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ORIGINAL CONTRIBUTIONS

A Pilot, Randomized Study in Women of Nutrition-Related Clinical Chemistry at 6 Weeks after Roux en Y Gastric Bypass: Comparison of Two Nutrition Support Plans

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Abstract

Background The current pilot study tested a twofold hypothesis: some nutrition-related chemical measures change by 6 weeks after Roux en Y Gastric Bypass (RNYGB); one of two nutrition support plans will prevent chemical signs of nutrition problems at 6 weeks better than the other. After RNYGB, nutrition support should begin right away. However, studies on nutritional status mostly examine subjects much later. In addition, little attention has been paid to optimizing nutrition support plans.

Methods Premenopausal females scheduled for RNYGB were given either a commercially available meal replacement product (2 servings/day) + other supplements or just a new meal replacement (2 servings/day). The latter included some nutrient versions that might enhance absorption. Blood and urine samples were taken before and 6 weeks after surgery.

Results In both groups, plasma vitamin D and B_{12} did not change, plasma osteopontin and vascular endothelial growth factor rose, while plasma retinol binding protein and a bone resorption marker declined. Copper status changes differed between groups based on plasma ceruloplasmin. Iron status improved in both groups (ferritin to c-reactive protein ratios). With the new formulation, magnesium status may have improved, urinary potassium rose, and blood sugar fell. In the other group, a liver damage marker increased, while homocysteine decreased.

Conclusions Nutrition-related parameters showed varying trends 6 weeks after RNYGB. Some of the trends were affected by the type of nutritional support provided.

Keywords Bariatric · Gastric bypass · Nutritional status · Vitamins · Minerals

Introduction

After Roux en Y Gastric Bypass (RNYGB), some nutrition-related parameters, such as body weight, blood sugar, and inflammation, are expected to improve. However, this may come with development of nutritional deficiencies which may result due to limited food consumption, poor compliance with nutritional support product recommendations, and reductions in certain nutrient absorptions [1, 2] (i.e., decreased fat absorption including fat-soluble vitamin D) [1–3]. Deficiencies of other nutrients reported include vitamin B_{12}, iron, and copper [1–4]. Also, some parameters can change that are influenced by overall nutrition including markers of inflammation, liver health, bone turnover, and heart disease risk.

Since prevention of nutritional problems is preferred practice, it would be useful to know how quickly nutritional problems develop after RNYGB and how quickly nutrition support

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products have impact. In the early postoperative period, high protein beverages or meal replacement products as well as vitamin and mineral supplements are recommended. It is assumed "normally nourished" pre-surgery subjects have substantial stores of nutrients, and that they are motivated to comply with nutritional recommendation. However, the idea that nutritional deficiencies only develop later in the postoperative period lacks verification; published studies on nutritional problems after bariatric surgery have only examined subjects months to years after the surgery has occurred. Moreover, these studies have not assessed the adequacy of the nutritional support regimens. The amounts and specific forms of certain nutrients may or may not provide optimum nutrition in the early post-surgery stage. Therefore, it should be determined whether nutritional problems develop shortly after surgery if nutrition support products are given.

The current study tested a twofold hypothesis: some nutrition-related chemical measures can change by 6 weeks after Roux en Y Gastric Bypass (RNYGB); one of two nutrition support plans will prevent chemical signs of nutrition problems at 6 weeks better than the other.

Methods

Subjects

All research subjects signed a Review Board approved consent form. Premenopausal females who were being scheduled for RNYGB were offered study participation. Subjects were not excluded for type 2 diabetes. For the group designated below as standard products, 6 subjects had diabetes; the other group had 5. All subjects had normal renal function. Other than diabetes, recruited subjects did not have any major systemic diseases like rheumatoid arthritis or hepatitis. Comorbidities that were accepted were depression, moderately high blood pressure, asthma, acid reflux, degenerative disk disease, dyspnea upon exertion, and osteoarthritis. Patients underwent RNYGB with a complete division of the stomach to create a proximal pouch of approximately 60–90 cc. A roux limb of 100 cm was utilized and the pancreaticobiliary limb was 50–75 cm. Common channel was not measured. An approximately 1–1.5 c. gastrojejunostomy was performed along the lesser curve. Study participants donated pre-surgery urine and blood samples as part of the usual preoperative procedure (7–10 days of the scheduled surgery).

