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Lack of Association Between Insulin Sensitivity and Colorectal Adenoma Risk

Rebecca L. Sedjo,

Department of Community and Behavioral Health, Colorado School of Public Health, University of Colorado Denver, Aurora, Colorado, USA

Ralph B. D'Agostino Jr.,

Department of Biostatistical Sciences, Division of Public Health Sciences, Wake Forest University School Health Sciences, Winston-Salem, North Carolina, USA

Dennis Ahnen,

Department of Gastroenterology and Hepatology, University of Colorado Denver, Aurora, Colorado, USA

Theodore R. Levin,

Kaiser Permanente Division of Research, Oakland, California, USA

Steven M. Haffner,

Department of Medicine and Clinical Epidemiology, University of Texas Health Science Center, San Antonio, Texas, USA

Janet A. Tooze, and

Department of Biostatistical Sciences, Division of Public Health Sciences, Wake Forest University School Health Sciences, Winston-Salem, North Carolina, USA

Tim Byers

Department of Epidemiology, Colorado School of Public Health, University of Colorado Denver, Aurora, Colorado, USA

Abstract

Insulin resistance is thought to mediate the association between obesity and colorectal neoplasia, but no prior studies have assessed stimulated insulin sensitivity as a risk factor for colorectal neoplasia. This prospective study examined the association between insulin sensitivity measured directly using the frequently sampled intravenous glucose tolerance test (FSIGT) and later risk of colorectal adenomas. Among participants with a range of glucose tolerance levels enrolled in the Insulin Resistance Atherosclerosis Study, colonoscopies were conducted on 600 participants ages 50 yr, regardless of symptoms, about 10 yr after the first FSIGT and 5 yr after the second.

Multiple logistic regression analyses were used. Within this cohort, diabetes was not associated with colorectal adenoma risk [~ 10 yr prior to colonoscopy adjusted odds ratio (OR_{adj}) 1.00; 95% confidence interval (CI), 0.62–1.62 or ~ 5 yr prior to colonoscopy OR_{adj} 0.96; 95% CI, 0.62–1.50]. Among non-diabetic participants, insulin sensitivity was not associated with colorectal adenoma risk at either prior study visit [lowest vs. highest insulin sensitivity, ~ 10 yr prior to colonoscopy OR_{adj} 0.93; 95% CI 0.50–1.71 and ~ 5 yr prior to colonoscopy OR_{adj} 0.74; 95% CI, 0.38–1.46]. These results suggest that factors other than insulin sensitivity mediate the relationship between obesity and colorectal neoplasia.

INTRODUCTION

Lifestyle factors such as obesity and physical inactivity are associated with an increased risk for colorectal neoplasia (1). These same factors influence the development of a diminished biological response to insulin, termed insulin resistance. Observations of these shared common risk factors led researchers to speculate that the associations observed between colorectal neoplasia and obesity and/or physical inactivity may be mediated through increased concentrations of circulating insulin and/or other factors related to insulin resistance (2,3). Adding support to this theory, some studies have found that individuals with diabetes mellitus are at increased risk for colorectal cancer (4), and that long-term insulin therapy is associated with risk for both colorectal adenomas and cancer among persons with type II diabetes (5,6). A meta-analysis reported a 35% increase in colorectal cancer risk with elevated circulating insulin or C-peptide levels, a cleavage product of proinsulin (7). Colorectal adenomas, the precursor lesions for most colorectal cancers (8), have also been found to be modestly associated with elevated insulin or C-peptide in some (9–13) but not all (14–16) studies.

Limited data exist on the risk of colon carcinogenesis relative to a more direct measure of insulin resistance. Using data from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Limburg and colleagues (17) reported an increased colorectal cancer risk with serum insulin and insulin resistance, as estimated by the homeostatic metabolic assessment (HOMA-IR), in age-adjusted models. However, after adjustment for other factors, including tobacco use and body mass index, these associations became attenuated and nonsignificant. Only one previous study addressed colorectal adenoma risk with insulin resistance as measured by HOMA-IR (18). Using a cross-sectional design, Kang and colleagues (18) reported a statistically significant dose–response relationship between elevated HOMA-IR and colorectal adenoma prevalence. Because it is not feasible to use the gold standard hyperinsulinemic-euglycemic clamp in large population-based studies (19), these studies used the HOMA-IR method to measure basal insulin resistance. The HOMA-IR method calculates basal insulin resistance based on fasting insulin and glucose concentration from a single sample. No data are currently available that assess the risk of colorectal neoplasia with a method that determines stimulated insulin resistance, such as the frequently sampled intravenous glucose tolerance test (FSIGT) that utilizes serial sampling following a glucose load to determine insulin sensitivity, the reciprocal of insulin resistance (19).

