Correlation study of metformin drug with vit.B12 and folic acid in women suffer of type 2 diabetic disease

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Abstract

Background: Diabetes mellitus is the most well-known endocrine disorder to date. Year after year, the prevalence of type 2 diabetes (T2D), which accounts for more than 90% of all diabetes cases, rises fast. Metformin is the most generally prescribed oral diabetes medication, and it is used to treat all diabetics worldwide in combination with diet and exercise. Though evidence shows that using metformin for a long time might cause vitamin B12 and folic acid deficiency, only a few studies have done in this regard. Materials and methods: Participants were divided into two groups: diabetic females (MET) (n = 60) and healthy control females (n = 25). All diabetic patients receiving Metformin (500 mg twice daily) were further divided into two groups based on treatment duration: less than 2 years and more than 2 years. Serum vitamin B12, folic acid, T3 and T4 levels were tested in the subjects. Results: the level of serum Folic acid in diabetic females with duration of metformin treatment more than 2 years was (77.05 ± 2.61), while its level in diabetic females with duration of metformin less than 2 years was (130.55 ± 1.86) both were significantly lower (p<0.001) than its level in healthy control (426.47 ± 32.51). Student’s t-test demonstrated a very significant drop in blood folic acid levels in diabetic females who had used metformin for more than 2 years compared to females who had used metformin for less than 2 years. Conclusion: To determine the risk of B12 and B9 deficiency in Diabetic females taking metformin, compared to the healthy control group.

Keywords: cobalamin; Metformin; B9; body max index. Diabetes mellitus type 2.

1. INTRODUCTION

Metformin is the greatest anti-diabetic medicine for those with type 2 diabetes mellitus (T2DM), making it an important part of T2DM treatment 1. This medication is generally well tolerated (with a few side effects) and has a considerable influence on the future risk of T2DM complications 2,3. Despite its numerous health benefits, metformin can potentially have serious side effects. People usually disregard or ignore such concerns since the advantages exceed the risk  4,5 Vitamin B12 insufficiency is one unintentional consequence of these risk. Furthermore, it has been found that metformin can for unclear reason participate in lowering folate concentration 6.

Vitamin B12 commonly referred to as cobalamin, is water-soluble and important for the op-eration of the circulatory, neurological, and hematopoietic systems. Its role in DNA synthesis and fatty acid metabolism is well-documented 7.

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Vitamin B12 is responsible for important cellular functions like the chemical conversion of homocysteine to methionine and then to S-adenosyl methionine (SAM), which adds methyl groups to many essential substrates. Vitamin B12 promotes the alteration of methyl malonyl coenzyme A to succinyl coA, and if this process is hindered, methylmalonic acid (MMA) is accumulated in the bloodstream and the creation of neuronal membranes’ fatty acids is af-fected. Studies have proven that metformin (which is used to treat diabetes) can result in a vitamin B12 deficit. Metformin is known to cause vitamin B12 deficiency (VBD) in people with T2DM, although we don’t know the mechanism by which it does so. Small intestinal motility is altered, which in turn triggers bacterial overgrowth and hence vitamin B12 insufficiency. Others have to do with the modification of intrinsic factor levels and in stimulation of vitamin B12 absorption, and, finally, contact with the cubulin endocytic receptor. Besides this, the suppression of the terminal ileum's vitamin B12–intrinsic factor (IF) complex’s calcium-dependent absorption has been theorized. While metformin use results in a reduction in vitamin B12 levels that begins by the 4th month. Due to the huge liver stores of vitamin B12, clinical symptoms appear in just 5 years because the stores aren't quickly ex-hausted. Metformin also influences the effectiveness of Prandin in this case, and that is determined by the person’s age and how much of the medication they take. It is of clinical significance to measure V B12 insufficiency in patients with DM T2. Cases on metformin may mistake this condition for diabetic neuropathy due to their metformin treatment. In some patients, it can manifest as neuropathy 15. In addition, a deficiency in vitamin B12 has been linked to slower nerve conduction velocities and a weaker ability to detect light touch using monofilament detection. It could lead to inappropriate therapy for diabetic neuropathy by unessential use of tricyclic, antidepressants, anticonvulsants, and other medicines 14,17,18.

2. Materials and Methods

The research design was approved by the Institute Review Board at the University of Al-Nahrain’s College of Medicine. From 23/9 /2021 to 1/2/ 2022, sixty diabetic females were recruited from the affiliated Hospital of the College of Medicine at Al-Nahrain University. Each patient was enrolled in our study based on the decision of a specialist who used standard diagnostic criteria. These (60) diabetic females were divided into two groups based on the length of metformin treatment: group I had more than two years of metformin intake; group II had less than two years of metformin intake; and 25 healthy females served as controls.

