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"The Vitamin B12 Levels In Type 2diabetes Mellitus Patients on Metformin and Not on Metformin"

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ABSTRACT
Introduction- Metformin is the most commonly used first line oral hypoglycaemic agent in the treatment of type 2 diabetes mellitus. It is a known fact that age and the duration of diabetes can affect the vitamin B12 status of a patient. Vitamin B12 deficiency is assessed by estimating the Vitamin B12 levels. Low vitamin B12 level is may occur in diabetics due to Metformin therapy . Many cross sectional studies shows chronic metformin therapy reduced the vitamin B12 levels. Often the initial clinical signs are subtle in l vitamin B12 deficiency. Vitamin B12 deficiency mostly present with anaemia, peripheral neuropathy, and altered cognition. Most of the time vitamin b12 deficiency was not thought in such clinical situation. There is no acceptable universal recommendation to supplement vitamin B12, especially in the high risk populations. Studying of the biochemical profile to detect vitamin B12 deficiency in that populations will provide the useful data to support the need for supplementation Objective and methods-
1. To assess the vitaminB12 levels in type 2 diabetes mellitus patients on metformin and not on metformin.
2. To assess relationship between metformin therapy and development of vitamin B12 deficiency.
Results - The national health and nutritional survey done in US from 1999-2006 had document vitamin b12 deficiency is more in patients on metformin than non metformin group. The biochemical vitamin b12 deficiency is high in metformin group,and it is well corellated in our study and we found significant relation with duration of metformin >2 years had more deficiency by significant p values.
Conclusion- In the study, metformin therapy for >2 years had shows significant vitamin B12 deficiency and less than 6 months has no significant vitamin B12 deficiency.
Vitamin B12 deficiency in metformin group is associated with macrocytosis and longer the duration of metformin therapy has significant deficiency status.
The vitamin B12 is not much affected those who are not on Metformin therapy.
The serum vitamin B12 assay helps the patient on metformin therapy helps to asses the early vitamin B12 deficiency.
Keywords-Vitmin b12, DM , Metformin

I. INTRODUCTION

Metformin is the most commonly used first line oral hypoglycaemic agent in the treatment of type 2 diabetes mellitus. It is a known fact that age and the duration of diabetes can affect the vitamin B12 status of a patient.

Vitamin B12 deficiency is assessed by estimating the Vitamin B12 levels.

Low vitamin B12 level is may occur in diabetics due to Metformin therapy . Many cross sectional studies shows chronic metformin therapy reduced the vitamin B12 levels. Often the initial clinical signs are subtle in l vitamin B12 deficiency. Vitamin B12 deficiency mostly present with anaemia, peripheral neuropathy, and altered cognition. Most of the time vitamin b12 deficiency was not thought in such clinical situation. There is no acceptable universal recommendation to supplement vitamin B12, especially in the high risk populations. Studying of the biochemical profile to detect vitamin B12 deficiency in that populations will provide the useful data to support the need for supplementation.

As metformin been prescribed worldwide and the duration of treatment period increases,the prevalence of the metformin induced vitamin b12 deficiency is also increased. Although clinical entity of vitamin b12 deficiency related to metformin is a debate one vitamin b12 monitoring is important In a patient with type 2 diabetic mellitus patients on metformin therapy. Vitamin b12 is a water soluble vitamin plays important role in the nervous system.It has been equal priority in both developed and developing countries. It is attracting that,the world since the global crisis due to diabetes cripples not only the health but also the economy of every country. The risk factors are accessed by the development of the Type 2

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Diabetes can either be deferred or even prevented by healthy customs. The Greek Apollonius of Memphi first used the term "diabetes" or "to pass through" in 230 Bc1. The Indian physicians, Sushruta and Charaka were the first persons to identify Type 1 and Type 2 Diabetes as two separate conditions.

Diabetes is a multisystem disease that affect the metabolism of glucose which causes multiple irregularities in diabetic metabolism. Metabolism of the glucose is well organized by the multiple hormones and neurotransmitters in response to nutritional, emotional and environmental changes.The Unger, first labelled diabetes, as a "bi-hormonal" disease.

The American Diabetes Association(ADA) advises that biguanides like metformin is the primary therapy forT2DM .When used alone it will rarely causes hypoglycaemia. The most important is increases the sensitivity to insulin,weight loss and alters lipid profile. Metformin acts through the 53 enhancement of activated protein kinase of adenosine monophosphate (AMPK) system to decrease sugar levels in the blood. The main activity of the drug is on gluconeogenesis in the liver.Adverse events of the therapy are gastrointestinal disturbances ,it never disturbs the muscle gluconeogenesis called lactic acidosis in addition to vitamin B12 deficiency which is commonly overlooked and the monitoring is for clinical side-effect. Pflipsen et al. i indicated that 22% of cases had a vitaminB12insufficiency, and person who are prescribed the above drug has reduced vitamin B12 levels. While Lactic acidosis manifests in the setting of heart failure, renal failure and alcoholism, it is uncertain whether the vitamin B12 malabsorption is due to DM itself or to biguanides.

Ting et al. published that if metformin dvised for long eriod it causes decreased B12 levels. It is dependent on the amount of the drug.It signifies to identify the impact of B12 insufficiency. B12 is required for cellular repair,DNA synthesis and for the regular synthesis of RBC. VitaminB12 is necessary for the metabolism of transmitters like dopamine, monoamines and serotonin. Because of vitamin B12 deficiency, all of the above said neuro transmitters' synthesis are deficient which collectively end in neurocognitive or psychiatric manifestations, Axonal degeneration,demyelination and neuronal death. Vitamin B12 deficiency induced neuronal damage manifests mainly as autonomic neuropathy,peripheral neuropathy, sub-acute combined degeneration of the spinal cord. Chronic metformin use results in reduced vitamin b12 which can exacerbate or cause peripheral neuropathy that already due to DM. The action of the glycation end products on vascular endothelium of diabetics are more vulnerable for diabetic neuropathy.As a consequence, vitaminB12 deficiency–induced neuropathy may be confused with diabetic peripheral neuropathy. Recognizing the exact cause of neuropathy is crucial, because the simple vitaminB12 supplementation may revert neurologic symptoms improperly attributed to hyperglycaemia.

II. AIMS & OBJECTIVES

Metformin is the firstline drug therapy in type 2 diabetes mellitus patients as per ADA. The main adverse effect is vitamin B12 deficiency whic is almost forgotten and vitamin B12 screnning is rarely advised.

1. To assess the vitaminB12 levels in type 2 diabetes mellitus patients on metformin and not on metformin.
2. To assess relationship between metformin therapy and development of vitamin B12 deficiency.

