Vitamin B\textsubscript{12} Levels of Subjects Aged 0-24 Year(s) in Konya, Turkey

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ABSTRACT

Research reports indicate that vitamin B\textsubscript{12} levels show racial differences, which suggests that using the reference ranges of varied populations may lead to inaccurate results. This study aimed to determine normal serum levels of vitamin B\textsubscript{12} among children and young people in the Konya region of Turkey. It evaluated 1,109 samples; 54 were from cord-blood and 1,055 were from healthy subjects aged 0-24 year(s), who were admitted to primary healthcare centres. The normal reference levels obtained for vitamin B\textsubscript{12} at 2.5-97.5 percentile (P\textsubscript{2.5}-P\textsubscript{97.5}) range were 127-606 pg/mL for girls, 127-576 pg/mL for boys, and 127-590 pg/mL for the entire study group. The reported reference values for vitamin B\textsubscript{12} in other studies were higher than the current results. Vitamin B\textsubscript{12} levels vary from country to country; comparisons between countries may not be valid, and normal levels for each population should be obtained.

Key words: Childhood; Nutrition; Reference ranges; Vitamin B\textsubscript{12}; Turkey

INTRODUCTION

Vitamin B\textsubscript{12} is a water-soluble vitamin that is an essential co-factor in some biochemical reactions and required for the synthesis of both RNA and DNA. Its deficiency may cause disorders, especially in the haematologic, neurologic, and gastrointestinal systems. Deficiency in infancy may lead to mental retardation and may have lifelong effects (1).

Reports indicate that vitamin B\textsubscript{12} levels show racial differences; thus, using the reference ranges of varied populations may lead to inaccurate results (2-6). Therefore, normal levels that are valid for each population should be obtained. To the authors' knowledge, no research in the literature addressed reference ranges of vitamin B\textsubscript{12} for the population of Konya region of Turkey. The authors designed this work to determine the normal levels of vitamin B\textsubscript{12} in this region.

MATERIALS AND METHODS

The study was conducted during May 2006 to March 2007. It screened samples of 1,109 subjects aged 0-24 year(s) (560 boys, 549 girls), including 54 cord-blood samples. The cord-blood was obtained through the umbilical cord at the time of birth in the Department of Obstetrics and Gynaecology, Selcuk University Hospital in Turkey. The other subjects were patients admitted to primary healthcare centres for any complaint. The study followed the guidelines set forth in the Declaration of Helsinki, and the procedures were approved by the Ethics Committee of Selcuk University Meram Medical Faculty.

Blood samples were obtained from persons undergoing blood analyses for other reasons. Twenty-eight of the cord-blood samples were collected from male babies and 26 from females. The distribution of subjects by age was as follows:

- Newborn group (45 subjects; 23 boys, 22 girls)
- 1-12 month(s) (38 subjects; 17 boys, 21 girls)
- 13-24 months (52 subjects; 32 boys, 20 girls)
- 24 months to 24 years (20 boys and 20 girls for every year).

Samples were obtained after administering a questionnaire consisting of 16 items about conditions that can affect the status of vitamin B\textsubscript{12} to determine suitability of subjects for the study.

The first section of the questionnaire recorded age, sex, height, weight, body mass index [BMI: weight (kg)/height (m)\textsuperscript{2}] as well as occupation,
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Table 1. Nutritional status of the study group

| Food intake pattern                                      | Number | Percentage (%) |
|---------------------------------------------------------|--------|----------------|
| Frequency of meat consumption                           |        |                |
| Several times per week (>2/week)                        | 1,057  | 95.3           |
| Almost every day                                         | 52     | 4.6            |
| Meat consumption in the last 3 days                     |        |                |
| No                                                      | 174    | 15.6           |
| Yes                                                     | 935    | 84.3           |
| Red meat                                                | 538    | 48.5           |
| Fish                                                    | 177    | 15.9           |
| Poultry                                                 | 220    | 19.8           |
| Frequency of fish consumption                           |        |                |
| Never                                                   | 165    | 6.7            |
| Rarely                                                  | 338    | 30.4           |
| Once per month                                          | 344    | 31             |
| Once or more per week                                   | 262    | 23.6           |
| Frequency of offal consumption                          |        |                |
| Never                                                   | 752    | 67.8           |
| Rarely                                                  | 268    | 24.1           |
| Several times per month                                 | 89     | 8              |
| Foods consumed at breakfast                             |        |                |
| No breakfast                                            | 24     | 2.1            |
| Jam/Honey                                               | 60     | 5.4            |
| Butter                                                  | 45     | 4              |
| Cheese-yoghurt-egg                                      | 613    | 55.2           |
| Olive                                                   | 152    | 13.7           |
| Mother’s milk                                           | 59     | 5.3            |
| Other’s milk                                            | 52     | 4.6            |
| milk+supplements                                        | 104    | 9.3            |
| Drinks at breakfast                                     |        |                |
| Nothing                                                 | 31     | 2.7            |
| Tea                                                     | 783    | 70.6           |
| Milk                                                    | 239    | 21.5           |
| Fruit juice/Others                                      | 56     | 5              |

