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Abstract

Background—Dysregulation of the insulin-like growth factor (IGF) system, a common consequence of adiposity-induced insulin resistance, may be a key underlying mechanism linking excess body weight with colon cancer. Evidence has been derived from studies of cancer and polyps. Supporting data about aberrant crypt foci (ACF), putative pre-polyp changes, have been generated only from animal studies to date.

Methods—We randomly selected 26 patients with sex-specific elevated waist-hip-ratio (WHR) and 26 with normal values from a series of 150 patients seeking routine colonoscopy at the University of Connecticut Health Center. Cross-sectional analyses were performed of ACF number (<5, ≥5) in relation to total IGF1, IGF-binding protein-3 (IGFBP3), insulin, body mass index (BMI), WHR and waist circumference (WC). Visualized ACF in the 20 cm of the distal colon were counted using advanced endoscopic imaging.

Results—Patients with ≥5 ACF had higher BMI, WHR, and WC compared with patients with >5 ACF ($p = 0.04$, $p = 0.03$, and $p = 0.01$, respectively). IGFBP3 was reduced ($p = 0.02$) and IGF1:IGFBP3 molar ratio was greater ($p = 0.03$) in patients with ≥5 ACF. We did not observe significant associations between ACF number and insulin or total IGF1.

Conclusions—Our study provides the first report in humans of a possible association of ACF prevalence and IGF1 bioavailability as characterized by IGF1:IGFBP3 molar ratio and IGFBP3 level. More research is needed to determine whether this relationship is varied by ACF features (e.g., size, dysplasia, molecular changes), synchronous cancer and polyps, and is modified by colon cancer risk factors.

Keywords

Aberrant crypt foci; Obesity; Adiposity; Colon cancer; IGF1; IGFBP3; Insulin resistance; Metabolic syndrome

Introduction

Adiposity continues to attract attention in colorectal cancer (CRC) research as a potentially modifiable risk factor. Increasing evidence suggests that obesity-induced insulin resistance may be a core pathology linking excess body fat with colon cancer risk [1–3]. Insulin resistance, defined as cellular unresponsiveness to the effects of insulin, results in increasingly higher levels of insulin needed to achieve normal glucose levels [1, 4]. Clinically, insulin resistance is manifest as a cluster of metabolic abnormalities and a number of hypotheses have been put forth to explain the specific underlying mechanisms by which insulin resistance might increase colon cancer risk. Dysregulation of the insulin-like growth factor (IGF) system and hyperinsulinemia are considered key candidate processes [4].

IGFs are strong mitogens that play a pivotal role in cellular proliferation, differentiation, and apoptosis [4, 5]. The biological activity of IGFs is modulated by the actions of circulating IGF binding proteins (IGFBPs), local production of IGFs, IGFBPs and IGFBP proteases, and interactions with receptors [6]. The key function of IGF-binding proteins in the peripheral circulation is regulation of IGF availability [6]. More than 90% of IGFs are bound to IGFBP3 [5]. In the hyperinsulinemic state, circulating levels of free IGF1 rise because of

a decrease in IGFBPs [1]. Subsequent to IGF binding in colonocyte receptors, a number of actions may be prompted that favor tumor growth such as inhibition of apoptosis, promotion of cell proliferation, and angiogenesis [1, 7]. Hyperinsulinemia is thought to promote colon carcinogenesis through stimulation of cellular growth and inhibition of apoptosis. Other potentially carcinogenic effects of insulin resistance stem from abnormal levels of glucose and fatty acids, which include: altered intracellular signaling, chronic inflammation resulting from production of reactive oxygen species, and enhanced proliferation of transformed colonocytes due to increased energy supply [1].

CRC develops over many years, and a multi-step process has been posited involving transition from normal mucosa to early adenoma, then to late adenoma, and, lastly, to carcinoma [8]. Improved chromoendoscopy techniques have made it possible to locate and characterize pre-neoplastic changes in colon tissue. Known as aberrant crypt foci (ACF), these early lesions exhibit many molecular features of advanced colonic neoplasms, including cancer. In animal models, these surface abnormalities appear in the distal colon within two weeks after carcinogen treatment [9]. ACF can exhibit nuclear atypia and dysplasia [8, 10–13]. ACF also show increased proliferative activity, K-*ras* and B-RAF mutations, microsatellite instability as well as other genome-wide alterations [14–19] suggesting that they may be precursors of colon cancer. Human ACF share a similar histology to those in rodent models and are present in grossly normal-appearing colon tissue from CRC patients [20].

