Combination Treatment With Curcumin and Quercetin of Adenomas in Familial Adenomatous Polyposis

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Background & Aims: **Familialadenomatous polyposis (FAP) is an autosomal-dominant disorder characterized by the development of hundreds of colorectal adenomas and eventual colorectal cancer. Regression of adenomas in this syndrome occurs with the administration of nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors, but these compounds can have considerable side effects. We evaluated the efficacy of the combination of diet-derived nonprescription supplements curcumin and quercetin to regress adenomas in patients with FAP.** ***Methods:*** **Five FAP patients with prior colectomy (4 with retained rectum and 1 with an ileal anal pouch) received curcumin 480 mg and quercetin 20 mg orally 3 times a day. The number and size of polyps were assessed at baseline and after therapy. The Wilcoxon signed-rank test was used to determine differences in the number and size of polyps. Treatment side effects and medication compliance also were evaluated.** ***Results:*** **All 5 patients had a decreased polyp number and size from baseline after a mean of 6 months of treatment with curcumin and quercetin. The mean percent decrease in the number and size of polyps from baseline was 60.4% ($P < .05$) and 50.9% ($P < .05$), respectively. Minimal adverse side effects and no laboratory abnormalities were noted.** ***Conclusions:*** **The combination of curcumin and quercetin appears to reduce the number and size of ileal and rectal adenomas in patients with FAP without appreciable toxicity. Randomized controlled trials are needed to validate these findings.**

Familial adenomatous polyposis (FAP) is an autosomal-dominant form of hereditary colorectal cancer caused by germline mutation of the *Adenomatous Polyposis Coli* gene located on chromosome 5q21.[1] FAP is characterized by the development of hundreds of colorectal adenomas in adolescence.[2] Nearly all affected individuals will develop colorectal cancer by the 6th decade of life if prophylactic colectomy is not performed.[2]

Regression of adenomatous polyps in FAP was first noted in a case series by Waddell et al[3] in 1983. These investigators described decrease in adenomas with sulindac, a nonsteroidal anti-inflammatory drug. Subsequently, this observation was confirmed by randomized controlled studies with sulindac[4] and with celecoxib, a selective inhibitor of cyclooxygenase 2.[5] Although effective in adenoma regression, cyclooxygenase 1 and 2 inhibitors possess side effects that limit the use of these drugs as true chemopreventive agents.

Curcumin is the major yellow pigment extracted from turmeric, the powdered root of the herb *Curcuma longa*. Curcumin long has been used as a spice in Asia and is considered a safe food additive.[6] In murine models, this agent shows preventive activity in the initiation and progression stages of colorectal carcinogenesis.[6] Also, several reports using this compound in patients with colorectal cancer, and high risk for premalignant conditions, have stimulated interest in curcumin as a chemopreventive agent.[7,8] In patients with advanced colorectal malignancy refractory to standard chemotherapy, 5 of 15 individuals given daily oral curcumin had stable disease at 4 months of follow-up evaluation.[8] Also, histologic improvement of precancerous lesions in patients taking this agent was noted in 1 of 2 patients with resected bladder cancer, 2 of 7 with oral leukoplakia, 1 of 6 with gastric intestinal metaplasia, and 2 of 6 with Bowen's disease.

Quercetin belongs to a group of plant-derived polyphenolic substances known as flavonoids, recognized for their antioxidant properties. Rich sources of quercetin include onions, red wine, green tea, and St. John's wort. Quercetin appears to inhibit cell growth of human colon cancer cell lines[9] and colorectal neoplasia development in murine models.[10,11]

Because cell culture and animal evidence of chemopreventive activity exists against colorectal neoplasia for both curcumin and quercetin, each with potentially different mechanisms of action, these compounds were used together. Therefore, we evaluated the effectiveness and toxicity of the

Abbreviation used in this paper: FAP, familial adenomatous polyposis

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Table 1. Demographic Characteristics of Study Patients

Patient	Age, *y*	Sex, M/F	Surgical status	Baseline number of polyps	Baseline size of the largest polyp, *mm*
1	49	F	IAP	(15)	4
2	21	M	IRA	45	8
3	51	F	IRA	11	4
4	54	M	IRA	5	4
5	22	M	IRA	15	5

NOTE. Parentheses indicate ileal polyps.
IAP, total proctocolectomy with ileoanal pouch; IRA, colectomy with ileorectal anastomosis.

combination of curcumin and quercetin to regress intestinal adenomas in 5 patients with FAP.

Methods

Patients

Five white FAP patients with previous colectomy, 4 with ileorectal anastomosis and 1 with ileoanal pull through with ileal anal pouch, were enrolled in the study. Patients were recruited from the Cleveland Clinic in Weston, Florida. Inclusion criteria were patients with FAP who had undergone colectomy with retained rectum or ileal pouch who had 5 or more adenomas. Exclusion criteria included the use of nonsteroidal anti-inflammatory drugs for more than 1 week over the prior 3 months. The study was approved by the Cleveland Clinic Institutional Review Board, and informed consent was obtained from the patients.

