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Efficacy of oral compared with intramuscular vitamin B-12 supplementation after Roux-en-Y gastric bypass: a randomized controlled trial

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ABSTRACT

Background: After Roux-en-Y gastric bypass (RYGB), patients often develop a vitamin B-12 deficiency.

Objective: Our objective was to investigate whether oral supplementation increases and normalizes low vitamin B-12 concentrations (vitamin B-12 > 200 pmol/L) in RYGB patients as compared to intramuscular injections.

Design: A randomized controlled trial in RYGB patients with subnormal serum B-12 concentrations was performed. One group (IM B-12) received bimonthly intramuscular hydroxocobalamin injections (2000 μg as loading dose and 1000 μg at follow-up) for 6 mo. The second group (oral B-12) received daily doses of oral methylcobalamin (1000 μg). Serum vitamin B-12 was determined at baseline (T0) and at 2 (T1), 4 (T2), and 6 mo (T3) after start of treatment. Concentrations of the secondary markers methylmalonic acid (MMA) and homocysteine (Hcy) were measured at T0 and T3.

Results: Fifty patients were included and randomized, 27 in IM B-12 and 23 in oral B-12. The median vitamin B-12 concentration at T0 was 175 pmol/L (range: 114–196 pmol/L) for IM B-12 and 167 pmol/L (range: 129–199 pmol/L) for oral B-12. Vitamin B-12 normalized in all individuals, and there was no significant difference in vitamin B-12 between the two groups. MMA and Hcy concentrations decreased significantly after 6 mo within each group ($P < 0.001$ and $P < 0.001$ for MMA and $P = 0.03$ and $P = 0.045$ for Hcy, respectively). There was no significant difference between the groups at 6 mo for both MMA and Hcy ($P = 0.53$ and $P = 0.79$).

Conclusion: The efficacy of oral vitamin B-12 supplementation was similar to that of hydroxocobalamin injections in the present study. Oral supplementation can be used as an alternative to hydroxocobalamin injections to treat RYGB patients with low values of serum vitamin B-12. This trial was registered at clinicaltrials.gov as NCT02270749. *Am J Clin Nutr* 2018;108:1–7.

Keywords: vitamin B-12, cobalamin, Roux-en-Y gastric bypass, RYGB, deficiencies, supplementation

INTRODUCTION

The Roux-en-Y gastric bypass (RYGB) is an excellent procedure for sustained weight loss in morbidly obese patients (1). Despite the excellent results in terms of weight loss, however, the RYGB is known to cause vitamin B-12 deficiency in a significant number of patients in the first postoperative years (17–50%) (2–4). This is caused by severely impaired vitamin B-12 absorption.

When performing an RYGB, the stomach is reduced to a small pouch (30 cc) and a considerable part of the intestinal tract is bypassed. Consequently, there (most often) is no gastric acid or intrinsic factor (IF) available in the first part of the digestive tract (5, 6). IF is still produced in the remnant stomach, but it is now isolated from the food stream and thus does not bind to vitamin B-12. Gastric acid and IF are required to release vitamin B-12 from dietary protein and to form the IF–B-12 complex needed for absorption.

Vitamin B-12 deficiency has been associated with neurologic complications and macrocytic anemia, both of which require treatment (7, 8). The American Society for Metabolic and Bariatric Surgery advises that vitamin B-12 deficiency (serum vitamin B-12 < 200 pmol/L) resulting from RYGB be treated parenterally, sublingually, subcutaneously, orally, or via intramuscular injections (9). All our RYGB patients are advised to take specific multivitamin supplements every day postoperatively to prevent multiple postoperative nutrient deficiencies. Although these specific supplements effectively prevent most deficiencies, subnormal or deficient vitamin B-12 concentrations still occur

FitForMe provided the oral vitamin B-12 supplements (FitForMe Vitamin B-12) free of charge. It did not play any role in the design, implementation, analysis, and interpretation of the data.