Although there have been numerous studies of the relationship of the IGF system and insulin with colon cancer, precursor lesions have not been fully explored [21]. There is promising evidence for associations with colorectal adenomas [22–25], yet, to our knowledge, there have been no human studies that have examined ACF. Causal evidence has been reported from animal studies, however, which have linked development of ACF with experimentally modified levels of circulating IGF or insulin [26–32]. Genetically IGF1-deficient mice exposed to the colon carcinogen azoxymethane developed significantly fewer ACF than normal-IGF controls [32]. Transgenic mice programmed to produce above-normal IGFBP3 had significantly fewer ACF than wild-type mice after introduction of a carcinogen [26]. In studies of F344 rats treated with carcinogen, significantly larger ACF were found in rats injected with insulin post-carcinogen compared with controls who did not receive insulin [29], and in rats with experimentally induced insulin resistance compared with normal controls [30].

Should the impact of a dysregulated IGF system be observed in ACF, it might offer new insight into CRC etiology. In the cross-sectional study of 51 colonoscopy patients reported here, we examined ACF prevalence in relation to circulating levels of total IGF1, IGF-binding protein-3, insulin, as well as anthropometric measures of obesity such as body mass index (BMI), waist-hip-ratio (WHR), and waist circumference (WC).

Methods

Study population

We conducted a cross-sectional study of 51 patients from the consecutive pool of 150 patients receiving standard colonoscopy at the Colon Cancer Prevention Program of the University of Connecticut Health Center from November 2005 to April 2006. Patients attended the clinic for routine screening or surveillance due to a pathological finding (e.g., polyp) at a previous exam. From these, we randomly selected 26 patients whose WHRs were above normal for their sex and 26 patients with normal sex-specific WHR. Cut-points for elevated WHR (>0.90 for males, >0.85 for females) are in accordance with the criteria for central adiposity in the WHO definition of the metabolic syndrome [33]. One patient was

excluded because of missing data on ACF. Participants were selected from those who had provided consent for the ACF Study (IRB #03-203-2).

Patient data

Prior to the colonoscopy clinic visit, an Advanced Practice Registered Nurse (APRN) took measurements of weight, height, hip (i.e., widest torso circumference), and waist (i.e., narrowest torso circumference) as defined in Gram et al. [34]. At the colonoscopy exam, a fasting blood sample (three heparinized vials at 10 ml) was drawn from the intravenous line and transported to the research laboratory. Samples were separated into 0.5 ml aliquots and frozen at −80°C.

Colonoscopy procedure and ACF detection

As stated, standard colonoscopy was performed on all patients for clinical purposes. Colon preparation prior to the clinic visit was undertaken with polyethylene glycol-based liquid as described in our prior reports [14, 35]. ACF detection took place post-colonoscopy, and lasted up to 30 min during a pre-scheduled slot. The examination employed a magnifying colonoscope (Olympus Close Focus Colonoscope XCF-Q160ALE), which allows clear visualization from 2 to 100 mm at 60× magnification. The distal 20 cm section of colon including the rectum was examined after washing with 10–20 ml of 20% *n*-acetyl-cysteine followed by water wash to remove surface mucus. Then a freshly prepared solution of 0.5% methylene blue was applied for contrast staining using spray catheters. Endoscopists waited 2 min for absorption of dye. Under close focus magnification, a finding is accepted as an ACF if two or more crypts are darkly stained and have lumen diameters that are 1.5–2.0 times those of surrounding crypt lumens. On tangential view, ACF were required to be raised above the mucosal surface. If apparent on the monitor, the following criteria also were assessed to confirm identification: round, dilated, slit, or star-shaped lumen, or thick crypt walls having compressed lumens. To ensure that ACF were not double-counted or missed, endoscopists employed established inspection techniques such as dividing the colon into four quadrants or withdrawing the scope in a clockwise fashion. Narrow-band imaging (NBI) for detection of ACF was used for three patients, which is a non-dye imaging technique that enhances mucosal and vascular detail. In a repeated measures study (unpublished), our group found that ACF counts detected by NBI and CE are comparable when broad categories are reported, instead of actual count, such as the dichotomous classification scheme used in this current study. Inter-rater variability was addressed by the requirement that two raters, trained in ACF determination, confer and reach agreement on the determination of an ACF finding at the time of chromoendoscopy as visualized on a video monitor. ACF in the 20 cm distal region were counted and digital images captured. A maximum of 10 biopsy specimens of ACF were taken within the distal 20 cm using forceps (Precisor EXL, CR Bard) (Fig. 1).

