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A Study on Occurrence Rate of Metformin Induced Vitamin B_{12} Deficiency in Type-Ii Diabetes Mellitus Patients

[1]Mohammed Muzakkir SM, [1]Mohammed Shoaib C, [1]G Manasa, [1]K Thejasvi, [2]Mr. ANDREW.G. J, M. Pharm.
[1]5th Year Pharm-D Students, Department of Pharmacy Practice, TVM College of Pharmacy, Karnataka, Bellary-583103
[2]Asst. Professor. Department of Pharmacy Practice, TVM College of Pharmacy, Karnataka, Bellary-583103
In collaboration withDepartment of General Medicine, VIMS, Bellary District, Karnataka

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ABSTRACT
Aim and Objectives: The aim of this study is to observe the occurrence rate of metformin induced vitamin B12 deficiency in Type II Diabetes mellitus patients In VIMS Hospital Bellary, Karnataka.**MATERIALS AND METHODS:** Prospective observational study conducted for a period of 6 months among 70 Type 2 Diabetes mellitus patients.**RESULTS:** A total of 70 patients were enrolled in this study. Majority of patients were male n=41 (58%), and female were n=29 (41%). Among 70 patients Vit B12 status is as follows, 12 patients where Deficient, 26 patients were Normal, 20 patients were Borderline, 12 patients were Above Normal. The occurrence rate of Vit B12 Deficiency was higher in age group between 51-65 years n=36 (32.8%). **CONCLUSION:** According to results obtained from our study shows that patients with long term use of metformin therapy may have higher chances of vitamin B12 deficiency. Moreover, patients with low levels of vitamin B12 were suggested to take vitamin B12 supplements.

KEYWORDS: Diabetes mellitus, Vitamin B12, Metformin, Intrinsic Factor, Hypoglycemics, Peripheral neuropathy.

I. INTRODUCTION

Diabetes mellitus (DM): Diabetes mellitus comprises a group of common metabolic disorders that share the phenotype of hyperglycaemia. Several distinct types of DM exist and are caused by a complex interaction of genetics, environmental factors, and life-style choices. Depending on the etiology of the DM, factors contributing to hyperglycaemia may include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic deregulations associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system.

The worldwide prevalence of DM has risen dramatically over the past decades. Likewise, prevalence rates of IFG (initial fasting glucose) are also increasing. Although the prevalence of both Type 1 and Type 2 DM is increasing worldwide, the prevalence of Type 2 DM is expected to rise more rapidly in the future because of increasing obesity and reduced activity levels. DM increases with aging. In 2000, the prevalence of DM was estimated to be 0.19% in people <20 years old and 8.6% in people>20 years old. In individuals >65 years the prevalence of DM was 20.1%. The prevalence is similar in men and women throughout most age ranges but is slightly greater in men >60 years.

Type of Diabetes	Normal glucose tolerance	**Hyperglycaemia**	
		Impaired fasting	**Diabetes Mellitus**

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		glucose or impaired glucose tolerance	Not Insulininsulin required insulin required requiring for control for survival
Type 1 Type 2 Other specific types Gestational Diabetes Time (year)		- - - - - - - - - - - - - - - - -	
FPG (mg/dl) 2-h PG (mg/dl)	<100 <140	100–125 140–199	≥126 ≥200

Etiologic Classification of Diabetes Mellitus

I. Type 1 diabetes (cell destruction, usually leading to absolute insulin deficiency)
A. Immune-mediated
B. Idiopathic
II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance).

METFORMIN :

Metformin is the representative of the class Biguanide. The mechanism of action of biguanide is still not completely understood. However, the principle mode of action is via potentiation of insulin action at an unknown intracellular locus, resulting in decreased hepatic glucose production by both gluconeogenesis and glycogenolysis. Metformin also stimulates tissue uptake of glucose, particularly in muscle, and is thought to reduce gastro-intestinal absorption of carbohydrate. The action of metformin does not involve stimulation of pancreatic insulin secretion and therefore it is still a beneficial agent when β-cell function has declined. Another advantage of metformin over insulin secretagogues, and sulphonylureas, in particular, is that it does not cause hypoglycaemia and is not associated with weight gain. It has been shown that diabetes-related death was reduced by 42% in overweight subjects who took metformin for10 years, compared to those who took conventional therapies such as a sulphonylurea or insulin. Myocardial infarction was also reduced by 39% over the 10-year follow-up period. Consequently, metformin has become the first-line therapy for glycemic control when oral agents are indicated especially in overweight and obese patients.[1]

Name	Mechanism of action	Examples	Advantage	Disadvantage
Biguanide	Decreased hepatic glucose, weightloss, insulin resistance Increased glucose utilization	Metformin	Weight loss, improved lipid profile, no hypoglycaemia	Lactic acidosis, Diarrhoea, nausea

Adverse effects :

The most common adverse effects of metformin, affecting about a third of patients, result from gastro-intestinal disturbances including anorexia, nausea, abdominal discomfort and diarrhea. In some patients, diarrhea can be extreme

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and can preclude metformin use. However; the gastro-intestinal side effects are usually transient and can be minimized by starting with a low dose, increasing the dose slowly and administering the drug with or after food.Because of its relatively slow onset of action and gastrointestinal symptoms with higher doses, the dose should be escalated every 2 to 3 weeks based on SMBG measurements .The major toxicity of metformin, lactic acidosis, can be prevented by careful patient selection. Metformin should not be used in patients with renal insufficiency [serum creatinine>133 µmol/L (1.5 mg/dl) in men or >124 µmol/L (1.4 mg/dl) in women, with adjustments forage], any form of acidosis, congestive heart failure, liver disease, or severe hypoxia. Metformin should be discontinued in patients who are seriously ill, in patients who can take nothing orally, and in those receiving radiographic contrast materials. Insulin should be used until metformin can be restarted. Though well tolerated in general, some individuals develop gastrointestinal side effects (diarrhea, anorexia, nausea, and metallic taste) that can be minimized by gradual dose escalation.[2]

Vitamin B_{12}deficiency: As can occur in pernicious anemia causes a macrocytic anemia and may also damage the nervous system. Neurologically, it most commonly produces a spinal cord syndrome (myelopathy) affecting the posterior columns (loss of position and vibratory sense) and corticospinal tracts (hyperactive tendon reflexes with Babinski responses); it also damages peripheral nerves, resulting in sensory loss with depressed tendon reflexes. Damage to cerebral myelinated fibers may also cause dementia. The mechanism of neurologic damage is unclear but may be related to a deficiency of S-adenosylmethionine (required for methylation of myelin phospholipids) due to reduced methionine synthase activity or accumulation of methylmalonate, homocysteine, and propionate, providing abnormal substrates for fatty acids synthesis in myelin. The neurologic signs of vitamin B12deficiency are usually associated with macrocytic anemia but on occasion may occur in its absence.