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Abbreviations used: Hcy, homocysteine; HoloTC, holotranscobalamin; IF, intrinsic factor; IM B-12, group receiving bimonthly intramuscular hydroxocobalamin injections for 6 mo; MMA, methylmalonic acid; oral B-12, group receiving daily doses of oral methylcobalamin; RYGB, Roux-en-Y gastric bypass; T0, baseline; T1, 2 mo after treatment; T2, 4 mo after treatment; T3, 6 mo after treatment

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sometimes (10, 11), and additional treatment of vitamin B-12 deficiency is warranted. The conventional treatment method for vitamin B-12 deficiency in many countries includes regular intramuscular hydroxocobalamin injections, which is commonly regarded as the gold standard. However, these injections can be painful, and they require a considerable amount of time and effort from health care professionals. Oral supplementation is potentially more comfortable for patients, and makes regular medical visits unnecessary. A number of studies have suggested that oral supplementation can effectively increase vitamin B-12 concentrations (12, 13). Three randomized controlled trials have concluded that oral supplementation in patients with a normal gastrointestinal anatomy was as effective as conventional intramuscular injections in the treatment of low cobalamin concentrations or cobalamin deficiency (14–16). However, there remains doubt as to whether oral supplements are as effective as injections in RYGB patients whose nutrient absorption is severely altered. Therefore, this study prospectively investigated whether oral supplementation effectively increases and normalizes vitamin B-12 concentrations in vitamin B-12-deficient RYGB patients as compared to conventional treatment with intramuscular injections.

METHODS

Trial design

A randomized controlled trial was conducted that compared oral vitamin B-12 supplementation with intramuscular vitamin B-12 injections. The present study was approved by the Medical Ethics Committee and the institutional review board.

Participants

The trial was performed in the bariatric department of a general hospital that performed some 1200 bariatric procedures per year. Patients were recruited when they were diagnosed with a low value of vitamin B-12 (<200 pmol/L) during one of the standard control visits after RYGB surgery (17). These control visits took place at 6, 12, 24, and 36 mo after surgery. During this screening process, patients were excluded if there was an increase in their creatinine concentration (>150 μmol/L) or liver enzymes (>2 times the upper limit), if they had undergone previous gastrointestinal surgery other than RYGB, had a gastrointestinal disease or psychiatric issues, had used medication that influenced their bone metabolism, had already used a vitamin B-12 supplement other than the advised multivitamin supplements, or were pregnant.

Intervention

Different effective supplementation regimes have been described for treating vitamin B-12 deficiency with intramuscular injections and oral supplementation (9, 13, 16). Similar to the results from these previous studies, our own clinical experience showed that a single intramuscular loading dose of 2000 μg and follow-up doses of 1000 μg of hydroxocobalamin every 2 mo intramuscularly was adequate. Therefore, patients in the first group (IM B-12) received a loading dose injection of 2000 μg of hydroxocobalamin (Centrafarm services B.V.) at baseline followed by bimonthly injections of 1000 μg of hydroxocobalamin up until 6 mo. Patients in the second group (oral B-12) received 1000 μg of methylcobalamin (FitForMe Vitamin B-12) orally, once daily, for 6 mo. These oral supplements were tailored to meet the increased needs of RYGB patients, and did not contain other micronutrients.

TABLE 1
Study design with primary and secondary outcome parameters after supplementation[1]

	T0	T1	T2	T3
Serum vitamin B-12	X	X	X	X
Serum Hcy	X			X
Serum MMA	X			X

[1]Hcy, homocysteine; MMA, methylmalonic acid; T0, baseline; T1, 2 mo after starting treatment; T2, 4 mo after starting treatment; T3, 6 mo after starting treatment.

