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EXISTIRÁ UM PAPEL PROTETOR DA METFORMINA NA INCIDÊNCIA DE PÓLIPOS, ADENOMAS E CARCINOMA COLORRETAL?

DOES METFORMIN HAVE A PROTECTIVE ROLE IN THE DEVELOPMENT OF POLYPS, ADENOMAS AND COLORECTAL CARCINOMA?

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INTRODUCTION

Diabetes *Mellitus* is associated with a higher incidence of colorectal carcinoma (CRC) and its precursors[1]. Recent studies have highlighted a protective role of metformin in the development of polyps, adenomas[2] and CCR[3], however, data are conflicting[4] and in most studies the duration of metformin use is not well established, which might affect their conclusions. We aim at investigating a **possible protective role of metformin use for more than 5 years in diabetic patients in the development of polyps, adenomas and CCR**, as well as other factors which may influence these outcomes such as insulin or aspirin use.

METHODS

We performed a **retrospective observational study** on 548 patients followed in a **Diabetes *Mellitus* appointment** in our center with a **total colonoscopy** between 2015 and 2019, under therapy with either metformin or other antidiabetic agent for more than 5 years. We **excluded** 147 patients due to inadequate preparation, incomplete colonoscopy, personal history of inflammatory bowel disease, personal or family history of polyposis syndromes, family history of colorectal cancer and incomplete hospital records. Data regarding demographic and clinical characteristics and the number and type of polyps detected were collected from computer records. Statistical analysis was performed using Stata® 15 and a p-value <0.05 was considered statistically significant.

RESULTS

Table 1. Demographic and clinical characteristics of patients followed in a Diabetes *Mellitus* appointment with a total colonoscopy from 2015-2019.

Legend. DM – Diabetes *Mellitus*; HbA1c – glycated hemoglobin. NSAID – Nonsteroidal anti-inflammatory drugs; Q1-Q3 – interquartile range; SD – standard deviation. [a]p calculated using Student's t-test for two independent samples. [b]p calculated using Chi-squared test. [c]p calculated using Mann-Whitney's test.

	Total (n=401)	Metformin use		p value
		No (n= 141)	Yes (n= 260)	
Age (years) – mean ± SD	68.5 ± 9.2	68.6 ± 8.5	68.5 ± 9.6	0.936[a]
Male gender – no. (%)	228	92 (65%)	136 (52%)	**0.012[b]**
Type of DM – no. (%)				
Type 1	5 (1%)	5 (3.5%)	0 (0%)	**0.004[b]**
Type 2	387 (97%)	131 (93%)	256 (98%)	
Type 3c	9 (2%)	5 (3.5%)	4 (2%)	
Duration of DM (years) – median (Q1-Q3)	11 (6-18)	10 (5-19)	12 (7-17)	0.157[c]
Complications of DM – no. (%)				
Macrovascular	131 (33%)	57 (40%)	74 (28%)	**0.015[b]**
Microvascular	137 (34%)	65 (46%)	72 (28%)	**<0.001[b]**
Insulin treatment – no. (%)	145 (36%)	81 (57%)	64 (25%)	**<0.001[b]**
Other oral antidiabetics use – no. (%)	241 (60%)	56 (40%)	185 (71%)	**<0.001[b]**
Obesity – no. (%)	91 (23%)	27 (19%)	64 (25%)	0.212[b]
Hypertension – no. (%)	329 (82%)	116 (82%)	213 (82%)	0.931[b]
Current or former smoking – no. (%)	102 (25%)	36 (26%)	66 (25%)	0.974[b]
Alcohol abuse – no. (%)	63 (16%)	24 (17%)	39 (15%)	0.595[b]
Statins use – no. (%)	269 (67%)	91 (64%)	178 (68%)	0.435[b]
Aspirin/NSAID use – no. (%)	110 (27%)	43 (30%)	67 (26%)	0.311[b]
HbA1c level (%), mean ± SD	7.44 ± 1.72	7.41 ± 1.87	7.46 ± 1.64	0.795[a]

