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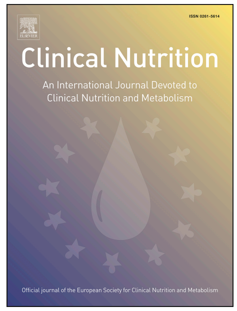


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Kemal Dogan, MD, Jens Homan, MD, Edo O. Aarts, MD, Hans de Boer, MD PhD, Cees J.H.M. van Laarhoven, MD PhD, Frits J. Berends, MD PhD

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# Long-term nutritional status in patients following Roux-en-Y Gastric bypass surgery

Kemal Dogan *MD*[1]; Jens Homan *MD*[1]; Edo O. Aarts *MD*[1]; Hans de Boer *MD PhD*[2]; Cees J.H.M. van Laarhoven *MD PhD*[3]; Frits J. Berends *MD PhD*[1]

[1]Department of Surgery and [2]Internal Medicine, Rijnstate Hospital, Arnhem, The Netherlands

[3]Department of Surgery, Radboud University Medical Centre, Nijmegen, The Netherlands

**Running title:** Vitamin status after Roux-en-Y gastric bypass.

**Corresponding author:**

K. Dogan, MD

Department of Surgery

Rijnstate Hospital, Postal number 1190, 6800 TA Arnhem, The Netherlands

Telephone number: +31 088 005 6909

Fax number: +31 088 0056627

E-mail: dogan.research@outlook.com

## ABSTRACT

**Background & Aims:** Roux-en-Y gastric bypass (RYGB) is an effective treatment for obesity. However, it also leads to multiple nutritional deficiencies. Much is known about the short term prevalence, but hardly any long term data is available on deficiencies. The aim of this study was to assess the long term outcome of nutritional status after RYGB.

**Methods:** We performed a retrospective analysis of prospectively collected data obtained from 51 morbidly obese patients who underwent a primary laparoscopic RYGB. Primary outcomes were iron, vitamin B12 and vitamin D deficiencies. Secondary outcomes were deficiencies of other vitamins and minerals and compliance of the patients to multivitamin use.

**Results:** The mean follow-up was 81±27 months. A total of 35%, 16% and 55% of the patients had deficiencies for iron, vitamin B12 and vitamin D respectively. Sixty-nine percent of patients used a (nonspecific) multivitamin supplement on a daily basis. Patients with multivitamin usage had a lower rate of iron deficiency (26% vs. 56%, p=0.034), vitamin B12 (11% vs. 25%, p=0.46) and vitamin D (46% vs. 75%, p=0.07), compared to non-compliant patients.

**Conclusions:** Nutritional deficiencies are common after a RYGB operation. Therefore, strict follow-up by a bariatric surgeon, endocrinologist or general practitioner is required, both short and long term.


**Keywords:** Morbid obesity; Bariatric surgery; Roux-en-Y gastric bypass; Vitamin; Nutrient; Deficiencies

## Introduction

The Roux-en-Y gastric bypass (RYGB) is one of the most frequently performed surgical procedures to induce sustained weight loss in morbidly obese patients. [1] In addition, it is an effective treatment to reduce obesity-related co-morbidities such as Type 2 Diabetes Mellitus (T2DM), hypertension and obstructive sleep apnoea syndrome. [2-5] However, due to alterations in the gastrointestinal tract after a RYGB procedure, patients are prone to develop nutritional deficiencies. These deficiencies can lead to serious hematological (i.e. anemia, leucopenia, thrombocytopenia), neurological (i.e. myeloneuropathy, Wernicke encephalopathy, paresthesia), and musculoskeletal (i.e. osteoporosis, bone pain, fractures) complications.[6] Most reported vitamin and mineral deficiencies are for iron (47-66%), vitamin B12 (37-50%), folate (15-38%), vitamin D (20-51%) and calcium (±10%).[7-17] Although there are numerous reports on deficiencies after RYGB, most only have a limited follow-up period and long-term follow-up studies are scarce.[18, 19, 20, 21] Daily use of multivitamin and mineral supplements is generally recommended to prevent postsurgical deficiencies.[22] Nevertheless it is often observed that patients' compliance to chronic use of medications drops over time. Additionally, patients lost to follow up most often not only have worse weight loss compared to other patients, but also experience more deficiencies.

