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ORIGINAL ARTICLE

Serological levels of IGF-1 and IGFBP-3 in patients with Barrett's esophagus and esophageal adenocarcinoma: Longitudinal study

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KEYWORDS
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Abstract
Background: Barrett's oesophagus (BE) is an entity with a known histological progression to malignancy. The Insulin-Like Growth Factor (IGF) system is involved in the carcinogenesis through obesity-related mechanisms that include IGF and it has been associated with several types of cancer.
Objectives: To evaluate the serological levels of IGF-1 and IGFBP-3 in patients with BE and esophageal adenocarcinoma.
Patients and methods: Prospective study of patients with BE and esophageal adenocarcinoma who underwent upper endoscopy between September 2012 and December 2015. A baseline determination of IGF-1 and IGFBP-3 was performed. We included a control group of patients without BE.
Results: 116 patients were included: 36 controls, 62 with BE (42 without dysplasia and 20 with dysplasia) and 18 with adenocarcinoma. IGF-1 and IGF-1/IGFBP-3 mol ratio showed a progression to high levels in BE and adenocarcinoma than in controls (IGF-1: 135.55 ± 66.07 ng/mL, 148.33 ± 81.5 ng/mL, 108.19 ± 46.69 ng/mL, respectively; $p = 0.049$) (molar ratio: 0.23 ± 0.91, 0.29 ± 0.11, 0.19 ± 0.06, respectively; $p = 0.001$), without differences between the histological

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types of BE. Fifty-four out of the 65 patients with BE were followed up (median of 58.50 months, range 12–113) and 11 of them (20.4%) presented progression to low-grade dysplasia ($n = 8$) or high-grade dysplasia/adenocarcinoma ($n = 3$), without differences in the IGF system compared with patients without progression.
Conclusions: Patients with BE and esophageal adenocarcinoma have changes in the IGF system although the serological levels of IGF-1 and IGFBP-3 do not correlate with histological progression of BE.

PALABRAS CLAVE
Esófago de Barrett;
Adenocarcinoma esofágico;
IGF-1;
IGFBP-3

Niveles séricos de IGF-1 e IGFBP-3 en pacientes con esófago de Barrett y adenocarcinoma de esófago. Estudio longitudinal

Resumen
Antecedentes: El esófago de Barrett (EB) es una entidad con una progresión histológica a malignidad conocida. Los factores de crecimiento insulínico (IGF, de Insulin-Like Growth Factor) están involucrados en la carcinogénesis asociada a la obesidad y se han asociado con el riesgo de padecer algunos tipos de cáncer.
Objetivos: Evaluar los niveles serológicos de IGF-1 e IGFBP-3 en pacientes con EB y adenocarcinoma de esófago.
Pacientes y métodos: Estudio prospectivo de pacientes con EB y adenocarcinoma de esófago explorados con gastroscopia entre Septiembre 2012 y Diciembre 2015 a los que se realizó una extracción de sangre para la determinación de IGF-1 e IGFBP-3. Se incluyó un grupo control.
Resultados: Se incluyeron 116 pacientes: 36 controles, 62 con EB (42 sin displasia y 20 con displasia) y 18 con adenocarcinoma. El IGF-1 y la ratio molar IGF-1/IGFBP-3 presentaron un aumento progresivo en los grupos con EB y adenocarcinoma comparado con los controles (IGF-1: 135.55 ± 66.07 ng/mL, 148.33 ± 81.5 ng/mL, 108.19 ± 46.69 ng/mL, respectivamente; $p = 0.049$) (ratio molar: 0.23 ± 0.91, 0.29 ± 0.11, 0.19 ± 0.06, respectivamente; $p = 0.001$), sin diferencias entre los diferentes grados histológicos. 54 de los 65 pacientes con EB fueron seguidos durante una mediana de 58.50 meses (12–113) y 11 de ellos (20.4%) presentaron progresión a displasia de bajo grado (n = 8) o displasia de alto grado/adenocarcinoma (n = 3), sin encontrar diferencias en el sistema IGF comparado con los que no progresaron.
Conclusiones: los pacientes con EB y adenocarcinoma esofágico presentan cambios en el sistema IGF aunque los niveles de IGF-1 y IGFBP-3 no se correlacionan con la progresión histológica del EB.

