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Original Article

# Circulating level of 25(OH)$D_3$ with risk factors of asymptomatic adenoma and proximal non-adenoma colorectal polyps

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ABSTRACT

*Background:* An inverse association between circulating vitamin D and adenoma risk has been reported, but less is known about proximal inflammatory-hyperplastic polyps.
*Purpose:* To investigate circulating 25(OH)$D_3$ and risk factors of proximal inflammatory-hyperplastic and adenoma colorectal polyps.
*Methods:* From January 2017 to June 2019, consecutive asymptomatic average-risk participants undergoing initial screening colonoscopy. Questionnaires provided information on colorectal polyp risk factors, and plasma samples were assayed for 25-Hydroxyvitamin-D – 25(OH)$D_3$. The colorectal polyps were assessed, and medical history and demographic data were obtained from each patient.
*Results:* Of the 220 asymptomatic subjects, the prevalence of proximal inflammatory-hyperplastic polyps and adenoma polyps were 16.8%; 18.1% and 22.2%, respectively. Multivariate analysis revealed that low vitamin D (25(OH)$D_3$ < 18 ng/mL, OR = 3.94; 95% CI: 1.81–9.51) and current/former smoking (OR = 6.85; 95% CI: 2.98–15.70), high body mass index (BMI > 24, OR = 5.32, 95% CI: 2.62–4.71) were independent predictors for proximal inflammatory-hyperplastic colorectal polyps (non-adenoma). Low vitamin D (25(OH)$D_3$ < 18 ng/mL, OR = 7.75; 95% CI: 3.19–18.80) and current/former smoking (OR = 3.75; 95% CI: 1.30–10.81), age over 60 years old (OR = 2.38, 95% CI: 1.02–5.57), were independent predictors for adenoma colorectal polyps.
*Conclusion:* Low vitamin D and smoking are common risk factors for both adenomatous and proximal inflammatory hyperplastic polyps. Old age and BMI are additional risk factors for the development of adenomatous and non-adenomatous colorectal polyps.



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## Níveis circulantes de 25(OH)D3 com fatores de risco de adenoma assintomático e pólipos colorretais proximais sem adenoma

*Palavras-chave:*
25(OH)D3 circulante
Fatores de risco
Adenoma
Pólipo proximal
Assintomático

RESUMO

*Justificativa:* Uma associação inversa entre a vitamina D circulante e o risco de adenoma foi relatada, mas há pouco conhecimento sobre os pólipos hiperplásico-inflamatórios proximais.

*Objetivo:* Investigar os níveis circulantes de 25(OH)D3 e os fatores de risco de pólipos colorretais hiperplásico-inflamatórios e pólipos adenomatosos no colo proximal.

*Métodos:* De janeiro de 2017 a junho de 2019, participantes consecutivos, de risco médio, assintomáticos e submetidos à colonoscopia para triagem inicial foram selecionados. Os questionários forneceram informações sobre os fatores de risco para pólipo colorretal, e as amostras de sangue foram analisadas para identificar a concentração plasmática de 25-Hydroxyvitamin-D-25(OH)D3. Os pólipos colorretais foram avaliados e a história médica e os dados demográficos foram obtidos de cada paciente.

*Resultados:* Nos 220 indivíduos assintomáticos, a prevalência de pólipos no colo proximal, tanto hiperplásico-inflamatórios quanto adenomatosos, foi de 16.8%, 18.1% e 22.2%, respectivamente. A análise multivariada revelou que nível baixo de vitamina D (25(OH)D3 < 18 ng/mL, OR = 3,94; IC 95%: 1,81–9,51), tabagismo atual/anterior (OR = 6,85; IC 95%: 2,98–15,70) e alto índice de massa corporal (IMC > 24, OR = 5,32, IC 95%: 2,62–4,71) foram preditivos independentes para pólipos colorretais hiperplásico-inflamatórios proximais (não adenomatosos). Nível baixo de vitamina D (25(OH)D3 < 18 ng/mL, OR = 7,75; IC 95%: 3,19–18,80), tabagismo atual/anterior (OR = 3,75; IC 95%: 1,30–10,81) e idade acima de 60 anos (OR = 2,38, IC 95%: 1,02–5,57) foram preditivos independentes para pólipos colorretais adenomatosos.

