Association between serum vitamin D and parathyroid hormone levels in Turkish patients with colonic polyps

Oyku Tayfur Yurekli[1], Tevfik Solakoglu[1], Roni Atalay[1], Aylin Demirezer Bolat[1], Fatma Ebru Akin[1], Eyup Selvi[1], Naciye Semnur Buyukasik[1], Osman Ersoy[1,2]

(1) Department of Gastroenterology, Research and Teaching Hospital, Ankara Ataturk, Ankara, Turkey ; (2) Department of Gastroenterology, Faculty of Medicine, Yıldırım Beyazit University, Altındağ, Ankara, Turkey.

Abstract

Epidemiological and investigational studies have proved that vitamin D is important in autoimmune processes and has anticancerogenic properties. But the interplay between serum vitamin D and parathyroid hormone (PTH) in colorectal polyps has been less clearly put forward. We evaluated serum vitamin D, PTH levels in Turkish people and tried to stratify colorectal polyps according to risk factors. Patients undergoing colonoscopy between January 2012 and March 2012 were considered to study serum vitamin D levels during winter. Study population comprised of 98 colorectal polyp and 197 normal colonoscopy patients. Results : Serum vitamin D levels were not different between the groups (mean vitamin D level in polyp group 14.3 ± 11.1 vs. 12.7 ± 6.74 the normal group, p = 0.12). Likewise serum PTH levels were not different between the groups Patients with polyps were further classified as high and low risk polyps. When discriminant function analysis was conducted, the effects of vitamin D or PTH levels were not again significant. During the study period 16 colorectal carcinoma cases were detected. Serum vitamin D or PTH levels were not significantly different between colorectal cancer or overall study group patients. Finally serum vitamin D levels were stratified into quartiles. Likewise there was not any significant difference between the groups. The present study suggests that serum vitamin D and PTH levels were not different between colorectal polyp and control groups. And serum vitamin D levels were significantly low in both groups suggesting a significant vitamin D deficient state in Turkish patients. (Acta gastroenterol. belg., **2015**, 78, **206-211**).

Key words : colonic polyp, vitamin D and PTH.

Introduction

Colorectal carcinoma is a common cause of mortality and morbidity in both sexes. As screening strategies have been implemented in most countries, efforts are concentrated on definition of preventive measures. Epidemiological studies have shown an inverse relationship between vitamin D status and colorectal carcinoma however, the association of vitamin D status with colorectal polyps, which are well defined precursors of colorectal carcinoma, have been less clearly identified. Additionally, colorectal polyps are not uniform in terms of size and histology resulting in different colorectal carcinoma risks.

Most epidemiological studies report inverse relationship between oral vitamin D intake and colorectal carcinoma risk (1,2). However more than 90% of vitamin D is synthesized in human body by action of sunlight. Therefore oral intake might be an insufficient marker of body vitamin D status. Studies measuring serum vitamin D levels also have some limitations. Some studies only used sigmoidoscopy for screening colorectal polyps (3,4) and some involved only one gender for screening purposes (5). Vitamin D is a steroid hormone and its levels are tightly regulated by PTH levels. However, most of the studies investigating the role of vitamin D in colorectal carcinogenesis did not measure serum PTH levels. Although Turkey is known to be a "sunny" country, people living in Turkey are generally vitamin D deficient. To the best of our knowledge this is the first study to investigate the relationships among colorectal polyps or carcinomas and vitamin D and PTH levels in Turkish people.

Patients and Methods

620 patients undergoing colonoscopy procedure between January and March 2012 were considered for this study. This period was chosen to be able to measure the patients' vitamin D levels in winter period. Screening colonoscopies are not as widely implemented as in other countries so patients presenting with irritable bowel syndrome like symptoms were included in this study. Additionally to be able to include advanced adenoma cases patients with anemia were also included in the study. Patients known to have or newly diagnosed with inflammatory bowel disease were excluded. Colonoscopies not reaching to the base of cecum were excluded. As vitamin D and PTH levels could be affected from renal function, patients with creatinin clerences below 50 ml/minute were excluded. Patients incidentally diagnosed with primary hyperparathyroidism were excluded. As a result 325 patients were excluded because of the aforementioned reasons. Health professionals interviewed all patients for family history of cancer, dietary supplement usage, lifestyle habits (i.e., smoking, alcohol consumption), nonsteroidal anti-inflammatory drug (NSAID) or acetylsalicylic acid intake. Patients' height and weight were measured as part of the physical examination. Body

Correspondence to : Oyku Tayfur Yurekli. Research and Teaching Hospital, Ankara Ataturk, Gastroenterology Clinic, Eskisehir Yolu, Lodumlu Mevkii No : 2 Bilkent/Ankara. E-mail : oykutayfur78@yahoo.com

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Mass Index (BMI) was calculated by dividing the weight measured in kilograms by the square of height in meters.

