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

Takuma Higurashi, Kunihiro Hosono, Hirokazu Takahashi, Yasuhiko Komiya, Shotaro Umezawa, Eiji Sakai, Takashi Uchiyama, Leo Taniguchi, Yasuo Hata, Shiori Uchiyama, Akiko Hattori, Hajime Nagase, Takaomi Kessoku, Jun Arimoto, Nobuyuki Matsuhashi, Yoshiaki Inayama, Shoji Yamanaka, Masataka Taguri, Atsushi Nakajima

Summary

Background The prevalence of, and mortality from, colorectal cancer is increasing worldwide, and new strategies for prevention are needed to reduce the burden of this disease. The oral diabetes medicine metformin might have chemopreventive effects against cancer, including colorectal cancer. However, no clinical trial data exist for the use of metformin for colorectal cancer chemoprevention. Therefore, we devised a 1-year clinical trial to assess the safety and chemopreventive effects of metformin on sporadic colorectal cancer (assessed by adenoma and polyp recurrence) in patients with a high risk of adenoma recurrence.

Methods This trial was a multicentre, double-blind, placebo-controlled, randomised phase 3 trial. Non-diabetic adult patients who had previously had single or multiple colorectal adenomas or polyps resected by endoscopy were enrolled into the study from five hospitals in Japan. Eligible patients were randomly assigned (1:1) to receive oral metformin (250 mg daily) or identical placebo tablets by a stratified computer-based randomisation method, with stratification by institute, age, sex, and body-mass index. All patients, endoscopists, doctors, and investigators were masked to drug allocation until the end of the trial. After 1 year of administration of metformin or placebo, colonoscopies were done to assess the co-primary endpoints: the number and prevalence of adenomas or polyps. Our analysis included all participants who underwent random allocation, according to the intention-to-treat principle. This trial is registered with University Hospital Medical Information Network (UMIN), number UMIN000006254.

Findings Between Sept 1, 2011, and Dec 30, 2014, 498 patients who had had single or multiple colorectal adenomas resected by endoscopy were enrolled into the study. After exclusions for ineligibility, 151 patients underwent randomisation: 79 were assigned to the metformin group and 72 to the placebo group. 71 patients in the metformin group and 62 in the placebo group underwent 1-year follow-up colonoscopy. The prevalence of total polyps (hyperplastic polyps plus adenomas) and of adenomas in the metformin group was significantly lower than that in the placebo group (total polyps: metformin group 27 [38·0%; 95% CI 26·7–49·3] of 71 patients, placebo group 35 [56·5%; 95% CI 44·1–68·8] of 62; p=0·034, risk ratio [RR] 0·67 [95% CI 0·47–0·97]; adenomas: metformin group 22 [30·6%; 95% CI 19·9–41·2] of 71 patients, placebo group 32 [51·6%; 95% CI 39·2–64·1] of 62; p=0·016, RR 0·60 [95% CI 0·39–0·92]). The median number of polyps was zero (IQR 0–1) in the metformin group and one (0–1) in the placebo group (p=0·041). The median number of adenomas was zero (0–1) in the metformin group and zero (0–1) in the placebo group (p=0·037). 15 (11%) of patients had adverse events, all of which were grade 1. We recorded no serious adverse events during the 1-year trial.

Interpretation The administration of low-dose metformin for 1 year to patients without diabetes was safe. Low-dose metformin reduced the prevalence and number of metachronous adenomas or polyps after polypectomy. Metformin has a potential role in the chemoprevention of colorectal cancer. However, further large, long-term trials are needed to provide definitive conclusions.

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Department of Gastroenterology and Hepatology (T Higurashi MD, K Hosono MD, H Takahashi MD, Y Komiya MD, S Umezawa MD, E Sakai MD, Prof A Nakajima MD) **and Department of Biostatistics** (M Taguri PhD), **Yokohama City University School of Medicine, Yokohama, Japan; Department of Gastroenterology, Chigasaki Municipal Hospital, Chigasaki, Japan** (T Uchiyama MD, L Taniguchi MD, Y Hata MD); **Department of Gastroenterology, Yokohama Rosai Hospital, Yokohama, Japan** (S Uchiyama MD, A Hattori MD, H Nagase MD); **Department of Gastroenterology, Hiratsuka City Hospital, Hiratsuka, Japan** (T Kessoku MD, J Arimoto MD); **Department of Gastroenterology, Kanto Medical Center, NTT East, Shinagawa, Japan** (N Matsuhashi MD); **and Department of Pathology, Yokohama City University, Yokohama, Japan** (Y Inayama MD, S Yamanaka MD)

Correspondence to: Prof Atsushi Nakajima, Department of Gastroenterology and Hepatology, Yokohama City University School of Medicine, 3-9 Fuku-ura, Kanazawa-ku, Yokohama 236-0004 Japan **nakajima-tky@umin.ac.jp**

