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Metformin for recurrent colorectal polyp or adenoma prevention after polypectomy in patients without diabetes mellitus: a prospective study

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To reduce the burden of colorectal cancer (CRC), the chemopreventive effects of 1-year metformin on polyps or adenoma recurrence in patients without diabetes mellitus (DM) who underwent polypectomy were evaluated. Patients without DM aged between 40 and 70 years old, with no polyp or adenoma after polypectomy, were randomly assigned to the control (no intervention), low-dose (500 mg/day), or high-dose (1,000 mg/day) metformin groups in a 1:1:1 ratio. After the 1-year intervention, the numbers of polyps and adenomas were measured and recorded, then resected. Plasma lipid and blood glucose were measured at baseline and 1-year follow-up. Data from the three groups were compared statistically. A total of 272 patients were enrolled in the analysis. In the control group, 48.9% of patients had adenoma recurrence, which was significantly higher than those in the low-dose (30.8%, p=0.012) and the high-dose (29.9%, p=0.009) metformin group. For the number of recurrent adenomas per subject, the difference between the control and the high-dose metformin groups was significant (0.86±1.09 vs. 0.47±0.83, p=0.020). No significant difference among the three groups and between baseline and 1-year follow-up was found in the lipid and glucose parameters. In conclusion, 1-year metformin use reduced the prevalence of recurrent adenoma significantly in patients without DM after polypectomy and may not be related to lipid and glucose metabolism.

Key words: chemoprevention; colorectal adenoma; colorectal cancer; colorectal polyps; metformin

Colorectal cancer (CRC) is the third most common malignancy and the second most common cause of cancer-related death [1]. Even though the rate of cancer-related mortality is declining since the screening and treatment continuously improve, the number of deaths is increasing with time and is estimated to rise by 60.0% and 71.5% for colon and rectal cancer from 2013 to 2035, respectively, due to population expansion and aging worldwide [2]. Therefore, new strategies to decrease the burden of CRC are required. Currently, the major method is early detection and removal of colorectal polyps and adenomas to block the adenoma-carcinoma sequence of CRC by colonoscopy [3, 4]. However, the possible complications of the procedure and healthcare resource consumption make an alternative strategy still desirable. Using chemopreventive agents to decrease the incidence of CRC and premalignant adenoma has garnered great attention recently [5]. A chemopreventive agent for cancer should have a good safety profile, availability, and affordability, considering the long-term use in the general population [6], and metformin may be an appropriate candidate.

Metformin is a biguanide derivative and also the most prescribed first-line glucose-lowering drug for diabetes mellitus (DM), which acts by suppressing hepatic gluconeogenesis and glycogenolysis, and increasing glucose uptake by muscle [7]. The mechanisms involved in the action of metformin vary. An important one is via affecting the AMP-activated protein kinase (AMPK) and subsequent mammalian target of rapamycin (mTOR) signaling pathways to inhibit mitochondrial respiration, then reduce cellular energy metabolism, protein synthesis, and cell proliferation [8]. Metformin also indirectly reduces insulin and insulin-like growth factor-1 (IGF-1) to inhibit cell proliferation [9].

An observational case-control analysis using a database of patients with DM conducted in 2005 is the first study to notice that metformin might have the potential to decrease cancer incidence [10]. Following this study, increasing

numbers of epidemiological and clinical studies demonstrated that metformin use is probably associated with the reduction of risk of various cancers in patients with DM, including CRC. More and more studies have observed that the protective effect of metformin also extends to colorectal adenoma formation [11]. Research for exploring the involved molecular mechanisms of metformin has also been performed intensively and found that the mechanisms of anti-DM and anti-CRC may be through the same or overlapped pathways. For example, through the AMPK/mTOR pathway, metformin inhibits the proliferation of CRC cells by suppressing mitochondrial respiratory complex I. Metformin is also found to induce oxidative stress, modulate inflammation, and lead to apoptosis and autophagy of CRC cells [8]. Subsequently, several systematic reviews and meta-analyses were conducted for this research hotspot [11–13]. Generally, metformin is considered a chemopreventive agent in these studies, however, it is not been recommended in any guidelines for cancer management until now because the conflict results still exist, including observational studies, randomized trials, and meta-analyses, no association between metformin and the risk of any malignancies was found in some studies [14–17].

Most studies focusing on the CRC preventive or therapeutic effects of metformin are with observational or retrospective design, which may have a time-related bias or un-adjusted cofounders to interfere with the results [14]. In addition, since metformin is a widely used anti-DM medication, leading the database research conducted in patients with DM is the most straightforward and convenient way. However, the characteristics of the two patient groups might not be the same, even though they are known to have overlapped risk factors and pathogenesis mechanisms. Moreover, DM itself is a risk factor for oncogenesis [18], further complicating the interpretation of the results of these studies. Therefore, studies with prospective and well-controlled designs in non-DM patients can provide data to complete the comprehensive prospect by combining with those using DM databases. Nonetheless, only one clinical trial conducted in Japan demonstrated that low-dose metformin (250 mg/day) for 1 year in non-DM patients showed prevention of recurrent polyps or adenoma after polypectomy until now [19].