*Conclusão:* Nível baixo de vitamina D e tabagismo são fatores de risco comuns para pólipos tanto adenomatosos quanto hiperplásico-inflamatórios proximais. Idade avançada e IMC são fatores de risco adicionais para o desenvolvimento de pólipos colorretais adenomatosos e não adenomatosos.



## Background

In 2006, colorectal carcinoma in Indonesia ranked third of all carcinoma cases found in men, and second in women, with 1.8/100.000 ratio, this number increased to 6 cases/100.000 individuals in 2012 and along with deaths related to colorectal carcinoma has reached 10% of all types of cancer.[1] Cause and death due to colorectal carcinoma can be prevented by proper diet planning, lifestyle modification, increased of vitamin D serum and colonoscopy screening according to the suggested recommendation.[2] In Indonesia, despite its tropical climate and abundance of sunlight does not guarantee an adequate intake of vitamin D, with plenty of cases found with vitamin D deficiency, especially in the elderly.[3]

The ecology and epidemiology data on the human for the last 2 decades shows that there is a negative correlation between sunlight exposure to the skin surface and the risk of colorectal carcinoma.[4,5] Cross-sectional and Case-control study also shows the relation between vitamin D deficiency and the risk of colorectal carcinoma.[6,7] While in cases of neoplastic colorectal polyp the result is inconsistent.[8] The American Association of Clinical Endocrinology, citing the historic definition by the Institute of Medicine, recommends the use of 25(OH)D as the diagnostic test of choice to evaluate at-risk individuals for vitamin D status. They have defined three thresholds of purported clinical significance, labeling "deficiency" at a level of <20 ng/mL, "insufficiency" is defined as the range between 21 and 29 ng/mL and "replete" as levels measuring >30 ng/mL.[9] Generally, the development of polyp to colorectal carcinoma takes a long time, which takes around 10–15 years to become colorectal carcinoma.[10] It is estimated that 20–53% of American adults above 50 years old have adenoma polyp, Hyperplastic polyp may develop into colorectal carcinoma via serrated adenoma.[10] The progress of a proximal hyperplastic serrated polyp and adenomatous polyp into colorectal carcinoma is continuously researched, with several factors of risks and those that related to the polyp development are genetic factors: epigenetic, age, family history, size of polyp (traditional risk factor); and vitamin D, calcium, Body Mass Index (BMI), smoking, eating habit, microbiota, micronutrients and physical activity (personalized risk factor).[11–15]

Currently, the risk factors for developing proximal hyperplastic polyps remain unclear, and the results of risk factors for adenomatous polyp in Asian countries are quite conflicting.[22] Indonesia, as a tropical country with plenty of sunlight, does not guarantee an adequate intake of vitamin D, with many cases of vitamin D deficiency found in the elderly.

Previous observational studies have reported an inverse association between 25(OH)$D_3$ concentration and risk of colorectal adenomas.[16,17] Little is known about the relationship between vitamin D and proximal hyperplastic polyps. A prospective analysis provides the opportunity to obtain a serum 25(OH)$D_3$ level at the time of colonoscopy, account for effects of previously described confounding variables, and test the hypothesis that a low vitamin D level is associated with an increased risk of colorectal proximal hyperplastic and adenomatous polyps.

## Patients and methods

### *Study participants*

We conducted a cross-sectional study using a consecutive series of subjects who underwent colonoscopy from January 2017 to June 2019, were invited to participate in this study. The study protocol was approved by institutional review boards of faculty of Medicine at Diponegoro University, all participants provided written informed consent. The eligible subjects were excluded if they reported symptoms of lower gastrointestinal tract disease, including rectal bleeding, marked change in bowel habits, or lower abdominal pain that would normally require medical evaluation. Other exclusion criteria were current participation in other studies, history of disease of the colon, prior colonic surgery, and colorectal examination within the previous 10 years.