The aim of this study was to assess the long-term nutritional status of morbidly obese patients who were initially lost to follow-up after laparoscopic RYGB (LRYGB), and also to evaluate the prevalence of deficiencies in patients who were compliant to multivitamin use compared to non-compliant patients.

## Materials and Methods

### *Patient selection and outcome*

Adult patients (age > 18 years) who underwent a primary LRYGB between January 2000 and December 2008 for severe obesity (BMI > 35 kg/m$^2$) or morbid obesity (BMI > 40 kg/m$^2$) according to international guidelines [23] with T2DM were invited to our outpatient clinic for a long-term follow-up visit. Patients were invited by a letter, followed by a reminder letter after no response. Finally, when patients still had not shown, they were contacted by phone and invited for the additional visit.

Patients with T2DM enroll a strict follow-up program by the endocrinologist, including extensive laboratory tests. The invited (study) patients followed this regular follow-up schedule. We obtained approval of the local board of ethics, although the study was a part of a regular follow-up protocol. The procedures followed were in accordance with the ethical standards the Helsinki Declaration of 1975 as revised in 1983.

*Surgical procedure:* an antecolic antegastric bypass was performed using a small gastric pouch of 30-50 ml and a fixed biliopancreatic limb (BPL) of 50cm. Patients with a BMI < 50kg/m2 received a Roux limb of approximately 100 cm and patients with a BMI > 50 kg/m2 received a Roux limb of 150 cm. All procedures were performed by two experienced bariatric surgeons.

The patients were selected from our prospectively collected database (Windows Excess 2000). Operation type and date, medical history, height (cm), weight (kg), BMI (kg/m2), weight loss expressed in percentage Excess Weight Loss (%EWL; defined as weight loss divided by excess weight based on BMI 25 kg/$m^2$; formula: ((pre-operative body weight – post-operative body weight) / (pre-operative body weight – ideal body weight)) * 100%) and percentage Total Body Weight Loss (%TWBL; defined as weight loss divided by pre-operative body weight; formula: ((pre-operative body weight – post-operative body weight) / pre-operative body weight) * 100%)), medication and multivitamin use, and laboratory tests were recorded at regular follow-up appointments. Regular follow-up was performed at 2, 3, 6, 9, 12, 18 and 24 months post-operatively. After 24 months, follow-up was conducted annually. Standard laboratory blood testing was performed preoperatively consisting of a complete blood count (XN-10 and XN-20, Sysmex Nederland B.V., The Netherlands), a mean cell volume (MCV) measured by hydrodynamic focusing (XN-10 and XN-20, Sysmex Nederland B.V., The Netherlands). Postoperative laboratory blood testing included hemoglobin (Hb) measured by colorimetric test (XN-10 and XN-20, Sysmex Nederland B.V., The Netherlands); MCV measured by hydrodynamic focusing (XN-10 and XN-20, Sysmex Nederland B.V., The Netherlands); iron, albumin, phosphate and magnesium measured by colorimetric test (Modular P800, Roche, Almere, The Netherlands); total-iron-binding-capacity (TIBC) is calculated via transferrin and measured by immunometric method (Modular P800, Roche, Almere, The Netherlands), ferritin, folate, vitamin B12, 25-hydroxyvitamin D (25-OHD) measured by electrochemiluminescence method (Modular E170, Roche, Almere, The Netherlands); parathyroid hormone (PTH) measured by chemiluminescence method (Immulite 2000 XPi, Siemens, The Netherlands); calcium measured by colorimetric test (BAPTA buffer, Modular P800, Roche, Almere, The Netherlands); vitamin A analyzed on an HPLC with UV-vis detector (Shimadzu Corporation, Japan); vitamin B1 analyzed on a HPLC with fluorescence detector (Shimadzu Corporation, Japan); vitamin B6 analyzed on a HPLC with fluorescence detector (Shimadzu Corporation, Japan); zinc analyzed by inductively coupled plasma mass spectrometry (Shimadzu Corporation, Japan).

