Possible protective role of metformin therapy on colonic polyps in acromegaly: an exploratory cross-sectional study

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Abstract

Context: Colonic polyps occur in 30–40% of acromegalic patients, increasing the risk of colon carcinoma. Although debated, there is emerging evidence that metformin may play a protective role in diabetic and non-diabetic patients with colonic polyps and its use in chemoprevention is currently explored.

Objective: Evaluate the prevalence of colonic polyps in acromegalic patients treated or not with metformin and explore its possible protective role.

Design: Exploratory cross-sectional study in two tertiary Italian referral centres.

Methods: Out of 153 acromegalic patients, we selected 58 patients (36–82 years; f: 33) who had at least one colonoscopy performed within the first 2 years of diagnosis. Presence of colonic polyps/cancer and related risk factors, current metformin and acetylsalicylic acid intake, disease duration, therapies for acromegaly, hormonal and metabolic parameters were assessed.

Results: An overall prevalence of 36% polyps was found. Based on the presence of polyps, we identified two groups, comparable for age, BMI, disease duration, glucose, insulin, HOMA-IR, HbA1c, GH and IGF-I levels. Of the patients with polyps (including three adenocarcinomas) only 24% were treated with metformin vs 57% of patients without polyps. Multivariate analysis confirmed a significant negative association between colonic polyps and metformin intake (OR: 0.22, 95% CI: 0.06–0.77, $P = 0.01$), whereas no significant association was found between polyps and age ($P = 0.10$), overweight/obesity ($P = 0.54$), smoking ($P = 0.15$), acetylsalicylic acid intake ($P = 0.99$), disease duration ($P = 0.96$), somatostatin analogues treatment ($P = 0.70$).

Conclusions: These findings, though deriving from an exploratory study, could suggest a protective role of metformin on the development of colonic polyps in acromegaly, and need to be confirmed in an extended study population.

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Introduction

First data showing a marked reduction in cancer incidence in type 2 diabetic patients treated with metformin were published in 2005 (1). To date, although both clinical and

in vitro studies have been providing increasing evidence of the potential protective role of metformin therapy on cancer development (2, 3, 4), such role is still debated and

published data are conflicting (5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17). Nowadays, more than 300 randomised clinical trials are ongoing, investigating the anticancer effect of metformin, mostly focusing on tumours for which diabetes and insulin resistance are known risk factors, such as colorectal cancer (18).

Metformin can provide anticancer activity either indirectly, by reducing insulin and insulin-like growth factors levels, or directly, by activating a number of pathways that lead to a reduction of protein transcription, cell growth and proliferation, such as activation of LKB1/AMPK pathway, induction of cell cycle arrest and/or apoptosis, inhibition of protein synthesis and inhibition of the unfolded protein response (UPR), activation of the immune system and eradication of cancer stem cells (3, 16, 17).

Among endocrine disorders, acromegaly displays a higher risk of colonic polyps and cancer. As known, this rare condition (prevalence 40–130 cases per million inhabitants) is characterised by chronic growth hormone (GH) and insulin-like growth factor 1 (IGF-I) hypersecretion, generally caused by a pituitary adenoma (19, 20, 21).

Although the real incidence of cancer in acromegalic patients is widely debated (22), there is general agreement on the increased risk of colonic polyps (up to 30–40%), with a consequent higher risk of cancer development (23, 24, 25, 26). Recent data from retrospective and prospective studies and metaanalyses indicate a 2.4-fold increased risk of colonic adenomas, a 3.7% prevalence of colorectal cancer with a 2.5-fold higher colon cancer-specific mortality rate in acromegalic patients compared to the general population (23, 24, 25, 26, 27, 28). In absolute terms, up to 45% of acromegalic patients might develop colonic polyps. Particularly at risk are male patients with more than 50 years of age, with a duration of disease of more than 5 years and a family history of polyposis (27, 28).