Regarding the knowledge from previous studies of metformin in reducing the risk of CRC, colorectal adenoma, and polyp, the chemopreventive effect of metformin on polyp or adenoma recurrence in non-DM patients with high risk was evaluated in the present study to expand the generalizability. Patients who were recommended a surveillance interval of 3 years were recruited for the relatively higher risk [4]. Metformin was administered for 1 year to observe the effect and safety in patients without DM, and the results of two doses (500 and 1,000 mg/day) that are the regular dose for DM treatment were compared for the possibility of dose-response. The prevalence and the number of polyps and adenomas at the end of the study and the adverse events during the study period were observed as outcomes to evaluate the effect and safety of metformin.

Patients and methods

Patients. Patients who attended our hospital from September 1, 2022, to August 1, 2023, for colorectal polypectomy were invited to participate in this study. The patients agreed to participate and signed the informed consent after being explained the study design and details, including possible advantages and adverse events. The inclusion criteria were: aged between 40 and 70 years old, with appropriate bowel preparation defined as the Boston Bowel Preparation Scale ≥7, found adenoma numbers >3 during polypectomy, no polyp or adenoma after polypectomy assessed by the physicians at the end of the procedure. The exclusion criteria were: had history of metformin allergy or intolerance; use non-steroidal anti-inflammatory drugs (e.g., aspirin) or berberine chloride or curcumin [20] for within 6 months before the starting of metformin treatment in this study or would be possible to use during the 1-year metformin treatment study period; had a history of colorectal surgery, malignant disease (excluding radical resection endoscopically). Patients who with DM, had a history of heart failure, renal failure or cirrhosis, familial adenomatous polyposis, inflammatory bowel disease, or were defined to be inappropriate candidates for this study by the investigators (e.g., those who cannot be followed up regularly) were also excluded.

Ethics approval and consent to participate. This study was ethically approved by the Institutional Review Board of our hospital (No. 2022-026) and prospectively registered in the Chinese Clinical Trial Registry (ChiCTR2200062649; August 14, 2022). All patients signed the informed consent after being explained the study design and details, including possible advantages and adverse events.

Interventions and measurements. The characteristics of resected polyps or adenomas at baseline were identified by certified pathologists. The demographic characteristics, medical and family history, and habits such as drinking and smoking of the eligible patients were collected at the first visit after the polypectomies. Meanwhile, the plasma lipid and blood glucose were measured. Homeostatic model assessment for insulin resistance (HOMA-IR) was calculated as fasting blood insulin (μU/ml) × fasting blood glucose (mmol/l)/22.5 [21]. Patients were randomly assigned by a computer-generated random number list into the control (no intervention), low-dose metformin (500 mg/day), or high-dose metformin (1,000 mg/day) groups in a 1:1:1 ratio. Metformin (Topfond Pharmaceutical Co., Ltd., Henan, China) intervention was started 1 week after polypectomy and continued for 1 year. Patients were followed up every 4 to 8 weeks by phone interview or outpatient visit. All adverse events were recorded and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) 5.0 [https://ctep.cancer.gov/protocoldevelopment/electronic_

applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf]. Patients would be withdrawn from this study if severe adverse events, defined as Grade ≥ 3, occurred.

After the 1-year intervention, colonoscopy examination and polypectomies, if any polyps or adenomas were found, were conducted. The healthcare givers (including physicians and nurses) who performed the final colonoscopy assessment were not informed which group the patients belonged to. Appropriate bowel preparation was defined as the Boston Bowel Preparation Scale ≥7. Total colonoscopy was performed according to the quality indicators to achieve the terminal ileum and with withdrawal time ≥6 minutes under narrow band imaging or blue light imaging models to identify each polyp or adenoma [22]. The numbers of polyps and adenomas were measured and recorded, then resected. The follow-up plasma lipid and blood glucose levels were also measured.

Statistical analysis. For the sample size estimation, at least 30 to 40 participants in each group are suggested for a pilot randomized controlled trial [23], and based on previous study for the effect of metformin on colorectal adenoma or polyps formation in post-polypectomy patients without DM, around 80 participants were enrolled and completed the study in each group [19]. With the assumption of a 20% dropout rate, we proposed to recruit 100 patients per group. All data were entered into SPSS 25.0 statistical software (IBM SPSS, Armonk, NY, USA) for statistical analysis. Continuous data are presented as mean with standard deviation (mean ± SD), and categorical data are presented by count and percentage. One-sample Kolmogorov-Smirnov test was used to assess the normality of the distribution when multiple comparisons were conducted using continuous data. The differences were tested by a one-way ANOVA test if normally distributed or by the Kruskal-Wallis test if non-normally distributed. The multiple comparisons of categorical data were performed by the chi-square (χ^2) test. A $p<0.05$ was considered statistically significant. The comparison of each two groups was performed using Bonferroni correction, and $p<0.0167$ was considered statistically significant.