The primary endpoint was the long-term nutritional status (deficiencies). The lower limit of normal was used to define deficiencies (normal ranges are presented in **Table 1a**). Anemia was defined using Hb level, and ferritin levels for iron deficiency (ID). Patients were subdivided into two groups: those who were still using multivitamin supplements at the follow-up visit (compliant) and those who did not (non-compliant). Type of multivitamin and amount of daily use were recorded based on questionnaires. Compliance was defined as reported use of multivitamin supplements on a daily basis, for at least 6 days a week.

*Statistical analysis*

Data were analyzed using IBM® SPSS® (version 20.0 for Windows). Results are presented as mean values ± standard deviation (SD) and range for normally distributed continuous data and median and inter-quartile range for skewed continuous data. Data normality was verified by both visual inspection and Shapiro Wilk testing. Differences between groups were tested using the unpaired *t*-test or the Mann-Whitney U test, as appropriate. The paired *t*-test or Wilcoxon signed ranks test was used to assess differences within groups. Categorical data are presented as frequencies and percentages and differences between groups are tested using the Chi square test or Fisher exact test. A $p < 0.05$ was considered significant.

**Results**

Eighty-nine patients were invited for a long-term regular outpatient follow-up visit. Twenty-five patients did not respond and 13 patients refused renewed follow-up for personal reasons. Fifty-one out of 89 (57.3%) patients agreed to participate and all were eligible for analysis. Thirty patients were female (58.8%). Patients had a mean age of 47.6±9.7 years, a baseline weight of 140.1±21.7 kg and a BMI of 46.3±6.2 kg/m2. The mean post-operative follow-up period was 81.4±27.1 months.

*Nutritional status and patients' compliance*

Forty-one (80.4%) patients used a supplement at least occasionally for the prevention and treatment of nutritional deficiencies, including multivitamin, iron, vitamin B12, cholecalciferol and/or calcium. Thirty-five (68.6%) patients were still using their multivitamin supplements at the last follow-up visit and were categorized as compliant patients. Sixteen (31.4%) patients were categorized as non-compliant.

Compliant patients used eight different commercially available multivitamin supplements. Only one of them was an optimized multivitamin supplement for bariatric surgery used by four patients. This supplement contained vitamin B12 of 350 mcg (14000% recommended daily allowance [RDA]), folate of 600 mcg (300% RDA), iron of 70 mg (500% RDA), vitamin B1 of 2.75 mg (250% RDA) and vitamin B6 of 2.8 mg (150% RDA) per tablet for usage of one tablet daily. All other (standard) multivitamin supplements contained vitamin B12 of 1-3 mcg (40% - 120% RDA), folate of 100-200 mcg (50% - 100% RDA), iron of 2.5-14mg (18% - 100% RDA), vitamin B1 of 0.6 – 3.3 mg (50% - 300% RDA) and vitamin B6 of 0.7 – 2.1 mg (50% - 150% RDA) per tablet. Half of the patients used one tablet per day, the other half used the multivitamin twice daily.

The laboratory results at the last follow-up are summarized in **Table 1** and **Table 2a and b**. Five (9.6%) patients had normocytic anemia preoperatively. At the last follow-up visit, anemia was present in 12 (23.5%) patients, in six (17.1%) compliant patients and in six (37.5%) non-compliant patients (p=0.11). None of the patients had used additional iron supplements. In seven patients, anemia was attributed to an iron deficiency (ID). Eleven additional patients had ID without anemia, meaning that eighteen patients had ID in total (35.3%). ID was more frequent in non-compliant than in compliant patients (56.3% vs. 25.7%, p=0.034).