Introduction

Colorectal cancer is a common neoplasm worldwide,[1] and both its prevalence and associated mortality are increasing. The removal of colorectal polyps reduces the risk of future development of colorectal cancer and advanced adenoma.[2] However, patients with polyps (adenomas or hyperplastic polyps) constitute a high-risk group for the development of metachronous colorectal polyps, colorectal cancer, or both.[3] Therefore, a change in approach from surveillance for early detection of cancer and adenomas (the latter often being treated by polypectomy) to new strategies for prevention, including chemoprevention, is needed to reduce the burden of this disease. Several large epidemiological and clinical

Research in context

Evidence before this study

We searched PubMed between Jan 1, 1990, and Sept 1, 2011, using the terms "colorectal cancer", "chemoprevention", "metformin", and "clinical trial". We searched for articles published in English only. We found no clinical trial data related to the use of metformin for colorectal cancer chemoprevention. As a preliminary study before considering long-term colorectal cancer chemoprevention trials, we devised a 1-year clinical trial to assess the safety and the chemopreventive effect of metformin against the development of metachronous colorectal adenomas or polyps in patients without diabetes post-polypectomy.

Added value of this study

To our knowledge, this is the first comparative randomised trial to assess the chemopreventive effect of metformin for metachronous colorectal adenomas and polyps. Low-dose metformin reduced the incidence and number of metachronous adenomas and polyps after polypectomy. The 1-year administration of low-dose metformin was safe for non-diabetic patients.

Implication of all the available evidence

Recent evidence indicates that metformin has a suppressive effect on tumorigenesis and cancer cell growth by activating AMPK and suppressing the mTOR pathway. Many metformin chemoprevention trials against various types of cancer are in progress. Our findings suggest that metformin has a potential role in the chemoprevention of colorectal cancer.

studies have assessed the possible preventive effects against colorectal cancer development of more than 200 agents, including fibre, calcium, and non-steroidal anti-inflammatory drugs, such as aspirin and selective COX-2 inhibitors.[4] Non-steroidal anti-inflammatory drugs, especially COX-2 inhibitors, administered either alone or in combination with other agents, have shown the most promise for reducing colorectal cancer risk. However, an increased risk of serious cardiovascular events is associated with the use of COX-2 inhibitors.[5,6] Because of the adverse cardiovascular effects of COX-2 inhibitors and the absence of demonstrable efficacy of other agents that had initially showed promise in this setting, new drugs are needed that are both safe and effective for colorectal cancer prevention. Colorectal cancer is associated with lifestyle-related diseases, such as diabetes mellitus and obesity.[7,8] Therefore, we postulated that these disorders might represent potential new targets for colorectal cancer chemoprevention.

Metformin is a biguanide derivative that is used widely to treat diabetes mellitus.[9] It reduces basal glucose output by suppressing gluconeogenesis and glycogenolysis in the liver and increasing glucose uptake by muscle. Because metformin does not directly stimulate insulin secretion, it is associated with a lower risk of hypoglycaemia than other oral antidiabetic drugs.[10] The molecular mechanism involved in the action of metformin is liver kinase B1-dependent activation of AMP-activated protein kinase (AMPK).[11,12] Patients with type 2 diabetes who are treated with metformin seem to be at a lower risk of developing cancer (including colorectal cancer) than those not treated with metformin.[13] This evidence suggests that metformin might be a candidate drug for colorectal cancer chemoprevention in patients with diabetes. However, because diabetes itself is a risk factor for cancer, treatment of diabetes might reduce this risk. Therefore, whether the suppressive effect of metformin against colorectal cancer is caused by a direct chemopreventive effect of the drug or is mediated by its antidiabetic effect remains unclear.

We have previously shown the chemopreventive effect of metformin against colorectal cancer in two models of colorectal carcinoma in non-diabetic mice,[14,15] which suggested the direct chemopreventive potential of metformin itself. We also did a trial involving non-diabetic human patients and showed that oral low-dose metformin (250 mg/day) was safe and suppressed the formation of colorectal aberrant crypt foci.[16] This clinical trial was the first to show that metformin has chemopreventive potential against colon carcinogenesis. However, the trial was limited by its short duration (1 month) and the use of human aberrant crypt foci as the surrogate biomarker of colorectal cancer; although these are regarded as a useful surrogate biomarker,[17] their biological significance remains controversial. Generally, in colorectal cancer chemoprevention trials, the incidence of polyps or cancer is set as the study endpoint. The incidence of colorectal cancer would be the most reliable endpoint but is unsuitable for colorectal cancer chemoprevention trials because of the low incidence of colorectal cancer in the general population and the long-term observation period that it would necessitate. Moreover, serious ethical issues would be involved in withholding endoscopic resection and waiting for polyps detected in annual colonoscopies to potentially develop into cancer.

To the best of our knowledge, no colorectal cancer chemoprevention trials using metformin in non-diabetic patients have been done. Consequently, the safety of the patients needs careful consideration in the design and execution of such a trial. We did a 1-year clinical trial to assess the safety and chemopreventive effect of metformin on sporadic colorectal cancer (assessed by adenoma and polyp recurrence) in patients with a high risk of adenoma recurrence as a preliminary study before considering long-term colorectal cancer chemoprevention trials.

Methods

Study design and participants

This study was a multicentre, double-blind, placebo-controlled, randomised trial of patients without diabetes with a recent history of colorectal polypectomy. The study was done at five hospitals in Japan (appendix).

