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Association of insulin and insulin-like growth factors with Barrett's oesophagus

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Abstract

Background—It is postulated that high serum levels of insulin and insulin growth factor 1 (IGF-1) mediate obesity-associated carcinogenesis. The relationship of insulin, IGF-1 and IGF binding proteins (IGFBP) with Barrett's oesophagus (BO) has not been well examined.

Methods—Serum levels of insulin and IGFBPs in patients with BO were compared with two separate control groups: subjects with gastro-oesophageal reflux disease (GORD) and screening colonoscopy controls. Fasting insulin, IGF-1 and IGFBPs were assayed in the serum of BO cases (n = 135), GORD (n = 135) and screening colonoscopy (n = 932) controls recruited prospectively at two academic hospitals. Logistic regression was used to estimate the risk of BO.

Results—Patients in the highest tertile of serum insulin levels had an increased risk of BO compared with colonoscopy controls (adjusted OR 2.02, 95% CI 1.15 to 3.54) but not compared with GORD controls (adjusted OR 1.55, 95% CI 0.76 to 3.15). Serum IGF-1 levels in the highest tertile were associated with an increased risk of BO (adjusted OR 4.05, 95% CI 2.01 to 8.17) compared with the screening colonoscopy control group but were not significantly different from the GORD control group (adjusted OR 0.57, 95% CI 0.27 to 1.17). IGFBP-1 levels in the highest tertile were inversely associated with a risk of BO in comparison with the screening colonoscopy controls (adjusted OR 0.11, 95% CI 0.05 to 0.24) but were not significantly different from the GORD control group (adjusted OR 1.04, 95% CI 0.49 to 2.16). IGFBP-3 levels in the highest

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Contributors AC, LL, GSC, WMG, DD and JW were responsible for the study design. GWF was responsible for recruitment of patients at the Cleveland Clinic site. BB and LB were responsible for data collection and patient enrollment. KBG and CLT were responsible for data analysis. AC is the principal investigator. All authors participated equally in the preparation of the manuscript.

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tertile were inversely associated with the risk of BO compared with the GORD controls (OR 0.36, 95% CI 0.16 to 0.81) and also when compared with the colonoscopy controls (OR 0.40, 95% CI 0.20 to 0.79).

Conclusions—These results provide support for the hypothesis that the insulin/IGF signalling pathways have a role in the development of BO.

INTRODUCTION

Obesity is an established risk factor for a number of cancers including oesophageal adenocarcinoma (OAC).[1–3] The obesity epidemic seen in developed countries has contributed, at least partially, to the increased incidence of OAC over the past three decades.[4–9] Barrett's oesophagus (BO), an acquired metaplastic columnar replacement of the normal stratified squamous epithelium of the distal oesophagus, is the only established precursor of OAC. Gastro-oesophageal reflux disease (GORD) is a strong risk factor for both BO and OAC and it is also more prevalent among obese subjects.[10] Studies examining the association of BO with obesity, as measured by body mass index (BMI), have found variable results with a meta-analysis reporting that increased BMI is associated with increased odds of BO.[11] Case-control studies that have looked specifically at fat distribution found that central adiposity, measured by an increased abdominal circumference or an increased waist-to-hip ratio (WHR), is associated with an increased odds of BO independent of BMI and GORD.[12, 13]

One plausible molecular mechanism for obesity-associated carcinogenesis is that central adiposity, which is hormonally active, promotes the release of free fatty acids, tumour necrosis factor α (TNFα) and resistins, inhibits the synthesis of adiponectins and ultimately leads to development of insulin resistance.[14] Increasing evidence from epidemiological studies suggests that increased levels of insulin promote carcinogenesis through its proliferative and anti-apoptotic actions and effects on the insulin growth factor family.[15–22] Insulin stimulates the production of insulin growth factor 1 (IGF-1) and downregulates production of insulin growth factor binding proteins 1 (IGFBP-1) and 3 (IGFBP-3). The net effect is an increase in 'bioavailable' IGF-1, which can bind to the insulin growth factor receptor complex and lead to post-receptor activation of the phosphoinositol-3-kinase (PI3K)/AKT/mTOR pathway as well as other pathways that participate in tissue proliferation.[23–25]

We hypothesised that higher serum levels of insulin and IGF-1 together with decreased serum levels of IGFBPs in the presence of central obesity could contribute to the development of BO. The aim of this hospital-based case-control study was therefore to compare serum levels of insulin, IGF-1, IGFBP-1 and IGFBP-3 in patients with BO with two separate control groups: subjects with GORD who did not have BO and screening colonoscopy controls.