The median serum vitamin B12 level was 348 [IQR 230 – 525] pmol/L. Eight (15.7%) patients had vitamin B12 deficiency, i.e. four (11.4%) in the compliant group and four (25%%) in the non-compliant group (p=0.46). One of these patients used additional vitamin B12 medication (orally) at the moment of laboratory test. Additionally, nineteen (37.3%) patients had started additional vitamin B12 supplementation after being diagnosed with a deficiency in the years after RYGB (commonly vitamin B12 injections for intra-muscular use). Thus in total 27 (52.9%) patients had developed vitamin B12 deficiency after the RYGB. Patients taking additional vitamin B12 medication had a significantly higher serum vitamin B12 level compared to patients without additional medication (median 533.5 [IQR339.3 – 1063.8] pmol/ vs. median 260.0 [IQR 213 – 378] pmol/L; p<0.0001).

Vitamin D deficiency was diagnosed in 28 (54.9%) patients, including 16 (45.7%) patients within the compliant group and 12 (75%) non-compliant patients (p=0.07). Seven (13.7%) patients used additional vitamin D supplements (oral cholecalciferol), and two of them had vitamin D deficiency. The mean serum 25-OHD tended to be somewhat higher for patients with additional vitamin D supplementation compared to non-users (62.4 ± 37.2 (range 11–109) nmol/L vs. 44.3 ± 23.0 (range 5–115) nmol/L; p=0.22). No hypocalcemia was found at the last follow-up visit. Twenty-four (47.1%) patients used calcium tablets or sachets (with or without cholecalciferol). Elevated PTH levels were found in seven (43.8%) non-compliant patients compared to ten (28.6%) compliant patients (p=0.286).

*Weight and nutritional status*

Both mean weight (-36.9±15.8kg) and BMI (-12.2±5.1 kg/m2) were significantly reduced ($p<0.0001$) compared to baseline. Overall mean %EWL was 59.9±24.5% and %TBWL was 26.3±10.2%, at the last follow-up. Thirty- one (60.8%) patients had an %EWL of > 50% ('successful'), while 48 (94.1%) patients had an 'acceptable' %EWL of >25%. [23]

Patients with successful weight reduction (*n*= 25; 80.6%) were more often compliant to multivitamin use than 'unsuccessful' patients (*n*=10; 50%; p=0.02). Patients with an EWL>50% had significantly higher 25-OHD levels (53.6±25.7 (range 11–115) nmol/L) than patients with an EWL<50% (37.2±24.0 (range 5–109) nmol/L; p=0.027). No significant differences were found for other vitamins and minerals.

*Hypervitaminosis vitamin B1 and B6*

The mean serum level of vitamin B1 was significantly higher in compliant patients than in non-compliant patients (175.5±44.7 (range 103–291) nmol/L vs. 133.5±26.5 (range 91–175) nmol/L; p=0.003). Additionally, hypervitaminosis of vitamin B1 was more common in compliant group (18 (51.4%) vs. 0 (0%), p=0.002).

The mean serum level of vitamin B6 for the compliant group was 88.5 [IQR 70.8 – 121.0] (range 48–1561) nmol/L, while the non-compliant group had a serum level of 52 [45.5 – 67] (range 31–106) nmol/L ($p<0.0001$). Thirteen (38.2%) vitamin users had hypervitaminosis of vitamin B6 compared to one (7.7%) non-compliant patient (p=0.072).

There was no significant difference in mean serum levels of vitamin A for patients with (1.9±0.7 (range 0.46–3.64) μmol/L) and without multivitamin supplements (2.3±0.9 (range 1.16–3.71) μmol/L; p=0.19). The number of patients suffering hypervitaminosis for vitamin A was four (14.8%) in vitamin users compared to two (18.2%) non-compliant patients (p=0.23).

## Discussion

It is known that patients who have undergone bariatric surgery are prone to develop nutritional deficiencies. [6-19] This can lead in worst case scenarios to serious irreversible complications such as blindness, encephalopathy and osteoporosis. [6] Use of (specialized) multivitamin supplements after RYGB surgery seems to be an important factor in managing these deficiencies. Therefore, multivitamin supplementation on a daily basis is advised in all bariatric guidelines. [6, 22] Some deficiencies, however, may be revealed many years after operation, making lifelong intake a necessity. The present study showed deficiencies of iron in 35%, vitamin B12 in 16% and vitamin D in 55% of patients after a mean 81 months.

