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Research Article

**CROSS-SECTIONAL ANALYSIS OF PREVALENCE OF  
VITAMIN B 12 DEFICIENCY IN DIABETIC POPULATION**Muhammad Muneeb<sup>1\*</sup>, Abid Ali<sup>2</sup>, Anam Shaikh<sup>3</sup>, Aatir H. Rajput<sup>4</sup>, Qirat Modi  
Shaikh<sup>5</sup>, Sadia Khan<sup>6</sup>, Ali Muntazir Naqvi<sup>7</sup>, Abeeha Batool<sup>8</sup><sup>1, 2, 3, 4, 5 & 6</sup>LUMHS Research Forum<sup>1 & 3</sup>Indus Medical College, Tando Muhammad Khan<sup>4</sup>Sir Cowasjee Jehangir Institute of Psychiatry, Hyderabad<sup>1, 2, 3, 4, 5 & 6</sup>Liaquat University of Medical & Health Sciences, Jamshoro<sup>7</sup>University of Karachi<sup>8</sup>Virtual University of Pakistan**Abstract:**

**Objective:** To determine the prevalence of vitamin B12 deficiency in diabetic population presenting at Liaquat University Hospital, Hyderabad.

**Methodology:** This observation- cross sectional study was conducted over 510 diabetic patients at Liaquat University Hospital Hyderabad. Patients above 45 years of age, of either gender, diagnosed with diabetes for more than 2 years duration were evaluated for serum vitamin B12 level. The data was analyzed in statistical software (SPSS) and the p-value  $\leq 0.05$  was considered as statistically significant.

**Results:** During seven month study period, total 510 patients with diabetes were evaluated, Vitamin B 12 deficiency was found in 183 patients i.e. 35.88% with a level of  $\leq 200$  pg/ml while 327 i.e. 30.6 % patients were having normal B-12 levels. Among Vitamin B12 Diabetic Population, 112 (61.2%) were males and 71 (38.8%) were females. Around 2/3<sup>rd</sup> of the patients were using metformin as hypoglycemic agent while the rest were on other oral hypoglycemic agents or on insulin. 81.17% patients were taking either H2 Blocker or Proton Pump Inhibitor, while around half (46.86%) were on multivitamins.

**Conclusion:** The Vitamin B12 deficiency in diabetic population was found to be 35.88%. This leads a serious concern for the primary care physician to look for vitamin B-12 deficiency even if the patient is asymptomatic for B12 deficiency.

**Key Words:** Diabetic population, Vitamin B12, Megaloblastic anemia.

**Corresponding author:****Dr. Muhammad Muneeb,**

Lecturer – Dept. of Forensic Medicine &amp; Toxicology

– Indus Medical College, TMK

Email: [muhammadmuneebchauhan@gmail.com](mailto:muhammadmuneebchauhan@gmail.com)

Phone: +92-331-3676651

QR code



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**INTRODUCTION:**

Diabetes is a metabolic syndrome that almost affects all bodily functions. It is mostly first encountered and treated by general practitioners and primary care physicians, who are required to properly manage both the disease and its numerous comorbidities. Vitamin B 12 deficiency is a potential comorbidity that is often unnoticed, in spite of the fact that many diabetic patients are at risk for vitamin B12 deficiency and associated problems. For instance, most widely used oral hypoglycemic agent is metformin and patients who are treated with it showed lowers serum vitamin B12 levels [1-4] and is associated with vitamin B 12 deficiency [1,5-7] Studies suggest the among the diabetic population that age more than 60, almost half suffered from metabolically confirmed B12 deficiency [8-10]. According to WHO criteria for screening for different diseases, earlier detection of disease at treatable stage leads to better prognosis of disease and is need of hour.

One of the most potential health concerns regarding vitamin B12 deficiency is neuropathy and it is evident from the scientific literature that almost 1/3<sup>rd</sup> of the diabetic patients older than 40 years of age have impaired sensation in feet [11]. Regrettably, the symptoms of diabetic neuropathy overlay with paresthesia, impaired vibration sense and impaired proprioception associated with lower levels of Vitamin B12 [12]. B-12 deficiency prompted nerve damage may be confused with or it may contribute to diabetic peripheral neuropathy [13] Identification of pinpoint cause of neuropathy is essential because simple vitamin B12 supplementation may reverse the neurologic symptoms inappropriately attribute to hyperglycemia.

Vitamin B12 deficiency is seen in normal clinical practice and observed in patients with various other pathologies [14]. Vitamin B12 deficiency often goes undetected with manifestations that range from asymptomatic to a wide spectrum of hematologic and/or neuropsychiatric features [15], Vitamin B12 deficiency is traditionally diagnosed

by biochemical assessment of serum B12 levels which is usually present in the setting of megaloblastic anemia but study showed that subclinical deficiency frequently presents with normal serum B12 levels and hematological parameter [16].

