Obesity Surgery (2018) 28:1916–1923
https://doi.org/10.1007/s11695-017-3102-y

ORIGINAL CONTRIBUTIONS

Oral Vitamin B_{12} Supplementation After Roux-en-Y Gastric Bypass: a Systematic Review

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Published online: 9 January 2018

Abstract

Background Many respectable guidelines recommend lifelong vitamin B_{12} injections for Roux-en-Y gastric bypass (RYGB) patients in the absence of lack of consensus on the efficacy of oral route of prophylaxis and the appropriate doses needed for this purpose. The purpose of this review was to examine the published English language scientific literature in accordance with PRISMA principles to find out if orally given vitamin B_{12} is adequate for prophylactic purposes in RYGB patients and the appropriate dosages needed for this purpose if it is.

Methods We examined the PubMed database for all English language articles examining various doses of oral vitamin B_{12} supplementation after proximal RYGB in adult patients. The search revealed 19 such articles.

Results The data suggest that oral vitamin B_{12} supplementation doses of ≤ 15 μg daily are insufficient to prevent deficiency in RYGB patients. Higher supplementation doses show better results and it appears that a dose of 600.0 μg vitamin B_{12} daily is superior to 350.0 μg daily suggesting an incremental dose-response curve. It further appears that supplementation doses of 1000.0 μg vitamin B_{12} daily lead to an increase in B_{12} levels and are sufficient for the prevention of its deficiency in most RYGB patients.

Conclusion The review finds that oral supplementation doses of ≤ 15 μg vitamin B_{12} daily are inadequate for prophylaxis of vitamin B_{12} deficiency in adult RYGB patients but doses of 1000 μg vitamin B_{12} daily might be adequate. Future studies need to examine this and even higher oral doses for vitamin B_{12} supplementation for patients undergoing RYGB.

Keywords Morbid obesity · Bariatric surgery · Gastric bypass · Roux-en-Y gastric bypass · Prophylaxis · Vitamin B_{12} · Micronutrient supplementation

Introduction

Vitamin B_{12} is an essential micronutrient. Its deficiency can lead to anemia and neurological dysfunction, which could be irreversible if untreated. Approximately 5.0–6.0% of patients considering bariatric surgery are deficient in vitamin B_{12} [1, 2] and Roux-en-Y gastric bypass (RYGB) further aggravates it [3] through a combination of decreased intake [4], lack of intrinsic factor, reduced gastric acid, and impaired absorption due to bypass of proximal small intestine. It is widely recognized that RYGB patients need additional vitamin B_{12} supplementation [5]. In the UK, the British Obesity and Metabolic Surgery Society (BOMSS) nutritional guidelines [5] recommend 3-month intramuscular injection for these patients and there is evidence to suggest that this is sufficient to prevent vitamin B_{12} deficiency in RYGB patients [6]. At the same time, regular lifelong injections pose an additional demand on already constrained healthcare resources and may put some patients off having a gastric bypass. It would hence be useful to understand if the same can be achieved through oral vitamin B_{12} supplementation and the dose needed for that purpose.

It is widely recognized that a 3-month injection of 1 mg vitamin B_{12} subcutaneously is sufficient to prevent vitamin

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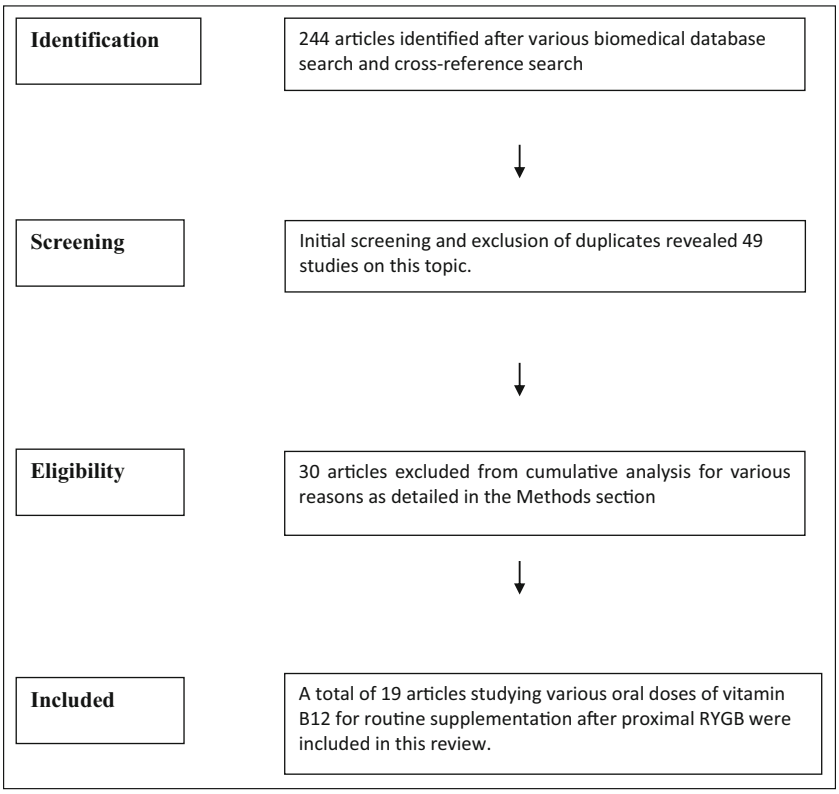