A clear liquid diet with no concentrated sugar was initiated on postoperative day (POD1). If this was tolerated on POD 2, the diet was advanced to full liquids with no concentrated sugar. If a full liquid diet was tolerated for two consecutive meals, the subjects were discharged home to consume a full liquid diet with follow-up scheduled for 1 week later. Patients consumed liquids for 3 weeks, followed by liquids + a pureed diet for another 2 weeks, and then a regular diet by 6 weeks post-surgery. The nutritional replacement products were delivered to the patient in the hospital prior to discharge. As part of the surgery approval process, patients completed at least three nutrition education classes focusing on food selection to achieve a protein intake of 1.2 g/kg ideal body weight (generally around 50–70 g). Patients kept dietary intake logs, and these were reviewed with the program dietitian at these visits. Although the pureed diet was not identical among study subjects, the protein goals (1.2 g/kg ideal body weight) and strategies recommended by the bariatric dietitian to achieve the goals were consistent. The protein goals were met mostly by the meal replacements, but pureed foods added to the protein intake (under 20% of total protein). This food intake, when compared to the nutrition support products supplied, was judged to supply only minor amounts of the nutrients that were studied here.

Subjects met with the medical team in an outpatient setting at 1 week and 6 weeks. Repeat blood and urine samples were obtained at 6 weeks following surgery. As a motivation for study participation, subjects were given nutrition support products without charge. At the 6-week visit, patients completed questionnaires regarding palatability and adherence with the nutritional supplement regiment. All subjects who appeared at the week 6 meeting indicated good compliance on their questionnaires. Since no payment or other reward incentives were given for attending the week 6 visit, subjects had no reason to make this visit unless they were compliant.

Nutritional Products

Subjects were randomly assigned to either standard products or a new product. Subjects in the first group were told to consume two meal replacement product servings/day + certain supplements (Table 1). These products were purchased from Bariatric Advantage (Aliso Viejo, CA). The meal replacement product was given to subjects as powder with a shaker and a measuring scoop. The subjects added powder + water to an 8 or 10 oz line on the shaker. Three flavors were provided in equal amounts (vanilla, chocolate, and strawberry). Participants assigned to the new product were told to take two meal replacement products per day (Table 2) and not to consume any other supplement products. The subjects prepared the product like the other group. Equal amounts of three flavors were given (vanilla, chocolate, and strawberry).

The new product was formulated by a research team member and prepared by two of them. Most vitamins and minerals were obtained as a premix from Fortitech, Schenectady, NY. Albion (Clearfield, UT) provided Iron Taste Free™, copper bisglycinate, and magnesium bisglycinate taste free. The methylcobalamin came from AIDP, City of Industry, CA. The debittered green tea extract was SynerTea™ from AMAX Nutrasource, City of Industry, CA. Calcium lactate

Table 1. Contents of the standard products. Meal replacement product—content per serving (2 servings consumed per day). Whey protein isolate—27 g protein; dietary fiber (undisclosed vegetable fiber)—5 g. Vitamin-minerals

- Vitamin A—2500 International Units
- Vitamin D—200 International Units
- Vitamin E—15 International Units
- Vitamin K—40 μg
- Vitamin C—30 mg
- B1–0.75 mg
- B2—0.85 mg
- B6—1.0 mg
- B12 as cyanocobalamin—3 μg
- Niacin—10 mg
- Biotin—0.15 mg
- Pantothenic acid—5 mg
- Folate—200 μg
- Iodine—75 μg
- Zinc as oxide—7.5 mg
- Sodium—320 mg
- Selenium as amino acid chelate—35 μg
- Manganese as ammoniate—1 mg
- Molybdenum—37.5 μg
- Calcium as dicalcium phosphate—150 mg
- Chromium as picolinate—60 μg
- Iron as ferronyl iron—6.3 mg
- Copper as gluconate—1.0 mg
- Magnesium as oxide—80 mg

Approximately 150–160 calories per serving depending on the flavor. Calcium lozenges—2 per day; calcium (as citrate)—500 mg. Iron supplement—2 tablets per day, chewable—iron (as Ferronyl® carbonyl iron)—18 mg; vitamin C—30 mg. Vitamin B12 supplement-1 per week, put under the tongue or between cheek and gum and allowed to dissolve over several minutes. Vitamin B12 (cyanocobalamin)—1000 μg; folic acid—200 μg. Vitamin D suppelement-1capsule per week—vitamin D3 (cholecalciferol, water-miscible "dry" vitamin D)—5000 International Units

was supplied by Purac of America, Linclonshire, IL. Nutriose® fiber was contributed by Roquette America, Keokuk, IA. Liquid micellular vitamins A and D were prepared in a single liquid preparation by 3Is, Wooster, OH. For this preparation, the study subjects used a marked dropper to add this liquid to one of the two daily servings of the meal replacement product.

Chemical analysis

Plasma glucose and alanine aminotransferase (ALT), plasma and red blood cell magnesium, and plasma and urine potassium were assessed using a Roche Cobas C111 Clinical Chemistry Analyzer (Indianapolis, IN). Plasma ceruloplasmin was measured by radial immunodiffusion using plates from The Binding Site, San Diego, CA.