On the day of the procedure, fasting serum was obtained to measure serum calcium, phosphorus, creatinine, vitamin D, parathyroid hormone (PTH), albumin and hemoglobin levels. > 20 ng/mL levels are accepted as normal values for vitamin D. For PTH, levels between 15-65 pg/mL are accepted as normal.

All colonoscopies were performed with a CV 180 (Olympus, Tokyo, Japan) by experienced gastroenterologists. During the procedure, the location, size and number of polyps were recorded. The location of the polyps was classified as "rectosigmoid", "descending colon", "transverse colon", and "right colon". The polyp size was estimated using open biopsy forceps. Patients with multiple adenomas were classified as "multiple" with different categories considering both size and location of the polyps. The most advanced pathology was recorded in the patients with multiple polyps.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviations while the categorical variables were presented as absolute values and percentages. The differences between patients were analyzed using student's *t* test for continuous variables and χ^2 test for categorical variables. 25(OH)D levels were stratified into quartiles and multivariate logistic regression analyses were performed to adjust for the differences in age, gender, BMI. Then, the association between serum vitamin D levels (as expressed in quartiles) and adenoma characteristics was examined. Next, polyps were further classified as high and low risk polyp (high risk polyps are defined by one of the following : more than 3 adenomatous polyps, polyp diameter > 10 mm or the presence of villous component). P values less than 0.05 were considered as statistically significant. The analyses were performed using SPSS version 21 (IBM Corporation, 2011).

Results

The characteristics of study population are presented in Table 1. The mean age of the study population was 53.4 ± 12.4 years (median = 53 ; range = 17-81 years). There were 122 females (41%) and 173 males (59%). 98 patients had colon polyps. Polyp and the normal colonoscopy group did not differ significantly with regard to BMI, smoking or alcohol intake status. However the mean age of the polyp patients were 57,76 ± 10.04 while mean age of the normal colonoscopy group was 51.21 ± 12.87 and the difference was statistically significant (p = 0.01). Mean serum 25(OH) D3 level was 13.23 ± 8.44 ng/mL in the whole study group. Serum vitamin D levels were not different between the groups (mean vitamin D level in polyp group was 14.3 ± 11.10 while 12.70 ± 6.74 in the normal group, p = 0.12). Similarly serum PTH levels were not significantly different between the groups (mean PTH level in polyp group was 61.32 ± 35.40 pg/mL while 55.84 ± 24.34 pg/mL in the normal group, p = 0.12).

Overall 98 patients had colonic polyps. As mentioned before the most advanced pathology was reported in patients with multiple polyps. Table 2 summarizes the distribution of polyps according to histology.

Univariate analyses did not reveal any relationship between the chance of having colon polyps and gender, smoking or alcohol intake. However age was found to be moderately correlated with colorectal polyp risk (Table 3).

Patients with polyps were further classified as high and low risk adenoma (high risk adenomais identified by one of the following : ≥ 3 adenomatous polyps, adenoma diameter > 10 mm or presence of villous component as suggested by US Multi-Society Task Force on Colorectal Carcinoma-AGA guideline published in 2012). 43 patients were classified as high risk and remaining 55 patients were classified as low risk. Only age variable was found to be related with the probability of having high risk polyp. Logistic regression analysis failed to show any effect of NSAID intake, smoking or family history, BMI on probability of having high risk polyp (Table 4). When discriminant function analysis was conducted, the effects of vitamin D (Wilks Lambda = 0.98 ; p = 0.149), PTH levels (Wilks Lambda = 1.00 ; p = 0.905), BMI (Wilks Lambda = 0.97 ; P = 0.09) were found to be insignificant meaning knowledge of vitamin D, PTH levels and BMI value is not useful for predicting whether the patient has risky polyp or not. However, the same

Table 1. — **Clinical characteristics and some laboratory values in polyp and normal colonoscopy groups**

