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Association of Serum Lipids and Glucose with the Risk of Colorectal Adenomatous Polyp in Men: A Case-Control Study in Korea

Previous studies on life style for colorectal cancer risk suggest that serum lipids and glucose might be related to adenomatous polyps as well as to colorectal carcinogenesis. This case-control study was conducted to investigate the associations between serum lipids, blood glucose, and other factors and the risk of colorectal adenomatous polyp. Male cases with colorectal adenomatous polyp, histologically confirmed by colonoscopy (n=134), and the same number of male controls matched by age for men were selected in hospitals in Seoul, Korea between January 1997 and October 1998. Serum lipids and glucose levels were tested after the subjects had fasted for at least 12 hr. Conditional logistic regression showed that there was a significant trend of increasing adenomatous polyp risk with the rise in serum cholesterol level (p_{trend}=0.07). Increasing trend for the risk with triglyceride was also seen (p_{trend}=0.01). HDL-cholesterol and LDL-cholesterol had increasing trends for the risk, which were not significant. In particular, it was noted that higher fasting blood glucose level reduced the adenomatous polyp risk for men (p_{trend}=0.001). This study concluded that both serum cholesterol and triglyceride were positively related to the increased risk for colorectal adenomatous polyp in Korea. Findings on an inverse relationship between serum glucose and the risk should be pursued in further studies.

Key Words: *Adenomatous Polyp; Body Mass Index; Cholesterol; Colon; Glucose; Risk Factors; Triglycerides*

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INTRODUCTION

Epidemiologic results from the countries with high incidence of colorectal cancer have shown that high fat diet, alcohol, physical inactivity, and obesity are associated with the increased risk of colorectal cancer (1-3). These factors which increase the risk of colorectal cancer are positively related to serum lipids and plasma glucose (4). There has been, however, a controversy on the association of low serum cholesterol with colorectal cancer. Previous studies on life style for colon cancer risk suggest that serum lipids might be related to adenomatous polyps, the presumed precursors of colorectal cancer (5). Studies on the relationship of serum lipids and glucose to colorectal adenomatous polyps may thus resolve this controversy.

Unfortunately, few studies have been done regarding the relationship between such risk factors and colorectal adenomatous polyp in Korea. This case-control study was conducted to investigate the associations between serum lipids, glucose, and other risk factors and the risk of colorectal adenomatous polyp.

MATERIALS AND METHODS

Subject selection

Cases were male patients with adenomatous polyps in the colon or rectum, whose histopathologic diagnosis and subsite information were confirmed through colonoscopy in the two hospitals in Seoul, Korea, from January 1, 1997 to October 31, 1998. Of all the eligible subjects (n=257), patients with self-reported past history of any other malignancies, and those who had liver diseases, heart diseases or a medication history of antihyperlipidaemic agents were excluded (n=96). A total of 134 cases were finally selected.

Controls were chosen in the same hospitals during the same period among males who had undergone the

Table 1. Age and educational attainments of male subjects (134 cases and 134 controls) in a hospital-based case-control study, Seoul, Korea, 1997-1998

Risk factors	Cases (%)	Controls (%)	*p*-values*
Age in years			
- 49	22 (16.4)	22 (16.4)	
50 - 59	47 (35.1)	47 (35.1)	ns
60 +	65 (48.5)	65 (48.5)	
Educational attainments			
primary school	31 (23.1)	28 (20.9)	
middle school	21 (15.7)	29 (21.6)	0.03
high school	30 (22.4)	45 (33.6)	
college +	52 (38.8)	32 (23.9)	

*p-values based on Chi-square test
ns: not statistically significant

colonoscopy and were found as having no polyps (n= 327). Under the same exclusion criteria, the same number of controls matched to case with regards to age (frequency) distribution were selected. General characteristics of the study subjects are seen in Table 1.

Exposure assessment

A questionnaire concerning life style, past history of illnesses, alcohol drinking habit, smoking history, and physical activity was given to each subject at the hospitals. A direct interview was done by a well-trained nurse interviewer under the informed consent from each interviewee. Current height, weight, and hip circumference were directly measured by the nurse.

