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METFORMIN THERAPY AND VITAMIN B12 LEVELS: A CASE CONTROL STUDY

General Medicine

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ABSTRACT

INTRODUCTION: Metformin is considered as the main drug of choice for the patients of type 2 diabetes mellitus. GI intolerance is a most common side effect seen in patients with long-term metformin therapy. Vitamin B12 deficiency can be a consequence of metformin therapy due to malabsorption. In this study we sought to estimate vitamin B12 levels in patients who were on metformin therapy.

MATERIAL AND METHODS: The study is a case control study. 30 patients were on Metformin for more than one year (CASES) and the other 30 were on other anti-diabetic drugs and/or insulin for more than one year (CONTROLS). Serum vitamin B12 levels were measured by radioimmunoassay method.

RESULT: In regard to vitamin B12 levels, this study clearly shows a decrease associated with Metformin therapy.

CONCLUSION: Type 2 diabetics on long term Metformin therapy were found to have significantly low levels of Vitamin B12 when compared to type 2 diabetics on other anti-diabetic drugs.

Hence Vitamin B12 supplementation should be considered in patients with long term metformin therapy.

KEYWORDS

Type 2 diabetes mellitus, vitamin B12, metformin

INTRODUCTION

The global diabetes prevalence in 2019 is estimated to be 9.3%.[1] It adversely affects cardiovascular, renal and neurological systems of each person significantly increasing the morbidity and mortality.[2]

Treatment of T2DM includes diet, exercise, medications and insulin. Metformin, a drug from the class Biguanides, remains the first choice of treatment according to American Diabetes Association (ADA). In addition, it is one of the few anti-hyperglycaemic agents associated with improvements in cardiovascular morbidity and mortality, which is a major cause of death in patients with type 2 diabetes.[3]

Metformin acts through decreased glucose output, increased insulin mediated glucose uptake in the peripheral tissues and increases intestinal glucose utilisation. The most common side effect of Metformin includes gastrointestinal distress, soft stools and diarrhoea.[4] These gastrointestinal side effects lead to malabsorption of Vitamin- B12 in a dose and time dependent manner.[5,6] On an average, 10% to 30% of the patients show malabsorptive deficiency of Vitamin-B12[7,8] and this risk increases with age.[9,10] This study focuses on estimation of Vitamin B12 levels in patients with T_2DM on Metformin therapy.

MATERIALS AND METHODS

The study is a case control study. 30 patients were on Metformin for more than one year (CASES) and the other 30 were on other anti-diabetic drugs and/or insulin for more than one year (CONTROLS). All the study population was above 30 years of age.

Exclusion criteria.

1) Patients who are on vitamin B12 supplementation
2) Patients who are on steroid therapy, oral contraceptive pills and diuretics
3) Pregnancy
4) Critically ill patients
5) Patients with tuberculosis
6) Patients with renal impairment

Method of collection of data

A detailed proforma was filled up for each patient, which included age, sex, IP and OP number, relevant present, past, personal history and clinical examination was done.

Venous plasma glucose was measured both fasting and prandial (120 min after a 75 g glucose load). HbA1C was measured by high performance liquid chromatography method.

Measurement of serum Vitamin B12

Serum Vitamin B12 concentration was measured in samples stored at -20°C collected from both cases and controls. Serum Vitamin B12 was measured by Radioimmunoassay method.

STATISTICAL METHODS APPLIED

Descriptive

The Descriptive procedure displays univariate summary statistics for several variables in a single table and calculates standardized values (z scores). Variables can be ordered by the size of their means (in ascending or descending order), alphabetically, or by the order in which you select the variables (the default).

Independent-Samples T Test

The Independent-Samples T Test procedure compares means for two groups of cases. Ideally, for this test, the subjects should be randomly assigned to two groups, so that any difference in response is due to the treatment (or lack of treatment) and not to other factors. This is not the case if you compare average income for males and females. A person is not randomly assigned to be a male or female.

In such situations, you should ensure that differences in other factors are not masking or enhancing a significant difference in means. Differences in average income may be influenced by factors such as education (and not by sex alone).