pg/mL respectively. Table 2 gives the vitamin B12 levels by age-group; Table 3 shows the results for cord-blood and newborns. Evaluation of these results revealed that vitamin B12 levels of both male and female subjects in the 1-5 year(s) old and the 6-11 years old groups were significantly higher than levels among the newborns (p<0.05 vs p<0.01). The levels in 1-5 year(s) old males and both 1-5 year(s) old and 6-11 years old females were significantly higher than the levels found in the 12-17 years old subjects (p<0.05). Additionally, the levels in the 1-5 year(s) old and the 6-12 years old females were significantly higher than the levels in 18-24 years old subjects (p<0.01).

Evaluation of the subjects according to gender revealed that vitamin B12 levels were significantly higher in females at the age of 7 and 14 years and in males at the age of 21 years when compared with the opposite gender (p<0.05). Considering correlations of vitamin B12 levels with age, height, weight, and BMI, a negative association was obtained with each (p<0.001).

Associations of educational status with vitamin B12 levels in fathers revealed that children of fathers who had high school education had significantly higher levels than children of fathers who were non-literate or who had a primary school education (286.6±147.5 pg/mL vs 248.2±133.7 pg/mL and 255.8±140.5 pg/mL respectively, p<0.05) while children of mothers with a university degree had significantly higher vitamin B12 levels than children of non-literate mothers (316.4±160.0 pg/mL vs 275.1±197.6 pg/mL respectively, p<0.05). Vitamin B12 levels showed no significant differences for the parents’ occupations or monthly incomes.

Dietary habits

Assessment of data showed no statistically significant difference for the frequency of red meat consumption. A significant difference did exist between subjects who never consumed fish and those who consumed it once or more per month (238.7±111.9 pg/mL vs 270.4±144.7 pg/mL and 285.0±151.4 pg/mL respectively, p<0.05). Vitamin B12 levels showed no difference between those who did or did not consume meals, including meat in the last three days. However, comparison of levels in subjects who received meals, including meat in the last three days, showed that subjects consuming fish had higher levels than did subjects receiving chicken (290.9±146.9 pg/mL vs 242.4±115.0 pg/mL respectively, p<0.05). No significant differences existed among the groups in terms of the frequency of offal consumption.

Subjects consuming butter at breakfast had higher vitamin B12 levels than those who never ate breakfast (303.9±187.9 pg/mL vs 220.0±89.1 pg/mL respectively, p<0.05). Subjects consuming milk at breakfast had significantly higher vitamin B12 levels when compared with those drinking tea or nothing (297.5±145.1 pg/mL vs 252.6±136.8 pg/mL and 244.8±75.3 pg/mL respectively, p<0.05).
Vitamin B$_{12}$ levels were significantly higher in infants [0-24 month(s), n=135] who were only on complementary feeding compared to those receiving only mother's milk (344.0±190.1 pg/mL vs 249.5±180.6 pg/mL respectively, p<0.05).

**DISCUSSION**

The reference levels of vitamin B$_{12}$ found in the current study were different from the levels found in studies conducted in other countries (Table 4). One of the characteristics of vitamin B$_{12}$ is that its normal values differ between races and societies (4,11,12). This characteristic property makes it necessary to determine the acceptable normal values of vitamin B$_{12}$ in each society. Carmel reported that the blacks have significantly higher cobalamin and transcobalamin (especially transcobalamin II) levels than whites do while the lowest levels were observed in India, Africa, and Pakistan (5). Recent reports show that vitamin B$_{12}$ levels in people of European societies are substantially higher (13,14). However, the results from this study show significant differences among the groups investigated with respect to the number and age of subjects. Furthermore, the methodologies used in the studies of different countries vary widely. This situation precludes the possibility of making a suitable comparison. Ortega et al. pointed out similar observations while evaluating relevant studies conducted in Spain (13).

