

## ARTICLE

# Vitamin B12 Deficiency in Patients with Type 2 Diabetes on Metformin Therapy

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## Abstract

**Background:** Vitamin B12 deficiency can cause peripheral neuropathy. Metformin use is associated with vitamin B12 deficiency. **Objective:** To define the prevalence of vitamin B12 deficiency in patients with type 2 diabetes mellitus (T2DM) and its possible relation to metformin therapy. **Patients and Methods:** A cross-sectional study of T2DM patients on chronic metformin therapy was conducted at Benghazi Diabetic Center during 2011. Demographic data, type, and duration of treatment reported adherence, and vitamin B treatment were all documented. History and examination for evidence of peripheral neuropathy were recorded. Serum vitamin B12 levels were measured (reference value 159-1000 pg/ml). **Results:** 500 patients were included of whom 175 were males (35%). Mean (SD) age was 58.6 ± 9.9 years and duration of diabetes 13.6 ± 8.4 years. Of these 358 (71.8%) were on insulin and metformin, 93 (18.6%) on sulphonylureas and metformin, 26 (5.2%) were on insulin and sulphonylurea and metformin triple

combination therapy, and 22 (4.4%) were on metformin monotherapy. Mean serum B12 level for all patients was 439 ± 212 pg/ml with males having significantly higher levels than females (512 ± 226 vs. 399 ± 193; p=0.001). Vitamin B12 levels were <159 pg/ml in 2%, <200 pg/ml in 7.4%, and <300 pg/ml in 30.8% of the patients. There was no significant difference in the B12 levels among patients who were adherent to metformin therapy and those who were not (432 ± 206 vs. 448 ± 219 pg/ml; p=0.4). Serum B12 levels were not different in the patient with history and/or examination suggestive of neuropathy and patients who have any (443 ± 216 vs. 423 ± 204; p=0.5). **Conclusions:** The prevalence of vitamin B12 deficiency in diabetic patients attending Benghazi diabetic center was dependent on the cut off points used. This is comparable with previous studies. No clear relationship was evident with metformin therapy nor with neuropathy.

**Keyword:** Diabetes, Vitamin B12 deficiency, Benghazi, Libya, Metformin, Neuropathy.

**Introduction**

Vitamin B12 deficiency is defined by the values of the serum levels cobalamin and also of homocysteine and methylmalonic acid which are the two components of the cobalamin metabolic pathway (1-3). Most guidelines define vitamin B12 deficiency on basis of serum cobalamin level <150 pmol/L on two separate occasions or cobalamin level <150 pmol/L and homocysteine level > 13 µmol/L or methylmalonic acid > 0.4 µmol/L in the absence of renal failure and folate and vitamin B6 deficiencies (4,5).

The most common cause of vitamin B12 deficiency, especially in elderly, is food-cobalamin malabsorption. This accounts for about 60%–70% of the cases. Long-term ingestion of the biguanides metformin can lead to food-cobalamin malabsorption (6). This may present without anemia and with features of peripheral neuropathy which may be misdiagnosed as diabetic neuropathy (7,8). We have undertaken this study to define the prevalence of vitamin B 12 deficiency in a sample of our patients with type 2 diabetes mellitus (T2DM).