Treatment with parenteral vitamin B12(1000 µg intramuscularly daily for a week, weekly for a month, and monthly for life for pernicious anemia) stops progression of the disease if instituted promptly, but reversal of advanced nervous system damage will not occur.[3]

The proposed mechanism to explain metformin induced Vit B12 deficiency among patients with T2DM patients:

Alteration in small bowel motility which stimulates bacterial over growth and consequential Vit B12 deficiency, competitive inhibition or inactivation of Vit B12 absorption alteration in intrinsic factor (IF) levels and interaction with the cubulin endocytic receptor. Metformin also has been shown to inhibit the calcium dependent absorption of the Vit B12-IF complex at the terminal ileum. This inhibitory effect is reversed with calcium supplements. [4,5]

II. REVIEW OF LITERATURE

- **Mayuresh D. Kiran et al.(2017)** Conducted A clinical study to determine metformin as a cause of serum vitamin B12 decrease and effect of combination of metformin and mecobalamin on serum vitamin B12 levels in type 2 diabetics 500 enrolled, 321 patients completed the study for duration of 6months, divided in two periods of 3 months each. At the end first period of 3months the vitamin B12 levels were compared form Metformin vs. that of otherantidiabetics. In second period of 3 months a combination of metformin andmecobalamin was given instead of plain metformin and vitamin B12 levels wererepeated at the end of this period. There was reduction in vitamin B12 levels with metformin with levels of 272.5pg/ml compared to 714.6pg/ml with other antidiabetics at the end of first period. The levels increased from 272.5pg/ml to 615.9 pg/ml at the end of second period after receiving the combination of metformin and mecobalamin.[6]

- **Rudra Prasad Roy et al.(2020**) conducted a study of Vitamin B12 deficiency and peripheral neuropathy in metformin-,treated early Type 2 diabetes mellitus. Itis a cross- sectional study involving randomly selected ninety patient's male 56, female 34 between age groups of 35 and 70 years, comparing those who had received >6 months of metformin Group A n = 35 with those without metformin Group B n = 35 and patients taking metformin with other oral hypoglycemicsagent Group C n = 20. Comparisons were made clinically, biochemically and with electrophysiological measures. Comorbidities contributing to neuropathy were excluded from the study.

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Group A patients were prone to develop peripheral neuropathy comparing Group B and Group C. There was insignificant low- level plasma folic acid in Group A (16.47 ng/ml) than in Group B (16.81 ng/ml) and Group C (22.50 ng/ml). There was significantly high level of Hcy in Group A (mean 17.35 µmol/L) and Group C (mean 16.99 µmol/L) than in Group B (mean 13.22 µmol/L). Metformin users even for 2 years showed evidence of neuropathy on nerve conduction velocity though their body mass index and postprandial blood sugar were maintained. There was significant difference in between groups regarding plasma, folic acid, and Hcy level as significance level <0.05 in all three groups.[7]

- **Davis Kibirige et al.(2013)** conducted Vitamin B12 deficiency among patients with diabetes mellitus: is routine screening and supplementation justified. Vitamin B12 is an essential micronutrient required for optimal hemopoetic, neuro-cognitive and cardiovascular function. Biochemical and clinical vitamin B12 deficiency has been demonstrated to be highly prevalent among patients with type 1 and type 2 diabetes mellitus. It presents with diverse clinical manifestations ranging from impaired memory, dementia, delirium, peripheral neuropathy, sub-acute combined degeneration of the spinal cord, megaloblastic anemia and pancytopenia. This review article offers a current perspective on the physiological roles of vitamin B12, proposed pathophysiological mechanisms of vitamin B12 deficiency, screening for vitamin B12 deficiency and vitamin B12 supplementation among patients with diabetes mellitus.[8]

- **Sampson Omagbemi Owhinet al.(2016)** conducted a study on Prevalence of vitamin B12 deficiency among metformin-treated type 2 diabetic patients in a tertiary institution, South-South Nigeria it is a case-control, prospective, analytical, observational study of 200 adult participants (100per group) attending the Endocrinology, Medical Out-patients Clinic of Irrua Specialist Teaching Hospital, Irrua, Edo State, Nigeria. The participants serum vitamin B12 levels were determined using an immunoassay technique. Data were presented using tables and charts. Chi-square test was used to compare non-continuous proportional variables. The prevalence of vitamin B12 deficiency was 41% and 20% among metformin-treated and metformin-naïve type 2 diabetes mellitus groups, respectively (p = 0.001). Borderline vitamin B12 status was present among 59% of metformin-treated group and 80% of metformin-naïve group (p = 0.001). Neither metformin-treated nor metformin-naïve groups had normal serum vitamin B12 levels.[9]

- **Serdar Oltet al.(2017)** conducted an Investigation of the vitamin B12 deficiency with peripheral neuropathy in patients with type 2 diabetes mellitus treated using metformin Patient's laboratory and electromyography (EMG) data were retrospectively reviewed. Patients with no EMG report and other necessary information were excluded from the study. Eighty-six patients with type 2 DM using metformin were included in the study. Of these patients, 26 were males and 60 were females. The mean age of the patients was 55.1±7.7 years. The mean body mass index of the patients was 29.1±9.01 kg/m2. The mean HbA1c level of the patients was 8.6%±2.1%. The mean duration of diabetes was 8.02±5.4 years. The incidence of vitamin B12 deficiency was 38.4%. Peripheral neuropathy was detected in 33.7% patients. There was no statistically significant difference in vitamin B12 levels between patients with peripheral neuropathy and those without peripheral neuropathy.[10]

- **Twinkal R. Upadhyayet al.(2016)** conducted an Association Between Serum B12 and Serum Homocysteine Levels in Diabetic Patients on Metformin. Mean s.B12 and s.Hcy levels of 30 cases (diabetics on metformin <5years) were compared with 30 diabetic controls not on metformin and 31 non diabetic controls and statistically analysed by ANOVA and post-hoc tests. No significant differences in either s.B12 mean or s.Hcy mean were found between cases and diabetic controls. s.B12 mean did not differ significantly but s.Hcy mean was significantly higher among no diabetics as compared to diabetic control. s. B12 level of Non-diabetic group was in borderline category while mean s. B12 levels of cases and diabetic control groups was in normal category but nearer to the lower cut off.

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Mean s.Hcy values in all the groups were high. Pearson correlation showed strong association between s.B12 and s.Hcy in all the groups. Additionally equation based on linear regression was derived to calculate either of the s.B12 or s.Hcy. On Receiver Operative Characteristic (ROC) curve, area under curve value was 0.842 for the value of s.Hcy.[11]

- **Amal N. Alshammariet.al.(2020)** conducted a Vitamin B12 deficiency and the knowledge and practice of physicians regarding screening for vitamin B12 deficiency among type 2 diabetic patients on metformin in selected hospitals in Riyadh, Saudi Arabia. We conducted a cross‐sectional study at the diabetic clinics of four hospitals in Riyadh, Saudi Arabia. Type 2 diabetes mellitus patients who were on metformin for at least 1 year were included in the study. Associations between B12 deficiency and age, duration of type 2 diabetes mellitus (T2DM), duration of use and dosage of metformin, and use of proton pump inhibitors (PPIs) were determined. Out Of 363 T2DM patients, 206 were males and 157 were females. There were 205 patients 56.5% who had a daily dose of 750 mg of metformin. The most commonly used oral hypoglycaemic agent was gliclazide only in 138 (38.4%) of patients. There were 107 patients (29.5%) who were on PPIs. There were 210 patients (57.9%) who were on vitamin B12 supplementation, of which 111 (30.6%) had a daily dose of 200 mcg. The use of vitamin B12 supplement, duration of T2DM and duration of metformin use was significantly higher among females. The use of vitamin B12 supplement was significant among patients who were 46 years old and above. There were only 16 patients (4.4%) who had available serum vitamin B12 levels. Only 44.0% of the physician respondents know the current recommendation of American Diabetes Association on vitamin B12 screening and supplementation among diabetic patients, and 21.0% never prescribe vitamin B12 to their patients.[12]

