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Evaluation of Serum Vitamin B12 Levels in Patients with Colon and Breast Cancer: A Case-Control Study

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ABSTRACT

Background: It has been shown that increased serum levels of vitamin B12 may be associated with some malignancies. This study aimed to compare the serum levels of vitamin B12 in patients with colon and breast cancer and healthy individuals.

Materials and Methods: In this case-control study, 140 patients with colon and breast cancer were compared with 140 healthy individuals matched in age, gender, and socioeconomic status. Serum levels of vitamin B12 were measured through the Electrochemiluminescence method in both groups. The normal serum level of vitamin B12 was between 200 and 800 pg/ml.

Results: Among 280 enrolled subjects, 60 had serum vitamin B12 levels higher than 800 pg/ml. Forty-six (32.9%) patients had high serum vitamin B12 levels, compared to 14 (10.0%) subjects in the control group (P = 0.001). The mean serum vitamin B12 level was significantly higher in the patients (380.4 ±540.2 pg/ml vs. 278.0 ±314.08 pg/ml, P =0.001). There was no statistically significant difference in serum levels of vitamin B12 in patients with breast and colon tumors (P = 0.8). A significant positive correlation was observed between serum levels of vitamin B12 and tumor stage (P = 0.001, r = 0.49).

Conclusion: The findings of this study showed that serum levels of vitamin B12 in patients with colon and breast cancer are higher than in healthy individuals and are positively associated with the stages of cancer.

Keywords: Vitamin B12; Breast cancer; Colon cancer

INTRODUCTION

Cancer is the third most common cause of death after cardiovascular disease and traffic accidents in Iran [1,2]. The worldwide prevalence of cancer is growing due to increasing life expectancy, particularly in developing countries[3]. It is estimated that 56% of cancer incidence and 64% of cancer deaths occur in developing countries[4].

Vitamin B12, or cobalamin, is one of the nutrients required for carbon metabolism and cell division[5]. Addition of vitamin B12, insulin, and epidermal growth factor to mouse 6T3 cells (embryonic fibroblasts) in a culture medium that was stopped at the G1G0 stage induces DNA synthesis in over 80% of cells[6]. Deficiency of this vitamin is mainly due to decreased intake or gastrointestinal absorption, and is observed more

commonly in the elderly, and causes neurological disorders, pernicious anemia, and increased risk of cardiovascular disease[7]. Elevated levels of vitamin B12 have been seen in alcoholism, autoimmune disease, solid tumors, especially hepatocellular carcinoma and hematologic malignancies[8]. Epidemiological studies have shown a higher prevalence of vitamin B12 deficiency in the Iranian population, which is more observed in men and women of childbearing age[9]. Furthermore, Vitamin B12 deficiency has been highly prevalent in Iranian immigrants to Australia[9]. Studies around the world suggest an association between abnormal levels of vitamin B12 and various cancers and even a role as a potential tumor marker or prognostic factor in a number of cancers [10,11].

Due to the enormous economic burden of cancer and lack of research on this concern in Iran, the present study attempted to assess serum vitamin B12 levels in patients with solid malignancies (i.e., breast and colon cancer) and healthy population.

MATERIALS AND METHODS

This case-control study was conducted on 280 participants at a clinic in Hamedan, located in western Iran, from April 2019 to June 2020. The Ethics Committee of Hamadan University of Medical Sciences approved the study, and written consent was obtained from all participants. Patients with breast or colon cancer referred to clinic and their family members were entered into this study. The cancer diagnosis was based on pathological findings and the approval of an experienced oncologist.

Patients with breast or colon cancer were assigned to the case group. For the control group, patients' family members without any malignancies were selected. Participants with blood cancers, liver cirrhosis, pernicious anemia, alcoholism, chronic liver and kidney disease, recent use of vitamin B12 supplement in any case (injectable, oral) in the last three months, use of proton pump inhibitor in the last month were excluded from the study. The participants in the case and control groups were matched regarding gender, age, and socioeconomic status. Vitamin B12 levels were measured under standard conditions through the Electrochemiluminescence (ECL) method. According to the kit instructions, the serum level of vitamin B12 between 200 and 800 pg/ml was considered as normal.

