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Serum Vitamin B_{12} Levels in Two Subpopulations of Healthy Workers in Israel: Differences by Land of Birth

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Abstract

Background: Clinical and subclinical vitamin B_{12} deficiency rates are lower in western populations compared to developing populations and cut-off points for defining deficiency are inconsistent.

Objectives: The present study was designed to examine variability in vitamin B_{12} blood levels in a heterogeneous population.

Methods: The present report is a cross-sectional analysis of serum vitamin B_{12} levels recorded for 1969 apparently healthy hospital workers employed at Tel Aviv Medical Centre, Tel Aviv, Israel, who underwent blood vitamin B_{12} tests evaluation as part of the routine occupational health evaluation. Data were extracted from the electronic employee medical record.

Results: Almost 73% of the study population was born in Israel, and 73.6% of the population was female. Serum vitamin B_{12} levels were significantly lower in Israeli born women than in women born outside of Israel: 294±119.9 vs. 320±121.7pmol/L. Land of birth and sex were significant, independent predictors of serum vitamin B_{12} levels even after controlling for age and year in which the serum vitamin B_{12} was measured. In a logistic regression model of serum vitamin B_{12} < 350 pmol/L, land of birth emerged as the only significant, independent predictor, such that being born in Israel increased odds of serum vitamin B_{12} < 350 pmol/L by a relative 44% (95% CI 17-78%, p=0.001).

Discussion: Wide serum vitamin B_{12} level variability in heterogeneous populations suggests that cut-offs for deficiency may need to be subgroup-specific in order to be clinically meaningful. It is not clear whether presently used clinical cut-offs are associated with increased morbidity in a given population.

Keywords: Serum vitamin B_{12}; Epidemiology; Occupational health

Background

In humans, vitamin B_{12} participates in two particularly important metabolic reactions. The methyl-cobalamin form of vitamin B_{12} serves as the cofactor of cytoplasmic methionine synthase, which catalyzes ultimately yields methionine [1]. It is thus not surprising that vitamin B_{12} deficiency is associated with elevated plasma homocysteine [2]. Coenzyme B_{12} (adenosyl-cobalamin) also serves as the cofactor of mitochondrial methylmalonyl-CoA, which is transformed to succinyl-CoA [3]. Micronucleus formation, an indicator of genetic instability, has been shown to be reduced when plasma vitamin B12 is > 300 pmol/L [4].

Vitamin B_{12} deficiency is typically defined as serum cobalamin levels < 148 pmol/L however, levels consistent with subclinical deficiency have not been defined [5]. Using this cut-off, however, variability in vitamin B_{12} deficiency rates has been reported. Predictably, clinical and subclinical deficiency rates are lower in western populations and higher in developing populations. Deficiency is exacerbated by vegetarianism. In India, for example, which is both developing and includes a large vegetarian population, 70% of adults and 80% of pre-school children are estimated to be deficient [6].

Use of this cut-off remains controversial, and would likely misclassify up to 50% of cases [3]. For this reason, a cut-off of 258 pmol/L has been proposed, particularly for use in older populations [7].

Variability in population levels and lack of clarity in defining deficiency are the basis for the present study, in which serum vitamin B_{12} levels were studied in a convenience sample of health care workers undergoing routine blood chemistry analysis in Israel. Using the actual serum cobalamin level and a variety of cut-offs, vitamin B_{12} levels were compared between health care workers born in Israel and those who immigrated to the country.

Methods

Study design

The present report is a cross-sectional study performed in 1969 apparently healthy hospital workers employed at Tel Aviv Medical Center, Tel Aviv, Israel.

Subjects and inclusion/exclusion criteria

Vitamin B_{12} tests were performed as part of the routine occupational health evaluation. In addition to serum B_{12} level, age, sex and location of birth were extracted from the electronic employee medical record.

Vitamin B_{12} assay

Vitamin B12 was assayed using the Siemens ADVIA Centaur XP Immunoassay System VB12, Siemens Healthcare Diagnostics, Siemens Healthcare Diagnostics Inc. Tarrytown, NY 10591-5097 USA.

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Ethics

The present study was approved by the Institutional Review Board of Tel Aviv Medical Center and the Israel Ministry of Health.