Results

Three hundred eligible patients were randomly assigned to the three groups in a 1:1:1 ratio, with 100 patients allocated for each group. Twenty-eight patients were excluded because of improper compliance (n=17), being prescribed NSAIDs due to cardiovascular diseases during the study period (n=2), or patients who decided to withdraw (n=9). A total of 272 patients were enrolled in the analysis; the patient numbers in the control, low-dose metformin, and high-dose metformin groups were 94, 91, and 87, respectively. The demographic characteristics (age, sex, and body mass index), habits (drinking and smoking), medical history (hypertension and hyperlipidemia), family history of CRC, and the Boston Bowel Preparation Scale at baseline are listed in Table 1. No significance of these patients' characteristics among the three

Table 1. Patients' characteristics at baseline.

	Control (n=94)	Low-dose metformin (n=91)	High-dose metformin (n=87)	χ^2/H	p-value
Demographic					
Age (years)	56.56±9.78	56.99±10.07	57.36±9.95	0.324	0.851
Sex [male/female (%)]	66/28 [70.2%/29.8%]	64/27 [70.3%/29.7%]	57/30 [65.5%/34.5%]	0.623	0.733
BMI (kg/m^2)	23.89±2.77	24.44±2.62	24.19±1.90	1.580	0.454
Drinking [n (%)]	23 [24.5%]	19 [20.9%]	22 [25.3%]	0.551	0.759
Smoking [n (%)]	27 [28.7%]	30 [33.0%]	28 [32.2%]	0.439	0.803
Hypertension [n (%)]	20 [21.3%]	27 [29.7%]	18 [20.7%]	2.515	0.284
Hyperlipidemia [n (%)]	25 [26.6%]	18 [19.8%]	21 [24.1%]	1.220	0.543
Family history of colorectal carcinoma [n (%)]	10 [10.6%]	6 [6.6%]	7 [8.0%]	1.005	0.605
Boston Bowel Preparation Scale	7.98±0.87	8.08±0.85	7.90±0.81	2.037	0.361
Characteristics of polyps or adenomas					
Number of polyps per subject (mean±standard deviation)	7.71±4.27	7.25±3.75	7.03±3.87	0.856	0.652
Number of adenomas per subject (mean±standard deviation)	5.80±2.71	5.52±2.58	5.49±2.70	1.056	0.590
Patients with high risk (≥ 10 adenomas) [n (%)]	12 [12.8%]	10 [11.0%]	13 [14.9%]	0.621	0.733
Histological type of adenomas [n (%)]*					
Conventional	516 [94.7%]	471 [93.8%]	459 [96.0%]	2.448	0.294
Tubular or tubulovillous	513 [94.1%]	469 [93.4%]	456 [95.4%]	1.812	0.404
Villous	3 [0.6%]	2 [0.4%]	3 [0.6%]	0.257	0.879
Serrated	11 [2.0%]	9 [1.8%]	6 [1.3%]	0.919	0.631
Adenoma type was not identified	18 [3.3%]	22 [4.4%]	13 [2.7%]	2.093	0.351

Note: *total numbers of adenomas in the control, low-dose metformin, and high-dose metformin groups are 545, 502, and 478, respectively

groups was found (Table 1). In addition, the characteristics of resected polyps or adenomas at baseline also showed no significant difference among the three groups, including the numbers of polyps/adenomas per subject, the numbers of patients with high risk, and histological types of adenomas (Table 1).

The recurrence of polyps or adenomas was observed by colonoscopy 1 year after metformin intervention. The prevalence rate of adenoma was significantly different among the three groups (p=0.010). In the control group, 48.9% (95% CI 38.6–59.2%, n=46) patients had adenoma recurrence, which was significantly higher than those in the low-dose metformin group (30.8%, 95% CI 21.1–40.4%, n=28, p=0.012) and the high-dose metformin group (29.9%, 95% CI 20.1–39.7%, n=26, p=0.009). There was no significant difference between the two metformin groups (p=0.898). The number of polyps per subject in the control, low-dose metformin, and high-dose metformin groups was 1.14±1.27, 0.91±1.30, and 0.74±1.08, respectively, however, no significant difference was found (p=0.072). With the same trend, the control group had the most numbers of recurrent adenomas per subjects as 0.86±1.09, followed by 0.58±1.01 in the low-dose metformin group and 0.47±0.83 in the high-dose metformin group with significant difference among the three groups (p=0.013), however, only the difference between the control and the high-dose metformin groups was significant (p=0.020). No differences between the control and the low-dose metformin groups or the two metformin groups were found (p=0.059 and 1.000, respectively). The prevalence rate of polyps and the location of polyps or adenomas were both not significantly different among the three groups and between each two groups (Table 2).