Fasting blood samples were taken at baseline and at 2 mo intervals up until 6 mo **(Table 1)**. Serum vitamin B-12 (expressed as pmol/L) was determined at each time point by electrochemiluminescence immunoassay (Roche Modular E170, Roche Diagnostics). The secondary parameters serum methylmalonic acid (MMA) (expressed as μmol/L) and serum homocysteine (Hcy) (expressed as μmol/L) were determined at baseline and after 6 mo. MMA was analyzed by means of isotope dilution liquid chromatography-tandem mass spectrometry and Hcy via enzymatic assay (Roche Modular P800 P5, Roche Diagnostics). Laboratory measurements in the IM B-12 group were taken just prior to their bimonthly injection to make sure that trough concentrations were measured and not peak concentrations. For the oral B-12 group, measurements were taken just prior to the intake of their oral supplement. A research physician administered the injections and monitored compliance in the IM B-12 group. Patients returned the empty oral supplement packages for monitoring compliance in the oral B-12 group.

At baseline, the patient's weight (kilograms) was measured. Height and weight were used to calculate the BMI in kg/m^2 and to determine the excess weight loss (percentage). Furthermore, patients were requested to report any existing comorbidities and their current medication and multivitamin use, and were asked not to use any vitamin B-12 supplements other than those advised in this study.

Outcomes

The main outcome was the increase and normalization of serum vitamin B-12 concentrations (>200 pmol/L) 2, 4, and 6 mo after supplementation. Secondary outcomes were effects on serum Hcy and serum MMA concentrations over 6 mo. Elevated Hcy and MMA concentrations were indicative of vitamin B-12 deficiency.

Sample size

The number of patients was calculated based on the assumption that there would be a 10% difference in low vitamin B-12 concentrations between the groups. In the control group, treated with vitamin B-12 injections, no vitamin B-12 depletion was expected (100% improvement). In the intervention group, which was treated with methylcobalamin, it was assumed that 10% of the low B-12 concentrations would persist (90% improvement). With a CI of 95%, an alpha of 5%, a power of 80%, and a noninferiority margin of 25%, 25 patients were required for each group.

TABLE 2
Baseline characteristics[1]

	IM B-12 ($n = 26$)	Oral B-12 ($n = 24$)	P
Age, y	41.6 ± 9.8	46.0 ± 11.9	0.16
Male/female, *n* (%)	5/21 (19/81)	8/16 (33/67)	0.26
Weight, kg	83.0 (65.1–119.8)	95.7 (72.2–136.7)	0.05
BMI, kg/m^2	29.2 ± 4.4	32.9 ± 4.5	0.01*
Time since surgery, mo	23 (5–49)	24 (4–39)	0.48
DM type 2, *n* (%)	1 (3.8)	2 (8.3)	0.60
Hypertension, *n* (%)	3 (11.5)	4 (16.7)	0.70
Hypercholesterolemia, *n* (%)	1 (3.8)	3 (12.5)	0.34
OSAS, *n* (%)	2 (7.7)	0 (0)	0.49
Arthrosis, *n* (%)	6 (23.1)	8 (33.3)	0.42
Vit B-12, pmol/L	175 (114–196)	167 (129–199)	0.45
Normal Vit B-12, *n* (%)	0 (0)	0 (0)	—
MMA, µmol/L	0.31 (0.10–1.53)	0.31 (0.13–0.73)	0.74
Normal MMA, *n* (%)	17 (65)	14 (58)	0.61
Hcy, µmol/L	11.4 (6.5–20.5)	11.3 (3.0–27.6)	0.92
Normal Hcy, *n* (%)	22 (85)	19 (79)	0.72

[1]Values are expressed as means ± SDs or median (range). Nominal data are expressed by *n* and percentage. The independent samples *t* test is used for normally distributed variables, the Mann-Whitney *U* test for nonnormally distributed variables, and the chi-square test or Fisher's exact test for nominal data. *Statistically significant. DM, diabetes mellitus; FFM, specific multivitamin supplement; Hcy, homocysteine; IM B-12, group treated with intramuscular hydroxocobalamin (2000 µg); MMA, methylmalonic acid; Oral B-12, group treated with oral methylcobalamin (1000 µg); OSAS, obstructive sleep apnea syndrome; Vit B-21, vitamin B-12.