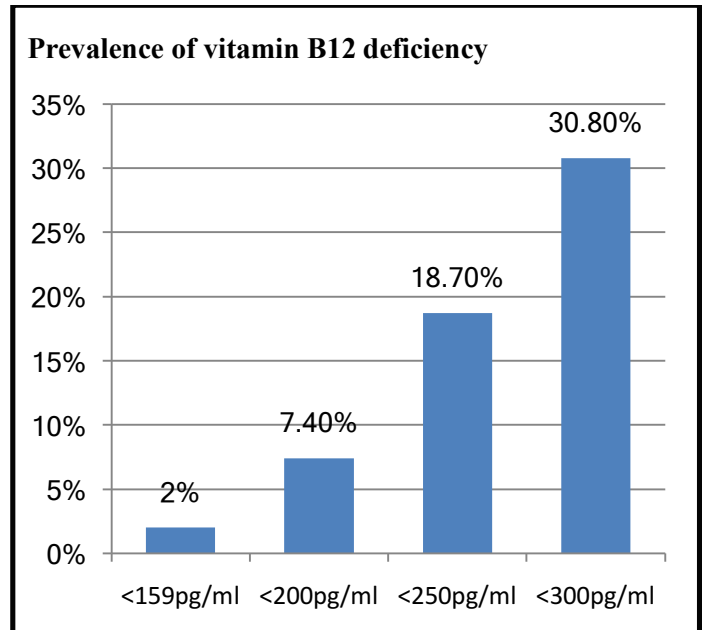
**Patients and Methods**

A cross-sectional study of T2DM patients was conducted at Benghazi Diabetic Clinic (BDC) during 2011. A convenience sample of 500 patients on metformin was recruited. They were 175 males (35%) and 325 females (65%). The mean age ± SD was 59 ± 10 years with no difference in age between genders. 460 (92%) were Caucasoid white, and 40 (8%) were black. 417 (83.4%) were Libyan nationals, and 83(16.6%) were non-Libyans (mostly Egyptians). 443 (88.6%) patients lived in urban Benghazi, and 57(11.4) resided in rural areas. Mean duration of T2DM was 13.6 ± 8.4 years.

Table 1 Number and percentage of the patients on various treatment regimens.		
Therapies	Number of patients	Percentage
Metformin and insulin	359	71.8%
Metformin and sulphonylureas	93	18.6%
Insulin; sulphonylurea and metformin	26	5.2%
Metformin monotherapy	22	4.4%

Most patients were on metformin/insulin combination followed by metformin/sulphonylureas combination. Use

of metformin alone was not common, but mostly in combination with another medication(s) (Table 1). Demographic data, type, and duration of treatment, adherence were recorded. History of peripheral neuropathy and vitamin B replacement was documented. History and examination features suggestive of peripheral neuropathy were identified. Vitamin B12 levels were checked using standard laboratory methods (reference value 159-1000 pg/ml). Student's T-test was used to analyze the associations between the subgroups and p<0.05 was considered statistically significant.



**Figure 1.** Prevalence of B12 deficiency determined at three different cut level points that are commonly-used in clinical practice.

**Results**

Mean B12 level for all 500 patients was 463 ± 467 pg/ml. Males had significantly higher levels than females (512 ± 227 vs. 399 ± 193 pg/ml, p<0.0001). Only 63 (12.6%) patients had a recent history of multivitamin or vitamin B complex intake. Mean serum B12 level for all patients was 439 ± 212 pg/ml with males having significantly higher levels than females (512 ± 226 vs. 399±193 pg/ml; p=0.001). Vitamin B12 levels were <159 pg/ml in 2%, <200 pg/ml in 7.4%, and <300 pg/ml in 30.8% of the patients (Figure 1). Although all patients in this study were prescribed metformin, 280 (56.8 %) reported being adherent to their regular daily metformin therapy as prescribed whilst the remaining 216 patients (43.2%) admitted to poor concordance with metformin. However, there was no significant difference in serum B12 levels

between those who were adherent to metformin) and those who were not ( $432 \pm 206$  pg/ml vs.  $448 \pm 219$  pg/ml;  $p=0.4$ ). 335 patients (67%) had history and/or examination findings suggestive of peripheral neuropathy. Mean serum B12 levels were not different in patients who had history and examination finding suggestive of neuropathy and patients who had none ( $478 \pm 552$  pg/ml vs.  $431 \pm 204$  pg/ml;  $p=0.29$ ). Mean serum vitamin B12 level in white patients was higher than in black patients ( $470 \pm 483$  pg/ml vs.  $384 \pm 214$  pg/ml;  $p=0.033$ ). There was a non-significant trend for mean vitamin B12 levels in patients of urban residency to be higher than in those of rural residency ( $476 \pm 489$  pg/ml vs.  $360 \pm 204$  pg/ml;  $p=0.08$ ).

