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A REVIEW ON METFORMIN INDUCED GASTRITIS AND VITAMIN B12 DEFICIENCY

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ABSTRACT

Diabetes is one of the major non-communicable diseases affects many individuals worldwide. A significant threat to global health is posed by the epidemic of diabetes mellitus and its sequelae. Adults with diabetes mellitus are expected to increase by 20% in wealthy countries between 2010 and 2030. Between 1980 and 2014, four times as many persons worldwide had diabetes mellitus. The number of individuals (20-79 years old) estimated to have diabetes mellitus, with a focus on the top three nations or territories for this statistic in 2015. Metformin-induced gastroenteritis Data indicates gastrointestinal (GI) problems). To Treat diabetes many treatments are available, if untreated will be devastating for the individual, including diabetic retinopathy, diabetic nephropathy etc. Out of the available therapies, metformin, a class of biguanide drug, is used regularly for the treatment of diabetes as it is economical and has weight-neutral effects. Due to long-term consumption of metformin, several side effects were implicated. Out of these side effects, gastroenteritis and Vitamin B12 are being overlooked. In this review we have highlighted metformin-induced gastroenteritis and deficiency of cobalamin and mentioned few clinical studies for the same.

KEYWORDS: Gastroenteritis, Vitamin B12, Metformin, Diabetic Nephropathy, Diabetic Retinopathy.

INTRODUCTION

Diabetes Mellitus (DM), also known as diabetes, is a metabolic disorder characterised by high glucose levels over a long period, a defect in insulin secretion, insulin activity, or both.[1] It is among the top 10 causes of death with cardiovascular disease (CVD), respiratory disease, and cancer, and it is one of the most significant global problems of the twenty-first century.[2] According to the World Health Organization (WHO), diabetes caused 1.6 million fatalities in 2019, making it the ninth biggest cause of noncommunicable disease (NCDs) deaths worldwide.[3] It is the most common endocrine condition, and by 2010, it is expected that more than 200 million people globally will have DM, with 300 million having the disease by 2025.[4]

Etiology

The Latin term "diabetes" comes from the Ancient Greek word "diabetes," which means "a passage through; a syphon.".[5] That term, with the planned meaning of "exorbitant release of urine," was used by the early first-century CE Greek physician Aretaeus of Cappadocia to describe the illness. The Latin word Mellitus, which means "Mellitus," is where the word Mellitus gets its name (i.e. sweetened with honey, nectar sweet).[6] Thomas Willis, who observed that diabetics' pee had a sweet flavour, added "Mellitus" to "diabetes" as an assignment for the infection in 1675. (Glycosuria). Ancient Greeks, Chinese, Egyptians, Indians, and Persians noticed that pee had a delicious flavour.[7]

History of Diabetes

Diabetes was one of the first diseases mentioned, with an original Egyptian copy from around 1500 BCE describing "excessively remarkable urine exhaustion".[8] Type 1 diabetes is the cause of the cases initially shown. Indian doctors identified the illness and called it madhumeha, or "nectar pee," after discovering the pee that would attract ants.[9] Aretaeus of Cappadocia, who first used the term diabetes in the second century AD, gave the first precise description of diabetes. Thomas Willis, who first used the term "Mellitus" in the 17th century, made a statement about the sweetness of diabetes patients' urine.[10] French physiologist Claude Bernard's research on the glycogenic function of the liver in the 19th century helped to shed light on the process of gluconeogenesis and advance the study of diabetes.[11] Minkowski and von Mering performed a pancreatectomy on a dog in 1889, and the dog developed diabetes, demonstrating that the pancreas was an internal secretory gland crucial for maintaining glucose homeostasis.[12] Frederick Banting and Charles Best extracted insulin from pancreatic islets. They administered it to type 1 diabetic patients in 1921, saving millions of lives and ushering in a new era in diabetes therapy.[13]

Classification of diabetes

Type 1 diabetes mellitus or Insulin Dependent Diabetes Mellitus (IDDM)

In this type, the pancreas either produces no insulin or does so improperly.[14] It is sometimes referred to as juvenile diabetes or early-onset diabetes. Type 1 diabetes is less pervasive than type 2 diabetes; in fact, it accounts for only 10% of all diabetes cases.[15] The exact cause of diabetes mellitus is unknown, but in most people, there is evidence of an autoimmune mechanism involving auto-antibodies that destroy beta islet cells.[16] Antibodies that recognise the autoimmune mechanisms that result in beta-cell death, such as those targeting anti-glutamic acid decarboxylase, islet cells, or insulin, are typically present in type 1 diabetes.[17] Insulin secretion is severely reduced or absent due to pancreatic β-islets cell destruction. Insulin injections are required as treatment.[16]