Laboratory methods

Blood specimens were available for 41 of the 51 participants. Total IGF1 (i.e., bound and unbound combined), IGFBP3 and insulin in plasma were measured using commercially available ELISA kits (DSL, Webster TX, 10-5600; DSL, Webster TX, 10-6600; Alpco Diagnostics, Salem NH, 28-10-1113-01; respectively). Results were reported as nanograms per milliliter (ng/ml) for IGF1 and IGFBP3, and milliunits per liter (mU/l) for insulin. The molar ratio of total IGF1 to IGFBP3 was employed as a surrogate measure of free IGF1 to mitigate concerns about specimen processing time. Recent findings suggest that results from commercially available ELISAs of free IGF1 tend to include increasing amounts of easily dissociable IGF1 as processing time increases whereas total IGF1 and IGFBP levels did not vary with processing time [36]. We computed the molar ratio by converting IGF1 and

IGFBP3 weight measurements into nanomoles per liter (nmol/l) using factors 0.13 and 0.25, respectively [37]. Standards and negative controls were included in all the ELISAs.

Variables and statistical analyses

The number of ACF were categorized into two groups (<5, ≥5), hereinafter referred to as low and high ACF. Biomarkers, BMI, WHR, waist circumference, and age were analyzed as continuous variables in the non-parametric Mann-Whitney U test for independent groups. BMI was defined as weight divided by height [2] (kg/m^2), and categorized according to the following established groups [33, 38] for use in descriptive analyses: Underweight (<18.5), Normal (18.5–24.9), Overweight (25.0–29.9), Obese I (30.0–34.9), Obese II (35.0–39.9), and Obese III (≥40.0). We examined WC and WHR as measures of central adiposity, due to recent evidence suggesting that central fat may be superior to BMI in estimating the etiologic role of excess fat in CRC [1]. Cut-points for elevated WHR (>0.90 for males, >0.85 for females) followed WHO criteria [33] and were employed in descriptive analyses. Sex-specific elevated WC was defined as >40 in (102 cm) waist for males and >35 in (88 cm) for females [38]. To identify linear associations among putative predictors of ACF prevalence, we calculated Spearman's ρ rank correlation coefficients among the following continuous variables: total IGF1, IGFBP3, IGF1:IGFBP3 molar ratio, insulin, BMI, WHR, WC, and age. SPSS version 16.0 was used, and tests were two-sided in all the analyses.

Results

Characteristics of the study sample are described in Table 1. Most participants (86.3%) were aged ≥50, and there was a roughly equal distribution of males and females. A majority of patients were either overweight or obese (79.5%) as defined by BMI, and there was a comparable distribution of patients in the sex-specific categories of WHR (normal and high) reflecting our participant selection procedure. Regarding WC, 66.7% of women had elevated waist sizes (>35.0 in) compared to only 37.0% of men (>40.0 in).

As reported in Table 2, ACF low and high groups (<5 and ≥5) did not vary by age. Having ≥5 ACF was somewhat more frequent in men than women (81.5% vs. 70.8%, respectively), but this difference was not statistically significant. The two ACF groups differed significantly with respect to anthropometric measures of excess body weight in analyses of males and females combined. Mean BMI in the low ACF group was 26.3 compared to 29.7 in the ACF high group ($p = 0.04$). Likewise, patients in the high ACF group tended to have higher WHR and WC ($p = 0.03$ and $p = 0.01$, respectively). Among females, those in the high ACF group tended to have significantly higher WHR values compared with females in the low ACF group (0.86 vs. 0.80, $p = 0.04$), with the mean WHR in the high ACF group being somewhat above the sex-specific cut-point (>0.85) for the elevated risk category of WHR. Although a similar pattern was observed among males regarding WHR, the differences did not reach statistical significance. Nor did stratification by sex regarding WC reveal statistically significant differences. Table 3 contains the correlation coefficients between biomarkers and adiposity measures. Insulin level was strongly correlated with BMI and WC, but not with WHR. Total IGF1, IGF1:IGFBP3 molar ratio, and IGFBP3 were found to not be significantly correlated with any of the three measures of adiposity.

