THE CURRENT SCENARIO OF VITAMIN B12 DEFICIENCY BY LONG TERM METFORMIN THERAPY IN DIABETES MELLITUS - TYPE 2 PATIENTS

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ABSTRACT
Since the history to this present date, Metformin falls under the category of commonly used anti – diabetic drugs in the therapy of type -2 diabetes mellitus (DM). The solidarity statement of American Diabetes Association and the European Association for the Study of Diabetes recommends Metformin therapy as the first line drug choice with lifestyle modification to treat type-2 DM. The pharmacology of this drug works by lowering, Mainly vitamin B12 is obtained from animal protein, during the metabolism process it is mediated by the action of pepsin and gastric acid, after which it binds to R protein, which is secreted by the salivary gland under hydrolyzed condition, it releases the vitamin B12 which binds to the intrinsic factor (IF) secreted by gastric parietal cells which in result leads to the formation of a complex which gets attached to the specific receptors of mucosa in the terminal ileum region, this stage is usually calcium mediated.

KEYWORDS: There have been some concern over the risk of vitamin B12 deficiency.

INTRODUCTION
Since the history to this present date, Metformin falls under the category of commonly used anti – diabetic drugs in the therapy of type -2 diabetes mellitus (DM). The solidarity statement of American Diabetes Association and the European Association for the Study of Diabetes recommends Metformin therapy as the first line drug choice with lifestyle modification to treat type-2 DM. The pharmacology of this drug works by lowering the
amount of glucose made by the liver and by making the body’s cells more sensitive to insulin. At the same time various complications were studied in patients who were in long term treatment for DM under Metformin therapy.\cite{1}

In recent years, there have been some concern over the risk of vitamin B12 deficiency in people who were taking Metformin. As a result a question embossed “So, why would taking Metformin possibly put you at a risk of vitamin B12 deficiency?”.

Mainly vitamin B12 is obtained from animal protein, during the metabolism process it is mediated by the action of pepsin and gastric acid, after which it binds to R protein, which is secreted by the salivary gland under hydrolyzed condition, it releases the vitamin B12 which binds to the intrinsic factor (IF) secreted by gastric parietal cells which in result leads to the formation of a complex which gets attached to the specific receptors of mucosa in the terminal ileum region, this stage is usually calcium mediated. When the vitamin B12 binds to the transcobalamin in the intracellular region it is referred to as ‘holotC’ where 90% of this will be taken up by the liver for the storage process. Any destruction caused during this process leads to the biochemical vitamin B12 deficiency. On the treatment therapy of Metformin, the metabolic process of vitamin B12 is usually disrupted.\cite{2,3}

Vitamin B12 plays an important role in managing the methylation process of homocysteine to methionine which is further activated to S-adenosyl methionine which actively donates its methyl group to methyl acceptors such as myelin, neurotransmitters and membrane phospholipids. It also acts as a cofactor in the conversion of methyl malonyl coenzyme A to succinyl CoA.\cite{4}

The signs and symptoms shown by classical vitamin B12 deficiency included anemia, peripheral neuropathy, depression, cognitive impairment.\cite{5,6}

Vitamin B12 being a water soluble vitamin was historically correlated with the hematological parameters but nowadays the status of Vitamin B12 can be measured by evaluating the active fraction, holotC and MMA which is a functional marker in patients taking Metformin for the treatment of diabetes mellitus.\cite{7}

According to some studies, between 10% and 30% of people who take Metformin on a regular basis have some evidence of decreased vitamin B12 absorption but exact cause still remains as anonymous.\cite{8}
Peripheral neuropathy has been presented as a result of Metformin-related B12 deficiency in case reports.\textsuperscript{[9]}

All current evidence on vitamin B-12 deficiency in Metformin treatment comes from short term studies. No long term, placebo controlled data on the effects of Metformin in patients with the concentrations of vitamin B12, having type 2 diabetes have been reported.\textsuperscript{[10,11]}

Lactic acidosis is unusual but probably a life-threatening complication of Metformin. The worldwide mortality of lactic acidosis is approximately found to be 50\%. A case report of Metformin-associated lactic acidosis, in a patient on Peritoneal Dialysis was reviewed in a former study and the modes of treatment to treat this complication were established.\textsuperscript{[12-19]}

**Characteristics of Type- 2 Diabetes Mellitus**

Diabetes has fastly gained the status of the potential epidemic population in India with more than 62 million diabetic individuals currently diagnosed with the disease per day. According to “The International Diabetic Federation” (IDF) the prevalence of diabetes in our country is predicted to grow double from 171 million in 2000 to 366 million by the year 2030.

