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ORIGINAL CONTRIBUTIONS

A Randomized Trial of a Novel Chewable Multivitamin and Mineral Supplement Following Roux-en-Y Gastric Bypass

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Abstract

Background Vitamin and mineral deficiencies are common following Roux-en-Y gastric bypass (RYGB) and can lead to significant morbidity, but little research on the efficacy of vitamin supplementation regimens exists. We compared the efficacy and tolerability of an investigational versus a standard multivitamin regimen in patients undergoing RYGB.

Methods Fifty-six patients, aged 18 to 65, were randomized to an investigational versus a standard multivitamin. Plasma levels of vitamins A, B-12, D, E-α, E-β/γ, thiamine, folate, iron, iron-binding capacity, iron saturation, prealbumin, and parathyroid hormone (PTH) were measured at 3 and 6 months postoperatively. Proteins induced by vitamin K absence (PIVKA), beta-carotene, coenzyme Q10, and mixed tocopherols were measured at 3 months postoperatively. Primary outcomes were differences in plasma levels at 3 and 6 months. Secondary outcomes were palatability, ease of use, and adherence.

Results Twenty-one patients were randomized to the standard regimen and 26 to the investigational multivitamin. Nine were lost to follow-up. At 3 months, plasma levels of PTH were lower ($p = 0.042$), and levels of vitamin D ($p = 0.033$), thiamine ($p = 0.009$), and beta-carotene ($p = 0.033$) were higher in the investigational multivitamin arm compared to those in the standard regimen arm. Patients receiving the investigational multivitamin reported higher taste satisfaction than those receiving the standard regimen ($p = 0.035$).

Conclusion The investigational multivitamin appears to be more effective than a standard multivitamin in maintaining therapeutic levels of clinically relevant vitamins and minerals, and was more palatable. Additional studies should be conducted to confirm these findings and refine the optimal dosing regimen.

Trial Registration www.clinicaltrials.gov under identifier NCT01475617

Keywords Multivitamin · Supplement · Nutritional deficiencies · Roux-en-Y gastric bypass · Randomized controlled trial

Introduction

Given the limited long-term effectiveness of traditional weight loss methods, bariatric surgery is increasingly becoming the preferred option for sustained weight loss. With the ascendancy of the laparoscopic approach, the two most common procedures are the Roux-en-Y gastric bypass (RYGB) and the vertical sleeve gastrectomy (VSG)

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[1]. While the VSG is growing in popularity, studies have demonstrated more durable weight loss and better resolution of obesity-associated comorbidities, such as type 2 diabetes, hypertension, and sleep apnea, with RYGB [2–5].

Vitamin and mineral deficiencies are common in individuals with obesity seeking bariatric surgery, and are further exacerbated by the surgery. This is especially true for RYGB patients, who experience more frequent and severe vitamin deficiencies [6]. RYGB intentionally induces a state of malabsorption by bypassing a large portion of the small intestine. In this procedure, a small portion of the stomach (the "gastric pouch") is divided from the remainder of the stomach and the attached duodenum. The proximal jejunum is then transected, and the distal portion of the jejunum, known as the Roux limb, is attached to the gastric pouch. Next, the remainder of the stomach along with the duodenum and proximal jejunum is reattached to the distal jejunum. Thus, undigested food bypasses the duodenum and passes directly into the jejunum, while pancreatic and biliary secretions travel through the duodenum unmixed with food, and only join with the undigested food in the distal jejunum. Because the presence of food in the duodenum stimulates the hormonal response of the body to feeding, the hormonal environment of the gastric bypass patient is dramatically altered, which most likely facilitates weight loss following RYGB [7–10], although the exact mechanisms are not fully understood [10]. Because pancreatic enzymes and bile are mixed with food for a shorter portion of the small intestine, absorption of calories is diminished, along with a decrease in the absorption of nutrients, especially fat-soluble vitamins A, D, E, and K. Poor absorption of vitamin B_{12}, calcium, folate, thiamine, and iron is common. Nutritional deficiencies, if left undiagnosed or untreated, can lead to serious and sometimes irreversible complications such as anemia, paresthesia, visual disturbances, and Wernicke's encephalopathy. To address these potentially severe consequences of nutritional deficiency, it is imperative that patient and provider be aware of the importance of proper vitamin supplementation. Nutritional guidelines have been published by the American Association of Clinical Endocrinology, the Obesity Society, and the American Society of Metabolic and Bariatric Surgery [11], which include recommendations for routine nutritional supplementation following restrictive and malabsorptive bariatric surgery, as well as biochemical surveillance of nutritional status postoperatively. However, there remains little prospective research on the optimal formulation of supplement regimens and on the efficacy of vitamin supplementation in this population. Formulations with better absorption and improved palatability have the potential to increase adherence and lessen the risk of nutritional deficiencies.

We performed an open-label randomized controlled trial comparing the efficacy and tolerability of an investigational chewable supplement (formulated with optimal vitamin and mineral content and designed for enhanced absorption) against the standard bariatric supplement used in patients undergoing RYGB at an academic bariatric surgical center.

