Increased Pulse Wave Velocity Reflecting Arterial Stiffness in Patients with Colorectal Adenomas

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Summary **The obese patients with diabetes or cardiovascular risk factors are associated with increased risk of colorectal cancer as well as adenomas under the shared pathogenesis related to atherosclerosis. Here we determined the association between increased arterial stiffness and colorectal adenomas incorporating parameters including age, gender, waist circumference, body mass index, lipid profiles, fasting glucose, and blood pressure. Subjects who simultaneously underwent colonoscopies and pulse wave velocity (PWV) determinations between July 2005 and September 2006 were analyzed, based on which the subjects were classified into two groups as patients group with colorectal adenomas ($n = 49$) and control group ($n = 200$) with normal, non-polypoid benign lesions or hyperplastic polyps. Uni- and multi-variate analyses were performed to calculate the odd ratio for colon adenomas. Based on uni-variate analysis, age, waist circumference, body mass index, heart-femoral PWV (hfPWV), and brachial-ankle PWV were significantly associated with adenomas ($p<0.05$) and multiple logistic regression analysis showed that the heart-femoral PWV, waist circumference, and the levels of LDL-C were significant risk factor for colorectal adenoma. However, arterial stiffness did not affect the progression of colon adenoma. The finding that hfPWV, reflecting aortic stiffness, was increased in patients with colorectal adenomas lead to conclusion that patients who have prominently increased arterial stiffness can be recommended to undergo colonoscopic examinations and at the same time we also recommend counseling about the risk for atherosclerosis in those who have colorectal adenomas.**

***Key Words*: risk factors, atherosclerosis, pulse wave velocity, colon adenoma**

Introduction

Many researchers have speculated that cancer may share several risk factors with cardiovascular disease [*1–4*]. That is, insulin resistance associated with metabolic syndrome is one of well-known risks for cardiovascular disease and cancer [*5*] and obesity has been linked to an increased risk for colorectal cancer and adenomas [*6–11*]. Therefore, an understanding of the risk factors for colorectal cancer and adenomas may guide the development of strategies targeted toward prevention.

Pulse wave velocity (PWV) reflecting arterial stiffness is a non-invasive method for assessing the early stages of atherosclerosis [*12*]. Aortic stiffness is assessed by measuring the carotid-femoral pulse wave velocity (cfPWV). The heart-femoral pulse wave velocity (hfPWV) is also positively correlated with the cfPWV [*13*]. The brachial-

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ankle PWV (baPWV) reflects the stiffness of both central elastic and peripheral muscular arteries, and correlates positively with conventional cfPWV [*12*, *14*]. Both baPWV and hfPWV are associated with cardiovascular risk factors as well as the metabolic syndrome [*14*, *15*].

Since a number of reports have shown that obesity and cardiovascular risk factors are associated with colorectal cancer as well as adenomas [*6*–*10*, *16*], in the current study, we determined the association between parameters related to obesity, cardiovascular risk factors, arterial stiffness and colorectal adenomas.

Materials and Methods

Subjects

Nine hundred two patients underwent colonoscopic examinations for screening purposes for colon adenomas or cancer during the study period. This study was conducted prospectively after approving Instutional Review Board (IRB of Dongguk University Ilsan hospital, Goyang, Korea). The study was in accordance with the ethical guidelines of the Helsinki Declaration (1989). The subjects completed a clinic survey to determine their eligibility. Six hundred fourteen patients were excluded because of a preference not to participate, inadequate eligibility, or the below exclusion criteria. The exclusion criteria included a history of colon cancer, prior colon surgery, prior colorectal polypectomy, a history of a cerebrovascular accident, a colon examination (sigmoidoscopy, colonoscopy, or barium enema) within the previous 5 years, a history of hypertension, diabetes mellitus, or hyperlipidemia which was being treated with medication, other chronic medical illnesses. Thirty-nine patients were dropped out because they did not undergo PWV determinations or omitted blood sampling. Finally 249 subjects were enrolled in the present investigation. The study subjects were divided into the following two groups according to the premalignant potential of the lesion; one was the case group had histologically-confirmed colorectal adenomas including tubulovillous adenomas or serrated adenomas and the other was the control group showing normal colonoscopic findings and non-polypoid benign lesions such as non-specific colitis or histologically-confirmed sporadic hyperplastic polyps.

