Micronutrient Absorption and Interactions After Bariatric Surgery

Taylor A. Brodie, MS, RDN, LD March 23rd 2023

Disclosures

• Employee of Celebrate Vitamins

Objectives

- Review physiological changes influencing micronutrient metabolism after metabolic and bariatric surgery (MBS)
- Reevaluate nutrient-nutrient interactions
- Explore the nutrigenomic and nutrigenetic influences on micronutrient metabolism

Introduction

- Micronutrient deficiencies are high among patients with obesity.
- Micronutrient deficiencies are high among patients who have had MBS.

Nutrient	Deficiency prevalence in those with obesity (pre-op surgical and nonsurgical)	Deficiency prevalence in those who have had MBS (varies by procedure) As high as 100%	
Vitamin D	As high as 90%		
Iron	14-45%	14-62%	
Thiamin	15-29%	As high as 45%	
Vitamin B12	2-18%	4-20%	
Folate	2-54%	As high as 65%	
Vitamin A	7-14%	As high as 70%	
Vitamin E	2.2%	0-65%	
Zinc	28-74%	19-70%	
Copper	As high as 70%	0-90%	

Parrot et al. SOARD. 2017; 13(5). 10.1016/j.soard.2016.12.018 Kaidar-Person et al. Obes Surg. 2008; 18(7). 10.1007/s11695-007-9349-y Kaidar-person et al. Obes Surg. 2008; 18(2). 101007/s11695-007-9349-y Isom & Majumdar, eds. Pocket Guide to Bariatric Surgery. 2022.

Introduction Cont.

Different Procedures \rightarrow Different Anatomy \rightarrow Different Impact on Micronutrient Status

- Size of the gastric pouch •
- Resection of antrum
- Length of bypassed intestine
- Length of the common channel
- Gastric emptying and transit time



RNY Roux-en-Y Gastric Bypass

DS Duodenal Switch

ASMBS Guidelines

Guidance for baseline micronutrient needs after surgery for majority of patients

4		SUBGERY FOR OBESITY AND RELATED DESLATES
ELSEVIER	Surgery for Obesity and Related Diseases 16 (2020) 175-247	
	Guidelines	
and nonsurgi 2019 upd Endocrinolo Society, Amo Medicine A	tice guidelines for the perioperative r ical support of patients undergoing ba ate: cosponsored by American Associ ogists/American College of Endocrino rican Society for Metabolic & Bariat Association, and American Society of	ariatric procedures – iation of Clinical ology, The Obesity tric Surgery, Obesity Anesthesiologists
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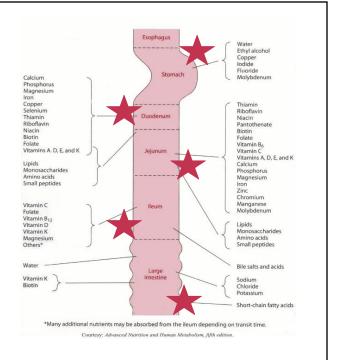
2019 ASMBS Guidelines for RNY

	Multivitamin (MVI)
Thiamin Folic Acid B12 Vitamin D Vitamin A Vitamin K Copper Zinc	At least 12 mg / day * 400 – 800 mg / day from MVI 800 – 1,000 mg / day total (female, child bearing age) Oral: 350 – 1,000 mg / day 3,000 UI (75 mg) 5,000 – 10,000 IU (1,500 – 3,000 mg) / day 15 mg / day 90 – 120 mg / day 2 mg / day from MVI 8 – 22 mg / day from MVI
∠inc to copp	er ratio: 8 – 15 mg of zinc for every 1 mg of copper Iron (from all supplements)
	At least 18 – 60 mg / day ** CANNOT take with Calcium
C	alcium (from food and supplements)
Calciu	1,200 – 1,500 mg / day Take in divided doses m Citrate may be taken with or without meals
	Other
Protein (often individualized)	Minimum of 60 g / day with some patients needing higher amounts of 80 – 90 g / day
Fluids (often individualized)	At least 50 oz / day to ensure adequate hydration
neuropathy, encephalopathy, a	loss, protracted vomiting, the need for parenteral nutrition, excessive alcohol, nd/or heart failure. At risk patients need at least 50 – 100 mg of thiamin daily.
	s and patients without a history of anemia) need 18 mg of iron from their ts (menstruating females who have had SG, RNY, or BPD / DS or those with anemia) need at least 45-60 mg of iron daily.