Introduction

Barrett's oesophagus (BO) is intestinal metaplasia replacing the normal squamous epithelium of the distal oesophagus. BO is a premalignant condition with a well-known sequence of histological changes, which can progress to adenocarcinoma through low-grade dysplasia (LGD) and high-grade dysplasia (HGD). When HGD is detected, the risk of malignant transformation is around 16–59% in five years, while the risk of progression to adenocarcinoma is 0.3% per year when there is no dysplasia.[1–3] For that reason, clinical guidelines recommend endoscopic surveillance with biopsies at regular intervals.[4,5] However, it is well known that the degree of compliance with the recommendations is variable and endoscopic biopsies have limited utility.[6,7] More precise methods are therefore needed to identify BO patients at higher risk of malignant progression in order to establish effective prevention measures.

The incidence of oesophageal adenocarcinoma has increased in developed countries in recent years.[8,9] This has been attributed to obesity and metabolic changes deriving from excess weight, regardless of whether or not the patient has gastro-oesophageal reflux disease (GORD), due to there being a molecular mechanism for carcinogenesis associated with obesity which leads to the development of insulin resistance.[10–12] Increased insulin levels promote carcinogenesis by stimulating the production of insulin-like growth factor 1 (IGF-1) and inhibiting the production of IGF-1 binding proteins (IGFBP-1 and IGFBP-3). The net effect is an increase in bioavailable IGF-1, which activates pathways involved in tissue proliferation, as it is a potent stimulator of mitogenesis.[13–15] For example, the association between IGF-1 levels and prostate and colorectal cancer and breast cancer in premenopausal women has already been demonstrated.[14,16]

The association of circulating levels of obesity-related biomarkers with the risk of BO and oesophageal adenocarcinoma has been studied previously, but results have been inconclusive and contradictory at times.[17–21] The aim of this study therefore was to measure serological levels of the IGF complex in patients with BO at different histological stages and oesophageal adenocarcinoma and look for any correlation between these biomarkers and histological progression.

Material and methods

Prospective study of a cohort of patients diagnosed with BO and oesophageal adenocarcinoma by endoscopy and histological confirmation at Hospital Clínic de Barcelona from September 2012 to December 2015 and with follow-up until March 2022. We included a control group consisting of patients without these disorders who underwent gastroscopy for other reasons during the same period. The patients agreed to take part in the study and signed an informed consent form. The study was approved by the Hospital Clínic Ethics Committee with reference 2012/7217.

The only exclusion criterion was the existence of a cancer other than oesophageal adenocarcinoma at the time of inclusion.

Endoscopy

Endoscopies were performed by expert endoscopists under deep sedation controlled by an anaesthetist. High-definition Olympus endoscopes (GIF-HQ190 or GIF-180, Olympus Corporation, Japan) were used. The diagnostic criteria for BO used were those of the American College of Gastroenterology (ACG) and the European Society of Gastrointestinal Endoscopy (ESGE)[4,5] which require the presence of gastric-like mucosa in the distal oesophagus with a biopsy demonstrating intestinal metaplasia. Both digital (Narrow Band Imaging or NBI) and conventional (acetic acid) chromoendoscopy techniques were used, as well as near-focus imaging to assess the mucosal and vascular patterns. BO was classified based on its endoscopic length according to the Prague classification. Biopsies were obtained following the Seattle protocol: biopsies from the four quadrants and every 1—2 cm along the length of the possible columnar epithelium. The biopsies were processed using the standard technique and reviewed by an independent pathologist who was blinded to the serological results, classifying the dysplasia according to the Vienna classification.

A follow-up endoscopy was subsequently carried out as indicated by the referring physician.

Blood analysis

All the patients had blood samples taken at the time of the baseline endoscopy. The samples were centrifuged and the serum was extracted and stored at −80° in the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) [August Pi i Sunyer Biomedical Research Institute] sample bank. IGF-1 and IGFBP-3 were measured with the ELISA technique. According to our laboratory's reference, the range of normal values for IGF-1 were 34—128 ng/mL and for IGFBP-3 were 0.7–2.3 mcg/mL. To assess the bioavailability of IGF-1, the IGF-1/IGFBP-3 mol ratio was calculated with the formula [IGF-1 (ng/mL) × 0.13]/[IGFBP-3 (ng/mL) × 0.035]. To calculate the amount of IGFBP-3, the molar difference was used with the formula (IGFBP-3)-(IGF-1).[22]

Statistical analysis

Continuous variables are expressed as mean ± standard deviation and range. Univariate analysis was performed using the Chi-square test and Student's *t*-test for categorical and continuous variables respectively. Multiple comparisons were made using the ANOVA test. A p value <0.05 was considered statistically significant. The statistical software SPSS (version 25.0) was used.