Colonic polyps development in acromegalic patients may be influenced first of all by elevated GH and IGF-I levels, stimulating epithelial cell proliferation and inhibit apoptosis, and also by the high prevalence in these patients of impaired glucose tolerance and diabetes, both conditions associated to colorectal cancer development (27, 29). Whereas much has been published about metformin and colorectal cancer (30), no information is available on the effect of metformin on neoplastic colonic lesions development specifically in acromegalic patients.

The main aims of this exploratory study were to confirm the high prevalence of colonic neoplasms in a

cohort of acromegalic patients and to explore the possible protective role of metformin in this disease.

Subjects and methods

In this exploratory cross-sectional study, the clinical archives of two major Italian tertiary pituitary referral centres (Genova and Napoli) were searched to identify all acromegalic patients who had performed at least one colonoscopy within the first 2 years of diagnosis, from 2000 to 2015. In detail, we excluded from the analysis patients who refused the endoscopic examination, patients who performed colonoscopy more than 2 years after the diagnosis of acromegaly, patients who underwent other screening procedures such as virtual colonoscopy or entero-CT and patients who did not perform the examination due to other comorbidities/frailties of the patient. Moreover, we excluded patients with unreliable examination including colonoscopy early stopped and/or conducted in poor bowel toilet conditions. Furthermore, we considered ineligible those patients who had a negative colonoscopy, performed for other reasons, within 2 years before the diagnosis of acromegaly.

For each patient, the following information was retrieved and filed in a dedicated computerised database: (1) family history or others risk factors for colonic polyps/cancers; (2) smoking history; (3) time since clinical onset of acromegaly (estimated disease duration); (4) therapies for acromegaly; (5) BMI, biochemical, hormonal and metabolic parameters (GH, IGF-1, glycaemia, insulin, HbA1c, HOMA-IR) at time of colonoscopy; (6) previous or concomitant use of acetylsalicylic acid; (7) current use of metformin at the time of colonoscopy; current use of metformin was defined as continuous metformin therapy for a minimum of six months prior to colonoscopy (metformin therapy was started in these patients only for insulin resistance or diabetes management); (8) colonoscopic findings. According to endoscopic examination we recorded: (a) presence/absence of colonic polyps and cancer; (b) macroscopic characteristics of the lesions found at colonoscopy (sessile or pedunculated), (c) histological characteristics of removed lesions (hyperplastic or adenomatous, tubular or villous, low grade or high grade dysplasia polyps). Patients were divided into two groups based on the presence (=cases, namely 'polyp') or absence (=controls, namely 'no polyp') of colonic neoplasia. Approval from the Medical Ethical Committee of both centres, as well as patients' informed

consent to use the data for research purposes, were obtained.

Statistical analysis

We performed descriptive statistical analysis of parameters evaluated in the two study-groups; values are expressed as mean $\pm$ s.d.

T-test was used to compare the distribution of patient characteristics in two groups, such as age, sex, BMI, disease duration and GH, IGF-I, glycaemia, insulin, HbA1c and HOMA-IR values.

Associations between categorical variables were assessed by two-tailed Fisher test or Chi-square test.

Due to the retrospective study design, the extent of the risk has been calculated and expressed as odds ratio (OR) (95% CI). Odds ratios (ORs) and the corresponding 95% CIs were calculated by means of an unconditional logistic regression model, with the case/control status as the dependent variable and the following as covariates: age, sex, overweight/obesity, duration of acromegaly, smoking habit, current/previous SSA therapy, current/previous use of acetylsalicylic acid, and current/previous use of metformin. The final model was arrived at by means of a stepdown procedure (<0.1) based on the likelihood-ratio test between the models with and without each covariate, one at a time.

Significance was defined for $P < 0.05$, always considering two-tailed *p* values. All statistical analyses were performed using software IBM – SPSS Statistics (version 22).

Results

Out of 201 acromegalic patients in active follow-up at two centres, 58 met the inclusion criteria for colonoscopy and resulted eligible for the study (33 females; mean age: 57 ± 11.6 years; age range: 36–82 years). A flow chart shows all acromegalic patients screened during the recruitment period, and the proportion of patients excluded from the final analysis with the reasons of exclusion (Fig. 1). Previous and ongoing treatments for acromegaly at the time of endoscopy are shown in Table 1.