Information adopted from Mechanick et al SOARD. 2020; 16:175-247

Absorption Considerations

- Loss of Absorption Site
- Nutrient Status & Absorption
- Dose-Dependent Absorption
- Competitive Transporters
- Enteroplasticity
- Absorption in Large Intestine
- Nutrient-Nutrient Interactions
- Genetic Considerations



Nutrient Status and Absorption

- Homeostasis Mechanisms
 - Feedback mechanism meant to increase absorption during low concentrations and decrease absorption to avoid toxicity
- Transporter number, efficiency and/or gene expression is altered based on concentration
 - Iron hepcidin*
 - Copper hCtr1

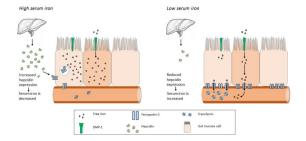


Image from Cornelissen et al EBioMedicine. 2019;47. doi: 10.1016/j.ebiom.2019.08.014.

Gropper et al. Advanced Nutrition and Human Metabolism. 7th Edition. 2008. Tapiero et al. Biomed Pharmacether. 2003; 57(9). doi: 10.1016/s0753-3322(03)00012; Cornelissen et al. EBioMedicine. 2019;47. doi: 10.1016/j.ebiom.2019.08.014.

01	Inverse relationship between dose and absorption	 Vitamin B12 Pantothenic Acid Vitamin C Vitamin E Copper Magnesium
02	Absorption rate decreases after saturation threshold	 Calcium - 400-500mg Magnesium - 500mg Vitamin B12 (IF Threshold 1-2mcg) Riboflavin - 27mg
03	Alters transporter transcription	 Zinc - ZIP4 Biotin - SMVT Thiamin - ThTr2

Competitive Transporters

DMT1 - Divalent Metal Transporter 1

- Thought to also transport various other metal cations
 - Cadmium: lettuce, spaghetti, bread, potatoes
 - Preference for Fe(2+)
 - Other Minerals: Copper, Manganese, and Zinc
- Also influenced by hepcidin concentrations

SMVT - Sodium Dependent Micronutrient Transporter

- Biotin
- Pantothenic Acid
- Iodide

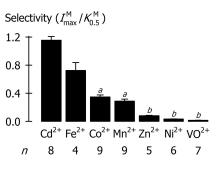


Figure from Shawki et al., *Curr Top Membr.*, 2012; 70. DOI: 10.1016/B978-0-12-394316-3.00005-3

Shawki et al. *Curr Top Membr.* 2012;70. doi: 10.1016/B978-0-12-394316-3.00005-3. Lefebvre et al. *Nutrients.* 2021;13(8):2516. doi: 10.3390/nu13082516.

Enteroplasticity

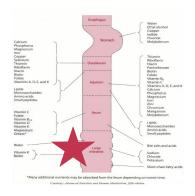
- Changes in Morphology
 - The adaptation of gastrointestinal cell to change structure and function in response to stimuli. This could be changes in the following:
 - Proliferation
 - Villus Height
 - Crypt Depth
 - Mucosal Surface Area
 - Intestinal Weight
- RNY:
 - Rodent models have seen roux-limb and common channels with increased bowel width, villus height, crypt depth, and cell proliferation. In contrast, the biliopancreatic limb only increased bowel length.
 - In humans, roux-limb enterocytes caused hypertrophy with increased cell proliferation and crypt depth.

Seeley et al. *Cell Metab.* 2015;21(3). Doi: 10.1016/j.cmet.2015.01.001. Camastra et al. *Eat Weight Disord.* 2022;27(2). Doi: 10.1007/s40519-021-01194-5.