The dissemination of health services and increase in general knowledge among the population has served to increase the number of those benefiting from preventive health services. This has facilitated a decrease in the incidence of various diseases, such as avitaminosis A and D, which were previously prevalent. At the same time, vitamin B$_{12}$ deficiency has attracted increased attention. Vitamin B$_{12}$ deficiency was found in 11% of the Guatemalan school children (15). Vitamin B$_{12}$ deficiency is also not rare in Turkey (16).

A review of studies conducted on vitamin B$_{12}$ levels among children show different results as shown in Table 4. In the study of Davis et al., infants of 4-37 weeks had higher 95% CI limit and mean value

### Table 2. Serum vitamin B$_{12}$ levels (pg/mL) of subjects aged 1 month to 24 years

| Age               | Gender | Number | Median | P$_{10}$ - P$_{90}$ | P$_{5}$ - P$_{95}$ | P$_{2.5}$ - P$_{97.5}$ |
|-------------------|--------|--------|--------|---------------------|-------------------|----------------------|
| 1-12 month(s)     | Male   | 17     | 210    | 143-400             | 140-418           | 140-418              |
|                   | Female | 21     | 243    | 134-560             | 122-647           | 121-655              |
| 1-5 year(s)       | Male   | 112    | 264    | 146-493             | 133-588           | 110-681              |
|                   | Female | 100    | 268    | 175-526             | 132-625           | 125-686              |
| 6-11 years        | Male   | 120    | 235    | 151-420             | 140-466           | 133-557              |
|                   | Female | 120    | 264    | 152-426             | 138-468           | 109-589              |
| 12-17 years       | Male   | 120    | 200    | 142-378             | 130-397           | 116-570              |
|                   | Female | 120    | 215    | 141-381             | 133-451           | 128-615              |
| 18-24 years       | Male   | 140    | 232    | 147-359             | 137-425           | 126-473              |
|                   | Female | 140    | 217    | 143-330             | 134-399           | 127-449              |
| Total             | Male   | 509    | 229    | 147-410             | 136-465           | 127-576              |
|                   | Female | 501    | 233    | 148-400             | 134-498           | 127-606              |

P=Percentile

### Table 3. Serum vitamin B$_{12}$ levels (pg/mL) in cord-blood and in newborns

| Source of blood | Gender | Number | Median | P$_{10}$ - P$_{90}$ | P$_{5}$ - P$_{95}$ | P$_{2.5}$ - P$_{97.5}$ |
|-----------------|--------|--------|--------|---------------------|-------------------|----------------------|
| Cord-blood      | Male   | 28     | 181    | 127-613             | 121-740           | 119-1,060            |
|                 | Female | 26     | 170    | 148-300             | 147-1,089         | 147-1,500            |
|                 | Total  | 54     | 174    | 147-417             | 126-793           | 121-1,335            |
| Newborns        | Male   | 23     | 181    | 132-429             | 119-700           | 116-532              |
|                 | Female | 22     | 206    | 137-750             | 127-1,178         | 126-1,230            |
|                 | Total  | 45     | 194    | 135-446             | 127-775           | 121-1,178            |

