Association Between Markers of Glucose Metabolism and Risk of Colorectal Adenoma

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BACKGROUND & AIMS: Diabetes is a risk factor for colorectal cancer. We studied the association between markers of glucose metabolism and metabolic syndrome and the presence of colorectal adenomas in a large number of asymptomatic men and women attending a health screening program in South Korea. We also investigated whether these associations depend on adenoma location. **METHODS:** In a cross-sectional study, we measured fasting levels of glucose, insulin, hemoglobin A_{1c}, and C-peptide and calculated homeostatic model assessment (HOMA) values (used to quantify insulin resistance) for 19,361 asymptomatic South Korean subjects who underwent colonoscopy examinations from January 2006 to June 2009. Participants completed a standardized self-administered health questionnaire and a validated semiquantitative food frequency questionnaire. Blood samples were collected on the day of the colonoscopy; fasting blood samples were also collected. Robust Poisson regression was used to model the associations of glucose markers with the prevalence of any adenoma. **RESULTS:** Using detailed multivariable-adjusted dose-response models, the prevalence ratios (aPR, 95% confidence interval [CI]) for any adenoma, comparing the 90th with the 10th percentile, were 1.08 (1.00–1.16; $P = .04$) for fasting glucose, 1.07 (0.99–1.15; $P = .10$) for insulin, 1.09 (1.02–1.18, $P = .02$) for HOMA, 1.09 (1.01–1.17; $P = .02$) for hemoglobin A_{1c}, and 1.14 (1.05–1.24; $P = .002$) for C-peptide. The corresponding ratios for nonadvanced adenomas were 1.11 (0.99–1.25; $P = .08$), 1.10 (0.98–1.24; $P = .12$), 1.15 (1.02–1.29; $P = .02$), 1.14 (1.01–1.28; $P = .03$), and 1.20 (1.05–1.37; $P = .007$), respectively. The corresponding ratios for advanced adenomas were 1.32 (0.94–1.84; $P = .11$), 1.23 (0.87–1.75; $P = .24$), 1.30 (0.92–1.85; $P = .14$), 1.13 (0.79–1.61; $P = .50$), and 1.67 (1.15–2.42; $P = .007$), respectively. Metabolic syndrome was associated with the prevalence of any adenoma (aPR, 1.18; 95% CI, 1.13–1.24; $P < .001$), nonadvanced adenoma (aPR, 1.30; 95% CI, 1.20–1.40; $P < .001$), and advanced adenoma (aPR, 1.42; 95% CI, 1.14–1.78; $P = .002$). Associations were similar for adenomas located in the distal versus proximal colon. **CONCLUSIONS:** Increasing levels of glucose, HOMA values, levels of hemoglobin A_{1c} and C-peptide, and metabolic syndrome are significantly associated with the prevalence of adenomas. Adenomas should be added to the list of consequences of altered glucose metabolism.

Keywords: Colon Cancer; Risk Factors; Glycosylated Hemoglobin; Epidemiology.

The global prevalence of diabetes is rapidly increasing, with a projected surge in the number of people with diabetes from 366 to 552 million between 2011 and 2030.[1] In addition to its direct health consequences, diabetes is a risk factor for other diseases such as colorectal cancer.[2] Pooled analyses have shown a 20% to 30% increased risk of colorectal cancer for patients with diabetes compared with those without it and a 50% to 60% increased risk for patients on insulin therapy.[3–7] Possible mechanisms for the link between diabetes and colorectal cancer include insulin resistance/hyperinsulinemia, hyperglycemia, inflammation, and oxidative stress.[8,9]

Although diabetes is an established risk factor for the development of clinically manifest colorectal cancer, the literature on the association between markers of glucose metabolism and colorectal adenomas, which are pathological precursors of colorectal cancer, is more limited and inconsistent.[10–19] Our objective was to determine the association between markers of glucose metabolism, including fasting glucose, insulin, hemoglobin A_{1c} (HbA_{1c}), homeostasis model of risk assessment – insulin resistance (HOMA-IR), and C-peptide levels as well as metabolic syndrome, and the risk of colorectal adenomas in a large sample of asymptomatic men and women attending a health screening program. We additionally investigated whether these associations were modified by adenoma location.

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Abbreviations used in this paper: **BMI, body mass index; CI, confidence interval; HbA_{1c}, hemoglobin A_{1c}; HOMA-IR, homeostasis model of risk assessment – insulin resistance; IGF, insulin-like growth factor; NSAID, nonsteroidal anti-inflammatory drug.**

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Subjects and Methods

Study Population

We conducted a cross-sectional study of 21,688 consecutive routine colonoscopies performed during health screening examinations at the Center for Health Promotion of the Samsung Medical Center (Seoul, South Korea) between January 2006 and June 2009.[20] The Center for Health Promotion provides regular health checkups that include screening colonoscopy examinations for adults. We excluded 2327 colonoscopies for one or more of the following reasons: repeated colonoscopy (n = 1188), diagnostic or therapeutic (nonscreening) colonoscopy (n = 817), insertion failure (n = 11), incomplete colonoscopy (n = 168), history of colorectal cancer or colorectal surgery (n = 66), inflammatory bowel disease (n = 29), history of biopsy with diagnosis of adenocarcinoma or lymphoma (n = 26), and non-Korean participants (n = 49). For participants with repeated colonoscopies, we selected the first colonoscopy for the present analysis. The final sample size was 19,361 participants.