Bacterial Fermentation of Nutrients

The following nutrients are thought to be produced by microorganisms in the large intestine:

- Vitamin K
- Biotin
- Folate
- Riboflavin
- Pantothenic Acid



Gropper et al. Advanced Nutrition and Human Metabolism. 7th Edition. 2008.

Colonic Absorption - Vitamins

Nutrient	Notes
Thiamin Diphosphate (TDP)	Energy-dependent transport.
Riboflavin	Smaller doses absorbed by Riboflavin Vitamin Transporters (RFVT) 1 and 3
Nicotinic Acid	Absorbed via high affinity carriers
Pantothenic Acid	Bacteria produced pantothenic acid is absorbed via shared multivitamin transporter (SMVT)
Folate	Absorbed via active transport with Bidirectional Reduced Folate Carrier
Biotin	Carrier-mediate enzymes absorb biotin and providing nutritional value
*Vitamin K (Menaquinones)	Passively diffused after produced by certain colonic bacteria and providing nutritional value

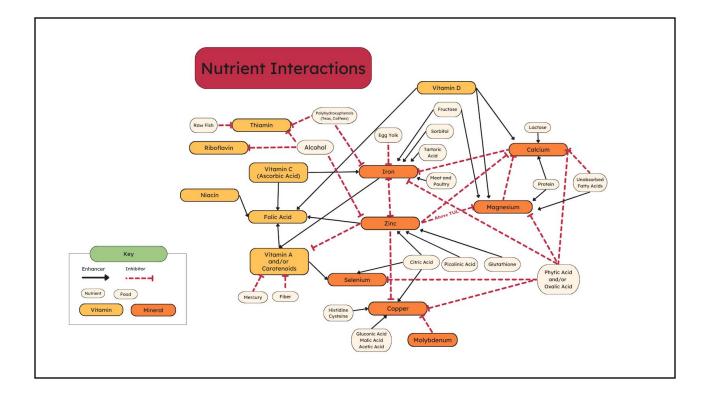
Gropper et al. Advanced Nutrition and Human Metabolism. 7th Edition. 2008. Said HM. Biochemical Journal. 2011;437(3). doi:10.1042/BJ20110326

Colonic Absorption - Minerals

Nutrient	Notes
Calcium	Microbiota separates calcium bound to fermentable fiber. May contribute 4-10% of total dietary calcium absorption
Magnesium	Absorption in colon likely when absorption is limited in small intestine
Zinc	Absorption in colon hypothesized during deficiency

*It is unclear how colonic absorption influences nutrient status

Gropper et al. Advanced Nutrition and Human Metabolism. 7th Edition. 2008. Schafer AL, J Steroid Biochem Mol Biol. 2017;173:202. doi:10.1016/J.JSBMB.2016.12.012



Calcium & Iron

- Calcium between 300-600mg has shown to inhibit heme and nonheme iron absorption after dietary and supplemental intake.
- Why? Here are a few hypotheses:
 - Calcium may decrease DMT1 expression and move away from apical membrane
 - Calcium causes ferroportin to relocate from basolateral membrane to cytosol
 - Change in membrane fluidity

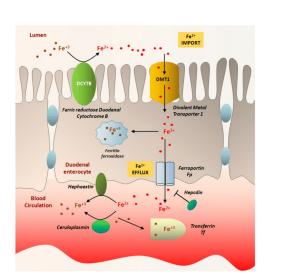


Image from Bjørklund et al 2020;94(3). doi: 10.1007/s00204-020-02652-2.

Gropper et al. Advanced Nutrition and Human Metabolism. 7th Edition. 2008. Shawki & Mackenzie. Biochem Biophys Res Commun. 2010;393(3). doi: 10.1016/j.bbrc.2010.02.025.