Randomization

Participants were enrolled by the research physician. Fifty eligible patients signed informed consent in duplicate, were invited for baseline measurements, and were randomized into one of two treatment groups by computer (Research Manager version 5.12.1.0, a validated program with block randomization, using a block size of 10). Patients were treated for their low vitamin B-12 by the research physician with the supplement that was assigned by the randomization procedure.

Statistical analysis

Data were analyzed using IBM SPSS (Version 21.0 for Windows). Results were presented as means ± SDs for normally distributed continuous variables; otherwise, medians and ranges were used. Normally distributed continuous variables were tested between the groups by independent-sample *t* tests and within the groups by paired-sample *t* tests. For nonnormally distributed continuous variables, a Mann-Whitney *U* test was performed for differences between the groups, and a related-samples Wilcoxon signed rank test was used for within-group differences. Chi-square tests and Fisher's exact test were performed for nominal data. An ANOVA test (2-factor repeated measures analysis) was performed to compare the serum vitamin B-12 concentrations after 2, 4, and 6 mo of treatment between the two treatment groups. A *P*-value of <0.05 was considered statistically significant.

RESULTS

Finding suitable patients for this study took longer than expected, because of the introduction of preventive specific multivitamins for RYGB patients in our clinic. These tablets contained 350 µg of vitamin B-12 and reduced the expected number of patients tested with low vitamin B-12 by two-thirds (9, 10). Fifty patients were included, 26 in the IM B-12 group and 24 in the oral B-12 group. The baseline table described the characteristics of the patients that were included in the study (**Table 2**). Compliance was defined as using the medication for ≥6 d/wk. Patients who took less were categorized as non-compliant. In the oral B-12 group there was sufficient compliance in 19 patients. Two patients were non-compliant during the first part of the study, but after 2 mo took the methylcobalamin tablets correctly. One patient from the oral B-12 group was non-compliant and forgot to take her medication daily in the first 2 mo of the study. This patient was switched to the IM B-12 group with a treatment with hydroxocobalamin injections and completed the study. Because of the switch of treatment of this patient, the IM B-12 group ultimately contained 27 patients and the oral B-12 group contained 23 patients in the follow-up.

Vitamin B-12

The changes in vitamin B-12 concentrations in both groups are shown in **Figure 1**. There was a significant increase within each group 2 mo after supplementation ($P < 0.001$ and $P < 0.001$). The repeated measures analysis showed that there was no interaction between time and change from baseline. After 6 mo of treatment, all patients had normal vitamin B-12 concentrations (**Table 3**).

MMA

The mean MMA concentration was significantly decreased after 6 mo within each group (**Figure 2**, $P < 0.001$ for both groups).

There was no significant difference in change from baseline to 6 mo between IM B-12 and oral B-12 [median change:

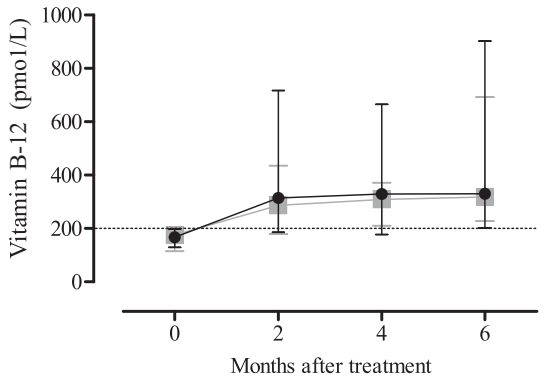

FIGURE 1 Vitamin B-12 concentrations. Values are median vitamin B-12 concentrations with range throughout the study period in both treatment groups. Grey squares represent intramuscular B-12 injection treatment (2000 µg, $n = 27$) and black dots represent oral treatment with methylcobalamin (1000 µg, $n = 23$). At 6 mo the number of patients in the intramuscular injection group was 26. *P*-interaction for time by repeated measures ANOVA for vitamin B-12 was not significant ($P = 0.75$).