Statistical analysis

Data were stored in Excel spreadsheet (Microsoft Inc., USA) and analyzed on SPSS v21 statistical analysis software (IBM Inc., USA). Continuous variables (age, vitamin B_{12} levels) were assessed for normality using the Kolmogorov-Smirnov test and found to be approximately normally distributed. These are described as mean ± standard deviation and compared by land of birth (Israel vs. outside of Israel) using the t-test for independent samples. Results and age were compared across year of test using one-way analysis of variance (ANOVA) and post hoc pair wise analysis was performed using Bonferroni's test. This test was also used to compare means by sex. Associations between continuous variables were described using Pearson's correlation coefficients. Nominal data such as sex, land of birth and categorized serum B_{12} levels using a variety of cut-offs are described as frequency counts and presented as n (%). Associations between nominal variables and land of birth and, separately, sex, were assessed using the chi square test. A model of vitamin B_{12} level was developed using linear regression including land of birth, age, sex and year of test as covariates. Similarly, models of vitamin B_{12} cutoffs (< 148 pmol/L [5]; < 184 pmol/L [8]; and < 248 pmol/L [7]) were developed using logistic regression analysis and odds ratios with 95% confidence intervals were calculated. All tests are two-sided and considered significant at $p<0.05$.

Results

Vitamin B12 evaluations from 1969 Tel Aviv Medical Center health care workers performed between January 1, 2010 and October 31, 2013 at the study site were included. For individuals with more than one vitamin B_{12} analysis, only the first measure was included to avoid the bias introduced by repeated measures in certain individuals. Thus, the dependent variable can be defined as the first measure of vitamin B_{12} available for a subject from January 10 2010-Oct 31, 2013. The study population was comprised of 1449 women and 520 men aged 46.8±12.8 and 51.1±12.9 years, respectively. Women were significantly younger than men, $p<0.0001$. Almost 73% of the study population was born in Israel (n=1436), while the rest were born outside of Israel. Sex distribution did not differ significantly by land of birth, with women comprising 73.6% of the Israeli-born population and 71.7% of the group born outside of Israel (p=0.24).

The study population is described by land of birth (Israel vs. outside of Israel) and sex in (Table 1). Among both men and women, subjects born in Israel were significantly younger than those born outside of Israel. No significant difference in serum vitamin B_{12} levels was detected by land of birth among men, but Israeli-born women had significantly lower serum vitamin B_{12} levels than women born outside of Israel. Serum vitamin B_{12} levels were 301.1±120.9 pmol/L in women vs. 287.2±109.9 pmol/L in men, p=0.02 in the total study population, a difference apparently driven by the significant by-sex difference observed in subjects born outside of Israel (p=0.006). Among Israeli-born subjects, the by-sex difference in serum vitamin B_{12} was not significant (p=0.27).

(Table 2) examines study population characteristics by year of test. Serum vitamin B_{12} levels differed marginally across years, but age of the participants declined significantly over time. Age was significantly, positively associated with serum vitamin B_{12}: r=0.19, p=0.03. Sex differed significantly by year, driven by the decline in % females in 2012. Distribution of participant land of birth did not differ significantly across time.

In light of their associations with serum vitamin B_{12}, land of birth, age, sex and year of test were included as covariates in a linear regression model of serum vitamin B_{12}. As can be seen in (Table 3), land of birth (using born in Israel as the indicator) and sex (using male sex as the indicator) emerged as significant, independent predictors of serum vitamin B_{12} levels.

Characteristics of the study population are compared by selected serum vitamin B_{12} cutoffs in (Table 4). Differences in serum vitamin B_{12} were not detected by land of birth using the 148 pmol/L or the 184 pmol/L cutoffs; however, significantly more Israeli-born subjects had serum vitamin B_{12} levels less than 248 pmol/L. Differences by sex were not detected using any of the cutoffs. Age of subjects with serum vitamin B_{12} < 148 pmol/L was significantly younger than those with higher levels, but age did not differ significantly by either of the other two cutoffs. The proportion of subjects with serum vitamin B_{12} levels less than 148 pmol/L did not differ by year; however, the proportion of subjects differed significantly by year for the 184 pmol/L and 248 pmol/L cutoffs. In both cases, the difference is driven by significantly lower proportion of subjects below the cut-off value in 2011.