### *Study design*

All subjects were carefully queried regarding the presence of abdomen symptoms in the previous 1 month, and subjects who responded negatively were classified as asymptomatic subjects and enrolled for this study. All the participants received anthropometric and blood biochemical tests, which included fasting serum 25(OH)$D_3$, and received total colonoscopy. Colonoscopies were performed by one experienced endoscopists with the Fujinon 4450 FICE EC 590 WR (Fujinon Corp., Tokyo, Japan) after the subjects had fasted overnight. Bowel preparation was performed with oral laxatives using the same protocol as that used for diagnostic colonoscopy. The patients were carefully examined for a colorectal mucosal lesion. During a colonoscopy, the location, size, and number of colorectal adenomas were recorded. The polyp size was estimated using open-biopsy forceps. All visible polyps were removed and examined histologically by the pathologist. The pathology types of colorectal polyps were subsequently categorized into inflammatory, hyperplastic and adenomatous polyps. Any result of a tissue biopsy, which was read as positive for adenoma of any grade, was counted as adenoma, whereas simple inflammatory-hyperplastic polyps, were considered non-adenoma.

### *Statistical analysis*

The Chi-square test or Fisher's exact test was employed to investigate the relationships between the rate of colorectal polyps and clinical characteristics. These variables included the following: gender; age; educational status; BMI; NSAID use; family history of colorectal cancer; smoking status; exercise habit, and metabolic syndrome. A p-value less than 0.05 was considered significant. Significant variables revealed by univariate analysis were subsequently assessed by a stepwise logistic regression method to identify independent clinical factors predicting the presence of colorectal polyps in asymptomatic subjects.

**Table 1 – Demographics and endoscopic findings of asymptomatic colorectal polyps subjects (n = 220).**

| Clinical characteristics | |
|---|---|
| Age, mean (SD) yr | 59.3 ± 5.50 |
| Gender, n (%) | |
| Male | 111 (50.5%) |
| Women | 109 (49.5%) |
| Body mass index (kg/m$^2$) | 24.4 ± 1,21 |
| Family history of colon polyp, n (%) | |
| No | 54 (24.5%) |
| Yes | 166 (75.5%) |
| Smoking | |
| Current | 35 (15.9%) |
| Former | 51 (22.2%) |
| No | 134 (60.9%) |
| Physical activity | |
| No | 14 (6.4%) |
| ≤3 times per week | 131 (59.5%) |
| >3 times per week | 75 (34.1%) |
| Educational level, n (%) | |
| Middle school | 23 (10.5%) |
| High school | 152 (69.5%) |
| University | 44 (21.0%) |
| Colonoscopic findings, n (%) | |
| Normal | 121 (55.0%) |
| Colorectal polyps | 99 (45.0%) |
| Pathological type | |
| Inflamation polyp (proximal) | 37 (16.8%) |
| Hyperplastic polys (proximal) | 40 (18.2%) |
| Adenomatous polyp (proximal and distal) | 49 (22.2%) |
| Location | |
| Proximal colon | 78 (61.9%) |
| Distal. colon | 22 (17,5%) |
| Only both | 26 (20,6%) |
| Serum 25(OH)$D_3$, Mean (SD) | 18.9 ± 4.74 |

## Results

### *Patient demographics and colonoscopy characteristics*

From January 2009 to December 2011, 1899 asymptomatic subjects mean age, 59.3 ± 5.50 years; age range, 48–76 years; male/female, 111/109) were recruited for this study. Among them, (45.0%) had colorectal polyps (Table 1). The prevalence of inflammatory, hyperplastic polyps, and adenomatous polyps were 16.81%, 18.18% and 22.27%, respectively.