Venous blood (10 ml) was collected from the study subjects after overnight fasting; serum was separated and store at −20°C and analyzed later. All measurements were performed in Al-Nahrain teaching hospital which consists of estimating serum insulin, folic acid, B12, T3, T4 by using immunoassay method (ELISA). Vitamin B12 decrease if the concentration in serum <200 pg/dl and borderline decrease if 200–300 pg/dl. Concentrations >300 pg/dl is normal 19. BMI was measured as weight (in kilograms) divided by height (in meters) squared for all subjects. BMI= Weight (kg) / Height (m²) 20. Exclusion criteria Patients who had un-dergone gastrectomy, had smaller-scale bowel resections, suffered from liver illness, had chronic kidney disease, or had hypothyroidism were excluded from this research. Patients were also eliminated if they had taken a recent vitamin B12 supplement orally or intramus-cularly, if they were using histamine two receptor blockers, or if they were vegetarians.

Statistical analysis

All Analyses were conducted by SPSS (version 25.0). The patients were analyzed using a histogram with a normal curve that revealed where in the distribution of vitamin B12 levels folic acid, T3, and T4 were. To clarify, t-tests and Mann Whitney U were employed to identify disparities in variable means. Statistically significant P-values were ones under 0.05.

3. Results

3.1. Subsection

Obese diabetic individuals all have Vitamin B12 insufficiency. The patients were categorized by the length of time they had been taking metformin, as the time period is believed to be correlated with the long-term effects of the drug. Long-term metformin users had lower mean vitamin B12 levels than those who had used metformin for two years or less, as seen in Table 1. Metformin had no significant effect on the average of folic acid, T3, and T4 levels; the findings were the same regardless of the period of treatment.

3.2. Tables

Table 1: Features of the patients and levels of T3, T4, B12, folic acid according to duration of metformin intake.

<table>
<thead>
<tr>
<th>Feature</th>
<th>&lt;2 year (n=30)</th>
<th>&gt;2 year (n=30)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>26.20 ± 6.11</td>
<td>25.26 ± 4.40</td>
<td>0.550</td>
</tr>
<tr>
<td>BMI</td>
<td>28.86 ± 4.04</td>
<td>26.32 ± 2.11</td>
<td>0.004</td>
</tr>
<tr>
<td>Insulin</td>
<td>35.73 ± 24.89</td>
<td>22.25 ± 7.86</td>
<td>0.007</td>
</tr>
<tr>
<td>T3</td>
<td>1.13 ± 0.27</td>
<td>1.1463±0.30</td>
<td>0.835</td>
</tr>
<tr>
<td>T4</td>
<td>88.59 ± 11.92</td>
<td>83.74±2 11.72</td>
<td>0.067</td>
</tr>
<tr>
<td>B12</td>
<td>130.55 ± 10.18</td>
<td>77.05±2 14.29</td>
<td>0.000*</td>
</tr>
<tr>
<td>Folic acid</td>
<td>2.09 ± 0.62</td>
<td>2.0580±0.65</td>
<td>0.799</td>
</tr>
</tbody>
</table>

Table 2: Features of the patients and levels of T3, T4, B12, folic acid according to duration of metformin intake <2-year comparison healthy control.

<table>
<thead>
<tr>
<th>Feature</th>
<th>&lt;2 year (n=30)</th>
<th>Control (n=30)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>26.20 ± 6.11</td>
<td>29.60 ± 5.34</td>
<td>0.064</td>
</tr>
<tr>
<td>BMI</td>
<td>28.86 ± 4.04</td>
<td>24.68 ± 3.24</td>
<td>0.00*</td>
</tr>
<tr>
<td>Insulin</td>
<td>35.73 ± 24.89</td>
<td>11.85 ± 3.09</td>
<td>0.00*</td>
</tr>
<tr>
<td>T3</td>
<td>1.13 ± 0.27</td>
<td>1.50 ± 0.39</td>
<td>0.00*</td>
</tr>
</tbody>
</table>
Patients with type two diabetes were more likely to have vitamin B12 deficiency. In addition, Vitamin B12 levels decreased in patients taking metformin for a long time had reduced B12 and folic acid levels, and this trend has been growing over the years. It has been theorized that this problem could have originated with any one of the following: a change in the way the small intestine moves (which could lead to bacteria overgrowth, thus causing vitamin B12 deficiency), a decrease in the amount of intrinsic factor (which would lead to vitamin B12 deficiency as well), a change in the ability of cubilin, an endocytic receptor, to absorb vitamin B12 or interference with the calcium-dependent absorption of the intrinsic factor complex at the terminal ileum. Our observation also suggests that the vitamin B12 storage in the liver is depleted, most likely due to a long duration of metformin intake. Twana et al agree with our study which found vitamin B12 and folate deficiency in type 2 diabetic patients. De-Jager et al found an increase in the probability of vitamin B12 insufficiency by 2.88 has been seen for a daily dose of 1 gram of metformin. Patients taking 1000mg of metformin per day may be at a lower vitamin B12 level, as observed in comparison to healthy females. This might explain why many additional reports have observed the same findings. Despite the unknown method, our finding suggests that high doses of metformin increase vitamin B12 absorption inhibition and could thus lead to fast vitamin B12 depletion in patients who are using metformin.

