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REVIEW ARTICLE

Different Supplementation Regimes to Treat Perioperative Vitamin B12 Deficiencies in Bariatric Surgery: a Systematic Review

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Abstract Vitamin B12 dosage in multivitamin supplementation in the current literature is quite variable. There is no consensus about the optimal treatment of vitamin B12 deficiency. A systematic literature search on different supplementation regimes to treat perioperative vitamin B12 deficiencies in bariatric surgery was performed. The methodological quality of ten included studies was rated using the Newcastle Ottawa scale and ranged from moderate to good. The agreement between the reviewers was assessed with a Cohen's kappa (0.69). The current literature suggests that 350 μg oral vitamin B12 is the appropriate dose to correct low vitamin B12 levels in many patients. Further research must focus on a better diagnosis of a vitamin B12 deficiency, the optimal dose vitamin B12 supplementation, and clinical relevance next to biochemical data.

Keywords Bariatric surgery · Vitamin B12 supplementation · Vitamin B12 deficiency · Methylmalonic acid

Introduction

Vitamin B12 deficiencies are common after bariatric surgery. Schilling et al. estimated the prevalence of vitamin B12 deficiency to be 12–33% [1]. Other researchers have suggested a much greater prevalence of vitamin B12 deficiency in up to 75% of postoperative Roux-en-Y gastric bypass (RYGB) patients. However, most reports have shown approximately 35% of postoperative RYGB patients as vitamin B12 deficient [1–6]. Experts have noted the significance of a functional/subclinical deficiency in the low-normal vitamin B12 range (defined as vitamin B12 levels between 140 and 200 pmol/l) that does not exhibit clinical evidence of deficiency. The methylmalonic acid (MMA) assay is the preferred marker of vitamin B12 status because metabolic changes often precede low vitamin B12 levels in the progression to deficiency. The evidence for the optimal vitamin B12 supplementation regimen after bariatric surgery is lacking [9]. The dose of vitamin B12 in multivitamin (MV) supplementation in the current literature shows a wide range of variety. There is also no consensus about the optimal treatment of a vitamin B12 deficiency.

This systematic review specifically focuses on vitamin B12 supplementation regimes after bariatric surgery. To disclose, we studied the current scientific knowledge regarding the following:

- the effect of additional vitamin B12 supplementation in this patient population
- the effect of different vitamin B12 supplementation regimens on blood levels of vitamin B12

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Methods

A systematic multidatabase literature search was conducted. The patient population of interest were all patients before or after bariatric surgery. The intervention studied was vitamin B12 supplementation compared to no supplementation (or different supplementation vitamin B12 regimen). Outcome measures were blood levels of vitamin B12.

Pubmed, Embase, Medline, and The Cochrane Library were searched from the earliest date of each database up to December 2015. The search string used for the literature search used the following keywords and was modified for each database: bariatric surgery OR metabolic surgery OR sleeve gastrectomy OR roux-en-y gastric bypass OR mini gastric bypass OR omega loop gastric bypass OR biliopancreatic diversion OR duodenal switch OR single anastomosis duodeno-ileal bypass AND vitamin B12 supplementation AND blood levels vitamin B12.

Authors HS and SP screened and selected studies on the basis of title and abstract, separately. After primary selection, authors (HS and SP) reviewed the full text of the selected studies and determined suitability for inclusion, based on the established selection criteria. For further eligible studies, cross-references were screened. Disagreements were solved by discussion with each other and the senior author (JS) until consensus was reached.

Inclusion Criteria

- Randomized controlled trial, prospective or retrospective cohort study
- Patients who were scheduled for bariatric surgery or patients postbariatric
- All surgical procedures were included (Laparoscopic Gastric banding, Vertical Banded Gastroplasty, Roux-en Y Gastric Bypass, Omega Loop Bypass, Duodenal Switch, biliopancreatic diversion, single anastomosis duodeno-ileal bypass)
- Outcome measure of interest was vitamin B12 levels

Exclusion Criteria

- Cross-sectional studies
- Studies looking at prebariatric and/or postbariatric patients with renal insufficiency
- Postbariatric body contouring surgery and vitamin B12 supplementation

For rating the methodological quality, the Newcastle-Ottawa scale for non-randomized trials (NOS) was used [10]. Stars awarded for each quality item serve as a quick visual assessment. Stars are awarded such that the highest quality studies are awarded up to nine stars. The NOS assigns up to a maximum of nine points for the least risk of bias in three domains: (1) selection of study groups (four points), (2) comparability of groups (two points), and (3) ascertainment of exposure and outcomes (three points) for case–control and cohort studies, respectively.