### *Risk factors for the development of colorectal proximal non-adenoma polyps*

Table 2 shows the results of univariate analysis for the risk factors for the development of proximal non-adenoma polyps. Low serum 25(OH)$D_3$, current/former smoking and high BMI

**Table 2 – Univariate analysis of the risk factors for the development of colorectal non-adenoma polyps (n = 181).**

| Principal parameter | Non-adenoma n = 60 | Normal n = 121 | p-value |
|---|---|---|---|
| Gender, n (%) | | | 0.999 |
| Male | 31 (31.7%) | 61 (50.4%) | |
| Female | 29 (48.3%) | 60 (49.6%) | |
| Age (years) | 61.0 ± 5.7 | 57.8 ± 4.5 | 0.012 |
| BMI | 24.7 ± 1.0 | 24.1 ± 1.3 | 0.002 |
| Family history of colon polyp, n (%) | | | 0.736 |
| No | 16 (26.7%) | 28 (23.1%) | |
| Yes | 44 (73.3%) | 97 (76.9%) | |
| Smoking | | | 0.000 |
| Current | 22 (36.7%) | 10 (8.3%) | |
| Former | 14 (23.3%) | 26 (21.5%) | |
| No | 24 (40.0%) | 85 (70.2%) | |
| NSAID use, n (%) | | | 0.084 |
| No | 45 (75.0%) | 104 (86.0%) | |
| Yes | 15 (25.0%) | 17 (14.0%) | |
| Physical activity | | | 0.673 |
| ≤3 times per week | 36 (60.0%) | 78 (64.5%) | |
| >3 times per week | 24 (40.0%) | 43 (35.5%) | |
| Educational level, n (%) | | | 0.166 |
| Middle school | 8 (13.3%) | 8 (6.6%) | |
| High school | 44 (73.4%) | 90 (74.4%) | |
| University | 8 (13.3%) | 23 (19.0%) | |
| Metabolic syndrome, n (%) | | | 0.532 |
| No | 58 (96.7%) | 1 (0.8%) | |
| Yes | 2 (3.3%) | 120 (99.2%) | |
| Serum 25(OH)D3 | 17.4 ± 3.05 | 20.4 ± 4.59 | 0.000 |

BMI, Body Mass Index, indicating weight in kg divided by body surface area; NSAID Nonsteroid Anti-Inflammatory Drug.

**Table 3 – Independent risk factors for the development of proximal non-adenoma polyps.**

| Clinical variable | Coefficient | SE | OR (95% CI) | p-value |
|---|---|---|---|---|
| Age > 60 y/o | 0.610 | 0.414 | 1.84 (0.81–4.14) | 0.140 |
| BMI > 24 kg/m$^2$ | 1.729 | 0.511 | 5.32 (2.62–4.71) | 0.000 |
| Current/former smoking | 1.953 | 0.429 | 6.81 (3.03–16.35) | 0.000 |
| Serum 25(OH)$D_3$ < 18 ng/mL | 1.423 | 0.423 | 4.15 (1.81–9.51) | 0.001 |

CI, Confidence Interval; BMI, Body Mass Index, indicating weight in kg divided by body surface area (Body Mass Index).

were significantly associated with non-adenoma polyp formation. Multivariate analysis with stepwise logistic regression showed that low serum 25(OH)$D_3$ (<18 ng/mL), current/former smoking and high BMI (>24 kg/m$^2$) were independent predictors for asymptomatic non-adenoma colorectal polyps (Table 3).

### *Risk factors for the development of colorectal adenoma polyps*

Table 4 displays the results of univariate analysis for the risk factors for developing colorectal adenoma polyps. Low serum 25(OH)$D_3$, old age, high BMI and current/former smoking were significantly associated with adenoma polyp formation. Multivariate analysis revealed that lower serum 25(OH)$D_3$ (<18.1 ng/mL), age over 60 years old, and current/former smoking were independent predictors for asymptomatic adenoma polyps (Table 5).