All the statistical methods were carried out through the SPSS for windows (version 16.0). P value <0.05 was considered as significant.

RESULTS

In this study, Vitamin B12 levels were done in 60 diabetic patients of which 30 patients were on only Metformin (CASES) and 30 patients were on anti-diabetic drugs other than Metformin.

Table 1: Age distribution among cases and controls

Age distribution among cases and controls			
Age Groups (years)	CASES	CONTROLS	TOTAL
<65	20 (33.3)	20 (33.3)	40 (66.6)
≥65	10 (16.6)	10 (16.6)	20 (33.3)
TOTAL	30	30	60

Majority of the cases and controls were less than 65 years of age which constituted to 66.6% of the total group.

Table 2: Sex wise distribution of cases and controls

Sex wise distribution of cases and controls				
SEX		Group		Total
		Case	Ctrl	
	MALE	16	16	32
				53.3%
	FEMALE	14	14	28
				46.7%
TOTAL		30	30	60
				100.0%

There were 16 male and 14 female in both cases and controls

Table-3: Mean age among cases and controls

Mean age among cases and controls					
	Group	N	Mean	Std. Deviation	Std. Error Mean
Age	Case	30	57.8000	16.15742	2.94993
	Control	30	58.7667	10.47389	1.91226

In this study, the mean age of the cases was 57.8±16.15 (SD) years and of the controls was 58.7±10.47(SD) years.

Table-4: FBS among cases and controls

FBS among cases and controls					
	Group	N	Mean	Std. Deviation	Std. Error Mean
FBS	Case	30	120.6333	34.62358	6.32137
	Control	30	149.9000	42.47786	7.75536

In this study, mean FBS among the cases was 120.63±34.62(SD) mg/dl whereas that of controls was 149.9±42.47(SD)mg/dl..

Table-5: PPBS among cases and controls

PPBS among cases and controls					
	Group	N	Mean	Std. Deviation	Std. Error Mean
PPBS	Case	30	184.2000	56.09192	10.24094
	Control	30	215.3333	67.35564	12.29740

In this study, the mean PPBS among the cases was 184.2±56.09(SD) mg/dl, whereas among the controls was 215.33±67.35 (SD)mg/dl.

Table-6: HbA_1C among cases and controls

HbA_1C among cases and controls					
	Group	N	Mean	Std. Deviation	Std. Error Mean
HbA_1C	Case	30	6.7633	1.30503	.23826
	Control	30	7.1517	1.32811	.24248

In this study, the mean HbA1C among the cases was 6.76±1.3 (SD)%, whereas among the controls was 7.15±1.32 (SD) %.

Table-7: S. Creatinine among cases and controls

S. Creatinine among cases and controls					
	Group	N	Mean	Std. Deviation	Std. Error Mean
S.Creat	Case	30	.8923	.14915	.02723
	Control	30	1.0300	.19853	.03625

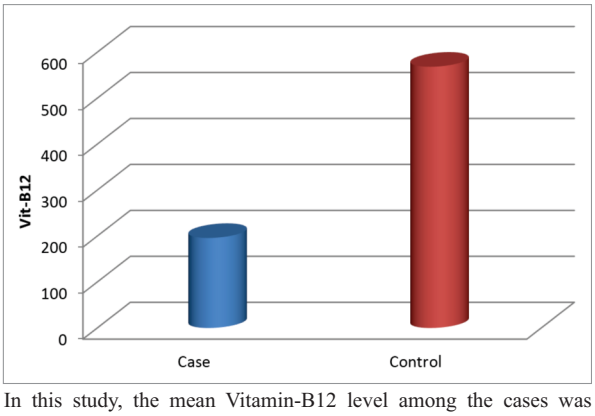
In this study, the mean S. Creatinine among the cases was 0.89±0.14 (SD) mg/dl, whereas among the controls was 1.03±0.19 (SD) mg/dl.