This current study investigates the relationship between a direct measure of insulin sensitivity and colorectal adenoma risk using the prospective Insulin Resistance and Atherosclerosis Study (IRAS) cohort, in which detailed individual physiologic measures of insulin sensitivity were made at two points within 10 yr prior to a colonoscopic examination.

MATERIALS AND METHODS

IRAS is a multicenter prospective cohort study of the association between insulin-resistance and atherosclerosis among non-Hispanic White, Hispanic, and African-American men and women (20). Briefly, participants with a range of glucose tolerance status (normal, impaired glucose tolerance, and diabetes) as determined using a 2-h, 75-g oral glucose tolerance test and categorized based on consensus criteria (21) were recruited from 4 centers. Similar protocols were used to collect data at the baseline (1992–1994, approximately 10 yr before the colonoscopy) and second study visits (1997–1999, approximately 5 yr before the colonoscopy). Between 2002 and 2004, all surviving participants who were ≥50 yr of age were invited to have a screening colonoscopy except those with serious concurrent illnesses

(22). Institutional Review Boards of all collaborating organizations approved the protocol, and participants signed informed consents before enrollment.

Of the 1,625 IRAS participants examined at baseline (1992–1994), 80% ($n = 1,308$) completed the second exam. Of the 1,226 remaining participants in 2002, 999 participants were contacted for eligibility, of which 197 were ineligible due to comorbid conditions ($n = 35$) or recent colon screening ($n = 162$). Thus, of the 802 eligible subjects, 605 consented and underwent a colonoscopy, of which 5 were excluded from the analyses due to missing or indeterminant histologic results. Therefore, analyses of the relationship between prior measures of insulin sensitivity and risk for colorectal adenomas were performed on 75% (600/802) of the eligible study population. Participants who had a colonoscopy procedure were on average younger ($P < 0.01$), less likely to be diabetics ($P < 0.01$), current smokers ($P < 0.01$), and to have a baseline BMI of $\geq 30 \text{ kg/m}^2$ as compared to those eligible subjects who did not undergo a colonoscopy.

Data Collection

At all 3 study visits, demographics, smoking practices, previous colorectal screening, and other lifestyle factors were collected via interviewer-administered questionnaires and anthropometric measures via trained staff. Height was measured to the nearest 0.1 cm and weights were measured to the nearest 0.1 kg. Physical activity was measured using a 1-yr recall of all activities based on modifications of a structured instrument (23–25) at baseline and the second visits.

Insulin sensitivity was determined using the frequently sampled intravenous glucose tolerance test (FSIGT) with a minimal model analysis (19) at the baseline and second visits after a 12-h fast. The FSIGT was measured as follows: a 0.3 g/kg in 50% glucose solution was injected at 0 min followed by the introduction of 0.03 U/kg human insulin at 20 min. Circulating glucose and insulin concentrations were measured at standard intervals from –5 to 180 min, and calculation of insulin sensitivity was conducted using a mathematical model (MINMOD, version 3.0, 1994) of whole-body kinetics (19). The 12-sample FSIGT was chosen for this study because it is comparable to the hyperinsulinemic-euglycemic clamp with an overall correlation of 0.55 (26) and can be conducted feasibly in large epidemiologic studies (19).

At the colonoscopy visit, experienced endoscopists performed colonoscopies following a standard prep. The cecum was reached in over 96% of participants. Location and size of all visible polyps were recorded, removed, and sent to local clinical laboratories, where standard histologic evaluation was performed.