Participants in the high ACF group tended to have greater IGF1:IGFBP3 molar ratios (i.e., representing more unbound IGF1) compared to the low ACF group ($p = 0.03$), although the spread of data points was wide in both ACF groups (Fig. 2a). We found a significant inverse association between ACF number and circulating levels of IGFBP3 ($p = 0.02$), yet there is notable overlap of these two distributions also (Fig. 2c). Levels of either total IGF1 (Fig. 2b) or insulin (Fig. 2d) were found not to differ significantly between ACF high and low groups.

Discussion

Our study offers the first report in humans, to our knowledge, of a possible association of IGF1 bioavailability and prevalence of ACF. Our findings are consistent with those of several animal studies that have demonstrated a causal link between aberrations in the IGF system and ACF count [26–30, 32]. Our findings with respect to central adiposity are consistent with a recent human study by Takahashi et al. [39]. who reported that a relatively high level of visceral fat was associated with increased ACF count. Further, our study is coherent with the long-standing epidemiological evidence of a link between excess body weight and CRC [1] and the accumulating evidence regarding other forms of early neoplasia [1, 40].

Our findings also reflect the growing body of knowledge regarding the IGF system and human colorectal neoplasia. Several human studies have reported evidence of a link between aberrations in the IGF system and incidence of colorectal adenomas, particularly advanced adenomas [22–24]. A recent case-control study, however, of 756 colonoscopy patients reported that hyperinsulinemia and hyperglycemia, but not IGF abnormalities, were associated with increased risk of colonic adenoma [21].

The non-significant difference in mean insulin levels between participants with low and high ACF counts (4.2 vs. 7.1 mU/l, respectively, $p = 0.20$) was not supportive of animal reports linking increased levels of circulating insulin with development of ACF. This is troubling because hyperinsulinemia, a hallmark of insulin resistance, is considered a likely biological mechanism of increased risk for colon cancer and adenoma [1, 21]. The association between insulin and ACF seen in controlled animal studies, however, may be challenging to replicate among free-living humans due to high intra-individual variation in insulin level. IGF1 and IGFBP3 levels, on the other hand, have shown high reproducibility in repeat assessments over long periods of time [41, 42]. Insulin levels tend to be labile even when measured in the fasting state, and particularly if the length of the fasting period was not standardized [43] as in our study. Also, insulin measured after preparation for a colonoscopy may not reflect true levels because of the physiological stress encountered from prolonged fasting and severe bowel evacuation. Clarification of this methodological question is warranted in order to determine how best to obtain representative insulin levels in patient-based colonoscopy studies. Perhaps, obtaining fasting insulin levels prior to colonoscopy preparation may be one solution. Further, lack of statistical significance might be explained in part by misclassification of insulin status in some patients who may have been approaching Type-2 Diabetes and, thus, had comparatively low levels due to progressive loss of beta-cell function [44]. Prior hyperinsulinemia might have accounted for ACF prevalence in those patients. Clinically confirmed diagnoses of pre-diabetes/insulin resistance is recommended for future studies. Lastly, as our findings showed a somewhat suggestive mean difference (non-significant) in insulin level between low and high ACF groups, it is conceivable that hyperinsulinemia may exert a comparatively smaller effect which our modest sized study might have been underpowered to detect.