Laboratory assay and measurement

The fasting glucose and lipid profiles were measured by the hexokinase method (Roche Diagnostics, Indianapolis, IN) on a Hitachi 7600 automated chemistry analyzer (Hitachi, Tokyo, Japan). The body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. The waist circumference (cm) was measured at the mild point between the lower margin of the ribs and the upper margin of the iliac crest during minimal respiration.

The measurement of pulse wave velocity (PWV)

The PWV (cm/sec) was measured using an automatic waveform analyzer (VP-2000; Colin Co., Komaki, Japan), which simultaneously records pulse waves, blood pressure, electrocardiogram (ECG), and heart sounds. Cuffs with an oscillometric pressure sensor were applied to the extremities, ECG electrodes were attached to both wrists, and a microphone for phonocardiography was placed at the second intercostal space on the left border of the sternum. Tonometric sensors were placed on the left common carotid and left femoral arteries. Pulse waves were recorded when the carotid and femoral pulse waves, ECG, and phonocardiogram were stable. Pulse waves were stored for a sampling time of 10 s with automatic gain analysis and quality adjustment. Recordings were done two times consecutively. Values at the second recording were used to eliminate error caused by physical stress. The wave form analyzer automatically determines the time intervals between the following: the second heart sound and the dicrotic notch of the carotid pulse (ΔThc); the foot of the carotid pulse and the foot of the femoral pulse (ΔTcf); and the foot of the brachial pulse and the foot of the ankle pulse (ΔTba). The sum of ΔTcf and ΔThc is the time for pulse waves to travel from the heart (aortic orifice) to the femoral artery (ΔThf). Also, the wave form analyzer automatically determines the distances between the two recording sites on the basis of the subject's height using the following formulas: the distance from the heart to the femoral artery (Lhf) = 0.5643 × height (cm) – 18.381; and the distance from the brachium to the ankle (Lba) = 0.5934 × height (cm) + 14.4014. PWVs were calculated automatically according to the following equations: hfPWV = Lhf/ΔThf; and baPWV = Lba/ΔTba [*13*, *14*]. For the analysis, the baPWV was used as the mean value of the right and left sides. To assess the reproducibility of the PWVs, two different observers measured the PWVs repeatedly in 30 consecutive subjects. The first observer measured the PWVs twice at intervals ≥5 min; after an additional interval of ≥5 min, the second observer measured the PWVs once. At each measurement of PWVs, the cuffs were wrapped again. Tonometric sensors and a microphone for phonocardiography were also positioned again. The Pearson's correlation coefficients for intra-observer reproducibility of the hfPWV and baPWV were $r = 0.912$ and $r = 0.976$, respectively. The corresponding coefficients of variation were 4.5% and 2.6%, respectively. The Pearson's correlation coefficients for inter-observer reproducibility of hfPWV and baPWV were $r = 0.802$ and $r = 0.972$, respectively. The corresponding coefficients of variation were 5.8% and 3.3%, respectively [*17*].

Colonoscopy

Colonoscopic examinations were performed by one experienced endoscopist who had performed >40,000

Table 1. Baseline demographic, laboratory, and anthropometric characteristics of controls and adenomas with statistical difference between groups

	Control (n = 200)	Adenoma (n = 49)	p value
Age (years)	50.10 ± 9.74	53.92 ± 10.55	**0.02**
Male gender (n)	119 (59.5%)	39 (79.6%)	**<0.01**
BMI (kg/m^2)*	24.1 ± 2.6	25.3 ± 2.5	**0.01**
Waist circumference (cm)	80.36 ± 12.46	87.11 ± 9.67	**<0.01**
Total cholesterol (mg/d*l*)	199.8 ± 37.3	191.4 ± 34.1	0.16
Triglycerides (mg/d*l*)	148.0 ± 32.1	153.73 ± 36.3	0.81
LDL-C (mg/dl)†	133.3 ± 36.0	127.1 ± 30.8	0.28
HDL-C (mg/dl)‡	56.1 ± 15.6	52.6 ± 15.9	0.18
Fasting glucose (mg/dl)	66.87 ± 23.67	60.02 ± 23.29	0.08
hfPWV (cm/sec)§	840.92 ± 151.11	931.31 ± 178.31	**<0.01**
baPWV (cm/sec) ‖	1316.55 ± 239.97	1436.94 ± 262.79	**<0.01**
Systolic BP (mmHg)	125.42 ± 18.40	131.13 ± 24.49	0.09
Diastolic BP (mmHg)	74.19 ± 8.72	74.09 ± 8.20	0.95