Blood samples were collected from all the subjects after 12 hr-fasting. All assays were conducted by medical technologists who were not aware of case-control status. Serum cholesterol and triglycerides (Tg) were measured by enzymatic methods (Boehringer Mannheim, FRG), and high density lipoprotein cholesterol (HDL-C) was measured directly with the determiner HDL-C diagnostic kits (Kyowa Medex, Japan) using a Hitachi 747 automatic chemistry analyzer. Low density lipoprotein cholesterol (LDL-C) values were calculated from total cholesterol, high density lipoprotein cholesterol (HDL-C), and triglyceride (Tg) concentrations using the Friedewald formula (6). Serum levels of bile acid and glucose were also measured by the enzymatic method using the same autoanalyzer.

Data analysis

The data set contained 161 matched pairs (134 pairs for males; 27 pairs for females). Risk factors including serum lipids and glucose were compared between cases and controls in unmatched manner, stratifying by sex. Adjusted risks were expressed as odds ratios (OR) and 95% confidence intervals (CI), which were derived from the regression coefficients and standard errors in the conditional logistic regression models. Possible confounders such as age, family history of colorectal cancer, education level, alcohol drinking habit, body mass index, and some serologic markers were included simultaneously in the model (7).

All continuous variables were categorized for the risk estimates as follows: total cholesterol (below 199 mg/dL, 200-249 mg/dL, 250 mg/dL and above), Tg (below 99 mg/dL, 100-149 mg/dL, 150 mg/dL and above), HDL-C (below 43 mg/dL, 44-54 mg/dL, 55 mg/dL and above), LDL-C (below 94 mg/dL, 95-119 mg/dL, 120 mg/dL and above), and glucose (below 90 mg/dL, 91-108 mg/dL, 109 mg/dL and above). The PC-SAS and the EGRET systems were used for the statistical analysis (8, 9).

RESULTS

Table 2 shows the odds ratios of some factors related to the risk of colorectal adenomatous polyp in both sexes. Neither body mass index nor waist-to-hip ratio was related to the risk of adenomatous polyp. Current drinkers had 1.6 time-higher risk of adenomatous polyp (95% CI: 0.99-2.63). Smoking, however, was not associated with the risk. A family history of colorectal cancer was moderately related to the risk of adenomatous polyp with borderline significance (OR=2.54, 95% CI: 0.90-6.52).

Table 3 shows means and standard deviations of the serum lipids and glucose in men. The mean value of serum triglyceride concentration was higher for cases than for controls ($p<0.01$). There were no significant differences between cases and controls with regard to other serum lipids. Meanwhile, the mean value of serum glucose level was much lower for cases than for controls ($p<0.01$).

Table 4 shows adjusted odds ratios for the risk of

Table 2. Risk factors related to colorectal adenomatous polyp in male (134 cases and 134 controls) interviewed at the hospitals in Seoul, Korea, 1997-1998

Risk factors	OR* (95% CI)*	*p* for trend†
Body mass index, kg/m^2		
- 22.1	1.0	
22.2 - 24.9	0.57 (0.21-1.74)	0.08
25.0 +	0.42 (0.18-1.21)	
Waist-to-hip ratio		
- 0.90	1.0	
0.91 - 0.94	2.58 (1.11-6.88)	ns
0.95 +	1.60 (0.56-4.32)	
Cigarette smoking		
no	1.0	
yes	1.32 (0.70-2.16)	
Alcohol drinking		
no	1.0	
yes	1.61 (0.99-2.63)	
Family history of colorectal cancer among the first-degree relatives		
no	1.0	
yes	2.54 (0.90-6.52)	

*Odds ratios were adjusted for all covariates listed in the table, in addition to serum cholesterol, serum glucose and serum triglyceride level, and their 95% confidence intervals were based on regression coefficients and standard errors of the conditional logistic regression models

†*p*-values were derived from the likelihood ratio test for a linear trend based on the logistic regression models

Table 3. Means and standard deviations of serum lipids and glucose levels between 134 colorectal adenomatous polyp cases and 134 controls for men interviewed at the hospitals in Seoul, Korea, 1997-1998