METHODS

Study population

Study patients were recruited at two hospitals within the Case Comprehensive Cancer Center, University Hospitals Case Medical Center and Cleveland Clinic between January 2005 and May 2009. Potential participants were recruited at the time of their endoscopy visit for evaluation of GORD or screening for colorectal cancer. Study patients who completed upper endoscopy had four quadrant biopsies taken at 2 cm intervals along the tubular oesophagus above the squamocolumnar junction as part of the study protocol. Case subjects had at least a 1 cm segment of columnar mucosa identified at endoscopic examination and intestinal metaplasia present on histopathological examination. Prevalent and incident BO

cases were eligible for recruitment. Two separate control groups were recruited from University Hospitals Case Medical Center and Cleveland Clinic endoscopy centres during the same time period. The first control group comprised subjects with symptoms of GORD who had no evidence of BO on endoscopic and histopathological examination. Biopsies were obtained from GORD control subjects only if the endoscopist suspected the presence of columnar epithelium in the distal oesophagus. These GORD controls were enrolled within 2 weeks of recruiting cases of BO. GORD controls were matched with cases primarily for ethnicity, gender and age (±5 years). We had difficulty with recruitment of subjects for the GORD control group and matching them appropriately to the BO cases. Matching criteria were therefore relaxed to help with study accrual and recruitment of female African-American patients with GORD was allowed. As a result of this, matching of BO cases with the GORD controls was ineffective, potentially leading to confounding of examined associations. This problem was addressed by adjustment for relevant variables in multivariate logistic regression models and by conducting subgroup analyses. The second control group was recruited from patients undergoing screening colonoscopy and is referred to as the screening colonoscopy controls. These individuals were recruited during the same time period as the cases. Owing to inadequate matching, subgroup analyses were performed with screening colonoscopy controls matched 2:1 to BO cases based on ethnicity, gender and age. Individuals were excluded from all study groups if they had a previous diagnosis of cancer other than that of non-melanoma skin cancer, a history of diabetes mellitus, a history of previous surgery for obesity or active participation in chemoprevention trials. In addition to these exclusion criteria, individuals were excluded from the screening colonoscopy control population if they had a history of colon polyps or inflammatory bowel disease.

Baseline characteristics, anthropometric and serum measurements

All study patients underwent an initial structured interview. At this visit, basic demographic information and anthropometric measurements were obtained by a trained nurse. Collected data included subject age, gender, race, weight (kg), height (cm), waist circumference (cm) and hip circumference (cm). Subject weight was obtained on a levelled platform scale. Waist circumference was measured at the narrowest part of the torso. Hip circumference was measured at the level of the greatest lateral extension of the hips, using the greater trochanter as an anatomical landmark.[26] Study subjects with WHR >0.90 were considered to have central adiposity. Our definition of central adiposity was different from the one used by the WHO where the cut-off for defining central adiposity is 0.90 for men and 0.85 for women.

All subjects provided fasting venous blood samples at the time of initial interview or subsequent endoscopy. Subjects were instructed to fast after midnight and endoscopic procedures as well as blood sampling were completed during morning endoscopy blocks. The collected blood was divided into multiple aliquots, spun for 15 min at 600*g* and aliquots of plasma, serum and concentrated buffy coat were prepared and stored at −70°C. Specimens were processed within 4 h of blood sampling. Haemolysed, icteric or grossly contaminated samples were discarded. Serum glucose concentrations were determined on the YSI 2300 Stat Plus Glucose and Lactate Analyzer (YSI, Yellow Spring, Ohio, USA). Serum insulin concentrations were measured by the radioimmunoassay method using the Siemens analyser (Siemens Medical Solutions Diagnostics, Los Angeles, California, USA). Serum concentrations of IGF-1, IGFBP-1 and IGFBP-3 were measured by a two-step immunoassay (Diagnostic Systems Laboratories, Webster, Texas, USA). In addition to kit controls, aliquots of in-house serum controls were used to determine assay performance for all serum markers. Coefficients of variation (CV) were calculated for serum markers by summing intra-assay and inter-assay variability. CVs for glucose, insulin, IGF-1, IGFBP-1 and IGFBP-3 were 3.53%, 14%, 12%, 9.7% and 7.8%, respectively. Hyperinsulinaemia was defined as a value in the highest tertile of serum insulin measured in non-diabetic study

individuals. Insulin resistance (IR) was estimated based on Homeostatic Model Assessment (HOMA).[27] This model estimates insulin resistance from basal insulin and glucose concentrations using the following formula: HOMA-IR = FPI × FPG/405, where FPI is fasting plasma insulin concentration (μIU/ml) and FPG is fasting plasma glucose (mg/dl). Estimates from the HOMA model correlate well with measurements obtained from the euglycaemic clamp.[28]

Statistical methods

Simple descriptive statistics were performed to describe the frequencies of risk factors among cases and controls. Differences in the distribution of baseline characteristics between the case subjects and controls were compared using the t test for continuous data or the Pearson χ^2 test for categorical data. Continuous variables were explored as such and also grouped into tertiles. Division of variables into tertiles was performed based on distribution of the measurements in the control population for the given analysis (either all controls or the colonoscopy controls matched to the cases). Univariate and multivariate logistic regressions were performed to calculate ORs and the associated 95% CIs. OR estimates were adjusted for age, gender (male vs female), race (white vs non-white) and WHR. Models unadjusted for WHR were analysed. For variables that were grouped into tertiles, OR and the associated 95% CIs were calculated by comparing each of the two higher tertiles with the referent lowest tertile. p Values for trend across tertiles were calculated using tertile category numbers as continuous variables in respective multivariate regression models. All tests of statistical significance were two-sided and p values <0.05 were considered significant. Statistical analyses were performed in Statistical Analysis Systems software package V.9.2 (Cary, North Carolina, USA).