Two authors (HS and SP) separately assessed the NOS scale of the included studies. A Cohen's kappa score was calculated to determine the level of agreement between authors HS and SP. A Cohen's kappa score <0.20 indicates a poor agreement, 0.21–0.40 a fair agreement, 0.41–0.60 a moderate agreement, 0.61–0.80 a good agreement, and 0.81–1.00 a very good agreement [16].

Measurement Unit of Vitamin B12 Levels

All the included vitamin B12 levels were calculated in one general unit (pmol/L), if possible.

Results

The primary literature search produced 532 results, including 37 duplicates. After selection on title and abstract, 19 studies were found possibly relevant. Nine studies were excluded, 5 of them were conference abstracts, 2 of them were not online available, 1 study did not use MV supplementation, and 1 study consisted of a survey among bariatric surgeons. Due to heterogeneity in patient populations, the small sample size of the included studies and lack of standardized reporting of outcome measures (type of supplementation regime and dose of vitamin B12 in the prescribed supplementation), a meta-analysis was not conducted. In total, 10 studies were included in this systematic review.

Figure 1 outlines our search strategy. The methodological quality of the included studies ranged from moderate to good, indicated by the NOS scale (Table 1). A Cohen's kappa of 0.69 reflected a good agreement between authors HS and SP. Table 2 gives an overview of the results of the included studies.

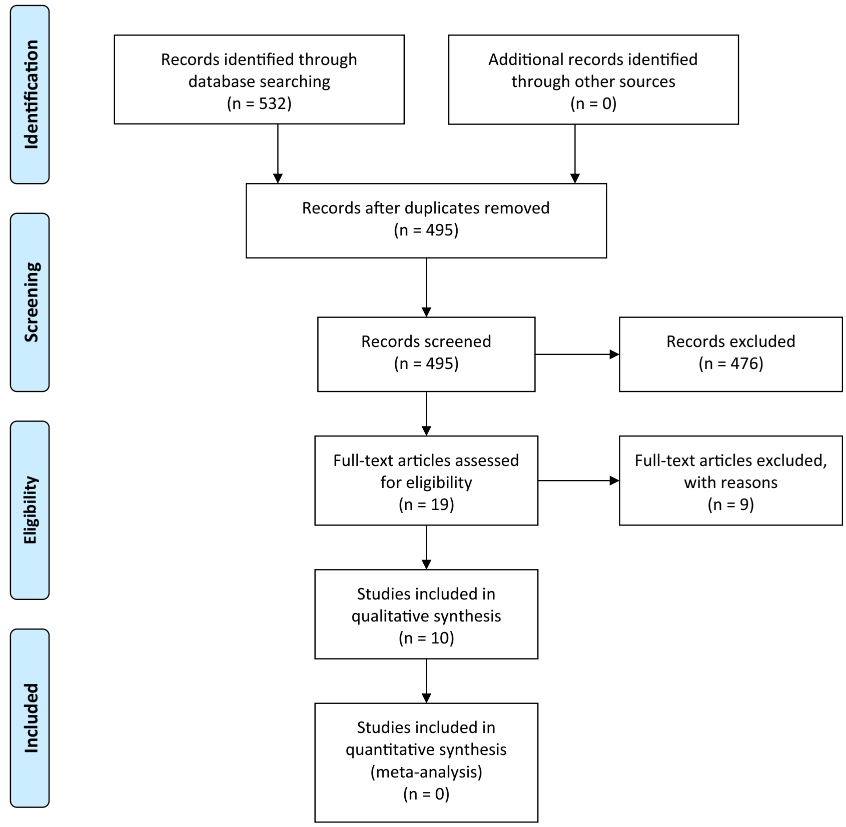
Study Characteristics

Of all the included studies, 1 study was a triple-blind randomized controlled trial [23], 4 studies were prospective cohort studies [9, 11, 12, 15], and 5 studies were retrospective cohort studies [6, 13, 14, 17, 18]. In total, 10 studies consisted of 1277 participants.

Intervention and Follow-up Length

The length of the intervention ranged from 3 months to 10 years postoperative. Intervention and follow-up length of all studies were described in Table 3.

Fig. 1 PRISMA Flowchart



Vitamin B12 Supplementation

In 8 studies, the dose of vitamin B12 in the MV supplementation was different (Table 4). The studies of Ramos et al. [18] and Brolin et al. [6] lacked the dose of vitamin B12 of MV supplements.

