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Circulating Concentrations of C-Peptide and Colorectal Adenoma

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Hyperinsulinemia may increase the risk of colorectal neoplasia because of its mitogenic and antiapoptotic properties, which have a growth-promoting effect. We examined the association between circulating concentrations of C-peptide, a biomarker of insulin secretion, and colorectal adenoma prevalence in a case-control study of Korean adults. A total of 364 participants (112 cases and 252 controls) were included. Participants who underwent a colonoscopy completed questionnaires and provided blood samples. We used multivariate logistic regression models to obtain odds ratios (ORs) and 95% confidence intervals (CIs) for colorectal adenoma. Circulating concentrations of C-peptide were not associated with colorectal adenoma; the multivariate OR (95% CI) was 0.95 (0.51-1.75) comparing the highest tertile with the lowest tertile (p for trend = 0.91). When we used a conditional logistic regression model by fasting status and sex matching, there was still no association (OR = 0.92; 95% CI = 0.43-1.99) when comparing the highest tertile with the lowest tertile. We observed no association between circulating concentrations of C-peptide and colorectal adenoma prevalence in Korean adults.

Key Words: C-peptide, Colorectal adenoma, Hyperinsulinemia

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Introduction

Colorectal cancer is the third most common type of cancer in Korea [1]. The incidence rate of colorectal cancer consistently increased by 5.9% annually from 1999 to 2010 [1]. Several epidemiologic studies suggest that obesity, physical inactivity, and the Western dietary pattern—rich in refined grain and sugar, red/processed meat and energy-dense food—are associated with an increased risk of colorectal cancer [2]. The potential hypothesis suggested that these lifestyles may increase colorectal tumorigenesis through alterations in the metabolism of insulin and insulin-like growth factors (IGFs) [3,4]. Insulin is a known key regulator of energy metabolism and may increase the bioactivity of IGF-1 by inhibiting the production of the IGF-binding protein (BP)-1 and perhaps IGFBP-2 [5]. The anabolic signals of insulin and IGF-1 can promote tumor development by inhibiting apoptosis and increasing cell proliferation [6,7].

C-peptide is secreted by beta cells on an equal molar basis with insulin; therefore, it is regarded as a marker of insulin secretion [8]. Because of the possible link between hyperinsulinemia and cancer risk, several epidemiologic studies have explored whether circulating concentrations of C-peptide could be a potential predictor of several cancer risks, including cancers of the breast [9], prostate [10], pancreas [11] and endometrium [12]. A recent meta-analysis of prospective studies suggested evidence of an increased risk of colorectal neoplasia with increased C-peptide [13], but only a few Asian studies examined the association with colorectal cancer [2,14,15]. For colorectal adenoma, the evidence linking hyperinsulinemia is more limited.

Therefore, we examined whether circulating concentrations of C-peptide were related to colorectal adenoma in Korean adults.

Materials and Methods

Study Population and Case Ascertainment

The study participants were 382 men and women aged 45-71 years who underwent colonoscopy from August 2011 to September 2012 and provided blood samples after re-invitation at a university hospital in Daegu, city of Korea. Participants were excluded if they had any type of cancer (n = 14) or had an energy intake beyond the mean energy intake by more than three standard deviations (n = 4). As a result, a total of 364 participants were included.

The sizes, subtypes, and number of colorectal adenomas were determined through a colonoscopy and pathological examination. Polyps were classified as adenomatous, hyperplastic, or other non adenomatous. Only adenomatous polyps were included as cases. We included both first and recurrent adenomas (n = 17; 4.7%). Adenomas were classified to the right colon if participants had at least one adenoma at the cecum, ascending colon, hepatic flexure, or transverse colon. Adenomas were classified to the left colon if participants had at least one adenoma at the splenic flexure, descending colon, sigmoid colon, or rectum [16]. Of 364 participants, a total of 112 cases and 252 controls were included in the analysis. To minimize the influence of fasting status or sex, we performed 1:1 matching by fasting status and sex and examined the association in the additional analysis. Written informed consent was obtained from all participants. This study was approved by the Institutional Review Board of Daegu Catholic University Medical Center.

Measurement of C-peptide

Blood samples were drawn from the participants, centrifuged, and sent on ice to the Neodin medical institute between January and February 2013. Serum concentrations of C-peptide were measured by the electrochemiluminescence immunoassay (ECLIA) method by using a Cobas 6000 at Neodin medical institute (Seoul, South Korea). All laboratory technicians were blinded to the case status. The intra-assay coefficient of variations (CV) was 2.5-3.5%.

