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Basic Study

Plasma MMP-2 and MMP-7 levels are elevated first month after surgery and may promote growth of residual metastases

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Abstract

BACKGROUND

MMP-2 also known as gelatinase A and MMP-7 (matrilysin) are members of the zinc-dependent family of MMPs (Matrix metalloproteinase). MMP-2 and MMP-7 are remodeling enzymes that digest extracellular matrix; MMP-2 is extensively expressed during development and is upregulated at sites of tissue damage, inflammation, and in stromal cells of metastatic tumors. MMP-7 is expressed in the epithelial cells and in a variety of cancers including colon tumors. Plasma MMP-2 and MMP-7 levels were assessed before and after minimally invasive colorectal resection for cancer pathology.

AIM

To determine plasma MMP-2 and MMP-7 levels before and after minimally invasive colorectal resection for cancer pathology.

METHODS

Patients enrolled in a plasma bank for whom plasma was available were eligible. Plasma obtained from preoperative (Preop) and postoperative blood samples was

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used. Only colorectal cancer (CRC) patients who underwent elective minimally invasive cancer resection with preop, post-operative day (POD) 1, 3 and at least 1 late postop sample (POD 7-34) were included. Late samples were bundled into 7 d blocks (POD 7-13, 14-20, *etc.*) and treated as single time points. Plasma MMP-2 and MMP-7 levels were determined *via* enzyme-linked immunosorbent assay in duplicate.

RESULTS

Total 88 minimally invasive CRC resection CRC patients were studied (right colectomy, 37%; sigmoid, 24%; and LAR/AR 18%). Cancer stages were: 1, 31%; 2, 30%; 3, 34%; and 4, 5%. Mean Preop MMP-2 plasma level (ng/mL) was 179.3 ± 40.9 ($n = 88$). Elevated mean levels were noted on POD1 (214.3 ± 51.2 , $n = 87$, $P < 0.001$), POD3 (258.0 ± 63.9 , $n = 80$, $P < 0.001$), POD7-13 (229.9 ± 62.3 , $n = 65$, $P < 0.001$), POD 14-20 (234.9 ± 47.5 , $n = 25$, $P < 0.001$), POD 21-27 (237.0 ± 63.5 , $n = 17$, $P < 0.001$), and POD 28-34 (255.4 ± 59.7 , $n = 15$, $P < 0.001$). Mean Preop MMP-7 level was 3.9 ± 1.9 ($n = 88$). No significant differences were noted on POD 1 or 3, however, significantly elevated levels were noted on POD 7-13 (5.7 ± 2.5 , $n = 65$, $P < 0.001$), POD 14-20 (5.9 ± 2.5 , $n = 25$, $P < 0.001$), POD 21-27 (6.1 ± 3.6 , $n = 17$, $P = 0.002$) and on POD 28-34 (6.8 ± 3.3 , $n = 15$, $P < 0.001$), *vs* preop levels.

CONCLUSION

MMP-2 levels are elevated for 5 wk and MMP-7 levels elevated for weeks 2-6. The etiology of these changes in unclear, trauma and wound healing likely play a role. These changes may promote residual tumor growth and metastasis.

Key Words: Effects of surgery; Colorectal resection; Colorectal cancer; Plasma MMP-2 and MMP-7 levels; Angiogenesis

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Core Tip: Our past studies have shown that the levels of 9 plasma proteins that play a role in angiogenesis have been shown to be elevated, *vs* baseline levels, for 2-5 wk after minimally invasive colorectal cancer resection (MICR). This group of proteins includes vascular endothelial-derived growth factor, placental growth factor, angiopoietin-2, soluble vascular adhesion molecule-1, monocyte chemo-attractant protein-1, chitinase 3-like-1, interleukin-8, CXCL16 and MMP-3 (matrix metalloproteinase-3). We have demonstrated that postoperative plasma from colorectal cancer (CRC) patients stimulates *in vitro* endothelial cell proliferation, migration, and invasion. This manuscript is to demonstrate that proangiogenic proteins, plasma MMP-2 and MMP-7 in CRC patients remain elevated for month after MICR.