Methods

The study was conducted at an academic institution that is accredited by the American College of Surgeons Bariatric Surgery Network. From February 2012 to April 2013, patients were recruited and consented after meeting a standard set of preoperative requirements, including meeting with a bariatric-registered dietitian and assessment by a clinical psychologist. Patients were eligible for the study if they were 18 to 65 years of age with a body mass index (BMI) greater than or equal to 35 kg/m^2 and were undergoing laparoscopic Roux-en-Y gastric bypass (LRYGB). Patients were excluded if they had used any nutritional supplements other than a multivitamin in the 3 months prior to surgery, if they were allergic to any component of the investigational or standard vitamins, or if they had documented levels of fat-soluble vitamins A, D, E, or K, or iron that exceeded the normal range. Patients who were nonadherent to their medical regimens, and pregnant or lactating women (up to 1 month prior to surgery) were also excluded. Following the standard of care, all bariatric patients underwent a one on one, 90-min session with our bariatric-registered dietician. During this session, the patients were educated regarding the specific dosing and frequency of the nutritional supplements they were required to take, as well as the timing of supplement intake to avoid incompatibilities (e.g., avoiding simultaneous iron and calcium intake). Once enrolled in the study, the research coordinator confirmed the patients' understanding of the required nutritional supplements and provided them with written instructions on administration (Appendix A). Patients were advised not to use dietary supplements other than a standard multivitamin for 30 days prior to the surgery. The study received investigational review board approval at our institution, and written informed consent was obtained from all patients before they underwent randomization. In accordance to the ethical obligations to patients and the research community, this trial was registered on the National Institute of Health web site, www.clinicaltrials.gov under identifier NCT01475617.

Study Design

Patients approved for LRYGB underwent a thorough history and physical exam by the patient's primary care

physician using a standard intake form. Demographics (age, sex, race, height, weight, and BMI) and medical comorbidities (hypertension, hyperlipidemia, type 2 diabetes mellitus, sleep apnea, GERD, and cancer) were documented. Informed consent was obtained up to 30 days prior to surgery. Between 30 and 0 days prior to surgery, baseline blood nutritional parameters were measured, consisting of serum iron, iron-binding capacity, and iron saturation, vitamin B_{12}, folate, thiamine, vitamin A, vitamin D, and vitamin E (as E-α, E-β/γ). Both vitamin E-α and vitamin E-β/γ were assessed individually because supplementation with vitamin E-α may cause a decrease in the blood concentration of vitamin E-β/γ. As part of the standard of care, participants had pre-surgical labs completed including a comprehensive metabolic panel, complete blood count, prothrombin time, activated partial thromboplastin time, and type and cross. Upon discharge after LRYGB surgery, patients were provided with a 3-month supply of either the investigational or standard supplementation regimen according to their treatment assignment. Blood nutritional parameters were re-evaluated at 3 and 6 months after surgery.

Randomization

After providing informed consent, consecutive patients were randomly assigned on the day of surgery in a 1:1 ratio to either the investigational vitamin regimen or the standard regimen using a computer-generated randomization scheme (Microsoft Excel 2007 data analysis tool pack) with a block size of four. Allocation was concealed by randomly generating the treatment assignment at the time of assignment. Each participant was provided a 3-month open-label supply of either the investigational vitamin regimen or the standard supplementation regimen.

Intervention

The interventional arm consisted of two investigational chewable tablets (Appendix B, Table 4) plus either three Nature Made® Calcium Softgels (600 mg calcium and 200 IU vitamin D per softgel) or six Vitamin Shoppe® calcium citrate tablets (250 mg calcium per tablet) per day. The standard arm consisted of two Flintstones Complete Multivitamins plus either three Nature Made® Calcium Softgels (600 mg calcium and 200 IU vitamin D per softgel) or six Vitamin Shoppe® calcium citrate tablets (250 mg calcium per tablet), as well as a Rexall Vitamin B12 (500 mcg per tablet) per day. Female participants in both interventional and standard arms who were anemic or were menstruating also received Twin Lab® Iron caps. Iron caps were not distributed to women who were postmenopausal unless they were anemic.

Nutritional Assessment at 3 and 6 months Post-Surgery

Following surgery, participants were scheduled for a free nutrition evaluation and visit with their surgeon at the 3- and 6-month postoperative visit. The nutritional evaluation was completed by a registered dietician within our Bariatric Center of Excellence and was part of the incentive for enrollment into the study. The participants were given a lab requisition to have their blood nutritional parameters measured at a participating laboratory facility 1 week prior to the scheduled 3- and 6-month postoperative visit. Participants were asked to fast for at least 8 h prior to having their blood specimens drawn. At 3 months, we assessed vitamins A, B_{12}, D, E-α, E-β/γ, thiamine, folate, iron, iron-binding capacity, iron saturation, prealbumin, parathyroid hormone (PTH), coenzyme Q10, β-carotene, and protein induced by vitamin K absence (PIVKA), a sensitive measure of vitamin K deficiency. The 6-month nutritional assessment included all these except coenzyme Q10, β-carotene, and PIVKA. All laboratory assays except coenzyme Q10, β-carotene, and PIVKA were part of the bariatric postoperative nutritional standard of care protocol.

To evaluate adherence, participants were asked to bring in their vitamin bottles to the 3- and 6-month scheduled visits. They also were asked to complete a questionnaire to evaluate taste and ease of taking the supplement regimen, recorded with 7- or 4-point Likert scales. At the 3-month visit, participants were given a second 3-month supply of supplements. On postoperative days 45 and 135, participants received a phone call from our research coordinator to assess adverse events and drug adherence and to reinforce adherence.

Outcome Measures

The primary outcomes were the blood concentrations of vitamins A, B_{12}, D, E-α, E-β/γ, thiamine, folate, iron, iron-binding capacity, iron saturation, prealbumin, and PTH, measured at both 3 and 6 months. PIVKA, beta-carotene, coenzyme Q10, and mixed tocopherols were measured at 3 months following surgery. The secondary outcomes were adherence and ease of use. Patients were asked if they found their supplements easy to use and if they were satisfied with the taste, aftertaste, and with the overall experience with their supplements, and their responses were assessed using Likert scales.