Study Design

Participants were examined by flexible sigmoidoscopy using an Olympus flexible sigmoidoscope (Olympus, Melville, NY) before administration (0 mo) and at 3-month intervals (range, 3–9 mo) after the initiation of treatment with curcumin and quercetin. The number and size of polyps were evaluated at each visit. Also, at each endoscopy examination, 2 polyps were sampled for histology with care taken not to remove the polyps. No effort was made to clear the rectum of polyps by polypectomy or excisional biopsy procedure. One observer (M.C.C.) performed all assessments. The endoscopist counted the total number of polyps in the entire circumference of the rectum from the ileorectal anastomosis to the anal verge or in the ileoanal pouch. The diameter of the largest polyp was measured in millimeters, with a graduated scale passed through the sigmoidoscopy biopsy channel.

Each patient received curcumin 480 mg and quercetin 20 mg orally 3 times a day using Oxy-Q tablets (Farr Laboratories, Santa Clarita, CA). Also, patients were instructed not to take nonsteroidal anti-inflammatory drugs during this trial. Patient compliance with drug administration was assessed by tablet count and monthly telephone contact. Safety was monitored by monthly telephone interviews and at follow-up visits. In addition, complete blood count was obtained and levels of glucose, blood urea nitrogen, serum creatinine, serum electrolytes, and bilirubin were measured at each visit. Adverse events were graded in accordance with the Common Toxicity Criteria of the National Cancer Institute.[12]

Statistical Analysis

The outcome variables analyzed were the number and size of polyps at the end of treatment. In addition, the percentage change from baseline in the number and size of polyps was evaluated. Mean, standard deviation, median, and range were reported where appropriate. Hypothesis testing was performed by Wilcoxon signed-rank test (pair analysis) using STATA 8.0 statistical software (STATA Corporation, College Station,TX).

Results

Clinical Effect

Table 1 shows the demographic characteristics of the study patients. Four of the patients had colectomy with ileorectal anastomosis and retained rectum and 1 had proctocolectomy with an ileoanal pouch. All patients had 5 or more polyps at baseline. Patients were treated for a mean of 6 months of therapy (range, 3–9 mo). Patient 1 was found to be noncompliant with scheduled treatment doses between 3 and 6 months of therapy. After re-instruction of the patient concerning the medication schedule, she was continued on therapy for an additional 3 months (months 6–9). Patient 5 was lost to follow-up evaluation after 3 months of treatment.

Figure 1 shows the polyp number for the 5 patients over the course of treatment with curcumin and quercetin. A decrease in polyp number from baseline was noted in 4 of 5 patients at 3 months and 4 of 4 patients at 6 months of treatment. Of note, polyp number in patient 1 paralleled medication compliance with resolution of polyps after 3 months, recrudescence of polyps between 3 and 6 months (medication noncompliance), and regression again by 9 months. Figure 2 shows representative endoscopic photographs of the retained rectum of patient 3 before and after treatment with curcumin and quercetin.

The mean decrease in polyp number from baseline with treatment was 60.4% ($P = .043$) (Table 2). The mean decrease in polyp size from baseline with treatment was 50.9% ($P = .039$).

Adverse Effects and Compliance

Few adverse side effects were reported with combination treatment with curcumin and quercetin. One patient reported a grade 1 episode of nausea and sour taste that occurred for 1–2 hours after pill ingestion and abated after 3 days without recurrence. One patient had a grade 1 self-limited episode of loose stools for 5 days during the study period. Abnormalities in laboratory study results were

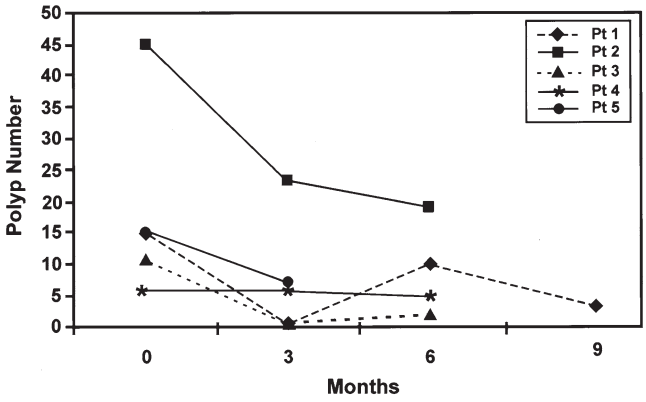

Figure 1. Polyp number after treatment with curcumin and quercetin. ◆, Patient 1; ■, patient 2; ▲, patient 3; ✱, patient 4; ●, patient 5.

not noted in any patient with curcumin and quercetin treatment. The compliance with scheduled drug doses by pill count was 92% (excluding the 3- to 6-month period for patient 1).