In our series, we found a total of 28 colorectal polyps among the 21 patients, mostly as sessile polyps ($n = 16$). As far as histological findings, we recorded a prevalence of hyperplastic polyps ($n = 13$, 46% of the total), followed by adenomatous polyps ($n = 10$, 36% of the total; 5/10

Figure 1

Flow chart of enrolled patients.

tubular, 3/10 villous and 2/10 tubulo-villous) (Fig. 2), without difference between patients treated or not with metformin. Histological report was unavailable for two lesions (micropolyps not recovered). None of the polyps analysed had a high-degree dysplasia. The endoscopic examination showed the presence of multiple polyps in five patients, including the two subjects with family history of colonic polyps (one with adenocarcinoma). In 3 out of 58 patients (5.2%) an adenocarcinoma (with or without accompanying polyps) was found at colonoscopy while in 18 cases (31%) only a benign polyp was detected, for an overall prevalence of colonic neoplasia of 36.2%.

The characteristics of the 58 patients according to the presence (polyp) or absence (no polyp) of colonic neoplasia are shown in Table 2. The two groups 'polyp' and 'no polyp' were comparable for several features (Table 2). Cases of polyp were more frequently males (12/21, 57.1%) than controls with no polyp (13/37, 35%) but the difference was not statistically significant (OR = 2.46 95% CI: 0.82–7.37, $P = 0.16$).

However, a striking difference between the two groups was observed in the proportion of patients with diabetes,

Table 1 Previous and ongoing treatments for acromegaly at the time of endoscopy.

Therapies	Number of patients
Neurosurgery	34
Somatostatin analogues (SSA)	32
SSA + cabergoline	6
SSA + pegvisomant	6
Cabergoline	1
Pegvisomant	1

Figure 2

Polyps subdivision according to histotype.

that was present in 6/21 (28.6%) cases and in 24/37 (64.9%) controls (OR: 0.22, 95% CI: 0.07–0.69, $P = 0.01$). This difference was reflected in the proportion of patients reporting current or previous use of metformin 5/21 (23.8%) and 21/37 (56.8%), respectively (OR: 0.24, 95% CI: 0.07–0.79, $P = 0.02$). The duration of metformin therapy changed from a minimum of 6 months to a maximum of 15 years prior to endoscopy, with an average duration of 3 years. The average dose of metformin was 1797 ± 926 mg for 'no polyp' and 1100 ± 540 mg for 'polyp', with no statistically significant difference between the two groups ($P = 0.12$). Four diabetic patients were on only diet-therapy, whereas four were taking other antidiabetic therapies in addition to metformin (1 sulfonylurea and 3 insulin). Only one patient among these latter had polyps at colonoscopy, while the others had a negative endoscopic exam.

Univariate analysis confirmed a significant negative association between the presence of polyps and metformin intake. Multivariate analysis (Table 3) as well confirmed a

significant negative association between the presence of colonic neoplasia and the use of metformin (OR: 0.22, 95% CI: 0.06–0.77, $P = 0.01$). No association was found between acetylsalicylic acid intake and polyps ($P = 0.99$). In the multivariate analysis, the only two variables with a protective role towards colonic polyps were metformin and female sex (OR: 0.37, 95% CI: 0.11–1.20, $P = 0.09$), the latter with a less strong degree. All other variables, age ($P = 0.10$), overweight/obesity ($P = 0.54$), smoking ($P = 0.15$), acetylsalicylic acid ($P = 0.99$), estimated disease duration ($P = 0.96$), somatostatin analogues treatment ($P = 0.70$) were excluded by the model (Table 3).

The degree of protection afforded by metformin appeared to be similar for hyperplastic and adenomatous polyps (OR=0.30 95% CI: 0.06–1.58 and OR=0.41 CI: 0.17–0.95, respectively).

None of the patients with multiple lesions were taking, or had previously taken, metformin.

