ASSOCIATION OF VITAMIN B12 DEFICIENCY AND METFORMIN USE IN PATIENTS PRESENTING WITH TYPE II DIABETES MELLITUS

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ABSTRACT

Objective: To compare the association of vitamin B12 deficiency and metformin use in patients presenting with type II diabetes mellitus.

Study Design: Case control study.

Place and Duration of Study: Department of Medicine, Military Hospital Rawalpindi from Apr 2017 to Sep 2017.

Methodology: All patients who fulfilled the inclusion criteria and visited OPD of department of Medicine Military Hospital Rawalpindi, were included in the study. After approval from the ethical review committee, informed written consent was taken from patients. The patients were divided into two groups group A (metformin use) & B (without metformin use). Outcome was checked by comparing both the groups for vitamin B12 deficiency.

Results: Two hundred and eighty patients with diabetes mellitus were included. One hundred and seventy one (61.07%) were males and 109 (38.93%) were females, with the mean age of 59.52 ± 12.441. Vitamin B12 deficiency in group I was seen in 30 (10.71%) and in 9 patients (3.21%) in group II (OR >1).

Conclusion: In conclusion, our study indicates that patients with type 2 diabetes mellitus treated with metformin should be screened for vitamin B12 deficiency, especially with longer durations of treatment.

Keywords: Diabetes Mellitus, Type 2, Metformin, Vitamin B12 deficiency.

INTRODUCTION

Diabetes mellitus (DM) is one of the oldest known diseases to mankind with clues found in old Egyptian manuscripts. However a clear differentiation between type 1 and 2 DM was not made until early 20th century.

Type II diabetes mellitus (T2DM) is a vastly spreading disease worldwide with >400 million people affected. In next 20 years this figure is likely to rise to more than 600 million. The condition is likely to deteriorate more in developing countries as compared to developed world. The prevalence of diabetes is almost equal in male and female population[1].

Similar is the state of affairs in our country. With increase in disease prevalence, the cost of treatment increases, not only of the disease itself but also all its related complications. This increasing cost is a burden on the already feeble economic state of Pakistan[2].

First line therapy for T2DM is Metformin. It is not only a potent antihyperglycemic but also reduces the cardiovascular risks associated with T2DM which are considered the main cause of mortality associated with the disease. On the other hand, malabsorption of vitamin B12 is also associated with Metformin use leading to clinical deficiency of mecobalamin. Additional intake of vitamin B12 is thus helpful in reducing the risk[3].

Study of literature shows that many genetic and environmental factors play a role in etiology/pathogenesis of DM[4]. Sedentary life style, family history of DM, diet related issues and lack of exercise are few of those risk factors. Complications of T2DM and B12 deficiency is more common in old age patients[5-7].

Mecobalamin is a significant nutrient factor for adequate functioning of cardiovascular, neurological and hemopoetic systems. Patients with long standing or severe and uncontrolled DM are particularly prone to B12 deficiency as stated

earlier. Few of the wide range of symptoms and manifestations include but not limited to anemia, pancytopenia, peripheral neuropathies, memory related issues and various types of neuro-degenerations[8].

De jegar *et al* reported that mecobalamin deficiency was observed in 9.9% patients with DM taking metformin while in 2.7% diabetic patients not taking metformin[9]. Reinstatler *et al* reported that vitamin B12 deficiency was observed in 5.8% patients with DM taking metformin while in 2.2% diabetic patients not taking metformin. This difference was although seems to be low but significant ($p<0.001$)[3].

Rationale of this study was to assess the association between vitamin B12 deficiency and metformin use in patients presenting with T2DM. Literature has showed that vitamin B12 deficiency is significantly associated with metformin use among diabetics. But, local evidence is missing in this regard. And because of this, the use and prescription of metformin is frequent. So we planned to conduct this study to find the association of vitamin B12 deficiency and metformin use. So that in future we may be able to recommend not to use metformin or if metformin is in use then periodic screening for vitamin B12 deficiency and supplementation must be given. This will help to improve our practice and reduce the complications of vitamin B12 deficiency in diabetics.

METHODOLOGY

This is a case control study including 280 patients presenting to department of Medicine, Military Hospital, Rawalpindi from Apr 2017 to Sep 2017.

Only those patients fulfilling the inclusion criteria were included in the study. Prior permission was taken from hospital ethics review committee vide letter number 8001/2/2017 dated 7 march 2017. Informed consent was obtained from patients. Sample size is calculated with 80% power of test, 5% level of significance and taking expected percentage of vitamin B12 deficiency i.e. 9.9% in cases and 2.7% in controls.

Demographic information including name, age, gender, BMI, duration of diabetes were noted. Patients of age 40-80 years of either gender presenting with type 2 diabetes (T2DM) were included using non probability, consecutive sampling technique. Patients taking oral metformin therapy for more than a year were included in case group. Patients not taking metformin therapy were included in control. Vitamin B12 deficiency was labeled if serumvitamin B12 <150pmol /l was recorded. Patients having documented deficiency and those already on vitamin B12 or multivitamins were excluded. Those having other comorbids like poor appetite, diarrhea/malabsorption state and history of abdominal surgery in the past were also excluded. Blood samples were obtained by using 3cc syringe. All samples were stored and sent to the armed forces institute of pathology (AFIP) laboratory for assessment of vitamin B12. Reports were assessed and if vitamin B12 <150pmol/l, then vitamin B12 deficiency will be labeled. All this information was recorded on proforma.