Calcium & Iron

- Relationship between Ca intake/supplementation on iron absorption, ferritin status, & hemoglobin levels.
 - Calcium intake was inversely related to iron absorption, but not ferritin or hemoglobin concentration.
 - Dose-response relationship was statistically significant for lower ferritin concentrations.
- Limitations and things to consider:
 - *Free-living population, including children.
 - Various calcium forms used, no indication of if taken with/without meals.

Abioye et al. J Nutr. 2021;151(5). doi: 10.1093/jn/nxaa437.

The Journal of Nutrition

ASN Nutrient Physiology, Metabolism, and Nutrient-Nutrient Interactions

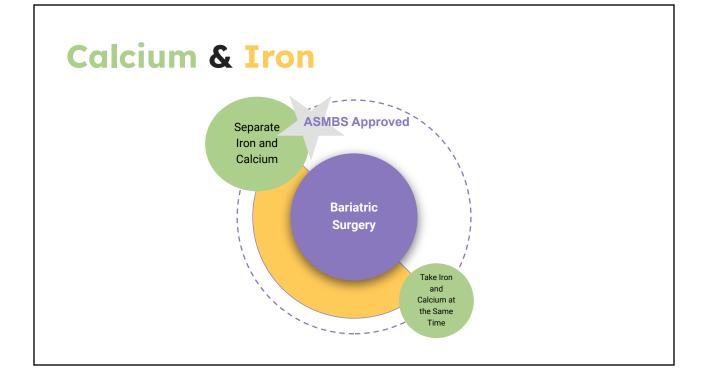
Studies: A Systematic Review and

Trials and Crossover Studies

Calcium Intake and Iron Status in Human

Dose-Response Meta-Analysis of Randomized

Ajibola Ibraheem Abioye,¹ Taofik A Okuneye,² Abdul-Majeed O Odesanya,³ Olufunmilola Adisa,⁴ Asanat I Abioye,⁵ Ayorinde I Soipe,⁴ Kamal A Ismail,⁷ JaeWon F Yang,⁸ Luther-King Fasehun,⁹ and Moshood O Omotayo^{18,11}



Vitamin C & Iron

- Vitamin C supports ferric \rightarrow ferrous iron conversion
 - 0 Needed for duodenal cytochrome b (DCYTB) and other ferrireductase
 - Increase Fe(2+) available to transport via DMT1
- Vitamin C complexes with ferric iron for membrane transport.
 - Fe(3+)-ascorbate complex 0

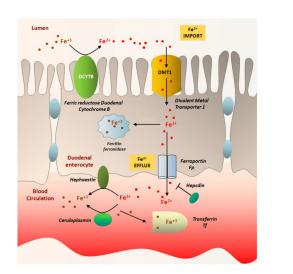


Image from Bjørklund et al 2020;94(3). doi: 10.1007/s00204-020-02652-2.

Gropper et al. Advanced Nutrition and Human Metabolism. 7th Edition. 2008. Kontoghiorghes et al. Medicines (Basel). 2020;7(8):45. doi: 10.3390/medicines7080045

Vitamin C & Iron

- After Bariatric Surgery
 - ASMBS recommended combination 0
 - Combination of Vitamin C and iron supplementation saw significant improvements in labs

Obesity Surgery, 9, 17-21

Iron Absorption and Therapy after **Gastric Bypass**

Barbara M. Rhode, PDt, MSc (Nutr); Chaim Shustik, MD, FRCP(C); Nicolas V. Christou, MD, PhD, FACS; Lloyd D. MacLean, MD, FRCS(C), FACS

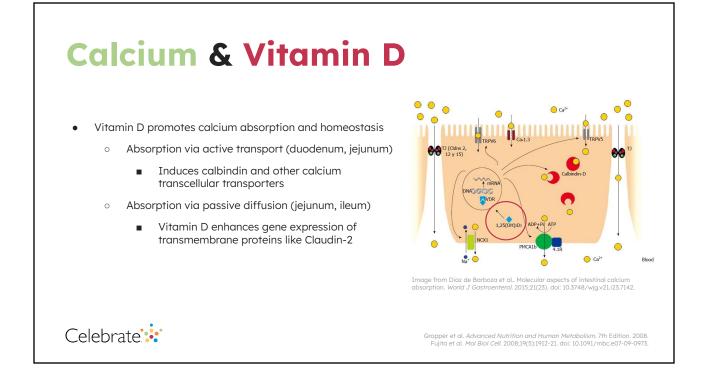
Department of Surgery and Division of Hematology, Royal Victoria Hospital, McGill University, Montreal, Quebec, Canada