P=Percentile
Table 4. Previous studies on vitamin B₁₂ levels among children

| Investigator, year | Country | Inclusion criteria | No. | Vitamin B₁₂ levels | Results |
|--------------------|---------|--------------------|-----|--------------------|---------|
| Hages M, 1985      | Germany | Good health and, for | 165 | 1-5 Y*: 591.7 (257-1,349) pg/mL | Higher in girls than boys, suggesting vitamin B₁₂ levels in girls have some hormonal influences |
|                    |         | girls, not during menstruation |    | 6-10 Y: 556.4 (234.4-1,349) pg/mL |         |
|                    |         | 11-15 Y: 468.1 (204.2-1,071.5) pg/mL |    | |         |
| Osifo BOA, 1986    | Nigeria | Good health and, for | 240 | 12-17 Y (GP): 615±258 (280-1,400) pmol/L | Levels were higher in infants being fed formula or cow's milk than fed breastmilk |
|                    |         | girls, not during menstruation |    | 12-17 Y (Male): 554±202 (290-1,150) pmol/L |         |
|                    |         | 12-17 Y (Female): 687±298 (280-1,400) pmol/L |    | |         |
| Davis RE, 1986     | Australia | Good health and receiving breastmilk | 223 | 4-37 weeks: 334 (120-800) pg/mL |         |
| Hicks JM, 1993     | USA     | Random              | 1,486 | 0-1 Y (Female): 168-1,116 pmol/L | In this country, daily vitamin B₁₂ intake is 8-9 mcg while 0.9-2.2 mcg is recommended. Levels are low in 0-18% of the subjects |
|                    |         | 0-1 Y (Male): 216-891 pmol/L |    | Levels are lower in boys |         |
|                    |         | 13-18 Y (Female): 158-637 pmol/L |    | Level of Italians with similar age-group were 520±190 pg/mL |         |
|                    |         | 13-18 Y (Male): 134-605 pmol/L |    | No difference between genders but levels decreased with age |         |
| Ortega RM, 2001    | Spain   | 76 studies reviewed | 1,490 | 0-15 Y: 679.7±127 pg/mL |         |
| Shen M-H, 2002     | Taiwan  | Maintaining usual diet in the last 3 days | 1,235 | 12-15 Y (Male): 444.8±158.4 pg/mL | Cord-blood levels are higher than levels in mothers |
|                    |         |                     |    | 12-15 Y (Female): 495.0±181.3 pg/mL | | |
| Leoncini R, 2004   | Mozambique | Healthy children on a standard diet | 173 | 6-16 Y: 782.7±537.1 pg/ml** |         |
| Huemer M, 2006     | Austria  | Good health and not receiving any vitamin or other drugs | 264 | 2-5 Y: 572 (202-1,345) pg/mL |         |
|                    |         |                     |    | 6-9 Y: 559 (201-1,050) pg/mL |         |
|                    |         |                     |    | 10-13 Y: 437 (163-889) pg/mL |         |
|                    |         |                     |    | 14-17 Y: 355 (142-736) pg/mL |         |
| Obeid R, 2006      | Germany | Children of healthy pregnant women over 17 years, premature and in-uteo growth-retarded babies also included | 92 | Cord-blood: 268 (88-1,018) pmol/L |         |
| McLean ED, 2007    | Kenya   | Randomly-chosen school children | 120 | 6-14 Y: 292±144 pmol/L | Nutrition with foods from animal source increases the levels |

*Folic acid and cobalamin units might have been mixed in the text; GP=General population; Y=Years old; α=Mean±SD; η=Mean±SD (Minimum-Maximum); θ=Mean (P₂₅-P₇₅); κ=Mean (Minimum-Maximum) π=P₂₅-P₉₇.₅; According to the international unit system, conversion coefficient pg/mL to pmol/L is 0.74' (pmol/L=pg/mLx0.74)
levels and lower 5% limit and mean value of vitamin B₁₂ when compared with our results (17). The values obtained in other studies (mean and percentage limit values), however, were higher than the values found in this study (8,13,18-24). These differences might be attributed to several factors, particularly the criteria and requirements for inclusion into the study. Davis et al. accepted only good health status and being breastfed as requirements for inclusion into the study (17). The vitamin B₁₂ levels in the infants’ blood and their umbilical cord are closely related to the level in the mothers’ blood (16,25). However, the drugs containing vitamin B₁₂ used during pregnancy and after giving birth and similar drugs that can be given to the infants have an increasing effect on vitamin B₁₂ levels. Among other researchers, only Huemer et al. indicated the absence of any vitamin drug as a requirement for inclusion in their study (22). Thus, differences in the inclusion criteria for study subjects could affect the study results.

Another reason for the differences observed between other studies and the current study can be nutritional habits. Disorders relating to excessive nutrition, such as obesity, are quite common in western societies; people in those societies are well-nourished, even excessively so. In Finland, subjects have been advised to take two mcg of vitamin B₁₂ daily, yet their daily vitamin B₁₂ intake was 7.4-11 mcg (12). The current study accepted consumption of red meat twice per week as an adequate nutritional sign of vitamin B₁₂ intake. The findings regarding the nutritional habits of the participants indirectly confirmed that they had consumed red meat at least twice per week. If participants reported that they had consumed red meat at least twice per week despite they had actually consumed less, their vitamin B₁₂ levels would be low. In that case, the vitamin B₁₂ levels in participants who stated that they had consumed meat daily and preferred fish and food of animal origin at breakfast should have shown a significant difference when compared with those who did not prefer these types of food. However, examination of the results showed no significant difference. Meat consumed in this quantity, together with the consumption of other foods of animal origin, maintained an adequate vitamin B₁₂ level but did not lead to a significant difference. This also shows that subjects who stated they consumed red meat at least twice per week were reporting accurately.

