Distinct dietary patterns lead to lower B12 intake in type 2 diabetes: a case-control study

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ABSTRACT

B12 deficiency has a higher prevalence in type 2 diabetes mellitus (T2DM) patients. The causes of this observation are poorly understood. Self-imposed (vegan/vegetarian) or advised dietary modification or intake of metformin could be contributing. Hence, we undertook this study to evaluate the dietary intake of Vitamin B12 in diabetes patients in comparison with age-matched healthy controls. Fifty T2DM patients (cases) and 50 age-matched volunteers (controls) aged 35-60 years were enrolled at a tertiary hospital, in New Delhi. Sociodemographic and dietary information was gathered and the average dietary intake of B12 was estimated using the Cobalamin Intake in North Indians-Food Frequency Questionnaire (COIN-FFQ) (developed and validated). Medical records were reviewed for biochemical parameters (HbA1c, lipid profile, and blood sugar) of the last three months. The mean age was 50.66±6.09 years (n=100) and the mean body mass index of 28.49±4.53 kg/m^2. The mean intake of dietary B12 was 3.2±1.7 µg/day and 3.8±1.4 µg/day (p=0.047) in diabetes patients and controls respectively. Thirty-six percent of diabetes patients did not meet the currently recommended daily dietary intake of B12 intake (vs. 14% of controls; p=0.011). Diabetes patients have a lower dietary intake of Vitamin B12 attributable to their distinctive dietary pattern. It is necessary to explore the factors leading to lower dietary B12 intake in diabetes patients.

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1. INTRODUCTION

The global diabetes prevalence in 2019 is estimated to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 [1]. Diabetes has been associated with several complications which affect a patient's health, productivity, and quality of life. B12 deficiency, with its associated consequences, is particularly common in vegetarian populations and in lower-income settings [2]. B12 deficiency and diabetes both are associated with significant neurological pathology, especially peripheral neuropathy [3]–[5]. Vitamin B12 replacement therapy has been shown to cause symptomatic improvement in patients with severe diabetic neuropathy [6]. Several systematic reviews and meta-analyses studied the efficacy of Vitamin B12 supplementation on diabetic peripheral neuropathy. It was found that the B12 supplementation increases the serum B12 level and improves neuropathy symptoms. It was also found that Vitamin B12 can improve neuropathic symptoms and reduce pain in patients with diabetic neuropathy [7]–[10].

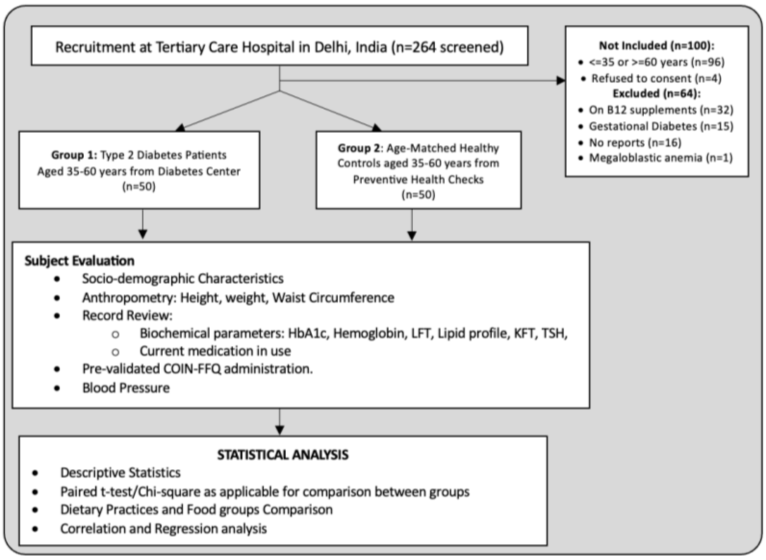
A high co-occurrence of B12 deficiency in diabetes patients has been reported in observational studies [11]–[13]. However, the reasons for such observation are poorly documented. This could be attributable to advised/self-imposed dietary restrictions/habits including veganism/vegetarianism. In addition, metformin is reported to further decrease B12 levels possibly due to poorer absorption [3], [14]. In the context of high co-occurrence and sinister consequences screening for B12 deficiency in diabetes patients in various clinical settings including India has often been debated [15], [16]. Since blood testing is associated with expense and inconvenience for patients and because the determinants of the higher deficiency prevalence in diabetes patients are poorly understood, we decided to explore the possibility of using a non-invasive, inexpensive, and convenient dietary assessment-based tool developed and validated by us earlier, Cobalamin Intake in North Indians by Food Frequency Questionnaire, (COIN-FFQ) [17].

