ORIGINAL ARTICLE

Cobalamin Deficiency in Metformin Treated Type 2 Diabetics Presenting at a Tertiary Care Hospital of Sindh

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ABSTRACT

Objective: To determine vitamin B_{12} levels in metformin treated type 2 diabetes mellitus and its correlation with dose and duration of metformin.

Methods: This Cross sectional study was conducted at Isra University Hospital, Hyderabad from June 2016 to December 2017. A sample of 200 type 2 diabetics was divided into 2 groups; Group 1 - type 2 diabetics taking metformin and Group 2 - type 2 diabetics without metformin were selected. Serum cobalamin levels were measured from the sera by ELISA assay kit (Chemiluminescence Technique using Abbot Architect 1000). Variables were statistically analyzed.

Results: Serum cobalamin in metformin treated diabetics was noted as 159.6±35.7 pg/dl compared to 232.5±28.51 pg/dl (P=0.0001). Serum cobalamin in male was 211.6±16.7 pg/ml compared to 135.35±15.51 pg/ml in female (P=0.0001). Cobalamin deficiency was noted in 49% metformin treated diabetics compared to 37% in no-metformin diabetics.

Conclusion: Long term metformin drug therapy is significantly associated with cobalamin deficiency. Cobalamin screening and supplements should be offered to metformin treated diabetics.

Key words: Cobalamin, Metformin, Type 2 Diabetics

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INTRODUCTION:

Diabetes Mellitus (DM) has emerged a challenging health problem throughout the World. Type 2 DM is metabolic disorder of glucose that is multiplying explicitly and has become a public health concern. In the United States, the DM is 6th leading cause of mortality[1]. DM is prevalent throughout the World; however its prevalence differs according to geographical areas and age groups. World burden of DM now approximates 450 million people. Of this, 35.4 million people are residing in middle-east and North African areas[2].

In Pakistan, the prevalence of DM varies in urban and rural areas. According a previous survey[3] the prevalence of DM was 7.7% in rural and 10.6% in urban population of Pakistan. Currently, Pakistan caters 7 million type 2 diabetics[1-3]. DM is associated with a number of vascular complications that include both micro-vascular and macro-vascular complications[4]. Metformin is a biguanide used as first line drug for diabetes therapy. Metformin is recommended as first line drug by both the American and European guidelines. Metformin is believed to prevent cobalamin absorption from the terminal ileum through inhibition of calcium dependent channels. Previous studies[5-7] concluded that the cobalamin deficiency occurs by prolonged use of metformin. Long term metformin use is linked to cobalamin deficiency; this is supported by observational and interventional studies[8,9]. Cobalamin catalyzes the conversion of homocysteine to methionine by remethylation reaction. Elevated homocysteine is a risk factor for the diabetes related micro-vascular and

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macro-vascular complications[10]. Euglcyemic effect of metformin is exerted through inhibition of liver gluconeogenesis, and an increased in glucose uptake by target cells. Metformin is proposed to inhibit the mitochondrial respiration that is essential for the hepatic gluconeogenesis[11]. Cobalamin deficiency manifests clinically as macrocytic megaloblastic anemia and peripheral neuropathy. Neuropathy may occur in the absence of hematological manifestations[12,13]. In Pakistan, the prevalence of DM is rapidly rising[3] compared to any other country in the World[14]. Risk of cobalamin deficiency in diabetics is multiplied by pre-existing dietary deficiency[15]. Bearing in mind a serious scenario of neglect, the present cross sectional study was conducted to determine cobalamin levels in metformin treated type 2 diabetes mellitus and its correlation with dose and duration of metformin presenting at our tertiary care hospital.

METHODS:

This present observational cross-sectional study was conducted at the Department of Medicine, Isra University Hospital. The study was conducted over duration from June 2016 to December 2017. Both admitted and Medical Outdoor patients were screened to fulfill the criteria. Patients were selected by non-probability convenient sampling, using proportions for the sample size calculation. A sample of 200 type 2 diabetics were divided into 2 groups; Group 1 - type 2 diabetics taking metformin (n=100) and Group 2 - type 2 diabetics without metformin (n= 100). Inclusion criteria were; volunteers of age 30-60 years, metformin dose 1-2 grams daily, metformin duration ≥ 2 years. Exclusion criteria were; strict vegans, age > 60 years, thyroid and liver disorders, anemia, malabsorption syndrome, alcoholism, renal disease, blood transfusion, and use of proton pump inhibitors. They were interviewed for the purpose of study, gain and losses and interest of the researcher. Volunteers were asked to abide by the protocol of study and were further directed that they can leave the study protocol without telling in advance. They were asked that they will not bear the expenses of blood investigations. All study subjects were interviewed in detail to meet the inclusion and exclusion criteria. Study subjects were asked for blood sampling. Hemoglobin, hematocrit and red blood cell counts were estimated by Cobas hematology analyzer. Serum cobalamin levels were measured. from the sera by ELISA assay kit (Chemiluminescence Technique using Abbot Architect 1000). Cobalamin categories were; >240pg/ml (normal), 170-240 pg/ml (borderline deficiency), <170 pg/ml (deficiency) and <100 pg/ml (severe deficiency).[16] Data was statistical analyzed.

