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ASSOCIATION OF ADULT OBESITY AND SERUM B12 DEFICIENCY - A CASE-CONTROL STUDY FROM INDIA

Internal Medicine

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ABSTRACT

Introduction: Vitamin B12, also known as cobalamin; has been implicated as an important factor in regulating various metabolic processes, thus playing a role in the etiology of obesity. **Objectives:** To assess whether obese adults are at an increased risk for vitamin B12 deficiency. This study aimed to assess the serum vitamin B12 status of obese Indians to see if there were any associations between body mass index (BMI) and serum B12 concentration. **Settings:** Medicine outpatient at a medical college university hospital. **Methods:** We included 224 adult participants aged ≥19 years. Overweight and obesity were defined as BMI ≥ 25-29.9 kg/m2 and ≥ 30 kg/m2 respectively. The study subjects were divided into 2 groups as normal BMI (< 25 kg/m2) group, and the obese BMI (≥ 25 kg/m2) group. BMI was calculated as weight in kilograms divided by height in meters square. Fasting venous blood samples were taken from the subjects for the estimation of serum B12 concentrations which were measured using the fully automated electrochemiluminescence immunoassay. Low serum B12 was defined concentration < 197 pg/mL, and B12 deficiency was defined as concentration below 150 pg/mL. The adjusted odds ratio (OR) and 95% confidence interval (CI) were obtained by the binary logistic regression method. The correlation between serum B12 and BMI was calculated using Pearson's correlation coefficient (r) across various BMI categories. **Results:** Serum B12 level was significantly lower among obese adults compared with non-obese adults. There were significant negative associations between BMI and serum B12 ($p = 0.004$). Pearson correlation coefficient was strongly negatively associated for BMI with serum B12 level ($r = -0.703$, $p < 0.00001$). **Conclusions:** Obesity in otherwise healthy adults was associated with an increased risk of serum B12 deficiency. A negative association was found between serum B12 concentrations in obese adult subjects. This association was more pronounced with higher grades of obesity; further research at a large scale is needed to understand the underlying mechanisms and its prevalence in the obese population. We recommend that the possibility of vitamin B12 deficiency should always be considered in obese adults.

KEYWORDS

Adult, Obesity, BMI, B12 Deficiency, Overweight, Vitamin.

INTRODUCTION

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health. In terms of body mass index (BMI) adult population is classified as overweight (BMI 25.0–29.9 kg/m2) or obese (BMI ≥ 29.9kg/m2) (1). The main causes of obesity include a sedentary lifestyle, advancing age, low socioeconomic status, and bad nutrition habits including irregular meal patterns with skipped meals among many adults (2). In 2016 worldwide 39% of adults aged ≥ 18 years were overweight and 13% were obese. The prevalence of overweight and obesity among children and adolescents aged 5-18 has risen dramatically from just 4% in 1975 to just over 18% in 2016 (3,4). Overweight and obesity are linked to more deaths worldwide than underweight. Globally more people are obese than underweight – this occurs in every region except parts of sub-Saharan Africa and Asia (4).

In India, according to the national family health survey 4 which was held in 2015-16; men and women overweight and obese are 18.9% and 20.6% respectively (5). Cerebrovascular diseases, insulin resistance, dyslipidemia, sleep apnea, hypertension, and diabetes are the major disorders associated with obesity due to the production of excessive adipokines (6). Also, obesity contributes to immune dysfunction and is a major risk factor for certain cancers such as hepatocellular, esophageal, and colon cancer (7).

Although it is hard to conceive of a nutritional deficiency occurring in subjects with excessive dietary and caloric intake, obese people tend to consume foods rich in carbohydrates and fat and thus are at increased risk of micronutrient deficiency. It is also observed that obese people have diets that are typically poor in balanced nutrition. Overweight and obesity have been shown to alter the absorption, distribution, metabolism, and/or excretion of micronutrients including folate, vitamin D, thiamine, calcium, magnesium, potassium, and B12(8). A poor nutritional status concerning vitamins affects mucosal integrity and can affect the absorption of other nutrients (9,10).