Hence, we conducted the current study to understand the differences in B12 deficiency prevalence between diabetes patients and healthy adults. We investigated the differences in dietary intake between the two groups. Additionally, we aim to delve into the determinants influencing any observed differences in dietary intake.

2. METHOD

A summary of the study flowchart is presented in Figure 1. Type 2 diabetes mellitus patients aged 35-60 years were screened for selection criteria at the Diabetes Centre at Sitaram Bhartia Institute of Science and Research, (a tertiary care hospital in New Delhi) as 'Cases'. Simultaneously, age-matched 'Controls' were screened from amongst healthy subjects reporting for preventive health checks. Pregnant or lactating mothers, those who are already on B12 supplementation, and patients having chronic health conditions like gastrointestinal problems, malabsorption, or use of any medication that inhibits B12 absorption were excluded. No financial rewards were given for their participation.

Basic baseline information including age, sex, education, type of family, food habits, lacto-vegetarian, ovo-lacto-vegetarian and non-vegetarian, smoking, alcohol use, medical history, duration of diagnosis of diabetes were recorded on a standardized pretested proforma after an informed written consent for all participants. The socioeconomic status of the participants was evaluated using the Kuppuswamy scale [18]. The Kuppuswamy scale score depends on education, occupation of the head of the family, and monthly household income of the family.



LFT: Liver Function Tests; KFT: Kidney Function Tests, TSH: Thyroid Stimulating Hormone: COIN-FFQ: Cobalamin Intake in North Indians-Food Frequency Questionnaire

Figure 1. Study flowchart

Weight was measured on a digital weighing scale, height was recorded using a SECA stadiometer, waist circumference was done at the level of the umbilicus using a measuring tape, and blood pressure using an OMRON digital instrument. Height, weight, and waist circumference were measured with minimal clothing and without shoes. Three consecutive BP values were recorded after 10-min rest at 10-min intervals in the sitting position as per World Health Organization recommendations [19], and the mean was used for analysis.

Reports of all blood investigations conducted in the last 3 months were noted including blood sugar (fasting and post-prandial), HbA1c, hemoglobin, liver function tests, lipid profile, kidney function tests, and thyroid stimulating hormone. Also, current medications like any insulin therapy, oral hypoglycemic drug, lipid-lowering drug, aspirin or blood thinning drug, antihypertensive agents, or any other medications in use were collected from records and by interview. The pre-validated COIN-FFQ [17] was then administered to all participants by a nutritionist researcher trained in its administration. The study was approved by the Institutional Ethics Committee of Sitaram Bhartia Institute of Science and Research, New Delhi (F.1/SBISR-EC/TH01/20), and the research was conducted according to the tenets of the Declaration of Helsinki. All participants gave their written informed consent.