Evidence for a role of the IGF system in CRC development is growing but clarification is still needed. In a meta-analysis of population-based studies of IGF1 and IGFBP3 in four cancer sites, Renehan [45] found that relatively high levels of circulating IGF1 were associated with increased risk of CRC [24, 46–49]. In contrast, there was no statistically significant association of CRC risk with levels of circulating IGFBP3 in the overall meta-analysis [45], yet two of the five studies included in the report observed statistically significant inverse associations [24, 46]. The other three studies reported null effects [47–49]. Dose-response trends were not found for either marker in any of the studies [45]. It has been suggested that sample medium used in studies (e.g., EDTA plasma, heparin plasma

sampling, serum sampling) could partly explain differences across studies given known variation between serum and EDTA plasma levels of IGF markers [45]. Also, concentrations of IGF peptides are known to vary markedly across ethnic groups [50, 51].

Our findings should be interpreted with caution. A key limitation is that the size of our study was small, suggesting the possibility of unreliable estimates. Also, as our findings were based on univariate analyses, multivariate methods are needed in the future to determine whether the observed relationships are maintained when established or emerging CRC risk factors are included in statistical models (e.g., family history of cancer, physical activity level, personal history of adenoma). Quality of the clinical history of the participants in our study was not adequately precise for use in analyses. It also would be of importance in future studies to examine epidemiologic correlates of IGF1 levels to help discern possible confounding in the association between the IGF system and ACF prevalence. Correlates with IGF1 levels have been reported in a number of studies. Among men, IGF1:IGFBP3 molar ratio was found to vary positively with dietary intake of specific animal proteins (i.e., milk, fish, poultry, but not red meat) [52]. IGF1 levels were reported to vary positively with total calorie consumption among men only [53] whereas this relationship was seen among women in another study [54]. IGF1 levels also were found to vary inversely with current hormone use among women in two studies [53, 55].

Surprisingly, Schoen [56] found that visceral adipose tissue was uncorrelated with IGF1, IGFBP3, or IGF1:IGFBP3 ratio in both men and women in a large community-based sample. The implication is that the link between excess body weight and disease does not necessarily involve aberrations in the IGF system. We also did not observe significant correlations between central adiposity and IGF markers. Yet our findings of potential associations of ACF prevalence with both adiposity and aberrant IGFBP3 levels suggest separate routes to early colorectal neoplasia. Multivariate analyses and follow-up studies, however, are needed to explore this suggestion.

Another potential limitation is that we examined ACF number at a single point in time only. A recent report suggests dynamic variation (i.e., appearance and disappearance) of ACF number from baseline to re-assessment 1 year later [57]. Investigators did not, however, examine putative explanatory variables such as weight gain or loss post-baseline. It should also be noted that ACF number based on a single measurement has been strongly correlated with presence of dysplastic foci, ACF size, and number of adenomas in a several studies [58, 59]. Nonetheless, fluctuation would suggest that broad categories of ACF number, as employed in our study, may be relatively more stable classifications of risk or interventional effect than would be the absolute number.

Another rationale for using broad count categories is that although ACF studies typically involve multi-rater consensus, as in our study, reliability of ACF determination remains to be quantified and standardized in the scientific arena [60].

Future analyses should take into account ACF size (i.e., number of crypts per focus) and presence of dysplasia, which are thought to be clinically important sub-characterizations [8, 58, 61]. There were no findings of dysplastic ACF in our study, so we could not address this question. Dysplastic ACF have been linked with a greater risk of synchronous advanced neoplasia, yet, typically, only a small proportion of ACF exhibits dysplasia [59]. Also, measurement of cellular activity in and nearby ACF is suggested for future investigations because membrane receptors as well as local marker expression mediate bioavailability of IGF1 in tissue.

A potential source of systematic bias may exist in studies of the relationship between obesity and ACF if obese individuals tend to have easier endoscopic exams, thus allowing more

time for detection of ACF. Difficulties in colonoscopy related to weight, however, appear to be limited to individuals with a BMI less than 22.0, and particularly so among females [62, 63]. The area of difficulty for most endoscopists is usually proximal to the hepatic flexure [64], which is beyond the area of the ACF exam in our study. A 30-min slot post-colonoscopy was scheduled for the ACF exam to afford adequate inspection time.

