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REVIEW ARTICLE
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REPERCUSSIONS OF METFORMIN ON VITAMIN B_{12} INSUFFICIENCY IN PERSON WITH TYPE 2 DIABETES MELLITUS: A REVIEW

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ABSTRACT
Diabetes mellitus is one of the common diseasesand its occurrence is rising worldwide. Metformin is a biguanide oral antidiabetic medication used to treat type 2 diabetes.The aim of the study is to perform a detailed analysis of metformin's impact on the incidence of vitamin B_{12} deficiency and on serum vitamin B_{12} levels.Numerous studies have shown that vitamin B_{12} deficiency is associated with impaired vitamin B_{12} absorption in metformin-treated patients with type 2 diabetes. Vitamin B_{12} deficiency can lead to severe complications for individuals with type 2 diabetes.In this review, we will look at how metformin affects vitamin B_{12}absorption and the mechanisms that may be involved.The physician should evaluate the patient's initial vitamin B_{12} level, regularly monitor vitamin B_{12} levels and nutritional status in metformin users, and provide vitamin B_{12} supplements as necessary.

Keywords: Type 2 Diabetes Mellitus, Vitamins, Metformin, Vit B12 Deficiency, Cognitive Impairment.

DIABETES MELLITUS
Chronic diabetes mellitus is caused by inadequate insulin production by the pancreas or by a genetic or acquired insufficiency in insulin production. Increased blood glucose levels from such a shortfall harm numerous bodily systems, including the blood vessels and nerves. Inadequate insulin action on the target tissues of the liver, adipose tissue, and skeletal muscle results in abnormalities in the metabolism of proteins, lipids, and carbohydrates.[1]

TYPES
- Type 1 diabetes (insulin-dependent): It is defined by autoimmune beta cell death, in which the pancreas fails to produce the insulin required for survival.[1] It is also known as Juvenile diabetes.[2]

- Type 2 diabetes (noninsulin-dependent): It results from the body's incapacity to react to the insulin that the pancreas produces. [1]
- Gestational diabetes: It is described as glucose intolerance, which is initially identified during pregnancy. Most women with gestational diabetes mellitus develop the illness during their third trimester of pregnancy.[3]
- Early-onset diabetes in adults.: Also known as monogenic diabetes, results from an inherited genetic mutation.
- Latent autoimmune diabetes in adults (LADA): It is triggered by autoimmune responses but progresses more gradually.[1]

PATHOGENESIS

Diabetes mellitus can arise from two main pathophysiologic pathways: insufficient insulin release and insulin resistance, the latter often leading to hyperinsulinemia. Insulin resistance may result from environmental factors and genetic defects. When their production fails to meet the needs of insulin-sensitive tissues, hyperglycemia occurs. A decrease in insulin sensitivity necessitates higher insulin production to keep glucose tolerance within normal limits; if insulin secretion drops below the fifth percentile for individuals with normal glucose tolerance, hyperglycemia will occur.

Type 1 diabetes mellitus arises from a marked deficiency of insulin in people with normal insulin responsiveness, whereas T2DM can develop due to insulin insensitivity combined with inadequate insulin secretion. T2DM is a polygenic condition affected by combination of inherited genes that increase the likelihood of emerging the disease. T2DM is the result of a genetic predisposition combined with environmental influences.[4]

Genetics:

1. Irregularities in beta cell function
2. Optimized pathways for nutrient use

Environmental:

1. Higher calorie consumption
2. Reduction in physical activities[4] Stress

SIGNS AND SYMPTOMS[5]

- Hyperglycemia
- Excessive urination
- Increased thirst
- Slow healing of cuts and wounds
- Fatigue
- Reduction of weight
- Blurring of vision

COMPLICATIONS OF DIABETES MELLITUS

I. **ACUTE COMPLICATIONS**

1.Hypoglycemia: It indicate confusion, lightheadedness, and fainting.

2.Diabetic ketoacidosis: This life-threatening condition is primarily associated with type 1 diabetes and is characterized by high blood sugar and ketone levels. [6]

II. **CHRONIC COMPLICATIONS.**

1.Cardiovascular disease: High risk of heart attack, stroke, and hypertension.

2.Neuropathy is nerve damage that causes pain, tingling, or loss of sensation, often in the foot.