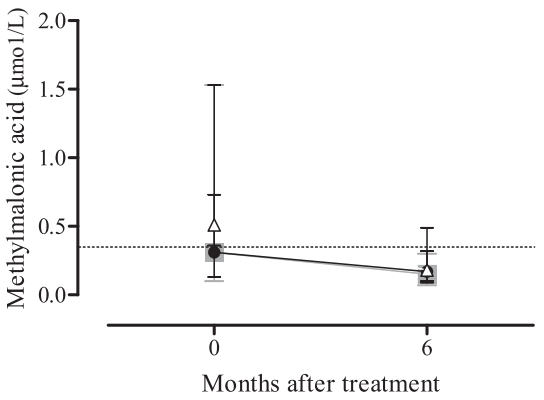

FIGURE 2 MMA concentrations. Values are median MMA concentrations with range at baseline and after 6 mo of treatment. Grey squares represent intramuscular B-12 injection treatment (2000 µg, $n = 27$) and black dots represent oral treatment with methylcobalamin (1000 µg, $n = 23$). Mean MMA concentrations decreased in both groups between 0 and 6 mo ($P < 0.001$ and $P < 0.001$, related samples Wilcoxon signed rank test). There was no significant difference between the groups in change of MMA concentration ($P = 0.53$, Mann-Whitney *U* test). The white triangles represent the total number of patients with raised MMA concentrations at baseline and their MMA concentration 6 mo after treatment ($n = 19$), which decreased ($P < 0.001$, related samples Wilcoxon signed rank test). MMA, methylmalonic acid.

–0.15 µmol/L (range: –1.34 to 0.04 µmol/L) compared with –0.13 µmol/L (range: –0.42 to 0.18 µmol/L), $P = 0.53$]. After 6 mo, MMA was normalized in all of the patients in the IM B-12 group and in 96% of the patients in the oral B-12 group ($P = 0.46$). Overall, MMA increased during the study in 5 patients, 4 of which stayed within the normal range (MMA < 0.35 µmol/L) and were in the IM B-12 group. The patient with MMA> 0.35 µmol/L was in the oral B-12 group.

Hcy

At baseline there was no significant difference in Hcy concentrations between men in the different treatment groups ($P = 0.83$) or between women ($P = 0.71$). The mean Hcy concentration decreased significantly after 6 mo in both the IM B-12 and oral B-12 groups ($P = 0.03$ and $P = 0.045$, respectively, **Figure 3**). There was no significant difference in change from baseline to 6 mo between IM B-12 and oral B-12 [mean change: –1.50 µmol/L (–7.5, 4.4) compared with –1.70 µmol/L (–10.0, 4.6), $P = 0.79$].

In the total group, Hcy was higher in 18 patients (36%, including 8 patients in the IM B-12 group and 10 in the oral B-12 group, $P = 1.0$) at T3 (6 mo after treatment) than at T0 (baseline). In 15 of these patients, the Hcy stayed within the normal range (Hcy < 16.4 µmol/L). One patient in the oral B-12 group had an Hcy value of 16.8 µmol/L.

TABLE 3
Number and percentage of patients with normal blood values after 6 mo[1]

	IM B-12 ($n = 27$)	Oral B-12 ($n = 23$)	*P*
Vitamin B-12, *n* (%)	26 (100)[2]	23 (100)	—
MMA, *n* (%)	27 (100)	22 (96)	0.46
Hcy, *n* (%)	25 (96)[2]	20 (87)	0.33

[1]Normalization was defined as vitamin B-12 ≥ 200 pmol/L, MMA < 0.35 µmol/L and Hcy < 13.4 µmol/L. *P*-values were analyzed by Fisher's exact test. Hcy, homocysteine; IM B-12, group treated with intramuscular hydroxocobalamin (2000 µg); MMA, methylmalonic acid; Oral B-12, group treated with oral methylcobalamin (1000 µg).

[2]$n = 26$.