*BMI; body mass index, †LDL-C; low density lipoprotein-cholesterol, ‡HDL-C; high density lipoprotein-cholesterol, §hfPWV; heart-femoral pulse wave velocity, ‖baPWV; brachial-ankle pulse wave velocity.

colonoscopies following bowel preparation with colonlyte (4 *l*/274.31 g; consisting of polyethylene glycol [3350.236 g], sodium bicarbonate [6.74 g], NaCl [5.86 g], sodium sulfate [22.74 g], and potassium chloride [2.97 g]). The colonoscopic examination was performed up to the cecal end or terminal ileum. An advanced adenoma was defined as ≥1 cm in estimated diameter (the largest size was used for multiple adenomas), containing >25% villous features, high grade dysplasia, or >3 adenomas.

Statistics

Statistical analysis was performed using the chi-squared test for comparison of discrete variables, such as gender, and the *t* test was used for comparison of continuous variables, such as age, waist circumference, BMI, lipid profiles, fasting glucose, blood pressures, and PWVs. The continuous variables measured in this study are expressed as the mean ± standard deviation. Multivariate analysis was performed using entered multiple logistic regression (p<0.3). Age, BMI, waist circumference, total cholesterol, low density lipoprotein-cholesterol (LDL-C), fasting glucose, systolic blood pressure, hfPWV, and brachial-ankle PWV (baPWV) were included as independent variables in a multiple regression model. For each variable, the odds ratio (OR) and 95% confidence interval (CI) are given. We examined the effects of confounding variables on the risk of colon adenomatous polyps with the Wald test for coefficient variables predicting risk at a significance level of 0.05. A two-tailed p value <0.05 was considered statistically significant. All analyses were performed with SPSS, version 12.0 for Windows (SPSS, Inc., Chicago, IL).

Results

Two hundred forty-nine subjects were enrolled in the present investigation (158 males and 91 females with a mean age of 51.8 ± 7.9 years). Uni-variate analysis of the risk for colorectal adenomas among the clinical factors, including age, gender, anthropometric parameters, lipid profiles, fasting glucose, blood pressure, and PWV, are shown in Table 1. As anticipated, age, male gender, waist circumference, BMI, hfPWV, and mbaPWV were significantly associated with colon adenomas (Table 1). However, no differences were identified for other factors such as lipid profiles, fasting glucose, and blood pressure. Based on the multiple logistic regression analsis of whole 249 patients, the hfPWV, but not the mbaPWV, was a significant risk factor (OR, 1.005; 95% CI, 1.001–1.008; p = 0.02) and waist circumference was a borderline significant risk factor (OR, 1.063; 95% CI, 1.000–1.133; p = 0.05) for adenomas (Table 2). When multiple regression analysis was done in patients with advanced colon adenoma, which was defined as ≥1 cm in estimated diameter, containing >25% villous features, high grade dysplasia, or >3 adenomas irrespective of adenoma size, only age was a borderline significant risk factor (OR, 1.243; 95% CI, 0.984–1.571; p = 0.06). (Table 3), signifying that though hfPWV contributed to colon adenoma, but not major factor.

Discussion

The incidence of colorectal cancer and adenomas is on very rise tendency because of the increase in the number of elderly group and the steeply increased prevalence of

Table 2. Odd ratio drawn from multiple logistic regression analysis between contributing parameters and colon adenoma

	Odds ratio (95% confidence interval)	*p* value
Waist circumference	**1.063 (1.000–1.133)**	**0.05**
hfPWV*	**1.005 (1.001–1.008)**	**0.02**
baPWV†	1.000 (0.997–1.002)	0.71
Age	1.002 (0.948–1.055)	0.95
Body mass index	0.960 (0.780–1.182)	0.7
Total cholesterol	0.974 (0.932–1.018)	0.25
LDL-C‡	**0.996 (0.941–1.055)**	**0.05**
Fasting glucose	1.015 (0.990–1.041)	0.24
Systolic BP	1.010 (0.990–1.030)	0.33

*hfPWV; heart-femoral pulse wave velocity, †baPWV; brachial-ankle pulse wave velocity, ‡LDL-C; low density lipoprotein-cholesterol.