Table 1 Assessment of methodological quality using the Newcastle-Ottawa scale for non-randomized trials [10]

Criteria	S1	S2	S3	S4	C1	O1	O2	O3	T
Aasheim et al. [11]	*	–	*	*	**	*	*	*	*8*
Brolin et al. [6]	*	–	*	*	**	*	*	–	*7*
Capoccia et al. [13]	*	–	*	*	**	*	*	*	*8*
Dogan et al. [23]	*	*	*	*	**	*	*	*	*9*
Donadelli et al. [9]	*	–	*	*	**	*	*	–	*7*
Gasteyger et al. [17]	*	–	*	*	**	*	*	–	*7*
Homan et al. (2016)	*	*	*	*	**	*	*	*	*9*
Moore et al. (2014)	*	–	*	*	**	*	–	*	*7*
Ramos et al. (2015)	*	–	*	*	**	*	*	–	*7*
Rhode et al. [12]	*	–	*	*	**	*	–	*	*7*

S1 representativeness, *S2* selection, *S3* ascertainment, *S4* demonstration, *C1* comparability, *O1* outcome selection, *O2* outcome follow-up, *O3* adequacy

[*] the study suffices in this criteria point

[**] the study suffices in this two criteria points

Outcomes of Laboratory Tests of Vitamin B12

Outcomes of laboratory tests are described in Table 5. All vitamin B12 levels were calculated in pmol/L, except the studies of Brolin et al. [6] and Ramos et al. [18], which was suspected to have used wrong measurement units for indicating a vitamin B12 deficiency. Therefore, the original measurement units of the studies were used in this paragraph. Reference ranges of vitamin B12 levels of all studies are described in Table 3.

Complaints and Clinical Effects

All included studies did not control the vitamin B12 deficient-related complaints. Clinical relevance of the deployed supplementation regime has not been studied in all manuscripts.

Discussion

This systematic review highlights the current evidence on the effects of MV or additional vitamin B12 supplementation in patients after bariatric surgery. Vitamin B12 supplementation has an effect on the intracellular vitamin B12 content, and in the optimal dosage, it can prevent vitamin B12 deficiency. However, vitamin B12 deficiencies preoperatively are not

Table 2 Overview of the study results of the included studies

Study (+design)	Participants *N* (male/female)	Characteristics	I: N (age ± SD) C: N (age ± SD)	Standard supplementation regime	Additional supplementation	Type of bariatric operation	Intervention/treatment	Outcome measures	Study results
Aasheim et al. [11] PCT	50 (18/32)	Patients who have had RYGB and a control group who only have had a life style intervention	I: 27 (44 ± ?) C: 23 (45 ± ?)	I: standardized supplements 1 pill/day; 1 μg B12. C: no supplements.	I: IM injections every 3 months (1 mg cyanocobalamin). C: no additional vitamin B12.	I: RYGB N: no operation	Biologic specimen collection and vitamin measurements were performed at baseline and 1 year after the intervention. Dietary intake was assessed by a structured interview performed in person by registered dieticians, at baseline and 1 year after intervention.	Blood tests	Vitamin B12 levels were increased ($p < 0.02$) in group I compared to group C during follow-up
Brolin et al. [6] RT	348 (?/?)	Patients with (morbid) obesity who have had RYGB as a primary or revisional surgery	I: 348 (? ± ?)	Oral MVI supplement daily; dose of MV was not mentioned.	Low serum levels of vitamin B12 were treated either with MV or an additional supplement. Dose of vitamin B12 used in this study 500 μg	RYGB: 321 Revisional surgery: 27 −24: some form of gastroplasty as their initial operation. −3 patients had revision of jejunoileal bypass.	During a 10-year period, a complete blood count and serum levels of iron, total iron-binding capacity, vitamin B12, and folate were obtained preoperatively and postoperatively at 6-month intervals for the first 2 years, then annually thereafter.	Blood tests	Vitamin B12 deficiency was recognized in 122 patients (37%). The incidence of vitamin B12 deficiency was significantly greater in the revision group. Taking standard MV did not prevent vitamin B12 deficiencies.
Capoccia et al. [13] RT	138 (28/110)	Patients with (morbid) obesity who have had LSG	I-a: 7 (36.7 ± 13.2) I-b: 29 (43.6 ± 10) I-c: 40 (44.4 ± 9.6) I-d: 33 (45.1 ± 12.8) I-e: 29 (43.7 ± 10.8)	Oral MV (1 tablet/day and provides 2.5 μg vitamin B12) for the first 6 months. Then, oral MV was stopped and 1000 μg/month of IM vitamin B12 were administered during all the follow-up period.	–	LGS	LGS patients with a standard MV were followed up with routine laboratory tests and anthropometric measurements and assessed for nutritional status every three months throughout 12 months.	Blood tests	Vitamin B12 was adequately supplemented for all the follow-up period. Greater weight loss does not require higher dosage of MV.
Dogan et al. [23] RCT	148 (46/104)	Patients who have had roux-en-y gastric bypass.	I-1: 74 (43.4 ± 10.0) I-2: 74 (45.3 ± 10.2)	I-1: Standard MV with a vitamin B12 dose of 12.5 μg/day. I-2: a vitamin B12 dose of 350 μg/day.	Vitamin B12 deficiency (levels <150 pmol/L) was corrected with IM injection of 1000 μg hydroxocobalamin once every 2 months for 12 months.	RYGB	Patient were randomized in 2 groups, receiving 2 different MV supplements (standard MV and WLS Forte). Standard laboratory blood tests were performed at baseline, 6 and 12 months postoperative.	Blood tests	Using WLS Forte supplements after RYGB results in fewer deficiencies in vitamin B12 levels compared with standard MV supplements.
Donadelli et al. [9] PCT	58 (12/46)	Patients with (morbid) obesity after RYGB	I: 58 (41 ± 10)	MV on daily basis with a vitamin B12 dose of 12 μg/day.	–	RYGB	Patients' blood vitamin concentrations were evaluated preoperatively and at 3, 6, and 12 months after surgery.	Blood tests	Vitamin B12 levels were significantly decreased and 7% of all patients had a vitamin B12 deficiency by 12 month postoperatively.
Gasteyger et al. [17] RT	137 (27/110)	Patients with (morbid) obesity after RYGB	I: 137 (39.9 ± 10)	A standardized MV between the 1st and 6th month postoperative. Dose of vitamin B12/day: 3 μg/day.	Specific substitutive treatments were prescribed as soon as the value was below the lower value of the reference range. Dose oral vitamin B12: 1 mg/month.	RYGB	Between 1st and 6th months postoperative, a standardized MV was prescribed for all patients. Specific requirements for additional substitutive treatments were systematically assessed by a blood sample at 3, 6, 9, 12, 18 and 24 months.	Blood tests	3 months after RYGB, 34% of all patients required at least one specific supplement in addition to MV. At 6 and 24 months, this proportion increased to 59% and 95%, respectively. Of all patients, 80% is using additional vitamin B12 after 24 months.
	137 (42/95)				Vitamin B12 deficiency (levels <150 pmol/L)	RYGB	12–36 months follow-up of the study of Dogan et al. [23].	Blood tests	In the first 3 years, 22 patients developed a vitamin B12