Type 2 diabetes mellitus or Non-Insulin Dependent Diabetes Mellitus

Adult-onset diabetes is another name for type 2 diabetes mellitus; against the backdrop of insulin resistance, the increasing insulin secretary malfunction.[18] Insulin resistance is a serious complication for people d of diabetes.[19] Long-term complications in the vascular system, kidneys, eyes, and neurons affect both forms and are the main contributors to morbidity and mortality from diabetes.[20] The causes are multiple-faceted, and potential complications include obesity, low physical activity levels middle-aged and older persons and genetics. As a result, these patients are more likely to experience macrovascular and microvascular problems.[21]

Epidemiology of diabetes

A significant threat to global health is posed by the epidemic of diabetes mellitus and its sequelae. In 2015, the International Diabetes Federation (IDF) estimated that one in every eleven adults aged 20 to 79 years (415 million adults) worldwide had diabetes mellitus.[22] By 2040, this figure is anticipated to climb to 642 million, with the most significant increases occurring that are experiencing economic transitions from low-income to middle-income status.[22] Since1990, there has been a substantial rise in the prevalence of diabetes-related disabilities, with increases among those between the ages of 15 and 69 showing the most significant rise.[23] According to the Global Burden of Diseases, Injuries, and Risk Factors Study 2015, a high fasting blood sugar level was the tenth most prevalent risk factor globally in 1990, the fourth most prevalent in 2005, and the third most prevalent in 2015, accounting for 143 million DALYs and a 22% increase in DALYs from 2005 to 2015.[24] The projected global prevalence of untreated adult cases of diabetes mellitus is 45.8% (or 174.8 million cases).[25] and complications are more likely to occur in those with undiagnosed and untreated diabetes mellitus than in those who are receiving treatment.

Between 1980 and 2014, four times as many persons worldwide had diabetes mellitus.[26] Adults with diabetes mellitus are expected to increase by 20% in wealthy countries between 2010 and 2030. In contrast, they are expected to rise by 69% in underdeveloped nations.[27]

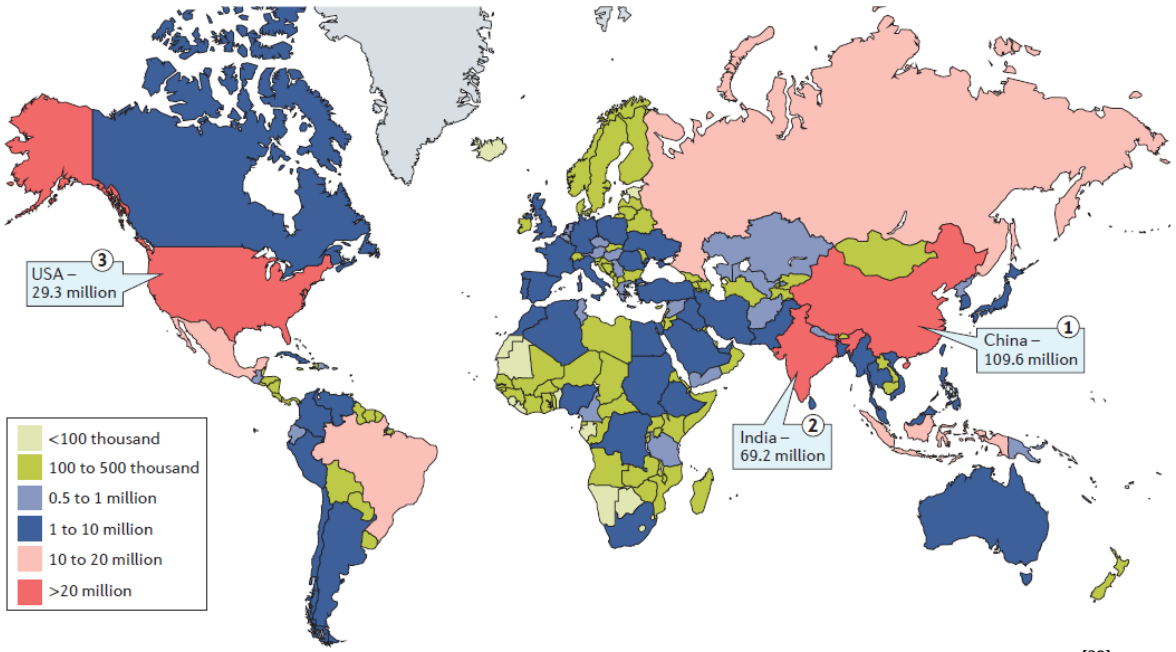

Figure 1: The top two major T2DM population centres worldwide are in China and India.[28]

