ORIGINAL ARTICLE

The prevalence of low vitamin B12 status in people with type 2 diabetes receiving metformin therapy in New Zealand—a clinical audit

Sylvan Haeusler, Amber Parry-Strong, Jeremy D Krebs

Abstract

Aim Metformin, the most common hypoglycaemic agent used in type 2 diabetes, is associated with reduced serum vitamin B12 concentrations. This cross sectional observational study determines the prevalence of low vitamin B12 status in people with type 2 diabetes on metformin therapy in both primary and secondary care in New Zealand.

Method All eligible patients seen in a secondary-care clinic over a 15-month timeframe were screened for low serum vitamin B12 concentrations. Additionally, patients from four primary health care providers were identified using metformin prescription data and offered the chance to participate in the audit.

Results Prevalence of serum Vitamin B12 level <220 pmol/L was 18.7%. Positive correlations were observed between B12 concentration, age and dosage and duration of metformin treatment. Māori and Pacific Islanders had higher mean serum B12 concentrations than Europeans but no difference in prevalence of low serum B12 concentrations.

Conclusion Low serum B12 concentration is a common occurrence in people with type 2 Diabetes treated with Metformin. Age is an important factor which explains some of this association. Systematic screening in those receiving metformin is advisable, particularly for patients older than 50 years.

Metformin is the first-line medication for patients with type 2 diabetes. Vitamin B12 (B12) is one of eight B group vitamins and plays an important role in haematopoiesis as well as key roles in brain and nerve function.

The association between metformin treatment and impaired serum B12 concentration was first reported in the 1970s. The prevalence of metformin associated vitamin B12 deficiency has generally been estimated to be 10–20% of treated patients, though the range is as low as 5% of treated patients and levels higher than 30%.

The mechanism for metformin-induced vitamin B12 deficiency remains unclear. Current evidence supports an effect of metformin on calcium channels and resultant impairment of calcium-dependent membrane activity in the ileum leading to malabsorption of vitamin B12 bound to intrinsic factors. A measurable reduction in serum vitamin B12 concentration can occur as quickly as 3–4 months after the initiation of the metformin therapy, while symptomatic deficiency may take as long as 5–10 years to manifest. The clinical consequence of B12 deficiency is macrocytic anaemia, but changes in cognitive function have been observed in 28–52% of patients with low B12 but no evidence of anaemia.

The prevalence of low serum B12 concentration in people using metformin in New Zealand is unknown. Furthermore, there are no data on rates of B12 deficiency in Maori or Pacific groups taking metformin, nor whether there are differences between those seen in a primary or secondary care environment.

The aim of this study was to estimate the prevalence of low serum B12 concentrations (<220 pmol/L) in those taking metformin and to compare this between ethnic groups and between primary and secondary care in New Zealand.
Methods

This is a cross sectional observational study of serum vitamin B12 concentration in patients taking metformin for management of type 2 diabetes, in primary and secondary care settings in New Zealand.

All patients attending the diabetes outpatient clinics at Wellington Regional Hospital and Kenepuru Hospital between February 2013 and April 2014 were reviewed. Additionally, patients enrolled in four primary health providers were included.

Through the practice management system (Medtech) an initial screen was conducted on the patient database of each practice for: Diagnosis of type 2 diabetes and prescription of metformin hydrochloride between February 2012 and February 2013. This produced a list of patients with a diagnosis of Type 2 diabetes who had received a prescription for metformin within the last year. These individuals were posted an invitation to join the study which included an explanation about the observed association between metformin and vitamin B12. In both groups patients were included if they had a diagnosis of type 2 diabetes and treatment with metformin for a minimum duration of 12 months. Those on current B12 treatment were excluded.

Data collected included age, duration and current dose of metformin therapy (mg/day), vitamin B12 concentration. Ethnicity was coded using the New Zealand Ministry of Health ethnic identifiers. Participants were grouped into 3 categories based on clinical relevance of serum vitamin B12 concentration: Vitamin B12 deficiency (<150 pmol/L), lowered vitamin B12 (150–219 pmol/L), and normal vitamin B12 (≥220 pmol/L). Outcomes assessed were prevalence of serum vitamin B12 <220 pmol/L, and factors predicting B12 status. Comparisons between primary and secondary care and between patient ethnicities were conducted.

