Effects of Supplemental Calcium and Vitamin D on Circulating Biomarkers of Gut Barrier Function in Colorectal Adenoma Patients: A Randomized Controlled Trial

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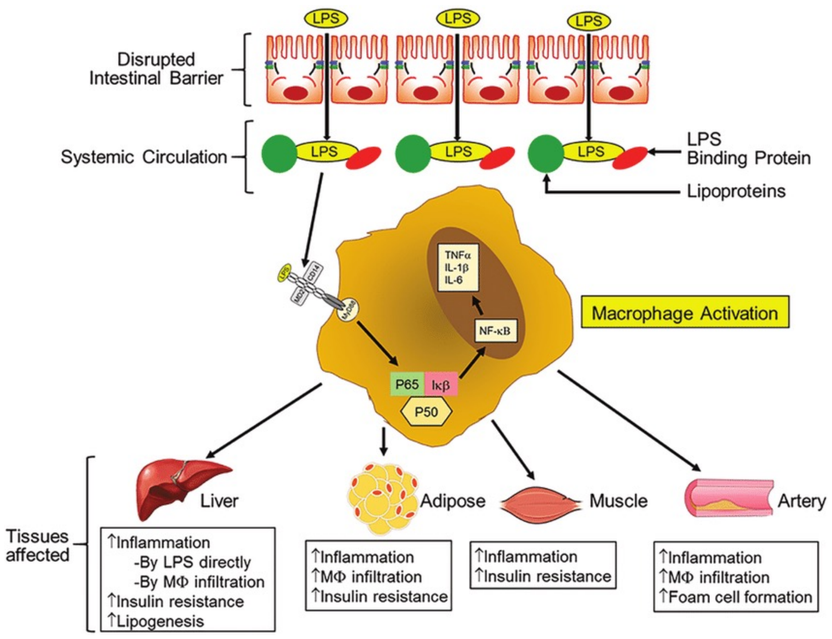
Introduction

- **Inflammation**, a potential factor contributing to gut barrier disfunction, is significant in colon carcinogenesis.
- On the other hand, **a weakened gut barrier** is more prone to the foreign antigens, causing endotoxemia and inflammation, which promotes colorectal cancer (CRC)
- **Lipopolysaccharide (LPS)-binding protein (LBP)**: A biomarker for activation of innate immune responses to microbial products and a marker of LPS.
- **Intestinal fatty-acid binding protein (IFABP)**: Elevated in conditions characterized by increased intestinal permeability



Reference
1. Ghosh, S. S., et al. (2020). PMCID: PMC7033038

Research Question

Does vitamin D and calcium supplementation affect the circulating biomarker of gut barrier function among individuals at high risk of CRC? If so, is there a difference in the treatment effect by BMI or pro inflammatory cytokine level?

Method

Parent Study

- 11-center, randomized, placebo-controlled, partial 2x2 factorial chemoprevention clinical trial, the Vitamin D/Calcium Polyp Prevention Study (NCT00153816).
- **Participants**: ages 45-75 years with at least one colorectal adenoma removed within 120 days prior to enrollment and with scheduled 3-year or 5-year colonoscopic follow-up examinations (patients were from 2 centers; Georgia and South Carolina).
- **Treatment Assignment**: "4-arm study": elemental Ca 1.2 g/d, vitamin D3 1,000 IU/d, both, or placebo; "2-arm study": women who declined to forego Ca supplementation were randomized to vitamin D or placebo

Adjunct Study

- **Participants**: 118 participants
- Blood was drawn at the baseline and 1-year follow-up
- LBP and IFABP level was analyzed through electrochemiluminescent Human LBP Assay Kit and ELISA

Statistical Analysis

- X^2 **Test** for categorical variables and **ANOVA or T-test** to compare baseline characteristics of participants across treatment arms.
- **Generalized linear model** (PROC MIXED) to compare the difference in biomarker levels between treatment groups
- **Stratified analysis** by median level of baseline serum 25-OH-vitamin D, total calcium intake, BMI and inflammatory biomarker (IL6) concentration.
- All analysis was done on SAS version 9.4.

Table 1. Selected baseline characteristics of the study participants[a]

Characteristic	Vitamin D & Ca (4-arm)					Vitamin D Only (2-arm)		
	Placebo (n=21)	Ca (n=17)	Vit D (n=20)	Ca + Vit D (n=19)	*P*	Placebo (n=22)	Vit D (n=19)	*P*
Age, yrs	60	59	59	58	*0.82*	58	59	*0.65*
Men, %	86	71	65	84	*0.36*	-	-	-
White, %	81	71	75	94	*0.28*	68	84	*0.29*
Smoking status, %								
Never	52	77	60	47	*0.30*	64	53	*0.21*
Former	33	18	40	47		36	32	
Current	14	6	0	5		0	16	
Family hx of CRC, %	10	6	17	5	*0.63*	5	11	*0.58*
ASA or NSAID users, %	67	94	60	58	*0.08*	50	47	*0.87*
BMI, kg/m^2	29	33	29	30	*0.09*	29	27	*0.29*
Advanced adenoma, %	38	12	20	26	*0.28*	9	16	*0.51*
Total energy, kcal/d	1,363	1,780	1,406	1,626	*0.07*	1,332	1,434	*0.57*
Total calcium, mg/d	639	976	649	692	*0.01*	1,076	1,227	*0.40*
Total vitamin D, IU/d	356	482	307	427	*0.28*	562	634	*0.54*
25-OH-D, ng/ml	23	24	24	23	*0.91*	25	26	*0.70*

[a]Data are shown as mean unless otherwise specified

Result

- LBP decreased in vitamin D group relative to the no vitamin D group after 1 year of supplementation.
- LBP did not change in calcium group relative to the no calcium group and in the vitamin D and calcium group relative to the calcium group after 1 year of supplementation.
- IFABP decreased in vitamin D group relative to the no vitamin D group after 1 year of supplementation.
- IFABP also decreased in vitamin D and calcium group relative to the calcium group while there was no change in the calcium group and no calcium group after 1 year of supplementation.
- LBP decreased in vitamin D group relative to the no vitamin D group, in participants with greater than or equal to median BMI but not in participants with less than median BMI.
- IFABP decreased in vitamin D group relative to the no vitamin D group and calcium and in the vitamin D group relative to the calcium group, in participants with less than median IL-6 concentration but not in participants with greater than or equal to median IL-6 concentration.

Conclusion: Overall, our study findings indicate decrease in LBP and IFABP concentrations with administration of vitamin D over 1 year. This effect was stronger among individuals with higher BMI for LBP and among individuals with lower IL-6 concentrations for IFABP. Our results suggest that vitamin D could potentially be used as a protective agent against gut barrier dysfunction and inflammation, which is associated with CRC risk. Final analyses are being prepared to be submitted to the AACR conference or to be published.