Table 3. Odd ratio drawn from multiple logistic regression analysis between contributing paramaetrs and advanced colon adenoma*

	Odds ratio (95% confidence interval)	*p* value
Age	1.243 (0.984–1.571)	0.06
weight	1.001 (0.953–1.052)	0.96
Waist circumference	0.964 (0.782–1.188)	0.73
Body mass index	1.082 (0.527–2.222)	0.83
Total cholesterol	0.981 (0.905–1.063)	0.63
Fasting glucose	1.036 (0.952–1.126)	0.41
hfPWV†	1.007 (0.997–1.016)	0.16
baPWV‡	0.998 (0.994–1.001)	0.24

*Advanced colon adenoma defined as "≥1 cm in estimated diameter, containing >25% villous features, high grade dysplasia, or >3 adenomas irrespective of adenoma size"; †hfPWV; heart-femoral pulse wave velocity, ‡baPWV; brachial-ankle pulse wave velocity.

obesity worldwide [*18–19*]. Similarly, the risk for cardiovascular diseases and metabolic syndrome also increased, based on the fact that these diseases share common causality and can be explained by inflammation, oxidative stress, and insulin resistance as for underlying pathogenesis [*10*]. In fact, recent reports have suggested that components of metabolic syndrome, obesity, or diabetes have a positive association with colorectal cancer or adenomas [*6–10*, *16*] and several studies have provided evidence that obesity or diabetes are associated with colorectal cancer [*6–10*]. As result, a positive correlation between atherosclerotic lesions and adenomatous polyps was found [*20*]. In this study, we focused on the association between PWVs and colorectal adenomas because many studies have examined the relationship between cardiovascular risk factors and colorectal adenomas [*6–10*] and we are very proud that our study might be the first investigation focusing on the association between arterial stiffness and colorectal adenomas.

Arterial stiffness plays an important role in the development of atherosclerosis, during which PWV is known to be an indicator of arterial stiffness and a marker of vascular damage [*12*]. Several studies have demonstrated that PWV is very useful for the diagnosis of atherosclerotic cardiovascular diseases [*12*]. Previous studies [*12–13*] have demonstrated that PWV is associated with hypertension, diabetes mellitus, hyperlipidemia, obesity, and smoking and we can add more evidence that PWV can be adopted as one of contributing parameters in predicting the risk of colorectal adenoma and contributing factor in adenoma generation. We examined the effects of confounding variables on the risk of colon adenomatous polyps through the OR, 95% CI, and Wald test for coefficient variables predicting risk at a level of significance of 0.05. Although old age, male gender, obesity-related markers, and diabetes are well-known risk factors for colon adenomas, no differences were identified as a function of lipid profiles, fasting glucose, and blood pressure in present investigation. Although the OR of hfPWV is 1.005, hfPWV had a significant contributing influence on the risk of colon adenoma based on the Wald test and only hfPWV had an effect on the risk for colon adenoma by the OR, CI, and Wald test. Due to small in numbers of advanced adenomatous polyps, 11 cases, limitation exists in documenting the exact risk factors for advanced polyps. Only age is a borderline risk factor for advanced colon adenomas. Though we excluded persons diagnosed with hypertension, diabetes mellitus, and hypertension who were treated with medications, a limitation of our study was that lifestyle risk factors such as exact amounts of alcohol consumption and cigarette smoking, objective assessment of physical activity, and component of diet were not calculated as confounding variables.

While cfPWV is an established method for measuring the PWV, a simpler method of measuring the baPWV and hfPWV has recently become available. Accumulated data indicate that determination of the baPWV and hfPWV may be similar to the cfPWV [*12*]. In contrast to the hfPWV, the baPWV includes peripheral components of the arterial tree. We have shown herein that the hfPWV is strongly associated with colorectal adenomas after adjusting for confounding factors, indicating that central arterial stiffness is associated with colorectal adenomas. Waist circumference was shown to be a borderline significant risk factor for adenomas. Both hfPWV and baPWV, indicating very early cardiovascular risk factors, and waist circumference, indicating central obesity, are associated with colon adenomas. We assumed that colorectal adenomas, central obesity, and very early cardiovascular risk factor were clustered in the same individual and these disease entities had the underlying same etiology in common.

In conclusion, patients who have prominently increased arterial stiffness can be recommended to undergo colonoscopic examinations and at the same time we also recommend counseling about the risk for atherosclerosis in those who have colorectal adenomas. However, more large sized analysis will be required to draw more solid guideline for colon adenoma in patients with high risk of atherosclerosis.

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References

[1] Bianchini, F., Kaaks, R., and Vainio, H.: Overweight, obesity, and cancer risk. *Lancet Oncol.*, **3**, 565–574, 2002.