In AJ institute of medical sciences and research centre, Mangalore.

DETAILS OF THE STUDY

Study design:-Observational cross section Study
Study period:- 12 months
Study area:- AJ institute of medical sciences and research centre
Study population:- All patients with type 2 diabetes mellitus on metformin and patients not on metformin depending on dosage and duration during the study period.
Consent:- Informed consent obtained from all subjects. Patient confidentiality maintained.
SAMPLE SIZE:- 110 patients who Satisfy the above criteria attending the Diabetolgy and medicine Out patient in department of General medicine in AJ institute of medical Hospital and research centre during the Study period.

INCLUSION CRITERIA:-

1. All patients with type 2 diabetes mellitus on metformin and patients not on metformin(dose and duration) Age group (18to 80 years).
2. Type-II DM who on metformin more than 6 months. Type-II DM who on metformin more than 2 year
3. Patients who are giving consent to participate in the study.

EXCLUSION CRITERIA:-

1.Patients who or on irregular treatment.

2.Anemia, pancytopenia, lactating mothers,
3.All Patients of age group less than 18 and greater than 80 years of age
withdiabetes mellitus
4.Patients not giving consent to participate in the study.
5.patients of gastritis.immune disorders, vegetarian diet, chronic ill nourished
patients, Chronic alcohol.

III. METHODOLOGY

All diabetic patients will be selected for the study. A detailed case history of each patient with reference to Name, Age, Sex, Address, Contact number, OP number occupation ,Presenting complaints with duration, treatment history , associated comorbid illness, history of any drug intake for other conditions ,Any similar complaints in the family members ,will be recorded. General , Systemic examination and vitals will be Done and recorded. Blood investigations such as Complete Blood Count, FBS,PPBS, VITAMIN B12. After obtaining a Proper Informed Written Consent from the patient ,blood vitamin b12 was taken and sent to laboratory... All patients participating in the study will be given Appropriate treatment and follow up will be made.

DATA ANALYSIS: Data was collected using predesigned proforma. Our study had 110 patients,of which 75 male and 35 female.All the patients recruited under the inclusion criteria.The patients separated intometformin group with duration and non-metformin group and in metformin group they further separated to <6months and >2years duration.The age groups are 10% in 30-40 years,31% in 41-50 years,36% in51-60 years,11% in 61-70 years,10% in 71-80 years. Of 75 males 51 in metformin and 24 were not in metformin.Of 35 females 25 on metformin and 10 are not in metformin.Based on duration of metformin ,71% are in metformin,29% are not on metformin in <6 months,in >2 years 65% are in metformin and 35% are not on metformin. The mean value for total count for metformin is 4957,those on non metformin found to be 7373.7. The p values shows significant ($p<0.001$).For heamoglobin the mean value for metformin is 4141,and non-metformin group is11.44.The p value had shown significant between these($p<0.001$). The mean platelet count on metformin group is 1.5 lakhs and 3 lakhs in non metformin groups.These also shows significant values ($p<0.001$). These three shows significant p value in metformin group compared to non metformin group. The p values calculated for finding the significance between the sex and vitamin b12 deficiency is not established. The number of males and females were not equal in our study .similarly based on age,patients are divided into subgroups and p value calculated and shows no significance.yet this may be differences among these populations in various other parameters like dosage calculation of metformin etc. The p value calculated for the duration of diabetes is calculated and it shows significant p values for > 2 years(Pearson chi-square=9.687;$p<0.001$) and no significance for <6 months(Pearson chi square 4.172,$p=0.041$). The more the mean duration of metformin therapy shows more development of vitamin b12 deficiency. The peripheral smears shows in metformin group 65%(22) had macrocytosis,15% microcytic normochromic,18% had normal,3% had microcytic hypochromic. The peripheral smear had shown significant p value.Those who are not on metformin 74% had normal,13% had microcytic hypochromic,12 had microcytic normochromic,1% had normocytic normochromic,the non metformin group shows No significant p values.

STATISTICS: The collected data were analysed with IBM.SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. To find the significance in categorical data Chi-Square test was used. In the above statistical tools the probability value 0.05 is considered as significant level

IV. RESULTS

All diabetic patients will be selected for the study. A detailed case history of each patient with reference to Name, Age, Sex, Address, Contactnumber, OP number occupation ,Presenting complaints with duration, treatment history , associated comorbid illness, history of any drug intake for other conditions ,Any similar complaints in the family members ,will be recorded. General , Systemic examination and vitals will be Done and recorded. Blood investigations such as Complete Blood Count, FBS,PPBS, VITAMIN B12. After obtaining a Proper Informed Written Consent from the patient ,blood vitamin b12 was taken and sent to laboratory... All patients participating in the study will be given Appropriate treatment and follow up will be made.

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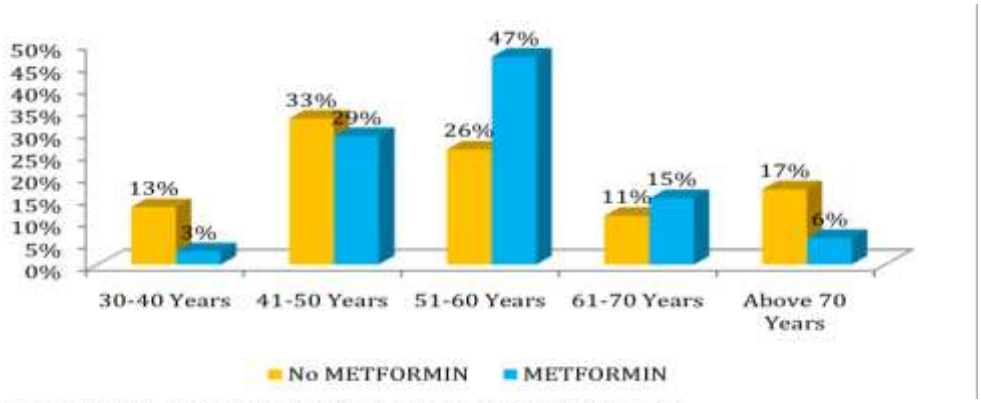
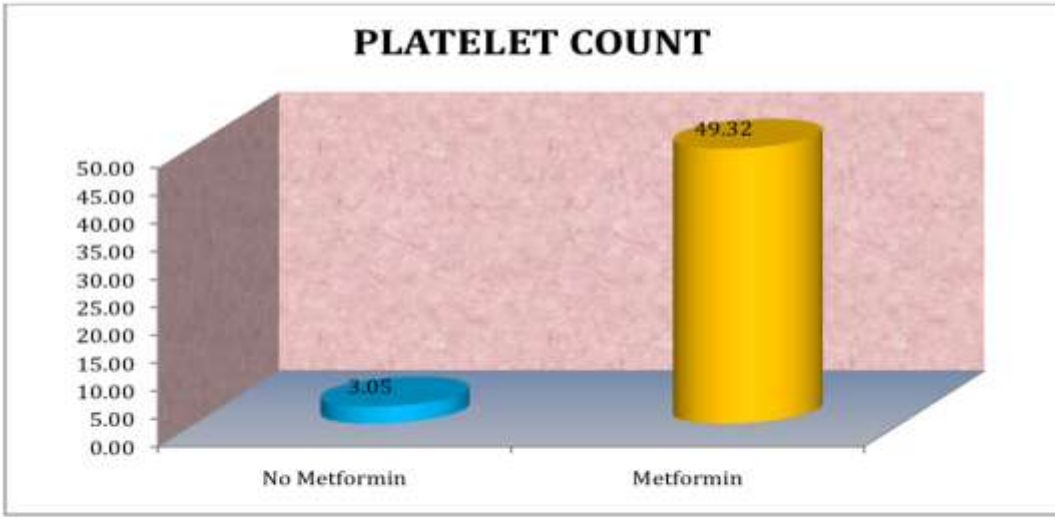