- **Moayadshahwanet al.(2018)** conducted a study on prevalence and risk factors of vitamin b12 deficiency among patients with type II diabetes on metformin: a study from northern region of united Arab emirates . A cross-sectional study was conducted on 213 patients having diabetes type II were randomly selected to be part of the study in Northern Regions of the UAE, from June 2014 to February 2015. The patients aged >45 years and who had taken metformin for at least 3 months were recruited with regular follow-up at the outpatient clinic. The patients were included in a survey after which they had their serum B12 levels measured. Serum B12 levels <150 pg/ml are defined as the B12 deficiency. Results: About 48% of diabetic patients had confirmed the B12 insufficiency through laboratory tests. The patients on metformin had statistically lower values of B12 (p=0.002). The majority of participants n (%) took metformin had neuropathy, hypertension, dyslipidemia, numbness or paresthesia, and depression, or mood changes 140 (70%), 183 (91.5%), 134 (67%), 136 (68%), 161 (80.5%), and 120 (60%), respectively.[13]

- **Priti Agarwal et al.(2016)** conducted A comparative study of levels of vitamin B12 in patients of type 2 diabetes mellitus on metformin and not on metformin at tertiary care center.The study group has 50 patients with a diagnosis of T2DM and a prescription history of metformin for ≥18 months and control group has 50 patients with diagnosis of T2DM and no history of metformin use in the past five years. The following data was recorded for each patient: age, sex, weight, height, body mass index (BMI), years with diabetes, total daily dose of and years on metformin. Serum vitamin B12 was measured using an immunoassay method. Data were statistically analyzed. Mean serum vitamin B12 levels in the study group was 431.84±265.76 and in control was 744.76±271.927 and the difference was statistically significant. Mean serum vitamin B12 levels in vegetarians (547.27±303.011) were significantly lower than in non-vegetarian (699.22±307.992) (p value 0.029). A significant negative correlation existed between the S. vitamin B12 and duration of diabetes (r= -0.445) by using Pearson's correlation coefficient in study group.[14]

- **Mohd Mahmood et al.(2017**) conducted Prescription Pattern Analysis of Antidiabetic Drugs in Diabetes Mellitus and Associated Comorbidities. A prospective observational study was conducted on inpatients admitted to

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various wards in a tertiary care hospital for period of 6 months between October 2016-March 2017. Prescriptions of the patients are collected in a designed questionnaire form and the relevant information is recorded and analysed. 235 patient prescription patterns were studied, out of which 62.97% were males and 37.02% were females. Most of the patients were in the age group of 41-60. Hypertension was the most commonly found co-morbid condition. Rapid acting insulin was mostly prescribed during hospital stay. Metformin was the commonly prescribed oral hypoglycaemic agent followed by glimepiride.[15]

- **Joyce Zalaket et al.(2017)** conducted Vitamin B12 deficiency in diabetic subjects taking metformin: A cross sectional study in a Lebanese cohort we conducted a cross sectional study on 200 Lebanese individuals. The cohort consisted of subjects with an established diagnosis of T2D and who have been on metformin for at least three months. The patients were subjected to a questionnaire, medical record review, and vitamin B12 level measurement. Thirty three percent of the subjects were found to have borderline values of the serum vitamin B12 (148e220 pg/dl) while 22.5% had a clear, deficiency (levels less than 148 pg/dl). We found a highly significant inverse correlation between the dose and duration of metformin treatment and the serum levels of vitamin B12. Furthermore, both borderline and low levels of vitamin B12 were associated with the presence of different neuropathies and macrocytic anemia in a dose dependent manner.[16]

- **Jolien de Jager et al.(2019)** Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial Multicentre randomised placebo controlled trial. Setting Outpatient clinics of three non-academic hospitals in the Netherlands. Participants 390 patients with type 2 diabetes receiving treatment with insulin. Intervention 850 mg metformin or placebo three times a day for 4.3 years. Main outcome measures Percentage change in vitamin B-12, folate, and homocysteine concentrations from baseline at4, 17, 30, 43, and 52 months. Results Compared with placebo, metformin treatment was associated with a mean decrease in vitamin B-12 concentration of −19% (95% confidence interval −24% to−14%; P<0.001) and in folate concentration of −5% (95% CI −10% to −0.4%; P=0.033), and an increase in homocysteine concentration of 5% (95% CI −1% to 11%; P=0.091). After adjustment for body mass index and smoking, no significant effect of metformin on folate concentrations was found. The absolute risk of vitamin B-12 deficiency (<150 pmol/l) at study end was 7.2 percentage points higher in the metformin group than in the placebo group (95% CI 2.3 to 12.1; P=0.004), with a number needed to harm of 13.8 per 4.3 years (95% CI 43.5 to 8.3). The absolute risk of low vitamin B-12 concentration (150-220 pmol/l) at study end was 11.2 percentage points higher in the metformin group (95% CI 4.6 to 17.9; P=0.001), with a number needed to harm of 8.9 per 4.3 years (95% CI 21.7 to 5.6). Patients with vitamin B-12 deficiency at study end had a mean homocysteine level of 23.7 µmol/l (95% CI 18.8 to 30.0 µmol/l), compared with a mean homocysteine level of 18.1 µmol/l (95% CI 16.7 to 19.6 µmol/l; P=0.003) for patients with a low vitamin B-12 concentration and 14.9 µmol/l (95% CI 14.3 to 15.5 µmol/l; P<0.001 compared with vitamin B-12 deficiency; P=0.005 compared with low vitamin B-12) for patients with a normal vitamin B12concentration (>220 pmol/l).[17]

- **AnuvarshaKatrothet al.(2018)** conducted a study on Diabetes Mellitus and Metformin: Fatal Vitamin B12 Deficiency Associated with Anemia and Sepsis in a Young Adult. Metformin is recommended as the first-line therapy to treat type 2 diabetes mellitus with better efficacy. We present a young adult with severe fatigue and dyspnea along with difficulty during the walk and tingling sensation in both the lower limbs. He had T2DM for 9 years and continuing metformin 1 g daily for five years. He presented to the hospital with untreated wounds over lower limbs. His haematological reports showed the megaloblastic anaemia and transfused with several pints of packed red blood cells (PRBCs). The patient developed sepsis during hospitalization and started on antibiotics. After several PRBC transfusions and aggressive treatment also patient did not improve and succumbed on 5th day of hospitalization.anemia. Metformin-induced