Vitamin B12 (B12) is an essential water-soluble vitamin also known as Cobalamin. B12 is manufactured by microorganisms present in the liver of animals bound to protein. B12 is involved in cellular energy production and epigenetic modulation processes, including DNA methylation, synthesis, and repair (11-13). B12 deficiency is mainly due to limited dietary intake of animal foods or malabsorption of the same (14). Previous studies have found that serum vitamin B12 deficiency is more common in obese individuals. However, the association between serum B12 concentrations and obesity has been inconsistent, although, B12 deficiency is more prevalent among the obese population (15-24).

A clinical study based on knowledge and information on serum B12 concentration among obese people in India is needed to reduce the risk of chronic diseases; especially coronary artery disease and diabetes mellitus, and improve quality of life. Our study is the first of its kind to describe the association of adult obesity with serum B12 concentration in India.

RESEARCH QUESTION

Does obesity is associated with the low level of serum vitamin B12?

AIMS AND OBJECTIVES

The current study aimed to assess whether obese adults are at increased risk for vitamin B12 deficiency. This study was conducted to investigate serum B12 status, clinical characteristics, and anthropometric measurements of healthy overweight and obese compared with healthy non-obese adults from Rajasthan.

METHODS

A. Settings

This is a hospital-based observational case-control study comparing 224 subjects with overweight and obese; and 170 subjects with normal BMI adults aged 19 years and above; over three years (from February 2018 to January 2021). The study participants, who came for routine

health check-ups; were randomly selected from medicine outpatient clinics at Pacific Medical College and Hospital (PMCH), Udaipur. PMCH is a tertiary care teaching hospital in Rajasthan, India. The participants were explained in detail the purpose of the study, and informed written consent was obtained. The study was approved by the institutional ethics committee.
The inclusion and exclusion criteria were defined as follows.

B. Inclusion criteria:
According to the world health organization (WHO), body mass index (BMI) is a simple index of weight-for-height that is used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his/her height in meters (kg/m2). Adults are of 19 years or more of age (4).

1. Overweight is a BMI greater than or equal to 25 but less than 30; and
2. Obesity is defined as BMI greater than or equal to 30.

Control non-obese group having BMI more than 18.5 and less than 25; and no other known chronic or acute illness.

C. Exclusion criteria:

1. Pre-existing diabetes, malignancy, anemia; or any other chronic or acute illness.
2. Post-surgical status of bariatric or other major gastrointestinal surgery.
3. Currently or in past on metformin, H2 blockers, and proton pump inhibitors for more than 4 weeks duration.
4. Currently or in past on fortified food, multivitamins, or B12 supplements.
5. Chronic alcohol use and dependence.
6. Pregnant females.

For this analysis, we initially identified 238 participants with complete information on serum vitamin B12 levels and obesity status. We then excluded 4 people who were using metformin for weight reduction for 2 months, 4 people who took B12 supplements, 2 females who reported pregnancy, and 4 people who started on herbal diets; resulting in 224 participants being finally included in our analysis.

D. Exposure and outcome analysis
Complete demographic details of all the participants were recorded in the study proforma. The body weight of each individual dressed in normal clothing was recorded by using Omron digital body weighing scale HN-283. Height measurements were taken by using an MCP wall-mounted stature scope height measuring scale for clinics according to the national health and nutrition examination survey anthropometry procedures manual (25). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters and rounded to 2 decimal places. The BMI classification was done according to WHO criteria: overweight = 25.0-29.9 kg/m2, obesity class I = 30.0-34.9 kg/m2, obesity class II = 35.0-39.9 kg/m2 and obesity class III ≥ 40.0 kg/m2; and normal BMI (non-obese) = 18.5-24.9 kg/m2. Waist and hip circumferences were measured to calculate the waist-hip ratio (WHR). As per WHO, WHR for males <0.95 and females <0.80 were considered normal (4).