2.1. Cobalamin Intake in North Indians-Food Frequency Questionnaire (COIN-FFQ)

Cobalamin Intake in North Indians-Food Frequency Questionnaire (COIN-FFQ) is a recently developed and validated Cobalamin Intake Food Frequency Questionnaire for North Indians by the same group of researchers. It is an easily administered, non-invasive and inexpensive tool to estimate the dietary intake of B12. It consists of 30 questions categorized into: i) Dairy & dairy products, ii) non-vegetarian foods, and iii) Vitamin B12 fortified foods/drinks. For each item, a commonly used portion size/quantity was listed along with a question frequency of consumption in the past three months. The frequency responses varied from "Never or less than once per month" to "Four or more times per day." Open-ended questions recorded brand names of potentially fortified products like protein supplements or breakfast cereals. The food frequency questionnaire has been previously validated comprehensively to check construct validity, reliability test, and internal consistency [17]. In summary, an initial construct of a draft food list was prepared which was refined using a market survey, followed by standardization of portion size, list finalization, and conversion to database. This was followed by a study on 115 volunteers to establish convergent validity($p=0.04$), discriminant validity($p<0.01$) test-retest reliability ($r=0.846$; $p<0.001$), and internal consistency (Cronbach's alpha 0.631). Using this pre-validated COIN FFQ dietary intake of various food items was then calculated using the values of B12 content of raw Indian foods converted to standardized cooked recipes with standardized portion sizes (household measures) pre-fed into an Excel database. The frequency of consumption was multiplied by serving size and B12 content to determine the nutrient contribution of each food item and that of the individual by summating all the items as is usual for FFQ-based calculations. The dietary habits of individuals were categorized using the following definitions:

i). Vegan: Consumed only plant-based foods in the last three months.
ii). Lacto-vegetarian: Consumed dairy food items along with plant-based foods in the last three months.
iii). Lact-ovo vegetarian: Consumed dairy food items and eggs along with plant-based foods in last three months.
iv). Non-vegetarian: Consumed poultry, red meat, seafood, and dairy food items along with plant-based foods in the last three months.

2.2. Sample size considerations

It was estimated that a sample size of 34 matched subjects in each group would be required to determine a mean difference of 0.5 µg/d in dietary intake between the two groups. Based on the earlier work on the subject, SD of 1.0 and with an alpha-error of 0.05 and 80% was assumed [20]. Hence, we chose to recruit 50 subjects in each group to account for local variations in intakes.

2.3. Statistical analysis

All data entry and data analyses were conducted using IBM SPSS Statistics version 26.0. Data entry and calculation for dietary B12 intake were done on MS Excel version 16. Continuous variables are reported as mean±standard deviation (SD). Categorical variables are reported in percentages. Means of continuous variables were compared using paired t-tests and dichotomous variables were calculated using Chi-square. p-values of <0.05 were taken as statistically significant.

3. RESULTS AND DISCUSSION

A total of 264 potential subjects were approached during the study period between Jun-Dec 2022. Ninety-six of the subjects did not meet the age criteria 4 refused consent and 64 were excluded (32 were on B12 supplements, 15 were having gestational diabetes mellitus, 16 did not carry the last three months' blood reports, and one was diagnosed with megaloblastic anemia). Hence, a total of 100 participants (50 type 2 diabetes mellitus and 50 age-matched non-diabetic healthy adults) were enrolled in the study. Table 1 presents a comparison of the socio-demographic profile of cases and controls. The study participants had a mean age of 50.66±6.09 years and a mean body mass index of 28.49±4.53 kg/m^2. Of the participants, 43% were male and 57% were female, and these differences were statistically comparable. There was a statistically significant difference in the mean waist circumference (6.37±2.22; p-value=0.06), mean systolic blood pressure (6.31±2.76; p-value=0.027), and mean diastolic blood pressure (3.68±1.52; p-value=0.019) between cases and control participants. The 88% of the study population belonged to the upper-middle socio-economic category of the Kuppuswamy classification. There was no significant difference between the baseline characteristics except for the intake of alcohol and other supplements. It was noted that 56% of diabetes cases were currently consuming alcohol as compared to cases (26%). Also, a higher proportion of diabetes patients were on other supplements like calcium, vitamin D, and/or multivitamins (40% vs 12.5%).

Table 2 compares the biochemical parameters of diabetes patients with those of age-matched control subjects. As expected, the HbA1c, fasting, and postprandial blood glucose of the diabetes patients were significantly worse than the case-control participants. Also, the sodium levels were lower in diabetes patients compared with healthy adults.