[2] Jee, S.H., Kim, H.J., and Lee, J.: Obesity, insulin resistance and cancer risk. *Yonsei Med. J.*, **46**, 449–455, 2005.

[3] Jee, S.H., Ohrr, H., Sull, J.W., Yun, J.E., Ji, M., and Samet, J.M.: Fasting serum glucose level and cancer risk in Korean men and women. *J.A.M.A.*, **293**, 194–202, 2005.

[4] Calle, E.E., Rodriguez, C., Walker-Thurmond, K., and Thun, M.J.: Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N. Engl. J. Med.*, **348**, 1625–1638, 2003.

[5] Alberti, K.G., Zimmet, P., and Shaw, J.: IDF Epidemiology Task Force Consensus Group. The metabolic syndrome—a new worldwide definition. *Lancet*, **366**, 1059–1062, 2005.

[6] Murphy, T.K., Calle, E.E., Rodriguez, C., Kahn, H.S., and Thun, M.J.: Body mass index and colon cancer mortality in a large prospective study. *Am. J. Epidemiol.*, **152**, 847–854, 2000.

[7] Nilsen, T.I. and Vatten, L.J.: Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: exploring the hyperinsulinaemia hypothesis. *Br. J. Cancer*, **84**, 417–422, 2001.

[8] Limburg, P.J., Vierkant, R.A., Fredericksen, Z.S., Leibson, C.L., Rizza, R.A., Gupta, A.K., Ahlquist, D.A., Melton, L.J. 3rd., Sellers, T.A., and Cerhan, J.R.: Clinically confirmed type 2 diabetes mellitus and colorectal cancer risk: a population-based, retrospective cohort study. *Am. J. Gastroenterol.*, **101**, 1872–1879, 2006.

[9] Frezza, E.E., Wachtel, M.S., and Chiriva-Internati, M.: Influence of obesity on the risk of developing colon cancer. *Gut*, **55**, 285–291, 2006.

[10] Komninou, D., Ayonote, A., Richie, J.P. Jr., and Rigas, B.: Insulin resistance and its contribution to colon carcinogenesis. *Exp. Biol. Med. (Maywood)*, **228**, 396–405, 2003.

[11] 2002 Annual report of the Korea central cancer registry. Available form: URL: http://www.yubang.com/down/2002cancer_regi_result.pdf

[12] Yamashina, A., Tomiyama, H., Arai, T., Hirose, K., Koji, Y., Hirayama, Y., Yamamoto, Y., and Hori, S.: Brachial-ankle pulse wave velocity as a marker of atherosclerotic vascular damage and cardiovascular risk. *Hypertens. Res.*, **26**, 615–622, 2003.

[13] Kim, Y.K.: Impact of the metabolic syndrome and its components on pulse wave velocity. *Korean J. Intern. Med.*, **21**, 109–115, 2006.

[14] Tomiyama, H., Yamashina, A., Arai, T., Hirose, K., Koji, Y., Chikamori, T., Hori, S., Yamamoto, Y., Doba, N., and Hinohara, S.: Influence of age and gender on results of noninvasive brachial-ankle pulse wave measurements—a survey of 12517 subjects. *Atherosclerosis*, **166**, 303–309, 2003.

[15] Wildman, R.P., Mackey, R.H., Bostom, A., Thompson, T., and Sutton-Tyrrell, K.: Measures of obesity are associated with vascular stiffness in young and older adults. *Hypertension*, **42**, 468–473, 2003.

[16] Ahmed, R.L., Schmitz, K.H., Anderson, K.E., Rosamond, W.D., and Folsom, A.R.: The metabolic syndrome and risk of incident colorectal cancer. *Cancer*, **107**, 28–36, 2006.

[17] Kim, Y.K., Lee, M.Y., and Rhee, M.Y.: A simple oscillometric measurement of pulse wave velocity: comparison with conventional tonometric measurement. *Korean J. Med.*, **67**, 597–606, 2004.

[18] El-Serag, H.B.: Obesity and disease of the esophagus and colon. *Gastroenterol. Clin. North Am.*, **34**, 63–82, 2005.

[19] Giovannucci, E.: Modifiable risk factors for colon cancer. *Gastroenterol. Clin. North Am.*, **31**, 925–943, 2002.

[20] Correa, P., Strong, J.P., Johnson, W.D., Pizzolato, P., and Haenszel, W.: Atherosclerosis and polyps of the colon. Quantification of precursors of coronary heart disease and colon cancer. *J. Chronic Dis.*, **35**, 313–320, 1982.