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Review Article

Dentistry Section

Long Term Use of Metformin and its Effect on Serum Vitamin B12 with its Oral Manifestations: A Review

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ABSTRACT

Metformin is the most frequently prescribed first line therapy for Type 2 Diabetes Mellitus (T2DM) and it is one of the fewer antihyperglycaemics associated with improvements in the morbidity and mortality of cardiovascular disease associated with T2DM. Although there are major beneficial effects but it is shown to have disadvantages with long-term use of metformin. Recent studies have shown that metformin induces malabsorption of Vitamin B12, which may increase the risk of developing Vitamin B12 deficiency. Vitamin B12 is one of the integral nutritional components that affect the oral health with individuals with decreased levels exhibit various oral manifestations such as glossitis, glossodynia, recurrent ulcers, angular cheilitis, dysgeusia, lingual paraesthesia, burning sensations and pruritis. Most of the vitamin B12 deficiencies are associated with malabsorption syndrome, gastrectomy cases, and elderly people. The prevalence of oral manifestations with regard to metformin induced Vitamin B12 has to be considered as new paradigm in routine diagnosis and investigations. This review likewise revolves around the mechanism involved in metformin induced vitamin B12 deficiency and possible implications in the diagnosis and management of oro-mucosal lesions associated with such deficiency.

Keywords: Antihyperglycaemics, Cobalamin, Oro-mucosal lesions, Type 2 diabetes mellitus

INTRODUCTION

Diabetes Mellitus (DM) is the commonest non communicable diseases in this era of development and globalisation. According to World Health Organisation (WHO) [1], the prevalence rate of Diabetes in India is 8.7% in the age group of 20-70 years. Diabetes affected 8.5 percent of persons aged 18 and above in 2014. Diabetes was the direct cause of 1.5 million fatalities in 2019, with 48 percent of all diabetes-related deaths occurring before the age of 70 years [2]. Diabetes caused a 5% rise in premature mortality rates (death before the age of 70 years) between 2000 and 2016. Diabetes-related premature mortality declined in high-income nations from 2000 to 2010, but then surged from 2010 to 2016. Diabetes-related premature mortality increased in lower-middle-income nations over both eras. In contrast, between 2000 and 2016, the global risk of dying from any of the four major non communicable illnesses (cardiovascular diseases, cancer, chronic respiratory diseases, or diabetes) between the ages of 30 and 70 fell by 18% [2]. The rising prevalence of diabetes amongst all other non communicable diseases in India is multifactorial, some of which constitute rapid urbanisation, sedentary sluggish lifestyle, unbalanced diet, usage of tobacco and alcohol consumption, obesity, lack of exercise etc. The Diabetes Research Centre in Madras conducted several investigations on the risk factors that contribute to T2DM in Indian population [3].

Previously DM was classified based on age at onset and therapy employed [4,5]. The American Diabetes Association [4,5] has revised the classification because each type could possibly have patients younger or older age group and the revised classification is based on the pathophysiology of DM and not the basis of treatment [5]. [Table/Fig-1] shows the revised classification of T2DM [4,5].

Non insulin hypoglycaemic therapies (non insulin hypoglycaemic agents) which are routinely used to treat hyperglycaemia in people with Type 2 Diabetes namely Biguanides (metformin), Sulfonylureas, Thiazolidinediones (e.g., pioglitazone), Alpha-glucosidase inhibitors (e.g., acarbose), Meglitinides (e.g., nateglinide), Dipeptidyl Peptidase (DDP)-4 inhibitors (gliptins), Glucagon-like peptide-1 agonists (exenatide, liraglutide), Amylin analogues (Pramlintide), Bile acid sequestrants (colesevelam) and Dopamine agonists (bromocriptine) [6-8].

Classification of diabetes
Type 1 diabetes (T1DM): (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency)
Type 2 diabetes (T2DM): (due to a progressive loss of β-cell insulin secretion frequently on the background of insulin resistance)
Gestational diabetes mellitus (GDM): (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)
Specific types of diabetes: due to other causes, e.g. monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the patients [MODY]), diseases of the exocrine pancreas (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation).