Table 2 (continued)

Study (+design)	Participants *N* (male/ female)	Characteristics	I: N (age ± SD) C: N (age ± SD)	Standard supplementation regime	Additional supplementation	Type of bariatric operation	Intervention/treatment	Outcome measures	Study results
Homan et al. [14] RT		Patients with (morbid) obesity after RYGB	I-1: 45 (46 ± 12) I-2: 64 (44 ± 9) I-3: 28 (43 ± 10)	I-1: Standard MV with a vitamin B12 dose of 12.5 µg/day. I-2: MV with a vitamin B12 dose of 350 µg/day. I-3: patients stopped using a supplement.	was corrected with IM injection of 1000 µg hydroxocobalamin once every 2 months for 12 months.				deficiency and were prescribed IM injections. At time of diagnosis 5 of this subset of patients were using WLS Forte, 15 were using an standard MV and 2 were nonusers. After exclusion of the IM injection users, a significant difference in estimated mean serum vitamin B12 concentrations was found between WLS Forte and standard MV ($p < 0.001$).
Moore et al. [15] PCT	22 (0/22)	Woman with (morbid) obesity after RYGB	I: 22 (41 ± 12)	MV with 350 µg vitamin B12 daily for 3 months	–	LGS: 11 RYGB: 11	Blood vitamin concentrations were measured preoperatively and 3 months postoperative.	Blood tests	Vitamin B12 levels were increased after 3 months.
Ramos et al. [18] RT	137 (24/113)	Patients with (morbid) obesity after RYGB	I: 137 (? ± ?)	MV Dose of vitamin B12 was not mentioned	–	RYGB	Personal information, anthropometric and laboratory data in the preoperative, 12, 24, 36 and 48 months postoperatively were done.	Blood tests	Vitamin B12 was decreased at 48 months postoperatively in females. The values are within the reference standards.
Rhode et al. [12] PCT	102	Patients after bariatric surgery	I-a:? (? ± ?) I-b:? (? ± ?) I-c:? (? ± ?) I-d:? (? ± ?)	Dose of crystalline vitamin B12 between 4 groups: I-a:100 µg I-b:250 µg I-c:350 µg I-d:600 µg	–	RYGB: 94 VBG: 8	Blood profiles were determined at the initial evaluation and then at 3 monthly intervals, producing a hematological profile for the 3-, 6-, and 9-month time point. All patients were given 350 µg of vitamin B12 per day for the first 3 months; patients were assigned on a sequential basis for the next 3 months to receive one of four dosage levels of crystalline vitamin B12—100, 250, 350, or 600 µg per day. For the last 3 months, they were instructed not to take any vitamin B12.	Blood tests	Serum vitamin B12 levels were greater than 150 pmol/L after 6 months in 83.3% of patients who received 100 µg; 92.3% of patients who received 250 µg; 94.7% after 350 µg and 95.2% after 600 µg ($p = 0.525$).