To clarify the chemoprotective mechanism of metformin, the plasma lipid and blood glucose parameters, including total cholesterol, creatinine, HbA1c, fasting glucose, fasting insulin, and Hb, were measured at baseline and 1 year after intervention. HOMA-IR was calculated based on the measurements. No significant difference among the three groups was found. In addition, no significant difference between baseline and 1-year follow-up of each parameter was observed (Table 3).

The adverse events during the study period were recorded. All were Grade 1 and occurred in the very early first or second week and were manageable. Loss of appetite, nausea, diarrhea, fatigue, and dizziness were reported. Significantly more events occurred in both metformin groups compared with those in the control group, however, no significant difference between the low- and high-dose metformin groups was observed (Table 4).

Discussion

In the present study, the results indicated that receiving metformin 500 and 1,000 mg/day after polypectomy for 1 year significantly reduced the prevalence of recurrent adenoma compared with no intervention. However, only patients who took 1,000 mg/day showed significantly decreased numbers of adenomas than those in the control group. Among the three groups, no difference in baseline characteristics, serum lipid, and blood glucose at two time points was found. In addition, differences in serum lipid and blood glucose between baseline and 1-year follow-up were non-significant in all participants, indicating that the effect of metformin on adenoma prevention may not be associated with the glucose-lowering ability, at least in non-DM patients.

Studies that evaluated the effect of metformin on CRC, colorectal polyps, and adenomas are mainly observational and may overestimate the protective effects due to time-related bias [14]. Within these studies, many are conducted using databases of DM patients because of the availability, which poses another challenge for generalizability. Prospective studies and clinical trials have higher evidence levels and no need to consider the immortal time bias issue from the misclassified definition of metformin exposure. However,

Table 2. Recurrence of polyps or adenoma 1 year after metformin intervention.

	Control (n=94)	Low-dose metformin (n=91)	High-dose metformin (n=87)	χ^2/H	p-value
Boston Bowel Preparation Scale	7.78±0.76	7.81±0.77	7.92±0.87	1.185	0.553
Recurrence type [n (%)]					
Polyps	50 [53.2%]	38 [41.8%]	33 [37.9%]	4.672	0.097
Adenomas	46 [48.9%]	28 [30.8%][a]	26 [29.9%][b]	9.168	0.010*
Number of polyps per subject (mean±standard deviation)	1.14±1.27	0.91±1.30	0.74±1.08	5.254	0.072
Number of adenomas per subject (mean±standard deviation)	0.86±1.09	0.58±1.01	0.47±0.83[b]	8.684	0.013*
Location of polyps or adenoma [n (%)]					
Left side	42 [39.3%]	31 [37.3%]	27 [42.2%]	0.682	0.711
Right side	30 [28.0%]	23 [27.7%]	19 [29.7%]	1.202	0.548
Rectum	35 [32.7%]	29 [34.9%]	18 [28.1%]	3.914	0.141

Note: *significance among the three groups; [a]significance between the control and low-dose metformin groups; [b]significance between the control and high-dose metformin groups

Table 3. Values of serum biological markers at baseline and 1-year follow-up.

		Control (n=94)	Low-dose metformin (n=91)	High-dose metformin (n=87)	H	p-value
Total cholesterol (mmol/l)	Baseline	4.60±0.95	4.63±0.86	4.56±1.01	0.713	0.700
	Follow-up	4.45±1.09	4.70±1.14	4.54±1.18	2.160	0.340
	p-value	0.341	0.698	0.913		
Creatinine (μmol/l)	Baseline	76.90±15.33	78.97±15.46	76.97±16.36	1.355	0.508
	Follow-up	79.04±20.72	76.08±19.92	78.61±21.73	1.151	0.562
	p-value	0.456	0.290	0.586		
HbA1c (%)	Baseline	5.30±0.68	5.35±0.61	5.24±0.64	1.418	0.492
	Follow-up	5.26±0.65	5.29±0.63	5.17±0.66	1.593	0.451
	p-value	0.659	0.436	0.426		
Fasting glucose (mmol/l)	Baseline	5.05±0.58	5.02±0.45	5.12±0.50	3.202	0.202
	Follow-up	5.12±0.80	5.04±0.70	5.09±0.84	0.799	0.671
	p-value	0.512	0.860	0.796		
Fasting insulin (μU/ml)	Baseline	5.65±1.48	5.52±1.83	5.65±1.64	0.870	0.647
	Follow-up	5.82±1.58	5.71±1.74	5.58±1.57	1.029	0.598
	p-value	0.469	0.509	0.794		
HOMA-IR	Baseline	1.27±0.38	1.23±0.40	1.28±0.38	1.353	0.508
	Follow-up	1.33±0.42	1.28±0.43	1.27±0.44	1.305	0.521
	p-value	0.351	0.463	0.851		
Hb (g/l)	Baseline	134.65±13.07	132.31±11.74	134.57±10.79	2.452	0.294
	Follow-up	135.38±13.54	131.78±12.88	133.71±13.63	3.833	0.147
	p-value	0.708	0.783	0.663		