Table 2 Contents of the New Product Powder. Content per serving (2 servings consumed per day). Whey protein proprietary combination—27 g protein. Dietary fiber (Nutriose soluble fiber)—5 g. Debittered green tea extract—350 mg of flavonoids. Vitamin-minerals

- Vitamin E—15 International Units
- Vitamin K—60 μg
- Vitamin C—30 mg
- B1—0.75 mg
- B2—0.85 mg
- B6—1.0 mg
- Vitamin B12 as methylcobalamin—500 μg
- Niacin—10 mg
- Biotin—0.15 mg
- Pantothenic acid—5 mg
- Folate—300μg
- Iodine—75 μg
- Zinc as gluconate—7.5 mg
- Sodium—320 mg
- Selenium as selenate—35 μg
- Manganese as chloride—1 mg
- Molybdenum—45 μg
- Calcium as lactate—540 mg
- Potassium as gluconate—0.65 g
- Iron as ferric triglycinate—25 mg
- Copper as diglycinate—1.25 mg
- Magnesium as diglycinate—200 mg

Approximately 150–155 Calories per serving depending on flavor. Separate; vitamin A and D in micelle form was provided as a liquid in a small bottle with dropper for daily serving; these were added to 1 of the 2 daily servings: vitamin A—5000 International Units/day, vitamin D—1000 International Units/day

Plasma 25-OH-vitamin D and ferritin were assayed using an EIA kit from Alpco, Salem, NH. Plasma cross-linked C-telopeptide of type 1 collagen (CTX), vascular cell adhesion molecules (VCAM-1), and homocysteine were determined using ELISA kits from My Biosource, San Diego, CA. C-reactive protein was assayed using an ELISA kit from BioVendor, Ashville, NC. Retinol binding protein (RBP) was quantitated with an ELISA kit from Arbor Assays, Ann Arbor, MI. Holotranscobalamin was measured using an ELISA kit from IBL International Corporation, Toronto, Canada.

Statistical Analysis

Changes within a group for the two time points were compared by paired t test (http://www.fon.hum.uva.nl/Service/Statistics/Student_t_Test.html). Net changes in one group were compared to changes in the other group by unpaired t test (http://www.fon.hum.uva.nl/Service/Statistics/2Sample_Student_t_Test.html).

Results

Subject characteristics are shown in Table 3. In each group, there were two subjects that did not finish because their compliance was altered by nausea (data from these four subjects were not used to construct Table 3). By 6 weeks post-surgery, mean weight loss for both groups was about 30 lbs. (Table 4). The mean percent weight loss for the new product was significantly higher than for the standard products. In both groups, at 6 weeks post-surgery, vitamin D status stayed the same while vitamin A status declined (based on plasma 25-OH-vitamin D and retinol binding protein, respectively)(Fig. 1). Blood sugar, a factor in cardiovascular disease [5], dropped significantly in the new product group, but not in the standard group (Fig. 1). Starting glucose varied widely among the subjects. The starting mean value was lower in the new product group, but that was mainly due to one high outlier (means did not statistically differ by unpaired t test).

Plasma CTX, a marker of bone resorption [6], declined in both groups (Fig. 2). This decline occurred consistently among subjects in both groups as evidenced by the very low p values for a paired t test (Fig. 2). In contrast, plasma osteopontin increased in both groups (Fig. 2). Plasma ALT activities, an inverse measure of liver integrity, [7] rose in subjects on standard products (Fig. 3). Values for plasma VCAM, an atherosclerosis contributor [8], rose in both groups (Fig. 3) Plasma homocysteine levels, which can be high in cardiovascular disease (CVD) [9], fell in both groups (Fig. 3). However, the change reached statistical significance only in the standard group.

In both groups, vitamin B_{12} status, based on plasma holotranscobalamin, did not change from pre-surgery to 6 weeks later (Fig. 4). Mean values for the ratio of ferritin to c-reactive protein, which was used as an iron status index, increased substantially in both groups (Fig. 4). Mean values for ferritin by itself had a small increase in both groups (data not shown). C-reactive protein concentrations decreased in both groups (Standard pre/post: 6.9 ± 0.7/4.9 ± 0.8; New pre/post: 6.1 ± 0.6/5.2 ± 0.8; mean ± SEM in mg/L). Ceruloplasmin, an indicator of copper status, [10, 11] dropped to some extent in the group getting the standard products (Fig. 4), but the change fell just outside the significance range by paired t test ($p = 0.065$). However, the change in values for the two groups was significantly different (Fig. 5).