[Table/Fig-1]: Classification of Diabetes [4,5]

The most widely recommended drug for T2DM patients is Metformin (1,1-dimethylbiguanide). It has a proven therapeutic effectiveness, has an excellent safety profile, is low-cost, and is suggested as the first-line oral medication in T2DM in combination with lifestyle changes [9].

METFORMIN IN THE MANAGEMENT OF T2DM

Galega officinalis (also known as goat's rue) is a traditional herbal medication in Europe that was discovered to be high in guanidine, which was proved to reduce blood glucose in 1918. In 1920s and 1930s, Metformin and other guanidine derivatives were used to treat diabetes, but they were phased out owing to toxicity and greater insulin availability. In the 1940s, Metformin was rediscovered while looking for antimalarial drugs, and was found to be effective for the treatment of influenza and also lowering blood glucose [10].

It does this by lowering hepatic glucose synthesis and intestinal glucose absorption. Metformin is an outstanding therapeutic option with a highly favourable risk-to-benefit ratio that was first licenced by the Food and Drug Administration in 1994 and commercialised in 1995. To reduce Gastrointestinal (GI) side-effects, start with the lowest effective dose (500 mg twice daily orally) and gradually increase dosage [11]. The first-line for management of T2DM is Metformin [12,13]. Since, its approval in the United Kingdom in 1958 and the United States in 1995, metformin has become one of the most extensively used medications in the treatment of T2DM, with dosages ranging from 500-2,500 mg/day [14]. According to the

American Diabetes Association/European Association for the Study of Diabetes guidelines, it is the first-line oral therapy medication for people with T2DM [15]. Metformin improves glycaemic control in people with T2DM by improving insulin sensitivity in the liver and other tissues. The major consequence is a reduction in hepatic glucose synthesis and an increase in glucose excretion in the skeletal muscles [16]. Metformin improves insulin suppression of endogenous hepatic glucose synthesis and clearance in the fasting state, but not insulin-mediated glucose absorption in peripheral tissues, according to a systematic review of in-vivo investigations in humans. Metformin works in the liver [17-21], small intestines [22-24], and skeletal muscles [25,26] to assist glycaemic control. [Table/Fig-2] Shows the mechanism of action of metformin at different sites to improve glycaemic control and lower plasma glucose [17-26].

Mechanisnm of action of metformin	
Liver	
1.	Metformin suppresses gluconeogenesis by activating the serine/threonine kinase 11-5' AMP (adenosine monophosphate) activated kinase signalling pathway in 2001 [17]
2.	Metformin inhibits mitochondrial electron transport complex I, which inhibits gluconeogenesis irrespective of the AMPK (AMP-activated protein kinase) pathway, using knockout mice cells in 2010 [18]
3.	It also decreased adenylyl cyclase and glucagon-induced gluconeogenesis through increasing cellular AMP [19]
4.	They discovered in 2014, Metformin also reduced Selenoprotein P, a hepatokinase that limits mitochondrial glycerol phosphate dehydrogenase and the conversion of lactate and glycerol to glucose by activating AMPK [20,21]
Small intestine	
1.	In 2004, Metformin was found to increase plasma Glucagon-like peptide-1 (GLP-1) to improve glycaemic control [22]
2.	In 2015, they found that Metformin stimulates duodenal AMP kinase and reduces glucose synthesis [23]
3.	Metformin Delayed Release (DR) works mostly in the ileum, stimulating L-cells to produce more GLP-1 in the blood, lowering glucose production as found in 2015 [24]
Skeletal muscles	
1.	Metformin, as reported in 1990, promotes Glucose Transporter Type 4 (GLUT4) translocation to the plasma membrane, resulting in increased glucose absorption [25]
2.	Metformin stimulates the AMPK alpha 2 pathway in skeletal muscle and improves glucose clearance, according to a 2002 study [26]

[Table/Fig-2]: Showing mechanism of action of metformin at different sites to improve glycaemic control and lower plasma glucose [17-26].

