Original article:

Study of Vitamin B12 deficiency in type 2 diabetes patients on long term metformin therapy

Dr Anu N Gaikwad, Dr. Anand Nandkumar Dugad*

Professor, Dept of Medicine, P Dr D Y Patil Medical College, Pimpri, Pune
Resident, Dept of Medicine, P Dr D Y Patil Medical College, Pimpri, Pune
Corresponding author*

ABSTRACT:

INTRODUCTION: Metformin is considered a cornerstone in the treatment of diabetes and is the most frequently prescribed first line therapy for individuals with type 2 diabetes. In addition it is one of the few antihyperglycemic agents associated with improvements in cardiovascular morbidity and mortality.

MATERIAL AND METHODS: The present study was a prospective type of study. Tertiary care hospital, Pad. Dr. D.Y. Patil Medical College, Hospital & Research Center Pimpri Pune 18.

Outpatient department of Medicine of tertiary care hospital. Registration of patients was from July 2014 to September 2016. They were registered when admitted under Medicine department. At the time of registration the patients with exclusion criteria were not enrolled for study.

RESULTS: Serum vitamin B12 among study population, were among cases majority 48% were below 200, followed by 34% more than 301 and only 18% in range of 201 to 300.
Among controls majority 78% were above 301, followed by 14% in range of 201 to 300 and only 8% were below 200. P value was highly significant.

CONCLUSION: It appears that vitamin B12 deficiency occurs commonly among patients with type-2 diabetes taking metformin therapy for longer duration and at higher dosage.
Outpatient department of Medicine of tertiary care hospital. Registration of patients was from July 2014 to September 2016. They were registered when admitted under Medicine department. At the time of registration the patients with exclusion criteria were not enrolled for study.

The main objective of this study was to determine Vitamin B12 deficiency in type2 diabetes patients on long term metformin therapy for >2years.

At the time of registration the baseline information was taken especially with respect to sociodemographic factors, clinical findings, and other investigations. Thus each & every patient was followed up in Medicine department till discharge. The data thus collected was analyzed the effect of long term use of metformin on vitamin B12.

**Study period:** July 2014 to September 2016

**Sample size:** 100. 50 cases and 50 controls.

**Study participant:** Patients having type 2 DM and on long term metformin therapy i.e. more than 2 years.

**Inclusion criteria:**
- Patients who have given written informed consent
- Patients with fasting blood glucose > 126mg/dl on two different occasions, post prandial >200mg/dl. HbA1C >6.5%, OGTT >200mg/dl.
- Type 2 Diabetic patients of age >18yrs
- Type 2 Diabetic patients on intake of metformin for >2yrs

**Exclusion criteria:**
- Patients who have not given written informed consent.
- Type 1 diabetes mellitus
- Diabetic complications
- Intake of calcium
- Malabsorption Syndrome
- Intestinal infection
- Partial/total gastrectomy
- Patients on vitamin B12 supplements
- Hypothyroidism

**Sampling technique:** The patients coming to Medicine outpatient department having the inclusion criteria were selected by simple random sampling.

**Data collection**

Written informed consent was taken from the participants. Two groups were made. One case group and one control group.

In case group 50 patients were selected having type 2 DM and were on long term metformin therapy for more than 2 years and control group had 50 patients without the disease. Pre designed questionnaire schedule consisting of standard questions related to socio demographic factors, environmental conditions, addiction among respondents, family size and so on, were interviewed. In addition, questionnaire also included questions on past and present medical history and health seeking behaviour.

Following main domains were covered in questionnaire:
- Fasting and post-prandial blood glucose
- Urine routine sugar
- Serum vitamin B12 levels
- Patients on long term metformin therapy, more than 2 years.

**Data analysis:**

The collected data was compiled in Microsoft Excel 2010 and analyzed using SPSS (Statistical
RESULTS:

Table 1: Symptomatology among the cases

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyuria</td>
<td>48</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>45</td>
</tr>
<tr>
<td>Tingling numbness</td>
<td>17</td>
</tr>
<tr>
<td>Burning feet</td>
<td>9</td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>6</td>
</tr>
</tbody>
</table>

Table shows Symptomatology among the cases, where majority 48 had Polyuria, followed by 45 had polydipsia, 17 had tingling numbness, 9 had burning of feet and 6 had visual disturbances.

Table 2: Co morbid condition

<table>
<thead>
<tr>
<th>HTN</th>
<th>Cases (n=50)</th>
<th>Percent</th>
<th>Controls (n=50)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>25</td>
<td>50%</td>
<td>19</td>
<td>38%</td>
</tr>
<tr>
<td>Absent</td>
<td>25</td>
<td>50%</td>
<td>31</td>
<td>62%</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100%</td>
<td>50</td>
<td>100%</td>
</tr>
</tbody>
</table>

Applying Chi square test, p value= 0.11, shows no significance

Table 3: Addiction among the study population

<table>
<thead>
<tr>
<th>Addiction</th>
<th>Cases (n=50)</th>
<th>Controls (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Smoking</td>
<td>17</td>
<td>12</td>
</tr>
</tbody>
</table>

Table shows Addiction among the study population, where among cases 17 were smokers and 11 were alcoholic.