Table 1. Baseline characteristics of cases and controls

Variables	Overall (n=100) Mean±SD	Diabetes (n=50) Mean±SD	Age-matched controls (n=50) Mean±SD	Mean Diff±SE	p-value*
Age, years	50.66±6.09	50.84±6.11	50.48±6.11	0.36±0.39	0.371
Gender; Male, n(%)	43(43)	21(42%)	22(44%)	-0.20±0.09	0.830
Height, cms	163.10±8.45	162.6±9.20	163.5±7.68	-0.85±1.4	0.571
Weight, kgs	75.57±11.67	75.67±12.6	75.47±10.7	0.19±2.20	0.928
Waist circumference, cms	102.40±10.48	105.3±11.5	99.34±8.36	6.37±2.22	**0.006**
Mean SBP, mmHg	125.16±12.88	128.3±12.5	122.0±12.4	6.31±2.76	**0.027**
Mean DBP, mmHg	82.32±7.69	84.16±6.79	80.48±8.14	3.68±1.52	**0.019**
BMI, kg/m^2	28.49±4.53	28.75±5.36	28.21±3.55	0.53±0.88	0.553
Socioeconomic socio-economic class[a] n(%)					
Lower middle	2(2)	2(4)	0(0)	-	0.360
Upper middle	88(88)	43(86)	45(90)	-	
Upper	10(10)	5(10)	5(10)	-	
Living in the owned house, n(%)	65(65)	32(64)	33(66)	-	0.567
Nuclear family, (n%)	73(73)	38(76)	35(70)	-	0.499
Food Habit[b] n(%)					
Lacto vegetarian	30(30)	16(32)	14(28)	-	0.733
Lacto-ovo vegetarian	13(13)	6(12)	7(14)	-	
Non-vegetarian	56(56)	27(54)	29(58)	-	
Current smoking status, n(%)	11(11)	5(10)	6(12)	-	0.865
Current alcohol status, n(%)	41(41)	13(26)	28(56)	-	**0.002**
Supplements[c], (n%)	26(26)	20(40)	6(12.5)	-	**0.002**

*Data analyzed using paired t-test and Chi-square, a=Kuppuswamy scale [18]; b=includes 1 ovo-vegetarian; c=includes any mineral and/or vitamins supplements except Vitamin B12

Table 2. Comparison of biochemical profile of the participants in the last three months

Biochemical parameters	units	n	Diabetes Mean±SD	Age-matched controls Mean±SD	Mean Diff±SE	p-value*
Haemoglobin	mmol/L	100	8.24±0.95	8.39±0.99	-0.14±0.18	0.441
Blood glucose (fasting)	mmol/L	92	9.18±3.41	5.92±0.68	3.28±0.51	<0.001
Blood glucose (PP)	mmol/L	50	12.54±5.62	6.37±1.57	6.55±1.21	<0.001
HbA1c	%	78	8.3±1.8	5.8±0.5	2.57±0.32	<0.001
Liver function test (serum)						
SGOT (AST)	U/L	92	27.8±10.2	31.4±12.6	-3.61±2.49	0.154
SGPT (ALT)	U/L	92	30.4±14.8	34.5±20.5	-4.04±3.62	0.270
Alkaline phosphatase	U/L	90	91.4±24.1	88.9±21.7	2.46±4.86	0.616
Total Protein	g/L	16	74.11±8.39	74.84±5.06	-5.84±1.75	0.012
Albumin	g/L	10	41.43±3.60	43.68±2.96	-3.00±1.52	0.119
Lipid profile (serum)						
Cholesterol-total	mmol/L	100	9.52±2.95	11.22±1.86	-1.70±0.51	0.002
HDL-cholesterol	mmol/L	90	2.45±0.68	2.91±0.74	-0.47±0.15	0.002
LDL-cholesterol	mmol/L	90	5.30±2.30	6.77±1.45	-1.60±0.41	<0.001
Triglyceride	mmol/L	94	9.49±4.78	7.81±2.86	1.70±0.79	0.036
Kidney function test (serum)						
Urea	mmol/L	94	4.04±1.57	3.77±1.06	0.23±0.26	0.384
Creatinine	µmol/L	94	73.03±42.91	70.54±15.52	2.50±6.86	0.717
Uric acid	mmol/L	38	0.13±0.03	0.14±0.03	-0.01±0.01	0.559
Sodium	mmol/L	62	137.8±2.5	139.5±2.0	-1.77±0.56	0.003
Potassium	mmol/L	58	4.6±0.4	4.5±0.5	0.11±0.11	0.356
Thyroid stimulating hormone (TSH, serum)	uIU/mL	66	3.1±2.8	2.8±1.5	0.30±0.57	0.604