Table-8: Vitamin-B12 levels among cases and controls

Vitamin-B12 levels among cases and controls					
	Group	N	Mean	Std. Deviation	Std. Error Mean
Vit B12	Case	30	195.9333	182.93016	33.39833
	Control	30	568.5000	459.33623	83.86294

p-value 0.00

Graph-1: Vitamin-B12 levels among cases and controls



In this study, the mean Vitamin-B12 level among the cases was 195.93±182.9 (SD) pg/ml whereas among the controls was 568.5±459.33 (SD) pg/ml.

Table-9: Classification of cases and controls in terms of Vit-B12 levels

Classification of cases and controls in terms of Vit-B12 levels			
Vitamin-B12(pg/ml)	Cases	Controls	Total
<210	21 (35)	7 (11.6)	28 (46.67)
≥210	9 (15)	23 (38.33)	32 (53.12)
Total	30	30	60

***number in bracket indicates %**

In this study, 70% of the cases were Vitamin-B12 deficient and 30% were sufficient whereas , among the controls, 23.2% were Vitamin-B12 deficient and 76.8% were sufficient.

DISCUSSION

In the present study, serum Vitamin B12 levels were estimated in type 2 diabetic patients of which 30 patients were on Metformin (CASES) and the other 30 were on other anti-diabetic drugs and/or insulin. (CONTROLS) .

In this study the mean age of the cases was 57.8±16.15 (SD) years and of the controls was 58.7±10.47(SD) years. And also, 53.3% were males and 46.7% were females in both the groups.

In regard to vitamin B12 levels, this study clearly shows a decrease associated with Metformin therapy. This result was expected because it is well documented in the literature that Metformin does cause a decrease in vitamin B12 levels in a time and dose dependent manner. In this study, the mean Vitamin-B12 levels among the cases were 195.93±182.9 (SD) pg/ml whereas among the controls was 568.5±459.33 (SD) pg/ml with 'p' value 0.00 showing major significance.

Our study had few limitations most notably, the sample size was small and may not truly reflect the whole group. Long standing diabetics are known to have gastro-intestinal disturbances related to autonomic neuropathy which can cause Vitamin-B12 deficiency which could not be ruled out.We, also could not rule out few other causes that hamper its absorption.

CONCLUSION

- Type 2 diabetics on long term Metformin therapy were found to have significantly low levels of Vitamin B12 when compared to type 2 diabetics on other anti-diabetic drugs.
- Hence Vitamin B12 supplementation should be considered in patients with long term metformin therapy.

REFERENCES

1. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition
2. National Diabetes Information Clearinghouse (NDIC). National Diabetes Statistics, 2011. NIH publication no. 11-3892, February 2011. http://diabetes.niddk.nih.gov/dm/pubs/statistics/. Accessed for verification October 5, 2011
3. Kuzminski AM, Giacco AJD, Allen RH, Stabler SP, Lindenbaum J.Effective treatment of cobalamin deficiency with oral cobalamin.Blood 1998;92:1191-8.
4. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy; a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes [published correction appears in *Diabetes Care*. 2006;29:2816-2818]. *Diabetes Care*. 2006;29:1963-1972
5. Ting RZ, Szeto CC, Chan MH, Ma KK, Chow KM. Risk factors of vitamin B12 deficiency in patients receiving metformin. *Arch Intern Med*. 2006;166:1975-1979.
6. Tomkin GH, Hadden DR, Weaver JA, Montgomery DA. Vitamin B12 status of patients on long-term metformin therapy. *Br Med J*. 1971;2:685-687.
7. Adams JF, Clark JS, Ireland JT, Kesson CM, Watson WS. Malabsorption of vitamin B12 and intrinsic factor secretion during biguanide therapy. *Diabetologia*. 1983;24: 16-18.
8. Bauman WA, Shaw S, Jayatilieke E, Spungen AM, Herbert V. Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. *Diabetes Care*. 2000;23:1227-1231.
9. Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Washington, DC, National Academy Press, 1998
10. American Diabetes Association. Standards of medical care in diabetes 2010. *Diabetes Care* 2010;33(Suppl. 1):S11–S61