Table 3 Study subjects characteristics

Group	N	Age	Weigh	BMI
Standard product	13	44 + 2	300 + 19	50 + 3
New product	13	41 + 3	298 + 9	47 + 2

For values other than *N*, numbers are the means ± SEM

Table 4 Weight loss 6 weeks after surgery

Group	Lbs Lost	% Lost
Standard products	29 + 3	9 + 2
New product	33 + 3	12 + 3*

Group, $p < 0.05$, one-tailed, unpaired *t* test

*Significantly different from standard products

Mean plasma potassium read between 264 and 270 pg/L in both groups, both before and after surgery (no significant changes; data not shown). In the new product group, plasma magnesium showed a small rise, but it fell just outside the statistically significant range (Fig. 6). Red blood cell magnesium also showed a small rise, but the increase fell just outside the significance range (Fig. 6). However, 2 subjects showed a large drop in values far above any other subjects in either group. These same subjects also showed large drops in red blood cell potassium (data not shown), which may indicate some trauma in cellular electrolyte metabolism. If these 2 subjects were excluded, a statistically significant increase in red blood cell magnesium was found (Fig. 6).

Discussion

The study tested the following hypothesis: chemical measures related to nutrition can change by 6 weeks, and one nutrition support approach will prevent nutrition problems better than a traditional approach. The hypothesis was partly confirmed. Some, but not all, measures related to nutritional status changed in at least one of the groups, and some differences were seen for the two nutrition support approaches. For part of the 6 weeks, subjects did eat some pureed food along with the nutrition support products (see "Methods" section). However, the low amount of pureed food would not be expected to contribute much to the total intake of the nutrients studied here.

The idea that preventing nutrient status declines by at least one of the nutrition support plans did not hold for vitamin A status (a decrease was seen for both groups). In contrast, vitamin D status remained constant in both groups. For the new product, the same micellular technology was used for vitamins A and D. Possibly, the technology works better for D, or storage dynamics may explain the different response. The liver, the main vitamin A storage site [12], may lose this vitamin to excretion more easily than adipose tissue, which contains substantial vitamin D [13]. The latter may gradually send D into plasma during initial weight loss. Still, in the present study, mean 25-OH-vitamin D was about 27 ng/ml, which is borderline low [14].

Despite no vitamin D change, values for CTX, a bone resorption maker [6], fell consistently in both groups. This

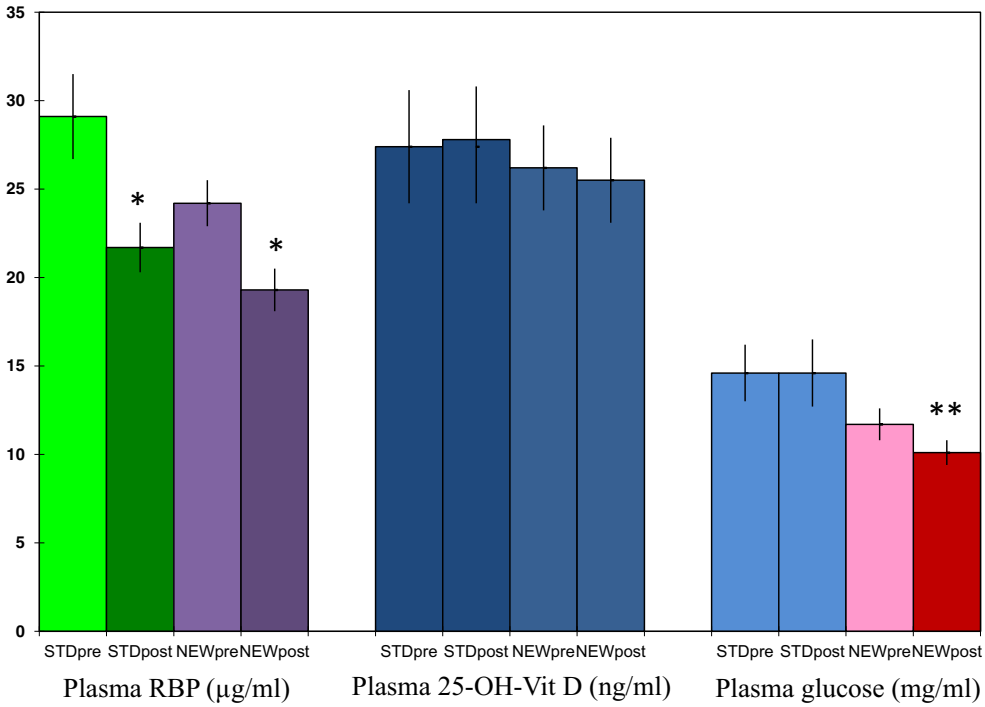

Fig. 1 Plasma retinol binding protein (RBP), 25-OH-vitamin D (25-OH-vit D), and glucose, pre- and 6 weeks post-surgery. Subjects consumed either standard (STD) nutrition support products or a new (NEW) meal replacement product. *Significantly different from pre-values, $p \leq 0.001$, two-tailed, paired t test. **Significantly different from pre-values, $p = 0.05$, two-tailed, paired t test

decrease, a desirable effect, may have resulted from a substantial intake of calcium in both groups. The new product group got all their supplemental calcium in the meal replacement product as calcium lactate. This form has high water solubility and tastelessness, both of which allow a fairly high dose in a nutrition beverage.