*Data analyzed using paired t-test and Chi-square
PP: post prandial

As reported in Table 3 mean dietary intake of dietary B12 by COIN-FFQ was significantly lower in the diabetes patients as compared to controls (3.2±1.7 and 3.8±1.4 (p=0.047)). B12 intake of lacto-vegetarian, lacto-ovo vegetarian, and non-vegetarian were 3.2±2.2 and 3.7±1.6; 3.2±1.1 and 3.3±1.3; 3.3±1.6 and 4.0±1.4 in diabetes and age-matched controls respectively. No significant differences were found based on dietary practices between the groups. However, the intake of several dairy products (cheese, cakes, and paneer) and animal-based foods (egg and prawn) was significantly lower in diabetes patients with a genetic tendency for lower intakes of animal-based foods in diabetes patients. A higher proportion (36%) of the diabetes participants were not meeting the daily dietary recommendation of Vitamin B12 intake i.e. 2.2 µg/day [21] through their diet as compared to controls (14%, p=0.011).

Table 3. Dietary B12 intake comparison

Variables	Overall (n=100) Mean±SD	Diabetes (n=50) Mean±SD	Age-matched controls (n=50) Mean±SD	p-value*
Dietary B12 intake (COIN-FFQ), µg/day	3.5±1.6	3.2±1.7	3.8±1.4	0.047
Dietary practices, n(%)				
Lacto-vegetarian	30(30)	16(32)	14(28)	0.733
Lacto-ovo vegetarian	13(13)	6(12)	7(14)	
Non-vegetarian	56(56)	27(54)	29(58)	
Food groups, n(%)				
Plain milk	65(65)	30(60.0)	35(70)	0.295
Milkshake	22(22)	8(16.0)	14(28)	0.148
Tea with milk	74(74)	43(86)	41(82)	0.585
Pudding	50(50)	23(46)	27(54)	0.424
Cheese	36(36)	12(24)	24(48)	0.012
Curd and curd drinks	95(95)	46(92)	49(98)	0.169
White butter	2(2)	0(0)	2(4)	0.153
Cakes	44(44)	16(32)	28(56)	**0.016**
Ice-cream	52(52)	22(44)	30(60)	0.109
Panner	86(86)	39(78)	47(94)	**0.021**
B12 fortified foods	30(30)	11(22)	19(38)	0.081
Egg	61(61)	25(50)	36(72)	**0.024**
Chicken	55(55)	26(52)	29(58)	0.546
Fish	38(38)	16(32)	22(44)	0.216
Red meat	27(27)	16(32)	11(22)	0.260
Prawns	15(15)	6(12)	9(18)	**0.041**

*Data analyzed using paired t-test and Chi-square; a=mean difference -0.59±0.29

To further understand the relationship between baseline determinants and the dietary intake of B12 by COIN-FFQ and to adjust the difference for potential confounders we conducted a correlation-regression analysis, see Table 4. The determinants were chosen based on the literature review and noted bi-variate correlations between dietary intake and potential co-variates. We used dietary B12 intake as the dependent variable with the assigned group, age, height, education level, monthly income, and smoking as independent variables. As presented in Table 4 the co-variate adjusted difference between the two groups was higher than the unadjusted differences. The covariate-adjusted mean difference in dietary B12 intake between the two groups was -0.873 (p=0.015; r^2=0.149).