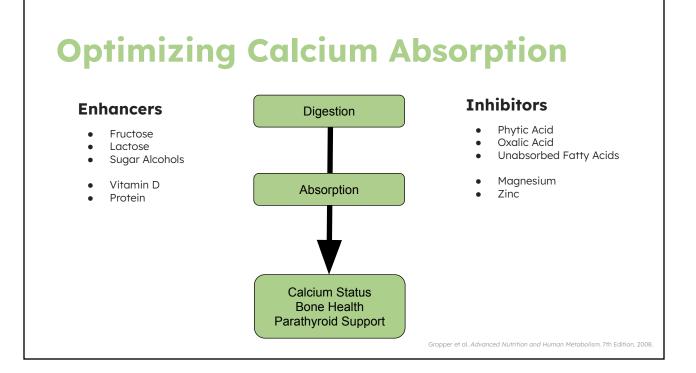
Iron Therapy after Gastric Bypass

Table 1. Response of hemoglobin and serum ferritin concentrations to ingestion of oral iron with and without vitamin C

Parameters	Pre	Iron	Iron + vitamin C
Hemoglobin (g/L)	116 ± 16*	$123 \pm 14^{\dagger}$	128 ± 14 [‡]
Serum ferritin (µg/L)	9.7 ± 6.2^{1}	14.8 ± 9.9^{1}	21.8 ± 13.7**
Anemia (%)	62	41	28

- $\label{eq:product} \begin{array}{l} *P < 0.01, \mbox{ pre versus iron}. \\ *P < 0.05, \mbox{ iron + vitamin C}. \\ *P < 0.05, \mbox{ pre versus iron + vitamin C}. \\ *P < 0.05, \mbox{ pre versus iron + vitamin C}. \\ **P < 0.01, \mbox{ iron versus iron + vitamin C}. \\ **P < 0.001, \mbox{ pre versus iron + vitamin C}. \end{array}$





Zinc & Copper . . . High intakes of zinc inhibits copper absorption . . Metallothionein (MT) copper bound to MT is unable to be absorped and is lost in the stool as enterocytes are shed Excess zinc upregulates metallothionein, 0 Zn Zinc which acts as a buffer with copper and reduces its functional use Associated with copper deficiency 0 0 0 overexpression of metallothioein protein in zinc excess state Prophylactic copper supplementation is effective without overexpression of MT ASMBS recommends 8-15mg zinc for every 0 1 mg copper Gastrointestinal circulation Image retrieved from Munie et al. (2021), Case Rep Nephrol Dial., 11(2). DOI: 10.1159/000512612

Gropper et al. Advanced Nutrition and Human Metabolism. 7th Edition. 2008. Gletsu-Miller & Wright. (2013). Adv. Nutr, 4. doi:10.3945/an.113.004341 Tapiero et al. Biomed Pharmacother. 57(9). DOI: 10.1016/s0753-3322(03)00012-x. Mechanick et al. (2019) Endocr Pract., 25(12). doi:10.4158/GL-2019-0406

Animal Proteins & Amino Acids

- Enhancers
 - Protein is thought to promote calcium & magnesium absorption/retention
 - Red meat, poultry, fish contain digestive products that may aid in iron absorption
 - Dairy proteins (casein, whey) may help increase passive diffusion of calcium
 - Sulfur-containing amino acids (Methionine, Cysteine) may promote bioavailability of minerals like zinc and selenium
- Inhibitor
 - Sulfur-containing amino acids may increase urinary excretion of calcium*
 - Raw fish contain thiaminases

Higdon & Drake. An Evidence-Based Approach to Vitamins and Minerals. 2nd ed. 2012. Gropper et al. Advanced Nutrition and Human Metabolism. 7th Edition. 2008. Schuchardt & Hahn (2017). Curr Nutr Food Sci. 13(4), DOI: 10.2174/157340131666170427162740 Melse-Boonstra, A. (2020). Font Nutr, 7(101). DOI: 10.3389/fnut.2020.00101.