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VitB12 deficiency was suspected because of long-term use of metformin. Coomb's test was negative. These all findings suggested the final diagnosis of 'Megaloblastic anemia' due to VitB12 deficiency.[18]

- **Lael Reinstatler et al.(2006)** Conducted a study Association of Biochemical B12 Deficiency With Metformin Therapy and Vitamin B12 Supplements. Analysis of data on U.S. adults $50 years of age with (n = 1,621) or without type 2 diabetes (n = 6,867) from the National Health and Nutrition Examination Survey (NHANES), 1999–2006. Type 2 diabetes was defined as clinical diagnosis after age 30 without initiation of insulin therapy within 1 year. Those with diabetes were classified according to their current metformin use. Biochemical B12 deficiency was defined as serum B12 concentrations #148 pmol/L and borderline deficiency was defined as .148 to #221 pmol/L. Biochemical B12 deficiency was present in 5.8% of those with diabetes using metformin compared with 2.4% of those not using metformin (P = 0.0026) and 3.3% of those without diabetes (P = 0.0002). Among those with diabetes, metformin use was associated with biochemical B12 deficiency (adjusted odds ratio 2.92; 95% CI 1.26–6.78). Consumption of any supplement containing B12 was not associated with a reduction in the prevalence of biochemical B12 deficiency among those with diabetes, whereas consumption of any supplement containing B12 was associated with a two-thirds reduction among those without diabetes.[19]

- **Moatassem S. Amer et al.(2015)** Conducted a study on Link between vitamin B12, type 2 diabetes mellitus, and bone mineral density in elderly patients. A case control study was conducted on 61 participants, 60 years of age, divided into 31 cases of patients with diabetes and 30 age-matched healthy controls. Patients receiving vitamin B12 supplements were excluded. The relationship between BMD and serum levels of vitamin B12 was examined. Borderline/deficient serum B12 status was more common in the control group; it was found in 53.33% of the controls and 25.80% of diabetic patients. The mean serum vitamin B12 concentration was 820.65 ± 544.77 pg/mL in patients with diabetes and 677.80 ± 619.89 pg/mL in healthy control participants (p ⅟4 0.34). Serum vitamin B12 concentration showed no significant difference between osteoporotic patients, osteopenic patients, and normal patients among the diabetic group.[20]

III. METHODOLOGY

Data collection form:
Demographic data, clinical data, and Treatment chart

Methods:
Patient information's will be collected from patient medical records

Study site:
The study will be carried out in the Department of General medicine, VIMS, Bellary District, Karnataka

Duration of study:
The study will be conducted for a period of six months

Study design:
A prospective observational study

Proposed Sample Size:
100 patients

Source of data:
Patient's profile sheets and laboratory investigation reports

Vitamin B12 assessing method:
Immunoassay system**:** ADVIA Centaur® XP
Vit B12 assessing kit: SIEMENS VB12 kit (ADVIA Centaur®**)**

Informed consent:
Will be given in written format

Study Criteria:
The study will be carried out by considering the following inclusion and exclusion criteria

Inclusion criteria:

- Both In-patient and Out-patient and either gender between the age group of 18years to 65 years
- Type II DM patients on metformin therapy with or without co-morbidities in the General Medicine Ward

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- Patients those who are newly to be detected with vitamin B12 deficiency on chronic metformin therapy
- Patients who are individually willing to participate in the study, and signed in the informed consent form

Exclusion criteria:

- Emergency ward patients
- The patients who are already found to be vitamin B12 deficiency and on metformin therapy
- Elderly patients

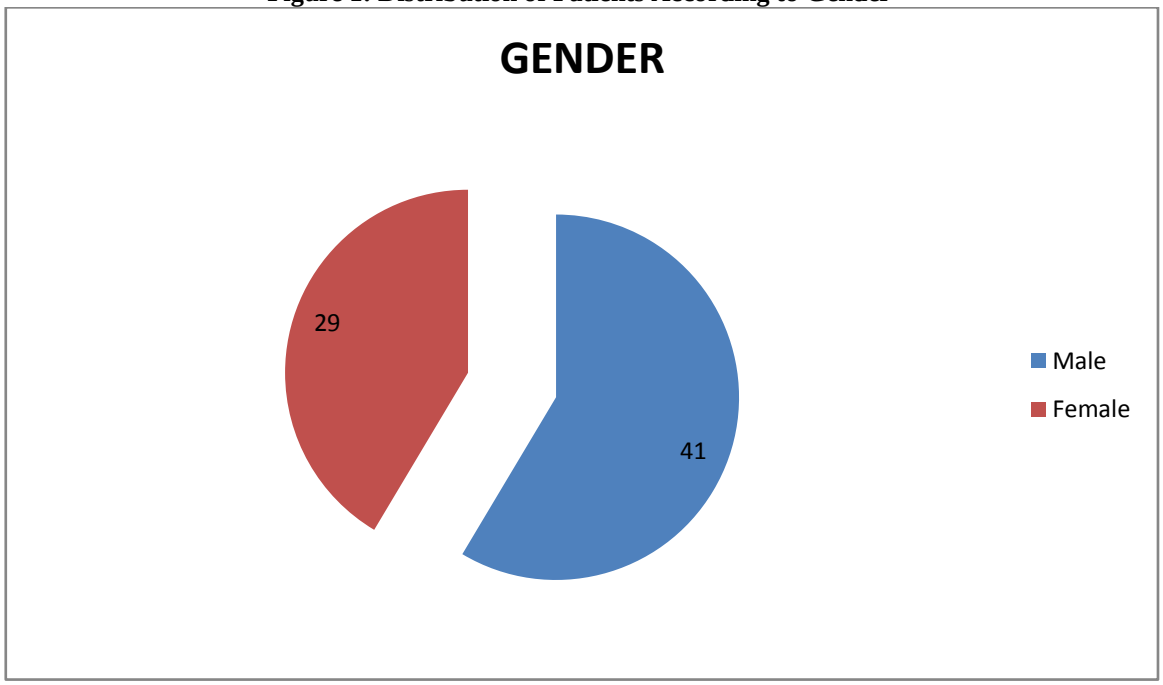
IV. RESULTS

A Prospective Observational study conducted in Department of General Medicine at VIMS from September 2019 to February 2020, Bellary,Karnataka. A total number of 70 patients have include during the study ,out of 70 patients 41 were males(58%) and 29 females(41%).