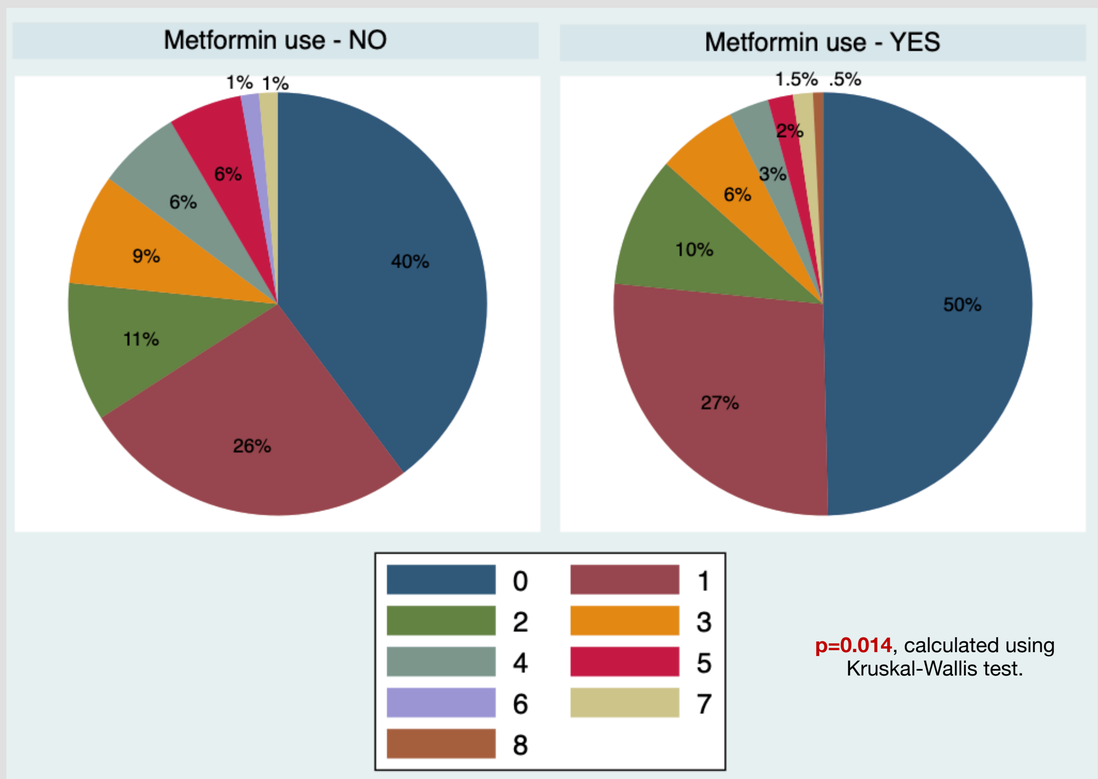

Figure 1. Number of polyps detected on total colonoscopy in each group.

In our regression analysis we considered the presence of more than one polyp on colonoscopy the outcome variable.

Table 2. Number and type of proliferative lesions detected on total colonoscopy.

Legend. Q1-Q3 – interquartile range; SD – standard deviation. *although data does not follow a normal distribution, it was reported using mean ± SD to facilitate comparisons between groups. **defined by at least 1 adenoma ≥ 10mm or with high grade dysplasia, or ≥ 5 adenomas, or any serrated polyp ≥ 10mm or with dysplasia[5]. [a]p calculated using Chi-squared test. [b]p calculated using Student's t-test for two independent samples.

	Total (n=401)	Metformin use		p value
		No (n= 141)	Yes (n= 260)	
Polyp detection rate – no. (%)	216 (54%)	85 (60%)	131 (50%)	0.058[a]
Number of polyps – mean ± SD *	**1.19 ± 1.62**	**1.45 ± 1.73**	**1.04 ± 1.54**	**0.014[b]**
Number of adenomas – mean ± SD *	0.68 ± 1.18	0.81 ± 1.24	0.61 ± 1.14	0.105[b]
High risk adenoma** – no. (%)	111 (28%)	38 (27%)	73 (28%)	0.810[a]
Colorectal cancer – no. (%)	43 (11%)	14 (10%)	29 (11%)	0.705[a]

Table 3. Multivariable logistic regression analysis of variables significantly influencing the presence of more than one polyp in colonoscopy.

This model has an area under the ROC curve of 0.7049 (acceptable discrimination).

VARIABLES	Odds Ratio	95% Confidence Interval	p value
Metformin use	**0.617**	0.384 – 0.992	0.046
Male gender	**2.281**	1.361 – 3.822	0.002
Age (years)	**1.028**	1.001 – 1.056	0.044
Current or former smoking	**2.087**	1.231 – 3.541	0.006
Hypertension	**2.175**	1.055 – 4.480	0.035
HbA1c	**1.142**	0.998 – 1.301	0.054

CONCLUSIONS

In our population of diabetic patients, the **number of polyps** detected on a total colonoscopy was **significantly inferior in the group under metformin**. In multivariable analysis on factors influencing the presence of more than one polyp on colonoscopy, we also found a **protective role of metformin**, whereas **male gender, age, smoking, hypertension and higher HbA1c levels** compose a greater risk in the development of more than one polyp. In our study, insulin, duration of diabetes, complications of the disease, obesity, statins or aspirin/NSAID use did not significantly influence the development of polyps.

Our conclusions support previous findings on metformin's protection in the development of colonic polyps. A larger sample size could possibly allow us to detect differences for more advanced lesions in the natural history of polyps, such as adenomas, high risk adenomas and CCR.

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