Phytic Acid

 Phytic acid chelates with various minerals including iron, calcium, magnesium, copper, zinc and selenium.

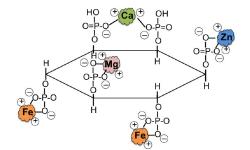


Figure 3. Phytic acid as chelator of divalent cations of iron (Fe²⁺), zinc (Zn²⁺), calcium (Ca²⁺), and magnesium (Mg²⁺).

Image retrieved from Majumder et al. 2019. Agronomy, 9, 803. 10.3390/agronomy9120803

Bronus, F. (2022). Nutrients 14(1), 25. DOI: 10.3390/nu14010025 Gropper et al. Advanced Nutrition and Human Metabolism. 7th Ed. 2018

Oxalic Acid

- Calcium and oxalic acid create CaOx salts in the intestine
 - Increases calcium excretion from fat malabsorption
 - Free oxalates bind with unabsorbed calcium and can contribute to kidney stone formation.
- Oxalic acid also inhibits zinc, nonheme iron, & magnesium.

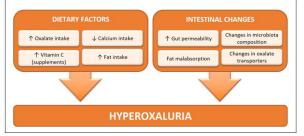


Image retrieved from Ormanji et al., *Nutrients*, 2020, 12(5); 1442. 10.3390/nu12051442

Ormanji et al., Nutrients, 2020, 12(5); 1442. 10.3390/nu12051442 Gropper et al. Advanced Nutrition and Human Metabolism. 7th Ed. 2018

Phytic Acid, & Oxalic Acid

- In most cases, no need to reduce whole grain and other foods high in fiber, phytates, or oxalates.
- Special attention to vegetarian/vegan patients, supplement schedules, excess of one food.
- Investigate extra Vitamin C supplementation

Decreasing Phytic Acid Content

- Food manufacturing and processing
- Cooking with heat
- Soaking beans

- Decrease High Oxalic Acid Foods
 - Teas
 - Rhubarb
 - Spinach
 - Beets
 - Turnips
 - Potatoes

Brouns F. Nutrients. 2021;14(1):25. doi: 10.3390/nu14010025. Ormanji et al. Nutrients. 2020;12(5):1442. doi: 10.3390/nu12051442. NIH ODS. Calcium - Health Professional Fact Sheet. 2021.

Sugars & Sugar Alcohols

- Fructose
 - \circ Reduce nonheme ferric iron \rightarrow ferrous iron or form chelates
 - Not likely to overcome inhibition of phytic acid or tannins in fruits
 - Thought to increase magnesium absorption
- Lactose
 - Thought to increase solubility of calcium
- Sugar Alcohols
 - Thought to increase iron absorption
 - Thought to improve calcium solubility

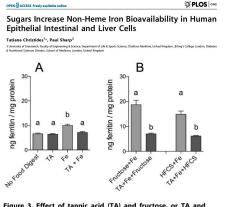


Figure 3. Effect of tannic acid (TA) and fructose, or TA and high-fructose corn syrup (HFCS), on iron-induced ferritin formation. Measurement of Caco-2 cell ferritin formation from digests

> Christides & Sharp. PlosONE 2013;8(12). DOI: 10.1371/jounral.pone.0083031 Gropper et al. Advanced Nutrition and Human Metabolism. 7th Ed. 2018

Nutrigenetics, Nutrigenomics & Nutrient Absorption

- Certain single nucleotide polymorphisms (SNPs) inform effectiveness of enzymes to support micronutrient absorption and utilization.
- Utilize knowledge to optimize dietary and supplement interventions