4. Discussion

The aim of the current study was to evaluate the risk of vitamin B12 and folate acid decrease in T2DM females and its association with metformin use duration. The study showed that diabetic patients were more likely to have vitamin B12 and folate acid deficiency based on duration of metformin use than control group. In addition, Vitamin B12 deficiency has been investigated by other researchers across the world.

Studies have found that diabetes patients with type two on metformin for a long time had reduced B12 and folic acid levels, and this trend has been growing over the years. It has been theorized that this problem could have originated with any one of the following: a change in the way the small intestine moves (which could lead to bacteria overgrowth, thus causing vitamin B12 deficiency), a decrease in the amount of intrinsic factor (which would lead to vitamin B12 deficiency as well), a change in the ability of cubilin, an endocytic receptor, to absorb vitamin B12 or interference with the calcium-dependent absorption of the intrinsic factor complex at the terminal ileum. Our observation also suggests that the vitamin B12 storage in the liver is depleted, most likely due to a long duration of metformin intake, Twana et al agree with our study which found vitamin B12 and folate deficiency in type 2 diabetic females. De-Jager et al found an increase in the probability of vitamin B12 insufficiency by 2.88 has been seen for a daily dose of 1 gram of metformin. Patients taking 1000mg of metformin per day may be at a lower vitamin B12 level, as observed in comparison to healthy females. This might explain why many additional reports have observed the same findings. Despite the unknown method, our finding suggests that high doses of metformin increase vitamin B12 absorption inhibition and could thus lead to fast vitamin B12 depletion in patients who are using metformin.

Regardless of the link establishment between metformin and vitamin B12 deficiency, the exact reason for this pathway has not been identified in the literature. The studies indicated that prevalence of vitamin B12 deficiency is between 5.8% and 52% worldwide. The present study found that longer use of metformin is associated with a greater level of vitamin B12 deficiency which is in agreement with the literature. However, this must be kept in mind that extended use of metformin in relation to vitamin B12 could result in a challenge of peripheral neuropathy in patients with non-insulin-dependent diabetes. Neuropathy is a complication making health abnormality among 30% of subjects with vitamin B12 deficiency and aged 40 years and older. It could lead to diminished sensory feeling of the feet of patients.

The evidence in the medical literature mentions that the long-term use of metformin affects on calcium-dependent vitamin B12 absorption. It has been documented that vitamin B12 is conversely associated with dose and duration of metformin in type 2 diabetic patients.

The literature supports concurrent intake of metformin and proton pump inhibitors or H2-blockers as the links with vitamin B12 deficiency. The reason backs this concept that reduction in gastric acidity has a key role in vitamin B12 malabsorption. The reduction in acidity occurs through acid discharge by the parietal cells in patients taking these two medications. The reduction in gastric acid created by parietal cells has a key role in vitamin B12 breakthrough. A number of reports claim that folate deficiency, common among diabetic patients, may increase the risk of diabetic nephropathy.

A lack of folic acid leads to problems in biochemical events like DNA methylation. Folic acid's role as a methyl donor makes it an important part of numerous biochemical reactions. Homocysteine has been discovered to be poisonous in many investigations. A shortage in folic acid leads to hyperhomocysteinemia, and this leads to the destruction of blood vessels and related consequences like blindness, kidney disease, and neuropathy. Diabetes-induced podocyte injury can be traced back to endothelial dysfunction and therefore albuminuria.

5. Conclusions

The conclusions of the current study was to evaluate the risk of vitamin B12 and folate acid decrease in T2DM females and its association with metformin use duration. The study showed that diabetic patients were more likely to have vitamin B12 and folate acid deficiency based on duration of metformin use than control group. In addition, Vitamin B12 deficiency has been investigated by other researchers across the world.

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References


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