because of the ethical consideration for intervention at the experimental stage of metformin prescription for cancer therapy, to ensure the most benefit and least harm to patients, metformin was used as an adjuvant therapy with standard treatment in refractory or later-stage CRC patients in most prospective studies, which is far away from the original purpose: use metformin as a chemopreventive agent, even this is reasonable considering the long duration for development or progression of CRC. Setting the CRC incidence as the primary outcome requires several years of evaluation. An alternative way to evaluate the effect of metformin for CRC by a prospective study is to use other colorectal neoplastic diseases as the endpoint of the study. Trials for colorectal polyps and adenomas, aberrant crypt foci, and familial adenomatous polyposis have been conducted in non-DM patients [19, 24, 25] because all these patients have a higher risk of developing CRC, and the major management is the same as routinely monitoring by coloscopic polypectomy. Using the three diseases as a shorter-term surrogate marker for CRC can maintain a lower dropout rate and better compliance. Moreover, according to the updated consensus for follow-up after colonoscopy and polypectomy, the frequency of this relatively safe, however invasive procedure is decided by the risk of recurrence and progression stratified by the numbers and advanced degree of polyps and adenomas [26]. Patients with the highest risk have to undergo colonoscopy and polypectomy annually, which is a burden on the healthcare system and patients. Metformin may provide the benefit of decreasing the frequency through reducing the prevalence and number of recurrent polyps and adenomas.

Table 4. Adverse events.

	Control (n=4)	Low-dose metformin (n=19)[a]	High-dose metformin (n=22)[b]
Loss of appetite	1	3	9
Nausea	–	5	5
Diarrhea	2	10	6
Fatigue	1	–	2
Dizziness	–	1	–
χ^2	16.337		
p-value	<0.001*		

Note: *significance among the three groups; [a]significance between the control and low-dose metformin groups; [b]significance between the control and high-dose metformin groups

Surprisingly, no significant difference was found in the prevalence of polyps among groups. CRC follows a linear progression from the normal epithelium to carcinoma transformation and metastasis. The absolute values of the prevalence and number of polyps and adenoma can observe the trends, the values of polyps are more than those of adenoma in all three groups, and the inhibition of metformin showed that the control group had the most recurrent subjects and numbers of both polyps and adenoma, followed by the low-dose (500 mg) and the high-dose (1,000 mg) metformin groups. Statistical significance may be gained from a larger

study population or a longer observation period. A retrospective study using data from a US veteran population showed conflicting results with that of the present study; metformin use is not associated with incident colorectal adenoma at interval colonoscopy after a successful prior coloscopic therapy, regardless of the prescription time. The authors tried to solve the potential for immortal time biases which may exaggerate the chemoprotective capability of metformin by requiring at least 6 month of metformin exposure for both index and interval colonoscopy, however, the authors concluded that the relatively short follow-up period (median follow-up period between baseline and interval colonoscopy = 4.5 years) may lead to that only the earliest stages of carcinogenesis can be observed [27]. Even though the study design is different between the two studies, considering the slow nature history of CRC progression, extending the observation period may be helpful for both studies. However, it is still possible that there is interference from other undiscovered confounders, for example, the metformin exposure dose was uncertain in this retrospective study. Well-controlled studies with better design should be conducted for further clarification.

The difference in HOMA-IR between the metformin and placebo groups in the low-dose metformin (250 mg) randomized trial conducted in non-DM patients was not shown in the present study. Because of the difference in HOMA-IR, the anti-CRC effect depended on the underlying metabolic alteration was suggested in the abovementioned trial [19]. However, even using higher doses (500 and 1,000 mg), the results of the trial did not repeat in the present study, which means that metformin did not attenuate insulin resistance. HOMA-IR is known to increase with age [28], since patients of the present study are younger than those in the trial (about 57 vs. 64 years) [19], metformin's effect on HOMA-IR may be insignificant in the younger population. Age can be adjusted to evaluate whether the indirect metabolic effect of metformin is the primary mechanism of prevention of polyps and adenoma recurrence. We assume the main mechanism may be the insulin-independent AMPK/mTOR pathway according to the HOMA-IR results. In a trial of using metformin to suppress colorectal aberrant crypt foci, no significant differences were observed in blood glucose, plasma lipid levels, or degree of insulin resistance in the metformin group between baseline and 1 month after treatment [24]. The molecular mechanism of metformin in inhibiting the production of aberrant crypt foci was clarified in the $APC^{Min/+}$ aberrant crypt foci murine model; metformin activated AMPK to inhibit the mTOR pathway [29]. Moreover, polyps removed from the metformin-treated patients with familial adenomatous polyposis showed significantly lower mTOR (p-S6) expression than those from the placebo group [25], and the same approach can be applied to identify the exact molecular mechanism in patients of the present study.