(Table 5) presents the odds ratios with 95% confidence intervals for predictor variables in logistic regression models of each of the serum vitamin B_{12} deficiency cutoffs. As can be seen, only age emerged as a significant predictor of serum vitamin B_{12} < 148 pmol/L, indicating that for each 1-year increase in age, odds of deficiency decline approximately 3% (95% CI 1%-5%, p=0.009). None of the studied

Characteristic	Land of Birth		
	Israel	Outside of Israel	Two-tailed significance
Women (n=1449)	n=1067	n=382	
Age (years)	45.3±12.2	51.2±13.5	<0.0001
Serum Vitamin B12 (pmol/L)	294.3±119.9	320.4±121.7	<0.0001
Men (n=520)	n=369	n=151	
Age (years)	48.2±12.3	57.9±11.9	<0.0001
Serum Vitamin B12 (pmol/L)	286.3±112.5	289.3±103.9	0.77

Table 1: Study population characteristics by land of birth and sex.

Year	N	Serum Vitamin B12 (pmol/L)	Age (years)	% Females	% Born in Israel
2010	821	293.6±116.7	51.3±12.6	76.7	72.1
2011	476	310.2±117.9	48.9±12.3	71.2	70.4
2012	384	292.2±127.0	44.9±11.9	69	74.2
2013	288	294.4±109.7	40.9±12.9	74.7	77.8
p-value		0.06*	<0.0001*	0.02**	0.13**

*Comparison across years calculated using one-way analysis of variance (ANOVA); in post hoc, pair wise testing, age differed significantly between each year and every other year

**Comparison across years calculated using the chi square test

Table 2: Mean serum vitamin B12 by year of test.

	Beta (standardized)	Significance
Age (years)	0.024	0.33
Male sex	-0.058	0.012
Born in Israel	-0.069	0.003
Year of test	0.01	0.681

Table 3: Linear regression model of serum vitamin B12 (pmol/L).

	Cut-off		
Characteristic	**<148 pmol/L**	**<184 pmol/L**	**<248 pmol/L**
Born in Israel (%)	2.7	8.1	46
Born outside of Israel (%)	2.8	2.5	37.5
p-value	0.91	0.21	0.001
Females (%)	2.9	10.6	42.6
Males (%)	2.3	10.8	46.9
p-value	0.48	0.89	0.09
Age (< cut-off)	43.8±13.6	47.1±13.9	47.9±13.1
Age (≥ cut-off)	48.1±12.9	48.1±12.9	48.0±12.9
p-value	0.02	0.31	0.87
Year of test			
2010 (%)	3.3	11.7	46
2011 (%)	1.3	6.9	35.3
2012 (%)	3.6	12.8	49.2
2013 (%)	2.4	10.8	43.8
p-value	0.11	0.02	<0.0001

Table 4: Characteristics of the study population by selected serum vitamin B12 cut-offs.

	Cut-off for vitamin B12 deficiency					
	<148 pmol/L		**184 pmol/L**		**248 pmol/L**	
Indicator:	**OR (95% CI)***	**p**	**OR (95% CI)***	**p**	**OR (95% CI)***	**p**
Sex (male sex as indicator)	0.92 (0.47-1.77)	0.79	1.05 (0.76-1.46)	0.77	1.19 (0.98-1.47)	0.09
Age (years)	0.97 (0.95-0.99)	0.009	0.99 (0.98-1.01)	0.42	1.002 (0.99-1.01)	0.68
Year of test	0.87 (0.67-1.12)	0.28	0.98 (0.86-1.13)	0.78	1 (0.92-1.09)	0.99
Land of birth (Israel as indicator)	0.79 (0.43-1.47)	0.46	1.2 (0.85-1.69)	0.3	1.44 (1.17-1.78)	0.001

*OR=Odds Ratio; 95% CI=95% confidence interval

Table 5: Logistic regression analysis of each of cutoffs for vitamin B12 deficiency as measured in serum showing odds ratios with 95% confidence intervals for each indicator.

variables significantly predicted serum vitamin B12 < 184 pmol/L. In the model of serum vitamin B_{12} < 350 pmol/L, land of birth emerged as the only significant, independent predictor, such that being born in Israel increased odds of serum vitamin B_{12} < 350 pmol/L by a relative 44% (95% CI 17-78%, p=0.001).