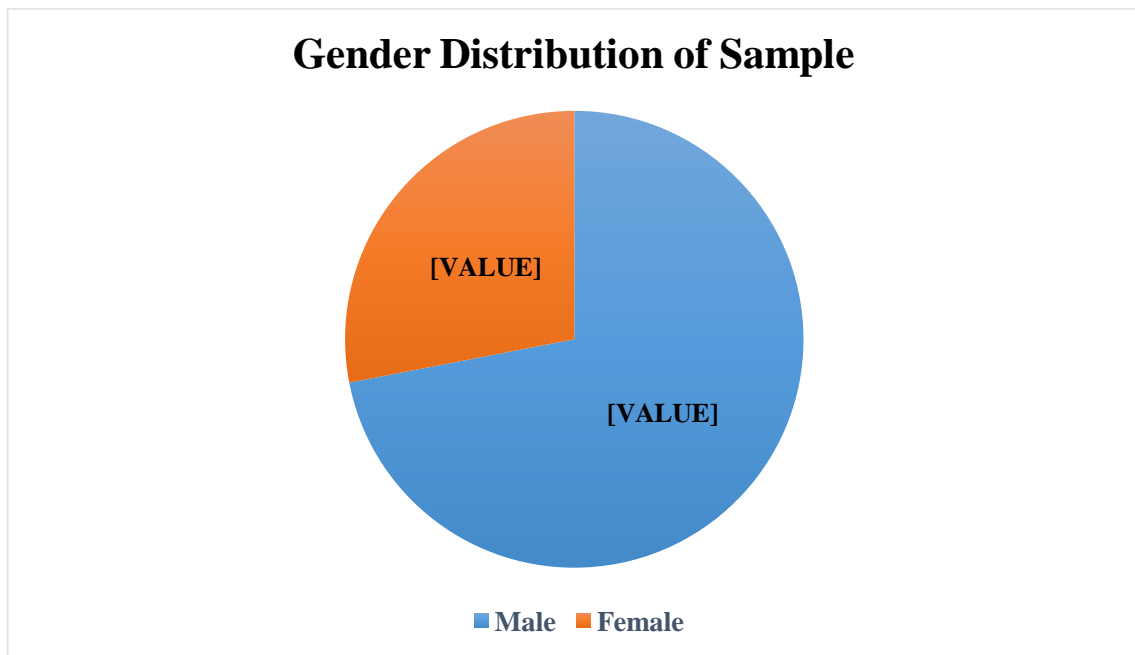
The present study was designed to investigate the serologic vitamin B12 deficiency in diabetic patients as the prevalence of diabetes in our setup is larger so it is expected that prevalence of vitamin B12 deficiency in diabetic population may be larger as compared to western population that's why such study was considered.