A network meta-analysis included 33 randomized controlled trials only to assess the efficacy in reducing the incidence of colorectal adenoma of all potential chemopreventive agents among patients previously undergone polypectomy. Metformin was identified as a promising drug among the 13 studied drugs [30]. To extend the implementation of metformin in the general population, more evidence is required. The authors suggested that studies focusing on the acceptability and tolerability of metformin should be performed in the future. In addition, optimal dose and duration have to be explored for balancing efficacy and possible adverse events since long-term use [30]. Metformin is considered a safe agent, however, investigation of the optimal dose is still insufficient to establish a conclusion, especially in observational studies, as the exposed dosage is usually uncertain. Most studies analyzed in a meta-analysis including 10 studies published from 2008 to 2016 did not provide data regarding the dose [12], in addition, no significant dose-response effect was found in the two metformin treatment groups in the present study; the difference between the low-dose metformin group and the high-dose metformin group was no significant (30.8% vs. 29.9%, p=0.898). Quantitative relationship between metformin dose and polyps and adenomas suppression needs further evaluation to clarify whether 500 mg metformin is already the plateau dose in this population, or the two doses are not in the linear line of the relationship between drug concentration and inhibition effect. Furthermore, a suitable stage dose of metformin is needed for patients with different levels of risk; stratified suggestions based on more convincing evidence, like the frequency of colonoscopic follow-up, may be necessary.

Some limitations should be noted for the interpretation of these results. The one-year observation period is relatively short when considering that colorectal adenomas or polyps may require several years to develop. Current clinical guidelines recommend a 1-year follow-up for patients with ≥10 adenomas, incomplete resection, or poor bowel preparation due to the high risk of missed lesions. For most patients, three to ten years of colorectal surveillance is considered according to the levels of risk [26]. Furthermore, a significant miss rate in the detection of colonic adenomas was noted previously, even quality-adjusted, back-to-back colonoscopies on the same day were conducted, especially when the lesions were smaller or the numbers were larger. For example, patients with ≥10 adenomas have a higher rate of recurrence; however, they also have a higher miss rate [31]. Thus, the possibility of recurrent polyps or adenomas may be that the missed lesions from the index colonoscopy cannot be ruled out. The present study was designed based on the randomized trial conducted in non-DM patients for the same reason as the ethical concern of long-term use of metformin for patients without DM [19]. Instead, patients with higher risk, i.e., had to undergo colonoscopic polypectomy, were enrolled. Patients with a higher risk than in the previous trial were included in the present study, indicated by the inclusion criteria that were aged between 40 and 70 years old and with adenoma numbers >3. Studies have shown that patients with higher

risk have a higher recurrence rate and can reach over 50% even only 1 year after the index colonoscopic polypectomy [19, 32]. Indeed, including the present study, both prospective studies still showed the chemopreventive character of metformin in patients without DM who had a higher risk of recurrent adenoma and comparable baseline characteristics in this short observation period [19], indicating the potential larger effeteness in a longer study period, especially in patients with higher risk. However, the possibility that the polyps or adenomas detected just 1 year after baseline may be the missed ones rather than new lesions should be kept in mind when interpreting the present results. In addition, since metformin was usually prescribed for patients with DM, the doses used in the present study for different populations may not be optimal. It's unclear why only the prevalence of recurrent adenoma was significantly different among groups, not both polyps and adenomas. The significance may be disclosed in a larger sample size. The results of plasma lipid and blood glucose monitoring indicate that the prevention effects may not be related to the glucose-lowering ability of metformin in the present study. The main pathway activated by metformin is the AMPK-mTOR signaling pathway; the alteration of the key components of this pathway could be assessed using the specimens from the patients to identify the molecular mechanism of the chemoprevention after exposure to metformin. Such as Complex I, MMP family, NF-kB, Complex IV, AMPK-dependent lysosomal pathway (AXIN/LKB1), and PD-1 have been reported to associate the therapeutic capability of metformin in malignancies [33], all these are valuable to be evaluated which one is the critical component in the recurrence of polys or adenoma.