Characteristics	Polyp group (n = 98)	Control group (n = 197)	P
Age (years)	57.76 ± 10.04	51.21 ± 12.87	0.01*
Gender (Female/male)	32/66 (32.7%/67.3%)	90/107 (45.7%/54.3%)	
Body Mass Index (kg/m^2)	28.63 ± 5.63	27.72 ± 4.47	0.16
Vitamin D (ng/mL)	14.3 ± 11.10	12.70 ± 6.74	0.12
PTH (pg/mL)	61.32 ± 35.40	55.84 ± 24.34	0.12
Hemoglobin (g/dL)	14.61 ± 2.10	14.28 ± 1.97	0.19
Albumin (g/dL)	4.66 ± 0,46	4.71 ± 0.42	0.35

Note: * indicates the difference is significant at p < .05.

Table 2. — **Distribution of polyps according to histology**

Polyp type	Number	%
Tubular adenoma	62	63.2
Tubulovillous adenoma	18	18.3
Villous adenoma	4	4.3
Hyperplastic polyp	14	14.2

analysis revealed that age was a significant predictor of having high risk polyp (Wilks Lambda = 0.92 ; p = 0.012). Accordingly, as the age of the patient increases, the probability of having risky polyp increases. This fact is also supported by the mean difference of age in high risk and low risk polyp groups. (Mean age for high risk polyp group = 60.55 ; mean age for low risk polyp group = 55.01).

Since the study period was relatively short in order to measure levels during the winter months only 16 colorectal carcinoma cases could be identified. These patients were separately analyzed and compared with the study group. Serum vitamin D and PTH levels were not significantly different between the groups. Similarly no differencewas detected after patients were classified as normal, polyp or cancer groups (the p values were 0.35 and 0.12 for vitamin D and PTH respectively). Table 5 presents some of the laboratory values between cancer and non-cancer patients. As expected mean age of cancer patients was significantly higher and mean albumin and hemoglobin levels were significantly lower than the study group.

The literature about the association of colorectal adenoma or carcinoma with serum vitamin D levels mostly analyzed data by stratifying vitamin D levels into quartiles. So we stratified serum Vitamin D levels into quartiles. Table 6 presents the distribution of the patients' vitamin D levels in each quartile Similarly no difference was observed between the groups.

Lastly multiple regression analyses were performed to search for the influence of vitamin D quartiles on the probability of having high risk polyp after controlling for age, gender, BMI, smoking, alcohol intake. No significant effect could be detected as well.

Discussion

Calcium and vitamin D have long been considered pivotal in bone metabolism. Yet being a steroid hormone, vitamin D is thought to play important roles in autoimmune processes and cancer. Calcium and vitamin D have multiple anticancerogenic properties such as induction of differentiation, inhibition of cellular proliferation and induction of apoptosis (6,7,8). Multiple cell types including colorectal cells harbor vitamin D receptor and 1-α hydroxylase, a key vitamin D metabolizing enzyme converting 25(OH)D to active 1,25-(OH)2D (7). In rats deletion of vitamin D receptor gene caused an imbalance between proliferation and apoptosis, increased oxidative DNA injury and increased carcinogenesis in epithelial tissues (9). Multiple studies have shown an inverse correlation between calcium and vitamin D levels and breast, pancreas and vulvar carcinoma development (10,11). However, recently Vitamin D has failed to show any protective property against cancer development (12,13). Some interventional studies e.g Women's Health Initiative Investigation also failed to show any protective effect of supplemental vitamin D in colorectal cancer development (14). However the dose was lower than the dose used in polyp recurrence trials, patients were younger and time period was relatively short possibly preventing any protective effect to be detected.

Potential protective role of vitamin D was first suggested in 1980 by Garland after the observation of different mortality ratios of cancer in places with different altitudes (15). Vitamin D is mainly synthesized in human body by sunlight through UV-B radiation. By UV-B radiation 7-dihydrocholesterol is converted to vitamin D in skin. Then 25 hydroxylation takes place in liver and finally active vitamin D is synthesized by 1 α hydroxylation. UV-B radiation decreases by increasing altitude. This may be the cause of increased cancer incidence and mortality in high altitude places (15).