TABLE 10: DISTRIBUTION BASED ON PLATELET COUNT

On metformin		N	Mean	SD	Std.error mean	t value	p value
PLATELET COUNT	No	76	3.01	0.69	0.079	7.490	p<0.001
	Yes	34	1.71	1.12	0.19		



Based on the distribution the mean platelet count is decreased in patients on metformin group compared to non metformin group.the p value is significant between platelet and metformin group.

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TABLE 2: DISTRIBUTION BASED ON SEX

			ON METFORMIN		Total
			No	Yes	
SEX	Male	Count	51	24	75
		% within ON METFORMIN	67.1%	70.6%	68.2%
	Female	Count	25	10	35
		% within ON METFORMIN	32.9%	29.4%	31.8%
Total		Count	76	34	110
		% within ON METFORMIN	100.0%	100.0%	100.0%

Pearson Chi-Square=0.131 p=0.717

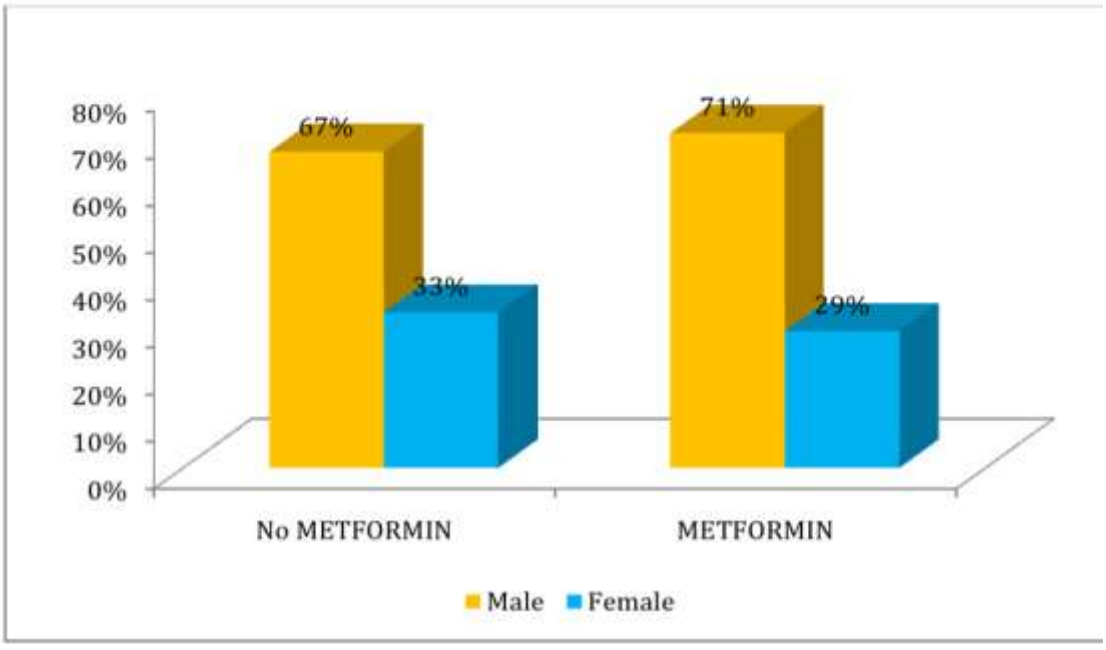

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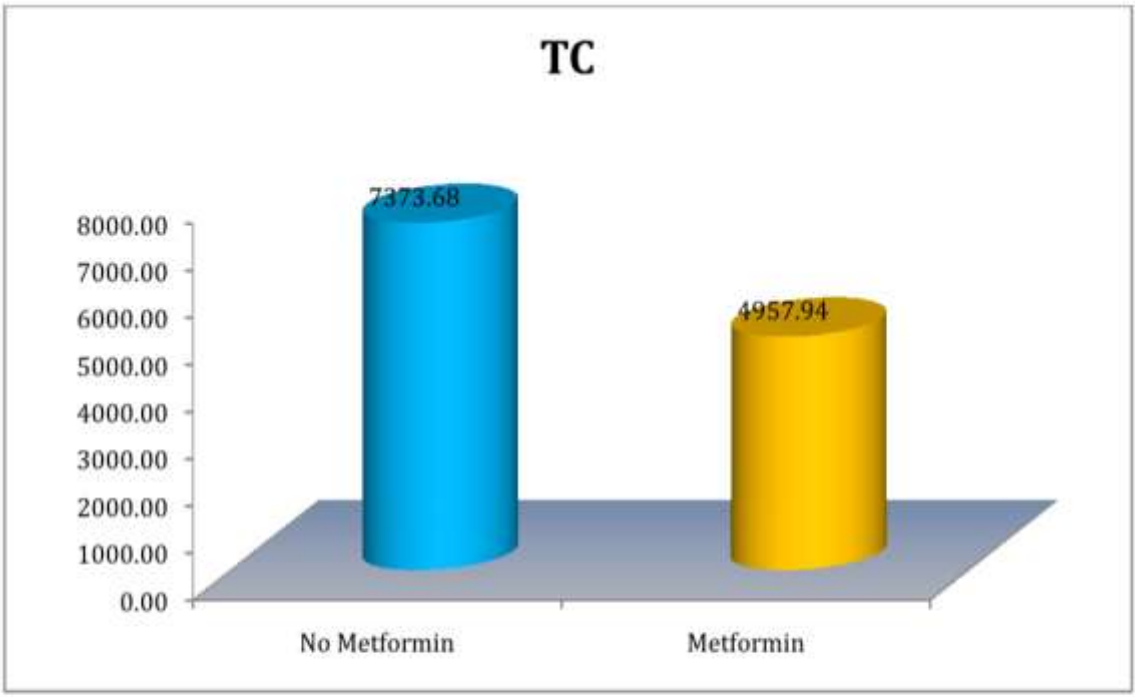
TABLE 6: DISTRIBUTION BASED ON TOTAL COUNT

On metformin		N	Mean	SD	Std.error mean	t value	p value
TC	No	76	7373	2337	268	4.704	p<0.001
	Yes	34	4957	2802	480		



Based on this distribution the mean total count is decreased in patients using metformin group. The p values is significant between the total count and metformin therapy.