All adult patients (aged ≥20 years) scheduled for polypectomy were recruited for the study. The inclusion criteria were: no colorectal polyps present after polypectomy, age 40–80 years on the date of informed consent, and willingness to provide written informed consent. We set the age criterion for inclusion based on the low likelihood of people less than 40 years of age developing colorectal adenomas and polyps, the diagnostic history of polyps in young people related to familial adenomatous polyposis or hereditary non-polyposis colorectal cancer, and the increased frequency of complication among elderly patients (≥80 years).

The exclusion criteria were: a history of diabetes mellitus (use of medication or glycated haemoglobin [HbA_{1c}] levels greater than 6·5%); a history of regular use (defined as at least once per week) of non-steroidal anti-inflammatory drugs, including aspirin; a history of bowel surgery; a history of malignant disease (excluding carcinoma in situ that had already been resected); a history of heart failure, renal failure, liver cirrhosis, or chronic hepatic failure; a history of familial adenomatous polyposis; a history of hereditary non-polyposis colorectal cancer; a history of inflammatory bowel disease; pregnancy or the possibility of pregnancy; and patients judged to be inappropriate candidates for the trial by the investigators (eg, those doing night-shift work or those whose address meant they would have a difficult journey to the hospital).

All eligible patients underwent an interview at their first visit to the outpatient clinic after polypectomy (which included questions about past history, medication, family history, and smoking/drinking habits) and laboratory tests. The study protocol complied with the Declaration of Helsinki and the Ethics Guidelines for Clinical Research published by the Ministry of Health, Labour and Welfare of Japan. Approval for this study was obtained from the Ethics Committee of Yokohama City University Hospital on July 7, 2011. All participating patients provided written informed consent for participation in the study. The protocol and informed consent forms were approved by the institutional ethics committees at each of the participating institutions. The trial results were reported in conformity with the Consolidated Standards of Reporting Trials 2010 guidelines. This trial protocol has been published[18] and is available online.

Randomisation and masking

Registration, randomised allocation, and data collection were done at the Yokohama City University Hospital. The investigators sent the patient details to the central registration centre by fax. After an eligibility check, the patients were randomly assigned in a 1:1 ratio to receive metformin or placebo at the central registration centre by a computer programme using a stratified randomisation method, with stratification by institute, age (<65 *vs* ≥65 years), sex, and body-mass index (<25 *vs* ≥25 kg/m²). In this way, patient assignment was hidden from the investigators. The randomisation centre allocated to each patient a numbered treatment pack that contained all the drugs or placebos needed to complete a course of the trial treatment for that patient.

See **Online** for appendix

Metformin was purchased from Dainippon Sumitomo Pharma Co, Ltd (Osaka, Japan). The placebo (250 mg lactose plus magnesium stearate) was purchased from Kokando Co, Ltd (Toyama, Japan). All trial drugs were packaged identically and identified only by number. Drug allocation was masked from all patients, endoscopists, doctors, and investigators until the end of the trial.

Procedures

Patients were instructed to take one tablet of the trial drug orally after breakfast every day and to visit the hospital every 4 weeks for assessment of their symptoms and to receive a new supply of study drug. The participants were also interviewed and monitored regarding drug compliance and they confirmed that they had not used prohibited agents (aspirin or other non-steroidal anti-inflammatory drugs). Outpatient clinic doctors monitored compliance by counting the empty drug packages returned by the patients at each visit to the outpatient clinic. Fasting blood glucose, fasting blood insulin, HbA_{1c}, total cholesterol, low-density lipoprotein cholesterol, blood urea nitrogen, and creatinine were checked every 8 weeks during follow-up and at the 1-year endoscopy. Metformin is known to improve insulin resistance and metabolic status through the activation of AMPK. Insulin resistance was calculated using the homoeostasis model assessment (HOMA-IR, calculated as fasting blood insulin [μU/mL]×fasting blood glucose [mg/dL]/405).[19] At each follow-up visit to the outpatient clinic, adverse events were monitored by the physician and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events [NCI-CTCAE] version 4.0. If serious adverse events or less than 80% drug compliance were confirmed in a patient, that patient was withdrawn from the trial. Physical examinations (bodyweight and body-mass index) were done at baseline.

Endoscopic examinations and polypectomies were done using colonoscopes (models H260AZI, PCF-260AZI, CF-Q260AI, and CF-H260AI; Olympus [Tokyo, Japan]). 1 day before endoscopy, patients were instructed to consume a low-residue diet (to reduce the number of bowel movements) and received 5 mg of oral sodium picosulfate. On the day of the endoscopy, patients received 2 L of polyethylene glycol. If the bowels were insufficiently clear, an additional 1–2 L of polyethylene glycol was given to ensure adequate bowel cleaning. At the time of the initial polypectomies, the endoscope

For the **protocol** see https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000006724&language=J

was inserted into the caecum, and the entire colorectum was observed carefully as the endoscope was withdrawn. If any polyps were detected, polypectomy was done. After 1 year of administration of metformin or placebo, the same endoscopists did the endoscopic examinations. If a polyp was detected during that repeat colonoscopy, a biopsy or magnified observation was done. Ten endoscopists from the trial sites did the polypectomies and endoscopic examinations.