Metformin

The most popular diabetes medication on the market is metformin, used primarily in obese and overweight people and the ideal remedy for monotherapy. A member of the biguanide class of drugs, metformin (1.1-dimethyl biguanide hydrochloride) is a guanidine derivative.

Diabetes was treated with the bioactive component obtained from the French lilac plant (*Galega officinalis*) in mediaeval Europe. It is the sole biguanide derivative on the market and the only oral anti-diabetic medication used to treat Type-2 diabetes uncontrolled by a balanced diet, especially in obese people.[29] The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) both recommended it as the first medicine of choice because of its safety, affordability, and weight-neutral effects.[30] Metformin has been used in Europe since 1957 and in the US since1994, when the FDA approved it. However, significant developments in our understanding of the clinical pharmacokinetics of metformin have only been made in the last 20 years.[31]

Mechanism of action

Metformin improves insulin sensitivity and reduces hepatic gluconeogenesis by phosphorylating GLUT enhancer factors and increasing glucose absorption.[32] The weight-loss drug metformin also reduces blood LDL cholesterol and triglycerides in a moderate amount.[33] The Organic Cation Transporter-1 is used by metformin to get access to hepatocytes (OCT-1) and works by activating AMP-activated protein kinase, among the enzymes responsible for the generation of hepatic gluconeogenic genes, in addition to inhibiting mitochondrial complex one and the enzyme glycerophosphate dehydrogenase in the mitochondria.[34] These cause levels of glucose and HbA1c to decrease. Metformin has little effect on β cells if weight is not reduced and muscles' insulin sensitivity does not improve. In addition, HbA1c levels gradually climb after initially lowering. Enteroendocrine cells in the stomach emit the peptides glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), which are thought to play critical roles in the elimination of glucose after meals.[35] Glucose synthesis is lowered by reducing gluconeogenesis[36] or breaking glycogen.[37] Metformin increases the translocation of glucose transporters 1 and 4 to the plasma membrane in skeletal muscles and adipose tissues when insulin is present.[38] In the small intestine, metformin concentrations are higher. It may also reduce the amount of glucose absorbed in the gut, affecting postprandial hyperglycemia.[39]

The side effects of metformin

Metformin has a history of being safe and efficient and is typically well tolerated. But, due to the drug's detrimental consequences, many individuals cannot endure it. Consequently, thorough knowledge of metformin's side effects and safety is necessary for optimal use.[40] The adverse effects of taking oral metformin might vary from slight to severe. The typical adverse effects are asthenia, myalgia, upper respiratory tract infection, changed or metallic taste, heartburn, headache, agitation, chills, dizziness, fatigue, nausea, diarrhoea/constipation, and abdominal cramps or pain.

Metformin induced gastroenteritis

Data indicate gastrointestinal (GI) problems.[41] With metformin therapy are primarily encountered. Participants who took metformin reported experiencing GI symptoms on average 28 % more frequently than those who took a placebo (16 % more regularly, p=0.01) than those who took the latter.[42] The phenomenon underlying metformin-induced GI intolerance remains unknown. Several hypotheses have been put forth, including serotonin secretion stimulation in the intestines, changes to incretin and glucose metabolism, and bile salt malabsorption. There are certain structural parallels between metformin and 5-hydroxytryptamine 5-HT3 receptor selective agonists, which are both transported by the serotonin reuptake transporter (SERT). The symptoms of nausea, vomiting, and diarrhoea brought on by the release of serotonin (5-hydroxytryptamine (5-HT)) from the intestine are comparable to those associated with metformin intolerance. The altered serotonin transport or a direct metformin serotonergic action may be one of the underlying mechanisms of metformin-induced GI discomfort. Metformin increased the release of serotonin (5-HT) from enterochromaffin cells, according to a duodenal biopsy study on metformin-naive individuals.[43] Metformin is absorbed by SERT or Organic Cation Transporter (OCT1), which reduces serotonin transfer and causes GI side effects. Metformin inhibits intestine uptake of glucose, which occurs more distantly. It promotes the use of intestinal glucose, particularly anaerobic metabolism, which has been shown to lower glucose uptake in animals and people in recent studies.[44]