Osteopontin levels can rise with inflammation or obesity [15, 16]. However, here, rises in osteopontin were accompanied by decreases in body weight (Table 1) and the inflammation marker [17] plasma c-reactive protein (data not shown). This pattern resembled studies that look at subjects a year or more after bariatric surgery [18–20]. In one of these studies

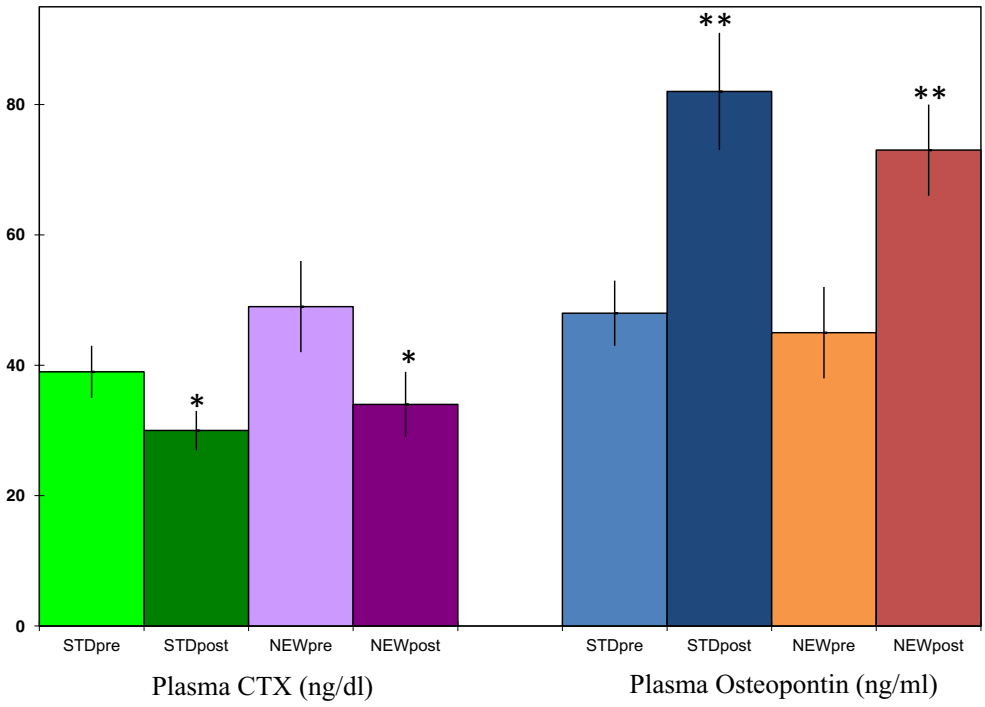

Fig. 2 Plasma cross-linked C-telopeptide of type 1 collagen (CTX) and osteopontin pre- and 6 weeks post-surgery. Subjects consumed either standard (STD) nutrition support products or a new (NEW) meal replacement product. *Significantly different from pre-values, $p \leq 0.01$, two-tailed, paired t test. **Significantly different from pre-values, $p \leq 0.0002$, two-tailed, paired t test