In conclusion, 1-year metformin use reduced the prevalence of recurrent adenoma significantly in patients without DM after polypectomy. The metabolic status represented by blood glucose, serum lipid, and HOMA-IR did not change with metformin. Metformin may be considered a safe and efficient chemopreventive agent for colorectal polyps and adenomas in the general population, regardless of the DM status.

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References

[1] BRAY F, LAVERSANNE M, SUNG H, FERLAY J, SIEGEL RL et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024; 74: 229–263. https://doi.org/10.3322/caac.21834

[2] ARAGHI M, SOERJOMATARAM I, JENKINS M, BRIERLEY J, MORRIS E et al. Global trends in colorectal cancer mortality: projections to the year 2035. Int J Cancer 2019; 144: 2992–3000. https://doi.org/10.1002/ijc.32055

[3] WINAWER SJ, ZAUBER AG, HO MN, O'BRIEN MJ, GOTTLIEB LS et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993; 329: 1977–1981. https://doi.org/10.1056/nejm199312303292701

[4] LIEBERMAN DA, REX DK, WINAWER SJ, GIARDIELLO FM, JOHNSON DA et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2012; 143: 844–857. https://doi.org/10.1053/j.gastro.2012.06.001

[5] KATONA BW, WEISS JM. Chemoprevention of Colorectal Cancer. Gastroenterology 2020; 158: 368–388. https://doi.org/10.1053/j.gastro.2019.06.047

[6] DAUGAN M, DUFAŸ WOJCICKI A, D'HAYER B, BOUDY V. Metformin: An anti-diabetic drug to fight cancer. Pharmacol Res 2016; 113: 675–685. https://doi.org/10.1016/j.phrs.2016.10.006

[7] AMERICAN DIABETES ASSOCIATION. Standards of Medical Care in Diabetes-2019 Abridged for Primary Care Providers. Clin Diabetes 2019; 37: 11–34. https://doi.org/10.2337/cd18-0105

[8] LI M, LI X, ZHANG H, LU Y. Molecular Mechanisms of Metformin for Diabetes and Cancer Treatment. Front Physiol 2018; 9: 1039. https://doi.org/10.3389/fphys.2018.01039

[9] YANG X, TAN SC, MOUSAVI SM, RAHMANI J, CLARK C et al. The influence of metformin on IGF-1 levels in humans: A systematic review and meta-analysis. Pharmacol Res 2020; 151: 104588. https://doi.org/10.1016/j.phrs.2019.104588

[10] EVANS JM, DONNELLY LA, EMSLIE-SMITH AM, ALESSI DR, MORRIS AD. Metformin and reduced risk of cancer in diabetic patients. BMJ 2005; 330: 1304–1305. https://doi.org/10.1136/bmj.38415.708634.F7

[11] NG CW, JIANG AA, TOH EMS, NG CH, ONG ZH et al. Metformin and colorectal cancer: a systematic review, meta-analysis and meta-regression. Int J Colorectal Dis 2020; 35: 1501–1512. https://doi.org/10.1007/s00384-020-03676-x

[12] JUNG YS, PARK CH, EUN CS, PARK DI, HAN DS. Metformin use and the risk of colorectal adenoma: A systematic review and meta-analysis. J Gastroenterol Hepatol 2017; 32: 957–965. https://doi.org/10.1111/jgh.13639

[13] DENG M, LEI S, HUANG D, WANG H, XIA S et al. Suppressive effects of metformin on colorectal adenoma incidence and malignant progression. Pathol Res Pract 2020; 216: 152775. https://doi.org/10.1016/j.prp.2019.152775

[14] YU OHY, SUISSA S. Metformin and Cancer: Solutions to a Real-World Evidence Failure. Diabetes Care 2023; 46: 904–912. https://doi.org/10.2337/dci22-0047

[15] FRANCIOSI M, LUCISANO G, LAPICE E, STRIPPOLI GF, PELLEGRINI F et al. Metformin therapy and risk of cancer in patients with type 2 diabetes: systematic review. PLoS One 2013; 8: e71583. https://doi.org/10.1371/journal.pone.0071583

[16] HOME PD, KAHN SE, JONES NP, NORONHA D, BECK-NIELSEN H et al. Experience of malignancies with oral glucose-lowering drugs in the randomised controlled ADOPT (A Diabetes Outcome Progression Trial) and RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) clinical trials. Diabetologia 2010; 53: 1838–1845. https://doi.org/10.1007/s00125-010-1804-y

[17] KOWALL B, STANG A, RATHMANN W, KOSTEV K. No reduced risk of overall, colorectal, lung, breast, and prostate cancer with metformin therapy in diabetic patients: database analyses from Germany and the UK. Pharmacoepidemiol Drug Saf 2015; 24: 865–874. https://doi.org/10.1002/pds.3823