Results

A total of 116 patients were included: 36 controls, 62 with BO (42 without dysplasia, 18 with LGD and 2 with HGD) and 18 with adenocarcinoma. Sixteen of the patients with BO were newly diagnosed and none of those under follow-up had previously received any endoscopic treatment. In patients with BO, a mean of 10.7 ± 8.9 (2–42) biopsies were performed. The mean age of the patients with BO was 58.69 ± 12.04 years and these patients took more proton pump inhibitors (85.48%) and had a higher prevalence of hiatus hernia (45%) than the control group (61.1% and 11.11% respectively) and patients with adenocarcinoma (38.89% and 16.67% respectively) ($p = 0.000$ and 0.019 respectively). In addition, patients with BO and adenocarcinoma were predominantly male (controls: 61.11%; BO: 84.65%; and adenocarcinoma: 94.44%; $p = 0.013$). There were no differences among the patients with BO according to whether or not they had dysplasia, except that the length was greater in the group with dysplasia (circumferential length without dysplasia: 1.36 ± 2.29 cm, dysplasia: 3.35 ± 3.67 cm; $p = 0.048$; and maximum length without dysplasia: 3.37 ± 2.72 cm, dysplasia: 5.3 ± 3.47 cm; $p = 0.032$). The patients with BO and dysplasia tended to be older (62.7 ± 11.43 years) than those without dysplasia (59.67 ± 11.98 years; $p = 0.07$). The patients' characteristics are shown in Tables 1 and 2.

There was an overall increase in IGF-1 serum levels in the groups with disease, although there was no difference between BO (135.55 ± 66.07 ng/mL) and adenocarcinoma (148.33 ± 81.50 ng/mL; $p = 0.733$) or when comparing BO and adenocarcinoma with the controls (108.19 ± 46.69 ng/mL; $p = 0.104$ and $p = 0.077$ respectively). In the case of the IGF-1/IGFBP-3 mol ratio, although there was also an overall increase, it was only significant comparing the adenocarcinoma group (0.29 ± 0.11) to the controls (0.19 ± 0.06; $p = 0.001$). In contrast, the molar difference (IGFBP-3)-(IGF-1) progressively decreased the more advanced the disease, with significant differences between patients with adenocarcinoma (46.09 ± 14.53) and BO (57.33 ± 17.47; $p = 0.029$) and controls (57.67 ± 14.49; $p = 0.039$) (Table 1, Fig. 1).

Within the BO group, there were no differences in IGF system values between patients with or without dysplasia (Table 2).

Patients with BO and HGD plus adenocarcinoma were treated at the time of diagnosis with the most appropriate

Table 1 Clinical and demographic characteristics of patients with BO, control group and adenocarcinoma.

	Control *n* = 36	BO *n* = 62	Adenocarcinoma *n* = 18	*p*
Age, years; mean ± SD (range)	59.67 ± 13.82 (32–82)	58.69 ± 12.04 (34–85)	60.78 ± 14.14 (28–86)	0.819
Gender, M; *n* (%)	22 (61.11)	50 (84.65)	17 (94.44)	0.013
BMI, kg/m^2; mean ± SD (range)	27.49 ± 4.93 (19.7–37.9)	26.74 ± 3.77 (17–39.2)	25.70 ± 3.342 (19.1–32)	0.315
Use of PPI; n (%)	22 (61.1)	53 (85.48)	7 (38.89)	0.000
Diabetes; *n* (%)	7 (19.44)	8 (12.9)	2 (11.11)	0.622
Glucose, mg/dl; mean ± SD (range)	110.19 ± 32.63 (65–219)	103.42 ± 20.77 (78–181)	105.39 ± 26.75 (83–185)	4.555
Symptoms of GORD; *n* (%)	16 (44.44)	26 (41.94)	9 (50)	0.600
Hiatus hernia; *n* (%)	4 (11.11)	27 (45)	3 (16.67)	**0.019**
IGFBP-3 (ng/mL)	2,049.44 ± 506.96	2,141.61 ± 600	1,867.78 ± 541.70	**0.191**
IGF-1 (ng/mL)	108.19 ± 46.69	135.55 ± 66.07	148.33 ± 81.50	**0.049***
Molar ratio	0.19 ± 0.06	0.23 ± 0.91	0.29 ± 0.11	**0.001****
Molar difference	57.67 ± 14.49	57.33 ± 17.47	46.09 ± 14.53	**0.026** ***

BMI: body mass index; BO: Barrett's oesophagus; GORD: gastro-oesophageal reflux disease; PPI: proton pump inhibitors; SD: standard deviation. The values in bold represent statistically significant differences.