Statistical Analysis

A participant's adenoma status was defined based on the highest-grade lesion identified. Participants classified with "adenomas" had tubular, tubulovillous, or villous histology; the presence of high-grade dysplasia was noted. Participants classified with "no adenoma" had no polyps or only hyperplastic polyps.

Tertiles of insulin, glucose, and insulin sensitivity were created based on the distribution in the group without adenomas at each time point. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2) and then classified into categories based on the World Health Criteria (27): normal ($<25.0 \text{ kg/m}^2$), overweight ($25.0\text{--}29.9 \text{ kg/m}^2$), and obese ($\geq 30.0 \text{ kg/m}^2$).

Differences between participants with and without an adenoma were assessed by χ^2 analyses for categorical variables of study center, age, sex, race/ethnicity, smoking status at

time of colonoscopy, previous screening status, total energy expenditure in 1997–1999, and BMI in 1997–1999. As the range of insulin sensitivity is limited in diabetics (26), FSIGT values were analyzed only among the nondiabetic participants. The associations between adenoma prevalence and insulin, glucose, insulin sensitivity (among nondiabetics only), and diabetes were performed using multiple unconditional logistic regression analyses controlling for age, sex, previous screening history, race/ethnicity, study center, and smoking. Adjusted odds ratios and 95% confidence intervals were estimated. As circulating insulin concentrations are believed to be an intermediary step between obesity and the development of colorectal neoplasia (2,3), these factors were not included in the models. To further assess possible effect modification, multiple logistic regression analyses of the associations between insulin measures and colorectal adenoma risk were also conducted, stratifying by BMI and total energy expenditure. The change in insulin sensitivity over time was calculated by subtracting the baseline values from the subsequently measured values. This difference was then assessed as a predictor factor of adenoma risk, adjusting for the covariates listed above as well as for baseline insulin sensitivity. *P* values for linear trend were calculated by treating categorical measures as continuous in the logistic models. All analyses were conducted using 2-sided statistical tests with an alpha level of 0.05 and performed using Intercooled Stata version 9 (StataCorp, *Stata Statistical Software: Release 9*, College Station, TX, StataCorp LP, 2005).

RESULTS

The analytic cohort had a mean age of 64 yr, 54% were women, 38% were White, non-Hispanic, 27% were Black, 35% were Hispanic, and 11% reported a previous colorectal polyp. Among the 136 participants found to have a polyp, there were 381 polyps with mean size of 4.0 mm (SD = 3.8); 126 (33.1%) were hyperplastic, 194 (50.9%) were tubular = adenomas, 24 (6.3%) were tubulovillous adenomas, 5 (1.3%) were villous adenomas, 3 (0.8%) were unable to be determined, and 29 (7.6%) were other types. Adenoma prevalence was higher among men, among older participants, and among those with previous colorectal screening in which polyps were detected (Table 1). Adenoma prevalence was lower in the Colorado study center among both Hispanics and non-Hispanic Whites (data not shown).

No significant association was observed between adenoma prevalence and fasting insulin, glucose, or diabetes (Table 2). Among nondiabetic participants, categorical variables of insulin sensitivity measured about 5 and 10 yr before colonoscopy were not associated with adenoma prevalence. As expected, FSIGT values were inversely correlated with fasting insulin at about 5 yr ($r = -0.36$, $P < 0.01$) and about 10 yr ($r = -0.27$, $P < 0.01$) among nondiabetics. There was no suggestion of an increased adenoma risk when the analysis was stratified by gender, race/ethnicity, BMI, or total energy expenditure, and when the change in insulin was evaluated (data not shown).

DISCUSSION

Despite some prior studies suggesting an association between colorectal adenoma risk and indicators of hyperinsulinemia, our findings—using a direct measure of insulin resistance, both at about 5 and 10 yr prior to a screening colonoscopy—do not support a role for long-standing insulin resistance in colorectal adenoma development. This study had 80% power to detect an odds ratio of 1.5 or greater, yet none of the point estimates for the FSIGT association approached this value. Of the 8 previous studies evaluating the relationship between colorectal adenoma risk and circulating insulin or C-peptide concentrations (9–16), 5 reported a modestly positive association (9–13), while 3 reported no association (14–16). While fasting insulin is an adequate surrogate measure of insulin sensitivity among normal glucose tolerant participants, its value is questionable among participants with impaired