[18] SOLTANI G, POURSHEIKHANI A, YASSI M, HAYATBAKHSH A, KERACHIAN M et al. Obesity, diabetes and the risk of colorectal adenoma and cancer. BMC Endocr Disord 2019; 19: 113. https://doi.org/10.1186/s12902-019-0444-6

[19] HIGURASHI T, HOSONO K, TAKAHASHI H, KOMIYA Y, UMEZAWA S et al. Metformin for chemoprevention of metachronous colorectal adenoma or polyps in post-polypectomy patients without diabetes: a multicentre double-blind, placebo-controlled, randomised phase 3 trial. Lancet Oncol 2016; 17: 475–483. https://doi.org/10.1016/s1470-2045(15)00565-3

[20] CHEN CY, KAO CL, LIU CM. The Cancer Prevention, Anti-Inflammatory and Anti-Oxidation of Bioactive Phytochemicals Targeting the TLR4 Signaling Pathway. Int J Mol Sci 2018; 19: 2729. https://doi.org/10.3390/ijms19092729

[21] WALLACE TM, LEVY JC, MATTHEWS DR. Use and abuse of HOMA modeling. Diabetes Care 2004; 27: 1487–1495. https://doi.org/10.2337/diacare.27.6.1487

[22] REX DK, SCHOENFELD PS, COHEN J, PIKE IM, ADLER DG et al. Quality indicators for colonoscopy. Gastrointest Endosc 2015; 81: 31–53. https://doi.org/10.1016/j.gie.2014.07.058

[23] HERTZOG MA. Considerations in determining sample size for pilot studies. Res Nurs Health 2008; 31: 180–191. https://doi.org/10.1002/nur.20247

[24] HOSONO K, ENDO H, TAKAHASHI H, SUGIYAMA M, SAKAI E et al. Metformin suppresses colorectal aberrant crypt foci in a short-term clinical trial. Cancer Prev Res (Phila) 2010; 3: 1077–1083. https://doi.org/10.1158/1940-6207.CAPR-10-0186

[25] PARK JJ, KIM BC, HONG SP, SEO Y, LEE HS et al. The Effect of Metformin in Treatment of Adenomas in Patients with Familial Adenomatous Polyposis. Cancer Prev Res (Phila) 2021; 14: 563–572. https://doi.org/10.1158/1940-6207.CAPR-20-0580

[26] GUPTA S, LIEBERMAN D, ANDERSON JC, BURKE CA, DOMINITZ JA et al. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2020; 158: 1131–1153.e1135. https://doi.org/10.1053/j.gastro.2019.10.026

[27] KRIGEL A, NGUYEN STT, TALUKDER N, HUANG CH, BUITRAGO C et al. Metformin Use Is Inversely Associated with Prevalent, but Not Incident Colorectal Adenomas. Dig Dis Sci 2022; 67: 4886–4894. https://doi.org/10.1007/s10620-021-07336-0

[28] YANG H, GONG R, LIU M, DENG Y, ZHENG X et al. HOMA-IR is positively correlated with biological age and advanced aging in the US adult population. Eur J Med Res 2023; 28: 470. https://doi.org/10.1186/s40001-023-01448-1

[29] HOSONO K, ENDO H, TAKAHASHI H, SUGIYAMA M, UCHIYAMA T et al. Metformin suppresses azoxymethane-induced colorectal aberrant crypt foci by activating AMP-activated protein kinase. Mol Carcinog 2010; 49: 662–671. https://doi.org/10.1002/mc.20637

[30] HEER E, RUAN Y, MAH B, NGUYEN T, LYONS H et al. The efficacy of chemopreventive agents on the incidence of colorectal adenomas: A systematic review and network meta-analysis. Prev Med 2022; 162: 107169. https://doi.org/10.1016/j.ypmed.2022.107169

[31] AHN SB, HAN DS, BAE JH, BYUN TJ, KIM JP et al. The Miss Rate for Colorectal Adenoma Determined by Quality-Adjusted, Back-to-Back Colonoscopies. Gut Liver 2012; 6: 64–70. https://doi.org/10.5009/gnl.2012.6.1.64

[32] GAO QY, CHEN HM, SHENG JQ, ZHENG P, YU CG et al. The first year follow-up after colorectal adenoma polypectomy is important: a multiple-center study in symptomatic hospital-based individuals in China. Front Med China 2010; 4: 436–442. https://doi.org/10.1007/s11684-010-0200-9

[33] AMENGUAL-CLADERA E, MORLA-BARCELO PM, MORÁN-COSTOYA A, SASTRE-SERRA J, PONS DG et al. Metformin: From Diabetes to Cancer-Unveiling Molecular Mechanisms and Therapeutic Strategies. Biology (Basel) 2024; 13: 302. https://doi.org/10.3390/biology13050302