* Control vs adenocarcinoma ($p = 0.077$), control vs BO ($p = 0.104$), BO vs adenocarcinoma ($p = 0.733$).

** Control vs adenocarcinoma (**$p = 0.001$**), control vs BO ($p = 0.088$), BO vs adenocarcinoma ($p = 0.058$).

*** Control vs adenocarcinoma (**$p = 0.039$**), control vs BO ($p = 0.995$), BO vs adenocarcinoma (**$p = 0.029$**).

Table 2 Demographic and clinical characteristics of patients with BO separated according to whether or not they have dysplasia (including low and high grade).

	Intestinal metaplasia *n* = 42	Dysplasia *n* = 20	*p*
Age, years; mean ± SD	59.67 ± 11.98	62.7 ± 11.43	0.070
Gender, M; *n* (%)	33 (78.57)	17 (85)	0.549
BMI, kg/m^2; mean ± SD	27.14 ± 3.83	25.91 ± 3.59	0.233
Use of PPI; *n* (%)	35 (83.33)	18 (90)	0.486
Diabetes; *n* (%)	6 (14.29)	2 (10)	0.687
Glucose, mg/dl; mean ± SD	92.38 ± 36	90.05 ± 44.59	0.826
Symptoms of GORD; *n* (%)	20 (47.62)	6 (30)	0.295
Hiatus hernia; *n* (%)	18 (42.86)	8 (40)	0.685
Prague C, cm; mean ± SD (range)	**1.36 ± 2.29 (0–9)**	**3.35 ± 3.67 (0–11)**	**0.048**
Prague M, cm; mean ± SD (range)	**3.37 ± 2.72 (5–12)**	**5.3 ± 3.47 (1–12)**	**0.032**
IGFBP-3	2160 ± 557	2103 ± 695	**0.730**
IGF-1	136.24 ± 68.38	134.10 ± 62.62	**0.906**
Molar ratio	0.23 ± 0.09	0.24 ± 0.9	**0.743**
Molar difference	57.89 ± 16.11	56.17 ± 20.45	**0.721**

BMI: body mass index; BO: Barrett's oesophagus; GORD: gastro-oesophageal reflux disease; PPI: proton pump inhibitors; Prague C: circumferential length; Prague M: maximum length; SD: standard deviation. The values in bold represent statistically significant differences.

technique (endoscopic or surgical) and were excluded from the follow-up. Of the 60 patients without dysplasia or with LGD, five were lost to follow-up with no further endoscopy and one patient with LGD was treated with radiofrequency, leaving 54 patients who had endoscopic surveillance for a median of 58.50 months (12–113) and who had a mean of 4.2 ± 2.3 endoscopies (2–10) (Fig. 2), with adequate follow-up intervals in 42 of them (78%); in 27 of the 38 without dysplasia (71%) and in 15 of the 16 with LGD (94%). During follow-up, 11 of them (20.4%) had progression to LGD ($n = 8$) or HGD/adenocarcinoma ($n = 3$), with a median of 30 months (12–112). The number of patients per year of follow-up required to detect an adenocarcinoma was 270. Fig. 2 shows a flowchart of the patients included in the study.