A stomach-derived orexigenic peptide called ghrelin is discovered in amounts that vary in connection to food intake, obesity, and diabetes management, indicating a possible physiological function. There is a pre-prandial peak and a postprandial reduction in plasma ghrelin levels. However, there are contradictory studies regarding how metformin treatment for type 2 diabetes affects ghrelin concentrations: a correlation with elevated plasma ghrelin concentrations has been discovered[45], following a glucose load, with reduced plasma ghrelin levels[46] and without any notable modifications.[47]

Case Studies adapted from Subramaniam et al. 2021[48]

Case Study 1

A 63-year-old woman with 17 years of documented diabetes and decent glycemic control had an unexpected weight loss of 10 kg the previous year. She experienced developing dyspepsia and sporadic, self-limiting, small-volume, painless diarrhoea at the same time. She had a healthy diet and lifestyle. She underwent evaluations from a primary care physician, a gastroenterologist, and a psychiatrist for the aforementioned problems and was diagnosed with diabetic diarrhoea. Her BMI was determined to be 23.5 kg/m2, and her blood pressure was normal. She had no lymphadenopathy, and an

examination of her systems revealed nothing unusual than distal sensory neuropathy in her lower extremities. She underwent an evaluation due to a concern for autonomic neuropathy. She had a sinus rhythm on an ECG, no postural drop in blood pressure, and normal heart rate fluctuations with heavy breathing.

Metformin discontinuation was tested in this study. Within the first week, she improved. She gained weight, the diarrhoea subsided, and the dyspepsia subsided since her last check-up. She failed to control her blood sugar with higher doses of a sulfonylurea or a sodium-glucose cotransporter 2 (SGLT2) inhibitor. Therefore, a combination of insulin degludec and insulin as part was administered.

Case Study 2

A 74-year-old woman with type 2 diabetes for a long time approached for treatment. She had been experiencing bouts of moderate, watery, solid, and unformed diarrhoea brought on by meals for 1.5 years, along with faecal incontinence. A gastroenterologist extensively examined her, identified her as having irritable bowel syndrome, and recommended an antipsychotic to treat it.

She was examined and found thin, normotensive, and free of any signs of poor assimilation. Tests of her involuntary physiologic processes and anal tone both came back normal. She was advised to stop taking metformin for a few weeks. Instead, a small amount of sulfonylurea was administered. During her most recent appointment, she had gained weight, and her diarrhoea had significantly improved.

Case Study 3

Despite eating enough calories, a 60-year-old man with long-standing diabetes who did not smoke was concerned about gradual, accidental weight loss without any constitutional symptoms. A gastroenterologist examined him for this issue, but there was no underlying cause.

He was found to be extremely sick and to be free of organomegaly and lymphadenopathy. After a few weeks of the trial of not consuming metformin, he began to exhibit improvements in his condition. He gained about three kilogrammes since his previous visit.

Table 1: Patient Information for Cases 1–3 for metformin induced gastroenteritis in detail.