RESULTS

Demographics

The final study group comprised 135 individuals with BO, 135 with GORD and 932 screening colonoscopy controls. In our analyses, variables of interest were compared between BO cases and each of the control groups individually. In the matched subgroup analyses the study group comprised 91 individuals with BO and 182 screening colonoscopy controls (1:2 ratio). Baseline patient characteristics are shown in table 1.

Serum insulin and insulin resistance

Mean unadjusted serum insulin levels (table 2) in BO cases were not statistically different from those of the GORD control group (10.2 μIU/ml vs 9.1 μIU/ml, p = 0.33). In contrast, mean unadjusted serum insulin levels (table 2) were significantly higher in BO cases than in the screening colonoscopy control group (10.2 μIU/ml vs 7.4 μIU/ml, p = 0.001). In adjusted models (table 3), being in the highest tertile of serum insulin did not significantly increase the risk of BO compared with GORD controls (adjusted OR 1.55, 95% CI 0.76 to 3.15). Being in the highest tertile of serum insulin was associated with a twofold increase in odds for BO (adjusted OR 2.02, 95% CI 1.15 to 3.54) when BO cases were compared with the screening colonoscopy control group (table 3). However, the odds for BO were not significantly increased in the highest tertile of serum insulin compared with the matched colonoscopy controls.

IR was approximated from the homeostatic model for assessment of insulin resistance (HOMA-IR). In adjusted models, being in the highest tertile of HOMA-IR increased the odds of having BO more than twofold (adjusted OR 2.23, 95% CI 1.26 to 3.95) compared with the screening colonoscopy controls (table 3). However, BO case status was not

significantly associated with increased HOMA-IR when compared with the matched colonoscopy controls.

IGF-1 and IGFBP levels

Statistically significant differences were observed in the mean unadjusted IGF-1, IGFBP-1 and IGFBP-3 levels between the three study groups (table 2). Mean (SD) IGF-1 concentrations were highest in GORD controls (194.1 (71.4) ng/ml) and lowest in the screening colonoscopy controls (116.5 (42.7) ng/ml). Levels of IGFBP-1 were not significantly different in BO cases and GORD controls. Mean serum levels of IGFBP-1 in screening colonoscopy controls were significantly lower than those in BO cases or GORD controls. Mean (SD) IGFBP-3 levels were similar among the GORD controls and the screening colonoscopy controls (3721 (876) ng/ml and 3623 (833) ng/ml, respectively) but markedly increased compared with those observed in BO cases (3200 (945) ng/ml).

In the multivariate regression analyses comparing cases with GORD controls, there was no association between serum IGF-1 levels and BO (table 4). Increasing levels of serum IGFBP-3 did show an inverse association with BO in the highest tertile (adjusted OR 0.36, 95% CI 0.16 to 0.81). In comparison with the screening colonoscopy controls (table 4), a fourfold increased odds of BO was seen for those in the highest tertile of serum IGF-1 (adjusted OR 4.05, 95% CI 2.01 to 8.17). A statistically significant inverse association for BO was seen for those with the highest serum levels of IGFBP-1 (adjusted OR 0.11, 95% CI 0.05 to 0.24). Increasing levels of serum IGFBP-3 also showed an inverse association with BO (adjusted OR 0.40, 95% CI 0.20 to 0.79). This association was further strengthened by mutual adjustment of IGFBP-3 for IGF-1 and IGFBP-1 (table 5). Finally, an increased molar ratio of IGF-1:IGFBP-3 (surrogate for bioavailable IGF-1) was also associated with an increased odds for BO (adjusted OR 4.72, 95% CI 2.24 to 9.92). In the subset analysis of BO cases compared with matched screening colonoscopy controls, BO cases in the highest tertile of serum IGF-1 (table 4) also had an approximately sixfold increase in odds of having BO. Increased levels of IGFBP-1 and IGFBP-3 also had inverse associations with case status in the matched subset analysis, similar to the associations seen when all BO cases were compared with the larger group of all screening colonoscopy controls (table 4). The association between BO case status and serum markers was also repeated without adjustment for WHR. Estimates from these models are shown in table 6. Models unadjusted for WHR gave similar results to the WHR adjusted models. Comparisons of GORD controls and screening colonoscopy controls are shown in table 7.

DISCUSSION

This hospital-based case-control study found that subjects with BO have increased levels of insulin and IGF-1 compared with screening colonoscopy controls, supporting the hypothesis that higher levels of these growth factors associated with obesity contribute to the development of BO. IGFBP-1 and IGFBP-3, the two major insulin growth factor binding proteins, both showed inverse associations with BO in comparison with the screening colonoscopy controls. The molar ratio of IGF-1 to IGFBP-3, a surrogate measure for bioavailable or unbound IGF-1, was also increased in BO cases compared with colonoscopy controls with increasing odds across tertiles, consistent with this hypothesis.