Berchtold P et al., reported vitamin B12 malabsorption in patients treated with metformin for as little as three months in 1969 [14]. Based on a cross-sectional study, Tomkin GH et al., suggested annual serum B12 testing for all patients on long-term metformin medication as early as 1971 [15]. Since then, cross-sectional, retrospective, and longitudinal observational studies [27,28] as well as case reports [29,30] have revealed that long-term metformin use and vitamin B12 deficiency are linked [31,32]. However, there have been few prospective placebo-controlled trials to determine the risk of vitamin B12 deficiency in metformin-treated individuals, and none specifically in prediabetic persons. The majority of randomised trials on this topic have been modest or short-term (six months) and have mostly involved patients with type 2 diabetes [33]. [Table/Fig-3] shows the previous studies about Metformin Induced Cobalamin Deficiency (MICD) and the prevalence according to those studies [14,15,28-30,34-36].

Authors and place	Year and type of study	Known prevalence rate of Metformin Induced Cobalamin Deficiency (MICD)
Berchtold P et al., [14] in Chicago, USA	1969 and a case report	Reported that vitamin B12 malabsorption in patients treated with metformin for as little as three months
Tomkin GH et al., [15] in Boston, USA	1971 and review article	Based on a cross-sectional study, annual serum B12 testing for all patients on long-term metformin medication.
de Groot-Kamphuis DM et al., in Tehran, Iran [27] and Kos E et al., in San Jose, USA [28]	• 2013 and an analytical case-control study • 2012 and a review article respectively	• In their study, the overall prevalence of vitamin B12 concentrations <150 pml/l was 9.7% • In type 2 diabetes patients not taking metformin the prevalence was 4.4% compared with 14.1% in metformin users. • Their study by Kos E et al., confirms the higher prevalence of vitamin B12 deficiency in metformin-treated patients with type 2 diabetes than in those not treated with metformin and Vitamin D insufficiency is not a clinical problem in metformin-treated type 2 diabetic patients, and metformin has no effect on vitamin D deficiency therapy in these individuals.
Tung ML and Tan LK [29] in Rochester, USA and Liu KW et al., [30] in Hannover, Germany	• 2014 and a review article • 2006 and a review article respectively	In their Reviews and case reports they found that "Metformin's adverse effects such as lactic acidosis and Gastrointestinal (GI) side-effects are well-known. The accompanying vitamin B12 deficiency, on the other hand, is less widely known."
Sampson Omagbemi Owhin et al., in Nigeria [34]	2019, case-control, prospective, analytical, observational study	• In their study, they reported that vitamin B12 deficiency was found in 41% of metformin-treated type 2 diabetic patients and 20% of non metformin type 2 diabetes patients, respectively. • Vitamin B12 deficiency was found in 59 percent of metformin-treated patients and 80 percent of non metformin patients.
Gayathri Devi Krishnan et al., in Malaysia [35]	2020 and original research	In their study, Vitamin B12 deficiency was found in 28.3% of metformin-treated individuals with type 2 diabetes.
Miyan Z and Waris N in Karachi, Pakistan [36]	2020, and a prospective multicentre observational study	Their study revealed that overall, metformin users had considerably greater B12 deficiency (200 pg/mL) than non metformin users, but metformin users had significantly lower B12 insufficiency (200–300 pg/mL) than non metformin users.

[Table/Fig-3]: Showing the previous studies about Metformin Induced Cobalamin Deficiency (MICD) and the prevalence according to those studies [14,15,28-30,34-36].