Table 1: Distribution of patients According to Gender

GENDER	TOTAL NUMBER	PERCENTAGE
Male	41	58%
Female	29	41%

Figure 1: Distribution of Patients According to Gender



In this study among 70 subjects prevalence of Type 2 Diabetes mellitus was more in age group between 51-65 years

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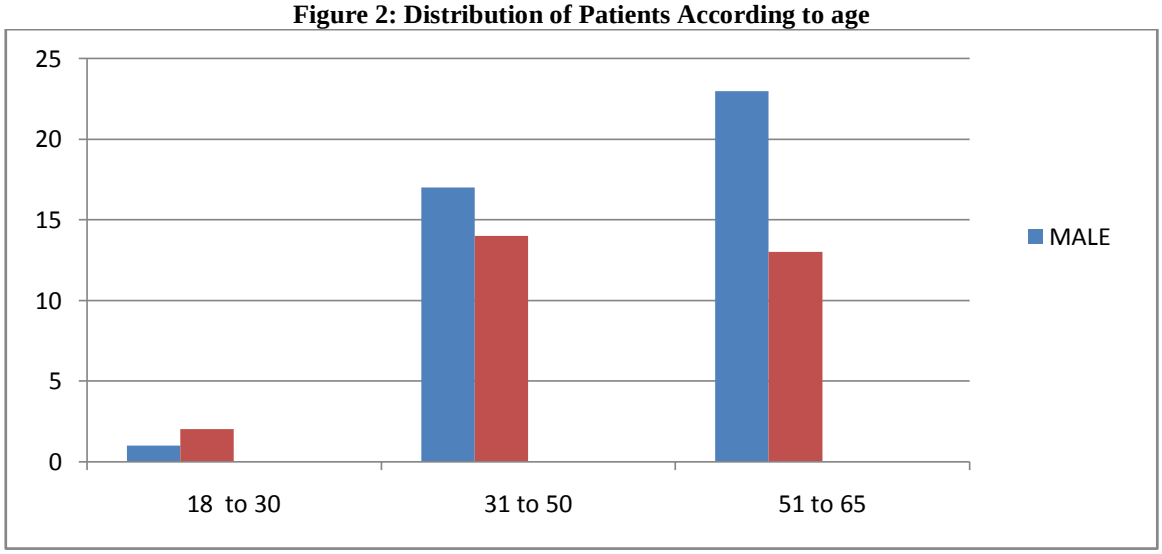
TABLE 2: Distribution of Patients According to age

AGE GROUP (IN YEARS)	MALE (n=41)	FEMALE (n=29)	TOTAL (n=70)
18-30	1	2	3
31-50	17	14	31
51-65	23	13	36

Figure 2: Distribution of Patients According to age



In this study among 70 patients, 14 male patients were diagnosed as Type 2 Diabetes mellitus and 29 male patients were diagnosed as Diabetes mellitus with Co-Morbidities, whereas 10 female patients were diagnosed as only Type 2 Diabetes mellitus and 17 female patients were diagnosed with Diabetes mellitus with Co-Morbidities.

TABLE 3: Distribution of Patients According to Diagnosis

GENDER	DIABETES MELLITUS	DM WITH CO-MORBIDITIES	TOTAL
MALE	14	29	43
FEMALE	10	17	27

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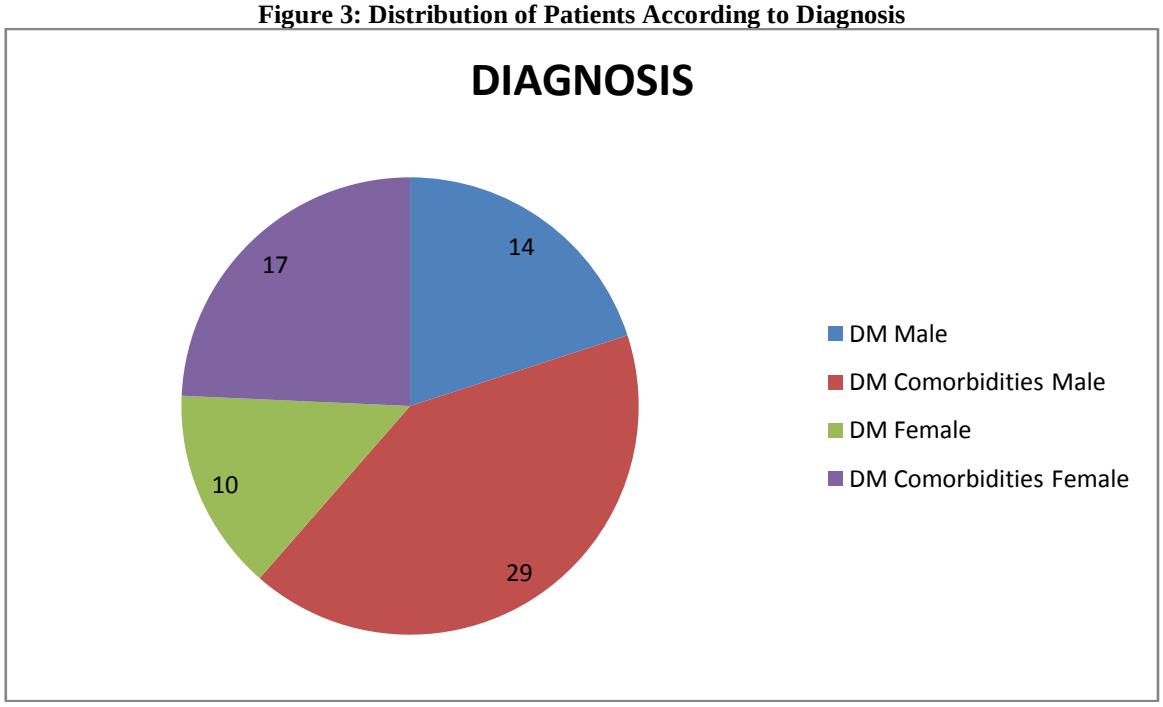
Figure 3: Distribution of Patients According to Diagnosis

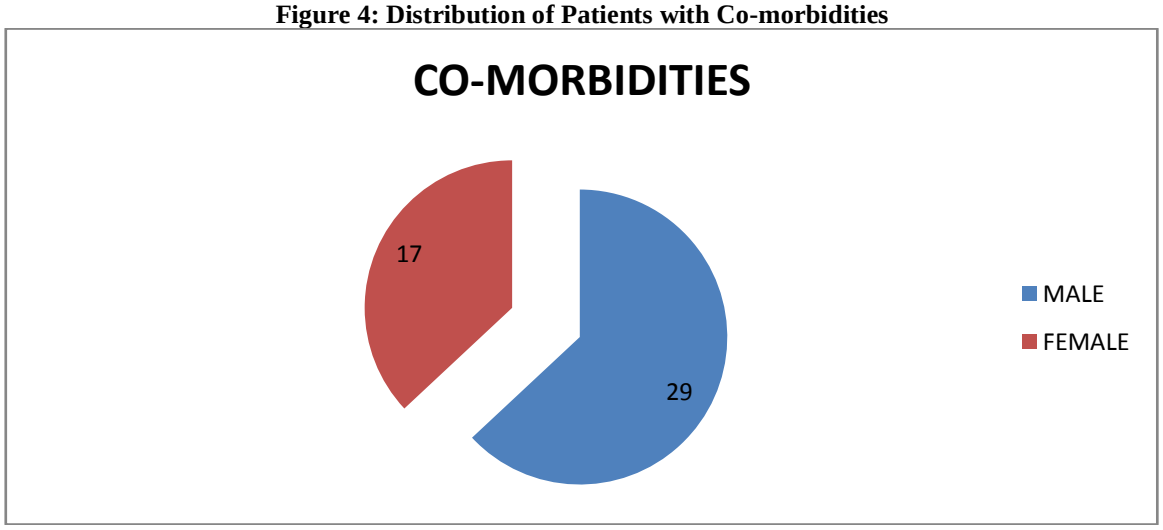


In this study among 70 patients, 46 patients were Diagnosed with Comorbidities among them 29 (41.27) were male and 17 (24.28) were female.