I intervention group, *C* control group, *PCT* prospective cohort trial, *IM* intramuscular, *MV* multivitamin, *RYGB* Roux-en-Y gastric bypass, *LGS* laparoscopic gastric sleeve, *DRI* dietary reference intake, *RT:* retrospective cohort trial, *BMI* body mass index, *VBG* vertical banded gastroplasty

Table 3 Intervention, follow-up length, and reference range of vitamin B12 levels of all included studies

Aasheim et al. [11]	Dietary intake and blood tests were performed until 1 year after intervention. Reference range: [a]
Brolin et al. [6]	Blood tests at 6-month intervals for the first 2 years postoperatively, then annually thereafter for 10 years. Reference range: 210–700 pg/dl
Capoccia et al. [13]	Blood tests and nutritional status postoperative every 3 months throughout 12 months. Reference range: [a]
Dogan et al. [23]	Blood tests preoperatively and at 6th and 12th months. Reference range: ≤150 pmol/L
Donadelli et al. [9]	Blood tests preoperatively and at 3rd, 6th, and 12th months. Reference range: 130–650 pmol/L
Gasteyger et al. [17]	Blood tests at 3rd, 6th, 9th, 12th, 18th, and 24th months. Reference range: 133–675 pmol/L
Homan et al. [14]	Blood tests were done at 12th and 36th months postoperatively. Reference range: ≤150 pmol/L
Moore et al. [15]	Blood tests only 3 months postoperatively. Reference range: < 200 μg/mL deficient; 677 μg/mL > 95th percentile
Ramos et al. [18]	Blood tests at the 12th, 24th, 36th, and 48th months. Reference range: ≥ 250 mg/dl
Rhode et al. [12]	Baseline blood tests and 3rd, 6th, and 9th months after treatment. Reference range: 150–600 pmol/L

[a] Reference range was not mentioned in the study.

uncommon in morbidly obese people. In the study of Dogan et al. [23], vitamin B12 deficiency was diagnosed in 9 patients (6.1%) and 3 patients (5.2%) in the study of Donadelli et al. [9] had a vitamin B12 deficiency in the preoperative period. This is not clearly reported in the other 8 studies.

There is no consensus about the optimal dosage of vitamin B12 supplementation after bariatric surgery worldwide. ASMBS guidelines advise oral vitamin B12 supplements of 350 to 500 μg, and if necessary, intramuscular (IM) injections of 1000 μg per month [24]. The ACCE/TOS/ASMBS guidelines advise that oral supplementation with crystalline vitamin B12 at a dosage of 1000 μg daily or more may be used to maintain normal vitamin B12 levels. Intranasally administered vitamin B12, 500 μg weekly, may also be considered. Parenteral (IM or sub-cutaneous) vitamin B12 supplementation, 1000 μg/month to 1000–3000 μg every 6 to 12 months, is indicated if vitamin B12 sufficiency cannot be maintained using oral or intranasal routes [25].

However, definitive conclusions cannot be made after this systematic review, because of the heterogeneity of MV supplementation or additional vitamin B12 IM injection regimes and timing of this additional vitamin B12 IM injections. Besides that, all the included studies did not control the vitamin B12 deficient-related complaints. Clinical relevance has not been studied in all