Fig. 1 PRISMA flow chart for article selection

B_{12} deficiency in RYGB patients [6] but it is unclear if the same can also be achieved through oral supplementation and the oral dosages needed if that is the case. Recent guidelines by the American Society for Metabolic and Bariatric Surgery (ASMBS) suggest an oral dose of 350–500 μg vitamin B_{12} daily for all bariatric surgery patients [7]. The guidelines do not make any distinction between different procedures and it is unclear if these doses are sufficient for all RYGB patients.

The purpose of this review was to identify the appropriate dose of oral vitamin B_{12} supplementation after RYGB. We investigated the entire English language scientific literature on oral vitamin B_{12} supplementation and deficiency after RYGB in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Methods

An online search of PubMed was carried out using keywords like "bariatric surgery," "gastric bypass," "Roux en Y Gastric Bypass," and "B12," and to identify all English language articles specifically examining doses of oral vitamin B_{12} supplementation after proximal RYGB in adult patients. Articles were also identified from references of relevant articles. Last of these searches was carried out on 22 September 2017. Review articles were excluded as were those that pooled results with different procedures together [8, 9]. Articles on distal RYGB [10] and banded RYGB [11] were also excluded. Articles that reported on vitamin B_{12} deficiency without clearly mentioning the supplementation dosages had to be excluded as these would not allow us to determine the appropriate supplementation dose for oral vitamin B_{12} supplementation after RYGB. Case reports were also excluded. Finally, we excluded articles where authors had evaluated non-oral routes for supplementing vitamin B_{12} as the purpose of this review was to ascertain the effectiveness of oral route for supplementation of vitamin B_{12}. A total of 19 articles were included. Figure 1 gives a PRISMA flow chart for article selection.

Results

Studies on Oral Vitamin B_{12} Supplementation in Doses up to 15.0 μg Daily

Table 1 [12–21] summarizes studies that examined oral vitamin B_{12} in supplementation doses of up to 15.0 μg daily. It would appear from these studies that even in the early period after RYGB when the body reserves of vitamin B_{12} are unlikely to have been exhausted, these oral doses of vitamin B_{12} are insufficient for the prevention of vitamin B_{12} deficiency. The data suggest that standard multivitamins do not contain dosages of vitamin B_{12} sufficient enough to prevent deficiency in RYGB patients.

Table 1 Studies on oral vitamin B_{12} supplementation in doses of up to 15.0 μg daily

