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Plasma insulin, glucose, IGF-I, IGF-II, and IGFBP-3 and risk of recurrent colorectal adenomas

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Abstract

Aim—Insulin and insulin-like growth factors (IGF's) are associated with an increased risk of colorectal adenomas. The association with recurrent adenomas is inadequately studied. We prospectively examined the relationship between insulin biomarkers and the risk of recurrent adenomas.

Materials and Methods—Our analysis included 167 subjects with one or more adenomas detected on a baseline colonoscopy who had a surveillance colonoscopy within three to five years. We measured serum biomarkers in all subjects at baseline. ELISA was used to measure fasting plasma insulin, IGF-I, IGF-II, and IGF binding protein-3. The hexokinase assay was used to measure fasting plasma glucose by and immuno-turbidimetric assay to measure hemoglobin A1C.

Results—Subjects with recurrent adenomas were more likely to be male, overweight and have ≥3 adenomas at baseline. We found no significant associations between insulin (OR=1.6, 95% CI 0.7-3.5), glucose (OR=1.4, 95% CI 0.7-3.1), IGF-I (OR=0.7, 95% CI 0.3-1.5), IGF-II (OR=1.0, 95% CI 0.5-2.3), IGFBP-3 (OR=0.1, 95% CI 0.5-2.1), or anthropometric measures and recurrent adenomas.

Conclusion—Our results do not support a role for insulin biomarkers and recurrent colorectal adenomas.

Keywords

insulin; colorectal adenoma; insulin-like growth factor

Introduction

Colorectal cancer (CRC) is the third leading cause of cancer death in men and women in the United States.[1] Obesity and type II diabetes are risk factors for development of CRC. Each condition is associated with increased serum glucose levels, hyperinsulinemia and insulin resistance.[2-7] Patients who use prescription insulins have a 3-fold increased risk of developing colorectal adenomas and CRC.[8] Insulin's role in carcinogenesis is proposed to be due to the hormone's positive effect on the growth and proliferation of cells.[9-11] Insulin has structurally related peptides, insulin-like growth factor (IGF) I and II, that have been shown to regulate cell proliferation and suppress apoptosis when bound to their receptors.[12] IGF binding proteins (IGFBPs), especially IGFBP-3, sequester and inhibit the actions of IGFs.[12]

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While a number of cross-sectional and prospective studies have shown a positive relationship between plasma insulin, IGFs and the risk of colorectal adenomas, and an inverse relationship with IGFBP-3, the results are inconsistent.[13-23] Some studies have reported no change in the risk of CRC or adenomas with insulin or IGFBP-3, while two papers reported that increased IGF-I was associated with decreased adenoma recurrence.[11, 15, 20, 24-31] Others observed that the association was dependent on the histologic grade of adenoma, with high levels of IGFBP-3 associated with decreased risk only for high grade adenomas.[13, 19] Most of these studies examined only one or two markers each, and no study prospectively investigated the effect of IGF-II on colorectal adenoma recurrence.

Patients with a history of colorectal adenomas are at increased risk for CRC. Guidelines recommend surveillance endoscopy to reduce the risk of CRC. Surveillance endoscopy is expensive and not without harm. Insulin biomarkers might help guide surveillance by helping to stratify risk. We prospectively evaluated a panel of markers in the insulin-IGF axis to test the hypothesis that insulin and IGFs concentrations would be associated with an increased risk of recurrent adenomas. We also hypothesized that concentration of IGFBP-3 would be inversely related to adenoma recurrence. Finally, we explored the relationship between diet, lifestyle and anthropometric measures to assess the risk of adenoma recurrence.

Methods

Study population

Our subjects were participants in the Diet and Health Study (DHS) III and IV. The DHS were cross-sectional studies to assess environmental and lifestyle factors associated with colorectal adenoma. The DHS methods have been published in detail elsewhere.[15, 32] Study subjects had a baseline outpatient colonoscopy in Diet and Health Study (DHS) III or IV between August 1998 and March 2000 and November 2001 and December 2002, respectively, at the University of North Carolina Hospitals (UNC). The DHS collected data on age, sex, educational background, BMI, race, smoking history, nonsteroidal anti-inflammatory drug (NSAID) use, and physical activity. Detailed information was obtained in a phone interview using a validated instrument.[15, 32] The DHS excluded: age <30 years, previous colon cancer, colon resection, polyposis or colitis.