The following two points can help explain the low values observed in our study:

(i) Ethnic diversity: Some researchers have noted differences in vitamin B₁₂ levels between the members of the white and black races (4,11,12). Kwee et al. reported vitamin B₁₂ levels of 382±131.3 pg/mL and 546±197.5 pg/mL in healthy white and black females respectively. They stated that the difference between the two races was significant (4). A similar characteristic might affect other societies, and one might question whether ethnic characteristics have affected the results of the current study. It would be presumptuous to provide a definitive answer to this question in view of the inadequate number of studies on the issue. However, evidence exists that would lead us to think the opposite. In a study conducted in Australia, 56 of the participants were Turkish (22). In that study, while the vitamin B₁₂ level of Turkish children was reported to be 592±70 pg/mL, that of Australian children was 469±79 pg/mL. This finding shows that Turkish people living in the same region with Australians and with similar opportunities for nutrition do not have low vitamin B₁₂ levels.

(ii) Vitamin B₁₂ content of nutrients: The source of vitamin B₁₂ is food of animal origin. Animals do not produce this vitamin themselves. Animals eat food containing B₁₂-producing bacteria; thus, the animals become sources of vitamin B₁₂ (26). One explanation of low levels of vitamin B₁₂ in humans could be low levels of cobalt in the soil, resulting in fewer microorganisms producing vitamin B₁₂ by using cobalt in the region’s soil. There is insufficient information to confirm or reject such a hypothesis.

Another reason for the different results among studies might be the differences between the methodologies used. The current study utilized the Beckman kits that are used in the biochemistry laboratory of the hospital for measuring vitamin levels. The reference range of 127-590 pg/mL obtained in the study was different from the reference range of the kits (180-914 pg/mL). The study by Christenson et al., conducted on 154 healthy subjects, investigated the reference ranges using two different kits. Reference ranges were found to be 116-817 ng/L with the SimulTRAC-S kit and 205-810 ng/L with the Quanaphase kit (27). It is remarkable that there is a substantial difference between these results. The reference ranges of the kits were 180-960 and >200 ng/L respectively. Furthermore, false positivity was detected in 9% of the subjects with the first kit. Thus, Christenson et al. suggested that studies on normal range be completed in a society before assays are used in the evaluation of patients;
the current authors support this idea (27). Kumar et al. compared three methods in a study conducted on the Indians, and they recommended radioisotope dilution assay as an accurate procedure for determining vitamin B₁₂ levels (28).

In the current study, we found that when the factors that can affect vitamin B₁₂ levels such as age, weight, height, and BMI increased, vitamin B₁₂ levels were significantly lowered. In line with the current findings, others have reported that vitamin B₁₂ levels significantly decrease with age (6,7,18,22,24,29). When subjects were stratified according to gender, it was found that vitamin B₁₂ levels were significantly higher in females at the age of 7 and 14 years and in males at the age of 21 years. However, the findings about the association of gender and vitamin B₁₂ levels are incompatible with the literature (6,8,11,18,20,22,29).

In this study, the serum level of vitamin B₁₂ was not affected by the parents’ occupations or the levels of family income. This finding gave rise to the thought that people living in the region had good awareness of nutritional issues. The finding that vitamin B₁₂ levels in children whose mothers had a university degree and whose fathers had high school education were significantly higher suggests education can be an effective factor in nutrition.

An interesting result of this research was that vitamin B₁₂ levels were significantly higher in subjects who consumed fish when compared with those who consumed chicken. No comparable result could be found in the literature. This situation can be explained because the vitamin B₁₂ level in fish is 10 times higher than in chicken (30). It is not surprising that infants taking complementary food had higher vitamin B₁₂ levels compared to infants who were only breastfed. Infants are generally given food prepared with milk as a supplement. The vitamin B₁₂ content in cow’s milk is 5 to 10 times higher than in human milk (30,31). The findings of the current study were supported by those of Davis et al. and Karademir et al. who reported that vitamin B₁₂ levels in infants who were only breastfed were lower when compared with levels in infants who were fed with cow’s milk and formula milk (17,32).

Conclusions

The results of this research suggest that vitamin B₁₂ levels vary among countries and that using reference ranges of varied populations may lead to inaccurate results. Therefore, the researchers advise that it would be beneficial to achieve normal levels that are valid for each population.

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