Most epidemiologic studies have shown that high vitamin D intake decrease colorectal carcinoma and adenoma risk by 20-30% (16). Cut-off value for vitamin D intake is 1000 IU/day in most of these studies. According to a metaanalysis performed in 2008 with respect to

Table 3. — **Univariate analyses on the association of risk of colorectal polyp with body mass index, gender, alcohol use, smoking status and age**

Variable	Number of Cases (n = 98)	Number of Controls (n = 197)	Univariate analysis	
			OR (95% CI)	P
Age	57.76 ± 10.04	51.21 ± 12.87	1.025 (1.006-1.044)	0.01**
Gender (F/M)	32/66 (32.7%/67.3%)	90/107 (45.7% / 54.3 %)	.774 (0.48-1.247)	0.29
Smoking status (smoker/nonsmoker/exsmoker)	15/65/18	32/141/24	1.21 (0.84-1.76)	0.31
Alcohol Intake (positive/negative)	8/90	16/181	0.95 (0.50-1.81)	0.87
Body Mass Index	28.63 ± 5.63	27.72 ± 4.47	0.95 (0.91-0.98)	0.16

Table 4. — **Analyses on the association of clinical parameters and some laboratory values with the probability of having high risk polyp**

Variable	Patients with high risk polyps (n = 43)	Patients with low risk polyps (n = 55)	Univariate analysis	
			OR (95% CI)	P
Smoking	4	11	0.378 (0.25-0.57)	0.08
NSAID	6	11	1.55 (0.79-1.89)	0.45
Family history	3	5	1.61 (1.45-1.98)	0.55
ASA	7	6	0.82 (0.75-0.94)	0.76

colorectal adenoma incidence between the lowest and the highest vitamin D intake group, 11% difference could be anticipated (17). Most studies about the protective role of vitamin D are mainly concerned with oral intake. However since vitamin D is mainly synthesized in human body through sunlight serum levels should also be evaluated.

Since 25 hydroxyvitamin D has 2-3 weeks long half-life it is a good marker for long term vitamin D status. Additionally in vitamin D deficiency renal 1 α hydroxylase activity is augmented with the help of an increase in serum PTH levels. This increase in serum PTH levels results in increased 1,25 dihydroxyvitamin D levels that may possibly cause an underestimate of the vitamin D deficiency. An important finding is that relationship between vitamin D levels and colorectal neoplasia has been shown in studies performed in winter months. No significant relationship was noted during summer (5,18).

After Garland's observation, multiple studies were performed to investigate the relationship between colorectal carcinoma and serum vitamin D levels. For instance, "Nurses Health Study", examined the relative risk ratio for colorectal carcinoma and found that the relative risk ratio was 0.53 between the highest and lowest serum vitamin D groups among 193 colorectal carcinoma cases (19).

A noteworthy study about the relationship of vitamin D levels with colorectal carcinoma was performed across the Europe in European Investigation into Cancer (EPIC) study. In this study 1248 colorectal carcinoma cases were matched with 1248 controls. Lower levels were found to be mildly related to increased cancer risk compared to the group with serum vitamin D levels 20-29 ng/mL (for levels < 10 ng/mL OR was 1.32 while for levels 10-19 OR was 1.28). Furthermore higher levels were found to be related to decreased relative cancer risk (for levels between 30-39 OR was 0.88and for levels > 40 ng/mL OR was 0.77) (20). From this study the optimum protective dose can be inferred to be 30 ng/mL. But some studies suggest that there is a 'U' shaped relationship between vitamin D levels and the cancer risk and optimal protective dose is referred as 16-32 ng/ml (21).

In 2011, the prominent studies investigating the relationship between serum 25 hydroxyvitamin D levels and colorectal cancer risk were reevaluated in a metaanalysis. All but one study showed an inverse relationship (22).

As we come to the relationship between serum vitamin D levels and colorectal adenomas results are more conflicting. Some studies are cross sectional while some others are concerned about adenoma recurrence making interpretation of the results even more difficult. Similar issues regarding the study designs are also true for adenoma studies. While some studies only used sigmoidoscopy for screening, the others only concerned one gender for investigation.