Overall, 9 patients had an increased Hcy concentration at baseline, 4 in the IM B-12 group and 5 in the oral B-12 group [median: 20.5 µmol/L (range: 17.6–27.6 µmol/L)], but these had decreased after 6 mo of treatment [$n = 9$, median: 15.0 µmol/L (range: 10.1–22.6 µmol/L), $P = 0.012$, Figure 3]. After 6 mo, Hcy was normalized in 25 (96%) patients in the IM B-12 and in 20 (87%) patients in the oral B-12 group ($P = 0.33$, Table 3).

Multivitamin supplementation

In the IM B-12 group at baseline, 23 subjects (88.5%) used daily multivitamin supplementation, 14 (54%) using the multivitamin supplements specific for RYGB patients, which contained higher doses of vitamin B-12 (10, 11), and 9 (34.6%) using standard multivitamins. In the oral B-12 group, 22 patients (92%) used multivitamins, 13 (54%) using the specific supplements and 9 (37.5%) using standard multivitamins ($P = 1.00$ compared with multivitamin use in IM B-12).

Vitamin B-12 concentrations were not significantly different between the specific multivitamin users and users of regular multivitamin supplements [median: 175 pmol/L (range: 124–196 pmol/L) compared with 164.5 pmol/L (range: 114–199 pmol/L) pmol/L, $P = 0.36$]. Nor was there a significant difference in Hcy [median: 11.8 µmol/L (range: 3.0–25.8 µmol/L) compared with 10.3 µmol/L (range: 6.7–27.6 µmol/L), $P = 0.56$]. The concentration of MMA was significant higher with the regular multivitamin supplements [median: 0.27 µmol/L (range: 0.1–0.57 µmol/L) compared with 0.37 µmol/L (range: 0.17–1.53 µmol/L), $P = 0.018$].

DISCUSSION

This study of RYGB patients with low vitamin B-12 concentrations ($n = 50$) showed that there was no significant difference in serum vitamin B-12 and MMA concentrations in patients

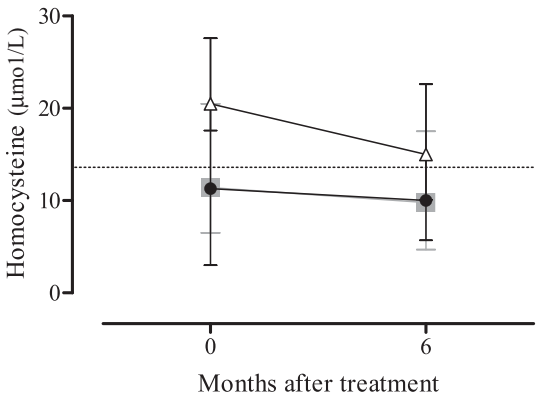

FIGURE 3 Hcy concentrations. Values are median Hcy concentrations with range at baseline and after 6 mo of treatment. Grey squares represent intramuscular B-12 injection treatment (2000 μg, $n = 27$) and black dots represent oral treatment with methylcobalamin (1000 μg, $n = 23$). At 6 mo the number of patients in the intramuscular injection group was 26. Hcy concentration decreased significantly in both groups ($P = 0.03$ and $P = 0.045$, related samples Wilcoxon signed rank test). There was no significant difference between the groups ($P = 0.79$, independent samples t test). The white triangles represent the total number of patients with raised Hcy concentrations at baseline ($n = 9$) and their Hcy concentration 6 mo after treatment ($n = 8$), which decreased ($P = 0.012$, related samples Wilcoxon signed rank test). Hcy, homocysteine.

receiving oral or intramuscular vitamin B-12 treatment after 6 mo. In addition, both treatments achieved normalization of the serum vitamin B-12 concentration (>200 pmol/L) in all patients within 6 mo of treatment. Within the oral B-12 group, one patient had persistently subnormal concentrations at T1 (2 mo after treatment) and one patient was low at T2 (4 mo after treatment). These deficiencies were caused by insufficient intake of vitamin B-12 tablets by these two patients ($P > 0.05$). Therefore, this study indicates that oral supplementation is similarly effective as intramuscular injections with adequate compliance.