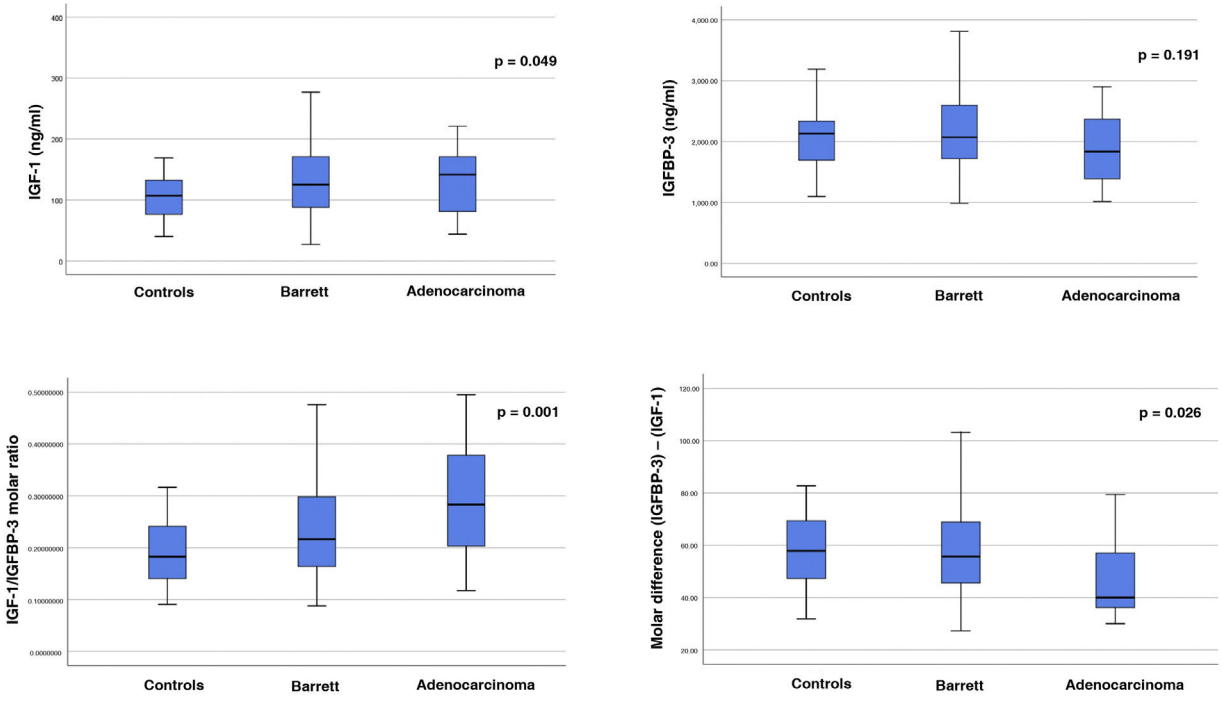

Figure 1 Serum IGF-1 and IGFBP-3 levels, IGF-1/IGFBP-3 mol ratio and IGFBP-3-IGF-1 mol difference in the controls, patients with BO and patients with adenocarcinoma.
IGF-1: control vs adenocarcinoma ($p = 0.077$), control vs BO ($p = 0.104$), BO vs adenocarcinoma ($p = 0.733$).
Molar ratio: control vs adenocarcinoma ($p = 0.001$), control vs BO ($p = 0.088$), BO vs adenocarcinoma ($p = 0.058$).
Molar difference: control vs adenocarcinoma ($p = 0.039$), control vs BO ($p = 0.995$), BO vs adenocarcinoma ($p = 0.029$).

Table 3 Characteristics of the 11 patients who had progression during follow-up.

Cases	Prague	Baseline	Follow-up	IGFBP-3	IGF-1	Molar ratio	Molar difference	Treatment	Progression time (months)
1	C3M5	LGD	HGD	2.05	173	0.31	49.26	RFA	22
2	C0M1	IM	LGD	2.55	101	0.15	76.12	No	83
3	C6M7	IM	LGD	1.73	89	0.19	48.98	RFA	12
4	C4M7	LGD	ADC	1.89	110	0.22	51.85	ESD	112
5	C0M3	IM	LGD	2.19	101	0.17	63.52	No	13
6	C3M4	IM	LGD	2.80	165	0.22	76.55	RFA	26
7	C3M4	IM	HGD	2.68	137	0.19	75.99	ESD	93
8	C3M7	IM	LGD	1.88	128	0.25	49.16	No	30
9	C3M5	IM	LGD	1.82	95	0.19	51.35	RFA	49
10	C9M10	IM	LGD	1.99	163	0.31	48.46	RFA	24
11	C1M3	IM	LGD	2.33	208	0.33	54.51	No	62

ADC: adenocarcinoma; ESD: endoscopic submucosal dissection; HGD: high-grade dysplasia; IM: intestinal metaplasia; LGD: low-grade dysplasia; RFA: radio frequency ablation.

