Original Research Article

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Vitamin B12 deficiency among vegetarian and non-vegetarian diabetic population receiving prolonged Metformin based oral hypoglycemic agents therapy

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ABSTRACT

Background: Diabetes is a group of metabolic disorder that share the phenotype of hyperglycemia. Over the period of time the metabolic dysregulation associated with diabetes mellitus causes secondary pathophysiological changes in multiple organs like heart, blood vessels, eyes, kidney and nerves resulting in various complications. However, a common potential interaction of metformin with vitamin B-12 is well documented but is poorly studied by the physicians who prescribe metformin to their diabetic patients. Since vitamin B-12 deficiency is common among vegan population as compared to population consuming food of animal origin (meat, fish and dairy products). But in this article, it has been studied that metformin cause vitamin B-12 deficiency even in non-vegetarian population. The aim of this study was to asses' vitamin B12 deficiency among vegetarian and non-vegetarian diabetic population receiving prolonged Metformin based oral hypoglycaemic agents therapy. It was a cross sectional study done in Department of Medicine, UPUMS, Saifai, Etawah, Uttar Pradesh, India.

Methods: Study done among patients of type 2 diabetes mellitus of age group 30-60 years on prolonged metformin based OHA therapy and having peripheral neuropathy were included in study. Data was analysed on SPSS Version 22.0 and p value obtained.

Results: Statistical analysis of 93 patients included in study showed that vitamin B12 deficiency is common among the vegetarian (56.52%) and non-vegetarian (35.71%) population but the difference is not statistically significant (p value=0.29) which is more in favour of metformin associated vitamin B12 deficiency in non-vegetarian population.

Conclusions: Vitamin B12 deficiency is common in diabetes patients on metformin based OHA therapy hence we recommend routine screening for Vitamin B12 deficiency in such diabetes patients.

Keywords: Diabetes Mellitus, Metformin, Vitamin B12, Peripheral Neuropathy, Non-vegetarian, Vegetarian

INTRODUCTION

The Greek physician Aretaeus (130-200CE) noted a disease with symptoms of constant thirst, excessive urination and loss of weight and named the condition "Diabetes" meaning "flowing through". Diabetes is known disease since 200 years and is characterized as group of metabolic disorder that share the phenotype of

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hyperglycemia state causing polydipsia, polyphagia and polyuria.

Thomas Cawley first reported the case of diabetes. Paul Langerhan's (1847-1888) first discovered the distinct tissue in the pancreas called as islet's of Langerhan's. Banting and John Macleod were awarded Nobel Prize in 1923 for the "Discovery of Insulin".

As per the available data, about 285 million people had diabetes till 2010 with 90% having type-2 Diabetes.² International Diabetes Federation estimate 381 million people having diabetes in 2013 and by 2030, the incidence will be doubled.³

In India, 7.1% of India's adult population is affected with diabetes i.e. nearly 62 million people are affected. The high incidence is due to combination of genetic susceptibility plus adoption of high calorie diet and sedentary life style by India's growing middle class.⁴

As per WHO, the diagnosis of diabetes is done by oral glucose tolerance test.⁵

Diabetes can be classified into the following general categories:⁶

- Type 1 diabetes (due to β-cell destruction, usually leading to absolute insulin deficiency)
- Type 2 diabetes (due to a progressive insulin secretory defect on the background of insulin resistance)
- Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes)
- Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced diabetes (such as in the treatment of HIV/AIDS or after organ transplantation).

Criteria for the diagnosis of diabetes⁷

A1C \geq 6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.* OR FPG \geq 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.* OR 2-h PG \geq 200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.* OR in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose \geq 200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

Regarding management of type-2 Diabetes, multidisciplinary approach is preferred. Life style intervention in high risk group results in 35-58% reduction in incidence of type-2 Diabetes.⁸

Over the period of time the metabolic dysregulation associated with diabetes mellitus causes secondary pathophysiological changes in multiple organs like heart, blood vessels, eyes, kidney and nerves resulting in various complications.⁹

Diabetes mellitus is an established leading known cause of neuropathy in the world. Neuropathy is a most common complication and greatest source of morbidity and mortality in diabetic patients. It is estimated that the prevalence of neuropathy in a diabetic patient is approximately 20%. In

Metformin is recommended as initial therapy after life style modification for type-2 diabetes. ^{11,12} In America metformin was approved in 1996 and since then its use is increased dramatically following UKPDS study, when it was found to be effective in decreasing diabetes related chronic complications and mortality in type-2 obese patients. ¹³

Metformin's best-known side effect i.e. metabolic acidosis almost never occur if metformin is used in appropriate manner. Other common side effect of metformin is gastrointestinal related and is overcome by initiating the drug at low dose or by giving the drug after the meal with sustained release preparations.¹⁴

Several cross-sectional studies 15-17 and case reports 18-20 have documented an increased frequency of vitamin B12 deficiency among type 2 Diabetes mellitus patients. Metformin use has been unequivocally demonstrated as the prime factor associated with vitamin B12 deficiency among patients with type 2 Diabetes mellitus.²¹⁻²⁴

However, a common potential interaction of metformin with vitamin B-12 is well documented but is poorly studied by the physicians who prescribe metformin to their diabetic patients. Since vitamin B-12 deficiency is common among vegan population as compared to population consuming food of animal origin (meat, fish and dairy products).

But in this article, it has been studied that metformin cause vitamin B-12 deficiency even in non-vegetarian population. So, a routine screening for vitamin B-12 level must be done in patients receiving metformin for treatment of type-2 Diabetes.

METHODS

This study was done on patients of Type 2 diabetes mellitus attending out door of Medicine Department of UPUMS Saifai, from October 2016 to April 2017.