The present study is the first randomized controlled trial comparing intramuscular and oral vitamin B-12 treatment in RYGB patients. The results of the current study are comparable to those of previous trials in subjects with low cobalamin concentrations or cobalamin deficiency but otherwise healthy subjects using different dosing schemes. Kuzminski et al. (16) studied the effect of 2000 μg cyanocobalamin orally per day for 4 mo compared to nine 1000-μg cyanocobalamin intramuscular injections spread over 4 mo on serum vitamin B-12 concentrations in vitamin B-12 deficient subjects in a randomized controlled trial. In the current study both treatment groups reached 100% normalization, suggesting they are equally effective based on vitamin B-12 concentrations. Castelli et al. (15) gave their subjects either 1000 μg cyanocobalamin orally every day or nine 1000-μg cyanocobalamin intramuscular injections spread over 3 mo. In both groups vitamin B-12 concentrations had normalized after 15 d, using an even higher cut-off value (>258 pmol/L). Some patients with gastrointestinal abnormalities such as the RYGB were included in that study and both treatments were considered effective.

Overall, the literature suggests that oral supplementation can be a suitable alternative to regular intramuscular injections in patients with a normal anatomy (14–16). In the previous randomized controlled trials cyanocobalamin was used as the supplement, whereas the current study used hydroxocobalamin and methylcobalamin. These forms of vitamin B-12 are very similar, and the form of choice for supplementation currently depends, for the most part, on the availability in the country where it is used.

Vitamin B-12 absorption can be impaired by certain medications. Acid inhibitors (e.g., omeprazole) result in reduced acid in the stomach. The lack of acid impairs the release of vitamin B-12 from dietary protein, so it cannot bind to IF and be absorbed in the ileum. Metformin therapy, an antihyperglycemic drug used against type 2 diabetes, has also been associated with reduced vitamin B-12 concentrations (18). Nevertheless, the mechanism is not entirely understood yet, and different mechanisms have been proposed. For example, metformin is suggested to interfere with intracellular calcium handling, disrupting calcium-dependent absorption of vitamin B-12 in the ileum (19). In the present study, 11 subjects used proton pomp inhibitors and 6 subjects used metformin. The RYGB most often resolves reflux issues and thereby reduces the need for acid inhibitors. Furthermore, the RYGB also helps patients to get rid of their diabetes, which makes antihyperglycemic therapy redundant.

The patients in both treatment groups received adequate therapy for their low vitamin B-12. Nevertheless, the current study also had limitations. There is currently no consensus on how to diagnose vitamin B-12 deficiency. As used in the present study, serum vitamin B-12 concentrations are routinely used in clinics as a first-line diagnostic test for vitamin B-12 deficiency. However, there is some debate about which cut-off values apply to normal vitamin B-12 concentrations. In the current study we used a cut-off of <200 pmol/L, based on the American Society for Metabolic and Bariatric Surgery guidelines (17). Generally, serum vitamin B-12 concentrations <148 pmol/L are thought to sensitively diagnose 97% of true vitamin B-12 deficiencies (20, 21). A higher cut-off value can reduce the specificity for diagnosing clinical deficiency to ∼65–90% with a cut-off value of 148 pmol/L (200 pg/mL) (20, 21). The largest problem with using vitamin concentrations to diagnose deficiency at present is the occurrence of false positive measurements. Serum vitamin B-12 concentrations are maintained at the expense of the tissue stores, hence deficiency might be present when serum vitamin B-12 is normal (13). Both MMA and Hcy are elevated in the case of vitamin B-12 deficiency. For this reason, additional measurements of MMA and/or Hcy are recommended for diagnosing clinical vitamin B-12 deficiency. It should be noted, though, that renal disease also increases MMA concentrations, and Hcy is not specific to vitamin B-12 deficiency. MMA is considered the best marker for vitamin B-12 deficiency but, owing to poor assay availability and its high cost, its clinical use is limited in the Netherlands. In the present study, it would have been helpful if additional Hcy and MMA measurements had been taken at 2 wk or 1 mo, instead of just at 6 mo, to see if patients' vitamin B-12 concentrations had already been corrected. Also, we were unable to ascertain the relative changes in vitamin B-12 concentration between the two groups within the first 2 mo. Selecting patients based on serum vitamin B-12 concentrations combined with MMA values might improve a future study design. It is also important to consider the costs of the laboratory tests. At present, the determination of serum vitamin B-12 concentration in the Netherlands costs €9. The current price to determine MMA concentration is €45, Hcy concentration costs €39, and holotranscobalamin (HoloTC) costs ∼€25.