Statistical Analysis

Descriptive analysis included the medians and standard deviations for continuous variables and proportions for

categorical variables. Univariate analyses comparing patient characteristics between treatment arms were conducted using Student's *t* tests for continuous variables and chi-square test or Fisher's exact test for categorical variables. We compared median measurements of nutritional status at baseline, 3, and 6-month follow-up between arms at each time point using the non-parametric Wilcoxon Rank Sum, which does not require assumptions about the distribution of nutritional measurements. In addition, as a sensitivity analysis, we also compared the percent below the cutoff for clinical deficiency for each bioavailability between the standard and the investigational arms prior to surgery and at 3 and 6 months after surgery. We also compared demographic and nutritional status at baseline of those who completed the study to those who were lost to follow-up, to determine whether those who were lost to follow-up were non-representative of the whole group.

We analyzed the ease of use of the different supplement arms by comparing the proportion of patients reporting favorable results on the recorded Likert scales, (e.g., responding to the question "How easy or difficult is it to use the medication(s) in their current format?" with "somewhat easy" or "extremely easy"), and testing for the difference in proportion having favorable report with Fisher's exact test. For statistical testing, $p < 0.05$ (2-tailed) was considered significant. All statistical analyses were performed using Stata statistical software (version 14, StataCorp, College Station, TX).

Table 1 Baseline characteristics of the participants

		Total ($n = 47$) mean ± SD, or %	Standard ($n = 21$) mean ± SD, or %	Investigational ($n = 26$) mean ± SD, or %	p[a]
Demographics					
Age (years)		43.1 ± 10.7	43.0 ± 12.1	43.2 ± 9.8	0.957
Female		78.7%	90.5%	69.2%	0.150
White		66.0%	61.9%	69.2%	0.758
Black		29.8%	33.3%	26.9%	0.752
Hispanic		4.2%	4.8%	3.8%	1.000
Weight (lb)		288.2 ± 49.3	278.6 ± 46.6	294.8 ± 50.9	0.650
Height (in.)		66.4 ± 3.5	65.4 ± 3.2	67.1 ± 3.7	0.108
BMI (kg/m^2)		46.2 ± 7.2	46.2 ± 7.8	46.2 ± 6.8	0.991
Medical history					
Hypertension		52.3%	55.6%	50.0%	0.767
Diabetes		43.2%	38.9%	46.2%	0.760
High cholesterol		34.9%	27.8%	40.0%	0.523
Gastroesophageal reflux		31.8%	27.8%	34.6%	0.748
Sleep apnea		36.3%	33.3%	38.5%	0.716
Cancer		4.5%	5.6%	3.8%	1.000
Irritable bowel syndrome		4.5%	5.6%	3.8%	1.000
Cholecystectomy		15.9%	22.2%	11.5%	0.419
Multiple comorbidities		34.9%	33.3%	36.0%	1.000
Vitamin levels	Normal range				
Vitamin A (μg/dL)	38–98	54 ± 22.9	48.0 ± 28.1	58.5 ± 18	0.386
Vitamin B_{12} (pg/mL)	200–900	344.0 ± 216.8	365.0 ± 187.8	326.0 ± 241.3	0.622
Vitamin D (ng/mL)	32–100	15.5 ± 6.0	16.5 ± 7.4	15.0 ± 4.5	0.380
Vitamin E-α (mg/L)	5.7–19.9	10.5 ± 5.2	9.9 ± 5	10.6 ± 5.4	0.571
Vitamin E-β/γ (mg/L)	0–4.3	2.2 ± 0.9	2.2 ± 0.7	2.1 ± 1	0.548
Thiamine (nmol/L)	66.5–200	133.0 ± 50	123.0 ± 44.4	134.0 ± 55.2	0.856
Folate (ng/mL)	5.3–24	13.3 ± 5.8	14.3 ± 6	12.7 ± 5.5	0.302
Iron (μg/dL)	67–185	62.0 ± 52	61.0 ± 40	62.5 ± 60.7	0.700
Iron-binding capacity (μg/dL)	250–450	356.0 ± 81.3	375.0 ± 93.1	336.0 ± 65.6	0.051
Iron saturation (%)	26–39	18.0 ± 14.7	18.0 ± 11.2	18.5 ± 17.1	0.923

BMI body mass index

[a] Comparisons between trial arms tested with Fisher's exact test, or Wilcoxon Rank Sum, where appropriate

Results

Seventy-two patients approved to undergo laparoscopic Roux-en-Y gastric bypass were screened for eligibility. Three patients declined to participate in the study, and eight did not meet inclusion or exclusion criteria. Of the 61 patients who were subsequently consented, five were not randomized: one was converted from laparoscopic to open procedure, two were converted from gastric bypass to vertical sleeve gastrectomy, one did not undergo surgery due to insurance issues, and one experienced a gastrojejunal leak. Of the 56 patients who were randomized on the day of discharge following surgery, one subsequently moved out of state (standard treatment) and eight were non-adherent to their vitamin regimen and required additional oral or IV therapy for one or more nutritional deficiencies including iron, thiamine, and vitamins A and D (5 standard treatment and 3 investigational), leaving 47 who were treated according to protocol (21 standard treatment and 26 investigational); this constituted the denominator for analysis. Baseline demographic characteristics, medical history, and vitamin levels of the 47 subjects who completed the protocol are described in Table 1. Most participants were Caucasian (66%) and female (79%), with a mean age of 43 years (24–65) and BMI of 46 kg/m^2 (35–65). A substantial number of participants had comorbidities, including hypertension (52%), diabetes (43%), and sleep apnea (35%); comorbid conditions were similar between the two arms. Baseline vitamin levels did not differ significantly between treatment groups. In addition, the fraction of participants with bioavailability below clinical cutoffs were similar for all vitamins across arms (not shown). Of 47 total participants, 35 were followed to 3 months, and 27 to the 6-month assessment (Fig. 1). Participants lost to follow-up at 3 and 6 months were similar demographically to those who completed the study, and loss to follow-up was similar in the intervention arm (23% lost at 3 months, and an additional 15% lost by