The Indian populations have been more prone to this disease due to the unique clinical and biochemical abnormalities which include increased insulin resistance, obesity (i.e. high waist circumference despite lower body mass index), lower adiponectin and due to the presence of high sensitive C-reactive protein levels.

Diabetes is a condition primarily defined by the level of hyperglycemia giving rise to risk of microvascular damage (retinopathy, nephropathy and neuropathy). It is associated with reduced life expectancy, significant morbidity due to specific diabetes related microvascular complications and diminished quality of life.

The type 2 DM also known as adult-onset or noninsulin-dependent diabetes, is usually marked as a stage of insulin resistance which thereby affects the glucose metabolism and at the same time it diminishes the β-cell mass and β-cell function thereby limiting the ability of the pancreas to maintain euglycaemia by increasing insulin secretion.

The below diagram represents the physiological changes that occurs during the abnormal increase of glycemic levels in the body.
The early manifestations of prediabetic dysglycaemia represent one or both of:

- impaired glucose tolerance (IGT), in which postprandial glucose control is impaired but fasting plasma glucose (FPG) is normal;
- impaired fasting glucose (IFG), in which a chronic elevation of FPG occurs in the absence of a deterioration in postprandial glucose control.\(^{[20]}\)

A simple blood test is sufficient to diagnose IFG, while a 75 g oral glucose tolerance test (OGTT) is required for the diagnosis of IGT. The originally used cutoff level for IFG (110 mg/dL [6.1 mmol/L]) was reduced to that shown in the below Table (100 mg/dL [5.6 mmol/L]) by an Expert Committee of the American Diabetes Association in 2003, in order to equalize the prognostic impact of diagnosis of IFG or IGT, in terms of the future risk of diabetes in a subject with either condition.\(^{[21]}\)

It should be noted that the World Health Organization (WHO) diagnostic criteria for IFG retains the 110 mg/dL (6.1 mmol/L) cutoff value for diagnosing IFG.\(^{[22]}\)

<table>
<thead>
<tr>
<th>Prediabetic state</th>
<th>FPG [mg/dl (mmol/L)]</th>
<th>2-h plasma glucose [mg/dl (mmol/L)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGT</td>
<td>&lt; 100 (&lt;5.6)</td>
<td>&lt;140(&lt;7.8)</td>
</tr>
<tr>
<td>IFG</td>
<td>100 – 125 (5.6-6.9)</td>
<td>140-199(7.8-11.0)</td>
</tr>
<tr>
<td>IGT</td>
<td>&lt;126 (&lt; 6.9 )</td>
<td>140-199(7.8-11.0)</td>
</tr>
<tr>
<td>Combined IFG/IGT</td>
<td>100-125(5.6-6.9)</td>
<td>140-199(7.8-11.0)</td>
</tr>
</tbody>
</table>

**TABLE**\(^{[23-27]}\)

FPG – fasting plasma glucose,
IFG- impaired fasting glucose,
IGT - impaired glucose tolerance,
NGT- normal glucose tolerance

**Principles for the Management of Type 2 – Diabetes Mellitus**

Since type 2 – DM is signature by the insulin resistance and b-cell dysfunction, life style modifications such as improved diet and regular moderate physical exercise with the aim of achieving weight loss in overweight helps to an extent.\[^{27}\] Those patients along with women, who were with a history of gestational diabetes, should be tested for the presence of causative agent for diabetes along with any other cardiovascular risk factors.\[^{28}\]

From various studies conducted, with evidence Metformin is the only optimal drug which remains as monotherapy.