Using the findings of previous studies considering the first type error of 5% and the second type error of 20%, using the standard formula and comparing the means in the two groups, and using the results of the study by Carmel et al. [12], the sample size was determined 140 in each group in this study. Qualitative data with percentages and ratios and quantitative data were displayed as mean and standard deviations. Mann-Whitney U test was used for comparing continuous variables, and the $\chi 2$ test was implemented to assess differences in the categorical variables. Odds ratio of hypervitaminemia B12 between two groups was calculated by binary logistic regression analysis. Pearson's correlation analysis was performed to find the relationship between serum levels of vitamin B12 and tumor stage. All P- values were two-tailed, and $P < 0.05$ was considered statistically significant. SPSS software (version 20, IBM Corporation, Armonk, NY, USA) was used for the statistical analysis.

RESULTS

Characteristics of studied participants are shown in Table 1. The mean age (± standard deviation) of participants in the case and control groups was 52.3 ±10.3 and 49.9 ±12.1 years, respectively (P =0.3). Two groups did not have a statistically significant difference in gender; 100 (71.4%) patients in case group and 90 (64.3%) participants in control group were female. In case group, 87 (62.1%) and 53 (37.9%) patients had breast and colon cancer, respectively. Among 280 enrolled subjects, 220 had serum levels of vitamin B12 less than 800 pg/ml, and 60 subjects had levels higher than 800 pg/ml.

The mean serum vitamin B12 level was significantly higher in the patients (380.4 ±540.2 pg/ml vs. 278.0 ±314.08 pg/ml, P value=0.001). There was no significant difference in mean serum vitamin B12 level between patients with breast and colon cancer (363.7 ± 543.8 pg/ml vs. 409.9 ±543.3 pg/ml, P value=0.8). In the case group, 46 (32.9%) patients had high serum vitamin B12 level, compared to 14 (10.0%) subjects in the control group. Binary logistic

regression analysis revealed the probability of high vitamin B12 in patients was 4.4 times that of healthy individuals (Table 2).

We found that patients with more advanced stages of cancer had higher serum levels of vitamin B12 (Table 3). Pearson's correlation coefficient showed a significant positive correlation between serum levels of vitamin B12 and tumor stage (r= 0.497, P=0.001) (Figure 1).

Table 1: Characteristics of studied participants

	Control group	Case group	P
Age (years)	49.9 (12.1)	52.3 (10.3)	0.30
Female (%)	90 (64.3%)	100 (71.4%)	0.20
Vitamin B12 (pg/ml)	278 (314.08)	380.4 (540.2)	0.001

Table 2: Comparison of serum levels of vitamin B12 classified into two groups

Vitamin B12	Control group	Case group	P (Chi^2)	OR (95 % CI)
	N (%)	N (%)		
High	14 (10)	46 (32.9)	0.001	4.4 (2.3-8.4)
Normal or low	126 (90)	94 (67.1)		

OR: odds ratio, CI: confidence interval

Table 3: Serum levels of vitamin B12 based on the cancer stage

Stage tumor	Mean	Standard deviation	P
I	331.3	278.3	0.001
П	294.4	216.8	
III	587.8	349.0	
IV	833.0	388.2	