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TABLE 24 : DISTRIBUTION BASED ON AGE

	ON_METFORMIN	N	Mean	Std. Deviation	Std. Error Mean	tvalue	p value
AGE	No	76	53.8684	11.88090	1.36283	0.448	0.655
	Yes	34	54.8824	8.56619	1.46909		

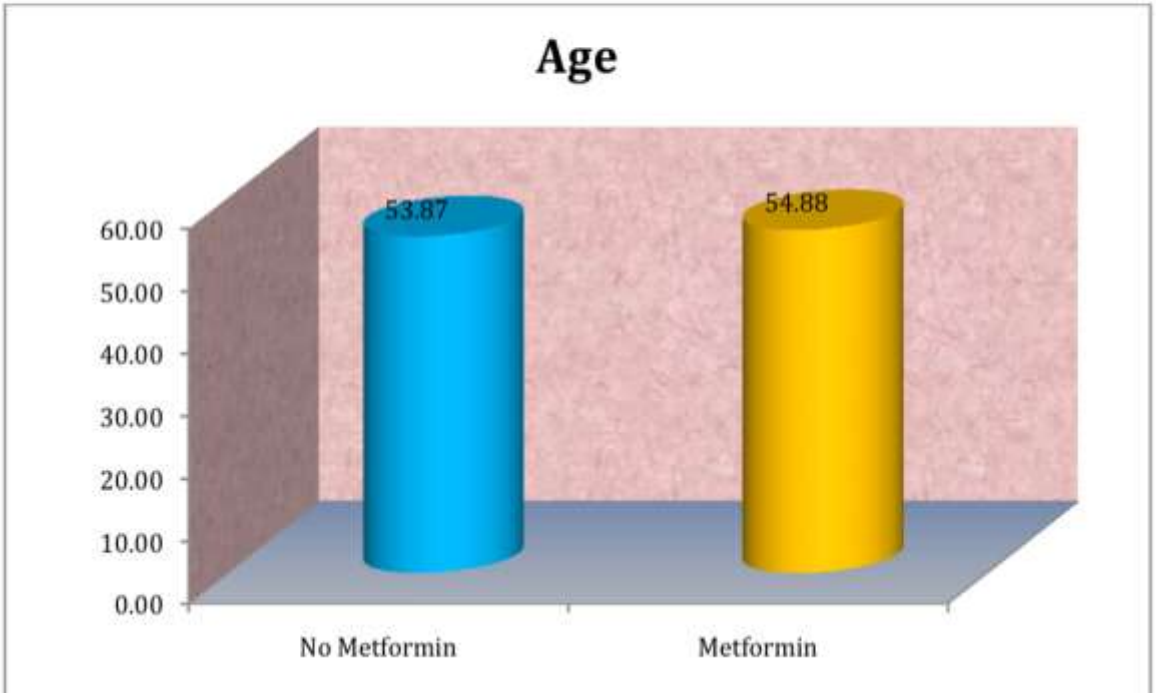

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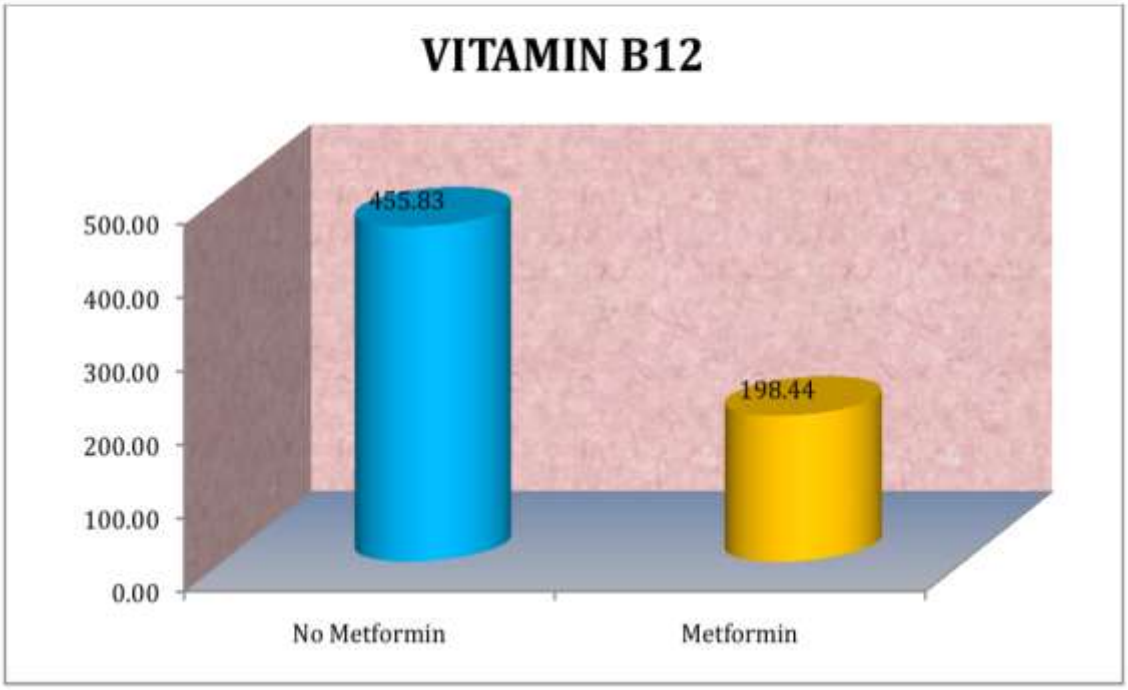
TABLE 22 : DISTRIBUTION BASED ON VITAMIN B12

On metformin		N	Mean	SD	Std.error mean	t value	p value
VIT B12	No	76	455.828	69.90	8.018	19.225	p<0.001
	Yes	34	198.441	51.71	8.868		



The mean vitamin B12 in metformin group is 198 and in non metformin group is 455.this shows vitamin B12 is moderately reduced in metformin group the p value is <0.001 and it shows significant between metformin and vitamin B12 deficiency.