VITAMIN B12 SERUM DEFICIENCY AND ITS IMPLICATIONS

Vitamin B12, also known as cobalamin, is a water-soluble vitamin that is essential for Deoxyribonucleic Acid synthesis, proper haemopoiesis, and neurological function. As a result, the clinical picture of vitamin B12 insufficiency is dominated by haematological and neurocognitive impairment [37]. Dietary vitamin B12 binds to the R-protein secreted by the salivary glands after it is released. Proteolytic breakdown of the vitamin B12-IF (intrinsic factor) complex is extremely difficult. The complex binds to specific receptors on the mucosa of the terminal ileum, a place where it can be found [37,38]. Vitamin B12, as a co-factor, facilitates the conversion of methyl malonyl coenzyme A (CoA) to succinyl-CoA in another important enzymatic route; resulting in an increase in serum methylmalonic acid (MMA). Following this, the neuronal membranes' fatty acid production is disrupted [39]. Vitamin B12 is also required for the production of monoamines, or neurotransmitters, such as serotonin and dopamine [40]. Vitamin B12 deficiency interferes with this production. Because of its cellular and vasculotoxic effects, hyperhomocysteinemia has been linked to an increased risk of cardiovascular events [41-43]. For absorption, vitamin B12 forms a compound with the cubulin (endocytic) receptor in the ileum. The ileal cell surface ordinarily takes this B-12 endocytic receptor complex via a calcium-dependent mechanism. Metformin binds to the B12-cubulin complex and gives it a positive charge, altering membrane potential and competitively repelling divalent calcium ions, limiting calcium-dependent uptake and resulting in B12 malabsorption, for which calcium supplementation has been used to treat some patients with metformin-induced B12 insufficiency [44,45].

Diagnosis of Metformin Induced Vitamin B12 Deficiency in T2DM

There are currently no published guidelines advocating for routine vitamin B12 deficiency screening in T2DM patients. However, it is

clinically reasonable to screen for vitamin B12 deficiency in type 2 diabetic patients prior to starting metformin and then annually in elderly patients with a history of long-term metformin use (≥3-4 years), high-dose metformin use (≥2 g/day), and clinically worsening diabetic distal polyneuropathy in the presence or absence of the discussed haematological abnormalities [46].

The method for detecting vitamin B12 insufficiency in diabetic patients and the general public is comparable. The preliminary screening step for vitamin B12 deficiency should be the measurement of serum vitamin B12 concentrations. Concentrations of less than 200 pg/mL are usually indicative of deficiency in vitamin B12 while values are >400 pg/mL ensure that there is no vitamin B12 deficiency [47]. In type 2 diabetes, patients with borderline serum vitamin B12 concentrations of 200-400 pg/mL and modest haematological symptoms, measuring serum MMA or homocysteine concentrations is a more sensitive and specific technique for screening. Serum homocysteine and MMA values of 5-15 mol/L and 0.28 mol/L, respectively, are considered normal [46,48]. Despite the fact that the medical literature is unclear about who should be monitored for MICD and how often, we believe that MICD should be suspected in all metformin-treated diabetic patients who have one or more of the following findings in their medical history, clinical signs, or laboratory studies:

- On a peripheral blood smear, oval macrocytic red blood cells ((Mean Corpuscular Volume (MCV) >100 fL) with or without anaemia. One of the characteristics of (cobalamin and folate insufficiency is an increase in red blood cell MCV (macrocytosis), while other reasons are also acquired (i.e., alcoholism, liver disease, hypothyroidism, myelodysplastic syndromes, drugs, etc.,) [46,48].
- On a peripheral blood smear, the presence of hypersegmented neutrophils (i.e., >5% of neutrophils with five lobes or 1% of neutrophils with 6 lobes) [48].
- An unknown cause of pancytopenia (a combination of anaemia, thrombocytopenia, and neutropenia).
- Unexplained neuropsychiatric symptoms, including dementia or weakness, sensory ataxia, and paresthesias, or clinically exacerbated established diabetic peripheral neuropathy [49,50].
- Elderly diabetic patients with long-term (≥3-4 years) high-dose (≥2 g per day) metformin use, especially if complicated by peripheral neuropathy, with or without haematological manifestations of cobalamine deficiency, and with or without everyday utilisation acid-suppressive drugs (as H2-receptor antagonists, antacids, proton pump inhibitors) [51]

SYSTEMIC MANIFESTATIONS OF VITAMIN B12 DEFICIENCY

[Table/Fig-4] shows different systemic manifestations of Vitamin B12 deficiency [46,52-58].