E. Method for estimation of serum B12 level
We obtained fasting venous blood samples of the study participants in a plain vial and the serum was stored at 2-8 0C and assayed for serum B12 levels. The serum B12 measurements were done with the Cobas e 411 analyzer (Roche Diagnostics) - a fully automated analyzer that uses a patented ElectroChemiLuminescence (ECL) technology for immunoassay analysis. This method has been standardized against the Elecsys serum vitamin B12 assay as per the WHO calibration and accuracy study (26). The range of normal level of serum B12 is 197-771 pg/mL (2.5th-97.5th percentile); with a median of 425 pg/mL. Values below 150 pg/mL are considered the B12 deficiency; while 150-197, pg/mL is a low B12 level. The range of detection of serum B12 in our method was 50 pg/mL to 2000 pg/mL.

F. Data collection: Both the group participants were clinically assessed, anthropometric measurements recorded and serum B12 concentration was estimated at the in-hospital biochemistry laboratory. These data were entered in the proforma.

G. Quality control of data: Serum B12 concentrations were randomly cross-checked with the PreciControl Varia kit provided with the test kits. We also sent random samples to the research laboratory of our medical college and were found to be comparable with biochemistry laboratory results.

STATISTICAL METHODS
Data were analyzed using a standard statistical method provided by SPSS software. The continuous variables age, WHR, and serum B12 of the two groups were analyzed using analysis of variance for comparison of the mean based on BMI categories. The continuous variables were stated as mean ± standard deviation (SD). The categorical variables were stated as a percentage. Adjusted odds ratio and 95% confidence intervals were obtained from binary logistic regression with low serum B12 concentration (<197 pg/mL) as a dependent variable; and sex, BMI, and WHR as predictors. Binary logistic regression was also performed with serum B12 and WHR as dependent variables and BMI as the main independent variable. P values below 0.05 were considered statistically significant. Correlation between serum B12 and BMI; and serum B12 and WHR were calculated using Pearson's correlation coefficient (r) across various BMI categories.

RESULTS
The study enrolled 394 patients, 224 cases of overweight and obesity (59.82 % males and 40.18% females), and 170 controls (59.41 % males and 40.59 % females). The mean age of the patients in the cases group was 40.37 ± 9.33 years, and in the control group was 39.10 ± 9.58 years (p=0.186; p > 0.05). Table 1 shows frequency distribution among cases and controls based on gender, age group, WHR, and serum B12 concentration range.

Table 1: Frequency distribution among controls and cases

Characteristics		Control group n= 170	Cases group n= 224	
		Normal (BMI 18.5-24.9) n= 170(%)	Overweight (BMI 25-29.9) n= 94(%)	Obese (BMI ≥30) n=130 (%)
Age Group	19-40 yrs.	84(49.41)	51(54.26	44(33.85)
	41-60 yrs.	86(50.59)	43(45.74)	86(66.15)
Gender	Male	101(59.41)	54(57.45)	80(61.54)
	Female	69(40.59)	40(42.55)	50(38.46)
WHR (Male)*	<0.95	87(86.14)	12(22.22)	0(0.00)
	≥0.95	14(13.86)	42(77.78)	80(100.00)
WHR (Female)*	<0.80	39(56.52)	8(20.00)	0(0.00)
	≥0.80	30(43.48)	32(80.00)	50(100.00)
Serum B12	≤150 pg/ml	11(6.47)	1(1.06)	73(56.15)
	151-197 pg/ml	15(8.82)	0(0.00)	21(16.15)
	>197 pg/ml	144(84.71)	93(98.94)	36(27.70)

*As per WHO, WHR for males <0.95 and females <0.80 were considered normal.

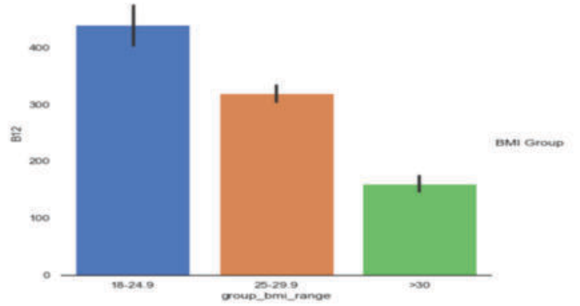

Figure 1: Serum B12 level among controls, overweight and obese group.