3. Retinopathy: It causes vision impairment
4. Nephropathy: renal damage that can lead to renal failure.
5. Dental problems: A progressive risk of periodontal disease and oral infections. [7]

TREATMENTS FOR DIABETES MELLITUS

I. ORAL HYPOGLYCEMIC AGENTS

i. Biguanide: Metformin
ii. Sulfonylureas: Tolbutamide, Glimepiride
iii. Meglitinide: Repaglinide, Nateglinide
iv. Thiazolidinedione: Pioglitazone
v. Dipeptidyl peptidase-4 inhibitors: Sitagliptin
vi. α-Glucosidase inhibitor**:** Acarbose, Voglibose

II. INSULIN THERAPY

i. Rapid acting: Insulin lispro, insulin aspart
ii. Short acting: Regular insulin
iii. Intermediate acting: Lente insulin, Isophane insulin
iv. Long acting: Insulin glargine, Insulin detemir [8]

DIAGNOSIS OF DIABETES MELLITUS

- Haphazard plasma glucose value: ≥ 200mg/dl
- Fasting blood plasma glucose value: ≥ 126mg/dl [9]
- OGTT value in venous plasma: (≥11.1mmol/l)[10]
- HbA1c level higher than 6.5% [9]

METFORMIN AS AN ANTIDIABETIC AGENT

Metformin (dimethyl biguanide) is an oral medication used to lower body fluid glucose levels in individuals having non insulin dependent diabetes mellitus.[11] Metformin is ineffective for patients with IDDS because their pancreas glands cannot produce insulin. [12]

MECHANISM OF ACTION

Metformin helps prevent blood glucose (sugar) levels from rising too high in a few distinct methods.

- Metformin reduces the quantity of glucose that is absorbed by the body from food and beverages. [12]
- Metformin aids in lowering the synthesis of glucose in the liver.[13]
- Metformin also improves the efficiency of your body's natural insulin. (Your body uses insulin, a hormone, to assist use glucose as an energy source.) [12]

DOSE

Oral administration form (prolonged-release tablets):
Grown ups

i. Metformin(Fortamet®): Start with 1000 mg once daily with dinner. Typically, the daily dose does not exceed 2500 mg.
ii. Metformin (Glumetza®): Start with 500 mg once daily with an evening meal. In most cases, the daily intake is limited to 2000 mg.
iii. Metformin with insulin: Start with 500 mg once a day. Typically, the daily dose does not exceed 2500 mg.

For oral dosage form (solution):

Mature person

i. Metformin alone: Start with 5 ml twice a day or 8.5 ml with meals. The daily intake is usually limited to 25.5 ml.
ii. Metformin with insulin: Start with 5 mL per day. The daily intake is usually limited to 25 ml.

Children aged 10 to 16 years
Initially, take 5 mL with meals twice a day.
Typically, the dosage is limited to 20 milliliter per day.

For oral dosage form (tablets):

Elder

i. Metformin alone: Start with 500 mg twice a day with morning and evening meals, or 850 mg with morning meal. Typically, the daily intake is limited to 2550 mg.
ii. Metformin with insulin: Start with 500 mg per day. Typically, the daily dose does not exceed 2500 mg.

Children 10 to 16 years of age

Initially, take 500 mg two times daily.

The dosage is normally no more than 2000 mg per day. [12]

SIDE EFFECTS[14]

- Gastro intestinal (Nausea, Vomiting)[14,15]
- Metformin associated lactic acidosis (MALA)[14,16]
- Abdominal pain
- Gas or feeling bloated
- Diarrhea

USES

1. Type 2 diabetes mellitus
2. Cardiovascular disease
3. Obesity [17]
4. Non- alcoholic fatty liver disease[18]
5. Anticancer[18,19]
6. Liver disease
7. Renal disease[19]

INTERACTIONS

Interaction of metformin with foods or drinks

Alcohol can raise the risk of lactic acidosis; metformin and food or drink interactions are unknown. While it's unknown if alcohol consumption will have any additional effects on metformin, it may have an impact on diabetes blood sugar levels. This could counteract the metformin's effects.