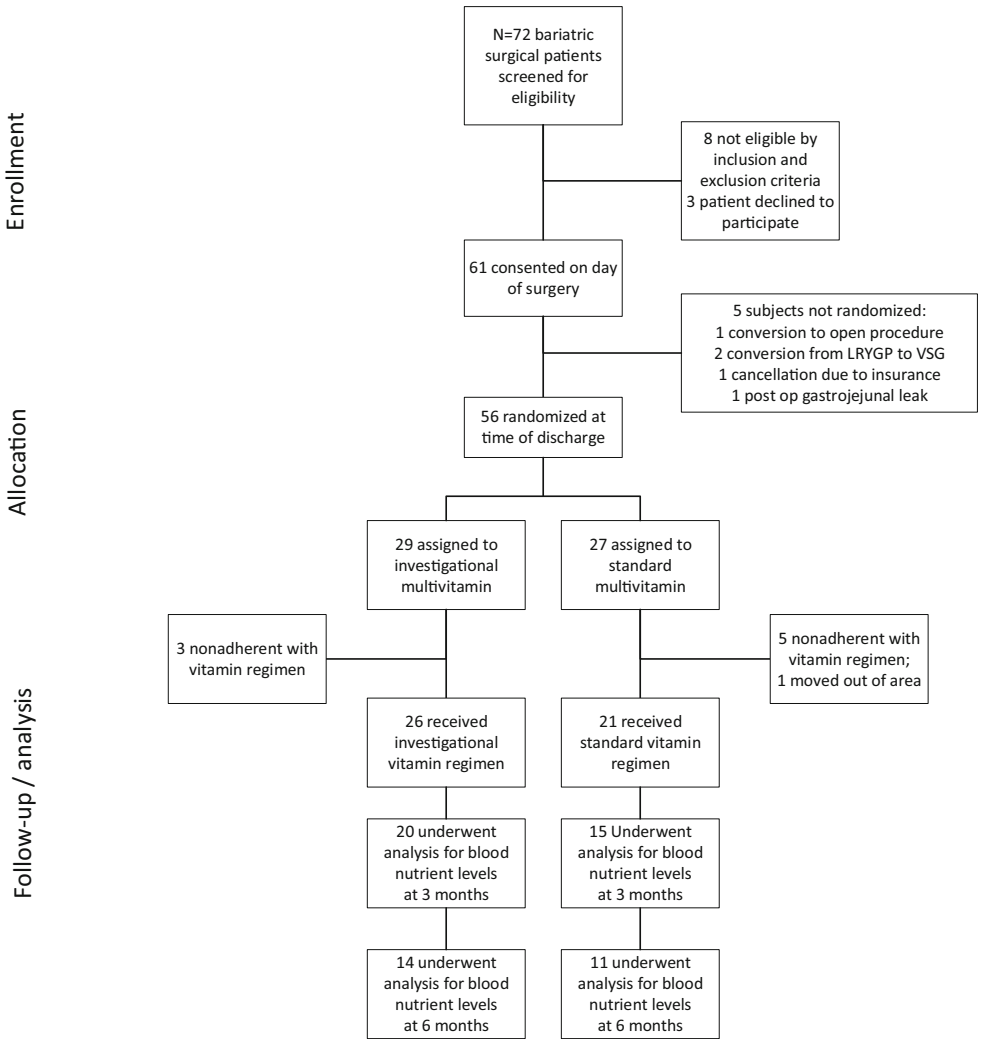

Fig. 1 Trial profile: enrollment, randomization, and follow-up of study patients

6 months) and standard arm (29% lost at 3 months, and an additional 5% lost at 6 months).

The primary outcomes, blood nutritional parameters at 3 and 6 months, are shown in Table 2. All nutritional parameters were not available for all patients due to laboratory and other errors; the number of measurements obtained for each parameter is indicated in the table. At 3 months, participants in the investigational group had higher vitamin D (33 versus 24 ng/mL, $p = 0.033$), thiamine (148 versus 109 nmol/L, $p = 0.009$), and beta-carotene (8 versus 4 dg/L, $p = 0.033$) and lower parathyroid hormone (29 versus 35, $p = 0.042$) levels than those in the standard regimen group. Participants in the investigational arm were more likely to be below the clinical deficiency for iron saturation (2 or 40% in standard arm below 20%, versus 8 or 100% below 20% in the investigational arm, not shown). At 6 months, there were no apparent differences in nutritional measurements between the two groups. However, vitamins D (40 versus 32, $p = 0.050$) and E-α (10 versus 8, $p = 0.050$) were higher in the investigational arm, at borderline statistical significance. Median blood levels of vitamin D, thiamine, and vitamin E-α and iron saturation over time are shown in Fig. 2 for those who were followed for at least 3 months.