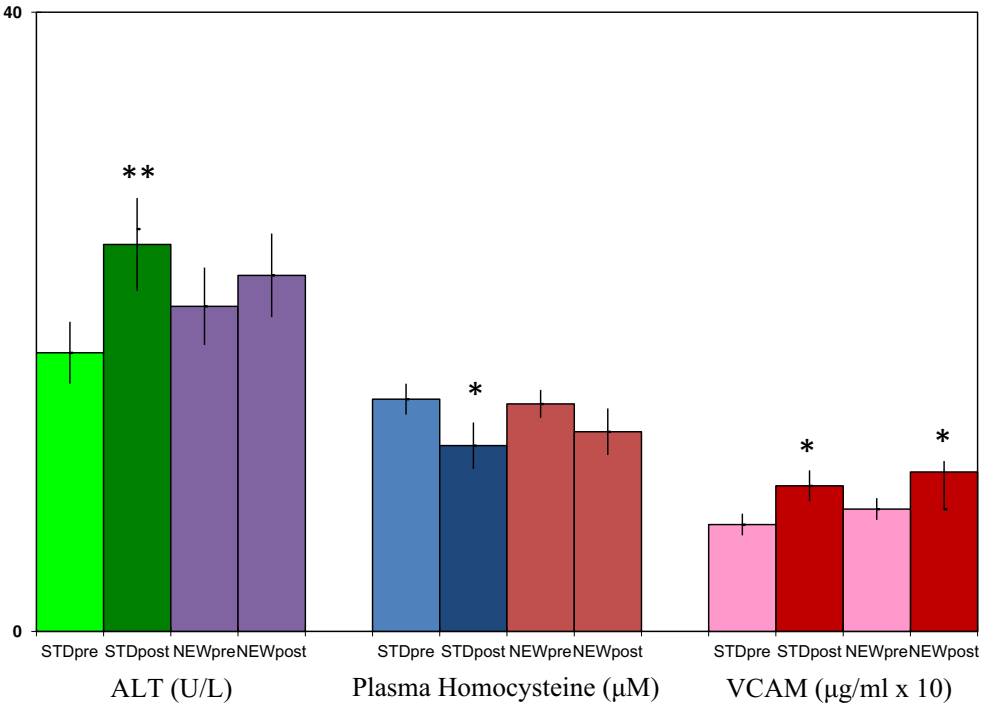

Fig. 3 Plasma alanine aminotransferase (ALT) activities, vascular cell adhesion molecules (VCAM-1), and homocysteine pre- and 6 weeks post-surgery. Subjects consumed either standard (STD) nutrition support products or a new (NEW) meal replacement product. *Significantly different from pre-values, $p \leq 0.001$, two-tailed, paired t test. **Significantly different from pre-values, $p < 0.05$, one-tailed, paired t test

[18], 15 months after bariatric surgery, plasma osteopontin changes parallel changes in bone turnover markers [18]. In contrast, here, osteopontin readings rose while readings fell for CTX. Osteopontin levels can also rise with poor insulin resistance [17], but with the new product, osteopontin levels increased while fasting blood sugar fell. Similarly, in two studies of people long after bariatric surgery [15, 16], osteopontin values did not correlate with measures of insulin resistance. Thus, rises in osteopontin after bariatric surgery occur despite trends that often predict the opposite.

Iron deficiency occurs commonly in premenopausal women after RNYGB [1, 2]. However, here, the iron given to both groups improved status based on the ratio of plasma ferritin to c-reactive protein. Ferritin values can reflect iron status, but

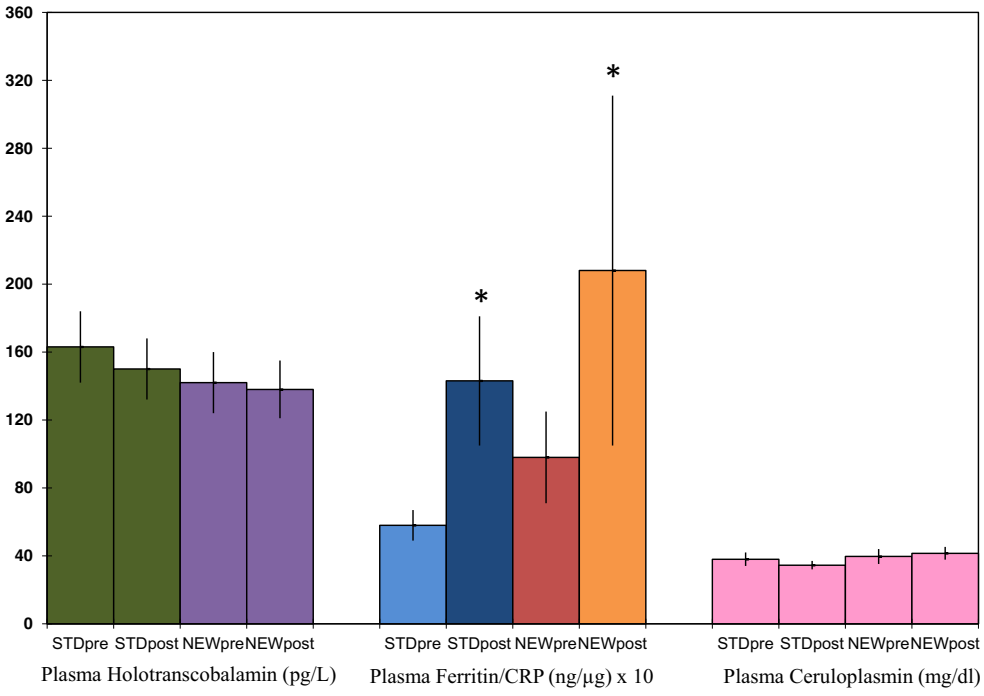

Fig. 4 Plasma holotranscobalamin, ferritin to c-reactive protein (CRP) ratio, and ceruloplasmin pre- and 6 weeks post-surgery. Subjects consumed either standard (STD) nutrition support products or a new [NEW] meal replacement product. For holotranscobalamin and ceruloplasmin, no significant changes pre- to post-surgery within treatment groups, paired t test. *Significantly different from pre-values, $p < 0.05$, two-tailed, paired t test