Adenoma detection rate variability is known to be related to endoscopic capability.[20] To minimise the occurrence of adenoma detection rate variability and missed polyps, all the endoscopists chosen were specialists with experience from more than 2000 procedures. Furthermore, all the endoscopists attended an initial meeting, during which definitions of the adequate procedures, such as preparation, caecal intubation, and withdrawal time, were provided. All the procedures were recorded on DVD, and all the adenomas or polyps were photographed. The number of polyps in each patient was counted by the operators during the colonoscopy procedure. To ensure accuracy, the number of polyps was counted again through observation of the recorded DVD by three masked expert endoscopists (KH, SUm, and ES). If these expert endoscopists judged a colonoscopic examination to have been inadequate in any case, that case was excluded before randomisation if assessed at enrolment or excluded from the analysis if asssessed at 1 year. The biopsied polyps were assessed by two expert pathologists (YN and SY).

The trial steering committee and data monitoring committee were located at the Yokohama City University School of Medicine, Yokohama, Japan. The committees consisted of Yutaka Natsumeda and four of his colleagues. The two committees constituted the management team, which monitored the data and the progress of the trial face-to-face or by telephone with each of the five sites every month.

Outcomes

The primary endpoint was the prevalence and number of colorectal adenoma or polyps upon endoscopic examination after the 1-year intervention. Secondary outcomes were drug safety; laboratory data (fasting blood glucose, fasting blood insulin, HbA_{1c}, total cholesterol, low-density lipoprotein cholesterol, blood urea nitrogen, and creatinine); and physical examination findings (bodyweight and body-mass index).

Statistical analysis

For the sample size estimation, we assumed that the prevalence of metachronous polyps 1 year after the treatment would be 31·3% in the metformin group and 54·2% in the placebo group, based on previous reports of the effect of metformin and sulindac on the development of aberrant crypt foci and polyps.[16,21] To detect a reduction in the incidence of metachronous polyps in the metformin group with a two-sided significance level of 5% and 80% power, we ascertained that a sample size of 68 patients per group was needed. With the assumption of a 10% dropout rate, we proposed to recruit 75 patients per group (150 patients in total). We compared the prevalence of polyps in the metformin and placebo groups using the χ^2 test. We calculated the 95% CI for the prevelance of total polyps in each group using the polyp prevalence and the standard error around the prevalence. We calculated the unadjusted risk ratio and 95% CI using the delta method. We compared the number of polyps in each group using the Mann-Whitney *U* test. For the remaining comparisons between the two groups, we used Student's *t* test. As a post-hoc analysis, we compared body-mass index, total cholesterol, low-density lipoprotein cholesterol, HbA_{1c}, fasting blood glucose, HOMA-IR, blood urea nitrogen, and creatinine between the recurrent patients (new lesions identified at 1-year endoscopy) and non-recurrent patients (no new lesions identified at 1-year endoscopy) in each group. We also compared these variables between baseline and 1 year in the recurrent patients and non-recurrent patients within each group with the paired *t* test. A post-hoc analysis to compare age, sex, smoking habits, and the findings of baseline colonoscopy (multiple or advanced adenoma or early carcinoma) in recurrent and non-recurrent patients in each group was also done because these factors are known to be related to adenoma recurrence.[22] We did a formal test of interaction within the metformin group using a linear mixed-effect model including time, group (recurrent or non-recurrent), and time-by-group interaction. To account for the possibility of confounding, we did a sensitivity analysis adjusted for baseline covariates (the family history of colorectal cancer and the history of hyperlipidaemia) using a multivariate risk ratio regression model. Our analysis included all the participants who underwent random allocation according to the intention-to-treat principle. A p value less than 0·05 was regarded as significant. We did not adjust for multiple comparisons. The analyses were done using SPSS version 17.0 and SAS version 9.2.

This trial is registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry, number UMIN000006254.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data and had final responsibility for the decision to submit for publication.

Results

Patient enrolment began on Sept 1, 2011, and the trial ended, with the final analysis done, on Dec 30, 2014. 498 patients were screened for eligibility, of whom 347 were excluded (figure 1). We excluded 183 patients

because of inadequate colon cleaning, such as an incompletely clean polypectomy, poor preparation, short observation time, or lack of insertion to the caecum (ie, if a patient's endoscopy had any of these characteristics, they were judged to have incomplete polypectomy).

The remaining 151 patients underwent randomisation: 79 were assigned to the metformin group and 72 to the placebo group (figure 1). 133 patients (71 in the metformin group, 62 in the placebo group) underwent 1-year follow-up colonoscopy (figure 1).

The median time from randomisation to 1-year colonoscopy was 373 days (IQR 358–388) in the metformin group and 371 days (355–385) in the placebo group. No patients were reported to have used prohibited agents, such as aspirin or other non-steroidal anti-inflammatory drugs, during the trial. All 133 participants underwent expert endoscopic assessment at 1 year (all procedures were judged to have been adequate [good preparation, insertion to caecum, and sufficient observation time]), and all patients were included in the final analysis.