**METHODOLOGY:**

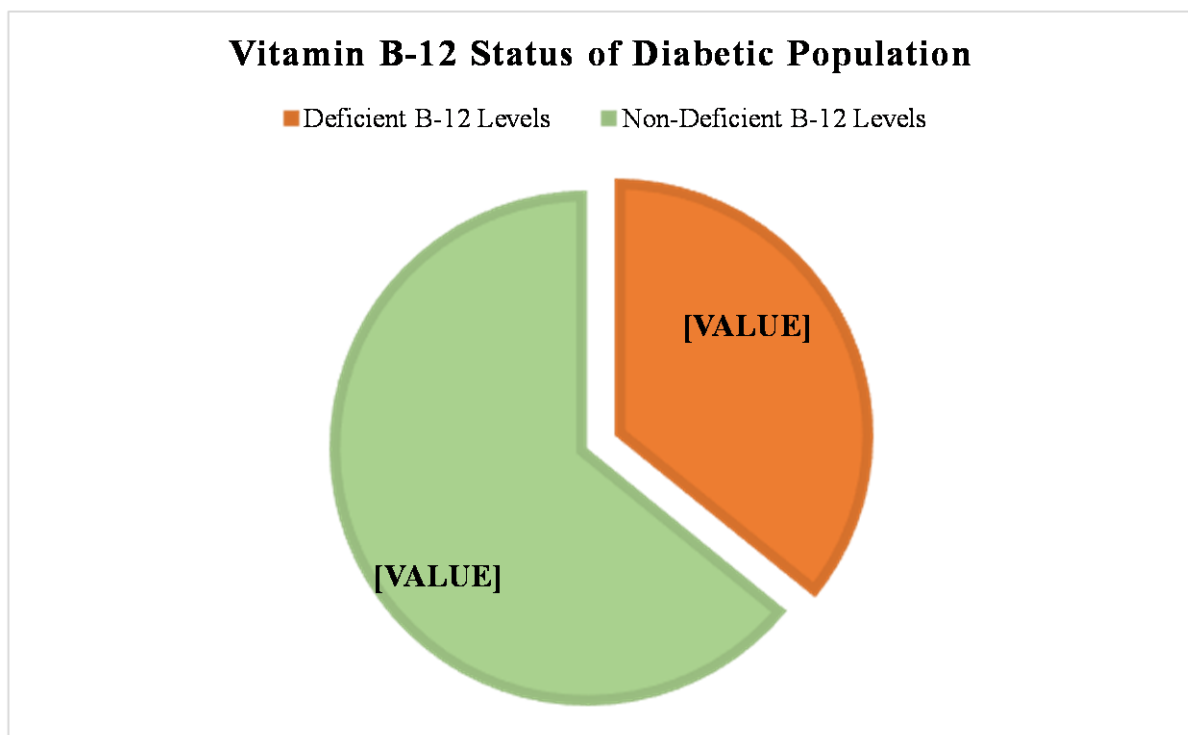
This study used a descriptive, cross-sectional design to determine the prevalence of Vitamin B-12 Deficiency among diabetic population, at Liaquat University Hospital Hyderabad. A sample of 510 diabetic patients with the age above 45 years, of either gender, chosen via consecutive sampling Non-probability, diagnosed with diabetes for more than 2 years duration were included in the study. An informed written consent was obtained from every participant prior to the study. Patients were asked about their age of onset of illness, duration of illness, type of diabetes diagnosed, type of regimen taking, sensory deficits and comorbid conditions. Patients were evaluated for serum vitamin B12 level in order to check for deficiency. Vitamin B12 deficiency was considered with level of  $\leq 200$   $\mu\text{g/ml}$ . Patients who are on vitamin B12 supplementation, malabsorption syndrome, those with history of resection of stomach or small intestine surgery, folic acid deficiency, pregnant ladies, alcoholics, anemia with the primary disease such as hepatic disease, hemolytic anemia, cancer, aplastic anemia, myeloproliferative disease, red cell aplasia, multiple myeloma, leukemia, and those using immunosuppressive or chemotherapeutic drugs were excluded from the disease. The data was obtained from 1<sup>st</sup> May, 2016 to 31<sup>st</sup> December, 2016 and was analyzed in statistical software (SPSS. V. 16.0) and MS. Excel 2013. P-value  $\leq 0.05$  was considered as statistically significant.

**RESULTS:**

During seven month study period, total 510 patients with diabetes were evaluated for vitamin B 12 deficiency with a mean age of  $56.32 \pm 9.3$ . Out of which 367 (71.96%) were males and 143 (28.04%) were females.