The mean was obtained for age, WHR, BMI, and serum B12 among cases and controls. The mean serum B12 level was significantly lower in the obese and overweight groups than in the control group; 160.7±83.14 pg/mL, 320.17±72.16 pg/mL, and 440.98±234.08 pg/mL respectively (p=0.000, p<0.001) (Table 2, Figure 2, 3). Serum B12 level in the obese patients was also significantly lower than in the overweight group (p=0.000, p<0.001). The adjusted Odds ratio was significant for BMI and gender (p=0.004 and 0.001 respectively) but the ratio was highest for BMI, and it was not significant for WHR ((p=0.439, p>0.005) (Table 3).

Table 2: Analysis of variance according to BMI category

Characteristics	BMI Category, mean± SD			p-value
	Normal (BMI18.5-24.9) n= 170	Overweight (BMI 25-29.9) n= 94	Obese (BMI ≥30) n= 130	
Age, yrs (mean±S.D.)	39.10±9.57	35.70±10.75	43.74± 6.29	0.000
BMI (mean±S.D.)	23.701.03	27.441.3	32.892.44	0.000
WHR (mean±S.D.)	0.8596±0.64	0.8991±0.68	0.9625± 0.5862	0.000
Serum B12, pg/ml(mean±S.D.)	440.98±234.08	320.17±72.16	160.7± 83.14	0.000

Table 3: Adjusted odds ratio about serum B12 deficiency for different variables (Results of Binary logistic regression)

Characteristics	Adjusted Odds Ratio*	95% Confidence Interval		P Value
Gender**	0.332	0.176	0.627	0.001
BMI	21.274	2.699	167.683	0.004
WHR	0.701	0.284	1.726	0.439

*Dependent Variable-Serum B12 Deficiency, **Reference category first i.e., male, control.

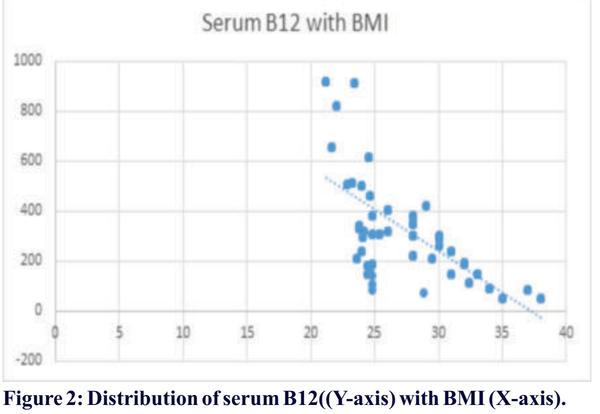

Figure 2: Distribution of serum B12((Y-axis) with BMI (X-axis).

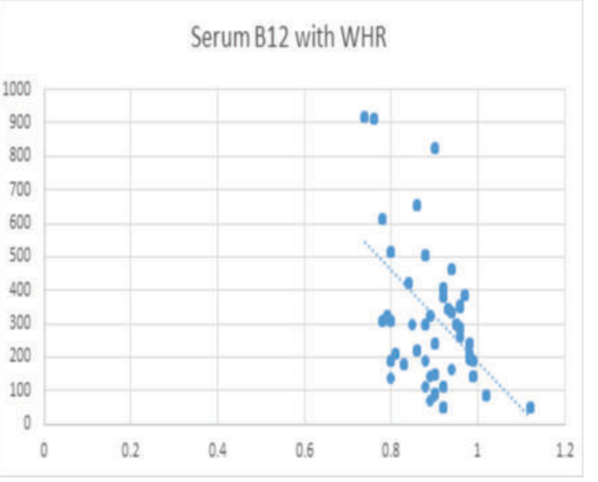

Figure 3: Distribution of serum B12 ((Y-axis) with WHR (X-axis).