Comparisons of insulin, IGF-1, IGFBP-1 and IGFBP-3 between BO cases and GORD controls showed that these two groups were fairly similar. Serum insulin levels and HOMA-IR were also similar between BO cases and GORD controls. IGFBP-3 was found to have an inverse association with BO case status compared with GORD controls. Serum levels of IGFBP-1 in BO cases did not differ from those in GORD controls. These results indicate that subjects with BO and those with GORD who do not have BO have similar BMIs,

similar proportions of central adiposity and fairly similar levels of serum insulin and bioavailable IGF-1.

Other observational studies have also examined the role of insulin in BO and oesophageal carcinogenesis. Ryan *et al*[29] found that individuals with long segment BO were significantly more obese and had higher fasting insulin levels than those with short segment BO, suggesting that obesity and elevated serum insulin levels play a role in the extent of metaplasia. Healy *et al*[30] examined the occurrence of the metabolic syndrome in subjects with BO and those with GORD and found that both groups were similar. In their study, insulin levels were actually higher in subjects with GORD than in those with BO (9.3 vs 7.5 mU/l, p = 0.02). Finally, Neale *et al*[31] recently reported that diabetes increased the risk of OAC compared with population controls, adding further support to the hypothesis that hyperinsulinaemia may mediate obesity-associated carcinogenesis.

Patients in the highest tertile of serum insulin were twice as likely to have BO than those in the lowest tertile compared with screening colonoscopy controls. Not surprisingly, increased HOMA-IR, a measure of insulin resistance, was also associated with a similar increase in the risk of developing BO. However, we found no significant differences in BMI, WHR, insulin levels and HOMA-IR of BO cases and GORD controls. Models adjusted and unadjusted for WHR did not give significantly different estimates of odds of BO. We cannot be certain whether the differences in raised insulin levels observed between BO cases and screening colonoscopy controls are simply associated with obesity and reflux or whether they contribute to the metaplastic process itself. Our case-control study design does not allow us to come to any conclusions about whether hyperinsulinaemia drives the progression from normal oesophageal tissue to BO or whether it is just reflective of the presence of metabolic syndrome in obese individuals with BO and GORD.

Postulating a relationship between IGF-1 and obesity-associated carcinogenesis is also reasonable given that obesity stimulates growth hormone secretion, which is the major determinant of serum concentrations of IGF-1. IGF-1 is important in tumorigenesis because of its role in the regulation of proliferation. IGF-1 activates the IGF-1 receptor (IGF-1R) family, which in turn triggers intracellular signalling cascades in the extracellular signal regulated kinase (erk) and phosphotidylinositol 3-kinase (PI3K) pathways, making insulin signalling both mitogenic and anti-apoptotic.[32–34] The differences in findings of observational studies examining serum levels of IGF-1 in relation to site-specific cancer risk may be because circulating levels of IGF-1 may not reflect tissue levels. Tissue levels of bioavailable IGF-1 and consequently IGF-1R activation are modulated by local paracrine concentrations of locally secreted IGFBPs.

Activation of the IGF-1R and systemic levels of IGF-1 may also be affected by polymorphisms in the receptor. One of the most common polymorphisms observed is G1013A. Healthy non-obese carriers of the A allele have lower circulating levels of IGF-1.[35] Obese individuals with the polymorphic A variant in IGF-1R are reported to have a fourfold increased risk for OAC (OR 4.81, 95% CI 1.09 to 21.15) whereas individuals with the G/G variant are not at increased risk of OAC (OR 2.69, 95% CI 0.41 to 17.62). Analysis of IGF-1R polymorphisms in BO cases has shown that, in comparison with asymptomatic population controls, obese individuals with the A variant were at threefold increased risk of having BO.[36] This effect is proposed to be mediated through altered receptor function due to gene transcription activity or mRNA stability.[37] McElholm *et al*[38] recently provided additional evidence for involvement of the IGF superfamily by identifying an IGF-1 (CA) microsatellite repeat that was significantly associated with reflux oesophagitis, and two single nucleotide polymorphisms—rs6214 and rs6898743—were associated with BO and OAC disease status, respectively. Polymorphisms in BO and GORD subjects were not

compared directly.[37] In contrast, Siahpush *et al*[38] found that circulating levels of IGF-1 or IGFBP-3 were not predictive of OAC risk or flow cytometric abnormalities in patients with BO followed long term. After adjustment for risk factors, higher levels of IGFBP-3 were associated with aneuploidy and the authors suggested that IGFBP-3 may have a role in early cancer development. Recent data also suggest that 75% of oesophageal adenocarcinomas overexpress IGF-1R,[39] and this over-expression—which is correlated with gender and depth of tumour invasion—is an independent predictor of survival in OAC.