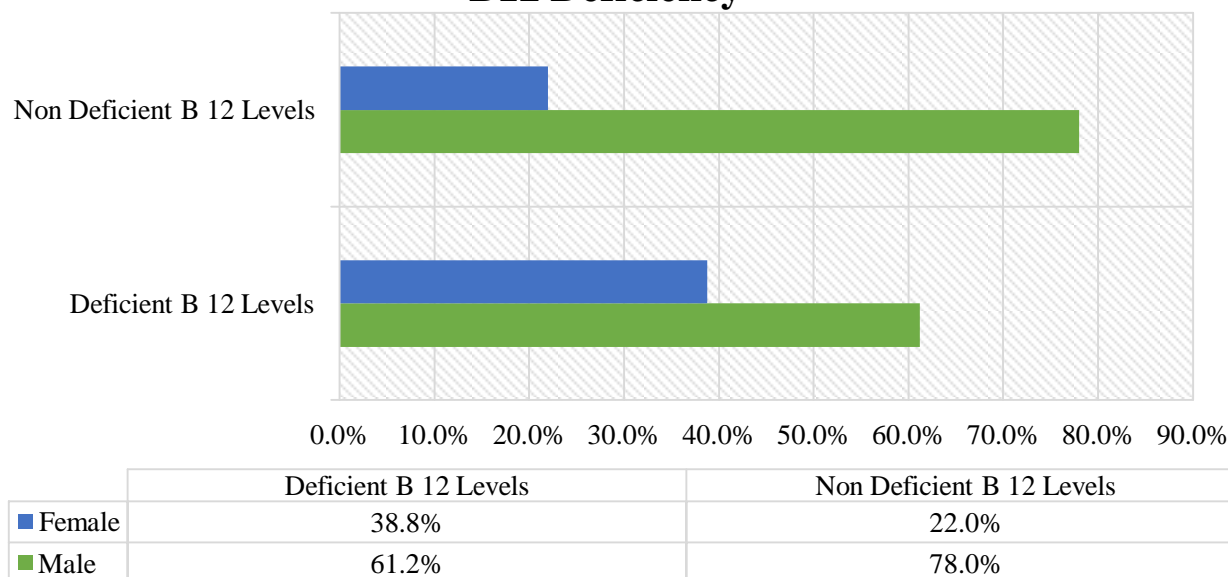


Vitamin B 12 deficiency was found in 183 patients i.e. 35.88% with a level of  $\leq 200$   $\mu\text{g/ml}$  while 327 i.e. 30.6 % patients were having normal B-12 levels.



The vitamin B12 deficiency was observed in 183 (35.88%) subjects of which 112 (61.2%) were males and 71 (38.8%) were females.

### The Distribution of Gender in Relation To Vitamin B12 Deficiency



Around 2/3<sup>rd</sup> of the patients were using metformin as hypoglycemic agent while the rest were on other oral hypoglycemic agents or on insulin. Majority of the population were on a dose of  $\geq 1000$ mg daily. 81.17% patients were taking either H2 Blocker or Proton Pump Inhibitor, while around half (46.86%) were on multivitamins.

**Table 1: Bivariate Association with Vitamin B12 Deficiency**

VITAMIN B12 DEFICIENCY				
	Yes n = 183	No n = 327	Total n = 510	P- Value
<b>Current Metformin Use</b>	0.67			
Yes	65.02% (119)	64.22% (210)	329	
[[No	34.97%(64)	35.77%(117)	181	
<b>Acid Blocker Use</b>	0.002*			
Yes	72.13%(132)	86.23%(282)	414	
[[No	27.86%(51)	13.76%(45)	96	
<b>Multivitamin Use</b>	0.04*			
Yes	60.1%(110)	39.45%(129)	239	
[[No	39.9%(73)	60.55%(198)	271	
<b>Calcium Use</b>	0.62			
Yes	26.23%(48)	34.86%(114)	162	
[[No	73.77%(135)	65.14%(213)	348	

\*p-value is statistically significant

**DISCUSSION:**

This is the very first cross sectional study in our Pakistan especially Sindh, as far we are aware of, which is designed to find out the prevalence of B-12 deficiency in patients with type 2 diabetes. In our study, we identified around 1/3<sup>rd</sup> of diabetic patients with B12 deficiency. Though it is probable to infer the prevalence of B-12 deficiency in diabetic patients from previous studies [8-11], we feel our study provided an estimate that is more generalizable to the diabetic population in our set up. With a prevalence of 35.88% physicians will need to consider the comorbid effects of B-12 deficiency in a population which is already at risk to neuropathic complications. More investigations are required to chart the full clinical impact of deficiency in these patients.

Despite that the clinical significance of a 35.88% prevalence of B-12 deficiency in the diabetic population is unknown, the impact B-12 deficiency may have as a cause of peripheral neuropathy in this population should be explored. 60% to 70% of diabetic patients have mild to severe forms of nervous system damage [11] the most common being peripheral neuropathy. The relatively high prevalence of B-12 deficiency found in this study makes it likely that at least a portion of peripheral Neuropathy cases in diabetic patients may be attributed to B-12 deficiency. Previous studies have demonstrated that supplemental vitamin B12 improved somatic and autonomic symptoms of diabetic neuropathy [17,18]. Testing for, and treating, B-12 deficiency in those patients with neuropathy may lead to improved clinical outcomes. Clinical trials are needed to further evaluate this link.

A number of studies demonstrate a prevalence of B-12 deficiency in the elderly that ranges from 12% to 23%.<sup>8, 10</sup> though the B-12 deficiency in our diabetic patients was in line with these results, it is important to note that the average age of our population was approximately 10 years younger than the average age of the elderly volunteers enrolled in these other studies. In addition, both bivariate and multivariate analyses demonstrated that age was not significantly associated with B12 deficiency. This suggests that diabetes, not age, may account for the 35.88% prevalence of B12 deficiency. Unfortunately, the ability to compare our prevalence results to the general population is limited because there are no published studies that examine the prevalence of B12 deficiency in the general population.