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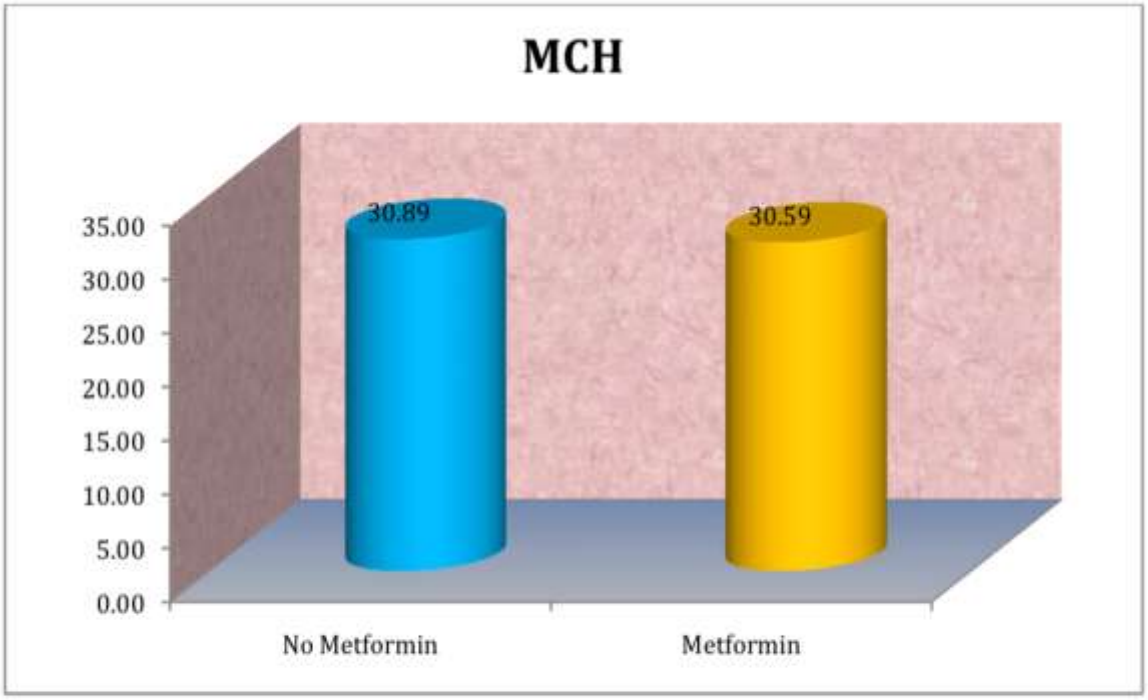
TABLE 9: DISTRIBUTION BASED ON MCH

On metformin		N	Mean	SD	Std.error mean	t value	p value
MCH	No	76	30.894	1.519	0.1742	0.881	.381
	Yes	34	30.588	2.016	0.3458		



The mean MCH value is almost same on both the groups.the p value is non significant. the p value is non significant.

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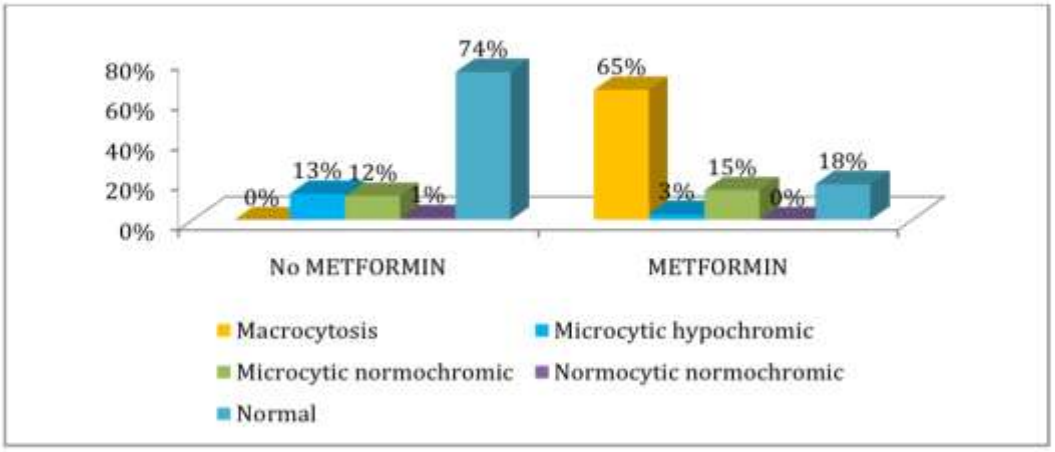
TABLE 5: DISTRIBUTION BASED ON PERIPHERAL SMEAR STUDY

PS * ON METFORMIN CROSSTABULATION

			ON METFORMIN		Total
			No	Yes	
PS	Macrocytosis	Count	0	22	22
		% within ON METFORMIN	0.0%	64.7%	20.0%
	Microcytic hypochromic	Count	10	1	11
		% within ON METFORMIN	13.2%	2.9%	10.0%
	Microcytic normochromic	Count	9	5	14
		% within ON METFORMIN	11.8%	14.7%	12.7%
	Normal	Count	56	6	62
		% within ON METFORMIN	73.7%	17.6%	56.4%
	Normocytic normochromic	Count	1	0	1
		% within ON METFORMIN	1.3%	0.0%	0.9%
Total		Count	76	34	110
		% within ON METFORMIN	100.0%	100.0%	100.0%

Pearson Chi-Square=65.315** p<0.001



Based on the study 65% patient on metformin therapy has macrocytosis picture.The 74% of patients on non metformin thearapy had normal picture.