	Age, years/ Sex	Diabetic Status at the Beginning of Symptoms (years)	Symptoms	Drugs at the First Signs and Symptoms	Weight, kg/BMI, kg/m2)	Mean A1C During Symptoms (%)	Complications	Tests	Endoscopy	Duration until Symptoms Disappear Upon Restricting Metformin	Months of Follow-up/Weight profile	Medication Upon Restricting Metformin
Case 1	63/ Female	17	Weight loss of 10 kg, ongoing pain-free diarrhoea, a year of dyspepsia	Vildagliptin 100 mg/day, metformin XR 2 g/day, glimepiride 0.5 mg/day, chlorthalidone 12.5 mg/day, rosuvastatin 5 mg/day	58/23.5	6.8	Moderate retinopathy without any albuminuria; both AJ absent; SW test sensation absent	TSH 3.2 mIU/ L; stool examination Normal. stool culture Negative. Chest radiography: normal. HIV: negative	Upper GI with duodenum Biopsy normal. colonoscopy normal	1 week	12/ gained 6 kg	Vildagliptin 100 mg/day, $I_{Deg}/_{Asp}$ 0.5 units/kg
Case 2	74/ Female	18	Pain-free postprandial diarrhoea with faecal incontinence, one and half years of dyspepsia	Metformin SR 1.5 g/day, Teneligliptin 20 mg/day, clopidogrel 75 mg/day, Nebivolol 5 mg/ day, calcium carbonate 500 mg/day, alprazolam 0.5 mg/day	65.4/ 21.5	6.4	No retinopathy, microalbuminuri. both AJ absent; SW test sensation present	TSH 4.5mIU/L. CEA normal. CT abdomen no Abnormality. stool examination: normal	Colonoscopy normal	5 days	6/gained 4.4 kg	Glimepiride 0.5 mg/day, teneligliptin 20 mg/day
Case 3	60/ Male	24	8 kg of body mass is lost in 8 months.	Glimepiride 2 mg/day, metformin SR 2 g/day, teneligliptin 20 mg/day, glargine insulin 16 units/day	63.6/ 23.1	7.5	No retinopathy, Microalbuminuria. both AJ absent; SW test absent sensation	SH 5.1 mI U/L; MRI abdomen Normal. chest radiography normal; HIV negative; FDG PET negative	Upper GI endoscopy normal	1 week	6/gained 3 kg	Glimepiride 4 mg/day, basal bolus insulin 0.4 units/kg

AJ, ankle jerk; CEA, carcinoembryonic antigen; CT, computed tomography; FDG PET, fluorodeoxyglucose positron emission tomography; GI, gastrointestinal; IDeg/Asp, degludec/aspart insulin coformulation; SR, sustained release; SW, Semmes-Weinstein monofilament; TSH, thyroid-stimulating hormone; XR, extended-release.

The Function of Vitamin B12 in Physiology

Vitamin B12 plays a crucial role in conversion of homocysteine to methionine through methylation and coenzyme A (CoA) is changed to succinyl-CoA through methylation.[49] Methionine is then transformed into S-adenosyl-methionine (SAM), which donates methyl groups to numerous neurotransmitters, including myelin and membrane phospholipids.[49] Enzymes involved in the synthesis of fatty acids, deoxyribonucleic acid (DNA), and other compounds require vitamin B12 as a cofactor. Hematologic and neurological symptoms can result from vitamin B12 deficiency.

Metformin-induced Vitamin B12 (Cobalamin) deficiency

The risk for cobalamin deficiency is one under-reported side effect of metformin therapy. Cobalamin uptake in the terminal ileum is hypothesised to be reduced by metformin.[50] Ileal cobalamin permeability is a calcium-dependent mechanism, and one reasonable assumption is that metformin competes with calcium for the mucosal cell membrane, resulting in vitamin B12 deficiency.[50] In accordance with the latest study, 5.8-33% of all persistent metformin users have a deficiency of vitamin B 12.[51,52] Regular cobalamin deficiency monitoring for individuals with type 2 diabetes is not typically prescribed by standardised criteria.[52,53] According to earlier research, using metformin was linked to higher severity of vitamin b12 deprivation.[54,55] The large number of studies had small numbers of participants.[54,56,57] or did not consider the daily average daily dosage, cumulative dose, and time frame of metformin use.[55] Just two previous reports examined the relationship between the daily dose of metformin and cobalamin deficiency, and they concluded that daily consumption had a stronger connection than the period of metformin use.[58,59] Research on the link between cobalamin deficiency and clinical manifestations in diabetic individuals taking metformin has yielded inconclusive results.[60,61]

Case Study 1

The two groups of 700 patients, those on metformin and those who weren't were separated. Cumulative metformin doses were documented in metformin-treated individuals based on dosage history and treatment duration. For all patients, serum Vit B12 levels were assessed.

Patients' vitamin B12 levels were graded as normal (20 pmol/L), borderline B12 insufficiency (150-220 pmol/L), and definitive deficit (150 pmol/L). The prevalence of vitamin B12 insufficiency increased by 11.16 % in individuals on long-term metformin treatment.

Case Study 2

The study included 34 healthy volunteers and 34 Type 2 diabetes patients who had been on metformin for at least six months. The levels of Vitamin-B12 were assessed form the blood samples collected.

In T2DM patients, the incidence of blood vitamin B12 insufficiency and borderline deficiency is 20.5%.