We limited our analysis to subjects with one or more adenomas detected during the baseline colonoscopy who returned for a surveillance colonoscopy. We only included subjects with insulin and insulin related biomarkers measured at the baseline colonoscopy. Recurrence was defined as a colorectal adenoma detected at the time of the repeat colonoscopy in subjects with an adenoma at baseline. A pathologist classified all polyps using standard pathologic criteria. Advanced adenomas were defined as villous histology, one or more adenomas larger than 1cm or more than three adenomas. The study was approved by the institutional review board at UNC School of Medicine.

Data collection

Study participants underwent colonoscopies after an overnight fast. At the time of the initial colonoscopy, the research assistant measured weight, height, waist-to-hip ratio and took blood samples. A telephone interview conducted within 12 weeks from the initial colonoscopy obtained information on diet and lifestyle factors. Dietary information was obtained using the Block food frequency questionnaire or NCI quantitative Diet History Questionnaire version 1.0.[15, 32]

Laboratory analysis

Blood samples were obtained at the time of the initial colonoscopy and processed to separate the plasma. Plasma was stored at -80°C in multiple aliquots until assayed to prevent repeated freezing and thawing. Fasting plasma insulin, IGF-I, IGF-II, IGFBP-3, were measured by ELISA as previously described using Diagnostic Systems Laboratory (Webster, TX).[15, 32] Fasting plasma glucose was measured by hexokinase assay (Sigma, St. Louis, MO) (DHS III), and hemoglobin A1C (HbA1C) (DHS IV) by immuno-turbidimetric assay (Ortho Clinical Diagnostics, Rochester, NY). As some subjects only had fasting glucose measured while others had HbA1C measured, we combined the glucose and HbA1C into one dataset for the baseline characteristics. To achieve this, we used a linear regression model as described by Rohlfing et al to convert HbA1c values into glucose equivalents using the following equation: mean plasma glucose (mg/dl)=(35.6 × HbA1c)–77.3.[33]

Statistical analysis

Baseline characteristics for recurrent and non-recurrent groups were compared using Fishers exact test for categorical variables and t-test (for means) and the Mann-Whitney test (for medians) for continuous variables. Insulin and related markers were log-transformed because those measures were not normally distributed. Then mean logs were compared via a t-test. Odds ratios and 95% confidence intervals were calculated to compare baseline tertiles of biomarkers to adenoma recurrence using logistic regression. Logistic regression models were run with follow-up adenoma as the response and baseline characteristic of interest as the predictor. Unadjusted models were run as well as models adjusting for age, race and sex. P-values < 0.05 were considered statistically significant. All analyses were performed using SAS Version 9.2 (SAS Institute, Cary, NC).

Results

We identified 403 subjects with one or more colorectal adenomas on baseline colonoscopy. Of these, 253 returned for a repeat colonoscopy. A total of167subjects had baseline plasma insulin, IGF-I, IGF-II and IGFBP-3 and glucose levels measured. Compared to those without recurrent adenomas, a higher proportion of subjects with recurrent adenomas were male, overweight and had ≥3 adenomas at baseline (Table 1). Although plasma levels of insulin were higher in those with recurrent adenomas compared to no recurrent adenomas, this was not statistically significant (p=0.16) (Table 1). IGF-I, IGF-II, IGFBP-3 and glucose at baseline were not significantly different between those with and without recurrent adenomas (Table 1).

While the risk of adenoma recurrence increased with increasing insulin and decreased with IGFBP-3, especially for those with baseline advanced adenomas, the trend was not statistically significant (p=0.32 and p=0.24 respectively) (Table 2). Similarly, IGF-I, IGF-II and glucose did not reveal any appreciable trends (Table 2).

When baseline anthropometric measures and adenoma characteristics were analyzed for adenoma recurrence, having 3 or more adenomas at baseline was significantly related to adenoma recurrence (OR=4.7, CI 95% 1.9-11.5)(Table 3). Adenoma size ≥1cm, BMI ≥25, villous histology, NSAIDs use, smoking, or calcium intake did not reveal significant associations (Table 3).

