Plasminogen activator inhibitor-1 is associated with the metabolism and development of advanced colonic polyps

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Implications of plasminogen activator inhibitor-1 (PAI-1) in colonic polyps remain elusive. A prospective study was conducted with 188 consecutive subjects who underwent colonoscopy at a tertiary referral center. Biochemical parameters, serum PAI-1 levels, PAI-1 single-nucleotide polymorphisms (rs-1799889), and colonic polyp profiles were analyzed at baseline and 24 and 48 weeks postpolypectomy. Of 188 patients (mean age: 56.8 years), 78.7% had adenomas; the median polyp number and size were 2 and 1.2 cm, respectively. Multivariate analyses revealed the following baseline associations: PAI-1 levels (95% confidence interval (CI) for estimated β: 0.012–0.223) and polyp pathology (0.294–0.63) with polyp size; polyp size (0.085–0.498) and platelet count (0.013–0.027) with PAI-1 levels. At 24 weeks postpolypectomy, homeostasis model assessment-estimated insulin resistance (HOMA-IR) and platelet count were independently associated with PAI-1 levels. Among patients with colonic adenomas, baseline PAI-1 levels (95% CI odds ratio: 1.06–1.686; cut-off value: >10.65 ng/mL, area under curve: 0.662, *P* = 0.032) and the PAI-1-rs-1799889 4G/4G genotype (0.036–0.912) were associated with high-grade dysplasia. Compared with baseline levels, repeated measures analysis of variance showed that PAI-1 levels increased, with concurrent increased HOMA-IR indexes, but decreased alanine transaminase levels and polyp size in follow-up colonoscopies at 24 weeks postpolypectomy. PAI-1 returned to baseline levels, and HOMA-IRs and triglyceride and/or high-density lipoprotein-cholesterol ratios decreased at 48 weeks postpolypectomy. Taken together, serum PAI-1 levels were positively associated with colonic polyp size and high-grade dysplasia, which was modulated by the PAI-1-rs-1799889 4G/4G genotype. The beneficial postpolypectomy inflammatory and metabolic alterations might be transiently counter regulated by elevated PAI-1 levels, with a link to HOMA-IR. (Translational Research 2018; ■■:■■-■■)

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in men and the second most common in women worldwide. Most CRCs arise from colonic polyps, particularly adenomatous polyps.[1] The detection rate for colonic adenomatous polyps is 28.5%.[2] The polyp size, number, and pathologic findings are crucial prognostic factors for CRC. For example, nonadvanced colonic polyps are defined as 1−2 adenomatous polyps each <10 mm in size,[3] and advanced colonic polyps are defined as any adenomatous polyp ≥10 mm in size or with >25% villous histology or high-grade dysplasia.[3] Colonoscopy is considered the gold standard for

detecting colonic polyps and affords clinicians an opportunity to initiate therapy through polypectomy and for histological diagnosis. However, colonoscopy does not allow detection of all colonic polyps. "Back-to-back" colonoscopies have indicated significant miss rates of 27% for polyps <5 mm and 6% for polyps ≥10 mm.[4] Moreover, the protection afforded by colonoscopy may be insufficient for proximal colon lesions. Missed lesions likely account for more than half of interval cancers diagnosed 3−5 years after the index procedure.[5] Thus, a noninvasive marker of advanced polyps may aid in decreasing the misdiagnosis rate of colonoscopy but is not currently available.

Obesity is a risk factor for adenomatous polyps,[6] and a link between obesity-related metabolic alterations and CRC development has been established.[7] Dysfunctional adipose tissue in obesity releases an altered profile adipokines, which may be crucial in establishing the peritumoral environment promoting tumor growth and progression.[8] Among adipokines, plasminogen activator inhibitor-1 (PAI-1), a single-chain glycoprotein with a molecular weight of 50 kDa that acts as a serine protease inhibitor (serpin),[9] is of particular interest. PAI-1 is a principal inhibitor of fibrinolysis due to its inactivation of plasminogen activators, including tissue-type plasminogen activator and urokinase-type plasminogen activator. PAI-1 is synthesized and secreted by ectopic fat depots, endothelial cells, hepatocytes, tumor cells, and inflammation-activated cells and is present as a stored product in platelets.[10] PAI-1 secretion is stimulated by insulin, free fatty acids, atherogenic lipoproteins, and chronic inflammation.[10] Consequently, PAI-1 levels are elevated during thrombotic, fibrotic, and cardiovascular events and in the presence of metabolic disorders and malignancies.[10] Specifically, an imbalance between plasminogen activators and PAI-1 exists in colonic neoplasia. This imbalance may further contribute to plasmin-mediated growth, invasiveness, and metastasis, supporting the malignant potential of colonic adenomas.[11] Furthermore, the link between PAI-1 and hypertriglyceridemia may accelerate intestinal polyp formation, as hyperlipidemia is associated with an increased colorectal tumor risk.[12] The situation is even more complicated when considering the PAI-1-associated genetic effects. A single guanosine insertion and/or deletion (4G/5G) polymorphism (PAI-1-rs-1799889) in the promoter region is associated with circulating levels of PAI-1 and gene−environment interactions.[10] The differences in PAI-1 levels between individuals with the 4G vs the 5G allele are more apparent in the presence of diseases that stimulate PAI-1 expression.[13] How the PAI-1-rs-1799889 genotype affects CRC prognosis remains controversial. For example, although negative impacts of the PAI-1-rs-1799889 4G/4G genotype on the survival of patients with CRC,[14] particularly proximal CRCs,[15] had been reported, another study failed to show any relationship between the PAI-1-rs-1799889 genotype and the stage, survival or tumor location of CRC.[16]

Accordingly, we sought to elucidate the implications of PAI-1 levels in colonic polyps after adjusting for crucial confounders, including metabolic and genetic profiles, in a prospective study of patients with colonic polyps who underwent polypectomy with an available pathologic diagnosis.

MATERIALS AND METHODS

Patients. This cohort study included subjects 18 years or older who underwent screening, surveillance, or therapeutic colonoscopy performed by experienced endoscopists using an electronic endoscopic reporting system to report data. Subjects with human immunodeficiency virus, hepatitis C infection, hepatitis B infection, hemochromatosis, malignancy, and inflammatory bowel disease; recipients of solid organ transplants; and patients on immunomodulatory agents, lipid-lowering, glucose-lowering or antihypertensive drugs were excluded.

Study design. One hundred and eighty-eight subjects were consecutively recruited from a tertiary referral center between December 2014 and March 2017. All 188 subjects were naïve patients who had never undergone polypectomy or colon surgery (13 received a screening colonoscopy, and 10 patients received surveillance colonoscopy due to a positive fecal occult blood test; the others [$n = 165$] received a therapeutic colonoscopy and were referred by the check-up department after a screening colonoscopy revealed polyps ≥0.5 cm [patients who had polyps <0.5 cm underwent polyp resection or their polyps were biopsied in the check-up department, but these patients were not referred for therapeutic colonoscopy and were excluded from the current study]). Patients received bowel preparation using a split-dose regimen of 2 L of a polyethylene glycol electrolyte solution. Sedation was performed by administering intravenous fentanyl and midazolam during the colonoscopy for patient comfort at the discretion of the endoscopist. Before colonoscopy, subjects were evaluated for body weight, body mass index, total cholesterol, triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), uric acid, homeostasis model assessment-estimated insulin resistance (HOMA-IR; fasting insulin [μU/mL] × fasting glucose [mmol/l]/22.5] index, C-reactive protein, carcinoembryonic antigen, neutrophil to lymphocyte ratio, alanine aminotransferase (ALT), estimated