The one patient who developed an adenocarcinoma had persistent LGD and had annual follow-up endoscopies after having refused radiofrequency ablative treatment. Endoscopic submucosal dissection was performed and the final histology was pT1b with 1500 μm involvement of the submucosa and lymphovascular invasion, for which he did subsequently have surgery. The characteristics of the patients with progression are shown in Table 3. There were no differences between patients who progressed and those who did not in IGF-1 or IGFBP-3 levels, IGF-1/IGFBP-3 mol ratio or molar difference (IGFBP-3)-(IGF-1). Age, body mass index, glucose, and BO length were also similar in the two groups (Table 4).

Discussion

The results of this study demonstrate that patients with oesophageal adenocarcinoma have a dysfunctional IGF system, supporting the hypothesis that these obesity-

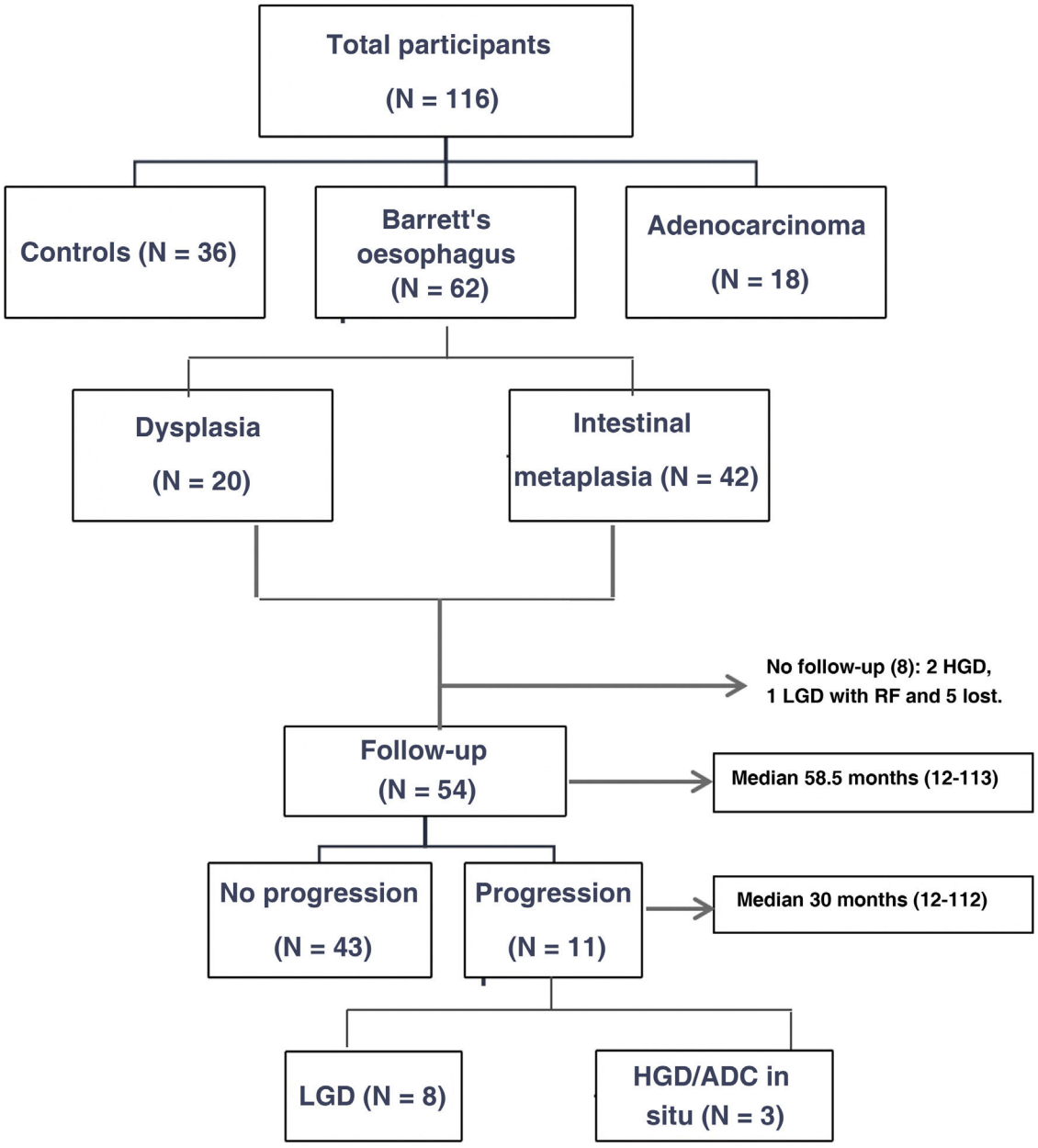

Figure 2 Flowchart of the study.