Table 1 shows the baseline characteristics of the participants. The incidence of polyps at the initial colonoscopy is shown in the appendix. The prevalence of total polyps (adenomas plus hyperplastic polyps) in the metformin group (27 [38·0%; 95% CI 26·7–49·3] of 71 patients) was significantly lower than that in the placebo group (35 [56·5%; 95% CI 44·1–68·8 of 62; p=0·034). The risk ratio (RR) for this difference was 0·67 (95% CI 0·47–0·97). Because the proportion of patients with a family history of colorectal cancer was lower in the metformin group than in the placebo group and the proportion of patients with a history of hyperlipidaemia was higher in the metformin group than in the placebo group (table 1), we did a sensitivity analysis adjusted for these characteristics (RR 0·64 [95% CI 0·43–0·96]; p=0·028). The prevalence of adenomas in the metformin group (22 [30·6%; 95% CI 19·9–41·2] of 71 patients) was also significantly lower than that in the placebo group (32 [51·6%; 95% CI 39·2–64·1] of 62; p=0·016). The RR for this difference was 0·60 (95% CI 0·39–0·92; p=0·016).

At the 1-year endoscopy, 110 polyps were found, of which 96 were adenomas and 14 were hyperplastic polyps. In the metformin group, there were 44 polyps at 1 year (37 adenomas and 7 hyperplastic polyps). In the placebo group there were 66 polyps at 1 year (59 adenomas and 7 hyperplastic polyps). The location and histology of the polyps did not differ significantly between the two groups (appendix) The median number of polyps was zero (IQR 0–1) in the metformin group and one (0–1) in the placebo group (p=0·041). The median number of adenomas was zero (IQR 0–1) in the metformin group and zero (0–1) in the placebo group (p=0·037).

A post-hoc analysis was done to compare age, sex, body-mass index, smoking status, multiple or advanced adenoma or carcinoma in situ at baseline, total

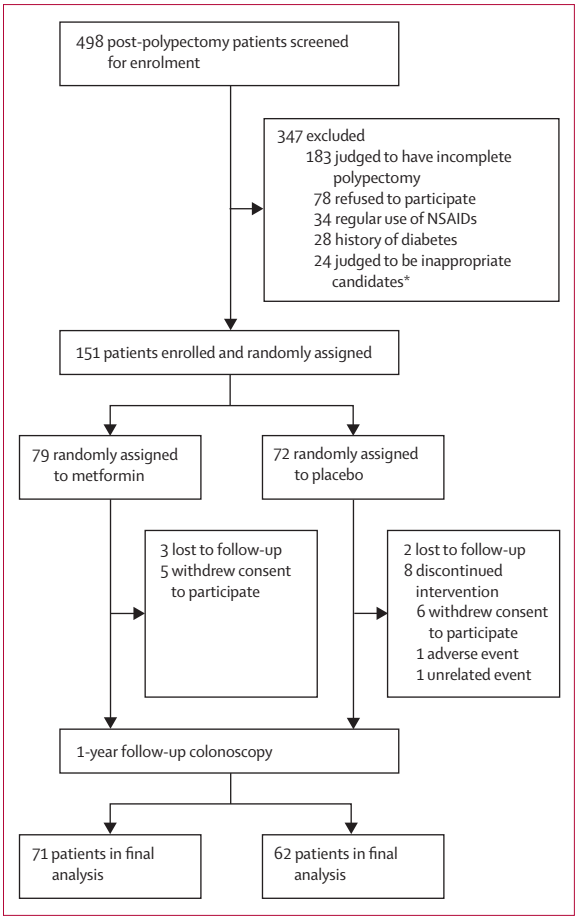

Figure 1: **Trial profile**
NSAIDs=non-steroidal anti-inflammatory drugs. *These patients were judged by the investigator to be inappropriate candidates for various reasons, including their job (eg, night-shift work) and address (eg, difficult journey to the hospital).

	Metformin (n=71)	Placebo (n=62)
Age (years)	64 (40–78)	63·5 (40–79)
Sex		
Male	54 (76%)	49 (79%)
Female	17 (24%)	13 (21%)
Body-mass index (kg/m^2)	23·1 (2·6)	23·9 (3·5)
HOMA-IR	1·43 (1·29)	1·83 (1·55)
Family history of colorectal cancer	8 (11%)	10 (16%)
Current smoker	23 (32%)	25 (40%)
History of hyperlipidaemia	15 (21%)	7 (11%)
History of hypertension	20 (28%)	20 (32%)
Multiple or advanced adenoma or carcinoma in situ findings at baseline colonoscopy	51 (72%)	43 (69%)

Data are median (range), mean (SD), or n (%). HOMA-IR=insulin resistance calculated using the homoeostasis model assessment. Multiple=more than three adenomas. Advanced adenoma=high-grade dysplasia, large size (>10 mm), or villous features.