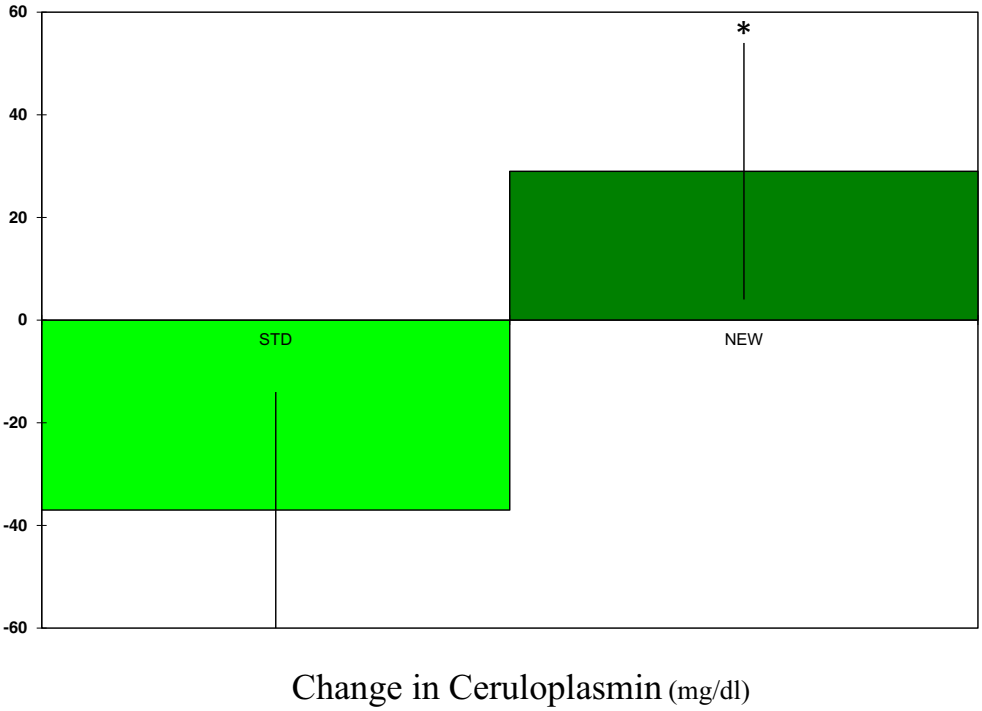

Fig. 5 Change in plasma ceruloplasmin from pre- to 6 weeks post-surgery. Subjects consumed either standard (STD) nutrition support products or a new (NEW) meal replacement product. *Significantly different between groups, $p = 0.05$, two-tailed, paired t test

also can be affected by inflammation [21]. Since c-reactive protein concentrations are influenced by inflammation [19], but not iron status, ferritin/c-reactive protein ratios can assess iron status during changing inflammatory states. Here, one group got iron mostly as ferrous fumarate lozenges. In the other group, iron was given in the meal replacement product as ferric triglycinate, a tasteless iron that can be added to a nutrition beverage in substantial amounts. This form may seem a bad choice for beverages since it dissolves poorly in water and absorbs poorly from a maize porridge [22]. Moreover, when drunk as a water suspension, this iron form, even with two rinses of the drinking vessel, gives less than half the absorption of ferrous sulfate [22]. To make matters worse, in this study's new product, iron and calcium are

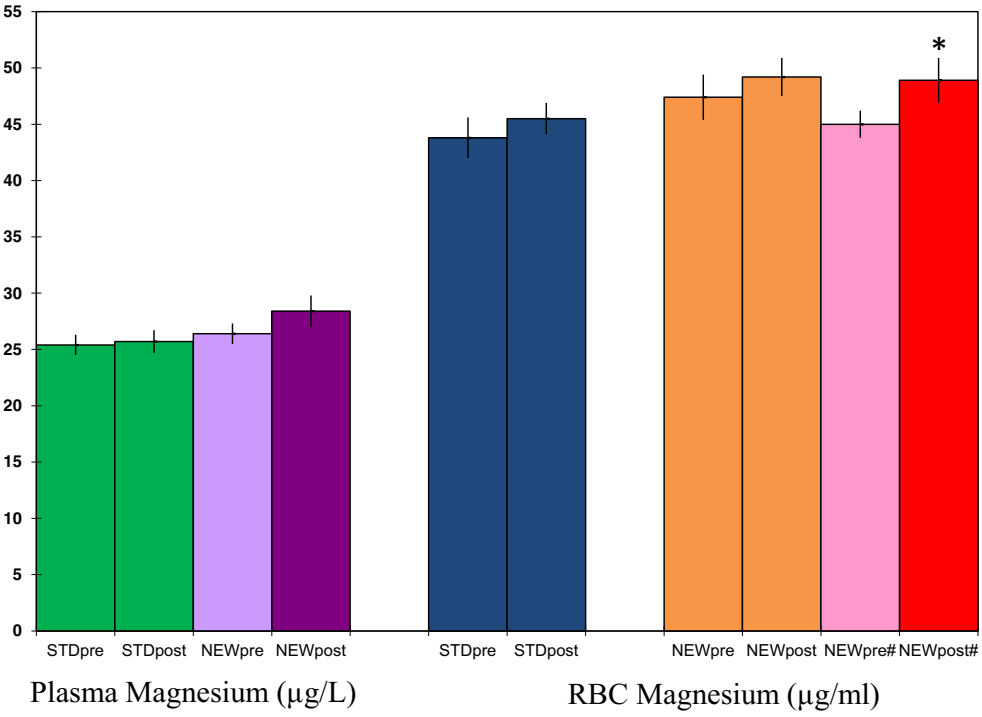

Fig. 6 Plasma and red blood cell (RBC) magnesium. Subjects consumed either standard (STD) nutrition support products or a new (NEW) meal replacement product #Data calculated with two subjects excluded. *Significantly different from pre-values, $p = 0.01$, two-tailed, paired t test