Author	RYGB characteristics	Daily supplementation dose of vitamin B_{12}	Important findings
Coupaye et al. [12] *N* = 43 Jan 2005–Jan 2012 Level III evidence Comparative study	Gastric pouch 15–20 ml AL 150 cm BPL NA	4.0 μg	Vitamin B_{12} levels dropped from a mean of 433.6 (± 229.2) ng/l before surgery to 355.8 (± 172.2) ng/l at 6 months, and 334.9 (± 160.4) ng/l at 12 months. Differences were statistically significant. Vitamin B_{12} deficiency prevalence increased from 7.0% before surgery to 12.0% at 6.0 months and 17.0% at 12 months
Coupaye et al. [13] *N* = 49 Jan 2004–June 2006 Level III evidence Comparative study	Gastric pouch 15–20 ml AL 150 cm BPL: NA	4.0 μg	The vitamin B_{12} levels dropped from 381 ± 171 ng/l before surgery to 308 ± 141 ng/l 12 months after RYGB. Intramuscular vitamin B_{12} injections had been started before the 1-year evaluation in 20 patients and at 1-year mark, and another 5 patients were found to be deficient in B_{12}
Dalcanale et al. [14] *N* = 75 Time: NA Level IV evidence Cohort study	NA	12.0 μg	61.8% of their patients were deficient in vitamin B12 at 83.4 ± 14.3 months after RYGB (minimum follow-up 5 years)
Donadelli et al. [15] *N* = 58 Time: NA Level IV evidence Cohort study	Gastric pouch: NA AL 100 cm BPL 100 cm	12.0 μg	The levels of vitamin B_{12} dropped from 442.1 ± 260.6 pg/ml before surgery to 372.5 ± 266.8 at 12 months ($p = <0.05$)
Gasteyger et al. [16] *N* = 137 Nov 1999–June 2004 Level IV evidence Cohort study	NA	3.0 μg	Over the next 2 years, 80.0% of the patients needed additional vitamin B_{12} supplementation in the form of injections
Gehrer et al. [17] *N* = 86 April 2004–Dec 2006 Level III evidence Comparative study	Gastric pouch: NA AL 150 cm BPL 50 cm	10 μg	Postoperatively (within 3-year follow-up), 58.0% of the patients developed vitamin B_{12} deficiency compared to 3.0% preoperatively
Provenzale et al. [18] *N* = 20 Time: NA Level IV evidence Cohort study	NA	10 μg (approx.)	Vitamin B_{12} levels decreased significantly from a mean of 385 pg/ml preoperatively to 282 pg/ml at 6 months and 234 pg/ml at 12 months. Five (27.8%) patients were deficient in vitamin B_{12} at 1 year compared to zero prior to surgery
Rhode et al. [19] *N* = 10 Time: NA Level III evidence Comparative study	Gastric pouch 10–15 ml AL 40 cm BPL: NA	4.0 μg	Vitamin B_{12} given in this dose to RYGB patients (19.4 ± 6.5 months after surgery) with a low serum vitamin B_{12} concentration did not increase B_{12} levels to the reference range though the levels increased slightly from 87 ± 25 pmol/l to 124 ± 43 pmol/l
Aarts et al. [20] *N* = 377 Jan 2005–Oct 2009 Level IV evidence Cohort Study	Gastric pouch 30 ml AL 100–150 cm	1.5 μg	By the end of the first year, 40.0% (152/377) of the patients had become deficient in vitamin B_{12}

Table 1 (continued)

Author	RYGB characteristics	Daily supplementation dose of vitamin B_{12}	Important findings
Vargas-Ruiz et al. [21] *N* = 30 July 2003–Jan 2005 Level IV evidence Cohort study	BPL 40 cm NA	6.0 μg	Authors found that at 6 months and 1, 2, and 3 years, respectively, 3 (10%), 5 (16.6%), 10 (33.3%), and 3 (27.2%) patients developed vitamin B_{12} deficiency

AL alimentary limb, *BPL* bilio-pancreatic limb, *NA* not available

Studies on Oral Vitamin B_{12} Supplementation in Doses from 16.0 to 999.0 μg Daily

Table 2 [1, 4, 19, 22–24] summarizes studies that examined oral vitamin B_{12} in supplementation doses from 16.0 to 999.0 μg daily and shows better results than studies in Table 1. Results also appear better with a dose of 600.0 μg vitamin B_{12} daily [22] in comparison with 350.0 μg daily [1, 19, 23] suggesting an incremental dose-response curve in this dose range.

Studies on Oral Vitamin B_{12} Supplementation in Doses of 1000.0 μg Daily or More

Table 3 [25–27] summarizes studies that examined oral vitamin B_{12} in supplementation doses of 1000.0 μg daily. It appears that these doses lead to an increase in vitamin B_{12} levels and are sufficient for the prevention of deficiency in most patients. There is no study in the scientific literature examining prophylactic doses of > 1000.0 μg daily in these patients.

Discussion

There is little doubt that RYGB patients need vitamin B_{12} supplementation to prevent subclinical and clinical deficiency as many patients are already deficient in vitamin B_{12} at the time of surgery and RYGB leads to further reduction in intake and absorption of vitamin B_{12}. Though there is no doubt that vitamin B_{12} injections at regular intervals, as recommended by the BOMSS guidelines [5], are sufficient to prevent deficiency in these patients, it does involve regular visits to primary care and it is possible that some patients would prefer to avoid regular lifelong injections if possible.

It is worth mentioning in this context that recent ASMBS guidelines [7] recommend routine preoperative screening for vitamin B_{12} levels because "2–18% patients with obesity suffer from vitamin B_{12} deficiency and the prevalence increases to 6–30% in those taking proton-pump inhibitors." Preoperative screening seems logical for those patients who are not going to be routinely supplemented after surgery; however, there is likely to be a minimal benefit for those who would receive routine supplementation after surgery.