Inclusion criteria

- A case of type 2 Diabetes mellitus
- Age group 30-60 years
- All patients had symptoms of peripheral neuropathy
- All patients were taking Metformin based oral hypoglycemic agents (OHA) for 5 years or more.

Exclusion criteria

- Patients of type 2 Diabetes mellitus with altered sensorium, disturbed mental state, pregnant and lactating females
- Patients of type 2 Diabetes mellitus on drugs known to cause peripheral neuropathy like ATT, ART etc.
- Patients with renal failure, liver failure and cardiac failure
- Patients with known malignancy, transplant, septicaemia, tuberculosis, thyroid disorders and rheumatologic illness
- Patients with diabetes mellitus on drugs known to cause peripheral neuropathy like isoniazid, linezolid, metronidazole and phenytoin
- Patient having high risk category like HIV or alcohol
- Patients who denied for consent.

All patients satisfying inclusion and exclusion criteria were included in study. This was a cross sectional study.

All patients were subjected to a detailed history and thorough clinical examination including neurological examination after obtaining his/her informed consent.

Investigations

Fasting and post prandial blood sugar, serum creatinine, blood urea, complete blood count, HbA1C, TSH, Serum vitamin B12 levels. Normal range of vitamin B12 = 187-887 pg/mL (as per Institute laboratory).

Statistical analysis was done by SPSS version 22.0 and p value was obtained.

RESULTS

Total 93 patients were included in the study who satisfied the inclusion and exclusion criteria.

In this study, mean age was 51.24 years with minimum age 39 years and maximum age 60 years.

Out of total 93 patients, 51 patients (54.84%) were male and 42 patients (45.16%) were female (Figure 1). Sex ratio was 1:0.82.

Out of total 93 patients, 70 patients (75.27%) were non-vegetarian and 23 patients (24.73%) were vegetarian (Figure 2).

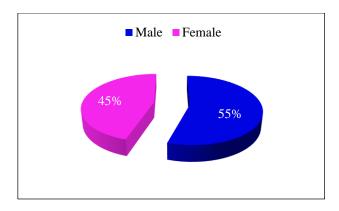


Figure 1: Sex distribution.

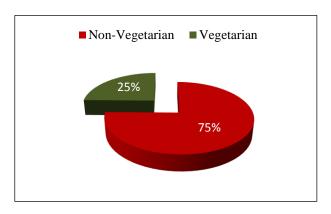


Figure 2: Dietary pattern

In the present study, minimum duration of Metformin based OHA therapy was 5 years and maximum duration was 16 years and average duration was 9.49 years (Figure 3).

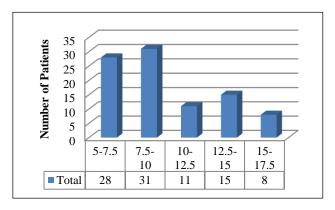


Figure 3: Duration of Metformin based OHA therapy.

In the present study, minimum dose of Metformin was 1.00 gram and maximum dose of metformin was 2.55 grams with average of 1.84 grams (Figure 4).

In the present study vitamin B12 deficiency was found in 38 patients (40.86%) out of total 93 patients.

Out of 38 patients with vitamin B12 deficiency, 25 patients were non-vegetarian and 13 patients were

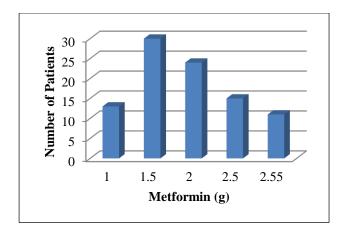


Figure 4: Dose of Metformin.

vegetarian. Among non-vegetarian patients, vitamin B12 deficiency was found in 35.71% (25 out of 70) patients and among vegetarian patients vitamin B12 deficiency was found in 56.52% (13 out of 23) patients but the association was statistically not significant (Table 1).

Table 1: Association of Vitamin B12 deficiency with dietary pattern.

| | Number of patients | Vitamin B12 deficient | P value |
|--------------------|--------------------|-----------------------------|---------------------------|
| Non- vegetarian | 70 | 25 | Fisher test p value=0.287 |
| Vegetarian | 23 | 13 | Chi square p |
| Total | 93 | 38 | value=0.375 |

Although vitamin B12 deficiency was more common among vegetarian than non-vegetarian patients of study population, the difference was considered to be statistically not significant by paired t test (p value=0.532).

DISCUSSION

In the present study vitamin B12 deficiency was found in 40.86% patients which was comparable to study done by Qureshi S et al.²⁵

Among vegetarian patients, vitamin B12 deficiency was found in 56.52% patients which was much higher than normal population and 35.71% patients had vitamin B12 deficiency among non-vegetarian patients. High incidence of vitamin B12 deficiency among non-vegetarian patients favor that use of Metformin was associated with vitamin B12 deficiency. Morar O et al, found vitamin B12 deficiency in 33% patients of diabetes mellitus on metformin therapy for more than 18 months.²⁶

Ting et al showed an increased risk of vitamin B12 deficiency associated with duration of metformin use and dose of metformin and found these parameters to be high risk factors for developing B12 deficiency.²⁷ In the

present study only those patients were included who were on metformin for more than 5 years and average duration of treatment was 9.49 years.

CONCLUSION

On the basis of the present study we conclude that Vitamin B12 deficiency is common in patients of diabetes mellitus on prolonged Metformin based OHA therapy. Deficiency is more common among vegetarian population on prolonged metformin therapy than nonvegetarian population but the difference is not statistically significant which is more in favor of Metformin associated Vitamin B12 deficiency in nonvegetarian population. Hence, we recommend routine screening for vitamin B12 deficiency in diabetes patients on Metformin based OHA therapy.

Due to small data and demographic variation among different regions of world, more research with greater number of subjects is needed to test this hypothesis.

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institutional ethics committee

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