Regular routine health screening is very common in South Korea due to the Industrial Safety and Health Law. This study used only de-identified medical records that were collected for administrative or clinical purposes as part of routine health screening examinations. The study was approved by the Institutional Review Board of the Samsung Medical Center, which waived the requirement of informed consent because the researchers only obtained de-identified routinely collected data from the institution's clinical data warehouse.

Data Collection

All participants completed a standardized self-administered health questionnaire as part of the screening program. The questionnaire asked for information on smoking, alcohol consumption, and exercise; medical history of diabetes, hypertension, hyperlipidemia, angina pectoris or myocardial infarction, colorectal polyps, colorectal cancer, and colorectal surgery; and family history of colorectal cancer. Medication history included current and regular (at least twice a week) use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and medications for diabetes and hypertension. Usual dietary intake was assessed by using a validated semiquantitative food frequency questionnaire that included 138 items from 17 major food categories.[21] Height and weight were measured by using an Inbody 720 machine (Biospace, Seoul, South Korea). Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters (kg/m^2). Waist circumference was measured at the midpoint between the inferior margin of the last rib and the superior iliac crest in a horizontal plane.

Participants were asked to fast for at least 12 hours and to avoid smoking on the morning of the examination. Fasting blood samples were obtained by a trained phlebotomist and immediately analyzed at the central laboratory of the Samsung Medical Center. Blood was collected on the day of the colonoscopy, and in 98.3% of the participants it was obtained after a bowel preparation. Fasting serum glucose level was measured by using the hexokinase/glucose-6-phosphate dehydrogenase method with a Hitachi 7600 Modular Dp-110 autoanalyzer (Hitachi, Tokyo, Japan). HbA_{1c} was determined by using high-performance liquid chromatography with a Tosoh Glycohemoglobulin Analyzer (Tosoh Bioscience Inc, Tokyo, Japan). Fasting insulin (DIAsource Insulin IRMA, DIAsource Immuno-Assays; DIAsource, Louvain, Belgium) and C-peptide (C-peptide IRMA; Immunotech, Prague, Czech Republic) levels were measured by using radioimmunoassay with a Packard Cobra II 5010 (Packard Instruments, Baltimore, MD). The interassay and intra-assay coefficients of variation for quality control specimens were 1.7% and 1.0% for fasting glucose, 2.5% and 2.5% for HbA_{1c}, 6.5% and 2.1% for fasting insulin, and 5.2% and 3.1% for C-peptide, respectively. History of diabetes was defined as self-reported diagnosis of diabetes or history of use of antidiabetic medication. HOMA-IR was calculated as follows: (Fasting Glucose [mg/dL] * Fasting Insulin [μU/mL])/405.

Metabolic syndrome represents an abnormal clustering of multiple metabolic risk factors.[22] Participants with 3 or more of the following 5 factors were classified as having metabolic syndrome : (1) central obesity, defined for Korean populations as having a waist circumference of $\geq$90 cm for male subjects and $\geq$85 cm for female subjects[23]; (2) a raised serum triglyceride level, defined as $\geq$1.7 mmol/L (150 mg/dL); (3) a low high-density lipoprotein cholesterol level, defined as $\leq$1.0 mmol/L (40 mg/dL) for male subjects and $\leq$1.3 mmol/L (50 mg/dL) for female subjects; (4) raised blood pressure, defined as a systolic blood pressure of $\geq$130 mm Hg, a diastolic blood pressure $\geq$85 mm Hg, or use of antihypertensive medication; and (5) a raised fasting blood glucose level, defined as $\geq$5.6 mmol/L (100 mg/dL) or use of antidiabetic medication.[22]

Twenty-six board-certified gastroenterologists performed the colonoscopies after bowel preparation with 4 L polyethylene glycol solution (CoLyte and CoLyte-F [Taejun, Seoul, South Korea] and Colonlyte [DreamPharma, Seoul, South Korea]). The size of each lesion was routinely estimated by using open biopsy forceps. Advanced adenomas were defined as adenomas with either a diameter $\geq$10 mm containing $\geq$25% of villous component or high-grade dysplasia. In addition, we classified sessile serrated adenomas as adenomas and large proximal hyperplastic polyps as nonadenomas.

A standardized electronic form was used to register colonoscopy results in the electronic medical records system. Endoscopists entered the results of the colonoscopy directly into these electronic forms during or immediately after the procedure. The following information was recorded: number of polyps, location and size of each polyp, family history of colorectal cancer, time and results of the last colonoscopy, bowel preparation, cecal insertion time, and withdrawal time. Biopsy samples were sent to the pathology department, where qualified pathologists assessed the histopathology of the polyp and entered the findings into the electronic medical record. All data used in this study were obtained from the electronic medical records stored at the clinical data warehouse of the institution.

Statistical Analysis

The primary outcome of the study was the presence of prevalent adenomas. The secondary outcomes were the presence of nonadvanced and advanced adenomas. Robust Poisson regression was used to model the associations of the individual glucose markers with the prevalence of any adenoma. We calculated prevalence ratios and 95% confidence intervals (CIs) of colorectal adenomas by comparing quartiles 2 to 4 of markers of glucose metabolism with the first quartile. For analysis of the secondary end points, we used multinomial logistic regression to estimate relative prevalence ratios for the