Assessment of Lifestyle and Anthropometric Factors

Participants were asked about their demographic characteristics including the type, frequency, and duration of exercise, alcohol and tobacco use, family history of colorectal cancer, menopausal status (in women only), use of hormone replacement therapy (in women only), nutritional supplement use, and dietary intake. Participants' height and weight were measured by using X-scan plus II professional (Jawon medical, Gyeongsan, South Korea). The waist circumference was measured at the midpoint between the lower margin of the rib cage and the upper margin of the iliac crest. The body mass index (BMI) was calculated by dividing the weight in kilograms by the square of height in meters. The metabolic equivalent of task (MET)-hours per week was calculated for physical activity, which was assessed using a list of questionnaire items similar, but modified, with the Minnesota Leisure Time Physical Activity Questionnaire.

Statistical Analysis

For participants' characteristics, we calculated the means and standard deviations (SD) of continuous variables and the frequencies and percentages of categorical variables. Differences in characteristics were calculated by either the t-test for continuous variables or chi-square test for categorical variables. We used logistic regression models to obtain odds ratios (ORs) and 95% confidence intervals (CIs) for colorectal adenoma. We adjusted for age (years, continuous), sex (men, women), waist circumference (cm, continuous), fasting status (<4, 4-8, >8 hours, unknown), alcohol consumption (nondrinker, past drinker, ≤4 drinks per month, ≥2 drinks per week), and pack-years of smoking (never, 1-<20, 20-<30, ≥30). Because additional adjustment for family history of colorectal cancer, red meat consumption, vegetables and fruits consumption, aspirin use and physical activity did not appreciably alter the association between C-peptide and colorectal adenoma, we

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did not include these factors in the analysis. We also examined whether associations varied by potential effect modifiers. Heterogeneity by each effect modifier was tested by including a cross-product term of the main exposure and interaction terms using the likelihood ratio test. We used the median of each C-peptide category as a continuous variable to test for linear trends. All p values were two-sided, and a p value < 0.05 was considered statistically significant. All analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Table 1 shows the study participants' characteristics by case status. Mean age was 60.3 years for the case group and 59.2 years for the control group. The proportion of men was higher in the case group (50.9%) than the control group (27.4%). Waist circumference was higher among the case group than the control group. The case group was more likely to smoke and drink alcohol, but less likely to use supplements than the control group.

Table 2 presents the multivariate ORs and 95% CIs for colorectal adenoma prevalence according to the tertiles of circulating C-peptide concentrations. We found no statistically significant association between circulating C-peptide concentrations and colorectal adenoma prevalence; multivariate ORs (95% CI)s were 0.77 (0.42-1.43) for the second tertile and 0.95 (0.51-1.75) for the third tertile of C-peptide levels (p for trend = 0.91). The associations remained non-significant when we stratified by sex or right/left colon. When we used a conditional logistic regression model by fasting status and sex matching (1 to 1 ratio matching), no association was observed (multivariate OR = 0.92; 95% CI = 0.43-1.99) when the highest tertile was compared with the lowest tertile. In the additional analysis including 261 participants (82 cases and 179 controls) who had been fasting more than four hours, C-peptide concentrations were not associated with colorectal adenoma (multivariate OR for highest tertile vs. lowest tertile = 0.74, 95% CI = 0.35-1.58). We also further examined whether the associations of circulating C-peptide with colorectal adenoma varied by age, sex, BMI, waist circumference, alcohol drinking status, smoking status, physical activity or red meat intake (Table 3). A lower prevalence of colorectal adenoma was observed among those who had ever smoked but not among those who never smoked (p for heterogeneity = 0.003). Other factors did not modify the associations.

Discussion

Our case-control study found no association between circulating levels of C-peptide and colorectal adenoma prevalence. When we examined the associations among men and women separately, we still found no statistically significant associations. We also found no associations when we stratified into right or left colon. The median values of C-peptide concentration were 4.3 ng/mL among male controls and 3.6 ng/mL among female controls, which were similar to those in the US Hawaiian multiethnic study [17], but higher than those in the Japan Public Health Center-based Prospective study [14].

The current evidence linking hyperinsulinemia to colorectal adenoma has remained inconsistent. A recent meta-analysis of nested case-control studies found an OR of 1.39 (95% CI = 1.04–1.87) for colorectal neoplasia [13] but no association for colorectal adenoma (OR = 1.42; 95% CI = 0.95–2.13) [13]. In this meta-analysis, two studies were included: the Nurses' Health Study, including 380 case-control pairs, found that high concentrations of C-peptide were associated with a risk of distal colorectal adenoma [18], whereas the CLUE II cohort (132 cases, 260 controls) found no association [19]. In the US Hawaiian population study, high plasma levels of C-peptide were statistically significantly associated with a risk of colorectal adenoma [17]. A review of the studies examining C-peptide and colorectal adenoma showed a more pronounced association for men than women [15,20]. However, our study observed no associations among men or women.