The association between IGF-1 and BO observed in this study is similar to the association of IGF-1 with neoplasms of the colorectum, prostate and breast.[16–22] In a systematic review and meta-analysis published by Renehan *et al*,[2] elevated serum IGF-1 levels increased the risk of cancer at multiple body sites. Pooled OR from cohort studies showed a 1.5–2-fold increased risk of cancer associated with elevated IGF-1 levels. Since the majority of cases in the study were prevalent cases of BO under surveillance, we cannot determine if high levels of insulin or IGF-1 are present prior to disease onset or even at disease incidence. Our results suggest that elevated IGF-1 is associated with a fourfold increase in the odds of BO in comparison with the screening colonoscopy controls (table 4). It is not clear why serum IGF-1 levels were highest in GORD controls. This is similar to the results reported by Healy *et al*.[30] Age, gender and circadian rhythms can affect serum IGF levels. It is possible that the differences in the baseline characteristics of the BO and the GORD study groups, as well as the time of day when blood specimens were collected, could contribute to the differences in the serum IGF levels. Intake of hormones by the women in the GORD control group could also have altered serum IGF-1 levels and biased our estimates. This study did not collect detailed information regarding medication intake or timing of laboratory blood collection and hence the role of these potential confounders cannot be assessed.

The study design included two control groups because the ideal control group for BO cases is difficult to define. We used the GORD control group because these subjects had upper endoscopy and it was unlikely that they had BO, given negative endoscopic and histopathological examinations. Our previous study showed that over 90% of BO cases seen in our endoscopy units report reflux symptoms.[40] We therefore felt it was important to capture a control group of patients who have reflux but do not have BO. However, this group is not representative of the general population and, since GORD is strongly associated with obesity, this control group is probably overmatched to our case group. The advantage of using the second screening colonoscopy control group is that it is more representative of the population seen for routine care in north-east Ohio and allows the identification of differences that would have been missed with the GORD controls alone. To ensure that our results were robust and not an artifact related to inadequate adjustment for differences between our BO cases and screening colonoscopy controls, we also performed a sensitivity analysis comparing BO cases with a matched subset of the colonoscopy controls (tables 3 and 4). Although the CIs were somewhat wider in this subset analysis, the associations were similar to the larger group and confirmed the validity of our broader comparative analysis. Selection bias may have occurred in the recruitment of BO cases, GORD and screening colonoscopy controls and affected the estimates of observed associations; however, this is a limitation of any case-control study.

In this study we did not have upper endoscopy information for all colonoscopy controls sufficient to definitively exclude the presence of GORD or BO. Misclassification in this control group would only have attenuated the examined differences slightly given the low population prevalence of BO, and would only bias the results towards the null, which is not observed here. Although there is a gradual increase in the OR across tertiles when comparing serum insulin levels and HOMA-IR (table 3) between BO cases and GORD controls, these differences are not statistically significant. Similar to the findings of Corley

et al,[12] in this study BO cases and the GORD control group had similar measures of central adiposity, suggesting that a much larger sample size would be required to rigorously test our hypothesis when comparing BO cases with GORD controls. Another important reason for choosing two control groups is the fact that GORD is strongly associated with BO as well as obesity. Excess weight—specifically, central adiposity—is an independent risk factor for BO and also GORD. Obesity may lead to BO through two separate pathways: the oesophageal reflux pathway and the insulin growth factor pathway. Addition of the second control group (ie, the screening colonoscopy controls) allowed us to examine the insulin/IGF axis separately from the obesity-reflux pathway. Misclassification could have also occurred in this study group and bias result estimates.

The results of this study potentially open up novel avenues of investigation. Given the association of increased insulin and IGF-1 with BO, the next step will be to evaluate the mechanisms and biological pathways that would account for these differences. Furthermore, it will be important to study interactions between inflammatory mediators produced by gastro-oesophageal reflux and the insulin/IGF pathway. Clearly, obesity is also associated with dietary changes and the results of this study suggest that it may be beneficial to study the role of diet, especially foods with a high glycaemic index, in oesophageal carcinogenesis. It would also be interesting to look at the impact of physical activity on the development of BO and progression through the spectrum of metaplasia. Most importantly, to determine the role of the insulin and IGF-1 pathways in oesophageal carcinogenesis, it will be necessary to examine molecular changes associated with activation of these pathways in BO.

In summary, evidence gathered from our study suggests that subjects with oesophageal intestinal metaplasia are exposed to elevated systemic levels of insulin and IGF-1 compared with screening colonoscopy controls, a reasonable surrogate for the population. Furthermore, the study suggests that IGFBP-3 has an inverse association with BO case status. Given the rising incidence of OAC as well as the obesity epidemic, it is important to focus research efforts on the IGF family and to continue exploring how interception of IGF molecular pathways could lead to possible disease prevention.

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Significance of this study

What is already known about this subject?

- Obesity increases the risk of cancer at multiple body sites including the oesophagus.
- Central accumulation of body fat increases the risk of gastro-oesophageal reflux and Barrett's oesophagus.
- Obesity is associated with increased insulin resistance.

What are the new findings?

- Increasing levels of serum insulin and insulin growth factor 1 are associated with an increased risk of Barrett's oesophagus in comparison with screening colonoscopy controls.
- High serum levels of insulin growth factor binding proteins 1 and 3 are associated with decreased odds of having Barrett's oesophagus.
- Insulin and insulin growth factor 1 may play a role in Barrett's oesophagus.

How might it impact on clinical practice in the foreseeable future?

- The insulin and insulin growth factor pathway may prove to be a target for the prevention of Barrett's oesophagus and oesophageal adenocarcinoma.