### Discussion

Most of the patients in the present study were on metformin combinations with insulin followed by sulphonylurea in line with common practices in many countries in the developing world. No patients in the sample were on the incretin-based therapies or thiazolidinediones reflecting the political situation in the country. Most of the patients using sulphonylurea were on glibenclamide, and very few were on glimepiride and newer incretin-based therapy agents. Lack of knowledge and experience by some of treating physicians or confidence about their safety could have contributed to the patterns of prescribing observed. This could have also been coupled with the interrupted availability or patient refusal of injections. The trends of metformin are fairly low considering its established benefits. This could be either due to the gastrointestinal side effect of metformin or the low patient education by the physician regarding the its benefit which is mostly caused by the overwhelming number of patients attending the clinics.

When the frequency of vitamin B12 deficiency was determined using different cut points; the frequency of vitamin B12 deficiency increased progressively from 2% to 30% (Figure 1). Unfortunately, testing for methyl malonyl co A was not feasible at our facility. We are not aware of any previous studies in Benghazi's general population on vitamin B12 deficiency to make comparisons. However, two previous studies from Libya had remarkably different findings (9,10). One study including Tripoli (the capital city) school children reported a total non-existence of B12 deficiency (9). Another study from Zleiten (a smaller town in the west of Libya) reported a very high prevalence exceeding 40% (10). However, findings of the present study remain comparable with studies in diabetic patients outside Libya using similar cut-off points (11).

The lower prescription rates for vitamin B12 or B complex supplement (12.6%) may be attributable to lack of knowledge regarding the association of metformin with vitamin B12 deficiency or the inconsistent international guidelines on the matter.

Despite the higher prevalence of peripheral neuropathy in our study (67%), there was no statistically significant difference between patients with and without peripheral neuropathy with regard to B12 levels ( $p=0.29$ ). The high percentage of neuropathy is most likely reflecting the chronic poor control of diabetes. A study conducted in Benghazi's Diabetes Center reported an alarmingly high prevalence of poorly controlled diabetes at 79.8% among T2DM patients, and this may explain why no impact of metformin on neuropathy (if any) was appreciated (12). Also, any degree of imbalance of the distribution of multivitamin or B complex treatment between groups, could mask any difference. Surprisingly there was no significant difference between those who were adherent to metformin and those who were not. However, perhaps other factors such as diabetic autonomic neuropathy affecting the level especially in the view of the high percentage of peripheral neuropathy which we observed during the study.

Females had significantly lower level of vitamin B12 than males in our study. Previous studies have not shown this difference. However, one previous study revealed an inverse relationship between body mass index (BMI) and vitamin B12 level (13). Another study showed Libyan females to have significantly higher BMI compared to males (13).

Our study showed a significantly lower level of vitamin B12 in black patients compared to white patients ( $P=0.03$ ) at variance with previous reports (14). Patients of urban residency had a non-statistically significant trend toward higher serum B12 levels compared to patients of rural residency ( $P=0.08$ ) while most of the previous reports showed lower B12 levels in urban areas (15).

In conclusion, the prevalence of vitamin B12 deficiency in diabetic patients attending Benghazi Diabetic Clinic was dependent on the cut-off points used and are comparable with previously reported studies. No clear relationship was evident with metformin therapy nor with presence or absence of neuropathy.

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### Disclosures

1. Authors contributions: jointly incepted, designed and conducted the survey jointly and produced the manuscript and approved its final version
2. Conflict of interest: None of the authors has any multiplicity of interests.
2. Funding: No funding received.
3. The study was conducted according to the ethical principles of the Declaration of Helsinki. All participants provided an informed consent prior to the study.

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