Data were analysed using SPSS v20.0 software. The primary outcome results are presented as arithmetic means. Assessment for significance between means was tested through application of t-test. Univariate analysis of variance (ANOVA) was used to assess between group interactions. Correlation was assessed using Pearson (for normal distribution, linear correlation) and Spearman (for non-normal, non-linear correlation) tests as specified. Continuous variables were log transformed wherever possible before running tests that require normal distribution of the data.

All tests were two-sided and p values of <0.05 were considered to be statistically significant. Logistic regression analysis was used for comparison of prevalence data due to the dichotomous property of the outcome variable. Stepwise forward multiple regression analysis was applied to identify variables that predict serum vitamin B12 concentration.

Ethics approval for the study was obtained from the Central Health and Disability Ethics Committee (reference: 12/CEN/65/AM02). The study was undertaken as a clinical audit and therefore did not require individual patient consent.

Results

Demographics

A total of 19,857 patients were reviewed from four primary health providers in the Wellington region and the Diabetes Outpatient Clinic at Wellington Regional Hospital (Figure 1).
The two study groups were similar in demographic composition but different in overall group size (Table 1). Patients screened from secondary healthcare were significantly younger than from primary health (p=0.008). Both groups had a higher percentage of men than women. There were no differences in distribution of ethnicity between the groups.
Table 1. Demographics of patient groups included in prevalence study. Mean (SD)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Primary Health n = 101</th>
<th>Secondary Health n = 246</th>
<th>Total Group n = 347</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men - n (%)</td>
<td>63.76 (10.55)</td>
<td>60.56 (11.28)*</td>
<td>61.50 (11.16)</td>
</tr>
<tr>
<td>Duration of metformin treatment (years)</td>
<td>7.65 (4.33)</td>
<td>7.60 (4.20)</td>
<td>7.61 (4.24)</td>
</tr>
<tr>
<td>Dosage of metformin (mg/day)</td>
<td>1848.51 (686.97)</td>
<td>2002.64 (775.69)</td>
<td>1957.78 (753.24)</td>
</tr>
<tr>
<td>Serum vitamin B12 (pmol/L)</td>
<td>348.98 (175.95)</td>
<td>363.83 (182.10)</td>
<td>359.51 (180.21)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Primary Health n = 101</th>
<th>Secondary Health n = 246</th>
<th>Total Group n = 347</th>
</tr>
</thead>
<tbody>
<tr>
<td>NZ European</td>
<td>46 (45.5%)</td>
<td>107 (43.5%)</td>
<td>153 (46.0%)</td>
</tr>
<tr>
<td>Other European</td>
<td>10 (9.9%)</td>
<td>23 (9.3%)</td>
<td>33 (9.5%)</td>
</tr>
<tr>
<td>NZ Maori</td>
<td>13 (12.9%)</td>
<td>27 (11.0%)</td>
<td>40 (11.5%)</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>10 (9.9%)</td>
<td>27 (11.0%)</td>
<td>37 (10.7%)</td>
</tr>
<tr>
<td>Indian</td>
<td>9 (8.9%)</td>
<td>29 (11.8%)</td>
<td>38 (11.0%)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (12.9%)</td>
<td>33 (13.4%)</td>
<td>46 (13.3%)</td>
</tr>
</tbody>
</table>

*p<0.05

Vitamin B12 concentration

The distribution of serum vitamin B12 concentration was skewed towards the lower range, with the peak located slightly higher than the 220 pmol/L level of lowered vitamin B12 status. The prevalence of lowered B12 concentration (<220 pmol/L) was 18.7% (Table 2).

The median deficient (<150 pmol/L) B12 concentration was 122.5 pmol/L and the median low B12 (150–219 pmol/L) concentration was 183 pmol/L (Figure 2).

Table 2. Number and percentage of patients in each serum vitamin B12 level category

<table>
<thead>
<tr>
<th>Vitamin B12 Level Status</th>
<th>Number of Patients n (% of group)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary Health n = 101</td>
</tr>
<tr>
<td>Deficient (&lt;150 pmol/L)</td>
<td>6 (5.9%)</td>
</tr>
<tr>
<td>Lowered (150–219 pmol/L)</td>
<td>16 (15.8%)</td>
</tr>
<tr>
<td>Normal (≥220 pmol/L)</td>
<td>79 (78.2%)</td>
</tr>
</tbody>
</table>

Note: No significant differences in B12 status between groups.
Effect of metformin dosage and duration

Univariate regression of duration of metformin with B12 concentration shows significant regression (p=0.023).