Discussion

Our study prospectively evaluated the contribution of insulin, glucose, IGF-I, IGF-II and IGFBP-3 to the risk of recurrent adenomas. We assayed these biomarkers as well as other

factors known to affect adenoma risk at the time of initial colonoscopy. We then determined whether baseline characteristics would predict future adenomas. Specifically, we tested the hypothesis that a single measure of circulating levels of plasma insulin and insulin related peptides would be positively correlated with risk of colorectal adenoma recurrence. Our results revealed that there was no significant association of insulin with adenoma recurrence. Likewise, there were no associations between IGF-I, IGF-II, IGFBP-3and recurrence. The only risk factor that predicted recurrence was ≥3 adenomas during the initial colonoscopy. We observed a trend toward recurrent adenoma risk with higher BMI which is consistent with the published literature.[34, 35] Likely because of small numbers, significant correlations were not found between smoking, calcium and NSAID use with recurrent adenomas even though smoking is reported to increase the risk while calcium and NSAID use decrease the risk of adenomas.[36-42]

Given the conflicting results of prior literature on effects of insulin, glucose, IGF-I, IGF-II, and IGFBP-3 on adenoma risk as well as inherent biases and limitations of cross-sectional studies, we evaluated these biomarkers in a prospective fashion. In our sample increasing insulin did not significantly increase the risk for adenoma recurrence. Biologically it is plausible that higher insulin levels increase the risk for adenoma formation. We previously demonstrated that increasing insulin was associated with decreased apoptosis, and these were associated with adenoma incidence.[15] Because all of the subjects in this study had adenomas, they were at the higher end of the risk spectrum and it may not have been possible to detect associations in this small study.

We did not observe any significant relationships between IGF-I and adenoma recurrence. This contradicts the result of two prospective studies that observed an inverse association of increasing tertiles of IGF-I with decreased risk of adenoma recurrence.[22, 23] A potential explanation could be the different patient populations in these studies. Hoyo et al demonstrated that serum IGF-I and IGFBP-3 differ by race and smoking status, and our study included higher proportion of African Americans than that of Jacobs et al.[23, 43]

We decided to evaluate the role of IGF-II because the risk for CRC has been shown to increase with higher quartiles of IGF-II.[27, 44] To the best of our knowledge, this is the first study prospectively evaluating the relationship between IGF-II and colorectal adenoma recurrence. We did not observe an association between IGF-II and adenoma recurrence in this study. As proliferating CRC cells are associated with overexpression of IGF-II and its receptors[45, 46], it is possible that the effects of IGF-II are more prominent late in the process of carcinogenesis rather than in the earlier stages of neoplasia, such as in colorectal adenomas.

Our current analysis had several strengths. This was a prospective study focusing on the temporal effect of insulin-IGF axis on colorectal adenoma recurrence. Further, we attempted to incorporate many relevant CRC and adenoma risk factors and investigated plasma insulin, glucose, IGF-I, IGF-II and IGFBP-3. However, as participants were volunteers and selected for initial colonoscopy, the conclusions may not be exactly generalizable to the entire population. Also, we only had one time point for biomarker collection and thus, were unable to assess the effect of change in the levels of these markers over time on the recurrent adenoma risk. Future studies could address the possible differential influence of insulin and IGF's on advanced adenomas at baseline and at follow up.

In conclusion, these data do not suggest a role of circulating insulin in the development of recurrent adenomas. The current study also does not support the use of a single measurement of IGF-I, IGF-II or IGFBP-3 in surveillance of recurrent colorectal adenomas. As such, these biomarkers are not likely to be useful to predict risk for recurrent adenomas.

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Table 1

Baseline characteristics of study participants who returned for follow up.