glucose tolerance and non-insulin-dependent diabetes (28,29). However, we observed no increase adenoma risk between insulin and adenomas by subgroups of glucose tolerance status. Previous in vitro (30) and in vivo (31,32) studies have demonstrated that elevated insulin concentrations promote colorectal cell proliferation. However, while an acute role in colorectal epithelial proliferation was observed for insulin concentration, it was not observed for insulin sensitivity (32). Additionally, the difference in our findings with the majority of others may be due to our measures of both fasting insulin and insulin sensitivity several years before colonoscopy, whereas several of the other studies showing an effect measured fasting insulin at the time of colonoscopy or later (9,10,12,18). The time period most relevant to colorectal neoplasia risk is unknown, but it is likely that exposure factors in the 5- to 10-yr time period before diagnosis should be relevant to the initiation of adenoma development (33).

Abdominal adiposity, commonly measured by the waist-to-hip ratio or waist circumference, has been more strongly linked to insulin resistance than is BMI (34). However, we previously reported that BMI measured at the time of colonoscopy was associated with an increased risk of colorectal adenoma in this cohort, but waist circumference and BMI measured at 5 and 10 yr were not and waist circumference measure at the time of colonoscopy was not (22). Obesity is known to increase the risk of colorectal adenomas and cancer (1), but it is accompanied by several factors apart from insulin resistance that are involved in the insulin pathways that could explain colorectal adenoma formation, such as various growth factors, their binding proteins, and factors involved in inflammation (7).

There are several strengths and limitations to consider when reviewing these findings. This study is the first, to our knowledge to address the relationship between the FSIGT direct measure of stimulation insulin resistance and colorectal adenoma prevalence. The FSIGT captures not only circulating insulin levels, but also a person's physiologic response to a glucose and insulin challenge, thus allowing for a more direct measure of insulin resistance. However, other factors such as IGF levels, which were not evaluated, may also contribute synergistically to increasing colorectal adenoma risk. Only participants who agreed to a screening colonoscopy were included in this analysis, of course, but the analytic cohort did represent a broad range of insulin sensitivities and there is no evidence to suggest that a systematic bias tied to FSIGT levels had occurred. Finally, as few cohort participants had advanced adenomas ($n = 39$), we were unable to fully examine the risk of advanced adenomas with insulin sensitivity.

In conclusion, these data do not support a direct role of insulin resistance in the 5 to 10 yr prior to colonoscopy in the development of colorectal adenomas. Mechanisms other than insulin resistance may mediate the role of obesity and related risk factors in the development of colorectal neoplasia.

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TABLE 1

Prevalence of any adenoma by demographic characteristics and risk factors among study participants

Characteristic/risk factor	Adenoma <i>n</i> / <i>N</i> (row %)	<i>P</i> value*
All subjects	136/600 (22.7)	
Center		
San Antonio, TX	38/144 (26.4)	0.01
San Luis Valley, CO	23/170 (13.5)	
Oakland, CA	42/156 (26.9)	
Los Angeles, CA	33/130 (25.4)	
Age, yr		
<60	34/220 (15.5)	<0.01
60–69	50/226 (22.1)	
70+	52/154 (33.8)	
Sex		
Males	74/274 (27.0)	0.02
Females	62/326 (19.0)	
Race/ethnicity		
White, non-Hispanic	54/230 (23.5)	0.84
Black	38/161 (23.6)	
Hispanic	44/209 (21.1)	
Smoking		
Never	59/289 (20.4)	0.45
Former	65/263 (24.7)	
Current	12/48 (25.0)	
Self-reported previous screening		
None	37/199 (18.6)	<0.01
Yes, without polyp	69/335 (20.6)	
Yes, with polyp	30/66 (45.5)	
Total energy expenditure (kcal/kg/yr) at 1997–1999		
<13,038	52/207 (25.1)	0.54
13,038–14,530	40/195 (20.5)	
>14,530	44/198 (22.2)	
BMI (kg/m ²) at 1997–1999 ^I		
Normal (<25)	22/119 (18.5)	0.34
Overweight (25–29)	55/256 (21.5)	
Obese (30+)	50/197 (25.4)	

* Pearson χ^2 test.^I *n* = 572 with BMI measures obtained.

