OH)D concentrations are known to induce the genomic regulation of fetal development and hence add to risk factors for childhood diseases (8). The Vitamin D Antenatal Asthma Reduction Trial (VDAART; registered at clinicaltrials.gov as NCT00856947) aims to supplement 25(OH)D in pregnant mothers to reduce the risk of asthma in their children. Therefore, the 25(OH)D concentrations in mothers may add some crucial findings in studies with children population. Fifth, interestingly, Welsh et al (9) explained 25(OH)D deficiencies as “reverse causality” in which there is a chance that poor health conditions will dictate low 25(OH)D concentrations, rather than the reverse. Conversely, studies suggest that 25(OH)D concentrations decrease significantly during the acute-phase response (10). In conclusion, all of these factors are crucial in the context of 25(OH)D-related population studies, potentiating the need for a multifaceted approach during further interventions.

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Fecal microbiota after gastric bypass in human obesity

Dear Sir:

I read with great interest in a recent issue of the Journal the important article by Kong et al (1), who extended by using a pyrosequencing method the results previously obtained with the reverse-transcriptase polymerase chain reaction method and showed an increase in fecal microbiota richness (diversity) but also described associations between fecal microbiota composition and white adipose tissue genes after Roux-en-Y gastric bypass (RYGB) in 30 obese women. They rightly discussed the role of hypochlorhydria and pH-induced changes in the gut oxidoreduction potential after RYGB, affecting aerobe or facultative anaerobe phyla, such as the phylum Proteobacteria, which represented 37% of the observed increased diversity; some modulated genera were presumed to be issued from periodontal and oropharyngeal environments because of modifications of gastric barrier and motility and eventually because of major changes in mastication recommended after bariatric surgery. They also observed a significant increase in Bacteroides, strict anaerobes of the phylum Bacteroidetes. My concern is with regard to 2 main points that the authors omitted to discuss.

First, whether fecal microbiota is an accurate reflection of what is happening within other microbial niches of the gut (2) warrants discussion. Indeed, the use of fecal microbiota as a surrogate for the entire gut microflora and the potential differences between specific anatomic sites are questions of special importance in the present case of profound structural changes in upper gut anatomy and continuity induced by RYGB. As recently outlined, fecal microbiota may not be representative of the microbiome in the 3 discrete upper gut sections of RYGB [ie, the Roux (alimentary) limb, the diverted gastroduodenojejunal limb, and the common limb], which may each contribute to distinct metabolic signals compared with feces (3). In RYGB rats, compared with sham-operated animals, the most substantial shifts in the microbiota composition were observed in the alimentary limb and the common channel, in association with reduced intestinal and serum dipeptidyl peptidase-IV activities, an enzyme that degrades gut peptides such as the incretin glucagon-like peptide-1. This recent finding is consistent with the modulation of jejunal microbiota altering the production or breakdown of gastrointestinal hormones known to control energy balance (3). Conversely, in a mouse model of RYGB that recapitulates many of the metabolic outcomes in humans, alterations to the gut microbiota were detectable throughout the length of the gastrointestinal tract but were most evident in the distal gut, downstream of the surgical manipulation site (4). Finally, after RYGB in rats, intestinal glucose metabolism was triggered by the exposure of the hypertrophic and hyperplasic jejunal Roux-limb to undigested nutrients and contributed to the improvement in glycemic control after operation; transcriptomic and metabolomic analyses showed that the rapid metabolic shift from an oxidative energy supply to an anabolic metabolism was only observed in the jejunum but not in the ileum or colon (5), a finding consistent with the view that the upper gut microbiota may be a key determinant of proper jejunal glucose metabolism.

The second point is that, in addition to considerably restricting stomach size (down to a 15–30-mL egg-sized gastric pouch), RYGB surgery creates an anatomic blind, stagnant loop including the diverted gastric and biliopancreatic limb (6, 7), a source of small intestinal bacterial overgrowth (SIBO) in the area of stasis but also in the neighboring Roux and common limbs, leading to the metabolically significant increase in fermentation potential (7, 8). SIBO, whose prevalence is much higher in anatomic blind loops than in achlorhydria of any origin without stasis, is most often infraclinical and has been reported in up to 47% of cases after RYGB reconstruction (8). SIBO, which is virtually absent after Billroth I gastrectomy (with gastroduodenal anastomosis), is very frequently found after Billroth II resection with gastrojejunostomy. The microbiota found in upper small intestinal SIBO complicating anatomic, postsurgical stagnant loops are colonic or fecal in type, and high concentrations (up to $10^{10}$ per ml of jejunal contents) of strict anaerobic, gram-negative flora such as Bacteroides of the phylum Bacteroidetes and of anaerobic Lactobacilli and Clostridia sp. predominate, in association with aerobic flora such as Escherichia coli, Streptococcus fecalis, and oropharyngeal flora.

In germ-free mice conventionalized with fecal microbiota, both transcriptomic and metabolomic analyses of the jejunal tissue references...

REFERENCES

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Fecal microbiota after gastric bypass in human obesity

Dear Sir:

We deeply appreciate the comments offered by Das et al, which summarize many of the critical issues highlighted in our article related to the association of serum 25-hydroxyvitamin D concentrations and risk of hospital-acquired bloodstream infections (1). These considerations are extremely important for the design of adequately powered, clinically meaningful, randomized, placebo-controlled clinical trials to investigate the effect of vitamin D supplementation on hospital-acquired infections.

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