Table 4 Dosage of vitamin B12 among the included studies

	Vitamin B12 per day in prescribed supplementation regime
Aasheim et al. [11]	1 μg oral vitamin B12 per day and 1 mg IM injection every 3 months
Brolin et al. [6]	The dose of vitamin B12 in de MV supplements was not mentioned in the study
Capoccia et al. [13]	First 6 months: oral MV with 2,5 μg vitamin B12 per day After 6 months: oral MV were stopped and IM injections with 1 mg/month were administered
Dogan et al. [23]	I-1:supplement with 350 μg vitamin B12 I-2: standard MV supplementation with 12,5 μg vitamin B12. Treatment of a deficiency: IM injections with 1 mg per 2 months for 12 months
Donadelli et al. [9]	12 μg oral vitamin B12 per day
Gasteyger et al. [17]	First 6 months: 3 μg oral vitamin B12 per day After 6 months: no MV, substitutive 1 mg/month oral vitamin B12 were prescribed below the lower reference range. When no satisfactory response was obtained, the doses were increased to IM injections. Dose of IM injections was not mentioned in the study.
Homan et al. [14]	I-1: supplement with 350 μg vitamin B12 I-2: standard MV supplementation with 12.5 μg vitamin B12. Treatment of a deficiency: IM injections with 1 mg per 2 months for 12 months
Moore et al. [15]	350 μg oral vitamin B12 per day for 3 months
Ramos et al. [18]	The dose of vitamin B12 in de MV supplements was not mentioned in the study
Rhode et al. [12]	First 3 months: 350 μg oral vitamin B12 per day. Thereafter, in the following oral dosage for the next 3 months:I-1: 100 μg I-2: 250 μg I-3: 350 μgI-4: 600 μg

MV multivitamin, *I-1-4* intervention group 1–4, *IM* intramuscular, *μg* microgram, *RDA* recommended daily allowance

Table 5 Outcomes of laboratory tests of vitamin B12

Aasheim et al. [11]	Vitamin B12 levels increases after intervention, compared with the control group ($P < 0.02$). Of 2 patients who developed vitamin B12 deficiency (compared with non in the control group), 1 reported not having had IM injections. Actual vitamin B12 levels were not mentioned in the study.
Brolin et al. [6]	Vitamin B12 levels were significantly lower than mean preoperative values only at 12 and 24 months after surgery. 37 % of the patients had a vitamin B12 deficiency and the incidence of vitamin B12 deficiency after surgery was significantly greater in the revision group ($p \leq 0.004$). There was no correlation between regular ingestion of MV supplementation and the potential for developing a vitamin B12 deficiency. In this study, more than 80% of the vitamin B12 deficiencies responded to oral supplementation (containing 500 μg vitamin B12). Actual vitamin B12 levels were measured but not mentioned in the study.
Capoccia et al. [13]	Vitamin B12 was adequately supplemented for all the follow-up period (before surgery and 12 months after surgery, 365.8 ± 193.7 and 360.8 ± 169.0 pmol/L, respectively). Baseline vitamin B12 levels: 317.3 ± 132.8, 286.0 ± 188.7, 376.8 ± 197.8, 517.3 ± 191.0, and 258.8 ± 303.5 pmol/L, for groups A, B, C, D, and E, respectively. Follow-up results 12 months after surgery: 338.7 ± 284.4, 349.8 ± 193.3, 268.6 ± 119.0, 284.4 ± 154.3, and 303.5 ± 187.0 pmol/L, for groups A, B, C, D, and E, respectively. Percentage deficiencies were not mentioned in the study.
Dogan et al. [23]	At baseline, vitamin B12 deficiency was diagnosed in 9 (6.1%) patients, that is, 5 (6.8%) patients in the standard MV group and 4 (5.44%) patients in the high dose group. These patients received IM injections by protocol. In total, 27 (18.2%) additional patients were treated with IM injections at any time during the 12-month follow-up: 17 (23%) in the standard MV group and 10 (13.5%) in the high dose group ($p = 0.14$). The results obtained after exclusion of these patients receiving IM injections: mean vitamin B12 serum levels decreased by 38.9 ± 141.3 pmol/L in the standard MV group and increased by 44.1 ± 138.8 pmol/L in the high dose group ($p < 0.001$) after 12 months, and as a result mean vitamin B12 blood serum levels at 6 months and 12 months were significantly higher with high dose compared with standard MV ($p < 0.05$). After 12 months, vitamin B12 deficiency had developed in 5 (7.9%) patients receiving standard MV versus 1 (1.6%) patient in the high dose group ($p = 0.207$).
Donadelli et al. [9]	Vitamin B12 levels remained constant up to 3 months (331.7 ± 183.9 pmol/L) until 6 months (295.8 ± 183.0 pmol/L) after surgery but were significantly decreased after 12 months (274.9 ± 196.9 pmol/L, $p \leq 0.05$ versus basal). 7% of patients had vitamin B12 deficiency 1 year after surgery.
Gasteyger et al. [17]	10% of all patients used additional vitamin B12 at 3 months, 28% at 6 months, 62% at 12 months, 72% at 18 months and 80% at 24 months.
Homan et al. [14]	In the first 3 years, 22 patients developed vitamin B12 deficiency and were prescribed IM injections. At time of diagnosis, 5 of this subset of patients were using high dose vitamin supplements, 15 were using a standard MV, and 2 were non-users. The difference in IM injection use between high-dose vitamin supplements (409 ± 25) and standard MV (330 ± 27) was significant ($p = 0.001$). After exclusion of the IM injection users, a significant difference in estimated mean serum vitamin B12 was found between high-dose vitamin supplements (335 ± 12) and standard MV (264 ± 12) ($p < 0.001$).- In total, 7 patients were diagnosed with a vitamin B12 deficiency at 36 months (3 in the standard MV group and 4 in the non-using group). Combining the IM injection users and the deficient patients resulted in a total of 29 patients with vitamin B12 deficiency throughout the study (5 while using high-dose vitamin supplements, 18 while using standard MV, and 6 while using no supplement). The difference between high-dose vitamin supplements and standard MV was significant ($p < 0.001$).
Moore et al. [15]	High-dose MV supplementation daily for 3 months resulted in a 48% increase of serum vitamin B12. A significant increase was seen in all patients after LSG (from 356.5 ± 93.0 to 466.4 ± 220.7 pmol/L, $p = 0.0336$) and in all patients after RYGB (from 377.1 ± 129.2 to 605.9 ± 295.2 pmol/L, $p = 0.033$).
Ramos et al. [18]	Male: Preoperative: 464.0 ± 140.6 mg/dL. Postoperative: 12 months: 373.8 ± 148.3 mg/dL, 24 months: 317.8 ± 163.7 mg/dL, 36 months 401.4 ± 352.0 mg/dL, 48 months: 354.4 ± 186.6 mg/dL Female: Preoperative: 512.5 ± 561.5 mg/dL Postoperative: 12 months: 395.6 ± 247.0 mg/dL, 24 months: 391.5 ± 212.9 mg/dL, 36 months 351.3 ± 177.1 mg/dL, 48 months: 395.8 ± 220.3 mg/dL Percentage of vitamin B12 deficiencies was not mentioned in the study.
Rhode et al. [12]	Serum vitamin B12 levels were <100 pmol/L at baseline and greater than 150 pmol/L after 6 months in 83.3% of patients who received 100 μg; 92.3% of patients who received 250 μg; 94.7% after 350 μg and 95.2% after 600 μg ($p = 0.525$).