Participants lost to follow-up at 3 months had lower baseline vitamin A (47 versus 64 μg/dL, $p = 0.023$) and

Table 2 Primary outcome: blood nutritional parameters at 3 and 6 months

	Normal bioavailable range	*N*	Standard regimen	Investigational regimen	p[a]
3 months			Median (SD)	Median (SD)	
Vitamin A (μg/dL)	38–98	31	39.5 (19.4)	57.0 (16.5)	0.565
Vitamin B_{12} (pg/mL)	200–900	35	649.0 (330.2)	759.5 (502.8)	0.271
Vitamin D (ng/mL)	32–100	32	24.0 (11.4)	33.0 (7)	*0.033**
Vitamin E-α (mg/L)	5.7–19.9	33	7.8 (4.9)	10.4 (3.7)	0.065
Vitamin E-β/γ (mg/L)	0–4.3	22	0.9 (0.7)	1.8 (0.6)	0.135
Thiamine (nmol/L)	66.5–200	31	109.0 (47.6)	148.0 (53.7)	*0.009**
Folate (ng/mL)	5.3–24	32	17.6 (6.5)	20.1 (5.7)	0.335
Iron (μg/dL)	67–185	33	54.0 (20.4)	55.0 (29.3)	0.638
Iron-binding capacity (μg/dL)	250–450	13	317.0 (26.8)	367.5 (47.8)	0.107
Iron saturation (%)	26–39	13	20.0 (4.1)	17.5 (2.4)	0.065
Prealbumin (mg/dL)	18–38	32	21.0 (5.1)	21.0 (4.4)	0.516
Parathyroid hormone (pg/mL)	10–65	34	34.5 (19)	28.5 (15.9)	*0.042**
Coenzyme Q10 (dg/L)	0.44–1.64	28	0.7 (0.2)	0.6 (0.3)	0.773
β-carotene (dg/L)	4–51	30	4.0 (2.1)	8.0 (12.9)	*0.033**
PIVKA (ng/mL)	0–2	25	14.6 (11)	4.9 (5.5)	0.459
6 months					
Vitamin A (μg/dL)	38–98	26	43.0 (20.9)	41.0 (17.2)	1.000
Vitamin B_{12} (pg/ml)	200–900	25	670.0 (358.1)	904.5 (341.2)	0.244
Vitamin D (ng/mL)	32–100	26	32.0 (11.4)	40.3 (18.9)	0.050
Vitamin E-α (mg/L)	5.7–19.9	25	7.5 (2.6)	10.4 (3.2)	0.050
Vitamin E-β/γ (mg/L)	0–4.3	13	1.1 (0.7)	1.1 (0.5)	0.616
Thiamine (nmol/L)	66.5–200	24	111.4 (27)	138.8 (48.2)	0.198
Folate (ng/mL)	5.3–24	23	18.8 (7.2)	20.0 (5.7)	0.526
Iron (μg/dL)	67–185	26	71.5 (32.7)	59.5 (50.2)	0.607
Iron-binding capacity (μg/dL)	250–450	7	325.5 (64.9)	236.0 (−)	0.286
Iron saturation (%)	26–39	7	22.0 (6.2)	21.0 (7.1)	0.845
Prealbumin (mg/dL)	18–38	27	18.5 (6.4)	21.5 (4.2)	0.111
Parathyroid hormone (pg/mL)	10–65	22	37.0 (10.4)	27.0 (14.4)	0.547

Differences significant at 0.05 are in italics

PIVKA Proteins induced by vitamin K absence

*$p < 0.05$

[a] Comparisons between trial arms tested with Wilcoxon Rank Sum

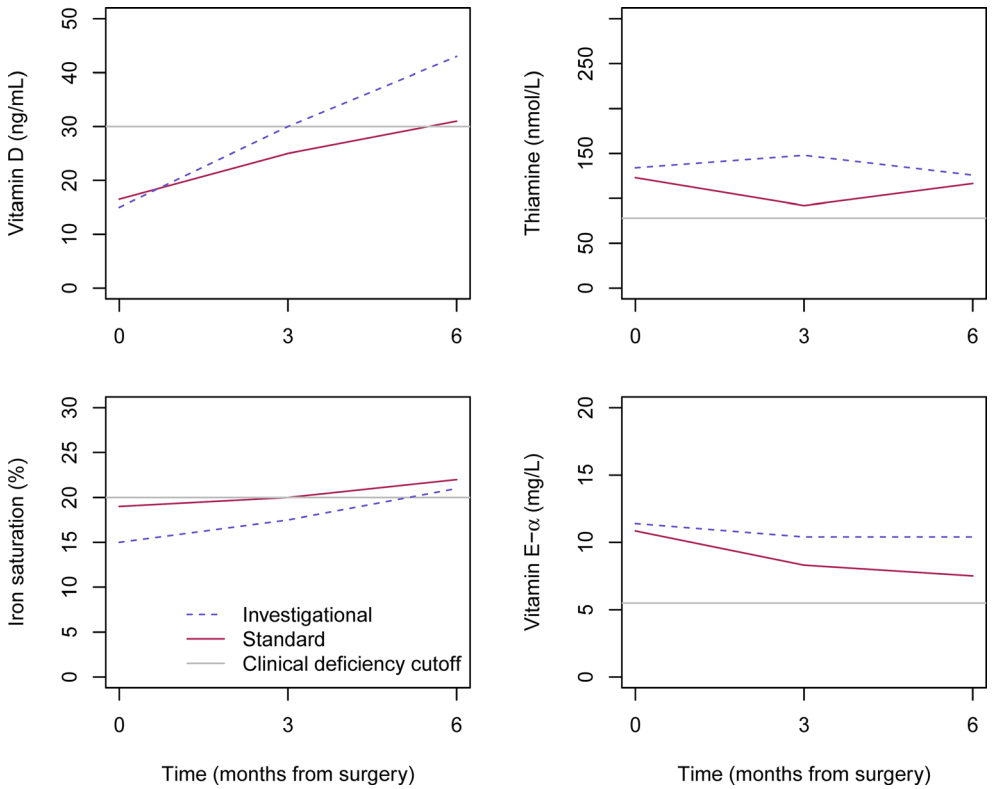

Fig. 2 Median blood nutritional parameters trends over time

E-α (8.6 versus 10.8 mg/L, $p = 0.004$) levels compared to those who did achieve 3-month follow-up (Appendix C, Table 5). Patients achieving 6-month follow-up had similar baseline vitamin levels to those who did not achieve 6-month follow-up. Patient adherence, indicated by the number of returned pills, was similar across supplement type. Patients were judged adherent if the number of returned pills at the time of their follow-up visit indicated that they had taken at least 75% of their assigned supplement during that period. One patient was non-adherent at 3 months, and six patients at 6 months; differences between treatment groups were not significant ($p = 0.394$ and 1.000 at 3 and 6 months, respectively).