*Anemia and related deficiencies*

In the current study, approximately a quarter of the patients had anemia at the last follow-up visit (mean 81 months). The reported prevalence of anemia after RYGB surgery in the literature varies from 20–50% after wide period of 12 to 120 months. [7, 18-21, 25-27] Patients developing anemia after RYGB operation, usually have iron, vitamin B12 or folate deficiency. [2, 7, 9, 17, 21, 25-27] Several studies reported that anemia and the related deficiencies were already present in a huge amount of patients prior to their operation. This suggest that anemia detected during the first post-operative year after RYGB may be related to the pre-operatively existing deficiencies. [7, 25-28] Weng et al. [25] reported in a systematic review twofold increase of anemia after 12 months of surgery. In line with this review, Van der Beek et al. [28] illustrated significantly higher incidence of deficiencies in pre-operatively deficit patients compared to patients without deficiency. However, pre-operative deficiencies may not influence the nutritional status on the long term which is observed in this study. Impairment in several anatomic and functional mechanisms after a RYGB operation may decline the absorbability of iron and vitamin B12, even on the long term. Iron deficiency after a RYGB is due to a combination of factors. Iron absorption is dependent on the pH of the stomach and uptake usually takes place through the intestinal wall of the duodenum and proximal part of the jejunum. The passage of iron through the small gastric pouch is too fast, while duodenum and jejunum are bypassed in gastric bypass surgery. Additionally, patient changes their dietary behavior with reduced caloric intake. Therefore, a higher intake of iron is usually needed to overcome these postsurgical impairments in iron absorption capacity. However, anemia may still persist after reduction of iron deficiency in gastric bypass patients. [27] This is probably due to the reduced availability of vitamin B12. Vitamin B12 is less available after RYGB due to the exclusion of the distal stomach, the site of the production of intrinsic factor, which is required for the uptake of vitamin B12 in the distal ileum. The available literature regarding postoperative vitamin B12 deficiency demonstrates a prevalence varying from 10% to 60%. [7, 17-19] Next to megaloblastic anemia, vitamin B12 deficiency can cause serious co-morbidities such as ataxia, optic atrophy, memory loss, and weakness, which reduce the quality of life of these patients. [6] The low percentage of vitamin B12 deficiencies in this study is due to the fact that 37% of the study group already used additional vitamin B12 medication due to deficiencies diagnosed in an earlier stage. This indicates that additional supplementation of vitamin B12 is important and that a standard multivitamin is completely insufficient to prevent vitamin B12 deficiency. Due to this substantial incidence of iron and vitamin B12 deficiency, the American Society for Metabolic and Bariatric Surgery (ASMBS) guideline advises daily use of additional iron of 45-60 mg orally and vitamin B12 of 1000 mcg orally. [22] Additionally, regular follow-up on the long term is required to detect iron and vitamin B12 deficiencies in an early phase.

*Vitamin D deficiency*

Vitamin D deficiency is one of the most commonly reported deficiencies in obese and bariatric patients. Obesity itself is associated with vitamin D deficiency as a result of several factors, including low exposure to sunlight, lack of vitamin D consumption and sequestration of vitamin D in adipose tissue. [29, 30]. Deficit vitamin D is related to decreased bone density, osteoporosis, an increased risk of fractures, muscle weakness or bone pain. [6] In the present study, 55% of the patients had vitamin D deficiency. In the literature, the short term prevalence of vitamin D depletion was demonstrated to be 58% preoperatively and 42% one year postoperatively. [31] Long term results on vitamin D deficiency are scarce and vary between 24% and 65%. [18, 19, 32] In this study a significantly higher 25-OHD level was found in patients with increased %EWL. Carlin et al. [29] support this finding and suggest that this may be due to better compliance with diet and vitamin supplements and because of a greater reduction in adiposity resulting in increased vitamin D availability. Calcium absorption is associated with 25-OHD levels and occurs in the duodenum and proximal jejunum. Since this part of the intestine is excluded by performing a RYGB, morbidly obese patients are also prone to develop calcium deficiency. Long-term results on calcium status in the literature show deficiencies in around 2% in patients after RYGB, which is consistent with the present study. [18, 19] Because of these deficiencies, additional calcium citrate of 1200-1500 mg per day and vitamin D of 3000 IU per day is advised in the ASMBS guidelines. [22]