Interaction of metformin with other medicines (drug interactions)

- Always inform your healthcare provider about all medications you are taking, whether they are prescribed or not.
- An inhibitor of carbonic anhydrase, like methimazole, acetazolamide (Diamox), or zonisamide (Zonegran).
- Diabetes medications, particularly insulin or those that raise insulin levels.[20]

INTRODUCTION TO VITAMINS

Vitamins are a class of highly intricate chemical compounds which are found in traces of food and are necessary for a healthy metabolism. Deficits in these nutrients can be treated by replenishing them, but their absence can lead to problems.[21]

Other necessary nutrients including nutritional minerals, vital fatty acids and indispensable amino acids, as well as many other nutritional compounds that support health but do not provide cells their structural integrity and energy, are not included in the category of vitamins.[22]

Vitamins are needed in very small quantities for their advancement, progress, well-being, and reproduction. Certain vitamins, such as vitamin C, cholecalciferol, and vitamin B_3, defy conventional definitions and aren't necessarily required to be present in food items.[21] Nutrients

are unable to synthesized by physique and need to be found from exterior origin.[23]Different types of vitamins, their sources and diseases are shown in Table 1.

OVERVIEW OF COBALAMIN

Cobalamin is a B vitamin vital in cellular biochemical processes, especially in genetic material formation, methyl group addition, and cellular powerhouse function.[24] Cyanocobalamin, similar to other members of the vitamin B complex, is essential for energy production and various biological functions; however, it has several distinct roles that set it apart from other B vitamins. i.e,

- About several ages cobalamin is able to kept in physique.
- Microorganisms such as bacteria and fungus synthesis this vitamin, which has a complicated structure and bigger molecule. Mushroom, a fungus, contains this vitamin.
- This vitamin is difficult to absorb.
- The daily requirement for this vitamin is really low.
- This vitamin, commonly known as cobalamin, contains the heavy metal cobalt.[21]

BIOLOGICAL IMPORTANCE

Vitamins are important in cardiovascular health, and cobalamin act a vital part in the manufacture of erythrocyte, that transfer O_2 through bloodstream with the help of hemoglobin.[21] Cobalamin plays a vital function in two essential metabolic processes: converting methylmalonyl CoA to succinyl CoA and producing methionine by methylating homocysteine.[25]

Vitamin B_{12} plays several crucial roles in the body. It recycles SAMe, a universal methyl group donor involved in neurotransmitter synthesis, highlighting its importance in methyl metabolism and brain health. B_{12} is also a co-factor for DNA production, alongside vitamins B_6 and B_9. A deficiency can cause macrocytosis, producing abnormally large blood cells.

In energy metabolism, B_{12} supports aerobic energy production by maintaining succinyl CoenzymeA. They additionally promotebone health, reducing the risk of osteoporosis. Deficiency is linked to various conditions, including atrophic gastritis, pernicious anemia, neuropathy, migraines, asthma, depression, memory loss, and Alzheimer's disease. [21]

DAILY REQUIREMENTS

The daily requirements for vitamin B_{12} can vary based on age, sex, and life stage. These values are based on recommendations from health authorities like the National Institutes of Health (NIH). It's important to ensure adequate intake, especially for populations at risk of deficiency. Daily requirements of different age groups are shown in Table 2.[26]

DIETARY SOURCES[27]

- Sardines
- Shrimps
- Chicken
- Salmon
- Beef
- Tuna
- Yogurt
- Cheese
- Cow’s milk
- Egg
- Lamb
- Scallops
- Turkey
- Mushroom
- Breakfast Cereals

DIETARY SUPPLEMENTS

Vitamin B_{12} is available in multivitamins,B complex supplements, and standalone B_{12} supplements. Vitamin B_{12} is available along with B vitamins and even higher, often 500 or 1000mcg, in pills that exclusively contain cobalamin.

Cyanocobalamin is found in dietary supplements. Additional forms include adenosylcobalamin, methylcobalamin, and hydroxycobalamin.[28]

NEEDS OF VITAMIN B_{12}

- DNA synthesis: Vitamin B_{12} promotes DNA production, which is the genetic material found in cells.
- Red blood cell formation: Vitamin B_{12} promotes development of red blood cells
- Nerve function: Vitamin B_{12} promotes healthy nerve cells
- Energy production: Vitamin B_{12} promotes conversion of food into energy
- Anemia prevention: Vitamin B_{12} helps prevent megaloblastic anemia,which causes weakness and fatigue.[29]