Table 1

Demographic variables by study group

	BO cases (N = 135)	GORD controls (N = 135)	Screening colonoscopy controls (N = 932)	Matched colonoscopy controls (N = 182)	p Value*	p Value†	p Value‡
Age	63.7 (11.2)	56.4 (11.1)	54.5 (8.9)	60.3 (10.18)	<0.0001	<0.0001	0.89
WHR	0.98 (0.06)	0.97 (0.07)	0.91 (0.09)	0.95 (0.09)	0.087	<0.0001	0.02
BMI	30.8 (5.7)	29.5 (5.6)	29.3 (6.9)	30.6 (6.0)	0.088	0.030	0.64
Gender (% female)	20.3%	40.0%	65.3%	29.7%	0.0003	<0.0001	0.12
Race (%)					0.0006	<0.0001	0.36
African-American	1 (0.7)	18 (13.3)	331 (35.8)	24 (13.2)			
White	126 (93.3)	112 (83.0)	574 (62.0)	157 (86.3)			
Other	1 (0.7)	0 (0)	27 (2.9)	0 (0.0)			
Unknown	7 (5.2)	5 (3.7)	0 (0)	1 (0.5)			

Values shown are mean (SD) or n (%).

*p Value of difference between BO cases and GORD controls.

†p Value of difference between BO cases and colonoscopy controls.

‡p Value of difference between BO cases and matched colonoscopy controls.

BMI, body mass index; BO, Barrett's oesophagus; GORD, gastro-oesophageal reflux disease; WHR, waist-to-hip ratio.

Table 2

Insulin and IGF measurements in BO cases and both control groups

	BO cases	GORD controls	Screening colonoscopy controls	Matched controls*	p Value†	p Value‡	p Value§
Insulin (μIU/ml)	10.2 (7.98)	9.1 (7.16)	7.4 (9.39)	7.9 (10.82)	0.33	0.001	0.082
HOMA-IR	2.78 (2.61)	2.23 (2.52)	1.86 (3.13)	1.84 (2.76)	0.13	<0.0006	0.013
IGF-1 (ng/ml)	173.4 (72.2)	194.1 (71.4)	116.5 (42.7)	119.3 (44.6)	0.03	<0.0001	<0.0001
IGFBP-1 (ng/ml)	14.7 (12.6)	14.5 (16.9)	30.1 (28.0)	29.7 (29.8)	0.88	<0.0001	<0.0001
IGFBP-3 (ng/ml)	3200 (945)	3721 (876)	3623 (833)	3475 (892)	<0.0001	<0.0001	0.16
Molar ratio of IGF-1:IGFBP-3	0.20 (0.07)	0.19 (0.06)	0.12 (0.03)	0.12 (0.04)	0.46	<0.0001	<0.0001

Values shown are mean (SD).

*BO cases (N = 91) were selectively matched and compared with colonoscopy controls (N = 182) for age and waist-to-hip ratio.

†p Value of difference between BO cases and GORD controls.

‡p Value of difference between BO cases and colonoscopy controls.

§p Value of difference between white male BO cases and matched colonoscopy controls.

BO, Barrett's oesophagus; GORD, gastro-oesophageal reflux disease; HOMA-IR, homeostatic model for assessment of insulin resistance; IGF-1, insulin growth factor 1; IGFBP-1, IGFBP-3, IGF binding proteins 1 and 3.

Table 3

Adjusted tertiles of insulin and HOMA-IR for BO cases compared with GORD controls, screening colonoscopy controls and matched colonoscopy control subset: analyses adjusted for age, gender, race (Caucasian vs other) and waist-to-hip ratio

Tertiles												
	1	**2**	**3**		**1**	**2**	**3**		**1**	**2**	**3**	
	BO cases vs GORD controls			**p Value***	**BO cases vs screening colonoscopy controls**			**p Value***	**BO cases vs matched colonoscopy controls**			**p Value***
Insulin												
Range, μIU/ml	<3.96	3.96–9.79	>9.79	0.21	<3.8	3.8–7.27	>7.27	0.007	<4.30	4.30–7.66	>7.66	0.08
Cases	48	40	45		47	23	63		22	14	41	
Controls	50	42	43		335	298	299		58	59	58	
OR (95% CI)	1.0 (referent)	1.26 (0.61 to 2.60)	1.55 (0.76 to 3.15)		1.0 (referent)	0.68 (0.34 to 1.35)	2.02 (1.15 to 3.54)		1.0 (referent)	0.56 (0.25 to 1.26)	1.68 (0.86 to 3.23)	
HOMA-IR												
Range	<0.90	0.90–2.22	>2.22	0.25	<0.74	0.74–1.58	>1.584	0.002	<0.91	0.91–1.64	>1.64	0.06
Cases	49	37	47		45	22	66		21	14	42	
Controls	50	42	43		335	299	298		58	59	58	
OR (95% CI)	1.0 (referent)	1.18 (0.56 to 2.46)	1.50 (0.75 to 3.03)		1.0 (referent)	0.64 (0.32 to 1.29)	2.23 (1.26 to 3.95)		1.0 (referent)	0.54 (0.23 to 1.24)	1.74 (0.90 to 3.38)	

* p Value denotes trend across tertiles.