RESULTS:

Age was 53.5±11.5 and 51.5±13.7 years in group 1 and 2 respectively (P=0.961). Male and female were noted as 53% and 47% vs. 51% and 49% in group 1 and 2 respectively (P=0.81). Systolic and Diastolic BP, body weight, hemoglobin, RBC counts and serum cobalamin are shown in table I. Serum cobalamin (mean± SD) in groups 1 and 2 were noted as 159.6±35.7 and 232.5±28.51 pg/dl respectively (P=0.0001). Serum cobalamin in male was 211.6±16.7 pg/ml compared to 135.35±15.51 pg/ml in female (P=0.0001). Cobalamin (Mean± SD) levels as normal, borderline deficiency, deficiency and severe deficiency (table II and graph I). Serum cobalamin >240 pg/ml, 170-240 pg/dl, <170 pg/dl and <100 pg/dl were noted 51%vs.63%, 23% vs. 19%, 12% vs.11% and 14% vs. 7% in groups 1 and 2 respectively (table III and graph II) (P=0.0001). In group 1 (metformin), 49% subjects revealed one or other type cobalamin deficiency, compared to 37% in group 2 (no-metformin) diabetics.

DISCUSSION:

The present small scale cross sectional study compared the serum cobalamin deficiency between metformin and no-metformin treated type 2 diabetic subjects. Being cheaper and effective drug, the metformin is one of first line drugs given as mono-pill or combined pill therapy. One of the potential adverse effects of long term metformin is serum cobalamin therapy. In present study, serum cobalamin deficiency was noted in 49% subjects

Table No: I Demographic characteristics and Lab findings (n=200)

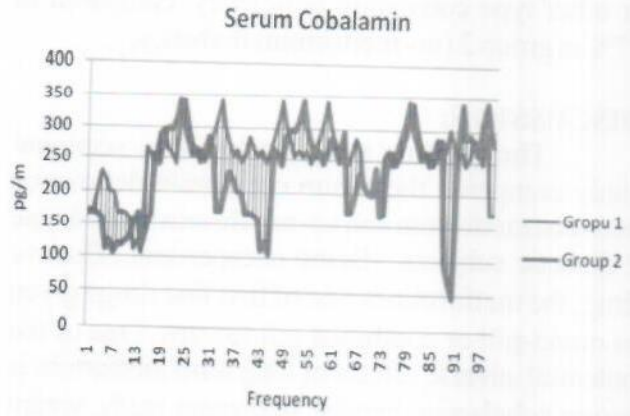
Variable	Group 1.	Group 2.	P-value
Age (years)	53.5 11.5	51.5 13.7	0.96
Male	53 (53%)	47 (47%)	0.81
Female	51 (51%)	49 (49%)	
Systolic BP (mmHg)	145.5 13.7	141.1 15.3	0.90
Diastolic BP (mmHg)	85.3 13.7	87.5 12.5	0.73
Body weight (Kg)	79.5 13.6	80.1 16.5	0.47
Hemoglobin (g/dl)	12.7 3.15	11.6 4.15	0.003
Hematocrit (Hct.) (%)	39.5 2.59	37.7 5.67	0.007
RBC ($x10^9$/ L)	4.21 0.91	4.81 0.75	0.008
Metformin duration (years)	4.1 1.3	4.3 1.1	0.81
Cobalamin (pg/dl)	159.6 35.7	232.5 28.51	0.0001

Table No: II Cobalamin levels in study subjects (n=200)