ETIOLOGY OF VITAMIN B_{12} DEFICIENCY

- Diet: Vegetarianism leads to a rise in dietary deficit of Vitamin B $_{12}$, which causes hypercysteinemia.[30]
- Medications: Vitamin B_{12} absorption may be hampered by medications such as proton pump inhibitors and H_2 blockers that have been taken for longer than a year. [31]
- Pernicious anemia: Pernicious anemia results from the nonappearance of internal aspect, that facilitates the uptake of cobalamin.[32]
- Medical conditions: Certain medical problems, such as Coeliac disease, type 1 diabetes, thyroid illness, Crohn's disease, and pancreatic abnormalities, can affect vitamin B_{12} absorption.
- Gastric surgery: Removing sections of the stomach or intestines can reduce the body's ability to make intrinsic factor and absorb vitamin B_{12}.

The body's vitamin B_{12} stores can last for several years, so it may take some time to notice difficulties after a dietary shift.

DIAGNOSIS OF COBALAMIN SHORTAGE

All individual with unaccounted anemia & nerve related symptoms, along with those at risk for vit B_{12} deficiency—such as older adults and individuals with intestinal disorders—should be assessed for vitaminB_{12} insufficiency.[33]

A wide range of served values for vit B_{12} and its biological indicators were determined:

- Vitamin B_{12} :100pmol/L & 350pmol/L
- Holotranscobalamine: 20-50pmol/l
- MMA: 0.210-0.470µmol/L
- Homocysteine: 10-21.6 µmol/l
- Serum folate: 3.7- 15.6nmol/L
- Erythrocyte count : 124- 397nmol/l[34]

SYMPTOMS OF VITAMIN B_{12}DEFICIENCY[35]

i. Anemia
ii. Fatigue and weakness
iii. Hyperpigmentation
iv. Headache
v. Mood changes
vi. Hairloss
vii. Memory loss
viii. Cognitive impairment

ix. Weight loss
x. Muscle weakness

PROCESS OF METFORMIN LEADING TO SHORTAGE IN COBALAMIN

Below mentioned are few of the hypothesized processes that could describe metformin triggered cobalamin insufficiency:

1. Interruption of Calcium-reliant attachment of IF - cobalamin combinations to cubilinprotein on absorptive cells in ileum & connection withcubilin membrane binding sites.
2. Alteration in intestinal motility, leading to bacterial proliferation that subsequently hinders the absorption of the IF – cobalamin combinations in lower part of the ileum.
3. Changes in the metabolic activity & uptake of bile acids result in reduced intestinal-liver circulation of cobalamin.
4. Elevated cobalamin levels in the liver results in modification in distribution and biochemical reactions of vitamin.
5. Reduced production of intrinsic factor by gastric acid-secreting cells. Importantly, primary process considered to explain metformin caused cobalamin insufficiency is suppression of calcium reliant absorption of IF - cobalamin complex in terminal ileum. In fact, calcium enrichment has been demonstrated to counteract this inhibitory effect.Proposed mechanisms underlying metformin caused cobalamin shortage is shown in Figure 1. [36]

Metformin is recognized to decrease cobalamin levels, despite its effectiveness in reducing blood glucose. An early disordered supervised test by De Fronzo*et al*. showed that dimethylbiguanide decreased plasma cobalamin concentration by 22% & 29% related to Glibenclamide& placebo. Numerous studies have since confirmed this adverse effect, with age, dosage, and treatment duration significantly affecting menace of cobalamin lack associated through metformin.

A likelihood proportion of 2.9 (95% confidence interval, 2.15-3.87) for evolving cobalamin deficiency was associated with each 1 gram/daytime surge in the metformin quantity amid 155 grown-up Chinese DM individuals on metformin & 310 reference group in a integrated retrospective comparative study. When Contrasting individuals who had taken dimethylbiguanide for $\geq$ 3 years to those who had not, the modified likelihood comparisonstood 2.4 (95% confidence interval, 1.46-3.91).

The reduction on cobalamin uptake & concentration after dimethylbiguanide therapy often begins as soon as fourth month. Medically noticeable symptoms of cobalamin insufficiency appear after 5 - 10 years, due to considerable bodily accumulation inhepatic organ that aren't rapidly exhausted.[37]

PREVALENCE OF METFORMIN INITIATED COBALAMIN INADEQUACY

The proportion of individuals undergoing long-term metformin treatment who are deficient in vitamin B_{12} varies from 5.8% to 30%. This study aimed to determine the prevalence of vitaminB_{12} insufficiency and the related factors in patients with type 2 diabetes mellitus (T2DM) who are using metformin.[38]

METHODOLOGY

Samples of T2DM patients are collected in order to evaluate the prevalence.Electronic medical records and a basic random sample approach are used to choose the participants.