This review shows that dosages of vitamin B_{12} contained in a standard over-the-counter preparation (Table 1) are insufficient following RYGB. When very low supplementation doses are used [20], a progressively increasing number of patients become deficient in vitamin B_{12} with an increasing duration of follow-up as their body stores get depleted. Since the vitamin B_{12} stores are expected to be even lower in bariatric surgery patients than the normal population, they may become deficient soon after surgery [20].

It is further evident that even doses many times higher than that contained in a standard multivitamin are also inadequate. In the randomized study by Dogan et al. [1] and their 3-year follow-up study [23], even when 350 μg of vitamin B_{12} daily supplementation was given following RYGB, a large number of patients become vitamin B_{12} deficient and needed further supplementation. At the same time, authors demonstrated a higher level and lower incidence of deficiency in the group given a higher dosage of 350 μg daily compared to the standard dose of 12.5 μg daily. Given these findings, it would be useful to examine even higher dosages. This is exactly what Boyce et al. [22] did and they reported a 0.6% deficiency rate at 12 months amongst patients recommended with 600 μg vitamin B_{12} daily.

Though the deficiency rate was very low with 600 μg daily [22], it would only be natural to examine if even higher dosages were more effective. The study by van der Beek et al. [28] can be useful to understand the effect of higher dosages of oral vitamin B_{12} in these patients. The authors [28] found that the oral dose of 1000 μg a day can successfully treat post-RYGB patient vitamin B_{12} deficiency in 86.0% of patients. This is slightly higher than 80.0% correction of vitamin B_{12} deficiency with an oral dose of 500 μg/day as observed by Brolin et al. [29].

Table 2 Studies on oral vitamin B_{12} supplementation in doses from 16.0 to 999.0 μg daily

Author	RYGB characteristics	Daily supplementation dose of vitamin B_{12}	Important findings
Rhode et al. [19] *N* = 10 Time: NA Level III evidence Comparative study	Gastric pouch 10–15 ml AL 40 cm BPL: NA	350.0 μg	In their study, 10 patients 19.4 ± 6.5 months after RYGB and a low serum vitamin B_{12} concentration first were given oral vitamin B_{12} at a dose of 4 μg/day for 3 months but without a significant increase in vitamin B_{12} levels (see Table 1). These patients were then given 350 μg/day oral vitamin B_{12} for 3 months. Authors found that this dose corrected vitamin B_{12} deficiency in 5 of the 10 patients. The levels of vitamin B_{12} levels increased from 124 ± 43 pmol/l to 214 ± 88 pmol/l
Boyce et al. [22] *N* = 309 Mar 2009–Apr 2010 Level IV evidence Cohort study	Gastric pouch: NA AL 150 cm BPL 80 cm	600.0 μg	At 12 months, only 1/176 (0.6%) developed vitamin B_{12} deficiency amongst those compliant with the preparation compared to 6/124 (4.8%) in those non-compliant
Dogan et al. [1] *N* = 128 June 2011–Mar 2012 Level I evidence Randomized controlled trial	Gastric pouch 30 ml AL 150 cm BPL 50 cm	350 vs 12.5 μg (RCT)	Patients were randomized to either a standard multivitamin containing 12.5 μg of vitamin B_{12} or an enhanced one containing 350 μg of vitamin B_{12}. There were 74 patients in each arm. After excluding patients who received vitamin B_{12} injections (21 in SMV and 15 in EMV), the mean vitamin B_{12} levels decreased by 38.9 ± 41.3 pmol/l in the SMV group after 12 months compared to an increase by 44.1 ± 38.8 pmol/l in the EMV group
Homan et al. [23] *N* = 128 June 2011–Mar 2012 Level I evidence Randomized controlled trial	Gastric pouch 30 ml AL 150 cm BPL 50 cm	350 vs 12.5 μg (RCT 3-year findings)	3-year results on the study by Dogan et al. [1] 29 patients developed vitamin B_{12} deficiency—5 of them were using the enhanced preparation and 18 the standard preparation, and 6 were not taking any multivitamin at all
Moore et al. [24] *N* = 11 July 2011–May 2013 Level IV evidence Cohort study	Gastric pouch 30 ml AL 125 cm BPL: NA	350 μg	Vitamin B_{12} levels increased from 511 ± 175 at baseline to 821 ± 4000 pg/ml at 3 months after surgery ($p = 0.033$)
Gesquiere et al. [4] *N* = Apr 2012–Jan 2014 Level IV evidence Cohort study	Gastric pouch: NA AL 120 cm BPL: NA	93.9 μg	The levels of vitamin B_{12} dropped significantly at 6 and 12 months after RYGB compared to baseline values. 24.0 and 23.4% patients, respectively, were deficient in vitamin B_{12} at 6 and 12 months compared to 3.8% before surgery