ORAL MANIFESTATIONS OF VITAMIN B12 SERUM DEFICIENCY

As aforementioned, vitamin B12 deficiency has an impact on oral health, and the following are some of the oral signs recorded in the literature such as glossopyrosis, glossitis, and glossodynia cause a beefy red tongue that appears smooth and shiny. Hunters' glossitis or Moeller's glossitis, which is related to pellagra's "Bald tongue of sand with", Recurrent Aphthous Stomatitis (RAS), Haemorrhagic gingiva, ulcerative gingivitis, gingival manifestations of Vitamin B12 deficiency, oral mucosa epithelial dysplasia, oral paraesthesia, and delayed wound healing and burning mouth syndrome [58-61].

Vitamin B12 Deficiency and Glossitis

Atrophic glossitis is caused by a vitamin B12 deficiency and manifests as a bright red, smooth, painful, and burning tongue [59-61]. Kim J et al., compared clinical aspects of vitamin B12 insufficiency patients with a medical history of gastrectomy to those without a history of gastrectomy in research including twenty-two individuals [62]. The most common symptom was depapillation of the tongue. They concluded that individuals with glossodynia, especially those with normal oral mucosa and/or no history of gastrectomy, should be evaluated for Vitamin B12 deficiency [62].

A case of a 61-year-old lady with a six month history of a persistent burning sensation on the tongue was described by Stoopler ET and Kuperstein AS in 2013 [63]. Glossitis was identified after clinical examination revealed depapillation of the tongue. Laboratory tests revealed macrocytic anaemia and low vitamin B12 levels, prompting the patient to have a vitamin B12 injection; which completely resolved her symptoms. They recommended that glossitis might be the only symptom, and that the oral physician should handle the situation properly [63].

Systemic manifestations of vitamin B12 deficiency	Literature search and review analysis
Haematological symptoms [52,53]	
-Megaloblastic anaemia -Pancytopenia (a combination of anaemia, leukopenia, thrombocytopenia)	• A serum vitamin B12 level of 200-900 pg/mL is considered normal, but a value of 300-350 pg/mL is recognised as a signal for good health in the elderly. • Low blood vitamin B12 levels or increased serum Methylmalonic Acid (MMA) and homocysteine levels are frequently used to make the diagnosis in the lab [52,53]. • Homocysteine elevation is a key indicator of vitamin B12 and/or folate insufficiency. Classic clinical signs such as megaloblastic anaemia, which are usually late clinical indicators of severe deficiency, do not always emerge with modest deficiencies [53].
Neurological manifestations [46,54,55]	
-Paraesthesia -peripheral neuropathy -Combined system disease (demyelination of dorsal columns and corticospinal tract)	• Vitamin B12 and folate deficiencies are frequently linked to depression, dementia, and mental impairment, especially in the elderly [54]. • The transmethylation of neuroactive components like myelin and neurotransmitters is dependent on vitamin B12 and folic acid (hypomethylation hypothesis) [55]. • There are various views on the relationship between depression and vitamin B12 and folate levels [55]. • Vitamins B12 and folate are involved in the synthesis of monoamine neurotransmitters like dopamine and serotonin, as well as single carbon transfer methylation reactions linked to their production. • These monoamine neurotransmitters are implicated in the pathophysiology of neuropsychiatric disorders like depression and psychosis [46].
Psychiatric manifestations [56,57]	
-Irritability, Personality changes -Mild memory impairment, Dementia -Depression -Psychosis	Consciousness disturbances, delirium, and cognitive impairment are all symptoms of mental illness or organic brain disease [56,57].
Cardiovascular symptoms [58]	
-Possible increased risk of myocardial infarction and stroke.	Vitamin B12 insufficiency is linked to a number of atherogenic processes, the majority of which are caused by hyperhomocysteinemia caused by vitamin B12 deficiency [58].