Data was entered and analyzed through in SPSS-20. Quantitative variables like age, BMI and duration of T2DM was presented as mean and standard deviation. Qualitative variables like gender and vitamin B12 deficiency was presented as frequency and percentage. Odds ratio was calculated to measure association between vitamin B12 deficiency and metformin use. OR>1 was considered as significant.

RESULTS

A total of 280 patients with diabetes mellitus were selected to conduct this study. A total of 171 patients (61.07%) were males and 109 patients (38.93%) were females. Group-I included 61 males (21.79%) and 79 (28.21%) females with mean age of 66.46 ± 10.39 years while group II included 111 male (39.6%) and 29 (10.3%) female patients with mean age of 67.38 ± 10.76years.

In group I the mean BMI was 31.514 ± 4.573 kg/m², while in group II the mean BMI was 31.77 ± 4.374 kg/m². In group I the mean duration of disease was 32.11 ± 8.66 months, while in group II

the mean duration of disease was 30 ± 6.66 months.

In our study the main outcome vitamin B12 deficiency in group I (study group) was seen in 30 patients (10.71%), while it as was seen in 9 (3.21%) patients in group II (control group).

The frequencies of age groups, gender, BMI, duration of disease were calculated according to vitamin B12 deficiency.

In our study vitamin B12 deficiency was

studies in middle aged patients depicted that metformin reduces vitamin B-12 levels however recorded concentrations were in the normal limit[10].

Keeping in view the results of the study, treatment duration was shown to be consistent risk factor for vitamin B12 deficiency even after adjusting the confounding factors.

In Korea, first line treatment for type 2 diabetes is life style modification along with met-

Table: Vitamin B12 deficiency between two groups (n=280).

	Vitamin B12 Deficiency	Groups		OR	*p*-value
		A (Metformin use) n (%)	B (without Metformin use) n (%)		
Vitamin B12 deficiency	Yes	30 (10.71%)	9 (3.21%)	OR 3.97	0.000
	No	110 (39.28%)	131 (46.7%)		
Duration of disease	(24-40) months Yes	24	7	31 82 (29.2%)	0.000 4.7048
	(24-40) months No	86	118		
	(41-55) months Yes	6	2	8 37 (20.71%)	0.000 1.6254
	(41-55) months No	24	13		
Gender	Male Yes	12	6	4.287	0.000
	Male No	49	105		
	Female Yes	18	3	2.5585	0.009
	Female No	61	26		
BMI	19-30 Yes	19 (6.78%)	5 (1.78%)	4.9543	0.000
	19-30 No	33 (11.78%)	43 (15.35%)		
	31-41 Yes	11 (3.92%)	4 (1.42%)	3.1454	0.005
	31-41 No	77 (27.5%)	88 (31.42%)		
Age	37-60 years Yes	12 (4.28%)	5 (1.78%)	2.6836	0.000
	37-60 years No	34 (12.14%)	38 (13.57%)		
	61-90 years Yes	18 (6.42%)	4 (1.42%)	5.5069	0.000
	61-90 years No	76 (27.14%)	93 (33.21%)		

common in group I (cases) and in age group of 61-90 years. It was predominant in female gen–der, more common in patients with BMI of 19-30 kg/m^2 and was more common in patients with 24-40 months duration of disease (table).

DISCUSSION

The vitamin B-12 deficiency associated with metformin therapy is not new and it has been discussed earlier in the literature. However, im-portant aspect here is that vitamin B12 deficiency is progressive.

Moreover, in some populations, the defici-ency reaches to a level necessitating replacement. This is also a new aspect. Although, previous

formin therapy[11-13], and metformin is the most commonly prescribed oral anti diabetic drug among 80.1% patients who are taking oral anti diabetic medication for type 2 diabetes mellitis[14].

In this study, 9.5% of patients on metformin had vitamin B12 deficiency. Data from the National Health and Nutrition Examination Survey was significant in this regard as it showed that patients with DM with metformin use had vitamin B12 deficiency in 5.8% patients while patients with DM without metformin use had this deficinency in 2.4% patients[15]. In a similar study in Brazil, the prevalence of vitamin B12 deficiency was 6.9% in type 2 diabetics on met-formin therapy[16]. The mean serum vitamin B12

levels in American adult patients with DM were 430.2 ± 13.0 pg/mL in those taking metformin and 524.0 ± 10.6 pg/mL in those who were not taking metformin and 475.3 ± 3.9 pg/mL in non-diabetic adults.