Discussion and conclusions

A unique opportunity to study the potential role of metformin as a cancer chemopreventive agent is offered by acromegalic patients, who have a 2.4-fold increased risk of colonic adenomas, a 2.5-fold increased colorectal cancer mortality rate, as compared to general population (23, 24, 25, 26, 27, 28, 29, 30, 31, 32) and often develop type II diabetes (29).

In this exploratory cross-sectional study, the overall prevalence of colonic polyps (36%) and cancer (5.2%) in 58 patients with acromegaly was in line with literature.

Similarly, mean age (over 50 years), estimated disease duration (more than 5 years) at the time of polyps' detection and prevalence of diabetes mellitus type 2 (51.7%) resulted in line with previously published data (21).

When patients with and without polyps were compared, the presence of diabetes and use of metformin were negatively associated with the presence of polyps, with odds ratios of controls, respectively. Since most diabetic patients (26 out of 30) were treated with metformin, and all patients treated with metformin received the drug for insulin resistance or diabetes, it was not possible to evaluate, statistically, which one of these two factors was independently associated with the presence of polyps: as a consequence, only biological plausibility dictated the choice to include metformin use instead of diabetes in multivariate analyses, which fully confirmed the negative association. It is known that the pathophysiology of diabetes facilitates the onset of cancer (14, 15).

Table 2 Demographics and patients' characteristics. Data are presented as n (%) or as mean $\pm$ S.D.

Characteristics	Group 1 ($n = 37$)	Group 2 ($n = 21$)	P value
Sex, n (%)			
Female	24 (64.9)	9 (42.9)	0.1
Male	13 (35.1)	12 (57.1)	
Age (y)	56.2 ± 2.0	57.6 ± 2.3	0.67
Disease duration (y)	12.5 ± 0.9	13.0 ± 1.6	0.78
Diabetes, n (%)	24 (64.9)	6 (28.6)	0.01
Smoking, n (%)	6 (16.2)	6 (28.6)	0.26
ASA, n (%)	6 (16.2)	3 (14.3)	0.85
Metformin, n (%)	21 (56.8)	5 (23.8)	0.02
Glycemia (mg/dL)	112.86 ± 4.84	103.52 ± 9.22	0.34
HbA1c (%)	6.7 ± 0.2	6.0 ± 0.3	0.18
HOMA-IR	5.1 ± 1.46	6.54 ± 3.15	0.64
BMI (kg/m ²)	28.8 ± 0.8	29.7 ± 1.3	0.54
GH (μ g/L)	10.29 ± 5.82	5.74 ± 2.01	0.46
IGF-I, $\times$ ULN	1.80 ± 1.49	1.88 ± 1.64	0.86

ASA, acetylsalicylic acid; HbA1c, glycated hemoglobin; IGF-I, Insulin like Growth Factor I; ULN, upper limit of normal.

Table 3 Univariate and multivariate analysis.

Risk factors	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Age	2.22 (0.37–13.12)	0.37	**	0.10
Female Sex	0.27 (0.07–1.07)	0.06	0.372 (0.11–1.20)	0.09
Overweight/obesity	0.74 (0.11–4.89)	0.78	**	0.54
Smoking	3.83 (0.67–21.94)	0.23	**	0.15
Disease duration	0.68 (0.22–2.12)	0.72	**	0.96
SSA therapy	0.92 (0.28–3.05)	0.85	**	0.70
Acetylsalicylic acid	0.86 (0.19–3.87)	0.85	**	0.99
Metformin	0.24 (0.07–0.79)	0.02	0.224 (0.06–0.77)	0.01

**Excluded from the final model.

SSA, somatostatin analogues.

Moreover, a recent retrospective study on a large number of acromegalic patients, showed that diabetic acromegalic patients may develop extra pituitary tumours and malignant neoplasms respectively twice and three times more frequently than those without diabetes (29). As stated before, in our series the vast majority of diabetic patients had a negative colonoscopy. According to this observation, patients with dual risk factors for polyps' development, such as diabetes and acromegaly, displayed a lower polyps prevalence compared with non-diabetic acromegalic patients, differently from the expected outcome. Since the only significant difference between the two groups was metformin intake, this finding could suggest that metformin therapy can be able to counterbalance the dual risk factor.