[Table/Fig-4]: Showing different systemic manifestations of Vitamin B12 deficiency [46,52-58].

In 2009, Pontes HA et al., reported on a 41-year-old female patient who followed a rigorous vegetarian diet [64]. On clinical examination, the tongue's dorsal and lateral margins exhibited pale mucosa, atrophic glossitis, and numerous erythematous patches and substantial B12 deficiency was discovered during a haematological investigation. Although history and clinical examination assisted in the diagnosis of megaloblastic anaemia, the authors advised to be keen about oral manifestations [64].

In 2009, Graells J et al., described four cases of oral linear lesions caused by vitamin B12 deficiency that were devoid of neurologic signs and anaemia [65]. They proposed that glossitis with linear lesions might be an early clinical symptom, and that serum levels should be checked even if anaemia is not present [65].

Hunter's Glossitis and Vitamin B12 Deficiency

Hunter's glossitis is a well-known oral symptom of B12 deficiency that begins as diffuse bright red areas ("beefy red") and proceeds to atrophic glossitis. The dorsal and ventral surfaces, as well as the tongue's edge, are the most common sites for lesions. The mucosa of the palatal, buccal, and labial mucosa can also be damaged, with lesions showing as linear, band-like, or irregular erythema [64]. As reported by Pontes HA et al., Graells J et al., in 2009 and Flores IL et al., the dorsal and ventral surfaces, as well as the tongue's margin, are the most common sites for lesions [64-66]. The mucosa of the palatal, buccal, and labial mucosa can also be damaged, with lesions showing as linear, band-like, or irregular erythema.

Recurrent Aphthous Stomatitis (RAS) and Vitamin B12 Deficiency

Vitamin B12 is a co-enzyme that helps in glucose metabolism, protein synthesis, and haematopoiesis. Changes in the oral mucosa, such as stomatitis and glossitis, have recently been reported to represent the sole early oral indication of vitamin B12 insufficiency. It's unknown what function vitamin B12 deficiency has in the aetiology of RAS. RAS cell-mediated immunity is thought to be reduced in people with RAS, and alterations in the oral epithelium of the tongue and buccal mucosa have been seen. These alterations resemble those found in the bone marrow and blood as a result of aberrant DNA synthesis [67-69].

The efficacy of daily dose in the therapy of people with RAS was investigated by Liu HL et al., in research published in 2013 [67]. The findings revealed a substantial improvement in RAS in the study group when compared to the control groups, indicating that supplementary medicines may be effective in both short and long-term RAS management.

In 2011, Qazi JA; conducted research on 65 RAS patients to validate the therapeutic benefits of Vitamin B12 in RAS patients [68]. Regardless of blood vitamin B12 levels, the number, length, and size of ulcers were reduced in the group treated with vitamin B12 1000mcg compared to the other group treated with 500 mcg. Regardless of their blood Vitamin B12 levels, the authors recommended that Vitamin B12 1000 mcg taken sublingually is a safe and effective therapy.

In 2010, Kozlak ST et al., conducted a study on the effects of dietary vitamin consumption in RAS patients [69]. The authors concluded that the existence of a deficit permits the development of an underlying inclination to ulceration, and that dietary intake may prevent instances of ulceration breakout in RAS patients.

Vitamin B12 Deficiency and Oral Premalignant Disorders and Malignancies

Several studies have found a link between low systemic levels of vitamin B12 and/or folate and an increased risk of cancer in oral epithelial tissues in those who are at risk [70]. Gorgulu O et al., conducted a study on 60 people in 2010 to investigate the role of serum homocysteine, folate, and vitamin B12 levels in the pathogenesis of Laryngeal Squamous Cell Cancer (LSCC) by measuring serum levels, and found that these levels are linked to metabolic changes in cellular metabolism, which lead to carcinogenesis [71]. In 68 Oral Submucous Fibrosis (OSMF) patients, Wang YP et al., looked at gastric parietal cell antibody positivity, serum iron, vitamin B12, and folic acid deficits [72]. However, the cause of lower serum levels of Vitamin B12 in OSMF patients remains unknown [72].