Serum B12 status (deficient, low, and adequately normal) was compared among cases and control groups. Accordingly, the percentage of patients with serum B12 deficiency in the cases (overweight_obese) group was quite higher than in the control group (42.41% versus 15.29 %) ($p<0.001$) (Table 4). Visual inspection of the scatter plot of the relationship between BMI and serum B12 among cases and controls is shown in Figure 4. Serum B12 was significantly lower in obese females compared to age-matched obese males. Also, the age group 41-60 years had significantly lower serum B12 than the age group 19-40 years among both cases and controls (Table 5).

Table 4: Comparison Of Serum B12 Deficiency Among Cases And Controls

Group Total	Sub Group	B12low and deficient(<197 pg/ml) n(%)	B12 Normal (≥197 pg/ml) n(%)	P (Chi-Square test)
n=394	Control n= 170	26(15.29)	144(84.70)	0.000
	Cases n=224	95(42.41)	129(57.60)	

Table 5: T-test For Comparison Of Means Of Two Groups

Characteristics	Control group n=170 (BMI 18.5-24.9)	Cases group n= 224 (BMI ≥25)	95% Confidence Interval		P Value
			lower	upper	
Age (mean±S.D.)	39.10±9.57	40.37±9.31	-3.15769	0.61662	0.186
WHR(all)	0.8596±0.64	0.9359±0.70	-0.08993	-0.06277	0.000
WHR(male)	0.90±0.04	0.96±0.07	-0.07907	-0.04925	0.000
WHR (female)	0.79±0.03	0.87±0.05	-0.11914	0.05055	0.000
Serum B12(all)	440.98±234.08	227.62±111.07	178.34326	248.39214	0.000
Serum B12(male)	407.0693±183.25	229.6866±100.00	140.5573	214.20818	0.000
Serum B12(female)	490.64±287.39	224.54±126.84	199.12778	333.05869	0.000
Serum B12(19-40 years)	510.52±264.01	266.02±105.23	186.45855	302.54696	0.000
Serum B12(41-60 years)	373.07±177.31	199.34±107.50	135.4187	212.03867	0.000

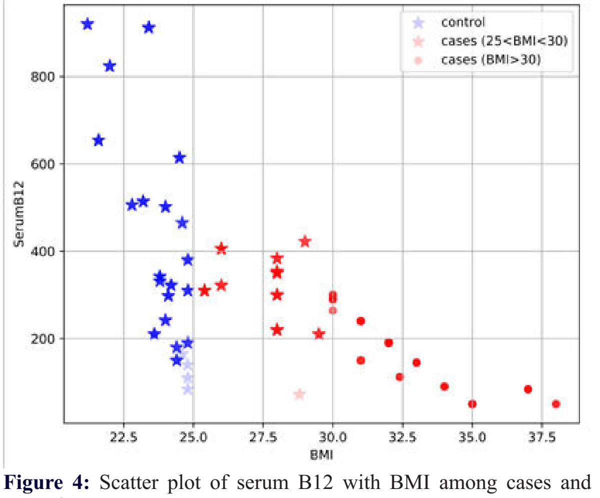

Figure 4: Scatter plot of serum B12 with BMI among cases and controls.

Relationship between BMI and serum B12

Pearson correlation coefficient was strongly negatively associated only for BMI with serum B12 level ®= -0.703, $p<0.00001$) (Table 6), although weak negative but statistically significant association was also found for age and WHR ($r = -0.397$, $p<0.00001$ and $r = -0.523$, $p<0.00001$; respectively). Spearman's Rho (rs) measures the strength and direction of the relationship between two variables. Among the cases group, BMI versus serum B12 the Spearman's Rho was rs = -0.89319, p (2-tailed) = 0. This shows the association between the two variables is statistically significant and the strength of association between the two variables is strong in the negative direction i.e. as BMI increases, there is a statistically significant decrease in serum B12 concentrations.