## Discussion

The increased understanding of vitamin D role shows that the role of vitamin D is not limited to bone disease, but also its connection to plenty of other chronic diseases such as colorectal carcinoma and adenoma polyp. The colon may produce 1α,25(OH)$_2$D$_3$ from 25(OH)D$_3$ locally to control the genes which prevent and suppress carcinogenesis.[18,19] 1α,25(OH)$_2$D$_3$ is an active biological form of vitamin D, with circulation time in blood around 4–6 h, and the number of concentrated 1α,25(OH)$_2$D$_3$ which is thousands less than 25(OH)D$_3$.[20] In addition, of the two forms of 25(OH)D measured in blood (D$_2$ and D$_3$), we used 25(OH)D3 as the primary measure of the vitamin D status in our analysis. Although 25(OH)D$_2$ contributes to the total circulating 25(OH)D, we expect this contribution to be minimal.[21,30]

To explain the relation between vitamin D and adenoma colorectal polyp, one case-control studies,[22] and two cohort

**Table 4 – Univariate analysis of the risk factors for the development of colorectal adenoma polyps (n = 160).**

| Principal parameter | Adenoma n = 39 | Normal n = 121 | p-value |
|---|---|---|---|
| Gender, n (%) | | | |
| Male | 19 (48.7%) | 61 (48.7%) | 0.854 |
| Female | 20 (51.3%) | 60 (51.3%) | |
| Age (years) | 61.5 ± 6.4 | 57.8 ± 4.5 | 0.002 |
| BMI | 24.8 ± 1.3 | 24.2 ± 1.2 | 0.012 |
| Family history of colon polyp, n (%) | | | |
| No | 10 (25.6%) | 28 (23.1%) | 0.750 |
| Yes | 29 (74.4%) | 93 (76.9%) | |
| Smoking | | | |
| Current | 7 (17.9%) | 2 (1.7%) | 0.001 |
| Former | 4 (10.3%) | 11 (9.1%) | |
| No | 28 (71.8%) | 108 (89.2%) | |
| NSAID use, n (%) | | | |
| No | 28 (71.8%) | 106 (87.6%) | 0.060 |
| Yes | 11 (28.2%) | 15 (12.4%) | |
| Physical activity | | | |
| ≤3 times per week | 28 (71.8%) | 77 (63.6%) | 0.460 |
| >3 times per week | 11 (28.2%) | 44 (36.4%) | |
| Educational level, n (%) | | | |
| Middle school | 7 (17.9%) | 8 (6.6%) | 0.011 |
| High school | 19 (48.7%) | 89 (73.6%) | |
| University | 13 (33.4%) | 37 (19.8%) | |
| Metabolic syndrome, n (%) | | | |
| No | 33 (84.6%) | 119 (98.3%) | 0.001 |
| Yes | 6 (15.4%) | 2 (17%) | |
| Serum 25(OH)$D_3$ | 16.2 ± 4.3 | 201 ± 4.9 | 0.000 |

BMI, Body Mass Index, indicating weight in kg divided by body surface area; NSAID, Nonsteroid Anti-Inflammatory Drug.

**Table 5 – Independent risk factors for the development of adenoma polyps.**

| Clinical variable | Coefficient | SE | OR (95% CI) | p-value |
|---|---|---|---|---|
| Age > 60 y/o | 0.870 | 0.432 | 2.38 (1.02–5.57) | 0.044 |
| BMI > 24 | 0.854 | 0.500 | 2.34 (0.86–6,36) | 0.093 |
| Current/former smoking | 1.324 | 0.540 | 3.75 (1.30–10.81) | 0.014 |
| Serum 25(OH)$D_3$ <18 ng/mL | 2.045 | 0.452 | 7.75 (3.19–18.80) | 0.000 |

CI, Confidence Interval; BMI, Body Mass Index, indicating weight in kg divided by body surface area (Body Mass Index).