TABLE 4: Distribution of Patients with Co-morbidities

GENDER	CO-MORBID PATIENTS	PERCENTAGE
MALE	29	41.27%
FEMALE	17	24.28%

Figure 4: Distribution of Patients with Co-morbidities



In this study among 70 patients 24 patients were diagnosed without Co-morbidities among them 14 (20%) were Male and 10 (14.28%) were Female.

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TABLE 5: Distribution of Patients without Co-morbidities

GENDER	WITHOUT CO-MORBIDITIES	PERCENTAGE
MALE	14	20%
FEMALE	10	14.28%

Figure 5: Distribution of Patients without Co-morbidities

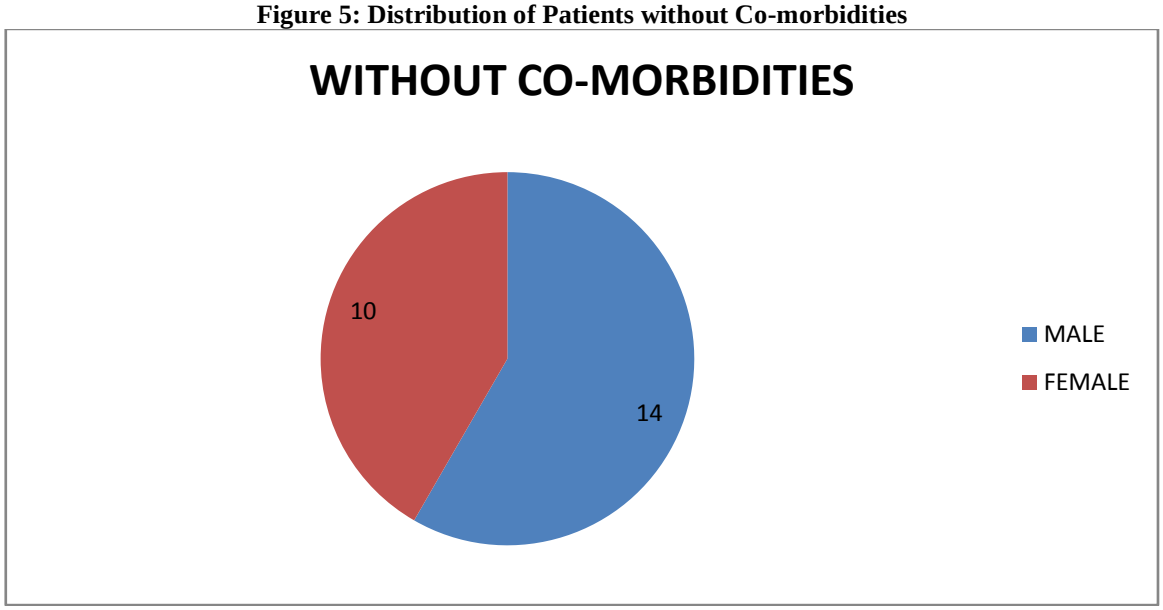

TABLE 6: Distribution of patients based on Co-Morbidities

CO-MORBIDITIES	MALE	FEMALE
Type 2 DM With Hypertension	17	8
Type 2 DM With Hypertension with IHD	2	4
Type 2 DM With Other (COPD, ARF, DKA, PTB, CLD, ALD, Anaemia, Hypothyroidism, Hypertensive Emergency, Diabetic Foot.	10	5

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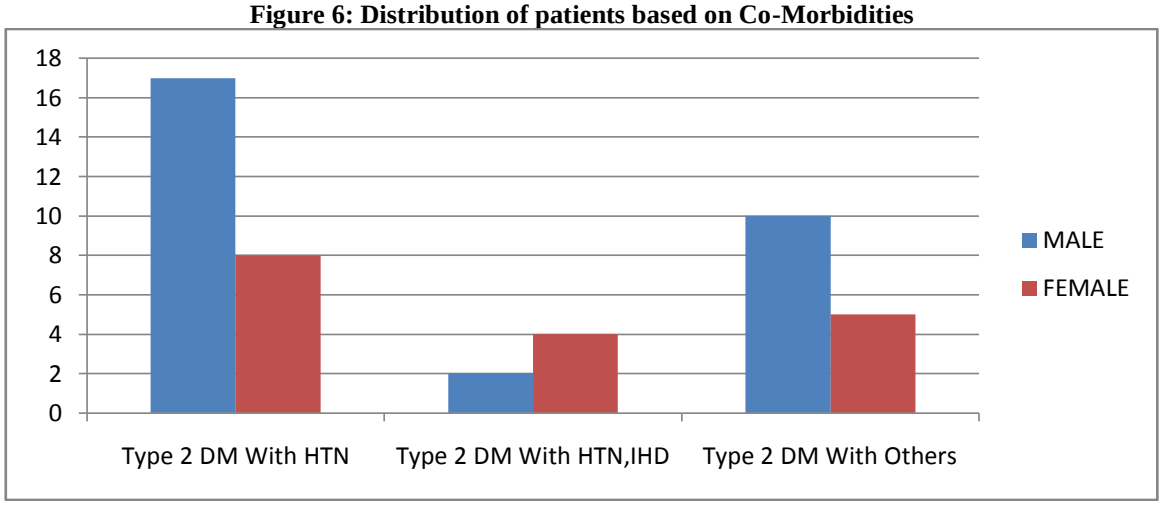
Figure 6: Distribution of patients based on Co-Morbidities



In this study population of Type 2 Diabetes Mellitus the most commonly prescribed hypoglycemics drug is Metformin followed Glimepiride is given more commonly in combination with Metformin followed by other less common hypoglycaemic drugs like pioglitazone, Voglibose and Vidagliptin.

TABLE 7: Distribution of patients according to type of Hypoglycemics prescribed.

Type of Hypoglycaemic	Number of patient prescribed
Metformin	70
Glimepiride	51
Pioglitazone	2
Voglibose	1
Vidagliptin	1

Figure 7: Distribution of patients according to type of Hypoglycemics prescribed.