Table 6: Correlation of serum B12 with Age, BMI, and WHR.

Parameter	Pearson Correlation Coefficient (r) with serum B12	p-value
Age	-0.397	<0.00001
BMI	-0.703	<0.00001
WHR	-0.523	<0.00001

DISCUSSION

Causes of Vitamin B12 deficiencies are multifactorial and associated with many health problems. The prevalence of obesity is increasing in the world (27-29). Therefore, both health problems have gained importance among non-communicable yet preventable diseases in the last decades. Disruption of B12 transport in the blood, or impaired cellular uptake or metabolism causes intracellular deficiency. Its deficiency is caused by inadequate intake, inadequate bioavailability, or malabsorption. The clinical B12 deficiency with classic hematological and neurological manifestations is relatively uncommon. However, subclinical deficiency affects between 2.5% and 26% of the general population depending on the definition used. Inadequacy of vitamin B12, ranging from varying degrees of insufficiency to outright deficiency, has a wide prevalence and affects individuals of all ages, but most particularly infants, children, adolescents, and women of reproductive age in populations in which dietary intake of B12-containing animal-derived foods are restricted. Diagnostic biomarkers for B12 status include decreased levels of circulating total B12 and transcobalamin bound B12, and abnormally increased levels of homocysteine and methylmalonic acid (MMA). However, the exact cut-offs to classify clinical and subclinical deficiency remain debated (30).

The current study mainly intended to understand the relationship between BMI and serum B12 concentrations among adult Indians. To the best of our knowledge, our study is the first study that investigated the association of serum vitamin B12 concentration with BMI and WHR in obese patients from north India. Thus, it is needed to understand the relationship between BMI and serum B12 levels in the Indian population with an intent to answer the above research question. The study indicated that serum vitamin B12 deficiency is common among obese, compared to non-obese individuals. It is not more frequent only in patients with obesity, but also in those who are overweight. The study has shown that serum B12 level was strongly correlated in the negative direction with BMI, and there was only a mild correlation between WHR and age.

Kaya et al. conducted a study on the association between insulin resistance, obesity, and vitamin B12 in patients with polycystic ovary syndrome. They concluded that obesity, insulin resistance, and elevated homocysteine level were associated with vitamin B12 deficiency (31). We investigated vitamin B12 deficiency in the general population in the present study and found a significant negative correlation of serum B12 with BMI, but not with WHR.

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Previously reported studies on the association between vitamin B12 and obesity in middle-aged women have shown a significantly lower vitamin B12 in obese women and a negative correlation with BMI (32). The current study investigated a correlation between vitamin B12 levels in both male and female patients with obesity and overweight, in addition to BMI and WHR. In our study, the relationship was significant across all the BMI categories and the strength of correlation (association) increased with the increase in the BMI category with an r of -0.703 in the obese category.

In previous studies, various results regarding serum B12 levels between male and female individuals were reported (33-35). In some studies, it was reported that vitamin B 12 deficiencies were associated with long-term use of metformin, histamine-2 blockers, and proton pump inhibitors (PPIs) (36,37). In the current study, we found no significant difference between B12 levels in males and females; although male subjects with obesity and overweight had more serum B12 levels, compared to female counterparts. Also, in the current study, we excluded the patients who had used metformin, PPIs, and H2-blocker agents for over four weeks duration. In recent studies, it was shown that gastro-oesophageal reflux disease secondary to helicobacter pylori infection was associated with serum B12 deficiency. It was known that the frequency of helicobacter pylori infection and dyspeptic symptoms in obese patients were common (38-40). Patients with obesity tend to use intermittently PPIs or H2-blockers to relieve dyspeptic complaints. Intermittent use can also cause serum B12 deficiency in obese people.