➢ Inclusion and Exclusion Parameters

The research involved individuals aged 18 and above with T2DM who had undergonedimethylbiguanide for at least six months. Exclusion criteria incorporated pregnant women, individuals with type 1 diabetes, those who had undergone prior bariatric surgery, patients with IBD, severe conditions (like long-term liver disease, cancer or renal disease), and those receiving vitamin B_{12} supplements or injections.

Method

An online cross-sectional assessment collected data from type 2 diabetes patients on sociodemographics, anthropometrics, lab results, smoking status, diabetes duration, comorbidities, surgeries, metformin use, and vitamin B_{12} consumption.

The assessment of nutritional consumption wereconducted employing a validated food frequency assessment tool and laboratory results.

- **Blood Sampling**

To assess vitamin B_{12} status blood specimens were obtained, alongside the data gathered from the web-based survey.

- **Statistical Analysis**

Information were presented as mean ± SD or as frequencies. Unrelated - examinations and Pearson chi-squared tests were employed for group comparisons, while multivariate logistic analysis were used to analyze odds ratios for cobalamin insufficiency.A p-value of less than 0.05 was regarded as having statistical importance.[39]

How to overcome metformin induced vitamin B_{12} deficiency

1. Consistent monitoring of plasma cobalamin levels.
2. Supplementation of vitamin B_{12}: Adenosylcobalamin and Methylcobalamin
3. Dietary modification: include more animal based food products.
4. Alternative medication: Sulfonylureas, Meglitinides and Insulin.
5. Monitoring ,cysteine levels: elevated level can indicate B_{12} deficiency.[40]

CONCLUSION

Metformin is an oral hypoglycemic drug classified as a biguanide, used to manage individuals with T2DM. Evidences have indicated a connection between metformin and lower blood plasma cobalamin levels. This study aims to analyze the effect of dimethyl biguanide on low serum cobalamin concentration and the associated consequences for diabetic patients.

The evidence presented in this report indicates a link among dimethylbiguanide usage & reduced cobalamin concentrations, which can result a significant deficiency or borderline status in some peoples with T2DM. The findings reveal a substantial decrease in cobalamin concentration in individual receiving metformin for over three years, suggesting the importance of monitoring B_{12} levels in those at greater risk of deficiency. Deficiency is associated with symptoms such as hair loss, hyperpigmentation, fatigue, mouth ulcers, and cognitive issues.

Regular monitoring of vitamin B_{12} levels and timely supplementation are essential strategies to reduce the risk of deficiency and its complications. Integrating awareness and screening into diabetes management protocols can enhance patient outcomes, ensuring improved long term well-being and life satisfactionfor individuals undergoing metformin treatment.

TABLE 1: TYPES OF VITAMINS

Sl no	TYPES	SOURCES	DISEASE
I	FAT SOLUBLE		
	Vitamin A(Retinol)	Sweet potato,Carrot	Night blindness
	Vitamin D(Cholecalciferol)	Sunlight , Fatty fish	Rickets
	Vitamin E (Tocopherol)	Nuts , Seed	Immune dysfunction
	Vitamin K (Menaquinone)	Egg York, Leafy greens	Bleeding disorders
	WATER SOLUBLE	Citrus fruits, Strawberry	Scurvy, Fatigue
II	Vitamin C (Ascorbic acid)	Grains, Nuts, Seeds	Beriberi
	Vitamin B_1 (Thiamin)	Dairy, Almonds	Dermatitis
	Vitamin B_2 (Riboflavin)	Meat, Fish	Dermatitis
	Vitamin B_3 (Niacin)	Avocado, Broccoli	Neurological problems
	Vitamin B_5 (Pantothenic acid)		Immune dysfunction
	Vitamin B_6 (Pyridoxine)	Meat, Fish, Banana	Anemia
	Vitamin B_9 (Folate)	Citrus fruit, Legumes	Anemia, Fatigue
	Vitamin B_{12} (Cobalamin)	Animal products	Hair loss , Dermatitis
	Biotin (Vitamin B_7)	Nuts, Seeds,Eggs	