Due to the small number of diabetic patients taking other antidiabetic therapies (including insulin), it was not possible to assess the presence of a correlation between the prevalence of polyps and other hypoglycaemic therapies.

In our study population, there is a trend towards a more frequent presence of polyps in the male gender, in line with that has already been suggested in acromegalic subjects and more strongly in the general population (28). Moreover, no significant difference was found between the two groups in GH and IGF-I values. These results confirm those of previous studies, where no correlation was seen between IGF-I levels and polyps detection at first colonoscopy, even though in a study higher IGF-I values were associated with a higher incidence of polyp recurrence at the endoscopic follow-up (23). Notably, mean GH and IGF-I values recorded in our series were higher than values recommended for disease control (33), since many patients performed colonoscopy near the diagnosis.

In our series, no relevant correlation was found between the presence of colonic polyps and overweight/obesity. The analysis on fasting insulin levels and

HOMA-IR, though limited by the proportion of missing data (due to retrospective nature of this study), failed to show differences between the two groups. To this regard, it must be considered that the role of insulin resistance in colonic polyps development in acromegaly is still debated. Two recent studies could not find any correlation between serum insulin levels and polyps in acromegaly (34, 35). In contrast, Colao *et al.* reported that an increase in fasting insulin levels is associated with an 8.6- to 14.8-fold increased risk of colonic adenomas (36).

Medical therapy for acromegaly was not correlated with polyps development (SSA, $P = 0.70$). Moreover, although published data suggest a protective effect of acetylsalicylic acid on colonic polyps, in our patients we did not find any significant correlation ($P = 0.99$). Similarly, although smoking is considered a risk factor, we failed to find any association between smoking and polyps ($P = 0.15$).

These results suggest that metformin use significantly affected the development of colonic polyps in our cohort of acromegalic patients, making speculate that a protective role of the drug in this setting can be hypothesized.

Colonic polyps development in acromegalic patients can have several causes: not only elevated GH and IGF-I levels and high incidence of impaired glucose tolerance as well as diabetes, but also genetic factors, increased large bowel length and/or altered bowel transit time, altered acid bile secretion, altered local immune response. As a consequence, extrapolation of the anti-tumour effect of metformin, observed in this specific setting, to the general population is absolutely not warranted.

We are aware that this study has some limitations, mainly due to its retrospective design (including the use of different hormonal assays, the variable dose and duration of metformin therapy and the lack of a third control group of acromegalic diabetic patients not-exposed to metformin). Conversely, the small sample size, due to the low incidence of acromegaly and the choice to include only

patients who underwent a reliable colonoscopy within two years of diagnosis, is due to the intent of evaluating a homogeneous population without interfering factors, and to make our cohort representative for only an exploratory study. Colonoscopy represents a screening procedure in patients with acromegaly, especially for patients with long term disease history and those with familiarity for colonic cancer. Indeed, acromegaly is reported among the conditions at high risk of colonic neoplasms for which the dedicated guidelines suggest performing colonoscopy at diagnosis. However, despite these evidences, being colonoscopy a rather invasive technique, still many patients refuse it. Moreover, for similar reasons, other patients were not eligible for the procedure. In this setting, when patients refuse or is not eligible, we may delay it or adopt alternative, although less effective, screening procedures. This is the main reason why we collected the data from 30% patients of the full cohort.

Keeping in mind these limitations our data suggest a possible protective role of metformin for preventing colon polyps in acromegalic patients. Such finding needs to be further assessed with prospective studies that include groups of non-diabetic acromegalic patients, as well as diabetic subgroups exposed and not-exposed to metformin.

In conclusion, despite these limitations, the study suggests a potential efficacy of metformin in preventing colonic polyps development in acromegalic patients.

This protective effect of metformin, once explored and confirmed in a larger population, possibly in a prospective setting, may open the perspective of a future application of metformin in chemoprevention in acromegaly, as well as in other populations with increased risk of colonic cancer.

Declaration of interest

All the authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this manuscript.

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