Hyperinsulinemia, reflected in high circulating concentrations of C-peptide, may increase cancer risk through promotion of the bioactivity of IGF-1. IGF-1 inhibits apoptosis and promotes proliferation [15]. Additionally, insulin may exert interaction with IGFBPs, which modulates the bioavailability of IGFs. Under low IGFBP levels, IGF mitogenic activity is expected to be high. Insulin decreases IGFBP-1 expression [21] and IGFBP-2 concentrations [22]. Increased bioactivity of IGF-1 partly by inhibiting the production of IGFBP-1 and IGFBP-2 could stimulate tumorigenesis. A direct mitogenic effect by increasing the activity of the Ras protein could be another potential mechanism, given that insulin increases the pool of farnesylated Ras protein [23,24].

The limitations of our study are as follows: the one-time measurement of C-peptide reduced our ability to evaluate associations between long-term circulating concentrations of C-peptide and colorectal adenoma. But C-peptide levels have previously been reported to be relatively stable [25]. We had a

Table 1. Characteristics of patients according to case status[*,†]

	Adenoma (n = 112)	No adenoma (n = 252)	p value[‡]
Age, years	60.3 ± 5.3	59.2 ± 5.0	0.06
Sex			<0.0001
Men	57 (50.9)	69 (27.4)	
Women	55 (49.1)	183 (72.6)	
C-peptide, ng/mL	4.7 ± 3.1	4.2 ± 2.2	0.10
Education			0.25
Elementary school graduate	16 (14.3)	33 (13.2)	
Middle school graduate	25 (22.3)	81 (32.4)	
High school graduate	50 (44.6)	100 (40.0)	
College graduate or above	21 (18.8)	36 (14.4)	
Waist circumference, cm	87.0 ± 7.8	84.2 ± 7.4	<0.001
BMI, kg/m^2			0.21
BMI < 23	33 (29.5)	73 (29.0)	
23 ≤ BMI < 25	32 (28.6)	94 (37.3)	
25 ≤ BMI	47 (42.0)	85 (33.7)	
Family history of colorectal cancer			0.33
Yes	6 (5.4)	8 (3.2)	
No	106 (94.6)	242 (96.8)	
Hormone replacement therapy (HRT)			0.95
Premenopausal status	3 (7.5)	11 (7.3)	
Postmenopausal status without HRT	24 (60.0)	94 (62.7)	
Postmenopausalstatus with HRT	13 (32.5)	45 (30.0)	
Smoking status			<0.0001
Non smoker	56 (50.9)	190 (76.9)	
Past smoker	37 (33.6)	39 (15.8)	
Current smoker	17 (15.5)	18 (7.3)	
Pack years (in smoker)	26.4 ± 13.4	25.9 ± 15.5	0.87
Alcohol drinking			0.01
Never drinker	41 (36.6)	137 (54.4)	
Past drinker	6 (5.4)	8 (3.2)	
Current drinker	65 (58.0)	107 (42.5)	
Physical activity (MET-hr/wk)	29.0 ± 32.0	25.9 ± 24.1	0.87
Supplement use			0.01
Yes	42 (37.5)	130 (51.6)	
No	70 (62.5)	122 (48.4)	
Red meat intake			0.12
≤1 serving/month	11 (10.1)	29 (11.6)	
2-4 servings/month	77 (70.6)	194 (77.3)	
≥2 servings/week	21 (19.3)	28 (11.2)	

BMI: body mass index, HRT: hormone replacement therapy, MET: metabolic equivalent of task.
*Values are presented as mean ± SD or n (column %); †The sum of number of participants for some variables did not match the total sample size because some participants did not provide information on these variables; ‡p values were based on chi-square test for categorical variables and t-test for continuous variables.