TABLE 2 : DAILY REQUIREMENTS

Age	Male (mcg)	Female (mcg)	Pregnancy(mcg)	Lactation(mcg)
Young infants	0.4	0.4		
Infants	0.5	0.5		
Toddlers	0.9	0.9		
School aged child	1.3	1.2		
Tweens	1.8	1.8		
Teens	2.5	2.4	2.7	2.8
Adults	2.4	2.3	2.6	2.9

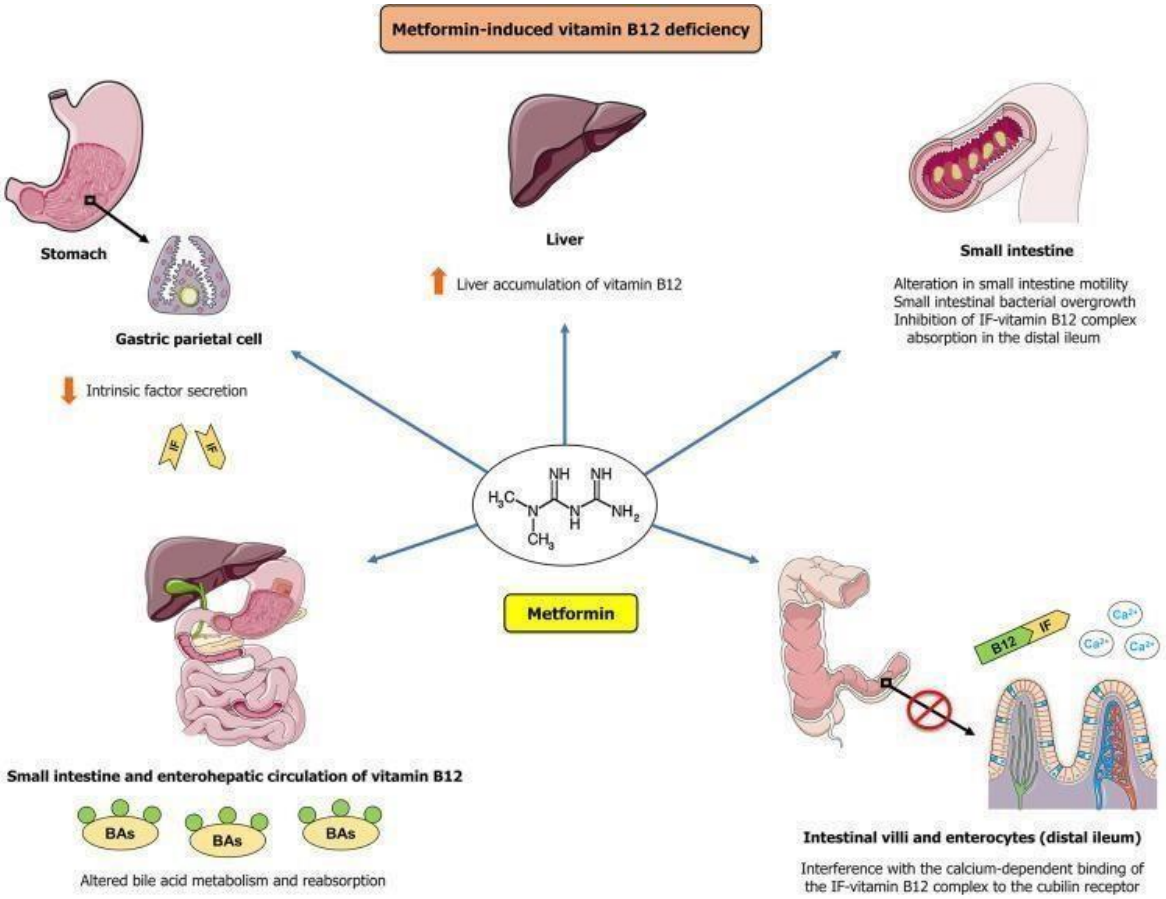

Figure 1: Proposed mechanisms underl

CONFLICTS OF INTEREST

There are no disclosed conflicts of interest for the authors.The manuscript's contents have been reviewed by all co-authors, who concur with its contents and have no financial interests to disclose.We confirm that the submission is our original work and isn't being considered for publication by another journal.

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