Participant satisfaction with supplement regimens was recorded at 3- and 6-month follow-up. Thirty-three patients reported satisfaction levels at 3 months, and 26 participants at 6 months. Patients in the investigational arm indicated higher satisfaction with the taste of the multivitamin compared to those in the standard group (90 versus 54%, $p = 0.035$), though overall satisfaction with supplement regimens did not vary between the groups either at 3 or 6 months (Table 3). There is no evidence that participants had a differential rate of side effects, with 2 (10%) and 1 (8%) reporting side at effects at 3 months, and 0 (0%) and 2 (18%) at 6 months, in the investigational and standard regimens, respectively.

Discussion

LRYGB is an accepted means of attaining sustained weight loss and resolution of cardiometabolic outcomes in individuals with severe obesity [12, 13]. However, successful long-term outcomes are critically dependent on attention to postoperative care, notably maintenance of adequate nutritional status. The malabsorption intentionally induced by LRYGB mandates the use of effective postoperative vitamin supplementation. In addition, many bariatric patients have pre-existing vitamin deficiencies, especially vitamin D deficiency, prior to surgery [14–16]. We compared an investigational multivitamin regimen with a standard regimen, for postoperative use in patients undergoing LRYGB, and found beneficial effects on several important nutritional parameters with the investigational regimen, including a 38% higher level of vitamin D at 3 months. Accompanying the increased bioavailability of vitamin D was an 18% lower parathyroid hormone level, confirming the physiologic significance of the increased vitamin D. Thiamine and beta-carotene levels were also significantly higher with the investigational vitamin. Vitamin B_{12} levels were 19% higher with the investigational vitamin; however, this difference was not statistically significant due to the large standard deviation in the B_{12} distributions. Importantly, from a convenience standpoint, B_{12} is incorporated in the investigational

Table 3 Satisfaction with supplement regimens at 3- and 6-month follow-up: percent agreeing with statement

	Standard vitamin		Investigational vitamin		
Item[a]	Number analyzed	Number (%) agreeing	Number analyzed	Number (%) agreeing	p^c
3-month follow-up					
This multivitamin is easy to use.	13	11 (85%)	20	17 (85%)	1.000
I am satisfied with the taste of this multivitamin.	13	7 (54%)	20	18 (90%)	*0.035**
I am satisfied with the aftertaste of this multivitamin.	13	8 (62%)	19	15 (79%)	0.427
I have experienced side effects as a result of taking this multivitamin.	13	1 (8%)	20	2 (10%)	1.000
Taking all things into account, I am satisfied with this multivitamin.	13	10 (77%)	19	17 (89%)	0.374
I am confident that taking this multivitamin is a good thing for me.	13	1 (8%)	20	0 (0%)	0.394
6-month follow-up					
This multivitamin is easy to use.	11	10 (91%)	15	13 (87%)	1.000
I am satisfied with the taste of this multivitamin.	11	9 (82%)	15	12 (80%)	1.000
I am satisfied with the aftertaste of this multivitamin.	11	8 (73%)	15	10 (67%)	1.000
I have experienced side effects as a result of taking this multivitamin.	11	2 (18%)	14	0 (0%)	0.183
Taking all things into account, I am satisfied with this multivitamin.	11	10 (91%)	15	14 (93%)	1.000
I am confident that taking this multivitamin is a good thing for me.[b]	11	10 (91%)	15	14 (93%)	1.000

Differences significant at 0.05 are in italics

*p significant at 0.05

[a] Items measured on a seven-point Likert scale, from "not easy to use" to "extremely easy to use" or "not satisfied" to "extremely satisfied;" responses shown as percent responding "somewhat easy to use" to "extremely easy to use" or "somewhat satisfied" to "extremely satisfied"

[b] Measured on a four-point Likert scale, from "not confident" to "extremely confident;" responses shown as percent responding "somewhat confident" to "extremely confident"

[c] Comparing distribution with Fisher exact test

preparation, obviating the use of a separate B_{12} supplement. Adherence literature has shown that a potential way to improve patient compliance to directives is to simplify their routine as much as possible [17].

In March of 2013, new clinical practice guidelines for the perioperative nutritional, metabolic, and non-surgical support of the bariatric surgical patient were released by the American Association of Clinical Endocrinologists (AACE), the Obesity Society (TOS), and the American Society for Metabolic and Bariatric Surgery (ASMBS). These guidelines included updated nutritional supplementation guidelines for patients undergoing bariatric surgery. Among these recommendations, vitamin D supplementation was increased from 1000 to 3000 IU of vitamin D_3 daily for all bariatric surgical patients. As well, the use of chewable or liquid multivitamins, rather than capsules or gel tablets, was recommended for a duration of 3 to 6 months rather than 4 weeks immediately following surgery [11]. The investigational supplement studied in our trial includes the recommended 3000-IU daily dose of vitamin D_3 (as well as vitamin B_{12}). By obviating the use of additional vitamin D and B_{12} supplements, administration is simplified. While we did not see significant differences in adherence in this study, the investigational supplement did result in higher vitamin D levels and lower PTH levels.