There are several possible explanations for the association between low serum B12 levels and obesity. One explanation is that low serum B12 levels would trap folate as 5-methyltetrahydrofolate, prevent the generation of methionine from homocysteine, and therefore reduce protein synthesis and lean tissue deposition (41-43). It could also be due to the adipocyte dysfunction linked to low serum B12 levels through cellular inflammation (18, 44). Another possibility is that obesity could lower serum B12 levels through decreased dietary intake or absorption, increased catabolism, sequestration in adipose tissues, or changes in the gut microbiota profiles which could affect the metabolism of vitamin B12 (45).

Interestingly, a recent study in the Danish population showed that lower serum B12 concentrations were significantly associated with higher BMI, but a genetic risk score related to serum B12 concentrations associated with variants was not associated with BMI (20). Also, there is clear evidence that low serum B12 level is a risk factor for neurological consequences such as cognitive decline and cerebral atrophy associated with aging (46); and incident dementia (47).

The findings of this study can be used for predicting the risk of new-onset cardiovascular events and diabetes among Indians in the future by using serum B12 status among various categories of BMI. Although, large-scale longitudinal studies are required to establish this relationship.

Strengths Of The Study

The major strength of this study is the utilization of obese adult subjects otherwise healthy. Our study was among the first studies to demonstrate the relationship between BMI and serum B12 among adult Indians. Also, this study is unique in the fact that it included medium sample size, and a broad range of serum B12 levels. Potential confounding effects from associated comorbid conditions, use of dietary supplements, and medications were excluded from the study that could have biased serum B12 status. Furthermore, the measurement of fasting serum B12 provides more reliable results for the true association with obesity than the dietary estimates.

Limitations Of The Study

The current study has certain limitations. First, the study was carried out on subjects who came for routine health check-ups; thus, it may not reflect true causality in the local population. Second, it is difficult to determine if obesity status alters serum B12 levels or if preexisting low levels of serum B12 cause obesity, though the inverse association of serum B12 levels with obesity supports the role of B12 in adipogenesis. Third, serum homocysteine and methylmalonic acid level were not measured in the study. Although homocysteine and methylmalonic acid are used for the determination of serum B12 deficiency. Fourth, although we have excluded cancer and gastric surgery, previously undiagnosed atrophic gastritis or pernicious anemia may have coexisted that could affect serum B12 absorption or body weight, or both. Thus the causal relation between serum B12 status and obesity necessitates further study involving a large database of the population.

CONCLUSION

In this Indian study, we demonstrated a significant negative correlation (association) between BMI and serum B12level. Our results reflect that overweight and obese individuals are at increased risk of inadequate or deficient serum B12 status. We could also establish the effect of age and level of BMI on the magnitude of correlation with a maximum negative correlation of BMI and serum B12 in the older (41–60 years) age group and individuals with high BMI, that is, obese (≥30 kg/m2) (figure 4). Our findings provide initial information on the relationship between BMI and serum B12level in the local population, which may be different from individuals of other ethnic groups and geographical regions.

In conclusion, a negative association between BMI for serum B12 level implies that people with higher BMI are at risk of deficiency of vitamin B12. Thus, obesity and overweight are additional risk factors for serum vitamin B12 deficiency. In obesity, the reason for serum B12 deficiency is multifactorial and modifiable. The clinicians should keep in mind that serum B12 levels may be lower than in non-obese people. They should check B12 levels in patients with obesity and overweight, although they are mostly asymptomatic or may have subclinical features. This study provides a platform for further research to provide more understanding in this context through prospectively planned larger and longitudinal studies. Also, further research is needed to determine the causality and the underlying mechanisms of low serum B12 concentrations among obese people.

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No funding was received for this study.

Declaration of competing interest

Competing interests: none to declare.

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Abbreviations

B12 = Vitamin B12, BMI = Body Mass Index, WHR = Waist Hip Ratio, WHO = World Health Organization, MMA = Methyl Malonic Acid; PPIs = Proton Pump Inhibitors.

Author Contributions

JV proposed the original study idea and design, drafted the original manuscript, and was the major contributor to the data analysis and writing of the manuscript. RKS and JCS assisted with editing the manuscript and reviewing the final article. KRS and SS assisted with data analysis and reviewed the results. All authors read and approved the final manuscript.

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