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EFFECT OF ANTI-DIABETIC DRUGS ON SERUM B12, MINERALS LIKE ZINC, MAGNESIUM, PHOSPHORUS AND CALCIUM IN TYPE II DIABETES MELLITUS (T2DM)

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ABSTRACT: Metformin, the first-line drug, can reduce hepatic gluconeogenesis and increase insulin sensitivity. At the molecular level, metformin inhibits the mitochondrial respiratory chain, which leads to an increase in adenosine monophosphate-activated protein kinase, which increases insulin sensitivity. Recent guidelines advocate metformin as the first-line agent that has a glucose-lowering effect concurrently with lifestyle modification. Metformin has long been shown to decrease vitamin B12 levels. Vitamin B12 is also an essential micronutrient required for optimal hemopoietic, neuro-cognitive, and cardiovascular function. Vitamin B12 deficiency has been highly prevalent among patients with type 2 diabetes mellitus. In this study, we want to figure out the association between metformin administration and VitB12 absorption defects in a diabetic patient pool on metformin alone and metformin with other combination drugs. Findings from this study indicate the role of metformin in vitB12 deficiency, uncontrolled glucose levels, and levels of serum Minerals in T2DM patients, gradually leading to microvascular and macrovascular complications even with one year of usage of drugs.

INTRODUCTION: Across the globe, the number of people with diabetes mellitus has quadrupled in the past three decades and is the ninth major cause of death. Around 1 in 11 adults worldwide now have diabetes mellitus, 90% of whom have type 2 diabetes mellitus (T2DM). India and China are the top two epicenters in Asia, showing major emerging T2DM global epidemics [1]. Diabetes is a multifactorial disease, and metformin is the first line of drug suggested.

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Metformin is a widely used drug with many benefits related to glucose metabolism and diabetes-related complications by improving peripheral insulin sensitivity [2, 3]. Physiologically, metformin reduces hepatic glucose production, yet not all of its effects can be explained by this mechanism, as there is increasing evidence of its vital role in the gut. At the molecular level, the findings vary depending on the dosage of metformin and the duration of treatment.

Metformin has been shown to act via both AMP-activated protein kinase (AMPK)-dependent and AMPK-independent mechanisms, by inhibition of mitochondrial respiration, but also perhaps by inhibition of mitochondrial glycerophosphate dehydrogenase and a mechanism involving the lysosome [4].

Vitamins and minerals exert important effects on the risk of diabetes mellitus and its progression and complications. The best recommendation should be to consume adequate quantities of those foods containing vitamins in sufficient amounts to guarantee an appropriate nutritional status [5]. Vitamin B12 is one of the nine water-soluble vitamins important for healthy body functioning. Vitamin B12 is an essential micronutrient required for optimal hemopoietic, neuro-cognitive, and cardiovascular function [6]. Since the effects are seen across a large range of functions, the symptoms of vitamin B12 deficiency can sometimes be very ambiguous. Intake of Vitamin B12 starts with ingestion and then digestion by saliva.

Once reaching the gut, the present acids release Vitamin B12 bound to proteins in food. The B12 can then bind to the intrinsic factor. Once bound to IF, Vitamin B12 is stable enough to travel into the intestines, where it can be absorbed into your body through its association with IF. Two very useful tests to distinguish between Vitamin B12 deficiency and folate deficiency are Methyl malonyl CoA (MMA) and homocysteine (HCY). The increase in methyl malonyl CoA and homocysteine levels is thought to be the root cause of any symptoms that accompany a Vitamin B12 deficiency.