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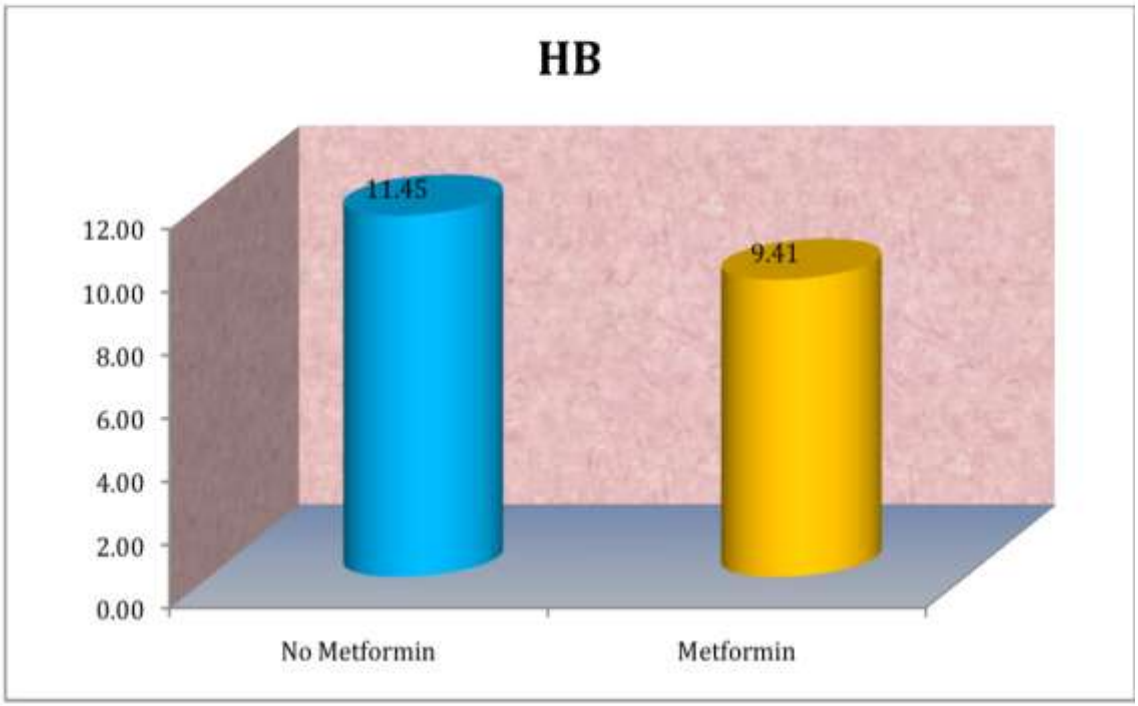
TABLE 7: DISTRIBUTION BASED ON HEMOGLOBIN

On metformin		N	Mean	SD	Std.error mean	t value	p value
Hb gm/dl	No	76	11.4	1.48	.1707	6.603	p<0.001
	Yes	34	9.4	1.49	.2568		



Based on this distribution the mean haemoglobin is decreased on patients using metformin therapy. The p value is significant between haemoglobin and metformin group.

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TABLE 1: DISTRIBUTION BASED ON AGE

			ON METFORMIN		Total
			No	Yes	
age group	30-40 Years	Count	10	1	11
		% within ON METFORMIN	13.2%	2.9%	10.0%
	41-50 Years	Count	25	10	35
		% within ON METFORMIN	32.9%	29.4%	31.8%
	51-60 Years	Count	20	16	36
		% within ON METFORMIN	26.3%	47.1%	32.7%
	61-70 Years	Count	8	5	13
		% within ON METFORMIN	10.5%	14.7%	11.8%
	Above 70 Years	Count	13	2	15
		% within ON METFORMIN	17.1%	5.9%	13.6%
Total		Count	76	34	110
		% within ON METFORMIN	100.0%	100.0%	100.0%

Pearson Chi-Square=8.057 p=0.089

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TABLE 4: DISTRIBUTION BASED ON DURATION >2YEARS

Crosstab

			ON METFORMIN		Total
			No	Yes	
DM >2yr	No	Count	8	12	20
		% within ON METFORMIN	10.5%	35.3%	18.2%
	Yes	Count	68	22	90
		% within ON METFORMIN	89.5%	64.7%	81.8%
Total		Count	76	34	110
		% within ON METFORMIN	100.0%	100.0%	100.0%

Pearson Chi-Square=9.687** p=0.001

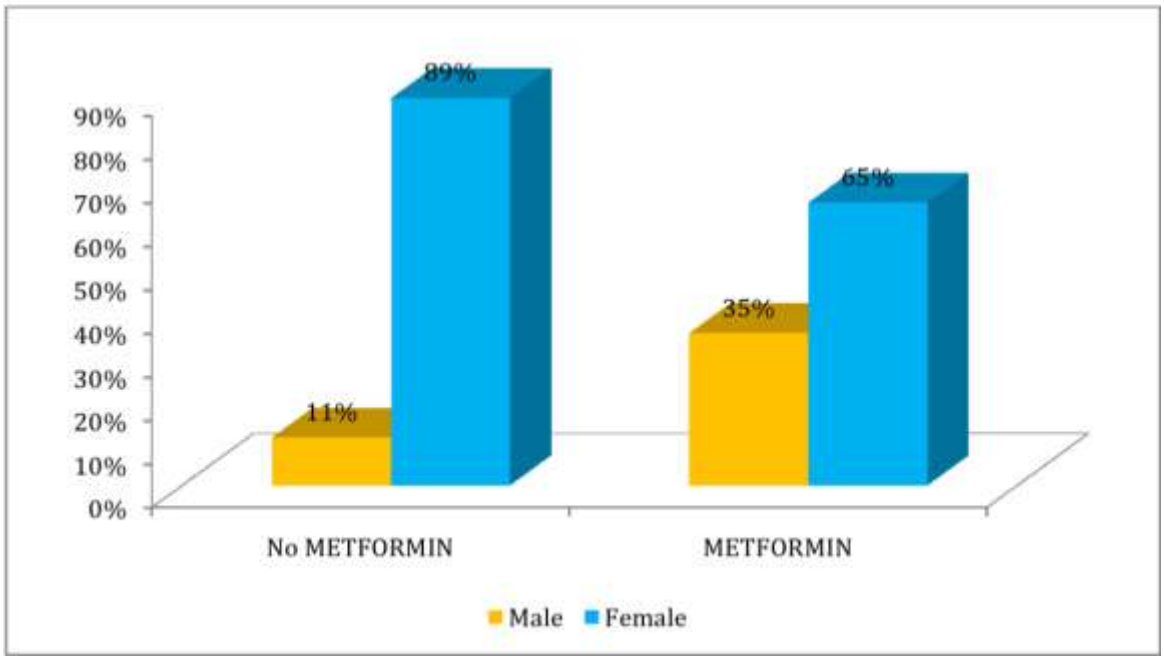

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TABLE 3: DISTRIBUTION BASED ON DURATION<6 MONTHS

Crosstab					
			ON METFORMIN		Total
			No	Yes	
DM <6mon	No	Count	66	24	90
		% within ON METFORMIN	86.8%	70.6%	81.8%
	Yes	Count	10	10	20
		% within ON METFORMIN	13.2%	29.4%	18.2%
Total		Count	76	34	110
		% within ON METFORMIN	100.0%	100.0%	100.0%