BO, Barrett's oesophagus; GORD, gastro-oesophageal reflux disease; HOMA-IR, homeostatic model for assessment of insulin resistance.

Table 4

Adjusted tertiles of IGF-1 and IGFBPs in BO cases compared with GORD controls, screening colonoscopy controls and matched colonoscopy control subset: analyses adjusted for age, gender, race (Caucasian vs other) and waist-to-hip ratio

Tertiles												
	1	**2**	**3**		**1**	**2**	**3**		**1**	**2**	**3**	
	BO cases vs GORD controls			**p Value***	**BO cases vs screening colonoscopy controls**			**p Value***	**BO cases vs matched colonoscopy controls**			**p Value***
IGF-1												
Range, ng/ml	<155	155–211	>211	0.10	<94.4	94.4–130.9	>130.9	<0.001	<95.3	95.3–133.1	>133.1	<0.0001
Cases	74	28	31		33	24	76		10	17	52	
Controls	49	42	44		311	310	311		61	60	61	
OR (95% CI)	1.0 (referent)	0.5 (0.25 to 1.05)	0.57 (0.27 to 1.17)		1.0 (referent)	1.77 (0.81 to 3.88)	4.05 (2.01 to 8.17)		1.0 (referent)	2.21 (0.87 to 5.56)	5.83 (2.54 to 13.36)	
IGFBP-1												
Range, ng/ml	<4.54	4.54–14.9	>14.9	0.94	<13.2	13.9–31.5	>31.5	<0.001	<13.8	13.8–29.3	>29.3	<0.0001
Cases	45	47	41		91	32	10		49	23	8	
Controls	49	42	44		318	306	308		60	61	60	
OR (95% CI)	1.0 (referent)	1.12 (0.57 to 2.44)	1.04 (0.49 to 2.16)		1.0 (referent)	0.34 (0.19 to 0.61)	0.11 (0.05 to 0.24)		1.0 (referent)	0.47 (0.24 to 0.91)	0.17 (0.07 to 0.43)	
IGFBP-3												
Range, ng/ml	<3327	3327–3977	>3977	0.02	<3286	3286–4020	>4020	<0.001	<3001	3001–3908	>3908	0.05
Cases	81	36	16		81	36	16		30	35	15	
Controls	48	42	45		313	309	310		61	60	61	
OR (95% CI)	1.0 (referent)	0.77 (0.38 to 1.57)	0.36 (0.16 to 0.81)		1.0 (referent)	0.92 (0.52 to 1.61)	0.40 (0.20 to 0.79)		1.0 (referent)	1.04 (0.54 to 2.00)	0.45 (0.20 to 0.98)	
Molar†												
Range	<0.15	0.15–0.21	>0.21	0.34	<0.104	0.104–0.119	>0.119	<0.001	<0.106	0.106–0.135	>0.135	<0.0001
Cases	51	43	39		30	8	95		6	11	61	
Controls	55	40	40		351	194	387		61	60	61	
OR (95% CI)	1.0 (referent)	1.71 (0.84 to 3.44)	1.41 (0.68 to 2.94)		1.0 (referent)	0.90 (0.31 to 2.52)	4.72 (2.24 to 9.92)		1.0 (referent)	2.36 (0.76 to 7.32)	16.82 (5.71 to 49.5)	

* p Value denotes trend across tertiles.

† Molar represents molar ratio of IGF-1 to IGFBP-3.

BO, Barrett's oesophagus; GORD, gastro-oesophageal reflux disease; IGF-1, insulin growth factor 1; IGFBP-1, IGFBP-3, IGF binding proteins 1 and 3.

Table 5

Multivariate odds of BO compared with screening colonoscopy controls, adjusted for other IGF biomarkers (lowest tertile set as baseline)

Tertile				
	1	**2**	**3**	**p Value (trend)***
IGF-1				
Range, ng/ml	<94.48	94.48–130.98	>130.99	<0.0001
Cases	33	24	76	
Controls	311	310	311	
OR (95% CI)	1.0 (referent)	3.27 (1.26 to 8.45)	10.5 (4.02 to 27.3)	
IGFBP-1				
Range, ng/ml	<13.2	13.92–31.49	>31.49	<0.0001
Cases	91	32	10	
Controls	318	306	308	
OR (95% CI)	1.0 (referent)	0.40 (0.20 to 0.78)	0.16 (0.06 to 0.40)	
IGFBP-3				
Range, ng/ml	<3286	3286–4020	>4020	<0.0001
Cases	81	36	16	
Controls	313	309	310	
OR (95% CI)	1.0 (referent)	0.41 (0.20 to 0.83)	0.05 (0.01 to 0.14)	

* Adjusted for age, gender, race (Caucasian vs other) and waist-to-hip ratio.

BO, Barrett's oesophagus; GORD, gastro-oesophageal reflux disease; IGF-1, insulin growth factor 1; IGFBP-1, IGFBP-3, IGF binding proteins 1 and 3.