associated biomarkers may contribute to the development of cancer. There is a tendency for these biomarkers to also be altered in BO. Our results are consistent as not only was IGF-1 elevated, but also the IGF-1/IGFBP-3 mol ratio, which is an indirect measure of the amount of bioavailable IGF-1, while the free ligand protein, represented by the molar difference (IGFBP-3)-(IGF-1), was decreased.

The relationship between IGF-1 and BO has been demonstrated in other studies. Greer et al.[17] found that elevated levels (in the highest tertile) of IGF-1 were associated with an increased risk of BO compared to controls who underwent screening colonoscopy and did not have GORD symptoms (OR 4.05; 95% CI: 2.01–8.17). However, when they compared the serum IGF-1 levels of BO patients to patients with reflux symptoms but without BO, they found no difference. The authors attributed these results to the fact that patients with BO and those with GORD symptoms had similar rates of obesity. In our case, almost 45% of the patients in the control group had reflux symptoms and body mass index, glucose levels and the prevalence of diabetes were similar in the two groups. Despite that, however, serum IGF-1 levels had a tendency to be higher in the BO group. As all of our cases had BO at the time of inclusion, we cannot know if they already had elevated IGF-1 levels before disease onset.

Apart from in BO, an association has also been described between IGF-1 levels and cancer in different locations.[14,16,23] In a study including 124 patients with oesophageal cancer (91 with adenocarcinoma and 33 with squamous cell carcinoma of the oesophagus), Doyle et al.[20] found an association with adenocarcinoma, but not with squamous cell carci-

Table 4 Comparative study of patients with BO who had progression during follow-up and those without progression.

	Progression $n = 11$	No progression $n = 43$	p
Age, years; mean ± SD	57.09 ± 12.64	58.23 ± 12.478	0.788
Gender, M; *n* (%)	10 (90.9)	35 (79.55)	0.382
BMI, kg/m^2; mean ± SD	26.27 ± 4.88	27.38 ± 3.23	0.365
Diabetes (%)	1 (9.09)	7 (15.9)	0.566
Glucose, mg/dl; mean ± SD	85.55 ± 31.8	91.88 ± 39.09	0.622
Hiatus hernia; *n* (%)	7 (63.64)	17 (53.13)	0.511
Prague C, cm; mean ± SD	3 ± 2.45	1.96 ± 3.21	0.325
Prague M, cm; mean ± SD	4.90 ± 2.43	3.95 ± 3.44	0.392
IGF-1	133.64 ± 38.91	137.23 ± 70.16	0.871
IGFBP-3	2173.64 ± 367.78	2153.16 ± 677.22	0.894
IGF-1/IGFBP-3 mol ratio	0.230 ± 0.619	0.233 ± 0.089	0.912
Molar difference IGFBP-3 − IGF-1	58.70 ± 12.01	57.52 ± 19.18	0.847

BMI: body mass index; BO: Barrett's oesophagus; Prague C: circumferential length; Prague M: maximum length.

noma. Moreover, in patients with adenocarcinoma, serum IGF-1 levels were higher in the obese patients who had an increased visceral fat area, supporting the theory that obesity increases the risk of adenocarcinoma. In our case, the patients with adenocarcinoma had higher levels of IGF-1 but no differences were found with the other groups in terms of body mass index or blood glucose levels. An increased expression of IGF-1 has also been reported in tumour tissues. The IGF-1 receptor is located on the cells and has mitogenic and tumorigenic properties; its involvement in the malignant progression of BO has been described.[24]