Improving adherence in our bariatric patient population is essential in preventing irreversible consequences from nutritional deficiencies. Strategies for improved adherence have included improved education and resources, improved follow-up methods, ease of treatment, and palatability. Palatability of chewable vitamins is especially important in the bariatric population, where supplementation is for a lifetime. The investigational preparation in this trial was rated higher at 3 months and comparable at 6 months, with similar overall satisfaction for both preparations. During our clinical trial, eight patients were non-adherent with supplementation during the first 3 months following surgery. Each of these patients was excluded from the study and subsequently received individualized therapy for their specific nutritional deficiencies, which included iron, thiamine, and vitamins B_{12}, A, and D. Iron, thiamine, and multivitamins were given as oral or IV infusions, and vitamin A and D deficiencies were treated with oral supplementation.

To our knowledge, only one other randomized controlled trial comparing vitamin supplementation regimens in bariatric surgical patients has been published, which used lower doses of vitamin D (500 IU) in the investigational supplement, as well as lower doses of vitamins B_{12} and A [18].

Pre-existing nutritional deficiencies in our study population were similar to those reported in other bariatric populations [14–16]. As such, our findings should be generalizable to these populations. Our study was limited by loss to follow-up in both arms in the study, which reached 45% by 6 months. This is a common problem among bariatric cohorts enrolled in longitudinal studies. However, loss to follow-up was similar across arms, and participants who were lost to follow-up were similar in their demographic profile and baseline nutritional status to those who achieved follow-up (Appendix C, Table 5). While our trial was not blinded, our primary outcome—blood nutritional parameters—was an objective measure and unlikely to be affected by the absence of blinding. In addition, participants did not report their diet or nutritional intake prior to measurement. As such, we were unable to account for dietary nutrition that may or may not contribute to the resulting lab parameters.

Conclusion

Participants undergoing RYGB are at high risk for nutritional deficiencies after surgery and consistent use of a multivitamin supplement is essential. In this trial, we found that the investigational vitamin supplement offered equal or better bioavailability and palatability than the standard regimen, with two fewer pills per day (due to the incorporation of vitamins D and B_{12} in the investigational supplement). Palatability and ease of use are important factors in maintaining long-term adherence and ensuring optimal outcomes. A supplement specifically formulated for the bariatric patient may offer advantages compared to over-the-counter standard vitamins [19]. Attention to detail in all aspects of care of the bariatric patient remains the best way to ensure consistently favorable outcomes, and selection of multivitamin supplements should be done thoughtfully. Future research in this area may include strategies to tailor nutritional supplementation to the precise needs of the individual patient.

Funding Information Study materials (drug) and/or additional financial support were provided by Yasoo Health Inc.

Compliance with Ethical Standards

Conflict of Interest Dr. Papas is the former medical director of Yasoo Health. All other authors declare that they have no competing interests.

Informed Consent Informed consent was obtained from all individual participants included in this study.

Ethical Approval This study was approved by the Institutional Review Board of the Johns Hopkins School of Medicine.

Appendix A

Healthy DIRECTIONS
Health Education Information from Johns Hopkins Bayview Medical Center

JOHNS HOPKINS MEDICINE
JOHNS HOPKINS BAYVIEW MEDICAL CENTER

Vitamin and Mineral Supplementation for Roux-en-Y Gastric Bypass

Multivitamin (MVI) with Minerals:

- **Take 1 or 2 MVIs every day for a lifetime. Serving size will depend on individual products. MVI(s) must provide at least 200% RDA for iron (36mg), folic acid (800mcg) and thiamine (3mg) and 2 mg of copper. It is best if MVI also contains selenium and zinc.**
- **Chewable and liquid vitamins are best absorbed. Suggest vitamins in this form for at least the first 3-6 months if not for a lifetime.** If you decide to switch to a pill form after 6 months, soft gels or capsules may be better absorbed than tablets.
- **Do NOT take MVI in gummy form**. Gummies do **NOT** have all the vitamins and minerals you need.
- Take with food (except dairy) to help with absorption.

Calcium:

- **Choose calcium citrate.** Avoid calcium carbonate (Tums®, Viactiv®, OsCal®, Caltrate®), calcium triphosphate, oyster shell, bone meal, etc.
- **Take 500-600 mg of calcium three (3) times per day** to equal at least 1,500 mg per day. Separate doses by at least 2 hours for maximum absorption. Look at the serving size on the label and adjust your dose to make sure you're getting 500-600 mg of elemental calcium each dose.
- **Chewable and liquid vitamins are best absorbed. Suggest vitamins in this form for at least the first 3-6 months if not for a lifetime.** If you decide to switch to a pill form after 6 months, soft gels or capsules may be better absorbed than tablets.
- **Chewy (NOT Gummy) calcium citrate supplements are acceptable. Do NOT take calcium in gummy form.** Gummies are not calcium citrate and are not the best absorbed.
- **Must contain Vitamin D.**
- **Take 2 hours apart from iron supplements or MVI with iron** for maximum absorption.

Iron:

- Menstruating women and/or patients with iron deficiency anemia need more iron.
- **If MVI contains iron- Take an additional 18-29 mg elemental iron per day. If MVI does not contain iron- Take 60-65 mg elemental iron per day.** Total intake should be 54-65 mg elemental iron a day.
- Taking Vitamin C at the same time as iron can increase absorption.
- **Chewable and liquid vitamins are best absorbed. Suggest vitamins in this form for at least the first 3-6 months if not for a lifetime.** If you decide to switch to a pill form after 6 months, soft gels or capsules may be better absorbed than tablets.