The minerals have an important role in glucose homeostasis. Understanding the impact of vitamin and mineral deficiencies and the potential utility of supplementation is relevant to the prevention and/or management of type 2 diabetes mellitus (DM) [6]. Minerals like magnesium in blood glucose regulation, phosphorus in impaired glucose tolerance, and calcium play an important role as a precursor in signalling cascades like insulin secretion by pancreatic beta cells and b12 absorption in the ileum as it is a calcium-dependent process and zinc in antioxidant function. Vitamins like b12 have a very important role in hematopoietic and neurocognitive properties. B12 deficiencies in diabetic subjects have been linked to oxidative stress and resulting in hyper-homocysteinemia and neuropathies [7, 8]. Patients receiving metformin have diminished B12 absorption and low serum total vitamin B12 and TCII-B12 levels because of a calcium-dependent ileal membrane antagonism, an effect reversed with supplemental calcium [9, 10, 11]. Metformin uses over time has been linked to biochemical B12 deficiency. Routine testing of vitamin B12 levels in metformin-treated patients should be considered. [12-15]. At 5 years (4.3 vs 2.3%; P =.02), low B12 (203 pg/mL) occurred more frequently in the metformin group, but not at 13 years (7.4 vs 5.4%; P =.12).At 5 years (19.1 vs 9.5%; P.01) and 13 years (20.3 vs 15.6%; P =.02), the metformin group had a higher prevalence of combined low and borderline-low B12 (298 pg/mL). Metformin use was associated with an increased risk of B12 deficiency (odds ratio, B12 deficiency/year metformin use, 1.13; 95% confidence interval, 1.06–1.20). Anemia prevalence was higher in the metformin group but did not differ by B12 status. Neuropathy prevalence was higher in the metformin group with low B12 levels [16, 17, 18].

Study Design and Methodology: This study was conducted through a collaboration between the physiology department of a teaching medical institute, the medicine department, and the Genetics Lab. Ethical approval for this study was received 007/02/2019-/IEC/SMHC-and the study was conducted from March 2019 to February 2021. Based on WHO and ADA guidelines for the screening of type 2 diabetes mellitus, the plasma glucose criteria, the fasting plasma glucose (FPG) value or the 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT), or A1C criteria, The present study recruited 500 participants between 30 and 65 years of age.

Patient pool who has been recently diagnosed as type 2 diabetics on metformin usage for more than 12 to 18 months. The study design was divided into 3 groups: A, B, and C. Group A consisted of 200 subjects with type 2 diabetes only on metformin with a daily dosage of 500 mg/day, and Group B consisted of 200 subjects with type 2 diabetes who were on both metformin with a daily dosage of 500 mg/day and other anti-diabetic drugs of around 2 mg/day. Both groups A and B had no other complications from diabetes. Group C included controls, consisting of 100 healthy individuals with no history of diabetes. The study included type 2 diabetics on metformin for more than a year and age-matched non-diabetic healthy volunteers as controls.

People on vitamin B12 supplements, calcium supplements, or proton pump inhibitors have no complications from liver diseases, renal diseases, gastrointestinal disorders, thyroid diseases, or parathyroid disorders. Strict vegetarians, alcoholics and smokers were excluded. A detailed clinical history, drug history, dosage of the drug, and B12 supplementation were documented in a structured proforma. The blood samples were collected from the subjects via vein puncture for fasting plasma glucose, glycated haemoglobin (HbA1c) and serum (creatinine, Zn, and magnesium (Mg)) were determined and quantified. Whole blood samples were collected into EDTA-coated vacutainers for quantification of glycated haemoglobin (HbA1c), zinc and magnesium in the blood. Fasting and postprandial plasma glucose were estimated using the glucose oxidase-peroxidase method. Serum magnesium was estimated on an automatic bioanalyzer (Beckman Coulter, Inc) [19, 20]. Serum zinc was quantified using an Abcam's Zinc Quantification Kit, and absorbance was checked at 560nm. Serum calcium, phosphorus, and vit B12 were measured with the Chemiluminescent Microparticle Immuno Assay, which is a modified and advanced form of the Enzyme-Linked ImmunoSorbent Assay (ELISA) technique. We ensured that the study complies with international ethical norms according to the Helsinki Declaration-Ethical Principles for Medical Research Involving Human Subjects (World Medical Association *et al.* 1964). All data were statistically analyzed and expressed as mean, and standard deviation. The mean was analyzed by one-way ANOVA (with a student T-test for comparison with controls). A Pearson correlation test was done to see the relationship between control subjects and diabetics.