*Hypervitaminosis*

Postoperative use of vitamin and mineral supplements is widely advised in bariatric patients to prevent serious co-morbidities as described above. Nevertheless, with the introduction of a multivitamin supplementation after bariatric surgery a new phenomenon was observed: hypervitaminosis. This is probably due to use of multivitamin use rather than the operations itself. Hypervitaminosis is also observed in patients after biliopancreatic diversion (with or without duodenal switch), which are malabsorptive procedures and associated with severe nutritional deficiencies. [33] The consequences of hypervitaminosis may be just as important as deficiencies; however, the clinical symptoms are rare or hard to recognize. For example, low serum vitamin B1 levels are associated with neurological abnormalities (i.e. Wernicke encephalopathy). [6] And the most common symptom of vitamin B6 hypervitaminosis is progressive neuropathy, since vitamin B6 plays a role in neurotransmitter synthesis. [34] In this study, serum vitamin B1 was most frequently elevated (51%) whereas vitamin B1 was deficient in only one (2%) patient. Furthermore, hypervitaminosis of vitamin B6 was seen in 14 (30%) patients in the present study, while no deficiencies of vitamin B6 were observed.

*Compliance and multivitamin supplements*

This study confirms that differentiated vitamin and mineral supplement regimes are necessary to prevent nutritional complications after bariatric surgery, especially in the long term. Despite a high compliance rate for regular supplements, high prevalence of nutritional deficiencies was observed. Regular supplements contain lower dosages of the vitamins and minerals advised in the ASMBS guidelines. [22] Therefore, regular supplements are insufficient to prevent these deficiencies. However, it is difficult to determine the optimal dosage of the supplements based on the present research (being a descriptive study). Recent randomized clinical trial showed that an optimized multivitamin supplement can reduce iron and vitamin B12 deficiencies after RYGB surgery. [35] This multivitamin supplement is effective up to 3 years after the operation. [36] However, additional prospective studies are needed to determine how to optimize nutritional deficiencies postoperatively in the long term, both for the specific nutrients as for the type of bariatric surgery and for the compliance status of patients. Obesity itself is accompanied by several deficiencies, and therefore preoperative screening and treatment are advised to reduce post-surgical complications. Hence, lifelong compliance of patients to multivitamin regimes is hard to achieve, with underestimation of the sometimes severe consequences of deficiencies by both patients and professionals. Patients with successful weight loss were more compliant to multivitamin regimes, probably due to greater self-awareness and the ability to achieve lifestyle changes. For some, financial reasons contribute to the cessation of vitamin use, since most patients have to pay for their own supplements. Despite these barriers, approximately two-third of the patients used a supplement in the present study. On the other hand, patients lost to follow-up (43%) are prone to be non-compliant and not able to achieve lifestyle changes. Therefore, this study may underestimate the deficiency rate.

*Limitations*

Some limitations must be pointed out regarding the present study. First, despite several attempts to reach all patients, a substantial lost to follow-up occurred which may have influenced the study outcomes, while we know that especially these patients do worse in terms of deficiencies. [20] It is sometimes hard to motivate patients to fill out questionnaires and to provide blood samples after several years of operation. Therefore, further studies with long term data are needed to detect the risks and consequences of bariatric surgery to increase awareness of the patients and to define optimal post-bariatric multivitamin supplements. Secondly, collecting data about the use of multivitamin supplements were based on the questionnaires and interviews. Therefore, the information may have inaccuracies. Finally, it was not possible to determine the optimal dosages of the individual vitamins or minerals because patients used multiple different multivitamin supplements.