Serum lipids*	Cases Mean±S.D.	Controls Mean±S.D.	*p*-values†
t-C, mg/dL	190.2±34.1	187.0±34.6	ns
Tg, mg/dL	229.3±146.5	147.6±84.7	<0.01
HDL-C, mg/dL	50.1±14.5	52.8±24.8	ns
LDL-C, mg/dL	105.0±25.8	108.7±33.3	ns
glucose, mg/dL	94.7±17.8	113.6±24.9	<0.01

*Total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol

†*p*-values based on Students' t-test

colorectal adenomatous polyp associated with serum lipids and glucose for men. Since the number of females was too small to ensure statistical stability, results on female subjects were not presented. Compared to subjects with low cholesterol concentrations, subjects with intermediate and high concentrations had adjusted odds ratios[OR] of 1.82 (95% CI: 0.88-3.76) and 2.44 (95% CI: 0.59-10.2), respectively. There was a borderline-significant trend of increasing adenomatous polyp risk with the rise of serum cholesterol level in men (p_{trend}= 0.07). The corresponding odds ratios for triglyceride were 1.41 (95% CI: 0.54-3.72) and 2.98 (95% CI: 1.22-7.29) for intermediate and high concentrations, respectively. An increasing trend in the risk with triglyceride was seen (p_{trend}=0.01). Both HDL-cholesterol and LDL-cholesterol had increasing trends for the risk, which were not statistically significant. In particular, it was noted that higher fasting blood glucose level reduced the adenomatous polyp risk (p_{trend}=0.001).

DISCUSSION

This study concluded that serum cholesterol and triglyceride were positively related to the increased risk of colorectal adenomatous polyp in Korea. With comparison to the mean values, level of cholesterol was not different between cases and controls in males. In the trend analysis with categorized variables, however, there was a significant trend in the risk of colorectal adeno-

Table 4. Adjusted odds ratios for the risk of colorectal adenomatous polyp associated with serum lipids and glucose among male subjects interviewed at the hospitals in Seoul, Korea, 1997-1998

Risk factors*	Categories	OR (95% CI)†	*p* for trend‡
t-C, mg/dL	–199	1.0	
	200–249	1.82 (0.88-3.76)	0.07
	250+	2.44 (0.59-10.2)	
Tg, mg/dL	–99	1.0	
	100–149	1.41 (0.54-3.72)	0.01
	150+	2.98 (1.22-7.29)	
HDL-C, mg/dL	–43	1.0	
	44–54	1.26 (0.52-3.08)	ns
	55+	2.23 (0.79-6.72)	
LDL-C, mg/dL	–94	1.0	
	95–119	1.66 (0.50-5.47)	ns
	120+	1.31 (0.38-4.53)	
s-Glucose, mg/dL	–90	1.0	
	91–108	0.43 (0.19-0.84)	0.001
	109+	0.12 (0.05-0.32)	

*Total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol
†Odds ratios were adjusted for age, education, family history of colorectal cancer, alcohol drinking, and body mass index, and their 95% confidence intervals were based on regression coefficients and standard errors of the conditional logistic regression models
‡*p*-values were derived from the likelihood ratio test for a linear trend were based on the logistic regression models

Table 5. Summary of epidemiologic findings on the association between serum glucose and the risk of colorectal cancer (based on 11 case-control studies selected)

Authors (yr)	Areas	Source population	No. of subjects	OR or RR†	Reference No.
Manousos et al. (1983)	Greece	hospital	100	0.35/0.40/0.70	(22)
Miller et al. (1983)	Canada	hospital	348	1.2/1.4/1.0/1.3	(24)
Pickle et al. (1984)	U.S.A.	hospital	58	1.4	(25)
Bristol et al. (1985)*	U.K.	hospital	50	1.6/3.6	(20)
Macquart-Moulin et al. (1986)	France	hospital	399	1.17/1.04/1.28	(26)
La Vecchia et al. (1988)	Italy	hospital	575	1.01/1.22	(27)
Tuyns et al. (1988)*	Belgium	community	453	1.30/1.68/2.31	(21)
Benito et al. (1990)	Spain	community	286	1.44/1.50/1.64	(28)
Bidoli et al. (1992)	Italy	hospital	123	1.5/1.6	(29)
Peters et al. (1992)	U.S.A.	hospital	746	1.0	(30)

*Studies of which 95% confidence intervals did not include 1.0
†Relative risk across categories of sucrose intake

matous polyp with total serum cholesterol increasing. Adjustment for potential confounders including alcohol drinking, body mass, and blood glucose level did not change the odds ratios (Table 4).