TABLE 2

The association between diabetes, insulin sensitivity, and colorectal adenoma prevalence risk among IRAS cohort study participants

Risk factors	Adenoma prevalence, <i>n/N</i> (%)	OR ¹	OR _{adj} (95%) ²
1992–1994 Clinical visit (~10 yr before colonoscopy)			
Fasting insulin, uU/ml ³			
Low (<11)	57/238 (24.0)	1.00	1.00
Medium (11–18)	33/177 (18.6)	0.81 (0.49–1.32)	0.83 (0.50–1.40)
High (>18)	46/184 (25.0)	1.20 (0.76–1.91)	1.05 (0.64–1.72)
<i>P</i> for trend		0.49	0.88
Fasting glucose, mg/dl			
Low (<96)	44/223 (19.7)	1.00	1.00
Medium (96–108)	43/178 (24.2)	1.19 (0.73–1.94)	1.15 (0.69–1.91)
High (≥ 109)	49/199 (24.6)	1.15 (0.71–1.85)	0.99 (0.60–1.63)
<i>P</i> for trend		0.59	0.95
Diabetes			
No	101/460 (22.0)	1.00	1.00
Yes	35/140 (25.0)	1.09 (0.69–1.72)	1.00 (0.62–1.62)
Insulin sensitivity ($S_i \times 10^{-4} \text{ min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}^{-1}$) ^{4,5}			
High (2.76–19.4)	34/148 (23.0)	1.00	1.00
Medium (1.24–2.75)	29/141 (20.6)	0.89 (0.50–1.58)	0.90 (0.49–1.63)
Low (0–1.23)	32/145 (22.1)	1.03 (0.59–1.81)	0.93 (0.50–1.71)
<i>P</i> for trend		0.92	0.81
1997–1999 Clinical visit (~5 yr before colonoscopy)			
Fasting insulin, uU/ml ⁶			
Low (<13)	53/221 (24.0)	1.00	1.00
Medium (13–20)	29/161 (18.0)	0.69 (0.41–1.16)	0.65 (0.38–1.12)
High (>20)	45/189 (23.8)	1.07 (0.67–1.72)	0.91 (0.55–1.49)
<i>P</i> for trend		0.84	0.65
Fasting glucose, mg/dl ⁷			
Low (<96)	34/192 (17.7)	1.00	1.00
Medium (96–112)	50/190 (26.3)	1.46 (0.87–2.44)	1.29 (0.76–2.19)
High (≥ 113)	42/191 (22.5)	1.21 (0.71–2.04)	0.99 (0.57–1.72)
<i>P</i> for trend		0.53	0.92
Diabetes ⁸			
No	84/388 (21.7)	1.00	1.00
Yes	44/188 (23.4)	1.03 (0.67–1.57)	0.96 (0.62–1.50)
Insulin sensitivity ($S_i \times 10^{-4} \text{ min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}^{-1}$) ^{4,9}			
High (1.68–18.3)	28/122 (23.0)	1.00	1.00
Medium (0.88–1.67)	25/119 (21.0)	0.85 (0.46–1.58)	0.87 (0.45–1.68)
Low (0.00–0.87)	25/119 (21.0)	0.90 (0.49–1.69)	0.74 (0.38–1.46)

Risk factors	Adenoma prevalence, <i>n/N</i> (%)	OR¹	OR_{adj} (95%)²
<i>P</i> for trend		0.75	0.38

¹ Adjusted for age at colonoscopy and sex using logistic regression.

² Adjusted for age at colonoscopy, center, race/ethnicity, smoking status at colonoscopy, sex, and previous screening (self-reported none, yes without polyp(s), yes with polyp(s)) using logistic regression.

³ *n* = 599.

⁴ As the range of insulin sensitivity is limited in diabetics, analyses were only reported among non-diabetic participants.

⁵ *n* = 434.

⁶ *n* = 571.

⁷ *n* = 573.

⁸ *n* = 576.

⁹ *n* = 360.