Its low cost, proven safety records, balance over weight and its positive outcomes with the cardiovascular events makes Metformin to be preferred as the initial drug of choice.\[^{29,30}\]

Metformin is prescribed by the health care professionals even when the eGFR level is between 45-60ml/min/1.73m\(^2\), with respect to the dose adjustment with the renal clearance level. In situations, where Metformin remains contraindicated or not tolerated the second option is to switch to sulfonylureas (particularly glibenclamide) due to the risk of hypoglycemia.\[^{19}\]

Considering the double and triple combination therapy, SGLT2 inhibitors in combination with Metformin along with other drugs can be used, but less efficacy is noted when SGLT2 inhibitors is been given as combination along with DPP-4 inhibitors or GLP-1 receptor agonist. From recent studies, the combination therapy for the treatment of type 2 – DM obtains the beneficial outcomes of achieving the target glucose level than the monotherapy, more quickly by a matter of weeks or even months.\[^{31,32,33,34}\]

In a recent studied conducted by the American Diabetes Association and the European Association in the year 2015, it was found that patient who showed no achievement in obtaining the Glycosylated hemoglobin (HbAtc) target after three months of oral combination triple therapy was moved to injectables, GLP-1 receptor agonist along with basal insulin was demonstrated, for patients taking basal insulin with one or more oral agents whose diabetes remained uncontrolled the addition of GLP-1 receptor agonist or mealtime insulin showed a
progressive outcome. In case of refractive patients, TZD or SGLT2 inhibitors were considered.

The remainder of this review will focus in details on the therapeutic profile of Metformin for the management of prediabetes and other insulin-resistant states that predispose to the subsequent development of type 2 diabetes mellitus.

**Drug Profile of Metformin**

*Brand Names:* GLYCIPHAGE (500mg), DIAFORMIN (500mg)

Metformin falls under the category of biguanides, which lower the glucose level by insulin like effects on the tissues. Phenformin and Metformin are drugs which were introduced in the 1950s. Phenformin was withdrawn in many countries and has been banned in India since 2003 as it was found as the main cause of lactic acidosis in patient who were in diabetes mellitus treatment.[12]

Metformin is reported to improve lipid profile as well in type 2 DM, they mark its advantage over sulfonylurea by absences of hypoglycaemic conditions in non-diabetic patients.

**Mechanism of Action**

- It suppresses the hepatic gluconeogenesis by the activation of AMP activated protein kinase enzyme.
- It inhibits the glucose absorption from the intestines.
- In the presence of insulin it stimulates the peripheral uptake of glucose in tissues.
- It stimulates the glycolysis in the tissues.
- Reduces the glycogen levels in plasma.

**Pharmacokinetics**

Metformin is well absorbed in gut, and it’s duration of action is 6-8 hours, the plasma t\(^{1/2}\) is usually 1.5 to 3 hours, the daily dose is usually 0.5- 2.5g and maximum 2 to 3 number of doses per day can be taken, it is usually not metabolized and excreted unchanged in urine and in case of renal failure this drug gets accumulated and increases the risk of lactic acidosis.

**Adverse Effects**

Abdominal pain, anorexia, nausea, metallic taste mild diarrhea and tiredness are the common side effects. Overdosing of Metformin can cause hypoglycemia.
Rare cases of lactic acidosis can be caused, as it is poorly concentrated in the hepatic cells. Alcohol ingestion can precipitate the lactic acidosis condition.

Vitamin B12 deficiency is also reported due to long term use, by interfering with the absorption of Vitamin B12.

**DISCUSSION**

Our studies on the various articles proved that the long term use of Metformin induces vitamin B12 deficiency in the type 2 DM. It was noted that it was not a momentary measure but persistent and grows slowly.

The mechanism of vitamin B12 deficiency with Metformin is undoubtedly due to malabsorption of vitamin B12 at its absorption site in the terminal ileum.[2,3] In initial studies it was believed that Metformin caused proliferation of bacteria in the small bowel either due to an effect on intestinal motility or an increased intestinal glucose level.[35,36] In current studies Metformin shows an effect on calcium dependent membrane action in the terminal ileum, absorption of the vitamin B12 in the intrinsic factor complex is calcium dependent and usually when metformin is administered it interfere this absorption.[10,37,38]

Among various articles there were few which well supported the theory of vitamin B12 deficiency, one among them was the study conducted in the year 2010 by, Jolien de Jagern and his team in three non-academic hospitals in the Netherlands, they performed a randomized placebo controlled study in 390 patients who were on drug therapy of 850mg of Metformin for 3 – 4 months and the result of Metformin showed a higher point of 7.2 % in deficiency to vitamin B12 with the placebo, thereby they came to the conclusion that the deficiency of vitamin B12 lead to the increase of homocysteine concentration up to 5 %.[10]

Basically homocysteine falls under the category of non-essential amino acid which contains the sulfur group that is usually formed as the result of demethylation pathway of the methionine, and they are usually dependent on the vitamins (folate, vitamin B6, B12) as a cofactor or co substrate.