Vitamin B12 Deficiency and Oral Lichen Planus (OLP)

In a study conducted by Chen HM et al., the relationship between iron, folic acid, and vitamin B12 deficiency and homocysteine level was assessed in 352 OLP subjects, and it was found that OLP patients had a higher frequency of haemoglobin, iron, or vitamin B12 deficiency, as well as abnormally elevated blood homocysteine level than control participants [73].

MANAGEMENT OF VITAMIN B12 DEFICIENCY

Patients in the United Kingdom are currently treated with injectable cobalamin according to the following guidelines, regardless of the underlying cause [74]. Hydroxocobalamin 1 mg on alternate days for two weeks is the standard prescription for people with no neurological damage, followed by three-monthly injections of hydroxocobalamin 1 mg [74]. If patients have pernicious anaemia, patients should follow this regimen for the rest of life. If the deficiency is caused by something else, treatment should be continued until the haematological indices improve significantly. If the patient has significant neurological symptoms, is present, or the diagnosis is unclear, he or she should be sent to secondary care. If there is a suspicion of malabsorption, gastric cancer, or celiac disease, patient should see a gastroenterologist. Treatment of underlying problems, such as antibiotics for bacterial overgrowth [75] and the discontinuation of offending medicines, can often be beneficial [74,75]. The discovery of an alternative IF-independent mechanism for vitamin B12 absorption 60 years ago resulted in the finding that big enough doses, in the range of 100-100,000 g (even though only 1% of the cyanocobalamin was absorbed), were sufficient to meet the daily need [76].

In two separate trials, Andrès E et al., proved the efficacy of oral cobalamin in alleviating both biochemical and clinical signs of vitamin B12 insufficiency [76,77]. Furthermore, in both groups, a similar proportion of participants showed improvement in neurological symptoms such as bilateral paraesthesia and ataxia (22 percent in the oral arm vs 27 percent in the intramuscular arm). Castelli MC et al., used a similar design to get similar results when they gave 1,000 g orally per day [78].

METFORMIN AND CANCER RISK

Metformin preferentially destroys cancer stem cells and inhibits tumour growth, according to Hirsch HA et al., [79]. Metformin was also found to have a synergistic effect with chemotherapeutic medicines in nude mice, reducing tumour bulk and prolonging remission. When compared to other antidiabetic medicines, meta-analyses of metformin and cancer risk in diabetic patients found that metformin users had a one-third lower total cancer risk and cancer mortality [79,80]. The results of trials comparing metformin to placebo or normal treatment, as well as trials lasting more than a year, did not favour metformin. The confidence intervals, on the other hand, were broad, and there was a lot of clinical heterogeneity between the studies when it came to the comparators. In addition, there was insufficient data to investigate particular cancer outcomes. Another significant drawback was the little follow-up time (average 4.1 years). Metformin's favourable effect on cancer risk was observed in most observational studies when the medicine was administered for more than five years [80,81].

CONCLUSION(S)

Analysis of serum Vitamin B12 in T2DM patients treated with metformin to rule out vitamin B12 deficiency in metformin-induced

cobalamin deficiency is highly essential to ensure general wellbeing to rule out all neuro-psychiatric ailments to oral manifestations. Few studies conclude any inter relationship between the above two factors and derive the results about the metformin induced vitamin B12 deficiency. To test the idea that metformin has an anticancer impact, long-term randomised clinical trials particularly designed to establish metformin's influence on cancer risk are much needed. The risk factors discovered have relevance for metformin-treated patients' screening and preventative methods for their general euphoria.

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