AL alimentary limb, *BPL* bilio-pancreatic limb, *NA* not available, *RCT* randomized controlled trial, *SMV* standard multivitamin, *EMV* enhanced multivitamin

If a dose of 1000 μg daily is successful for the treatment in the majority of patients, one can naturally infer that it would also be effective for prophylaxis. This is indeed what other authors have also suggested [25, 27]. But deficiency rates of nearly 6.0% seen by del Villar Madrigal et al. [26] in patients advised with 1000 μg vitamin B_{12} daily seem to contradict the assumption that a daily oral dose of 1000 μg is adequate for all post-RYGB patients for prophylaxis of vitamin B_{12} deficiency. However, these authors did not report compliance and it cannot hence be ruled out as a potential explanation of these observed

Table 3 Studies on oral vitamin B_{12} supplementation in doses of 1000.0 μg daily or more

Author	RYGB characteristics	Daily supplementation dose of vitamin B_{12}	Important findings
Aasheim et al. [25] *N* = 15 Feb 2006–Aug 2007 Level III evidence Comparative study	Gastric pouch 25 ml AL 150 cm BPL 50 cm	1000 μg	Vitamin B_{12} levels increased from 359 ± 150 pmol/l at baseline to 474 ± 209 pmol/l at 1 year. None of these patients was deficient in vitamin B_{12} at 1 year
del Villar Madrigal et al. [26] *N* = 486 2005–2012 Level IV evidence Cohort study	Gastric pouch 30 ml AL 150 cm BPL 50 cm	1000 μg	Vitamin B_{12} deficiency was seen in 19/320 (5.9%) (only two of these patients were anemic and they also had iron deficiency). Authors did not measure levels preoperatively and did not record compliance so the subclinical drop in vitamin B_{12} levels may not have been due to other factors
von Drygalski et al. [27] *N* = 1125 Time: NA Level IV evidence Cohort study	Gastric pouch 10–15 ml AL 75–150 cm BPL 20 cm	1000 μg	The mean vitamin B_{12} levels significantly increased (24–48 months after surgery) to 626 from 427 pg/ml at baseline

AL alimentary limb, *BPL* bilio-pancreatic limb, *NA* not available

discrepancies. At the same time, we cannot assume lack of compliance to be the reason for these observed findings. It is hence important to prospectively examine the adequacy of 1000 μg vitamin B_{12} daily given orally in these patients.

It has been suggested that though intrinsic factor-dependent absorption of vitamin B_{12} is reduced after RYGB, absorption of oral crystalline vitamin B_{12} can also take place through diffusion. But this route probably requires much higher dosages to be completely effective for prophylactic purposes [9]. It has been shown [30] that though absorption of food-bound vitamin B_{12} was severely impaired after RYGB, absorption of free vitamin B_{12} largely remained unchanged. On the basis of these data, authors suggested that daily supplementation using oral crystalline vitamin B_{12} was an acceptable route for supplementation for RYGB patients.

The studies in this review confirm that though proportionately very small, some absorption of vitamin B_{12} does take place in RYGB patients. Moreover, there is little doubt that intestinal adaptation takes place [31] after RYGB to maximize orally consumed vitamin B_{12} absorption.

It should hence follow that if we give a high enough dose of vitamin B_{12}, we should be able to use the oral route of supplementation in these patients. Since there are practically no side effects of an excess of vitamin B_{12} [32], we can trial even higher dosages that will not only prevent deficiency in all patients but also be permissive towards intermittent non-compliance. We probably over-supplement with parenteral injection too as we routinely see higher than normal levels of vitamin B_{12} in our practice with 3-month 1-mg intramuscular vitamin B_{12} injections.

Conclusion

Some absorption of orally administered vitamin B_{12} does take place in post-RYGB patients but the dosages needed are much larger than that contained in most standard over-the-counter multivitamin formulations. A dose of 1000 μg vitamin B_{12} daily seems adequate for prophylaxis in most RYGB patients but needs to be examined in prospective studies over longer periods of time. It is possible that even higher oral dosages may deliver better outcomes.

Author Contribution KM conceived the idea for the topic, performed the review, and wrote most of the manuscript. KM and AR independently searched for all the relevant articles. All other authors critically reviewed the manuscript and participated in the departmental discussions on the topic. All authors have seen the final version and approve of it.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Statement of Human and Animal Rights Not applicable.

Statement of Informed Consent Not applicable.

Abbreviations RYGB, Roux-en-Y gastric bypass; BOMSS, British Obesity and Metabolic Surgery Society; ASMBS, American Society for Metabolic and Bariatric Surgery; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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