Vitamin D:

- **Take 3,000 International Units of Vitamin D_3 per day.**
- **Chewable and liquid vitamins are best absorbed. Suggest vitamins in this form for at least the first 3-6 months if not for a lifetime.** If you decide to switch to a pill form after 6 months, soft gels or capsules may be better absorbed than tablets.
- Vitamin D is best absorbed when you take it with food.

Vitamin B12:

- **Take 500 mcg sublingual (under your tongue) tablet or liquid once a day or 1000 mcg sublingual tablet or liquid every other day. OR**
- **1000 mcg shot once a month** (injections prescribed by your primary care physician).
- **500 mcg nasal spray once a week** (available by prescription from your bariatric provider or primary care physician).

Suggested Timing of Supplements

	Extra Iron	No Extra Iron
Breakfast	500-600 mgs Calcium & B12	500-600 mgs Calcium & B12
Snack		
Lunch	500-600 mgs Calcium	500-600 mgs Calcium
Snack	500-600 mgs Calcium	
Dinner	Multivitamin(s) & Vitamin D	Multivitamin(s) & Vitamin D
Snack	Iron	500-600 mgs Calcium

**May take vitamin B12 at any time during the day as it does not interact with other vitamins or minerals.*

Please bring all vitamins and minerals to your appointment with the dietitian to assure you are taking the appropriate products and serving sizes.

Dietitian: _____

For more information, please contact the Johns Hopkins Bayview Medical Center's Clinical Nutrition Department at 410-550-1549.
To schedule an outpatient nutrition appointment with a dietitian, call 410-550-7728.

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Appendix B

Table 4 Formulation of multivitamin/mineral supplements and standard and investigational supplement regimens

	Standard[a,c]	Investigational[b,c]
Vitamin A	6000 IU	10,000 IU
β-Carotene	33%	75%
Palmitate	67%	25%
Vitamin C (sodium ascorbate)	120 mg	90 mg
Vitamin D_3	800 IU	1500 IU
Vitamin E		
d-α-Tocopherol	60 IU	150 IU
Other mixed tocopherols		30 mg
Vitamin K1 (phytonadione)		400 mcg
Thiamine (mononitrate)	3 mg	12.5 mg
Riboflavin (vitamin B_2)	3.4 mg	3.4 mg
Niacin (niacinamide)	30 mg	20 mg
Vitamin B_6 (pyridoxine hydrochloride)	4 mg	4 mg
Folic acid	800 mcg	800 mcg
Vitamin B_{12} (cyanocobalamin)	512 mcg	500 mcg
Biotin	80 mcg	600 mcg
Pantothenic acid	20 mg	20 mg
Iron[c]		
Ferrous fumarate	36 mg	36 mg
Iodine	300 mcg	150 mcg
Magnesium	40 mg	50 mg
Zinc		
Zinc amino acid chelate		15 mg
Zinc oxide	24 mg	
Selenium (selenomethionine)		70 mcg
Calcium	1500 mg	1500 mg
Copper	4 mg	2 mg
Manganese		2 mg
Chromium		120 mcg
Molybdenum		75 mcg
Sodium	20 mg	10 mg
Choline	76 mg	20 mg
Boron		2 mg
Coenzyme Q10		10 mg

[a] Two standard supplement tablets, plus calcium and vitamin B_{12}

[b] Two investigational supplement tablets, plus calcium

[c] A separate 18-mg iron fumarate tablet, once daily, was given only to female participants who were menstruating or anemic in both standard and investigational arms

Appendix C

Table 5 Baseline nutritional status prior to Roux-en-Y gastric bypass by loss to follow-up

		At 3 months			At 6 months		
	Total ($n = 47$) median (SD)	Follow-up ($n = 35$) median (SD)	No follow-up ($n = 12$) median (SD)	p^a	Follow-up ($n = 27$) median (SD)	No follow-up ($n = 20$) median (SD)	p^a
Vitamin A (μg/dL)	54.0 (22.9)	64.0 (25.0)	47.0 (11.0)	*0.023**	53.0 (20.9)	55.5 (25.7)	0.654
Vitamin B_{12} (pg/ml)	344.0 (217)	354.0 (232)	307.0 (162)	0.243	365.0 (222)	327.5 (212)	0.480
Vitamin D (ng/mL)	15.5 (6.0)	16.0 (5.4)	13.0 (7.7)	0.764	15.0 (5.2)	16.0 (6.9)	0.724
Vitamin E-α (mg/L)	10.5 (5.2)	10.8 (5.6)	8.6 (2.5)	*0.004**	11.4 (5.5)	9.2 (4.5)	0.086
Vitamin E-β/γ (mg/L)	2.2 (0.9)	2.3 (0.8)	1.8 (1.1)	0.745	2.3 (1.0)	2.0 (0.7)	0.119
Thiamine (nmol/L)	133.0 (50.0)	134.0 (49.5)	125.0 (53.1)	0.696	123.0 (36.9)	134.0 (61.9)	0.206
Folate (ng/mL)	13.2 (5.8)	13.0 (5.8)	13.5 (6.0)	0.855	12.6 (6.0)	14.7 (5.6)	0.719
Iron (μg/dL)	62.0 (52.0)	74.0 (58.5)	58.5 (18.7)	0.061	74.0 (61.7)	60.0 (34.3)	0.282
Iron-binding capacity (μg/dL)	356.0 (81.3)	356.0 (69.2)	334.5 (113.1)	0.809	342.0 (90.3)	356.0 (67.3)	0.306
Iron saturation (%)	18.0 (14.7)	18.0 (16.7)	17.5 (5.0)	0.202	18.0 (17.8)	17.5 (8.9)	0.372

Differences significant at 0.05 are in italics

*$p < 0.05$

[a] Comparison between nutritional status of regimens tested with Wilcoxon Rank Sum

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