Discussion

The present study suggests that land of birth and sex are significant, independent predictors of serum vitamin B_{12} levels even after controlling for age and year in which the serum vitamin B_{12} was measured. In the present study, serum B_{12} levels were elevated in women vs. men, a finding contrary to those of the Jackson Heart Study in which vitamin B_{12} levels were elevated in African American men vs. women [9]. The difference in serum vitamin B_{12} distribution by sex did not persist, however, when categorized by cut-offs. It is not clear whether clinical cut-offs are associated with increased morbidity in a given population, since variability in serum vitamin B_{12} levels across populations has been well-documented [10]. This may suggest a need to determine clinically-relevant cut-offs for each population, and possibly sub-groups in ethnically diverse populations such as Israel.

Surprisingly, the present study identified lower serum B_{12} levels in Israel-born subjects, who were significantly younger than subjects born outside of Israel. Further, a significant positive correlation was detected between serum B_{12} levels and age. This contrasts with reports of no association or inverse associations between B12 levels and age in other populations [9,11,12], or no change. On the other hand, age did not emerge as a significant predictor of serum vitamin B_{12} levels after controlling for age and land of birth.

Sources for variation in serum vitamin B_{12} levels include differences in dietary intake. Israeli adults have been shown to differ significantly in nutrient intake based on land of birth [13]. It is possible that vegetarianism and/or veganism are more prevalent among Israeli- than foreign born citizens, practices that would explain the between-group difference in serum vitamin B_{12} levels [14]. Another source of differences is B_{12} absorption. Systematic differences between Israeli- and foreign-born citizens in inflammatory bowel disease [15], chronic pancreatitis [16], parasitic or bacterial infection [16,17] might explain some of the between-group differences in serum vitamin B_{12} levels, though evidence of these differences was not found in the literature. Hereditary differences in B_{12} absorption such as intrinsic factor or transcobalamin deficiency or defect, would also account for some of the variability in serum vitamin B_{12} levels between groups [18]. Genetic variation may be associated with between-group differences in serum vitamin B_{12} levels. Single-nucleotide polymorphisms (SNPs), such as CUBN CD320 (associated with absorption and uptake); TCN1 and TCN2 (associated with transport), and FUT2 have been associated with differences in serum vitamin B_{12} levels in human populations [19,20], though not specifically in Israeli subgroups. While moderate to heavy alcohol use has been associated with reduced serum B12 [21], foreign-born Israelis report heavy and binge drinking more frequently than Israeli-born individuals [22,23]. Medications such as non-selective beta blockers [24], metformin [25] and protein pump inhibitors [26] have been associated with reduced serum B12 levels. But the Israeli-born subjects were younger, which might suggest lower use of these medications.

Findings must be considered in light of study limitations. It is possible that the between-group difference in serum vitamin B_{12} levels is attributable to selection bias in the study sample, though with a sample size of nearly 2000 subjects this seems unlikely. On the other hand, subjects clearly self-selected by seeking routine health evaluation (this is not a mandatory examination). It is possible that subjects with some underlying health condition or concern were more likely to participate in occupational health examinations than others, but there is no reason to suspect that this self-selection would systematically differ by place of birth. Both Israeli-born and foreign-born subjects volunteered, so unless there is a systematic difference in the way these two groups seek occupational health services, we can assume that the bias is non-differential, in which case it would bias the estimate of the between-group difference towards the null. In that case, our estimate of the association between land of birth and serum vitamin B_{12} levels would be an underestimate of the true association. Additionally, the study population is drawn from a convenience sample at a single center, which may restrict external validity. All included subjects were hospital personnel, which may further restrict generalizability, because hospital workers might be more informed and may have generally improved lifestyle habits vs. general population. But it still would not explain the measured between-group difference. Information on lifestyle, concomitant diseases, medications prescribed and other factors that could explain the observed between-group differences in serum vitamin B_{12} levels were not collected, so their impact on the findings cannot be evaluated. This is particularly important regarding a measure of dietary intake, since systematic between-group differences

in nutrition would provide a reasonable explanation for the observed differences in serum vitamin B_{12} levels.

Conclusions

Despite these the aforementioned study limitations, and in light of the robust sample size, we conclude that a between-group difference in serum vitamin B_{12} levels based on land of birth has been identified, and that further investigation is necessary to repeat the findings and identify underlying mechanisms. If confirmed, these findings suggest that a targeted, subpopulation-specific screening program may be needed for Israeli-born Israelis.

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