Patients on chronic metformin therapy seem to be at increased risk for B12 deficiency. Its use is

associated with lower serum vitamin B12 levels [1-4,6] and megaloblastic anemia [1]. Several studies associate metformin use with established clinical B-12 deficiency.<sup>1,5</sup> In fact, higher doses and longer treatment with metformin seem to be risk factors for such deficiency [19]. Although we found that patients using metformin had lower B12 levels. We did not find metformin use to be associated with overt B12 deficiency. In addition, there were no statistically significant metformin dose-dependent relationships, despite a trend between higher dosages of metformin use and B12 deficiency. Our study was not designed nor powered to find these secondary associations. As part of a post hoc analysis we did look at diabetic patients at risk for B12 deficiency to determine whether there was a significant association with metformin use. Current metformin use was associated with a significantly higher risk for B-12 deficiency when defined as a serum B12 level  $\leq 200$ pg/mL. Patients with B12 levels of 200 pg/ mL may be at risk for B-12 deficiency because tissue deficiency may occur despite normal serum B12 levels [9, 20-22]. Identification of patients "at risk" for B-12 deficiency as those with serum B12 equivalent to 350 pg/mL may help the clinician define a level to test for B-12 deficiency using specific tissue markers, especially among diabetics who are using metformin.

Our multivariate analysis looked for specific associations for B-12 deficiency. We entered into our model known and potential risk or protective factors for B-12 deficiency. Multivitamin use seemed to protect diabetic patients from B-12 deficiency. The effect of multivitamins raising serum B12 level is documented in the literature. Randomized trials in adults taking 6 to 9 mcg of B12 daily show effects of higher serum B12 levels compared with placebo [23,24]. There are no known studies specifically evaluating whether a daily multivitamin prevents B-12 deficiency. Our findings may be noteworthy because conventional treatment of B12 deficiency is with high dose oral supplementation or B12 injections [25] Yet, most multivitamin formulations typically contain 6 to 25 mcg of supplemental B12 [26,27], which seemed to be enough to protect against B12 deficiency in diabetic patients. Further research needs to be conducted before the validity of multivitamin use to prevent against B12 deficiency is confirmed. Other factors known to increase risk for B12 deficiency, such as advanced age was not significantly associated with B-12 deficiency, though usage of acid blocker seems to be a strong factor behind deficiency of B12.

Regarding gender distribution of present study, the vitamin B12 deficiency was more marked in males (65.8) with statistically significant difference ( $p=0.04$ ) whereas the female gender is predominant in the study by Gümürdülü *et al* [28].

There were several limitations to our study. Our study was a sample population from a government health care system. Liaquat University Hospital Hyderabad has been recognized as a major care provider in the chronic care model of diabetes. Subsequently, most patients had well-controlled diabetes. In populations with poorer glycemic control, our study may not be generalizable because the rates of metformin use may not be similar. However, a population with poorer glycemic control is at higher risk for neuropathy and may benefit even more from early identification of concomitant B12 deficiency. In addition, we only included diabetics older than 45, consistent with the age group of the majority of the diabetic population in the United States [13]. Overall, we feel our participants represent typical primary care diabetic patients who present to an outpatient clinic for ongoing care.

The cross-sectional nature of our study limits us to describing a population. Therefore, the findings relevant to our secondary aims were limited to associations. The primary objective, however, was to define the prevalence of B12 deficiency in the diabetic population, for which a cross-sectional study is appropriate. Additional studies will be needed to prove causation. In addition, defining B12 deficiency based solely on biochemical markers remains controversial [29-31]. Although elevations in methylmalonic acid have been correlated with clinical manifestations of B12 deficiency [17,18], we did not evaluate for evidence of megaloblastic anemia or neuropathic disease. Therefore, the clinical significance of metabolically confirmed B12 deficiency in our patient group is unknown. Finally, the B12 deficient patients identified in our study were not followed for treatment effect with supplemental vitamin B12 or to evaluate for normalization of B12 levels. Such follow-up would have helped confirm the diagnosis of vitamin B12 deficiency [32].

Therefore, it has been observed that prevalence of vitamin B12 deficiency is high in Pakistani population and the present study was specific and limited to evaluate vitamin B12 level in diabetic population subjects at a limited setup; hence several other multidisciplinary and more in-depth studies are required to screen diabetic patients for their vitamin B12 status from every aspect i.e.

diagnostic to treatment effects because the serious concern of neuropathy.

### CONCLUSION:

Vitamin B12 deficiency seems to be very common among diabetic population in our country. In present study vitamin B12 deficiency was observed in 1.3<sup>rd</sup> of the diabetic population (35.88%) patients with male predominance 112 (61.2%).

Therefore the medical community should seriously recognize that up to 1/3<sup>rd</sup> of their diabetic patients may have vitamin B-12 Deficiency: they should consider B-12 deficiency in the differential diagnosis when managing comorbidities of diabetes especially diabetic neuropathy.

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