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Table 2. Odds ratios and 95% confidence intervals for colorectal adenoma prevalence according to serum concentrations of C-peptide

	Circulating concentrations of C-peptide			
	Tertile 1	Tertile 2	Tertile 3	p for trend
All patients				
Median, ng/mL	2.1	3.9	6.4	
No. of case/control	37/84	31/91	44/77	
Model 1*	1.00	0.73 (0.41-1.31)	1.14 (0.66-1.99)	0.52
Model 2†	1.00	0.77 (0.42-1.43)	0.95 (0.51-1.75)	0.91
Men				
Median, ng/mL	2.1	4.3	7.6	
No. of case/control	18/24	22/20	17/25	
Model 1	1.00	1.43 (0.60-3.40)	0.90 (0.38-2.14)	0.72
Model 2	1.00	1.90 (0.67-5.40)	0.55 (0.19-1.58)	0.22
Women				
Median, ng/mL	2.0	3.6	5.9	
No. of case/control	21/58	12/68	22/57	
Model 1	1.00	0.48 (0.22-1.07)	1.06 (0.53-2.14)	0.68
Model 2	1.00	0.52 (0.23-1.17)	1.13 (0.53-2.41)	0.62
Right colon‡				
Median, ng/mL	2.1	3.8	6.4	
No. of case/control	22/84	22/91	26/77	
Model 1	1.00	0.87 (0.44-1.71)	1.10 (0.56-2.15)	0.72
Model 2	1.00	0.79 (0.38-1.65)	0.89 (0.43-1.87)	0.81
Left colon‡				
Median, ng/mL	2.1	3.9	6.4	
No. of case/control	19/84	16/91	25/77	
Model 1	1.00	0.79 (0.37-1.67)	1.24 (0.62-2.50)	0.47
Model 2	1.00	1.06 (0.47-2.38)	1.05 (0.47-2.32)	0.92

*Adjusted for sex (men, women), and age (continuous); †Adjusted for sex (men, women), age (years, continuous), waist circumference (cm, continuous), fasting status (<4, 4-8, >8 hours, unknown), alcohol drinking (nondrinker, past drinker, ≤4 drinks/month, ≥2 drinks/week), and pack-years of smoking (never, 1-<20, 20-<30, ≥30); ‡A total of 18 cases had both left and right colon adenomas.

small sample size, which may have lowered the power of our analysis. Additionally, the results may not be generalizable to the general Korean population. We cannot rule out the possibility that residual or unmeasured confounding factors remained.

One of this study's strengths is that all participants underwent a colonoscopy, which reduces the possibility of misclassification of outcomes. We were able to adjust for known confounding factors.

Conclusion

We found no association between circulating concentrations of C-peptide and colorectal adenoma in our study. However, further prospective studies with a large population are needed to elucidate the role of hyperinsulinemia in the colorectal adenoma-carcinoma sequence.

Table 3. Odds ratios and 95% confidence intervals according to C-peptide concentrations by major risk factors*

	Circulating concentrations of C-peptide		p for heterogeneity
	<median	≥median	
Age, years†			0.77
<60.0	1.00	0.92 (0.48-1.75)	
≥60.0	1.03 (0.52-2.03)	1.14 (0.57-2.27)	
Sex			0.80
Men	1.00	0.77 (0.36-1.64)	
Women	0.77 (0.29-2.08)	0.91 (0.34-2.46)	
BMI, kg/m^2			0.95
<25	1.00	1.14 (0.53-2.46)	
≥25	0.84 (0.43-1.64)	0.55 (0.27-1.11)	
Abdominal obesity‡			>0.9
Yes	1.00	1.17 (0.41-3.39)	
No	1.30 (0.60-2.82)	1.29 (0.60-2.81)	
Alcohol drinking			0.90
Never drinker	1.00	0.89 (0.43-1.85)	
Ever drinker	1.25 (0.62-2.54)	1.36 (0.67-2.75)	
Smoking status			0.003
Non smoker	1.00	1.40 (0.77-2.57)	
Ever smoker	4.23 (1.51-11.88)	1.95 (0.73-5.21)	
Physical activity, MET-hr/wk†			0.66
<20.9	1.00	1.19 (0.60-2.35)	
≥20.9	1.29 (0.65-2.54)	1.11 (0.57-2.15)	
Red meat intake, servings/wk†			0.68
<2	1.00	1.16 (0.68-1.97)	
≥2	2.53 (1.03-6.26)	1.13 (0.42-3.06)	

BMI: body mass index, MET: metabolic equivalent of task.
*Adjusted for sex (men, women), age (years, continuous), waist circumference (cm, continuous), fasting status (<4, 4-8, >8 hours, unknown), alcohol drinking (nondrinker, past drinker, ≤4 drinks/month, ≥2 drinks/week), and pack-years of smoking (never, 1-<20, 20-<30, ≥30); †Variables were categorized by median values; ‡Abdominal obesity was categorized to yes if waist circumferences were ≥90 cm for men and ≥85 cm for women.

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Conflict of interest

We declare that we have no conflict of interest.

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