Table 1: **Baseline characteristics**

	Metformin (n=71)			Placebo (n=62)		
	Non-recurrent (n=44)	Recurrent (n=27)	p value for non-recurrent *vs* recurrent	Non-recurrent (n=27)	Recurrent (n=35)	p value for non-recurrent *vs* recurrent
Age (years)	64 (40–78)	66 (46–78)	0·58	62 (40–79)	64 (41–78)	0·98
Sex			0·11			0·68
Male	30 (68%)	23 (85%)		22 (81%)	27 (77%)	
Female	14 (32%)	4 (15%)		5 (19%)	8 (23%)	
Body-mass index at baseline (kg/m^2)	23·0 (2·7)	23·4 (2·4)	0·61	23·3 (3·1)	24·3 (3·7)	0·16
Current smoker	13 (30%)	10 (37%)	0·51	10 (37%)	15 (43%)	0·64
Multiple or advanced adenoma or carcinoma in situ at baseline	31 (71%)	20 (74%)	0·74	13 (48%)	30 (86%)	0·0015
Total cholesterol (mg/dL)						
At baseline	204·3 (32·9)	190·9 (38·3)	0·13	195·4 (22·6)	209·8 (42·8)	0·38
At 1 year	200·9 (40·8)	206·9 (42·2)	0·57	213·6 (27·1)	206·5 (29·8)	0·38
p value (baseline *vs* 1 year)	0·36	0·0021		0·0027	0·60	
LDL cholesterol (mg/dL)						
At baseline	115·7 (29·4)	119·9 (37·3)	0·61	118·7 (22·1)	123·1 (36·9)	0·60
At 1 year	121·4 (34·3)	112·6 (33·8)	0·31	125·1 (29·6)	125·3 (27·2)	0·98
p value (baseline *vs* 1 year)	0·18	0·37		0·50	1·0	
HbA_{1c} (%)						
At baseline	5·44 (0·43)	5·55 (0·40)	0·33	5·57 (0·39)	5·50 (0·40)	0·53
At 1 year	5·51 (0·34)	5·61 (0·35)	0·27	5·51 (0·42)	5·61 (0·26)	0·38
p value (baseline *vs* 1 year)	0·131	0·131		0·537	0·167	
Fasting blood glucose (mg/dL)						
At baseline	100·4 (15·1)	101·6 (20·8)	0·78	101·6 (17·8)	102·9 (16·7)	0·78
At 1 year	99·9 (12·7)	103·1 (19·9)	0·42	103·9 (19·3)	98·2 (7·8)	0·14
p value (baseline *vs* 1 year)	0·33	0·64		0·59	0·061	
HOMA-IR						
At baseline	1·54 (1·41)	1·25 (1·08)	0·39	1·31 (0·73)	2·19 (1·84)	0·034
At 1 year	1·13 (0·78)	1·31 (0·91)	0·41	1·33 (0·83)	1·80 (1·68)	0·22
p value (baseline *vs* 1 year)	0·029	0·83		1·0	0·071	
Blood urea nitrogen (mg/dL)						
At baseline	13·1 (3·6)	14·0 (5·8)	0·39	13·8 (4·8)	13·5 (3·9)	0·79
At 1 year	12·8 (3·0)	13·3 (3·9)	0·51	12·3 (3·2)	13·2 (3·8)	0·28
p value (baseline *vs* 1 year)	0·43	0·62		0·086	0·72	
Creatinine (mg/dL)						
At baseline	0·78 (0·16)	0·83 (0·12)	0·23	0·78 (0·16)	0·77 (0·16)	0·87
At 1 year	0·78 (0·15)	0·85 (0·13)	0·060	0·77 (0·14)	0·79 (0·17)	0·75
p value (baseline *vs* 1 year)	0·95	0·23		0·65	0·067	

Data are median (range), mean (SD), or n (%). HOMA-IR=insulin resistance calculated using the homoeostasis model assessment. HbA_{1c}=glycated haemoglobin LDL=low-density lipoprotein.

Table 2: **Comparative analysis of non-recurrent and recurrent patients in each treatment group**

cholesterol, low-density lipoprotein cholesterol, HbA_{1c}, fasting blood glucose, HOMA-IR, blood urea nitrogen, and creatinine between non-recurrent patients and recurrent patients in each treatment group (table 2). A post-hoc analysis of changes in HOMA-IR from baseline to 1 year in the non-recurrent and recurrent patients in each group is shown in figure 2. In the metformin group, the mean HOMA-IR value in non-recurrent patients was lower after 1 year of treatment compared with baseline but was unchanged in recurrent patients (table 2, figure 2). We did a formal test of interaction within the metformin group using a linear mixed-effects model including time, group (non-recurrent or recurrent), and time-by-group interaction (p=0·141). In the placebo group, the mean HOMA-IR value in non-recurrent patients and recurrent patients was unchanged between baseline and 1 year (table 2, figure 2). In the placebo group, the mean baseline HOMA-IR value in recurrent patients was higher than that in non-recurrent patients, however, this value was similar in recurrent and non-recurrent patients in the metformin group (table 2, figure 2).

15 (11%) of patients had an adverse event, all of which were NCI-CTCAE grade 1 (table 3). One patient discontinued treatment due to an adverse event (diarrhoea; placebo group). The adverse events included abdominal pain, diarrhoea, rash, constipation, and alopecia. Median compliance with medication was 91% (IQR 89–98) in the metformin group and 92% (90–97) in the placebo group. No patients were removed from the trial because of poor compliance with study drug administration.