manuscripts. These data are needed to examine whether biochemical benefits of vitamin B12 supplementation are correlated with clinical improvement. Besides that, surgical techniques affect the absorption of vitamin B12. Intrinsic factor (IF) is produced by the parietal cells of the stomach, and IF is needed to absorb vitamin B12 in the terminal ileum.

In this review, laparoscopic sleeve gastrectomy (LSG), RYGB, and vertical-banded gastroplasty (VBG) are discussed. LSG patients have reduced production of stomach acid and reduced availability of IF. In RYGB patients, a vitamin B12 deficiency loss of IF and acid secretion in the stomach is expected. The remnant stomach and duodenum are eliminated from the digestion process as well. The VBG serve only to restrict and decrease food intake and do not interfere with the normal digestive process. In this procedure, the upper stomach near the esophagus is stapled vertically to create a small pouch along the inner curve of the stomach. The outlet from the pouch to the rest of the stomach is restricted by a band.

Two interesting findings were found in the included studies. First, in 4 included studies, a dose of 350 μg vitamin B12 per day was used [12, 14, 15, 23]. In the study of Moore et al. [15], vitamin B12 levels of all patients were increased 3 months postoperatively. In the study of Dogan et al. [23], high-dose vitamin B12 supplements result in fewer vitamin B12 deficiencies compared with standard MV supplements. The study of Homan et al. [14] showed that high-dose vitamin B12 supplement is more effective than is a standard MV supplement to reduce the number of patients with vitamin B12. In the study of Rhode et al. [12], serum levels of vitamin B12 were >150 pmol/L after 6 months in 95% of the patients.

Secondly, all the other studies used MV supplementation with a dose of vitamin B12 ranging from 3 to 12 μg per day [9, 17] or unknown dose of vitamin B12 [6, 18]. The studies of Brolin et al., Donadelli et al., and Gasteyger et al. showed many vitamin B12 deficiencies in the follow up [6, 9, 17]. Contrary results were found in the study of Ramos et al. [18]; the vitamin B12 levels are within the reference standards. However, the dose of vitamin B12 in his study was unknown.