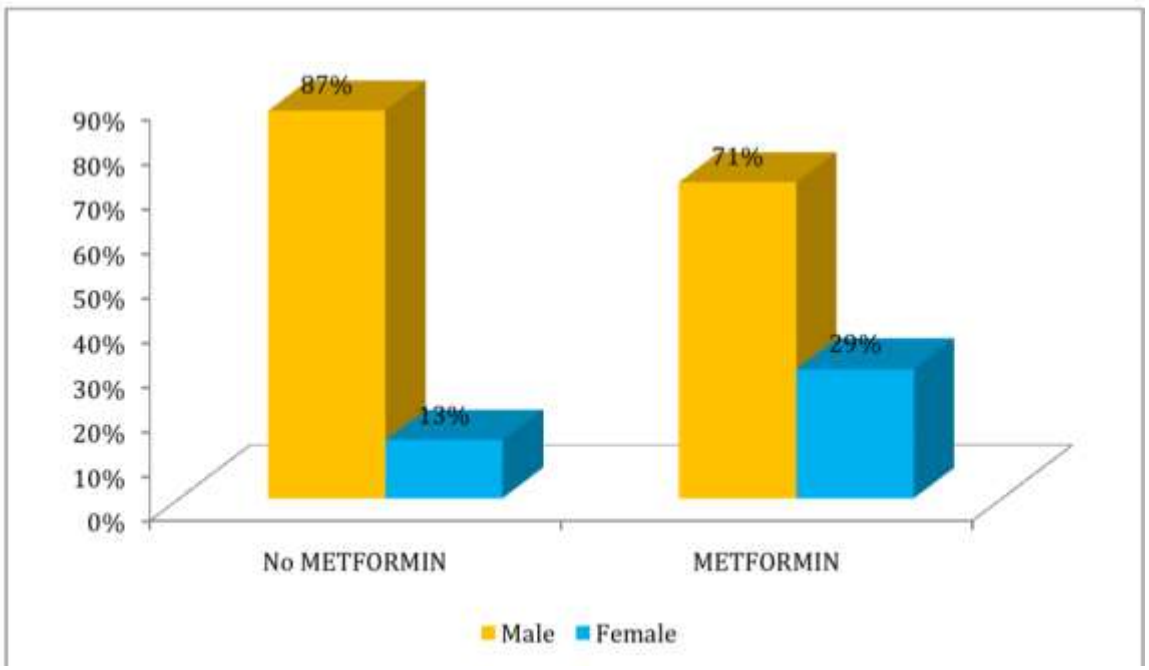

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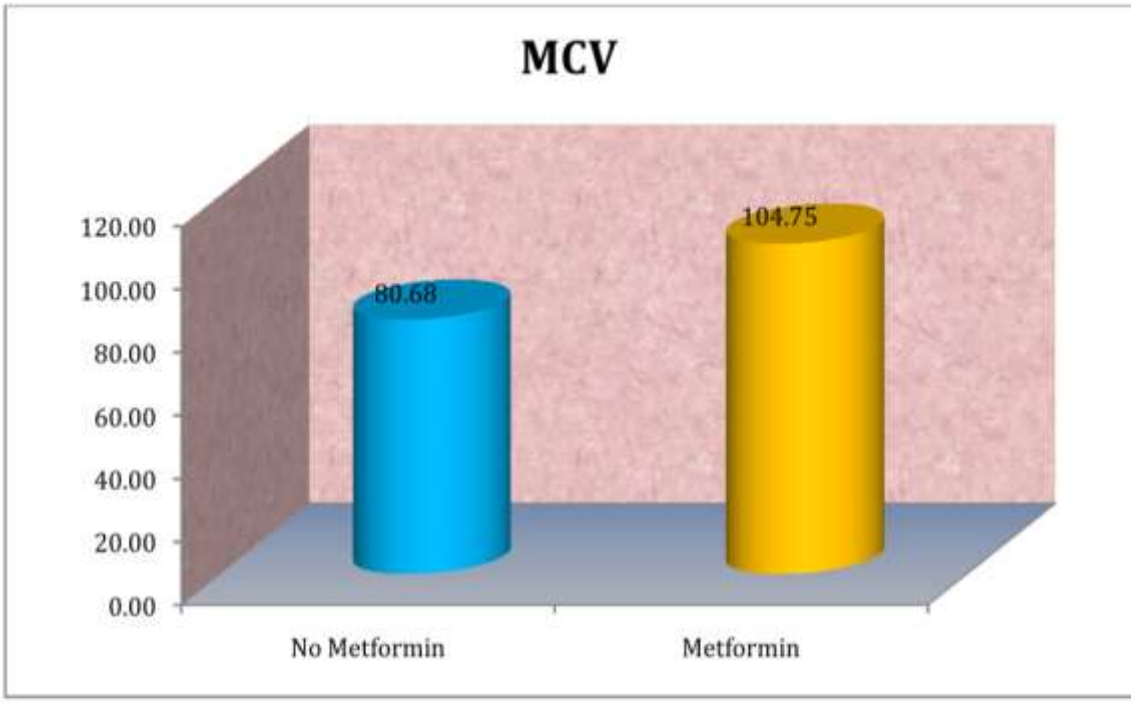
TABLE 8: DISTRIBUTION BASED ON MCV

On metformin		N	Mean	SD	Std.error mean	t value	p value
MCV	No	76	80.67	2.4144	0.2769	11.114	p<0.001
	Yes	34	104.74	18.6395	3.1966		



Based on this distribution the mean MCV value is higher in patients on metformin group. The mean value in metformin is 104.75 and in non metformin is 80.68.the p value is significant between metformin and mcv values.