Discussion

In this randomised phase 3 trial, metformin prevented both metachronous hyperplastic polyps and adenomas in non-diabetic patients post-polypectomy. Moreover, few adverse events occurred in the trial period. The safety results suggest that low-dose metformin intake for 1 year was safe for non-diabetic patients. This study is the first to our knowledge to assess the chemopreventive effect of low-dose metformin against metachronous colorectal adenoma or polyp formation.

In a colorectal cancer chemoprevention trial, Ishikawa and colleagues[23] reported that administration of 100 mg aspirin daily for 2 years reduced the risk of adenoma (RR 0·60 [95% CI 0·36–0·98]). Takayama and colleagues[21] reported that 150 mg sulindac daily for 2 months reduced adenoma and hyperplastic polyp recurrence 1 year later (RR 0·44 [95% CI 0·20–0·95]). So far, non-steroidal anti-inflammatory drugs, especially COX-2 inhibitors, have shown the most promise for colorectal cancer risk reduction, although they are associated with an increased risk of serious cardiovascular events.[5,6] In line with these findings, our results suggest that metformin has potential as a chemopreventive agent for colorectal cancer. For practical chemoprevention, a drug generally needs to have the following attributes: safety, good compliance, cost-effectiveness, and a clear mechanism of action. Metformin meets these criteria.

Metformin was first synthesised in the 1920s and has been used worldwide in the treatment of diabetes mellitus and for polycystic ovary syndrome and metabolic syndrome.[24] In our trial, the administration of low-dose metformin for 1 year to non-diabetic patients resulted in few adverse events, and all events were NCI-CTCAE grade 1, suggesting that low-dose metformin is safe. Additionally, metformin is an inexpensive drug. Chemopreventive agents usually need to be taken long term; therefore, an inexpensive drug is suitable for daily use. Finally, the drug mechanism has been well elucidated.[11] Recent evidence indicates that metformin has a suppressive effect on tumorigenesis and cancer cell growth.[25,26] In one study, metformin was shown to activate AMPK and consequently to reduce cellular proliferative activity, resulting in a general decrease in protein synthesis in vitro in human breast carcinoma cells.[25] Metformin has also been shown to inhibit the proliferation of human colon cancer cells.[26] Although several recent studies did not record any anticancer effect of metformin,[27–29] Sehdev and colleagues[30] reported that metformin use in the USA seems to be associated with a reduced risk of developing colorectal cancer in patients with diabetes.

In our study, the mean value of the HOMA-IR in non-recurrent patients in the metformin group was significantly lower at 1 year than at baseline. By contrast, the value of the HOMA-IR in recurrent patients in the metformin group was unchanged after 1 year of treatment. In the placebo group, the mean baseline HOMA-IR value in recurrent patients was significantly higher than that in non-recurrent patients. These results suggest that adenoma or polyp recurrence is associated with insulin resistance. Improvement in insulin resistance by metformin might lead to a reduction in

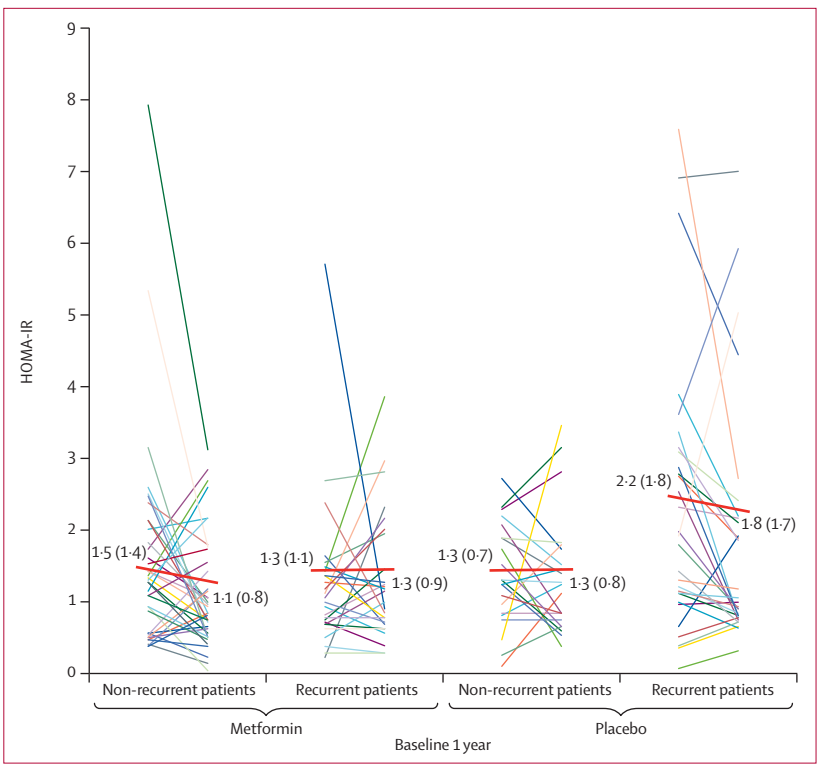

***Figure 2*: HOMA-IR insulin resistance values at baseline and 1 year for non-recurrent patients (no new lesions) and recurrent patients (adenoma or polyp recurrence)**
Red line represents change in mean HOMA-IR from baseline to 1 year. Data for these HOMA-IR values are mean (SD). HOMA-IR=insulin resistance calculated using the homoeostasis model assessment.