consumed simultaneously, which can further reduce iron absorption [23]. Despite these concerns, ferrous triglycinate in the new product gave good efficacy even without drinking vessel rinsing. Possibly, when this iron is mixed with whey protein + water, it suspends as small glycinate particles. These particles could enter intestinal cells with the amino acid pool formed as the protein digests. This co-absorption may be impervious to calcium interference.

RNYGB can hinder vitamin B_{12} absorption due to low mixing with intrinsic factor [1, 2]. In the present work, B_{12} status did not change 6 weeks after surgery. For the standard group, this vitamin was given sublingually. In the other group, high doses were added to the meal replacement product. The latter may give a very low percent absorption but give enough total absorption to preserve B_{12} status. This type approach has worked well for treating the B_{12} malabsorption syndrome pernicious anemia [24].

The new product was fortified with potassium. The dose fell below the US food label daily value (DV). However, an actual requirement for potassium remains unclear [5]. Mean plasma potassium did not change in either group. In contrast, urine potassium results did suggest that the added potassium did impact potassium status (data not shown).

Magnesium was given to the standard group as Mg oxide; the new product group got Mg glycinate. Mean plasma magnesium levels, which can be influenced by multiple factors [25], increased slightly, but just outside statistical significance, with the new nutrition product. Mean red blood cell magnesium also increased slightly, but also fell just outside the significance range. However, as noted above, significance occurred with the exclusion of two subjects showing a drop that greatly exceeded any other subject in either group. These same subjects also showed a big drop in red cell potassium; thus, abnormal cellular electrolyte metabolism may have been occurring. So, the red blood cell results could indicate that Mg glycinate helped magnesium status better than Mg oxide.

A fairly substantial copper deficiency appears sometimes after bariatric surgery [26, 27]. Milder copper deficiencies may occur more frequently. Here, mean values for plasma ceruloplasmin, which can reflect copper status [28], dropped in the standard product group, but the decrease was just outside the significance range. However, the change differed significantly between groups. Possibly, initial copper stores varied highly among individuals. So, a longer intervention may have showed more consistent separation between groups. Both groups received almost the same copper dose (2 mg standard vs 2.5 mg new). The standard group got copper gluconate, which so far, has not fared well in supplement studies [28, 29]. The new product group got copper glycinate, which has done well in multiple studies [ie. 10, 11, 30].

Three measures related to CVD were assessed. Plasma VCAM, which contributes to atherosclerosis [8], rose in both groups. VCAM can correlate with body mass index [31], but here, for unknown reasons, values rose despite body weight drops. Also here, plasma homocysteine values, which can be high in CVD [9], decreased in both groups (just outside significance for the new product, significant in the other group). Both groups got about the same dose of B-vitamins, which can affect homocysteine readings [9]. Since readings varied a lot, longer interventions may have given statistical significance in both groups. Fasting blood sugar, another factor in CVD [5], fell only in the new product group. This was possibly due to NUTRIOSE®, a fiber that improves insulin resistance in overweight people [32]. This fiber also caused modest weight loss in one study [33], which may be why the new product group lost a little more weight.

Many people who have bariatric surgery show nonalcoholic fatty liver disease that improves after surgery [34]. However, here, the subjects did not show very high values for ALT, a marker of liver injury [7]. In the standard products group, but not the new product group, ALT values actually rose 6 weeks after surgery. The difference between groups may result from differences in the types of copper and magnesium given. Both minerals can affect liver resistance to injury [35, 36]. Also, the new product had added potassium, which can affect liver health [37].

In summary, at 6 weeks post-RNYGB, some chemical signs of nutrition problems appeared despite use of nutrition support products. However, these products prevented some nutritional problems and improved status for others. For multiple measures, using the new nutrition product worked as well or better than multiple standard products. Using a single support product can simplify adherence to a nutrition support regimen.

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Compliance with Ethical Standards

The protocol was approved by the xxx Human Subjects Biomedical Institutional Review Board.

Conflict of Interest All but one author declare no conflict of interest. Robert DiSilvestro is president of Medinutra LLC, a company that after the study, has been developing a commercial product that overlaps the new product tested in this study.

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