RESULTS:

Biochemical Parameters:

TABLE 1: A COMPARISON OF FBS, PLBS, HBA1C, CALCIUM, PHOSPHORUS, VITAMIN B12, AND MICRONUTRIENT (ZINC AND MAGNESIUM) LEVELS BASED ON MEAN ± SD VALUES OF DIFFERENT VARIABLES BY GROUPS

Variables	Groups			F Value	*P-Value*
	Metformin (199)	Metformin And Other Drug (200)	Control (100)		
Age	49.3 ± 10.5	46.4 ± 10.70	48.5 ± 9.97	3.911	0.021
FBS	124.3 ± 61.65	127.0 ± 34.80	84.0 ± 11.635	34.297	0.000
Plbs	162.9 ± 78.09	173.4 ± 43.86	105.8±20.02	48.826	0.000
HBA1C	22.0 ± 83.72	159.0 ± 45.36	6.0±0.52	335.577	0.000
Calcium	8.2 ± 1.36	7.6 ± 1.75	9.0 ±1.60	27.656	0.000
Phosphorus	4.1 ± 1.45	3.4 ± 1.75	4.9 ±1.27	32.756	0.000
B12	163.1 ± 35.59	150.5 ±20.35	301.1 ± 47.51	747.776	0.000
Zinc	57.1 ± 11.58	56.2 ±10.47	96.9± 12.09	512.139	0.000
Magnesium	1.0 ± 0.24	1.0 ± 0.17	1.9± 0.15	851.594	0.000

TABLE 2: A COMPARISON OF FBS, PLBS, HBA1C, CALCIUM, PHOSPHORUS, VITAMIN B12), AND MICRONUTRIENT (ZINC AND MAGNESIUM) LEVELS BASED ON THE DISTRIBUTION (%) OF BIOCHEMICAL VARIABLES BY GROUPS

Variables	Cut Off Values	N	Groups					
			Metformin	Metformin And Other Drug	Control	Total	X^2	P Value
FBS	<100	211	35.5	28.6	83.0	42.3	146.9	0.000
	100-126	136	42.0	17.6	17.0	27.3		
	≥126	152	22.5	53.8	0.0	30.5		
PLBS	<180	242	52.5	23.1	91.0	48.5	124.935	0.000
	≥180	257	47.5	76.9	9.0	51.5		
HBA1C	<5.7	61	18.0	0.0	25.0	12.2	219.248	0.000
	5.7-6.5	72	10.5	0.0	51.0	14.4		
Calcium	≥6.5	366	71.5	100.0	24.0	73.3		0.000
	9.3 -9.9	52	9.0	2.5	29.0	10.4	50.743	
	<9.3 ≥10	447	91.0	97.5	71.0	89.6		
Phosphorus	2.5-4.5	321	68.5	72.9	39.0	64.3	35.793	0.000
	<2.5 ≥4.6	178	31.5	27.1	61.0	35.7		

B12	200-900	110	5.0	0.0	100.0	22.0	443.718	0.000
	<200 ≥901	389	95.0	100.0	0.0	78.0		
Zinc	75-125	103	3.5	0.0	96.0	20.6	434.320	0.000
	<75 ≥126	396	96.5	199.0	4.0	79.4		
Magnesium	1.7 – 2.2	105	2.5	0.0	100.0	21.0	469.658	0.000
	<1.7 ≥2.3	394	97.5	100.0	0.0	79.0		
	≥177	108	4.0	0.0	100.0	21.6		

TABLE 3: SHOWS THE STANDARD REFERENCE RANGE

I	FBS	< 100 mg/dl
II	PPBS	< 180 mg/dl
III	HbA1c	< 5.7% normal
	Prediabetic	-5.7- 6.4%
	Diabetic	-6.5%
IV	Vitamin B12	- 200 - 900 pg/ml
V	Calcium	- 9.3 - 9.9 mg/dl
VI	Magnesium	- 1.7-2.2 mg/dl
VII	Zinc	- 75 - 125 microgram/dl
VIII	Phosphorous	- 2.5 - 4.5 mg/dl

DISCUSSION: An escalating proportion of research on animals and clinical trials suggests that the key function of metformin is to decrease hepatic glucose production, mainly by suppressing gluconeogenesis [21–24]. The inhibitory effects on hepatic gluconeogenesis can be due to changes in enzyme activities or suppressed hepatic uptake of gluconeogenic substrates supported by research evidence [25]. Cellular uptake of metformin is facilitated by the chief expression of OCT1 (organic cation transporter 1) in the hepatocytes [26].