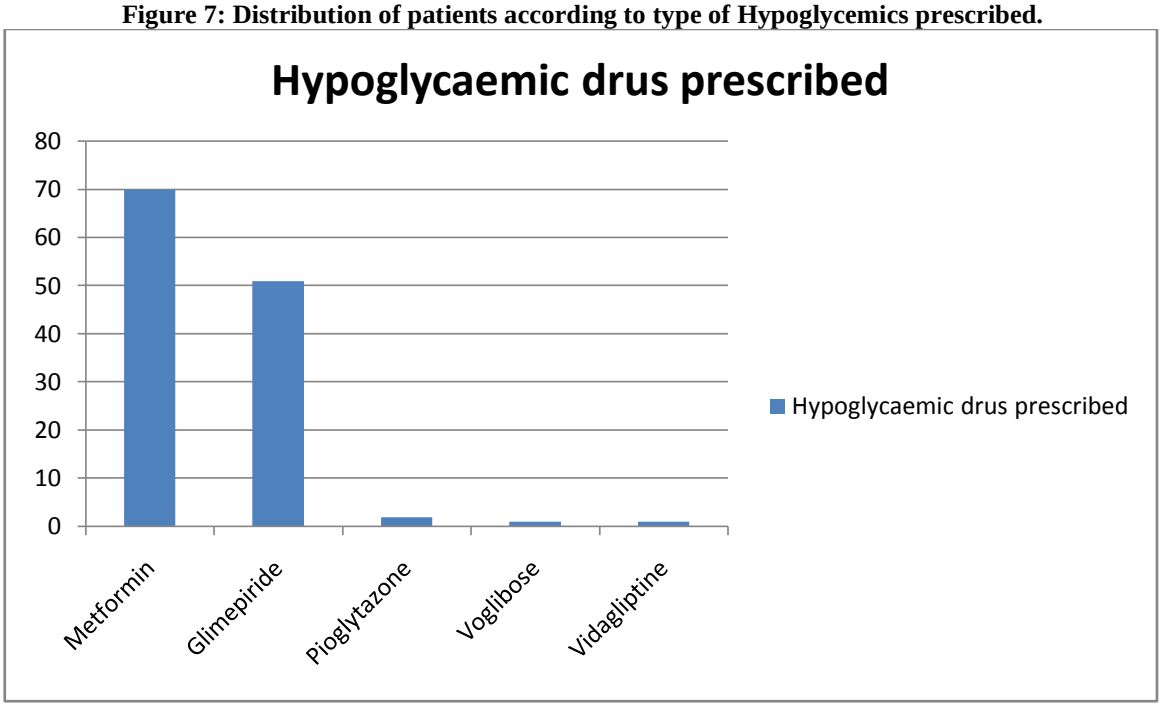


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TABLE 8: Distribution of patients based on combination of oral Hypoglycemics agents.

Other OHA's with Metformin	NUMBER OF PATIENTS
Only Metformin	11
Metformin + Glimepiride	48
Metformin + Glimepiride +pioglitazone	02
Metformin +Glimepiride +Vidagliptin	01
Metformin + Voglibose	01
Insulin along with OHA's	15

Figure 8: Distribution of patients based on combination of oral Hypoglycemics agents.

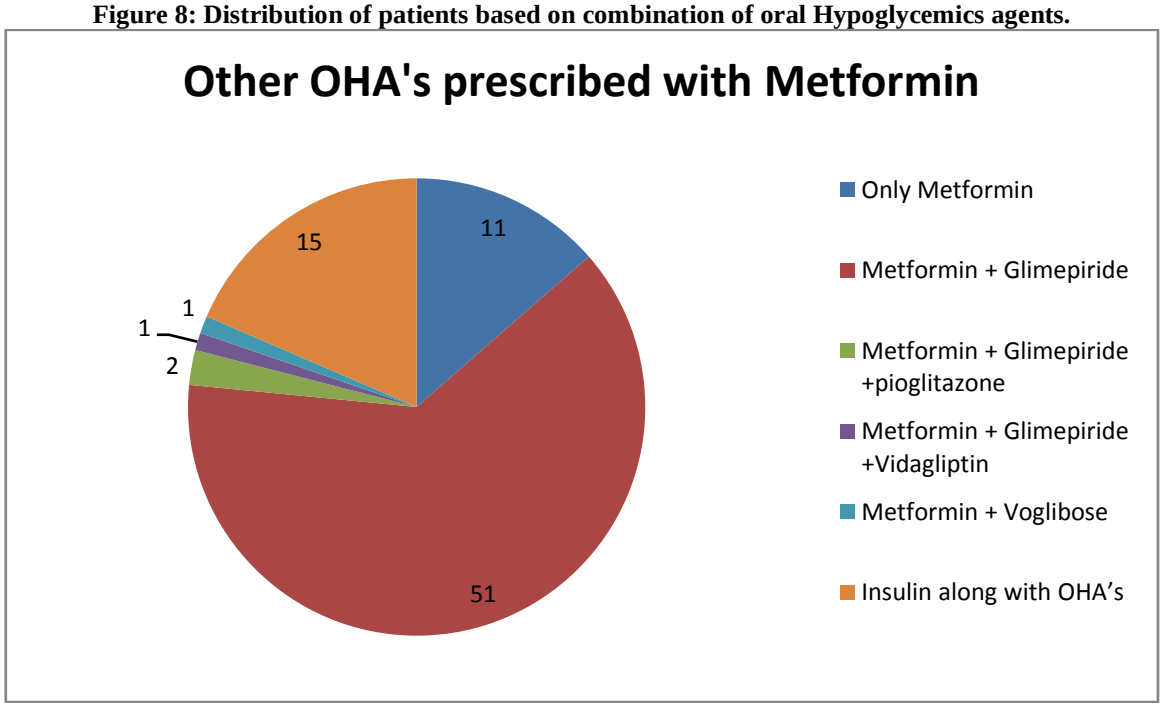

TABLE 9: Distribution of patients based on Vitamin B12 levels.

Vit B12 Category	Number of patients
Deficient (<211 pg/ml)	12
Normal (211-911 pg/ml)	26
Borderline (<350 pg/ml)	20
Above Normal (>911 pg/ml)	12

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Figure 9: Distribution of patients based on Vitamin B12 levels.