Genes to Consider -

- Vitamin D 25-Hydroxylase Enzyme is needed for the conversion of inactive 25(OH)D \rightarrow 1,25(OH)D in liver
 - Instructions provided by CYP2R1 Gene
- Vitamin D Receptor (VDR) transcription factor that regulates binding of active vitamin D.
 - Instructions provided by VDR Gene

SNP ID	Gene	p-Value (R/NR)	p-Value (S/D/I)	
rs10783219	VDR	0.6071	0.5330	
rs7139166	VDR	0.4249	0.6209	
rs731236	VDR	0.5133	0.0336	
rs757343	VDR	0.6023	0.6926	
rs10741657	CYP2R1	0.3748	0.4870	
rs10766197	CYP2R1	0.7235	0.3820	
rs12794714	CYP2R1	0.7221	0.8857	
rs1562902	CYP2R1	0.3136	0.1389	
rs10500804	CYP2R1	0.7443	0.8867	
rs1993116	CYP2R1	0.6900	0.6161	
rs7116978	CYP2R1	0.0727	0.0163	
rs10877012	CYP27B1	0.7108	0.3583	
rs4646536	CYP27B1	0.8004	0.8265	
rs703842	CYP27B1	0.7845	0.7230	
rs12785878	DHCR7/NADSYN1	0.9386	0.9820	_
rs3829251	DHCR7/NADSYN1	0.7488	0.4279	id
rs1155563	GC	0.9104	0.9904	
rs12512631	GC	0.3288	0.1126	
rs17467825	GC	0.0661	0.1188	
rs222020	GC	0.4039	0.4397	
rs2282679	GC	0.9068	0.7540	
rs2882679	GC	0.4395	0.6346	
rs3755967	GC	0.8826	0.5654	
rs4588	GC	0.2287	0.1922	-
rs7041	GC	0.1961	0.2328	
rs17219315	CYP24A1	0.6713	0.3635	
rs2244719	CYP24A1	0.7235	0.3820	
rs229624	CYP24A1	0.8586	0.8796	
rs2296241	CYP24A1	0.3863	0.4631	
rs2426496	CYP24A1	0.4395	0.6346	
rs4809960	CYP24A1	0.5668	0.1768	
rs6013897	CYP24A1	0.7249	0.9156	ie

Nutrigenetics - Vitamin D

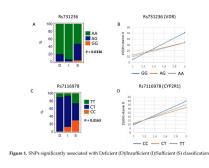
- Look at associations between genotype and response to vitamin D supplementation.
- Who may respond better to Vitamin D supplementation?
 - VDR Taq1 (rs731236) GG Carriers
 - CYP2R1 (rs7116978) CC Carriers
- How can we use this information to cater interventions?



MDPI

Brief Report The Role of Polymorphisms in Vitamin D-Related Genes in Response to Vitamin D Supplementation

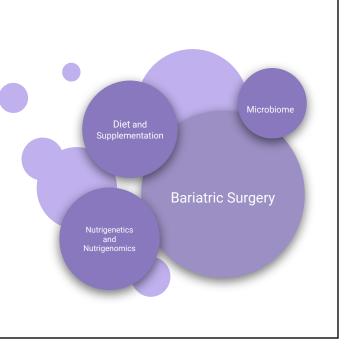
Sara Tomei ¹,*[®], Parul Singh ¹, Rebecca Mathew ¹, Valentina Mattei ¹, Mathieu Garand ¹[®], Mariam Alwakeel ²[®], Elham Sharif ²,*[†][®] and Souhaila Al Khodor ¹,*[†]



Tomei et al. Nutrients, 2020: 12(9): 2608. DOI: 10.3390/nu12092608

What to do?

- Use labs and clinical assessment to determine priorities.
- Emphasize importance of adequate diet recalls/journals to determine pertinent nutrient-nutrient interactions.
- Reevaluate the supplement schedule (with food, what food, empty stomach, etc.)
- Consider nutrigenomic testing to evaluate nutrient absorption SNPs.



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Thank You!

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