Homocysteine is synthesized by two metabolic pathways such as, remethylation and transsulfuration which are dependent on vitamin B12 and folate for methionine synthesis and on pyridoxal – 5- phosphate for cystathionine synthesis, when the diabetic patient has low
level of vitamin B12 it thereby causes the accumulation of homocysteine and thereby leading to the risk of cardiovascular diseases, stroke and venous thrombosis.

Such risk caused by hyperhomocysteinemia due to vitamin B12 deficiency in Metformin administrating patients was noted in a study conducted by Mahajan R and Gupta K in the year 2010, they recommended annual injections of vitamin B12 (in a dose of 1 mg) should be given to every patient on long-term Metformin therapy which will be more practical and cost-effective method as it will ensure replenishment of vitamin B12 stores for at least one year and they also obviate the need for annual screening of vitamin B12 levels.[40]

The study conducted by Donghoon Kang, Jae-Seung Yun and team during January 2012 to April 2014, in Korea came to a conclusion that patient above 60 years were most prone to induce vitamin B12 deficiency while taking Metformin in combination with higher dose of sulfonylurea than Metformin used along with insulin.[41]

In other various studies vitamin B12 deficiency is often preceded by the development of neuropathy, as in the nervous system vitamin B12 deficiency causes demyelination followed by axonal degeneration and neuronal death.

A team from Saudi Arabia, under the leadership of Najlaa Almaleki and Mohammad Ashraf during the year of 2009 – 2010, reported a case of Metformin-associated lactic acidosis in a patient with end-stage renal disease who was on peritoneal dialysis. The patient was successfully treated with hemodialysis. The mechanism of Metformin induced lactic acidosis was studied and it was explained as the conversion of glucose to lactate in the splanchnic bed and inhibition of hepatic gluconeogenesis from lactate, pyruvate, and alanine. Lactic acidosis usually occurs in comorbid conditions of renal, hepatic, cardiac and hemodynamic instabilities.[15,16]

When prevention considered, NICE recommends to review the dose of Metformin, if the value of serum creatinine > 130µmol/L or, if eGFR < 45ml/min /1.73m² at the same time NICE recommends to stop the usage of Metformin, if the serum creatinine value exceeds 150 µmol/L and if eGFR < 30ml/min /1.73m².[13,19]

In general, 1000µg of Vitamin B12 given annually is enough to replenish the body’s vitamin B12 stores in this category of patients, but there are no guidelines to address how often patients with Diabetes Mellitus should be supplemented with Vitamin B12.[42]
CONCLUSION

Metformin being a biguanide was first introduced in UK in the year 1958, and by the year 2009 the World Health Organization approved Metformin as the only oral Anti diabetic drug which showed maximum effectiveness in the treatment of Type 2 – Diabetes Mellitus.

Despite the advantages of this drug its long term usage resulted in Vitamin B12 deficiency. Annual measurement of serum vitamin B12 levels in patients on long-term Metformin therapy was recommended way back in 1970s. However, such facility for a large population of diabetic patients under Metformin therapy was in a dilemma.

Even though the Metformin showed a positive result in reducing the blood glucose level, the result of vitamin B12 deficiency in long term use of Metformin lead to the comorbid conditions such as hyperhomocystinemia, peripheral neuropathy, megaloblastic anemia, peripheral arterial thrombosis and lactic acidosis. While anemic conditions of vitamin B12 deficiency is reversible, the progress of the neuropathy is only arrested and not reversed with initiation of vitamin B12 therapy.

Even after measurement of low vitamin B12 levels, the differential diagnosis from other causes of vitamin B12 deficiency will be difficult to make.

REFERENCE


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