Case Study 3

There are 50 T2DM-diagnosed trial participants history of using metformin for almost 18 months. The control group includes 50 individuals with T2DM who have not used metformin in the last five years. Each patient's age, gender, weight, height, body mass index (BMI), years with diabetes, total daily dose of, and years of metformin were all recorded. An immunoassay approach was used to test the serum vitamin B12 levels.

The mean serum vitamin B12 levels in the study group were 431.841±265.76pg/mL., whereas the control group had 744.76 ±271.927pg/mL., a statistically relevant. Metformin was linked to a considerable reduction in vitamin B12.

Table 2: Patient Information for Cases with metformin induced Vitamin B12 deficiency

Authors/Year	Country	Duration of Study	Study Sample Age group (Years)	N	Time Frame for Metformin Consumption	Metformin Dosage	Primary characteristic: Deficiency of Vitamin B12
Farooq MD et al., 2022[62]	India	September 2014 to November 2016	M = 366 (52.29 %) mean age 50 ±1 F = 334 (47.71%) mean age 52.5 ±1	700 patients 451 (64.4%) [a] 249 (35.6%) [b]	Mean ± SD months 56 ± 5.9	Cumulative dose of metformin (g) Group 1: 4663 Group 2: 3637.9 Group 3: 2230.3	Group 1, 205 individuals are deficient of Vitamin B12 (<150 pmol/L) Group 2, 42 individuals are Borderline deficient of Vitamin B12 (150–220 pmol/L) Group 3, 204 individuals are Sufficient of Vitamin B12 (>220pmol/L) With an increase in metformin intake there is a direct correlation of Vitamin B12 deficiency compared to non-metformin controls.
Reddy S. et al., 2019[63]	India	6 Months	Mean ± SD Age 46.10±14.6 M = 36 (52.9 %) F =32 (47.1 %)	68 patients 34 (50%) [a] 34 (50%) [b]	≥ 6 months n = 3. 0.09 % 1 – 10 years n = 24. 70.5 % 11 – 20 years n = 5. 14.7 % 21 – 30 years n = 2. 0.6 %	NA	In comparison to non-metformin users, metformin users had a greater prevalence of B12 deficiencies. The amount and length of time people used metformin were linked to vitamin B12 insufficiency.
Agarwal P,et al., 2016[64]	India	1 year	Mean ± SD age 51.98 ± 5.17 [a] 49.28 ± 5.08 [b]	100 patients 50 (50 %) [a] M= 22 (44%) F= 28 (56%) 50 (50 %) [b] M= 24 (48%) F= 26 (52%)	≥18 months n = 50	≥2gm/day n= 50	With the use of metformin, it was discovered that Type 2 diabetes mellitus subjects exhibited B12 deficiencies. Metformin treated group was assessed to be Vitamin B12, 431.84± 265.76 pg/ml Control group 744.76±271.93 pg/ml.

All data are reported as mean ± SD unless otherwise stated. NA: not applicable; M = male; F = female. a: metformin user; b: non metformin user.

DISCUSSION

As we previously established, diabetes is a terrible health issue that affects people all over the world. In an effort to treat it, many individuals use metformin, a prolonged usage of which results in induced vitamin B12 deficiency and gastroenteritis.

Three case reports related to metformin-induced gastroenteritis and weight loss were used in this analysis of gastroenteritis to support our discussion. A 60-year-old male and 63-year-old female who were both experiencing consistent weight loss of 8 to 10 kg each gained weight after using metformin for a while and then stopping it. Next, a 74-year-old patient who had been experiencing diarrhoea for 1.5 years and had been using metformin was found to have gastroenteritis. Once the medication was stopped, the diarrhoea stopped in all of these cases, pointing to a potential connection between weight and diarrhoea. who was using metformin was found to have gastroenteritis after the drug was stopped. In each of these individuals, the diarrhoea disappeared, indicating a potential connection between weight reduction and gastroenteritis brought on by metformin use.

In this research of vitamin B12, we found that long-term treatment raised the risk of low vitamin B12 levels in the years 2016, 2019, and 2022. Three cases of controlled trials were conducted to determine whether there was a relationship between metformin use and vitamin B12 insufficiency. These studies involved 100, 68, and 700 T2DM patients who received long-term metformin treatment. The likelihood of metformin-induced vitamin B12 insufficiency was between 11 and 20 percent higher than in the control group.

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