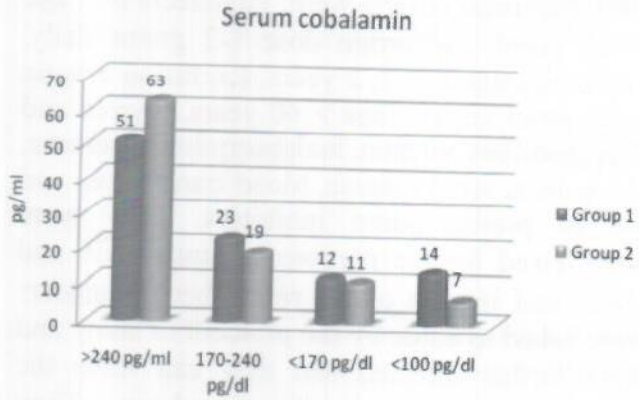
Cobalamin categories	Group 1	Group 2	P-value
>240 pg/ml	515.3 23.98	435.7 26.7	0.0001
170-240 pg/dl	181.83 11.5	176.35 17.3	
<170 pg/dl	131.13 15.6	115.27 17.5	
<100 pg/dl	70.85 15.8	82.51 8.98	

Table No: III Cobalamin deficiency in Study Subjects (200)

Cobalamin categories	Group 1.	Group 2.	P-value
>240 pg/ml	51%	63%	0.0001
170-240 pg/dl	23%	19%	
<170 pg/dl	12%	11%	
<100 pg/dl	14%	7%	
Total	100%	100%	



Graph I. Frequency distribution of serum cobalamin



Graph II. Bar graph showing cobalamin frequency between groups

revealed one or other type cobalamin deficiency in metformin group, compared to 37% in no-metformin diabetics. High frequency of 49% cobalamin deficiency may be because of nutritional deficiency that is prevalent among the general healthy adult population of Pakistan. The no- metformin diabetics shows frequency of 37% cobalamin deficiency this shows the prevalent cobalamin deficiency due to malnutrition[17-19]. Hassan N et al[20] conducted on the frequency of serum cobalamin deficiency in 27.5% patients being treated by metformin. The cobalamin deficiency reported by above study in contrast to the present study. Most probable reason of discrepancy is nutritional deficiency that is prevalent among the country[17-19]. Iftikhar et al[21] reported frequency of 31% of cobalamin deficiency among metformin treated patients that are also in contradistinction to 49% cobalamin deficiency of present study. This discrepancy is due to the metformin duration. Iftikhar et al studied metformin therapy of at 3 months that is in contradiction to present study of ≥2 years metformin duration. An Irish[22] study reported cobalamin deficiency of 31% in metformin diabetics compared to 9% no-metformin diabetics. In present study, 49% of metformin treated diabetics showed 49% cobalamin deficiency compared to 37% no-metformin diabetics. Ahmad et al[23] reported cobalamin deficiency in 38.1% of the metformin taking diabetic patients. This is close to 49% cobalamin deficiency of present study. However, the reason of low frequency of Ahmed et al[23] is small duration of metformin therapy by the diabetics they studied. Another study[24] conducted reported cobalamin deficiency in 36.8% of patients and cobalamin ranged as 125-250 pg/ml. In present study, serum cobalamin (mean± SD) in groups 1 and 2 were noted as 159.6±35.7 and 232.5±28.51 respectively (P= 0.0001) that is consistent finding. Another previous study[25] reported high frequency of cobalamin deficiency among diabetics with megaloblastic anemia taking metformin. The findings are in full agreement with the present study. Another previous study[26] from Netherland reported very low frequency of 9.7% in diabetic patients on metformin compared to 4.4% of diabetic patients' not taking metformin. The findings of above study are in contradistinction to present and previous studies[22-24]. One reason of contrary results is use of different cobalamin levels of deficiency. Above previous study[26] took cobalamin deficiency <150 pmol/l that is different from the present study. A recent study[27] from India reported cobalamin deficiency of 30% among metformin treated diabetics that are also inconsistent to the 49% cobalamin deficiency of present study. The reason is that the above study included a small sample of 50 diabetics in contrary to 100 metformin treated diabetics in the present study. Limitations of present study include 1st small sample size not representative of total population, 2nd nutritional deficiencies are prevalent in the country that might have affected the results as confounding factors. The results of present study cannot be generalized to large population and other geographical areas. However, strength of study is clear from its prospective cross sectional study design, inclusion and exclusion criteria. The present study is a contribution to the medical professional for the future studies to be conducted.

CONCLUSION:

The long term metformin drug therapy is significantly associated with cobalamin deficiency. Cobalamin screening is mandatory for the diabetics taking metformin for long durations. Cobalamin supplements be given to metformin treated diabetics to prevent irreversible neuropathic complications beside anemia.

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