Vitamin B12 Supplementation

Dose of vitamin B12 in the MV supplementation in all included studies is varied from 1 μg/day to high-dose supplementation with 350–600 μg/day. MV supplements with 350 μg vitamin B12 per day can maintain normal-high vitamin B12 levels in many patients [12, 14, 15, 23]. The body's storage will be depleted much faster in patients using standard MV supplementation with a low dose of vitamin B12. As regards the supplementation regimes with an oral vitamin B12 dosage <350 μg/day, eight of the included studies showed persistence of deficiencies even after a period supplementation of vitamin B12 [6, 9, 11–14, 17, 23]. In one study [6], no dosage of vitamin B12 was measured; in the other studies, the dosage of vitamin B12 was lower than <350 μg/day [9, 11–14, 17, 23]. In two included studies, IM injections belong to the standard MV supplementation regime with a low dose of vitamin B12 [11, 13]. The dose of the IM injections is equal but the frequency of the given IM injections is also different (Table 4). In the study of Aasheim et al. [11], two patients developed vitamin B12 deficiency and in the study of Capoccia et al. [13], vitamin B12 levels decreased in many patients, which suggests that both of this regimens were not optimal.

If MV supplementation with high dose of vitamin B12 may improve the vitamin B12 levels in many patients, IM injections as a standard regime is not necessary and because of this, many patients were unnecessarily loaded with IM injections. This seems like contradictory advice, but to determine whether IM injections of vitamin B12 are necessary, we need to focus on the combination of vitamin B12 and MMA. This is essential to assess whether there is an absolute functional deficiency of vitamin B12, because of the failure rate of the current vitamin B12 assays between 22 and 35% [7, 8, 19, 20] and therefore whether it is necessary to add IM injections to the standard supplementation regime. Besides that, these data are subjective and it is unclear if patients take their supplements daily. Lifelong compliance of daily supplement intake is hard to achieve. To measure adequate intake of MV supplementation, one can monitor the serum concentration of highly absorbable vitamins. Some investigators have reported that low folate levels reflect non-adherence to MV supplementation because the amount of the supplemented folic acid properly corrects low serum folate levels [9, 23]. Only two studies have looked at compliance of MV supplementation intake and distinction in processing these data [14, 23].

Outcomes of Laboratory Tests of Vitamin B12 and MMA

Vitamin B12 assays that are currently used to diagnose clinical vitamin B12 deficiency have a failure rate of 22–35% [7, 8, 19, 20]. This failure rate may be due to the fact that 80% of the vitamin B12 in plasma is bound to the transport protein haptocorrin. This percentage is biologically unavailable and cannot be absorbed by the cells, which means that plasma vitamin B12 concentrations poorly correlate with the bioavailable intracellular vitamin B12 content [8, 21, 22]. Measuring vitamin B12 is a poor predictor for a functional vitamin B12 status. In the study of Smelt et al. [8], more vitamin B12 deficiencies were found when MMA was included in the diagnosis. When a vitamin B12 level is between 140 and 200 pmol/l, additional MMA levels should be measured to determine whether there is functional vitamin B12 deficiency. In this review, no included study used the additional parameter MMA. Given the high failure rate of vitamin B12 assays, many vitamin B12 deficiencies will be untreated.

Study Limitations

First, the following limitations are present when evaluating the literature: (1) heterogeneous patient populations being studied, (2) non-comparable vitamin B12 from supplements being evaluated, (3) lack of many data (some studies lacked of gender, age, reference range of vitamin B12 levels, actual vitamin B12 levels after intervention, lack of dose of vitamin B12 in MV supplementation), and (4) lack of well-designed prospective cohort and randomized controlled studies for the right use of vitamin B12 in postbariatric patients. Secondly, only biochemical data was measured and clinical relevance was not demonstrated.

Conclusion

In bariatric surgery, vitamin B12 deficiencies have a high prevalence. Unfortunately, there is no consensus about MV supplementation and any additional vitamin B12 supplementation. The current literature suggests that 350 μg of oral vitamin B12 is the appropriate oral dose to correct low serum vitamin B12 levels in many patients. A lifelong follow-up regimen seems necessary, because MV supplementation with a high dose of vitamin B12 cannot prevent all deficiencies. Further research must focus on a better diagnosis of vitamin B12 deficiency with possible additional parameters like MMA, the right dose of vitamin B12 supplementation, and the clinical relevance beside biochemical data.

Compliance with Ethical Standards

Conflict of Interest Author 3 reports educational grants from Medtronic and FitForMe. Author 1 and author 2 have nothing to disclose.

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Ethical Approval For this type of study, formal consent is not required.

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Author Contributions

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