In a receny study patients with adenomatous and hyperplastic polyps were compared with control colonoscopy group. In this study no significant difference was found between the groups in terms of 25 hydroxyvitamin D (23). Another study similar to ours was published from Korea. In this study 143 colorectal adenoma cases were compared with 143 age and sex matched control patients. Median age of the patients was 58. Mean 25 hydroxyvitamin D level was 20.0 ± 11 ng/ml in adenoma group while it was 25.0 ± 20.0 ng/ml in the control group. The difference was statistically significant. This study was also performed during winter. Furthermore this risk reduction was more pronounced in proximal colon (24). Most studies about the adenoma risk were conducted on patients with gastrointestinal symptoms. This study was

Table 5. — **Comparison of some laboratory values between cancer and noncancer patients**

Variable	Cancer patients (n = 16)	Noncancer group (n = 295)	P value
Age	64,12 ± 10,36	53.4 ± 12.4	0,00
Hemoglobin	12,23 ± 2,41	14,50 ± 1,94	0,001
Albumin	4,11 ± 0,58	4,73 ± 0,40	0,001
Vitamin D	15,42 ± 18,77	13,12 ± 7,62	0,376
PTH	67,03 ± 59,41	57,18 ± 26,17	0,22

Table 6. — **Distribution of patients according to vitamin D quartiles***

Quartile of 25 (OH)D3*	Number of Cases	Number of Controls	Multivariate Analysis	
			OR (95% CI)	P
1st quartile (< 8.56 ng /ml)	24	48	1	
2nd quartile (8.56-10.11 ng /ml)	20	53	0.48 (0.24-0.98)	0.04
3rd quartile (10.12-14.53 ng /ml)	25	48	0.51 (0.25-1.03)	0.06
4th quartile (≥ 14.54 ng /ml)	27	46	0.69 (0.36-1.36)	0.28

* : Vitamin D levels of 4 patients were unavailable.

the first evaluating patients referred for screening colonoscopy.

Literature about parathyroid levels and colon cancer is relatively scarce. In patients with primary hyperparathyroidism colon carcinoma is long known to be more frequent (25). The reasons for the increased risk can be multiple : 1) Malignant colonic cells have been shown to express PTH receptor (26) 2) PTH can increase the hepatic production of insulin-like growth factor-1 (IGF-1) (27). 3) PTH can decrease luminal calcium concentrations by increasing calcium absorption. Calcium is a protective molecule for colonic cells from luminal cytotoxic agents. It also regulates cell cycle (28,29)

EPIC trial also investigated the relationship between serum parathyroid hormone levels and colorectal carcinoma risk. In the whole group serum parathyroid hormone levels > 65 ng/L were associated with increased colorectal carcinoma risk (RR : 1.41, 95 CI : 1.03-1.93) (30).

Although known as a ''sunny'' country people living in Turkey are generally vitamin D deficient. In a study concerning pregnant women in İzmir, one of the sunniest cities in Turkey, mean vitamin D levels were 11.5 ± 5.4 ng/mL. %50 of women had serum vitamin D levels < 10 ng/mL and in 90% of women serum levels were below 20 ng/mL (31). Also in another study conducted in western Turkey mean vitamin D levels in adult patients were found to be 16.9 ± 13.09 ng/mL, 75% of people were vitamin D deficient (< 20 ng/mL) (32). It is not known however this vitamin D deficient state would cause increased incidence of colorectal polyps or carcinomas. To our knowledge no study performed investigating the relationship between colorectal polyps or carcinomas and vitamin D and PTH levels in Turkish people was performed.

In this present study we aimed to determine whether serum vitamin D and PTH levels are related with colorectal polyp or carcinoma risk in patients undergoing colonoscopy procedure. The time period was chosen to be relatively short to be able to include patients during winter season as most of the studies showing a relationship were conducted during the winter months. We did not find any significant relationship between serum vitamin D or PTH levels and colorectal polyps or carcinomas. Different from most of the previous studies we tried to stratify colorectal polyps into high and low risk polyps however analyses did not show any significant relationship between neither of these hormones. Reasons for this observation can be multiple. First vitamin D deficiency is common in central Anatolia region since serum levels of vitamin D in polyp or control groups are around 12-14 ng/mL. This might have prevented any relation to be detected. Moreover, one measurement of serum vitamin D levels may not be reflecting long term vitamin D status. Being a cross sectional study, it is not helpful about giving information about long term follow up of the patients. We believe that prospective studies with longer follow up period could end up with different results.In addition our colorectal cancer group was relatively small. Extension of the study in colorectal cancer patients may reveal difference between the groups. Considering all of these limitations larger scale longitudinal studies with longer follow up are needed to clarify the relationship between colorectal polyp and carcinoma risk and serum vitamin D and PTH levels.

No potential conflict of interest relevant to this article was reported.

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