## Conclusion

RYGB Surgery results in significant sustained weight loss. However, it is accompanied by a high rate of nutritional deficiencies, especially of iron, vitamin B12 and vitamin D. Use of regular multivitamins does not completely prevent these deficiencies, since they do not meet the advised dosages in the ASMBS guidelines. On the other hand, hypervitaminosis may be observed for some vitamins. Although optimal regimes are not yet available, multivitamin supplementation, individualized for patients, should be implemented on a permanent basis for all patients after RYGB. New criteria to optimize such suppletion therapies should be researched. Bariatric surgeons, endocrinologists and general practitioners should be committed to a strict life-long follow-up.

**Conflict of interest statement and funding resources**

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**TABLE 1: Laboratory blood tests and number of deficiencies at the end of follow-up in total study group**

| | Normal range | No. of patients | Blood levels | SD/ IQR | Range | No. of deficiencies | % deficiencies |
|---|---|---|---|---|---|---|---|
| Haemoglobin (mmol/L) | F: 7.4-9.9<br>M: 8.4-10.8 | 51 | 8.4 | ±0.96 | 6.4 - 10.7 | 12 | 23.5 |
| Ferritin (µg/L) | 20-200 | 51 | 47* | 13 - 81 | 5.0 -350.0 | 18 | 35.3 |
| Folate (nmol/L) | 9.0-36.0 | 49 | 24.6 | ±10.0 | 8.0 - 45.3 | 1 | 2.0 |
| Vitamin B12 (pmol/L) | 200-640 | 51 | 348* | 230 - 525 | 83 – 1476 | 8 | 15.7 |
| Vitamin D (nmol/L) | >50 | 51 | 47.2 | ±26.1 | 5 - 115 | 28 | 54.9 |
| Parathyroid hormone (pmol/L) | 1.3-6.8 | 51 | 7.6 | ±10.1 | 1.6 – 74.9 | 0 | 0 |
| Calcium (mmol/L) | 2.10-2.55 | 50 | 2.32 | ±0.09 | 2.11 – 2.57 | 0 | 0 |
| Albumin (g/l) | 35-50 | 50 | 38* | 36.8 - 40 | 28 – 43 | 4 | 8.0 |
| Magnesium (mmol/L) | 0.71-0.93 | 49 | 0.79 | ±0.07 | 0.60 – 0.92 | 6 | 12.2 |
| Phosphate (mmol/L) | 0.87-1.45 | 49 | 1.00 | ±0.19 | 0.60 – 1.60 | 10 | 20.4 |
| Zinc (µmol/L) | 9.2-18.4 | 43 | 12.4 | ±1.4 | 9.3 – 14.8 | 0 | 0 |
| Vitamin A (µmol/L) | 1.05-2.80 | 38 | 1.98 | ±0.85 | 0.46 – 3.71 | 6 | 15.8 |
| Vitamin B1 (nmol/L) | 95-175 | 48 | 164.1 | ±44.5 | 91.0 - 291.0 | 1 | 2.1 |
| Vitamin B6 (nmol/L) | 25-100 | 47 | 78* | 57.0 – 114.0 | 31.0 – 1561.0 | 0 | 0 |

*Values are numbers (%), mean ± standard deviation (SD) for normal distributed variable, otherwise reflected as median (interquartile ranges (IQR) p25 – p75)*.*