As metformin dose is dependent on tablet strength, metformin dosages were assigned to six different categories dependent on the gram per day value. Serum vitamin B12 levels decreased progressively as metformin dose increased (ANOVA p=0.007) (Table 3).
Logistic regression shows significant effect of metformin dosage on prevalence of decreased serum Vitamin B12 level (<220 pmol/L) (p=0.004).

**Effect of ethnicity**

Vitamin B12 concentrations varied by ethnicity (ANOVA p<0.0005) (Table 4). However, the prevalence of low serum B12 (<220 pmol/L) is not significantly different across all ethnic groups (p=0.854).

### Table 4. Ethnicity dependent presentation of mean values of data for study group

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Serum vitamin B12 (pmol/L)</th>
<th>Metformin dosage (mg/day)</th>
<th>Duration of metformin treatment (years)</th>
<th>Prevalence of low vitamin B12 (&lt;220 pmol/L) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NZ European n=153</td>
<td>318.51 (129.93)</td>
<td>1908.50 (774.25)</td>
<td>7.58 (4.36)</td>
<td>21%</td>
</tr>
<tr>
<td>Other European n=33</td>
<td>330.94 (164.37)</td>
<td>1692.42 (644.46)</td>
<td>6.71 (3.88)</td>
<td>18%</td>
</tr>
<tr>
<td>NZ Maori n=40</td>
<td>429.70 * (193.11)</td>
<td>2206.25 (768.05)</td>
<td>7.63 (4.46)</td>
<td>13%</td>
</tr>
<tr>
<td>Pacific Islander n=37</td>
<td>472.65 * (188.33)</td>
<td>2022.97 (674.80)</td>
<td>6.84 (3.65)</td>
<td>8%</td>
</tr>
<tr>
<td>Indian n=38</td>
<td>374.63 (279.51)</td>
<td>1988.16 (729.35)</td>
<td>7.77 (4.24)</td>
<td>24%</td>
</tr>
<tr>
<td>Other n=46</td>
<td>351.83 (164.48)</td>
<td>2018.48 (778.77)</td>
<td>8.85 (4.19)</td>
<td>19%</td>
</tr>
</tbody>
</table>

* = p < 0.0005 for comparison with NZ European

**Effect of age**

Vitamin B12 concentrations reduced with age (ANOVA p=0.044) when patients were allocated into the following age groups: <50, 51–69, >70. Older age (uncategorised) predicted lowered serum Vitamin B12 status (<220 pmol/L) (logistic regression, p=0.011).
Table 5. Mean serum vitamin B12 (pmol/L) and prevalence of low serum vitamin B12 concentration dependent on age group categorisation

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Number of individuals (% of study group)</th>
<th>Mean serum vitamin B12 level (&lt;220 pmol/L) (SD)</th>
<th>Prevalence (%) of low serum vitamin B12 level (&lt;220 pmol/L) within age group</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>54 (15.6%)</td>
<td>394.96 (151.22)</td>
<td>5.6 %</td>
</tr>
<tr>
<td>51-70</td>
<td>210 (60.5%)</td>
<td>358.91 (192.00)</td>
<td>20.0 %</td>
</tr>
<tr>
<td>&gt;70</td>
<td>83 (23.9%)</td>
<td>337.95 (164.29)</td>
<td>24.1 %*</td>
</tr>
</tbody>
</table>

* p<0.05

Age was correlated with both dosage of metformin (mg/day) (Pearson correlation coefficient of -15.75, p<0.0005) and with duration of metformin treatment (years) (Pearson correlation coefficient of 0.259, p<0.0005). After adjustment for age, the effect of dosage remained significant (p<0.001) but the effect of duration of metformin on serum vitamin B12 was no longer significant (p=0.102).

**Discussion**

The New Zealand Ministry of Health Primary Care Handbook 2012 recommends metformin as the first line therapy for glycaemic control in type 2 diabetes once lifestyle modifications have been deemed ineffective. Although there are recommendations for the annual screening of serum B12 concentration in patients with type 2 diabetes on long-term metformin treatment; it was observed that this is not a common practice in primary health.