Overall, our study is the first report that lower circulating levels of IGFBP3 may be linked inversely to prevalence of ACF in humans. Our data also support recent findings of a positive association of ACF prevalence with central adiposity [39]. Our data add promising perspectives to the as yet small body of literature concerning epidemiological risk factors for ACF [59]. Findings require confirmation in larger studies of diverse populations that incorporate a wide range of circulating and tissue-based biomarkers, CRC risk factors, and, perhaps, multiple time points. We report this investigation as a first-generation epidemiological study of ACF so as to promote further characterization of these early lesions thought to be the potential markers of increased risk for advanced neoplasms including cancer.

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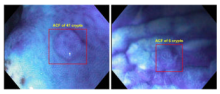

Fig. 1.
Endoscopic photographs of two ACFs detected by methylene blue dye[1]; [1]Visualization using Olympus Close Focus Colonoscope (XCF-Q160ALE)

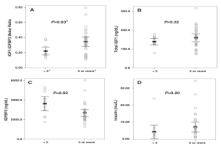

Fig. 2.

ACF number in relation to IGF1:IGFBP3 molar ratio, total IGF1, IGFBP3, and Insulin (n = 41)[1,2]; [1] Means and all data points displayed. [2] Error bars depict ±2 standard errors of the mean. [3] p-values derived from non-parametric Mann-Whitney U test of two independent groups (two-tailed test). [4] <5 ACF (n = 11). [5] Five or more ACF (n = 30)

Table 1

Characteristics of study participants (n = 51)

	***n* (%)**
Sex	
Male	27 (52.9%)
Female	24 (47.1%)
Age (years)	
39–50	7 (13.7%)
≥50	44 (86.3%)
Body mass index[a] (kg/m^2)	
Underweight (<18.5)	1 (1.9%)
Normal (18.5–24.9)	10 (19.6%)
Overweight (25.0–29.9)	19 (37.3%)
Obese I (30.0–34.9)	15 (29.4%)
Obese II (35.0–39.9)	4 (7.8%)
Obese III (≥40.0)	2 (3.9%)
Waist-hip-ratio[b]	
Male	
Normal (≤0.90)	14 (51.9%)
High (>0.90)	13 (48.1%)
Female	
Normal (≤0.85)	11 (45.8%)
High (>0.85)	13 (54.2%)
Waist circumference (in)[b]	
Male	
Normal (≤40.0)	17 (63.0%)
High (>40.0)	10 (37.0%)
Female	
Normal (≤35.0)	8 (33.3%)
High (>35.0)	16 (66.7%)

[a] Body mass index risk categories from National Institutes of Health[38]

[b] Waist-hip-ratio and Waist circumferences risk categories from Balkau et al. [33]

Table 2

ACF number in relation to age, sex, and adiposity (n = 51)

	ACF number		
	<5 (*n* = 12)	**≥5 (*n* = 39)**	***p*-value[a,b]**
Age (years)			
Mean	56.8 (10.9)[c]	57.7 (8.1)	0.72
Range	39–74	40–75	–
Sex			
Male	5 (18.5%)[d]	22 (81.5%)	0.37
Female	7 (29.2%)	17 (70.8%)	
Body mass index (kg/m^2)	26.3 (4.7)	29.7 (5.2)	0.04
Waist-hip-ratio			
All	0.83 (0.09)	0.88 (0.05)	0.03
Male	0.87 (0.05)	0.90 (0.05)	0.13
Female	0.80 (0.10)	0.86 (0.05)	0.04
Waist circumference (in)			
All	35.1 (5.3)	39.9 (5.5)	0.01
Male	36.6 (1.5)	40.6 (6.1)	0.17
Female	34.0 (6.8)	38.9 (4.8)	0.06

[a] Non-parametric Mann-Whitney *U*-test of two independent groups (two-tailed test)

[b] Pearson chi-square test for categorical data

[c] Mean (SD) for continuous variables

[d] *n* (%) for categorical data

Table 3

Spearman ρ correlation coefficient[a] matrix for biomarkers and adiposity measures (n = 41)

	Body mass index	Waist-hip-ratio	Waist circumference
Total IGF1	0.19	0.07	0.19
IGF1:IGFBP3 Molar ratio	0.21	−0.01	0.26
IGFBP3	−0.17	−0.15	−0.24
Insulin	0.49[b]	−0.02	0.40[c]

[a] Except where noted, $p > 0.15$;

[b] $p = 0.001$;

[c] $p = 0.01$