In the subgroup of patients with BO, we found no differences between those who only had intestinal metaplasia and those who already had some degree of dysplasia. The sequence of histological changes in the progression of BO to malignancy is well established.[1,25] The early detection of dysplasia is the objective for which patients with BO are periodically screened by endoscopy with biopsies, in order to detect malignant transformation in treatable phases. However, the utility of endoscopic biopsies is limited because they are not representative of the full length of the BO.[26,27] In recent years, progress has been made in the search for biomarkers to identify possible predictors of dysplasia and progression to malignancy. A 2017 meta-analysis[28] included 36 studies which had analysed 16 immunohistochemical biomarkers and identified an association between aberrant p53 expression and the risk of progression to HGD and ADC with an OR of 3.18. The use of a combination of p53 with other predictors of progression such as gender, histology or length of BO would allow for better risk stratification and early detection of lesions in patients at higher risk, reducing the costs associated with follow-up. Another more recent meta-analysis which included 19 studies[19] evaluated the association between 13 inflammatory and metabolic serological biomarkers related to obesity and the risk of BO/adenocarcinoma. When comparing the maximum with the minimum values, they found that the risk was increased with leptin (OR, 1.68; 95% CI: 0.95–2.97) and insulin (OR, 1.47; 95% CI: 1.06–2.00) for BO and with glucose (OR, 1.12; 95% CI: 1.03–1.22), C-reactive protein (OR, 2.06; 95% CI: 1.28–3.31), IL-6 (OR, 1.50; 95% CI: 1.03–2.19) and soluble TNF receptor 2 (OR, 3.16; 95% CI: 1.76–5.65) for adenocarcinoma. They found no association with IGF-1 or IGFBP-3.

The IGF system had no prognostic value with regard to the risk of BO progression in our series. Siahpush et al.[18] similarly showed that circulating levels of IGF-1 and IGFBP-3 were not predictors of adenocarcinoma development in 344 patients with BO followed up for a median of five years. In this series, 38 patients (11%) developed cancer during follow-up. However, patients with IGFBP-3 levels above the median almost tripled the risk of having aneuploidy, which would indicate a potential role for IGFBP-3 in the early stages of adenocarcinoma development. Other epidemiological studies on the association between IGFBP-3 serum levels and cancer risk have also produced inconclusive results, which have been attributed to differences in analysis methods or to the measurement of different fractions of the protein.[19]

The BO length has been related to the risk of progression, such that the recommended follow-up intervals are narrower in those of 3 cm or longer.[5] The low occurrence of progression in our series could explain the lack of significant differences between cases based on whether they progressed or not. With regard to the follow-up intervals, in our series compliance was better in patients with LGD than in those without dysplasia, with the general tendency being to shorten the intervals. This practice reflects the fear of progression to cancer among patients and their physicians and reinforces the need to find markers which help identify patients who really are at risk, in order to be able to avoid or space out follow-up in those not at risk.

Not only does the association between the IGF-1 system and BO have a role in diagnosis, but it also opens up some new therapeutic options. As hyperinsulinaemia and insulin resistance are mediators of carcinogenesis through the IGF system and have proliferative effects on oesophageal cells, dietary changes based on calorie and protein restriction have been shown to reduce cancer risk in experimental models with rodents.[29] Fontana et al. found a beneficial effect of a low protein diet administered for two years on inflammatory mediators, with a reduction in glucose levels, IGF-1 and IGF-1/IGFBP-3 mol ratio in patients with BO and obesity.[30]

One of the strengths of this study is the fact it is a prospective study with three well-characterised populations. Endoscopic follow-up of patients with BO was carried out within a specific programme by expert endoscopists and the histological analyses were performed by a pathologist expert in gastrointestinal disease. We aimed to rule out the possibility of a hidden cancer of another organ by determining various tumour markers. Although some patients had slight elevations of some tumour markers, none of them either had cancer or developed cancer in the following years. In addition, all blood samples were taken under similar conditions and measurements with the ELISA technique were made together on the same day to minimise possible variations in the way the technique was performed.

The study has the following limitations. First of all, there was a small number of patients and, although they were followed up for a long time, the number of cases with progression was also small. Secondly, the control group included patients with GORD and, as biopsies of normal Z-lines were not performed systematically, we cannot rule out that some had intestinal metaplasia. This could explain why we did not find differences in IGFBP-3 levels.

In summary, patients with BO and oesophageal adenocarcinoma have changes in the IGF system, although there are no differences between the different histological grades of BO and nor do levels correlate with the progression of BO. Our findings confirm the association between the IGF system and oesophageal adenocarcinoma, but cast doubt on the potential role of the IGF system as a biomarker of progression to cancer in patients with BO.

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Conflicts of interest

The authors have no conflicts of interest.

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