**TABLE 2a: Laboratory results in compliant and non-compliant patients for multivitamin supplements**

| | Compliant patients | SD/IQR | Range | Non-compliant patients | SD/IQR | Range | *p-value* |
|---|---|---|---|---|---|---|---|
| Haemoglobin (mmol/L) | 8.5 | ±0.85 | 6.6 – 10.7 | 8.1 | ±1.17 | 6.4 – 9.6 | 0.28 |
| MCV (fL) | 89.9 | ±5.23 | 78 – 99 | 88.2 | ±6.07 | 77 – 100 | 0.30 |
| Iron (µmol/L) | 14.1 | ±5.40 | 3.1 – 28.2 | 12.7 | ±4.62 | 4.0 – 22.0 | 0.38 |
| Ferritin (µg/L)* | 55 | 15 -95 | 10 – 350 | 17.5 | 12.3 – 66.8 | 5 – 142 | 0.161 |
| TIBC (µmol/L, 45-81) | 65.5 | ±11.28 | 39 – 87 | 73.2 | ±11.39 | 55 – 100 | **0.03** |
| Folate (nmol/L) | 27.6 | ±9.5 | 12.0 – 45.3 | 17.1 | ±6.57 | 8.0 – 29.5 | **<0.0001** |
| Vitamin B12 (pmol/L)* | 412.0 | 276 – 542 | 142 – 1476 | 239.5 | 198.8 – 371.3 | 83 – 1401 | **0.016** |
| Vitamin D (nmol/L) | 54.9 | ±23.8 | 17 – 115 | 30.3 | ±23.3 | 5 – 90 | **0.001** |
| PTH (pmol/L) | 5.9 | ±2.86 | 1.6 – 13.9 | 11.5 | ±17.2 | 2.0 – 74.9 | 0.22 |
| Calcium (mmol/L) | 2.32 | ±0.09 | 2.11 – 2.51 | 2.33 | ±0.09 | 2.20 – 2.57 | 0.921 |
| Albumin (g/l)* | 38 | 37 – 40 | 29 – 43 | 38 | 36 – 40 | 28 – 42 | 0.881 |
| Vitamin A (µmol/L) | 1.9 | ±0.89 | 0.46 – 3.64 | 2.3 | ±0.72 | 1.16 – 3.71 | 0.185 |
| Vitamin B1 (nmol/L) | 175.5 | ±44.7 | 103 – 291 | 133.5 | ±26.50 | 91 – 175 | **0.003** |
| Vitamin B6 (nmol/L)* | 88.5 | 70.8 – 121.0 | 48 – 1561 | 52 | 45.5 – 67 | 31 – 106 | **<0.0001** |
| Zinc (µmol/L) | 12.3 | ±1.48 | 9.3 – 14.8 | 12.7 | ±0.92 | 11.2 – 14.4 | 0.372 |
| Phosphate (mmol/L) | 0.99 | ±016 | 0.60 – | 1.04 | ±0.25 | 0.74 – 1.60 | 0.464 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | 1.28 | | | | |
| Magnesium (mmol/L) | 0.79 | ±0.08 | 0.60 – 0.92 | 0.79 | ±0.06 | 0.69 – 0.87 | 0.920 |

*Values are mean ±standard deviation (SD) for normal distributed variable, otherwise reflected as median (interquartile ranges (IQR) p25 – p75) *. MCV: mean cell volume, TIBC: total iron binding capacity, PTH: parathyroid hormone.*

**TABLE 2b: Number of deficiencies at the end of follow-up for compliant and non-compliant patients**

| | | Compliant patients | | Non-compliant patients | | |
|---|---|---|---|---|---|---|
| | Overall no. of patients | No. of deficiencies | % | No. of deficiencies | % | *P-value* |
| Haemoglobin | 51 | 6 | 17.1 | 6 | 37.5 | 0.112 |
| Ferritin | 51 | 9 | 25.7 | 9 | 56.3 | **0.034** |
| Folate | 49 | 0 | 0 | 1 | 7.1 | 0.341 |
| Vitamin B12 | 51 | 4 | 11.4 | 4 | 25.0 | 0.404 |
| Vitamin D | 51 | 16 | 45.7 | 12 | 75 | 0.051 |
| Parathyroid hormone | 51 | 0 | 0 | 0 | 0 | - |
| Calcium | 50 | 0 | 0 | 0 | 0 | - |
| Albumin | 50 | 3 | 8.6 | 1 | 6.7 | 1.000 |
| Magnesium | 49 | 5 | 14.3 | 1 | 7.1 | 0.659 |
| Phosphate | 49 | 5 | 14.3 | 5 | 35.7 | 0.108 |
| Zinc | 43 | 0 | 0 | 0 | 0 | - |
| Vitamin A | 38 | 6 | 22.2 | 0 | 0 | 0.150 |
| Vitamin B1 | 48 | 0 | 0 | 1 | 7.7 | 0.433 |
| Vitamin B6 | 47 | 0 | 0 | 0 | 0 | - |