In our study, vitamin B-12 deficiency in group I was seen in 30 patients (10.71%), while in group II, vitamin B-12 deficiency was seen in 9 (3.21%) patients as compared to Ko *et al* study, mean vitamin B-12 level in diabetic patients using metformin was 665.7 ± 246.7 pg/mL[16].

The pathogenesis of vitamin B-12 deficiency in metformin users is not fully understood but there are multiple factors that contribute towards this finding, i.e, small intestine bacterial over-growth, decreased gut motility, altered bacterial normal flora, inactivation of vitamin B-12 absorp-tion, all attributable to diabetes mellitus[17].

Vitamin B12 deficiency has multiple clinical implications. It can lead to bone marrow supp-ression with pancytopenia, multiple neurological lesions including optic atrophy, sensory ataxia and demyelinating peripheral neuropathy which is commonly mistaken for diabetic polyneuro-pathy[18]. Low vitamin B-12 levels are associated with decreased nerve conduction velocities and poor sensory perception by monofilament tes-ting[19]. In clinical practice this finding commonly leads to unjustified use of neuropathic pain medications[18].

The study focused on metformin usage and its associated vitamin B12 deficiency in the patients. Patients with metformin use have docu-mented deficiency of vitamin B12 and should thus be screened for it specially those on long term therapy.

CONCLUSION

Our study concluded that diabetic popu-lation on metformin therapy, should be screened for deficiency of vitamin B12, specifically with longer duration of treatment.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Akhtar S, Khan Z, Rafiq M, Khan A. Prevalence of type II diabetes in district dir lower in Pakistan. Pak J Med Sci 2016; 32(3): 622.
2. Zia A, Bhatti A, Jalil F, Wang X, John P, Kiani AK, et al. Prevalence of type 2 diabetes–associated complications in Pakistan. Intl J Diabetes Develop Count 2016; 36(2): 179-88.
3. Reinstatler L, Qi YP, Williamson RS. Asso-ciation of biochemical B12 deficiency with metformin therapy and vitamin B12 supp-lements: the National Health and Nutri-tion Examination Survey, 1999–2006. Diabetes care 2012; 35(2): 327-33.
4. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus present and future perspectives. Nature Rev Endocrinol 2012; 8(4): 228-36.
5. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. Puerto Rico Health Sci J 2013; 20(2): 1-7.
6. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: US department of health and human services, centers for disease control and prevention. Centers Dis Control Prevent 2011; 201(1): 2568-69.
7. Pawlak R, Parrott SJ, Raj S, Cullum-Dugan D, Lucus D. How prevalent is vitamin B12 deficiency among vegetarians?. Nutrition Rev 2013; 71(2): 110-17.
8. Kibirige D, Mwebaze R. Vitamin B12 deficiency among patients with diabetes mellitus: is routine screening and supplementation justified?. J Diabetes Metab Disord 2013; 12(1): 17-20.
9. De Jager J, Kooy A, Lehert P, Wulffelé MG, Bets D, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. Bio Med J 2010; 340: c2181.
10. American Diabetes Association. Standards of medical care in diabetes 2013. Diabetes Care 2013; 36(Suppl-1): S11-66.
11. Commiittee of Clinical Practice Guideline. Treatment guideline for diabetes. 4th ed. Seoul: Korean Diabetes Association; 2011.
12. Ko SH, Kim SR, Kim DJ, Oh SJ, Lee HJ, Shim KH, et al. Clinical practice guidelines for type 2 diabetes in Korea. Diabetes Metabol J 2011; 35(5): 431-36.
13. Chung HH, Moon JS, Yoon JS, Lee HW, Won KC. The relation-ship between metformin and cancer in patients with type 2 diabetes. Diabetes Metabol J 2013; 37(2): 125-31.
14. Reinstatler L, Qi YP, Williamson RS, Garn JV. Association of biochemical B12 deficiency with metformin therapy and vitamin B12 supplements: the national health and nutrition examination survey, 1999–2006. Diabetes Care 2012; 35(2): 327-33.
15. Nervo M, Lubini A, Raimundo FV, Faulhaber GA, Leite C, Fischer LM, et al. Vitamin B12 in metformin-treated diabetic patients: a cross-sectional study in Brazil. Revista Da Associacao Medica Brasileira 2011; 57(1): 46-49.
16. Ko SH, Ko SH, Ahn YB, Song KH, Han KD. Association of vitamin B12 deficiency and metformin use in patients with type 2 diabetes. J Korean Med Sci 2014; 29(7): 965-72.
17. Bell DS. Metformin-induced vitamin B12 deficiency presenting as a peripheral neuropathy. Southern Med J 2010; 103(3): 265-67.
18. Naha K, Dasari S, Vivek G, Prabhu M. Vitamin B12 deficiency: an unusual cause for recurrent generalised seizures with pancytopaenia. BMJ Case Rep 2012; 2012: bcr2012006632.
19. Leishear K, Boudreau RM, Studenski SA, Ferrucci L, Rosano C, De Rekeneire N, et al. Relationship between vitamin B 12 and sensory and motor peripheral nerve function in older adults. J Am Geriatrics Soc 2012; 60(6): 1057-63.

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