A rational accumulation of metformin in the liver could be higher compared to other tissues, leading to high micromolar concentrations in the per portal area. Research over a certain time period indicates metformin's action is targeted around the intestines by reducing the net glucose uptake and enhancing anaerobic glycolysis in enterocytes, causing an increased release of lactic acid in the liver. The molecular level findings vary depending on the dosage of metformin and the duration of treatment, with some differences between acute and chronic administration. Metformin has been shown to act via both AMP-activated protein kinase (AMPK)-dependent and AMPK-independent mechanisms; by inhibiting mitochondrial respiration and perhaps by inhibiting mitochondrial glycerol phosphate dehydrogenase [27]. Absorption of VitB12 is a multifactorial process and depends on factors like Haptocorrin (HC), also commonly known as the R-protein secreted by the salivary glands of the oral cavity, which binds to vitamin B_{12}, which is an intricate and necessary mechanism to protect against the acidic environment of the stomach. In this complex, Haptocorrin attaches to VitB12 to create a complex. This Haptocorrin–B_{12} complex passes *via* the pylorus to the duodenum, where HC is cleaved from the complex in the presence of pancreatic proteases. Intrinsic factor (IF) is a glycoprotein secreted by the gastric mucosa parietal cells, and the IF binds to the free vitamin B_{12} to form the VitB_{12}–IF complex. Then, the vitamin B12 is transported to the ileum by the ileal receptor (*i.e.,* Cubam), which comprises the Cubilin and Megalin complex and takes them up into the circulation *via* endocytosis-mediated absorption. Hence, as ileal vitB12 absorption is a calcium-dependent process, in our study, patients with type 2 diabetes developed a marked reduction in serum vitB12 and Ca levels in patients treated with metformin alone for T2DM.

Singh *et al.,* in their studies, showed that T2DM patients on metformin treatment had lower levels of B12. Similar findings were reported by Roy *et al.* that patients on metformin had a lower level of B12 [28]. According to the DPPOS study, an increased risk of B12 deficiency is shown to have an association with metformin [29]. A recent study from India has shown an association between metformin use and B12 levels. Similar studies by Den Elen *et al* on B12 deficiency in older adults with prolonged proton pump inhibitors and H2 blockers have also reported hypocobalinemi. A meta-analysis was done by Chapman et al. on the B12 lowering effect of metformin, which took approximately 6 weeks to 3 months after commencing metformin. All these studies correlated with our studies showing decreased B12 levels with oral anti-diabetic drug usage. We found that B12 levels had significantly decreased by about 82% in the metformin group and 62% in the associated anti-diabetic drug group compared with controls. According to Reinstatler *et al.,* metformin therapy is associated with a higher prevalence of biochemical B12 deficiency.

Bauman *et al.* reported that there is a 10–30% decline in VitB12 levels in people who are on metformin due to diminished ileal b12 absorption as it is a calcium-dependent process. In our study, we included screening for calcium levels in all the groups as it has a major role in the signalling cascade where it is shown to have 38% decreased levels of calcium in the metformin group, 58% in the associated antidiabetic drug group and it was normal in the control group. Our present study could find a widespread association between phosphorus levels and different groups. A study done by Ellen et al. suggested that there was no effect on phosphorus levels in the subjects who were on metformin. Anwar *et al*. subjects with T2DM showed higher levels of fasting blood sugars, postprandial blood sugars, and glycated haemoglobin levels, which are correlated with a reduction in serum levels of zinc and magnesium, showed a significant inverse correlation with glycaemic control when compared to controls. In our study, we included screening for both serum zinc and magnesium levels in all the groups and we tried to associate the levels of zinc and magnesium in the metformin group, other antidiabetic drug groups, and control group.

CONCLUSION: Vit B12 is a pivotal micronutrient required for maintaining essential functions such as haematopoiesis, neuro-cognition, and cardiovascular functions, but its deficiency in diabetic patients (type 1 and 2) results in diverse clinical manifestations (*i.e.,* megaloblastic anemia, dementia, peripheral neuropathy, nephropathy, disc degeneration, inflammatory bowel disease, and pancytopenia. Our retrospective study has given us important proof against the antidiabetic drugs commonly advised to T2DM patients for controlling their blood glucose levels. Still, instead, they are facing the inevitable consequence of being VitB12 deficient and its associated manifestations. Hence, periodical dosing of vitamin B12 should be performed in T2DM patients treated with metformin alone, especially if they have anemia, peripheral neuropathy, etc. Future large and well-designed studies on screening for vitamin B12 deficiency, vitamin B12 supplementation, and optimal supplementation dose among type 2 diabetic patients are warranted to help guide formulation of guidelines in diabetes clinical care.

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