	Metformin (n=71)	Placebo (n=62)
Abdominal pain	0	1 (2%)
Diarrhoea	1 (1%)	4 (6%)
Rash	2 (3%)	0
Constipation	3 (4%)	3 (5%)
Alopecia	0	1 (2%)

All adverse events were National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 grade 1.

***Table 3*: Adverse events**

adenoma or polyp recurrence even if the patients do not have diabetes mellitus. It might be possible to predict the chemopreventive effect of metformin by assessing the insulin resistance response. We have previously reported that metabolic factors, including high levels of fasting glucose, accelerate adenoma or polyp recurrence,[22] which is consistent with the results in this trial.

This trial has several limitations. First, we did not do a dose–response study of the effect of metformin on colorectal polyp formation. Previous trials of metformin for cancer prevention and adjuvant treatment have used high-dose metformin (500–2000 mg per day). However, high-dose metformin is associated with the risk of developing lactic acidosis and gastrointestinal adverse effects (including diarrhoea). Gontier and colleagues[31] reported results from a study in which patients treated with antidiabetic agents, including metformin, showed high and diffuse bowel uptake of ^{18}F-fluorodeoxyglucose. This finding suggests that AMPK is present in abundance in the bowel epithelium and that activation of AMPK by metformin upregulates the expression of glucose transporters. Thus, these results support the notion of metformin as a chemopreventive drug in the colorectum.

Second, repeat colonoscopy at 1 year might be too soon to allow reliable detection of differences between the treatment groups. However, no previous colorectal cancer chemoprevention trials have used metformin in non-diabetic patients, and a trial duration longer than 1 year presented ethical issues. To overcome this problem, we selected participants who were at high risk of adenoma and cancer recurrence: about 70% of patients in each group had multiple or advanced adenomas (high-grade dysplasia, adenomas larger than 10 mm in diameter, and villous features), which are known risk factors for colorectal cancer,[2] and surveillance after polypectomy is recommended for up to 3 years in these patients.[32] Indeed, in the placebo group, patients who had undergone resection of advanced adenomas or multiple adenomas had a high frequency of recurrence. However, no colorectal cancer was detected in any of our participants with the 1-year follow-up colonoscopy. Further long-term study is needed to ascertain whether metformin prevents colorectal cancer occurrence. Moreover, our study does not address whether metformin is effective for patients with an average risk of colorectal cancer, limiting its external validity.

Third, patients in our study did not receive a so-called clean colon confirmed colonoscopy after initial polypectomy, which means that polyps and adenomas might have been missed. However, clean colon confirmed colonoscopy is painful and time-consuming for participants. To minimise the occurrence of missed polyps, we selected expert endoscopists and we also excluded the patients who were likely to have had missed polyps by the DVD observer. Variability in adenoma detection rate is known to be related to endoscopic capability.[19] Furthermore, we excluded 183 patients who were judged to be likely to have missed polyps or adenomas based on the opinions of the endoscopic operators and observers. If we did inadvertently include participants with missed polyps, that effect would be partly mitigated by randomisation. Nonetheless, if many participants with missed polyps were included in the trial, that would reduce the chance of detecting a significant decrease in metachronous adenoma or polyps in the metformin group.

Fourth, despite no serious adverse events occurring in the 1-year trial period, this study was underpowered to detect rare adverse events. Long-term studies with larger populations are needed to confirm the safety of low-dose metformin and to detect rare adverse events.

Finally, this study was done in a small region of Japan and the sample size was not large. The recurrence rate in this study is higher than that reported in previous chemoprevention trials. However, many adenoma prevention trials, including that of the COX-2 inhibitor celecoxib, have been done in westernised countries. In a chemoprevention trial in Japan, Takayama and colleagues[21] reported that in patients who underwent polypectomy, the 1-year recurrence rate was 54·6%. Our results were similar to those obtained by Takayama and colleagues. To generalise the conclusions, multinational studies are needed, involving large sample sizes, many more institutions, and many more ethnic groups.

In conclusion, low-dose metformin is safe and effective in reducing the prevalence of metachronous adenomas and polyps in non-diabetic patients after polypectomy. Low-dose metformin might be more effective for patients who are insulin resistant, even if they do not have diabetes. The HOMA-IR could act as a suitable predictor of responders to metformin in chemoprevention for colorectal cancer. Metformin has potential in chemoprevention for colorectal cancer.

Contributors

TH and AN conceived the study. HT, TU, HN, SUc, TK, AH, and NM did the baseline polypectomy and repeat colonoscopy at 1 year. KH, SUm, and ES overviewed on a DVD recording to ensure the validity. YK, LT, YH, HN, TK, and JA recruited participants and follow-up at outpatient clinic. ES, YI, SY, and KH did the pathological analyses. MT analysed and interpreted the data. All the authors have read the final version of the report and approve its submission for publication.

Declaration of interests

We declare no competing interests.

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