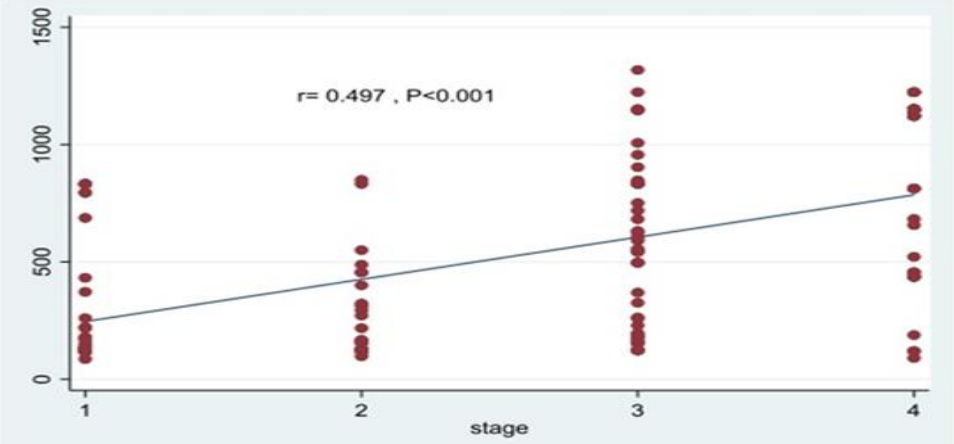

Figure 1. Correlation between serum levels of vitamin B12 and tumor stage

DISCUSSION

The findings of our study showed that the serum level of vitamin B12 in patients with colon and breast cancers was significantly higher than in the control group. Moreover, the level of vitamin B12 raised significantly with increasing stage of cancer. The chances of having vitamin B12 levels higher than 800 pg/ml in patients with both cancers was 4.4 times higher than in non-patients.

Some studies have shown that increased vitamin B12 is associated with liver cancer [13-15]. A research study by Arendt et al. [5] showed that elevated serum levels of vitamin B12 are associated with cancer risk. Gimsing et al.[16] also showed that increased serum levels of vitamin B12 could increase the risk of hematologic cancer.

In some studies, including the study of Ching-Yih Lin et al.[17], it has been shown that increased serum levels of vitamin B12 along with tumor markers are a predictor of poor survival in patients with hepatocellular carcinoma. A study by Hye Kyung Oh et al.[18] showed that increased serum levels of vitamin B12 reduced the survival rate of liver cancer patients.

Consistent with the present study's findings, a study conducted by Zulfiqar et al. [10] in France showed that the factors associated with increased serum levels of vitamin B12 are kidney failure, liver disease, and solid tumors. In their study, increasing the serum level of vitamin B12 raises the risk of blood cancers by 7.5 times. However, some other studies have shown that increased serum levels of vitamin B12 are associated with a reduced risk of prostate and lung disease[19, 20].

The mechanism of increased serum levels of vitamin B12 remains unclear, as there is no evidence that such an increase is related to intestinal absorption. Only injectable or high doses can increase serum levels. The pathogenicity of elevated serum levels of vitamin B12 and the risk of cancer have not yet been determined. Previous studies have shown that the risk of mortality in non-cancer patients surges with increasing serum levels of vitamin B12[19,21], indicating that its pathogenesis is unrelated to cancer.

One hypothesis for an increase in serum levels of vitamin B12 is a change in cobalamin metabolism. Cancer is thought to increase serum levels of vitamin B12 by altering cobalamin metabolism. This hypothesis was made because serum vitamin B12 levels increased over the next few years in patients with cancer, and as the years progressed with cancer, levels of this vitamin increased [5].

Like previous studies, our findings show that most patients and controls suffer from vitamin B12 deficiency[22, 23]. B12 deficiency can affect people of all ages, but the elderly, children, adolescents, and women of childbearing age are also at higher risk for deficiencies in populations that restrict their intake of vitamin B12-rich animal foods. We did not have enough information about patients' lifestyles, smoking status, obesity, and physical activity that may affect serum levels of vitamin B12.

CONCLUSION

The findings of this study showed that serum levels of vitamin B12 in patients with colon and breast cancer are higher than in non-patients and are positively associated with the stages of the cancer.

CONFLICTS OF INTEREST

The authors have no conflict of interests to disclose.