Characteristic	Recurrent adenomas (n=96)	No recurrent adenomas (n=157)	p value
Age (mean (SE))	60.4 (1.0)	58.6 (0.8)	0.17
Race (n (%))			
Caucasian	71 (82)	109 (76)	0.41
African American	16 (18)	34 (24)	
Gender (n (%))			
Male	63 (66)	80 (52)	0.03
Female	32 (34)	75 (48)	
Smoking (n (%))			
Never	39 (43)	68 (47)	0.47
Former	40 (44)	54 (37)	
Current	11 (12)	24 (16)	
Family history of CRC (n (%))	19 (21)	27 (19)	0.74
BMI (n (%))			
Normal	26 (28)	56 (38)	0.003
Overweight	42 (45)	35 (24)	
Obese	25 (27)	55 (38)	
Waist-hip Ratio (mean (SE))	0.965 (0.008)	0.943 (0.009)	0.08
Calories kcal/day (mean (SE))	1,737 (77)	1,777 (62)	0.76
Time to repeat colonoscopy, days (mean (SE))	1,231 (80)	1,275 (50)	0.64
Adenoma grade (n (%))			
Tubular	83 (86)	140 (89)	0.55
Villous	13 (14)	17 (11)	
# adenomas (n (%))			
1-2	62 (75)	132 (91)	0.002
≥3	21 (25)	13 (9)	
Adenoma size (mean (SE))			
<1cm	64 (67)	116 (75)	0.19
≥1cm	32 (33)	39 (25)	
Diagnosis of diabetes (n (%))	16 (18)	22 (15)	0.59
Alcohol grams per day (median (min, max))	1.5 (0, 63.3)	2.5 (0, 81.2)	0.88
Calcium mg per day (mean (SE))	901 (50)	984 (46)	0.23
NSAID use # per month (median (min, max))	0 (0, 122)	0 (0, 184)	0.69
Insulin, microunits/mL (mean (SE))†	2.10 (0.12)	1.90 (0.09)	0.16
IFG-I,ng/mL(mean (SE))†	4.88 (0.06)	4.90 (0.05)	0.85
IFG-II, ng/mL (mean (SE))†	6.29 (0.05)	6.32 (0.03)	0.57
IGFBP-3, ng/mL (mean (SE))†	7.81 (0.05)	7.78 (0.04)	0.64
Glucose, mg/dL (mean (SE))†	4.82 (0.03)	4.81 (0.03)	0.80

†Recurrent adenomas (n=67) and No recurrent adenomas (n=100) for insulin and other markers in the insulin-IGF axis. These were log transformed due to skewness of data.

Table 2

Odds ratios (OR) (95% CI) for adenoma recurrence risk according to tertiles of biomarkers.

	Reference	OR (95% CI) for all baseline adenomas		OR (95% CI) for only baseline advanced adenomas*	
Measure	**Tertile1**	**Tertile2**	**Tertile3**	**Tertile2**	**Tertile3**
Insulin	1.0	0.9 (0.4, 2.0)	1.6 (0.7, 3.5)	1.5 (0.3, 8.5)	2.9 (0.4, 21.8)
IGF-I	1.0	0.6 (0.3, 1.3)	0.7 (0.3, 1.5)	1.4 (0.3, 6.1)	0.5 (0.09, 3.0)
IGF-II	1.0	1.0 (0.4, 2.1)	1.0 (0.5, 2.3)	0.6 (0.1, 2.8)	1.1 (0.2, 6.1)
IGFBP-3	1.0	0.5 (0.2, 1.1)	1.0 (0.5, 2.1)	0.2 (0.03, 1.1)	0.6 (0.1, 3.2)
Glucose	1.0	0.8 (0.3, 1.8)	1.4 (0.7, 3.1)	0.4 (0.08, 2.3)	0.9 (0.2, 4.2)

Adjusted for age, race and gender.

*Advanced adenomas included villous histology, size >1cm or >3 adenomas.

Table 3

Baseline characteristics and OR (95% CI) for recurrence of adenomas.

	Unadjusted OR (95% CI)	Adjusted† OR (95% CI)
Villous histology		
No	1.0	1.0
Yes	1.3 (0.6, 2.8)	1.3 (0.5, 3.1)
# of adenomas		
1-2	1.0	1.0
≥3	3.5 (1.6, 7.3)	4.7 (1.9, 11.5)
Size of adenomas		
<1cm	1.0	1.0
≥1cm	1.5 (0.9, 2.6)	1.5 (0.8, 2.8)
NSAIDs >15 times/month		
No	1.0	1.0
Yes	1.0 (0.5, 1.7)	0.7 (0.4. 1.5)
Smoking		
Never	1.0	1.0
Former	0.8 (0.4, 1.8)	1.2 (0.6, 2.1)
Current	1.3 (0.7, 2.3)	0.9 (0.4, 2.0)
BMI		
Normal	1.0	1.0
Overweight, Obese	1.6 (0.9, 2.8)	1.6 (0.9, 3.0)
Calcium		
<1000mg/day	1.0	1.0
≥1000mg/day	0.9 (0.5, 1.6)	0.9 (0.5, 1.7)

†Adjusted for age, race and gender.