Only one of the four medical centres approached for recruitment had a regular serum B12 screening program for patients with type 2 diabetes who are taking metformin. In this study we recruited subjects from primary and secondary care. Subjects from secondary care may be considered to be more at risk due to a greater complexity of issues and co-morbidities. However this was demonstrated not to be the case.

The overall level of prevalence of reduced serum B12 concentration (<220 pmol/L) in patients with type 2 diabetes receiving metformin therapy in this study was 18.7% which is similar to results from other studies reporting between 5 and 36.8%. At the lower end of this range, in a North American group, Reinstatler et al reported a vitamin B12 deficiency in only 5.8% of patients with type 2 diabetes taking metformin compared to 2.4% of patients with type 2 diabetes not taking metformin. This is in contrast to a study in a Brazilian group by Nervo and colleagues. The threshold for deficiency in this study was higher (250 pmol/L vs 220 pmol/L) which may partially explain the high prevalence of decreased serum B12 of 36.8%. Differences between the two studies are also seen in the subsequent effect of vitamin supplementation. While supplementation with vitamin B12 in the American group did not result in a significant alteration to prevalence, in the Brazilian group an increase in Vitamin B12 intake was positively correlated to serum Vitamin B12 status. This suggests that impairment is linked closely to dietary malnutrition of Vitamin B12.

This study did not have a dietary intake component, however we can use Ministry of Health data to inform the discussion. The median daily dietary intake of B12 in New Zealand in the last National Nutrition Survey was 4.7 mcg for men and 3.3 mcg for women. The daily intake of participants in the Brazilian study was 2.25 mcg, less than the recommended daily intake of 2.4 mcg. While the American study does not include vitamin B12 intakes, it does note that 40% of people with diabetes were taking a supplement containing B12. While this data is not available for New Zealand,
supplement rates here in the general population vary between 2 and 11%, with people in the 31–50 year group reporting the highest supplement use.\textsuperscript{12}

The 2003–2006 American National Health and Nutrition Examination Survey (NHANES), reports the mean population serum Vitamin B12 level was 370 pmol/L compared with 355 pmol/L in the present study.\textsuperscript{13} Again this may reflect greater use of vitamin supplements in the US.

There are few data on Vitamin B12 status in the general population of New Zealand. Levels in non-vegetarian Seventh Day Adventists were reported to be 245 pmol/L, with an average age of 40.\textsuperscript{14} In an older group (age >65 years) 35.5% were observed to have a lowered serum Vitamin B12 concentration (<221 pmol/L).\textsuperscript{15} This compares with a rate of 24.1% in patients >70 years in the current study, reflecting again the influence of age alone on B12 status.

One of the unique aspects to this study is the consideration of ethnic differences in the New Zealand population, a factor that has not yet been explored in previous literature. Higher mean serum Vitamin B12 concentrations were seen in NZ Maori and Samoan groups compared to the other groups.

Dietary or genetic determinants may explain this observation.\textsuperscript{16} Data from the 2008/2009 New Zealand Adult Nutrition Survey showed that levels of Vitamin B12 consumption from red meat and seafood are higher in the Maori group than in the NZ European group.\textsuperscript{12}

A limitation of this study is the lack of a true New Zealand population denominator for prevalence of low vitamin B12 concentrations. Nor were we able to compare our results with those of a group with type 2 diabetes but not taking metformin. Despite this, it is clear that the prevalence of reduced B12 status in those with type 2 diabetes who are taking metformin is high and increases with age.

As this is a cross-sectional study and we do not have B12 concentrations prior to commencement of metformin, it cannot be concluded that metformin is causative of low B12 concentrations. Furthermore, the clinical implications of this are less clear, and whether supplementation of these individuals would be of benefit requires an intervention study.

While it is difficult to diagnose B12 deficiency based on physiological symptoms, further data on cell volume and presence of anaemia would also be useful. This would help to inform whether universal screening of those taking metformin is appropriate. Given the low rate of reduced B12 levels in those less than 50 years, it may be argued that screening could be safely restricted to those older than this.

Competing interests: Nil.

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References