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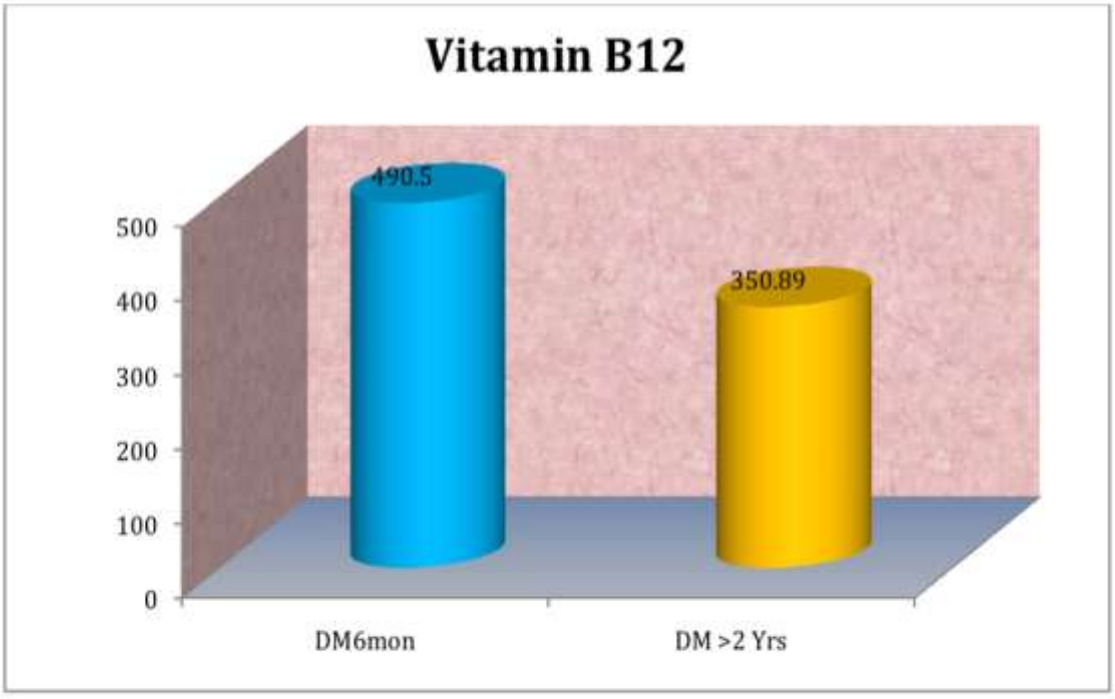
TABLE 25 : DISTRIBUTION BASED ON DURATION OF METFORMIN THERAPY

			Mean	Standard Deviation	Minimum	Maximum
	DM6mon	VITAMIN_B12	490.50	61.92	358.00	567.00
	DM >2 Yrs	VITAMIN_B12	350.89	134.88	117.00	567.00



Based on this distribution the vitamin b12 deficiency is more for .>2 years of metformin duration. The mean value is >2 years is 350 and <6months is 490.

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V. DISCUSSION

Metformin is the commonly used drug for the treatment of diabetic mellitus patients,and the drug mechanisms interact with vitamin b12 absorptionand cause vitamin b12 deficiency.In the observational cross sectional study,the serum vitamin B12 of type2 DM patients who on metformin for< 6months and more than 2 years, and not on metformin were measured.The results are correlated with various parameters like fbs,ppbs,mcv,mch,total counts,hb%, platelet count, peripheralsmear, etc. Our study had 110 patients,of which 75 male and 35 female.All the patients recruited under the inclusion criteria.The patients separated into metformin group with duration and non-metformin group and in metformin group they further separated to <6months and >2years duration.The age groups are 10% in 30-40 years,31% in 41-50 years,36% in51-60 years,11% in 61-70 years,10% in 71-80 years. Of 75 males 51 in metformin and 24 were not in metformin.Of 35 females 25 on metformin and 10 are not in metformin.Based on duration of metformin ,71% are in metformin,29% are not on metformin in <6 months,in >2 years 65% are in metformin and 35% are not on metformin. The age group didn't shows significant p value. The Pearson chi square for age is 8.057,p=0.089.The sex also shows no significant p value(Pearson chi square=0.131,p=0.717) The mean value for total count for metformin is 4957,those on non metformin found to be 7373.7. The p values shows significant (p<0.001).For heamoglobin the mean value for metformin is 4141,and non-metformin group is11.44.The p value had shown significant between these(p<0.001). The mean platelet count on metformin group is 1.5 lakhs and 3 lakhs in non metformin groups.These also shows significant values (p<0.001). These three shows significant p value in metformin group compared to non metformin group. The mean MCV value in metformin group was 104.75 and not on metformin is 80.68.There is significant p value(<0.001) in between vitamin b12 and metformin group. Totally 34 people found to be increase MCV with metformin group,in greater than 2 yrs of the duration. The p value shows significant corellation between metformin group based on duration and vitamin b12 deficiency.The mean MCH value is almost same for both the metformin and non- metformin group. There is non significant p values for MCH and vitamin b12 deficiency. The p values calculated for finding the significance between the sex and vitamin b12 deficiency is not established. The number of males and females were not equal in our study .similarly based on age,patients are divided into subgroups and p value calculated and shows no significance.yet this may be differences among these populations in various other parameters like dosage calculation of metformin etc. The p value calculated for the duration of diabetes is calculated and it shows significant p values for > 2 years(Pearson chi-square=9.687;p<0.001) and no significance for <6 months(Pearson chi square 4.172,p=0.041). The more the mean duration of metformin therapy shows more development of vitamin b12 deficiency.The peripheral smears shows in metformin group 65%(22) had macrocytosis,15% microcytic normochromic,18% had normal,3% had microcytic hypochromic. The peripheral smear had shown significant p value.Those who are not on metformin 74% had normal,13% had microcytic hypochromic,12 had microcytic normochromic,1% had normocytic normochromic,the non metformin group shows No significant p values. Similarly the correlation between LDH,FBS,PPBS,URIC ACID, TB, DB, SGOT, SGPT, ALP, CREATININE shows almost equal percentage distributions between the metformin based on duration and non metformingroup. The above said values had shows no significant p values. The national health and nutritional survey done in US from 1999-2006 had document vitamin b12 deficiency is more in patients on metformin than non metformin group. The biochemical vitamin b12 deficiency is high in metformin group,and it is well corellated in our study and we found significant relation with duration of metformin >2 years had more deficiency by significant p values.

Mathew c pflipse et al,shows high prevalence of vitamin b12 deficiency among 22% of diabetes with metformin therapy.In our study also had almostsame percentage of the metformin group patients affected.

Vineeta Shoba et al shows high prevalence of vitamin b12 deficiency indiabetes mellitus patients on metformin therapy. They assess more deficiencies on vegetarian but our study limits such things.

Ting et al, noticed that the metformin duration are main factors forVitamin B12 deficiency .This is similar to our study and shows associationbetween duration of metformin and with B12 levels.

VI. CONCLUSIONS

In the study, metformin therapy for >2 years had shows significant vitamin B12 deficiency and less than 6 months has no significant vitamin B12 deficiency. Vitamin B12 deficiency in

metformin group is associated with macrocytosis and longer the duration of metformin therapy has significant deficiency status. The vitamin B12 is not much affected those who are not on metformin therapy.

The serum vitamin B12 assay helps the patient on metformin therapy helps to asses the early vitamin B12 deficiency.

LIMITATIONS

1. constraints and financial constraints.

The sample size of this study is small because of time

2. Mainly the dosage of metformin is not calculated in our study. So the relationship between total cumulative dose and vitamin B12 deficiency is not established.

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