HoloTC (also called active vitamin B-12) is emerging as another potential marker for vitamin B-12 deficiency. HoloTC

reflects the amount of vitamin B-12 available to the body's cells. The literature suggests that HoloTC is also suitable for diagnosing vitamin B-12 deficiency (22). Although HoloTC appears to be a promising marker, its use is still explorative and further investigation is needed to justify its use as marker for clinical diagnosis for vitamin B-12 deficiency.

Although we performed a randomized controlled trial, the groups were not compared with placebo groups. Neither was the study blinded, which could have given the study more strength. However, blinding this study would be ethically problematic and clinically challenging, as it would mean that both groups would be given injections and tablets at the same time.

Another limitation is the design of the study, which was based on two different factors between the intervention arms, the route of administration (oral compared with intramuscular) and the form of B-12 used (hydroxycobalamin compared with methylcobalamin). Moreover, although vitamin B-12 was low in all of the patients studied, MMA was not elevated in all of the patients who were considered deficient at the start. This study was set up for the most common type of deficiency found in bariatric centers with adequate follow-up, in which patients have only minor or no clinical symptoms, and serum concentrations are lowered. The severity of the deficiency could theoretically vary and could therefore be a factor that influences the response to the two treatments. In severely deficient patients there could be a faster response in the intramuscular injection group. Therefore, in patients with a severe deficiency for whom a rapid response is required only intramuscular therapy should be considered. However, we compared MMA and Hcy concentrations before treatment, and there was no significant difference. We also saw hardly any severe deficiencies in our clinics, and there were none in the studied population.

This study indicates that both treatments could effectively increase and normalize serum vitamin B-12 concentrations in RYGB patients with low vitamin B-12 values over a period of 6 mo. Having a choice of treatment is convenient for optimizing the care of RYGB patients. For example, patients who are anxious about receiving injections can be offered the more comfortable, albeit more expensive, oral supplementation treatment. Conversely, patients with compliance issues can be prescribed bimonthly intramuscular injections to ensure control of the treatment. One possible problem area in terms of compliance is when patients have to take other tablets for various other deficiencies.

Nevertheless, it remains of the utmost importance to monitor vitamin B-12 status throughout the patient's life, especially in patients with oral supplementation, in whom compliance is harder to monitor.

The authors' responsibilities were as follows—WS, JH, and LvdM: were responsible for the continuation of the study and contributed significantly to the conception, design, and acquisition of all data; WS and JH: were involved with basic analysis, interpretation of data, and writing the results, and participated in drafting and revising the manuscript; IMJ and FJB: were responsible for the integrity of the work as a whole, contributed to this study from inception to writing of the manuscript, were involved throughout the whole process including preoperative management and postoperative follow-up, including requesting for blood withdrawals, and made an essential contribution to revising the manuscript; CJvL and EOA: were highly involved in writing and revising the article; EOA and JH: established the present research; and all authors: read and approved the final manuscript. Except for the delivery of free supplements from FitForMe, which provided the oral vitamin B-12 supplements (FitForMe Vitamin B-12), none of the authors received payment or services from a third party for this study. There were no relevant financial activities outside the submitted work. There were no patents relevant to the work. None of the authors have any relationships/conditions/circumstances that present a potential conflict of interest.

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