Discussion

In this study combination therapy with curcumin and quercetin appeared effective in reducing the number and size of adenomatous polyps in both the retained rectum and ileoanal pouch of patients with FAP with prior colectomy. Evidence of ileal adenoma regression is of clinical importance because recent reports highlight a risk for adenoma and adenocarcinoma development in the ileal pouch.[13] Of note, patient 1 developed an increase in polyp number between 3 and 6 months. Investigation revealed patient noncompliance with treatment dosing during this period. With re-establishment of compliance between 6 and 9 months, the polyp number again decreased. Curcumin, a food spice, is used commonly in Asian meal preparation and is considered to have an absence of side effects.[14,15] Also, quercetin, a dietary-derived supplement, has a dearth of reported adverse effects, although limited experience with this agent exists.[16] In contrast, agents previously shown to regress colorectal adenomas in FAP patients, including sulindac and cyclooxygenase-2 inhibitors, have defined toxicities. During this trial of curcumin and quercetin, study patients had virtually no adverse events and no perturbations in laboratory values.

Findings of adenoma regression in FAP patients with curcumin are consistent with the effect of this agent in animal studies of colorectal carcinogenesis. In azoxymethane-induced murine models, curcumin inhibited the incidence and multiplicity of colonic adenocarcinomas[15] and adenomas.[17] Inhibition of colonic neoplasia was noted in both the initiation and promotion/progression phase of colon carcinogenesis.[18] Some similar studies have been published with quercetin.[10,11] Also, in the murine model of FAP (Min mouse) curcumin significantly decreased tumor formation by 64%.[19] Few clinical trials of curcumin or quercetin exist. Sharma et al[8] treated 15 patients with advanced colorectal cancer refractory to standard chemotherapy with curcumin for up to 4 months and reported radiographically stable disease in 5 patients for 2–4 months of therapy.

The putative anticancer mechanisms of curcumin include up-regulation of carcinogen-detoxifying enzymes such as glutathione S-transferases,[20] antioxidation,[21] and suppression of the isoenzyme cyclooxygenase-2.[22] In a phase I clinical trial, orally administered curcumin produced a 57%–62% decrease in inducible prostaglandin E_2 levels as measured in blood leukocytes.[23] Of interest, an association between adenoma regression in FAP patients and prostaglandin levels has been noted in several recent studies of colorectal mucosal prostanoids after sulindac treatment.[24]

The potential anticarcinogenic mechanisms of quercetin are less well understood. Of interest, flavonoid compounds are able to target the function of ras gene products.[25] Quercetin specifically inhibits p21-Ras expression in human colon cancer cell lines and in primary colorectal cancers.[26]

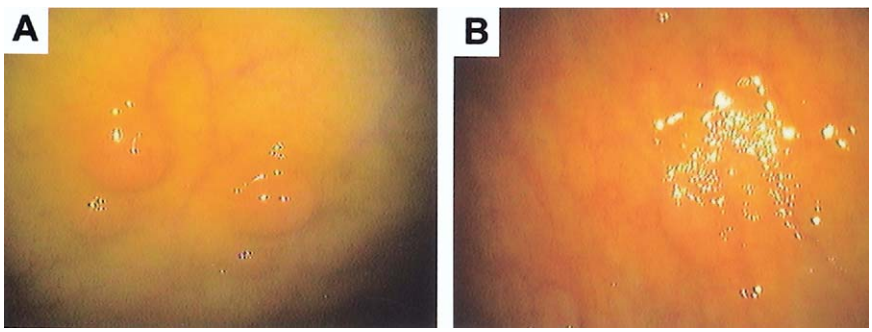

Figure 2. Endoscopic photographs of the retained rectal segment of patient 3 before and during treatment with curcumin and quercetin. (*A*) Before treatment, patient 3 had 11 adenomas averaging 4 mm in size. (*B*) At 3 months of treatment, the rectum was polyp free.

Table 2. Effect of Curcumin and Quercetin on Polyp Number and Polyp Size

	Mean (SD)	Range of polyps	Percent reduction from baseline	*P* value[a]
Polyp number				
Baseline	23.7 (18.6)	11–45		
Treatment	7.2 (6.8)	2–19	60.4	.043
Polyp size (*mm*)				
Baseline	5.3 (2.3)	4–8		
Treatment	2.7 (.9)	2–4	50.9	.039

[a]*P* values determined by Wilcoxon signed-rank test.

In summary, the potential use of curcumin and quercetin as chemopreventive agents against colorectal neoplasia is supported by animal studies and this human observational data. However, these findings need validation in a randomized, double-blind, placebo-controlled trial.

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