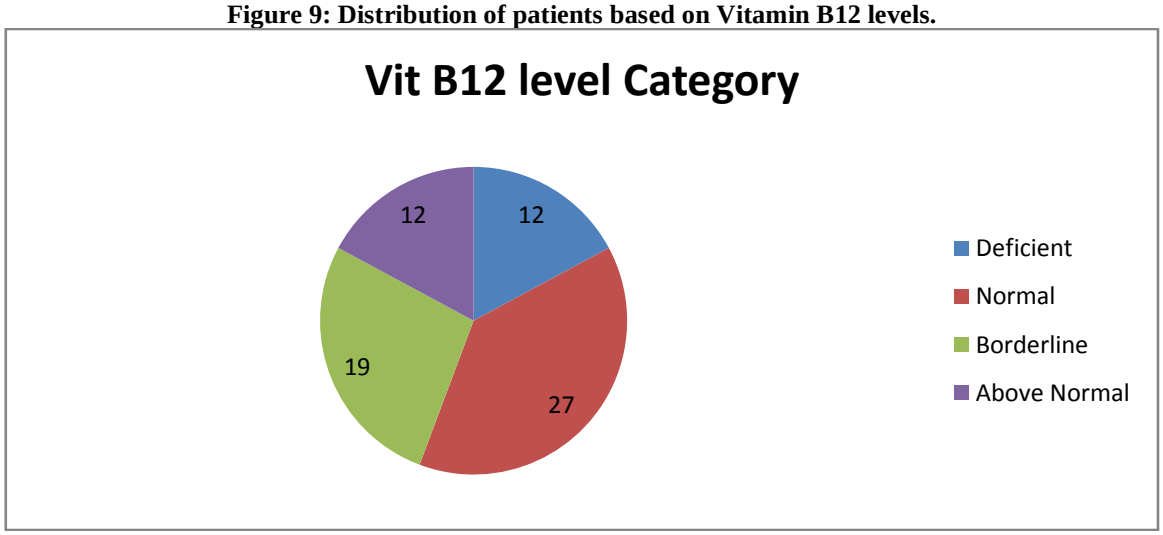
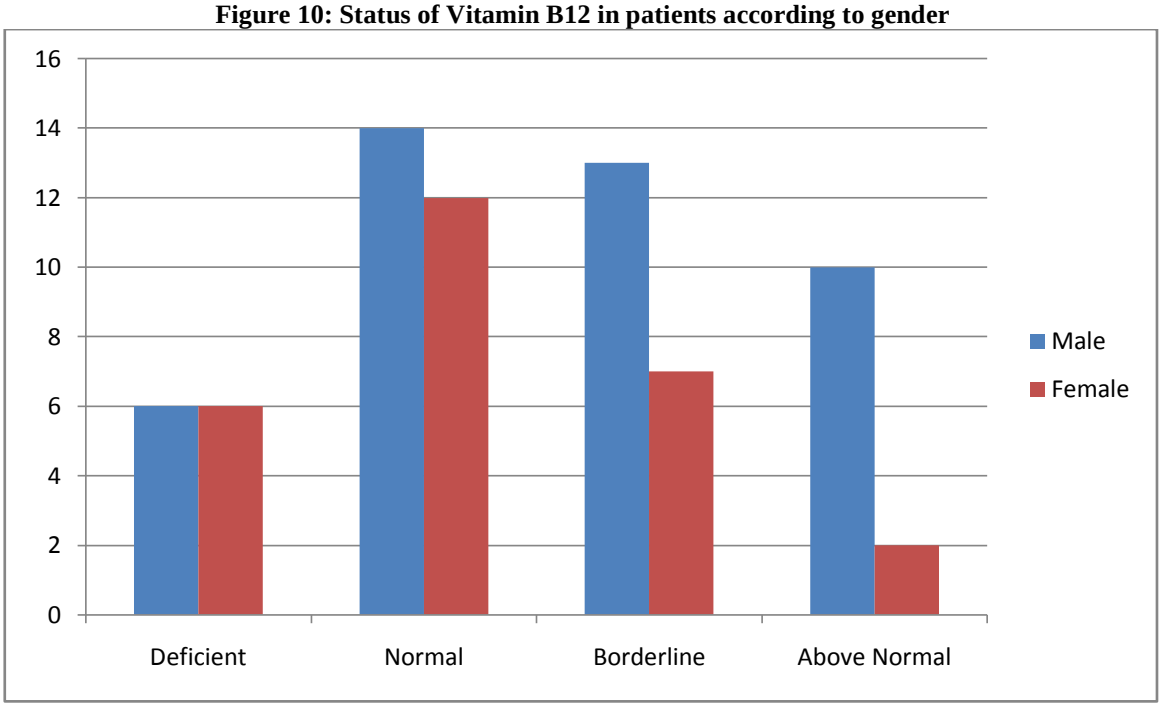


TABLE 10: Status of Vitamin B12 in patients according to gender

Vit B12 Category	Male	Female
Deficient (<211 pg/ml)	06	06
Normal (211-911 pg/ml)	14	12
Borderline (<350 pg/ml)	13	07
Above Normal (>911 pg/ml)	10	02

Figure 10: Status of Vitamin B12 in patients according to gender



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V. DISCUSSION

A prospective observational study was conducted for period of 6 months in tertiary care teaching hospital at VIMS, ballari. The aim of the study is to observe occurrences rate of metformin induced Vit B12 deficiency in type II DM patients.

Metformin plays an important role in the type II DM Patients, which has more safety and efficacy than other oral hypoglycaemic agents. Metformin has its benefits and eventually same harmful effects induces Vit B12 deficiency that cause to neurological problems like paraesthesia, ataxia, peripheral neuropathy.

In our study total 70 patients were assessed among them 43 male and 27 females, where as in 43 males, 14 with DM and 29 DM with co-morbidities. In 27 females, 10 with DM and 17 DM with co-morbidities. Prevalence of type II DM is more in male than female in the age group of (51- 65 yrs.). A similar study was conducted by **Joyce Zalatet et al**. on **vitamin B12 deficiency in diabetic patients taking metformin.**Across-sectional study conducted for 6 months in 200 subjects where 22.5 % of subjects had clear deficiency of vitamin B12 and 33% of subjects found to have borderline vitamin B12.

Another similar study was conducted by **Mayuresh D. Kiran et al.** on a clinical **study to determine metformin has a cause of serum vitamin B12 decrease and effect of combination of metformin and mecobalamin on serum vitaminB12 levels in type 2 diabetics. A systematic multi-centred, comparative clinical study was planned with observational dual objective. A total of T2DM patients were recruited for the study.**A total of 500 subjects were included in the study and the study was conducted for the period of six months. There was reduction in vitamin B12 levels with metformin with levels of 272.5pg/ml compared to 714.6pg/ml with other anti-diabetics at the end of 1st period. The levels increased from 272.5pg/ml to 615.9pg/ml at the end of second period after receiving the combination of metformin and mecobalamin.

Most commonly prescribed oral hypoglycaemic drugs to patients were metformin, glimepiride followed by pioglitazone, Voglibose, Vidagliptin.

Our study reveals that among 70 patients, 12 patients were found to be Vit B12 deficient whereas 5 male and 7 females. 19 patients were found to be borderline vitamin B 12 levels whereas 13 male and 7 females.

VI. CONCULSION

A Prospective observational study was conducted for a period of six months at VIMS, ballari. Total 70 patients were assessed among them 43 male and 27 females. Whereas 12 patients were found to be vitamin B12 deficiency and 19 patients were found to be borderline vitamin B12 levels. Prevalence of type II DM is more in male than female due to social habits and life style (alcoholic and smokers).

According to results obtained from our study shows that patients with long term use of metformin therapy may have chances of vitamin B1 deficiency. Moreover, patients with low levels of vitamin B12 were suggested to take vitamin B12 supplements.

All the type 2 Diabetes Mellitus patients who are on metformin must be counselled degrading the possible side effects of long-term metformin usage and should also be counselled regarding the management of vitamin B12 deficiency through supplementation and dietary modifications

As a pharmacist it is also concluded that all these observations lead us to make strong recommendations for type II DM patients to screen their vitamin B12 levels regularly on long term use of metformin therapy.

STRENGTHS AND LIMITATIONS

STRENGTHS

- Our study helps us to produce the knowledge and information about Metformin and vitamin B12 deficiency.
- It mainly highlights the adverse effects of long term usage of metformin
- This study create awareness of health in the future perspective in Diabetic population
- The study also focused on providing counseling regarding adverse effects of Metformin and its management through pharmacological and non- pharmacological approach.

WEAKNESSES

- The study only focused on specific ADR of specific drug (Metformin induced vitamin B12 deficiency)
- Time consuming
- Expensive

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