Table 4. Regression model

Model	Unstandardized coefficients (B)	Std. error	Standardized coefficients (B)	t	Sig.
Group*	-0.873	0.352	-0.265	-2.484	**0.015**
Age	0.037	0.026	0.138	1.433	0.155
Height	0.038	0.02	0.195	1.889	0.062
Smokers[a]	0.755	0.451	0.168	1.674	0.097
Education[b]	-0.49	0.475	-0.117	-1.032	0.305
Employed[c]	-0.806	0.515	-0.170	-1.565	0.121

*Diabetes vs. age-matched controls; dependent variable: dietary B12 intake through COIN-FFQ, r2 =0.149; a=smokers vs. non-smokers; b=graduation or above graduation; c=employed vs. non-employed

Our study records that the dietary intake of Vitamin B12 is lower in diabetes patients compared with healthy subjects. The intake of milk products, cakes, and eggs was noted to be lower amongst diabetes patients reflecting one of the unintended consequences of self-modifications/dietary advice. This is one of the first studies reporting the differences in dietary intake of B12 and related food patterns. The study is strengthened by the paired comparison of the intakes of diabetes patients with age-matched controls using a tool developed and validated in the same setting. However, the subjects were recruited from a tertiary hospital catering to middle- and higher-income patients potentially limiting the generalizability of findings. Although the study does not provide direct biochemical correlates of the changes in intake, the assessment tool (COIN-FFQ) has been previously reported to have high specificity (94.44%; cut-off-3.26 μg/d) and high predictive value (70.37%; cut-off 6.98 μg/d) for detecting biochemical B12 deficiency of serum B12 level.

Several studies reported to have a higher prevalence of B12 deficiency in diabetes patients [22]–[24]. A study from South India on 1,500 subjects reports that the mean levels of Vitamin B12 significantly decreased with increasing degrees of glucose tolerance (normal glucose tolerance 444±368; prediabetes 409±246; T2DM 389±211 pg/ml, p=0.021). The prevalence of absolute Vitamin B12 deficiency (<191 pg/mL) was significantly higher among individuals with Type 2 diabetes mellitus (18.7%) followed by prediabetes (15%) and normal glucose tolerance (13.7%) [p for trend=0.05]. Vegetarians had twice the risk of Vitamin B12 deficiency compared to non-vegetarians. The risk of having Vitamin B12 deficiency was 1.7 times higher (CI 1.03–2.87, p=0.037) in those people having a lesser dietary intake of Vitamin B12 (<1.2 μg/d) compared to patients having a higher intake of dietary Vitamin B12 (>2.2 μg/d) [25].

Many of these studies have related such deficiency to metformin intake [2], [11], [15], [26]. It is also reported without metformin intake as in the South Asian studies [23], [27], [28]. The concept of plant-based diets has become increasingly popular due to the purported benefits for both human health and environmental impact. Several studies, while reporting the metabolic benefits of plant-based diets have commented on the deterioration in B12 deficiency and the need for supplementation [29], [30]. One such study on 138 volunteers conducted at the University of Helsinki a partial replacement of animal protein foods with plant protein foods over 12 weeks led to a marked decrease in the intake and status of Vitamin B12 [31]. In a study from Germany 53 healthy omnivore participants were randomized to a controlled un-supplemented vegan diet (n=26) or meat-rich diet (n=27) for four weeks. Vegan diet intervention led to a significant reduction in cholesterol intake and adequate profiles of nutrient and micronutrient status. A lower intake of Vitamin B12 was observed in the vegan diet, which was mirrored by a lower concentration of serum Vitamin B12 and reduced holo-transcobalamin (Holo-TC) after four weeks [29]. In this context, the current study also highlights that diabetes patients have lower B12 intake related to lower intake of animal-based foods including meats and dairy products i.e. more dominantly plant-based diet. This could be related to dietary beliefs in the community or dietary advice received as part of the management of the dietary intake in B12.

4. CONCLUSION

The study aimed to investigate the dietary intake of vitamin B12 among diabetes patients and its dietary correlates using the COIN-FFQ. When compared to people without diabetes, our hypothesis predicted that people with diabetes would have lower dietary intakes of B12. Our findings substantiate this hypothesis and shed light on important considerations for public health policy and clinical practice. For example, should dietary screening for B12 intake be utilized more widely in diabetes practices as a low-cost way of deciding on supplementation? Should routine B12 testing be recommended especially amongst predominantly vegetarian patients or should routine supplementation with B12 be practiced for vegetarian diabetes patients? While the findings of the study are suggestive, more research is required to provide evidence-based guidance on clinical situations.

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