REFERENCES

1. Kolahdoozan S, Sadjadi A, Radmard AR. Five common cancers in Iran. Arch Iran Med. 201013(2):143-6.
2. Amirkhah R, Naderi-Meshkin H, Mirahmadi M, et al. Cancer statistics in Iran: Towards finding priority for prevention and treatment. Cancer Press. 2017;3(2):27-38.
3. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin . 2015;65(2):87-108.
4. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90.
5. Arendt JFB, Pedersen L, Nexo E, et al. Elevated plasma vitamin B12 levels as a marker for cancer: a population-based cohort study. J Natl Cancer Inst. 2013;105(23):1799-805.
6. Mierzejewski K, Rozengurt E. Stimulation of DNA synthesis and cell division in a chemically defined medium: effect of epidermal growth factor, insulin and vitamin B12 on resting cultures of 3T6 cells. Biochem Biophys Res Commun. 1976;73(2):271-8.
7. Green R, Allen LH, Bjørke-Monsen AL, et al. Vitamin B_{12} deficiency. Nat Rev Dis Primers. 2017;3:17040.
8. Andrès E, Serraj K, Zhu J, et al. The pathophysiology of elevated vitamin B12 in clinical practice. QJM. 2013;106(6):505-15.

9. Benson J, Phillips C, Kay M, et al. Low vitamin B12 levels among newly-arrived refugees from Bhutan, Iran and Afghanistan: a multicentre Australian study. PLoS One. 2013;8(2):e57998.
10. Zulfiqar AA, Andres E, Lorenzo Villalba N. [Hypervitaminosis B12. Our experience and a review]. Medicina (B Aires). 2019;79(5):391-6.
11. Cappello S, Cereda E, Rondanelli M, et al. Elevated Plasma Vitamin B12 Concentrations Are Independent Predictors of InHospital Mortality in Adult Patients at Nutritional Risk. Nutrients. 2016;9(1):1.
12. Carmel R, Eisenberg L. Serum vitamin B12 and transcobalamin abnormalities in patients with cancer. Cancer. 1977;40(3):1348-53.
13. Lildballe DL, Nguyen KQT, Poulsen SS, et al. Haptocorrin as marker of disease progression in fibrolamellar hepatocellular carcinoma. Eur J Surg Oncol. 2011;37(1):72-9.
14. Nörredam K, Chainuvati T, Gimsing P, et al. Plasma cobalamin and transcobalamin in patients with primary carcinoma of the liver. A study from Thailand. Scand J Gastroenterol. 1983;18(2):229-32.
15. Wheeler K, Pritchard J, Luck W, et al. Transcobalamin I as a "marker" for fibrolamellar hepatoma. Med Pediatr Oncol. 1986;14(4):227-9.
16. Gimsing P, Overballe-Petersen C, Hippe E. Cobalamin and cobalamin-binding proteins in plasma related to the clinical condition in chronic myelogenous leukemia. Leukemia. 1995;9(9):1604-9.
17. Lin CY, Kuo CS, Lu CL, et al. Elevated serum vitamin B(12) levels in association with tumor markers as the prognostic factors predictive for poor survival in patients with hepatocellular carcinoma. Nutr Cancer. 2010;62(2):190-7.
18. Oh HK, Lee JY, WK Eo, et al. Elevated Serum Vitamin B(12) Levels as a Prognostic Factor for Survival Time in Metastatic Cancer Patients: A Retrospective Study. Nutr Cancer. 2018;70(1):37-44.
19. Collin SM, Metcalfe C, Refsum H, et al. Circulating folate, vitamin B12, homocysteine, vitamin B12 transport proteins, and risk of prostate cancer: a case-control study, systematic review, and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2010;19(6):1632-42.
20. Johansson M, Relton C, Ueland PM, et al. Serum B vitamin levels and risk of lung cancer. JAMA. 2010;303(23):2377-85.
21. Dou J, Xu W, Ye B, et al. Serum vitamin B12 levels as indicators of disease severity and mortality of patients with acute-on-chronic liver failure. Clin Chim Acta. 2012;413(23-24):1809-12.
22. Stabler SP. Clinical practice. Vitamin B12 deficiency. N Engl J Med. 2013;368(2):149-60.
23. Hunt A, Harrington D, Robinson S. Vitamin B12 deficiency. Bmj. 2014;349:g5226.