Table 6

Adjusted tertiles of insulin, HOMA-IR, IGF-1 and IGFBPs in BO cases compared with GORD controls, screening colonoscopy controls and matched colonoscopy control subset: multivariate analyses not adjusted for waist-to-hip ratio

Tertiles	1	2	3		2	3		2	3	
	BO cases vs GORD controls			p Value (trend)*	BO cases vs screening colonoscopy controls		p Value (trend)*	BO cases vs matched colonoscopy controls		p Value (trend)*
Insulin, OR (95% CI)	1.0 (referent)	1.11 (0.58 to 2.12)	1.15 (0.61 to 2.14)	0.65	0.55 (0.30 to 1.00)	1.64 (1.01 to 2.67)	0.04	0.63 (0.29 to 1.37)	1.87 (0.99 to 3.53)	0.03
HOMA-IR, OR (95% CI)	1.0 (referent)	0.95 (0.49 to 1.84)	1.09 (0.59 to 2.03)	0.76	0.52 (0.28 to 0.95)	1.74 (1.07 to 2.84)	0.02	0.66 (0.31 to 1.43)	2.00 (1.05 to 3.79)	0.02
IGF-1, OR (95% CI)	1.0 (referent)	0.43 (0.22 to 0.83)	0.54 (0.28 to 1.06)	0.44	0.69 (0.37 to 1.30)	1.78 (1.04 to 3.03)	0.01	1.86 (0.77 to 4.44)	5.75 (2.57 to 12.8)	<0.001
IGFBP-1, OR (95% CI)	1.0 (referent)	1.07 (0.57 to 2.02)	0.87 (0.46 to 1.67)	0.69	0.26 (0.15 to 0.45)	0.07 (0.03 to 0.16)	<0.001	0.41 (0.21 to 0.77)	0.14 (0.05 to 0.33)	<0.001
IGFBP-3, OR (95% CI)	1.0 (referent)	0.65 (0.35 to 1.22)	0.30 (0.14 to 0.64)	0.02	0.69 (0.41 to 1.14)	0.30 (0.16 to 0.56)	0.0001	1.11 (0.60 to 2.09)	0.45 (0.21 to 0.95)	0.05
Molar,† OR (95% CI)	1.0 (referent)	1.16 (0.62 to 2.19)	1.11 (0.58 to 2.13)	0.73	0.33 (0.13 to 0.83)	1.91 (1.10 to 3.30)	0.003	2.36 (0.76 to 7.32)	16.81 (5.71 to 49.5)	<0.001

*Adjusted for age, gender and race (Caucasian vs other).

†Molar represents molar ratio of IGF-1 to IGFBP-3.

BO, Barrett's oesophagus; GORD, gastro-oesophageal reflux disease; HOMA-IR, homeostatic model for assessment of insulin resistance; IGF-1, insulin growth factor 1; IGFBP-1, IGFBP-3, IGF binding proteins 1 and 3.

Table 7

Tertiles of insulin, HOMA-IR, IGF-1 and IGFBPs in GORD controls compared with screening colonoscopy controls: multivariate analyses not adjusted for waist-to-hip ratio

Tertiles				
	1	**2**	**3**	**p Value (trend)***
Insulin, μIU/ml				
Range	<3.8	3.8–7.27	>7.27	0.73
Cases	50	42	43	
Controls	335	298	299	
OR (95% CI)	1.0 (referent)	0.98 (0.62 to 1.54)	1.08 (0.69 to 1.71)	
HOMA-IR				
Range	<0.74	0.74–1.58	>1.58	0.78
Cases	50	42	43	
Controls	335	299	298	
OR (95% CI)	1.0 (referent)	0.97 (0.61 to 1.53)	1.07 (0.68 to 1.69)	
IGF-1, ng/ml				
Range	<94.5	94.5–130.9	>130.9	0.08
Cases	49	42	44	
Controls	311	310	311	
OR (95% CI)	1.0 (referent)	0.77 (0.48 to 1.22)	0.66 (0.40 to 1.05)	
IGFBP-1, ng/ml				
Range	<13.9	13.9–31.5	>31.5	0.57
Cases	49	42	44	
Controls	319	306	308	
OR (95% CI)	1.0 (referent)	0.84 (0.53 to 1.34)	0.87 (0.55 to 1.38)	
IGFBP-3, ng/ml				
Range	<3286	3286–4020	>4020	0.76
Cases	48	42	45	
Controls	313	309	310	
OR (95% CI)	1.0 (referent)	0.91 (0.56 to 1.46)	0.93 (0.58 to 1.49)	
Molar ratio of IGF-1 to IGFBP-3				
Range	<0.103	0.103–0.119	>0.119	0.0008
Cases	55	40	40	
Controls	351	194	387	
OR (95% CI)	1.0 (referent)	1.06 (0.66 to 1.69)	0.45 (0.27 to 0.72)	

* Adjusted for age, gender, race (Caucasian vs other)

BO, Barrett's oesophagus; GORD, gastro-oesophageal reflux disease; HOMA-IR, homeostatic model for assessment of insulin resistance; IGF-1, insulin growth factor 1; IGFBP-1, IGFBP-3, IGF binding proteins 1 and 3.