Most studies have failed to demonstrate an inverse association of total serum cholesterol with colorectal adenomatous polyp (10-13). However, few studies have found similar findings to ours on positive relationship of serum cholesterol to polyp risk (14, 15). As the controversy on the relationship of low serum cholesterol with colorectal cancer, this issue regarding the association of high cholesterol with the increased risk of colorectal adenomatous polyp should be further investigated.

Current study showed that mean values of triglycerides were significantly different between cases and controls in men. Such increasing trend in the colorectal risk was also observed when the variable was categorized. There have been several studies which reported that serum triglycerides were related to the increased risk of adenomatous polyps (10, 13, 16, 17). Direct evidence of an association between serum triglyceride and adenomatous colorectal polyps has been observed in studies conducted in Toronto (18). Although other studies did not observe such relationship (12), most of the studies reported the positive

association.

It has been suggested that serum triglyceride concentration may be positively associated with bile acid synthesis. Furthermore, serum triglyceride and fecal bile acids may be biologically related to each other (19). An increase in bile acids, synthesized and secreted may provide abundant substrates for the formation of secondary bile acids and therefore promote carcinogenesis in large bowel (13). We measured serum bile acids, instead of fecal bile acids, in some patients, but found no relationship to the risk of colorectal adenomatous polyp.

This study showed that both HDL-cholesterol and LDL-cholesterol showed increasing trends for the risk of colorectal adenomatous polyp, which were not statistically significant. Bayerdorffer et al. reported a positive association between LDL-cholesterol and adenomatous polyps, and a negative association between HDL-cholesterol and the polyps (15). Some researchers found a significant relationship with HDL-cholesterol in their initial report (16). However, they did not find any significant relationship with HDL-cholesterol and LDL-cholesterol in other reports (12). Several authors also found no association of HDL-cholesterol with colorectal polyps (13). It is suggested that colorectal adenomatous polyps may be related to neither HDL-cholesterol nor LDL-cholesterol.

In particular, it is noteworthy in the present study that high blood glucose levels may reduce the colorectal adenomatous polyp risk in men. Most of the previous studies did not observe the risk of colorectal adenomatous polyp with regard to serum glucose. Two studies reported a positive relationship between them (20, 21), and only one study observed an inverse relationship with glucose levels (22), which was similar to our results.

This hospital-based case-control study is internally valid because the cases and controls were selected from the same source population. In addition, the strength of this study lies on the fact that cases, as well as controls, were confirmed as having or not-having the lesion through the same diagnostic procedure of colonoscopy. Therefore, it is highly unlikely that the study results might be affected by misclassification bias. Since both cases and controls visited this hospital to be tested by the colonoscopy, it is hardly feasible for an individual to be differentially allocated to case group or control group. This fact seems to favor to a certain extent an unbiased selection of the study subjects.

The major limitation of the present study is that the number of cases and controls was too small to ensure the comparability between subsites of the colon. In addition, it is known that serum triglycerides usually shows a non-differential misclassification due to intra-individual variation, including physical activity, obesity, and diet, compared to other serum lipids (13). Although potential confounding effects such as obesity and diet have been adjusted in the multivariate analysis, we cannot rule out the possibility of biological variation of triglycerides due to exercise. In addition, the present study has a weakness of time relationship between exposure and disease occurrence. It is possible that serum lipid levels changed subsequently to cases confirmed as having a polyp. In spite of the limitations, it is noticeable that the present study has examined the polyp and their relationship to cholesterol and other serum lipids, which may thus provide a clue to resolve the colorectal cancer-cholesterol controversy.

We concluded that both serum triglyceride and cholesterol are a potential risk factor for colorectal adenomatous polyp in men. Findings on an inverse relationship between serum glucose (which might be a potentially protective factor) and the risk of polyps, should be pursued in further studies. Further large-scale epidemiologic studies should be followed, in which differences in age, gender and subsites are taken into account (23).

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