Table 4: Duration of DM in years

<table>
<thead>
<tr>
<th>Duration</th>
<th>Cases (n=50)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>23</td>
<td>46%</td>
</tr>
<tr>
<td>&gt;5</td>
<td>27</td>
<td>54%</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100%</td>
</tr>
</tbody>
</table>

Mean duration among cases was $6.18 \pm 2.64$

Table shows Duration of DM in years, where majority 54% had duration >5 years and 46% had <5 years.
Table 5: Serum vitamin B12 among study population

<table>
<thead>
<tr>
<th>Serum vit B12</th>
<th>Cases (n=50)</th>
<th>Percent</th>
<th>Controls (n=50)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td>24</td>
<td>48%</td>
<td>4</td>
<td>8%</td>
</tr>
<tr>
<td>201 to 300</td>
<td>9</td>
<td>18%</td>
<td>7</td>
<td>14%</td>
</tr>
<tr>
<td>&gt;301</td>
<td>17</td>
<td>34%</td>
<td>39</td>
<td>78%</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100%</td>
<td>50</td>
<td>100%</td>
</tr>
</tbody>
</table>

Mean serum vitamin B12 of cases was 271.75 ± 184.21
Mean serum vitamin B12 of controls was 410.45 ± 154.34
P value= 0.00009, shows significance.

DISCUSSION

In our study, majority 48 had Polyuria, followed by 45 had polydipsia, 17 had tingling numbness, 9 had burning of feet and 6 had visual disturbances.

In a case report by Dacid S.H. a 69-year-old white male who had well-controlled type 2 diabetes (HbA1c 6.0%) for six years developed numbness in his feet, which he thought was due to diabetes. bilateral loss of pinprick and vibration sense to just above the ankles bilaterally. However, both ankle jerks were present and brisk. The physical findings were consistent with vitamin B12 deficiency rather than diabetic neuropathy. While vitamin B12 deficiency is associated with a macrocytic and megaloblastic anemia, the anemia is often preceded by the development of neuropathy. While the anemia of vitamin B12 deficiency is reversible, the progress of the neuropathy is only arrested and not reversed with initiation of vitamin B12 therapy. In the nervous system, vitamin B12 deficiency causes demyelination followed by axonal degeneration and neuronal death—not only in peripheral nerves but also in the posterior and lateral columns of the spinal cord and the cerebrum. Clinically, the earliest manifestations are numbness and paresthesias in the feet, which, unless the vitamin B12 deficiency is corrected, can be followed by weakness, ataxia, sphincter disturbance, and changes in mental status.

Co morbid condition

In our study, 50% had HTN and 50% dint. Applying Chi square test, p value= 0.11, shows no significance.

Addiction

In our study, 17 were smokers and 11 were alcoholic.
Study by M S Amer et al showed that 19.35% were smokers.
Duration of DM in years

In our study, majority 54% had duration >5 years and 46% had <5 years.
Mean duration among cases was 6.18 +2.64.
Study by PflipsenM et al 6 showed that mean duration of DM was 8.3 years.
This is also mentioned in a review article by Davis Kibirige et al 7 that risk of developing metformin associated vitamin B12 deficiency is greatly influenced by increasing age, metformin dose and duration of use.
In a case control study by Ting R et al 8 showed an increased risk of vitamin B12 deficiency associated with current dose and duration of metformin use despite adjustment for many potential confounders. This study also found clinically important and statistically significant association of vitamin B12 deficiency with dose and duration of metformin use.
Study by Lael R et al showed that mean years of DM were 12 years.9

Serum vitamin B12

In our study, majority 48% were below 200, followed by 34% more than 301 and only 18% in range of 201 to 300.
Among controls majority 78% were above 301, followed by 14% in range of 201 to 300 and only 8% were below 200. Mean serum vitamin B12 of cases was 271.75+184.21. Mean serum vitamin B12 of controls was 410.45+154.34. P value= 0.00009, shows significance.
In one early randomised controlled trial by DeFronzo et al.10 metformin decreased the serum vitamin B12 levels by 22% and 29% compared to placebo and glyburide respectively.
In another randomised, placebo controlled, double blind trial by De-Jager J et al 11 showed that in patients with type 2 diabetes being treated with insulin, those additionally treated with metformin had a seven percentage point greater absolute risk of vitamin B-12 deficiency than those treated with placebo during 4.3 years of follow-up.
Niafar et al 9 studies were selected with a total of 8,089 patients. 19 studies were rated intermediate or high quality. Primary outcome suggested increased incidence of Vit B12 deficiency in metformin group (OR = 2.45, 95 % CI 1.74–3.44, P < 0.0001.) 12

CONCLUSION
It appears that vitamin B12 deficiency occurs commonly among patients with type-2 diabetes taking metformin therapy for longer duration and at higher dosage.

BIBLIOGRAPHY