studies that use subject selected at random on chemoprevention experiment showed that there is a relation/association between adenoma and concentration of serum 25(OH)$D_3$.[23,24] The majority of the previous studies investigated only the risk of distal adenomatous colorectal on a specific population, with the most participant on both of these studies were symptomatic or was a high-risk individual who required colonoscopy evaluation. The research that we conducted was focused on serum 25(OH)$D_3$; with results of serum 25(OH)$D_3$ in normal colonoscopy group 20.4 ± 4.5 ng/mL, adenoma polyp 16.2 ± 4.3 ng/mL and non-adenoma proximal polyps 17.4 ± 3.3 ng/mL (Tables 2 and 3) for individuals with asymptomatic who undergone first colonoscopy, while research by Hong SN in Korea found adenomatous group 20 ± 11 ng/mL and control group 25 ± 2 ng/mL.[8] Risk estimation of adenoma polyp incidence in this research is that if the serum of 25(OH)$D_3$ < 18 ng/mL will have a risk of colorectal polyp 7.7 times compared to serum 25(OH)$D_3$ ≥ 18 ng/mL and 3.3 for non-adenoma polyp. Jacob et al. reported that serum 25(OH)$D_3$ below 20 ng/mL increases the frequency of polyp incident.[34] McCullough et al. reported that serum 25(OH)D3 below 12 ng/mL elevated risk of colorectal carcinoma by 31% (OR = 1.31, 95% CI: 1.05–1.6) while serum 25(OH)D3 above 30 ng/mL lowered the risk by 19% (OR = 0.81, 95% CI: 0.67–0.99).[25] Prospective data are needed to distinguish between association or a causative role of vitamin D in the pathogenesis of neoplastic polyps.

In this study, smoking is an independent risk factor for developing both adenoma and proximal non-adenoma polyps with odds ratios between 3.75 and 6.81, respectively. In previous studies, cigarette smoking has consistently been a risk factor for colorectal adenoma.[13,26,27] Several known or probable human carcinogens are present in cigarette smoke, including polycyclic amines, aromatic amines, and benzene.[13] Martinez et al. reported that APC and KRAS mutations were found in 36% and 61% of the hyperplastic polyps of smokers but were absent in nonsmokers.[28] Recent studies also demonstrated that smoking is associated with DNA hypermethylation, which has been implicated in the pathogenesis of hyperplastic polyp.[29]

This study revealed a strong positive association between BMI and both adenoma and proximal non-adenoma colorectal polyps. Previous studies indicate a higher BMI considered as overweight or obesity has revealed associations with the risk of colorectal adenomas and hyperplastic polyps.[30,31] High BMI levels have been more strongly associated with advanced lesions than with no advanced, tubular adenomas.[32] The mechanism by which obesity increases the risk of asymptomatic colorectal polyps is unknown. Possible explanations include the inflammation, oxidative stress, and insulin resistance in obese subjects.[33]

Our study also showed that old age was independent predictors for developing adenomatous colorectal polyps in asymptomatic subjects. Advanced age is a well-known risk factor for the development of colorectal adenomas and advanced neoplasm. In this study, age over 60 years old was an independent predictor for developing asymptomatic colorectal adenomatous polyp whereas it was not a risk for the development of hyperplastic polyp. The findings were supported by a previous study.[34] Many recommendations suggest that those aged 50 years old and more to have a colonoscopy screening since there are plenty of colorectal carcinoma cases found in those aged more than 50 years old The trend of increase in colorectal carcinoma for below 50 years old patient, which leads to the American Cancer Society (ACS) recommendation to do colonoscopy screening at 45 years old, is still debatable.[35]

Despite its contributions, this study had certain limitations. First, the self-selection bias of the population in this trial was possible because all enrolled subjects had undergone self-paid health examination and likely had better economic status than the general population in Semarang–Indonesia (Table 1). Second, the studied subjects may differ from the subjects in primary care hospitals because our hospital is a tertiary care center.

## Conclusion

In conclusion, the prevalence of colorectal polyps in asymptomatic subjects is 45.0% in Semarang–Indonesia. Low serum 25(OH)$D_3$ and smoking are common risk factors for both adenomatous and proximal non-adenoma polyps. Advanced age and BMI are additional risk factors for the development of adenoma and proximal non-adenoma polyps of colorectal.

## Conflicts of interest

The authors declare no conflicts of interest.

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