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INTRODUCTION

Colorectal cancer (CRC) accounts for almost 900000 deaths per year worldwide[1,2]. Despite advances in surgery as well as in medical and radiation oncology, recurrence and mortality rates remain high. As regards surgery, there is evidence that tumor resection may indirectly or directly stimulate the growth of residual cancer early postop *via* unclear mechanisms[3-8]. Among other suggested explanations, persistently elevated blood levels of proangiogenic proteins during the early postoperative (Postop) period[9,10] has been proposed as a potential cause of increased tumor growth post-surgery.

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In the past decade the levels of at least 9 plasma proteins that play a role in angiogenesis have been shown to be elevated, *vs* baseline levels, for 2-5 wk after minimally invasive CRC resection. Included on this list are vascular endothelial-derived growth factor (VEGF), angiopoietin-2 (Ang-2), placental growth factor (PIGF), soluble vascular adhesion molecule-1 (sVCAM-1), monocyte chemotactic protein-1 (MCP-1), matrix metalloproteinase-3 (MMP-3), chitinase 3-like 1 (CHI3L1), interleukin 8 (IL-8) and CXCL16[11-15]. The added finding that plasma from the second and third postop weeks stimulates *in vitro* endothelial cell (EC) proliferation, migration and invasion (all critical to angiogenesis) suggests that post resection plasma is proangiogenic[16,17]. It has been suggested that these systemic changes may stimulate tumor angiogenesis in patients who harbor unknown micrometastases after the primary tumor has been removed.

MMP-2 and MMP-7 are two proteins that play a role in angiogenesis whose postop levels have not been thoroughly studied. Both are members of the diverse zinc dependent MMP family that breaks down extracellular matrix (ECM) proteins. Based on their specific substrate specificities MMP-2 and MMP-7 are grouped in the gelatinase and matrilysin sub families, respectively[18,19]. MMP-2 degrades gelatin and the following ECM components; collagen (types IV, V, VII and X), decorin, elastin, and fibronectin[20,21]. MMP-2 promotes tumor cell invasion and metastasis because of its high specificity for type IV collagen[22,23]. MMP-2 ECM degradation releases VEGF and transforming growth factor β (TGF- β), thus, increasing their bioavailability [24,25]. Transformation of TGF- β into its active form is further supported by MMP-7 [26]. Of note, MMP-2 overexpression has been noted in a variety of cancers and has been associated with tumor progression[27-30].

Most MMPs are synthesized in the stroma, however, MMP-7 is produced in normal large bowel epithelium as well as in cancer cells and is associated with tumor invasion and metastasis by virtue of the damage it incurs to the basement membrane. MMP-7, like MMP-2, has a high affinity for numerous ECM proteins[31,32]. MMP-7 is capable of shedding of bioactive cell-surface molecules such as epidermal growth factor (EGFR)[33], heparin binding EGFR (HB-EGFR)[34], Fas-Ligand[35,36] and E-cadherin [32,37]. MMP7 related vascular basement membrane degradation has been shown to facilitate hematogenous metastasis[38].

Elevated MMP-2 and MMP-7 activity has been linked to a poor prognosis in many cancers including CRC[27,28,38-47]. As mentioned, the impact of MICR for CRC on plasma levels of MMP-2 and MMP-7 is unknown. This study's purpose was to evaluate plasma MMP-2 and MMP-7 levels during first month after MICR for CRC.

MATERIALS AND METHODS

Study population

CRC patients undergoing elective minimally invasive colorectal resection (MICR) at Mount Sinai West Hospital and New York Presbyterian Hospital between 2007 and 2014 who were enrolled in an IRB approved data/plasma bank (Institutional Review Board of the Mount Sinai School of Medicine, New York; IRB reference NO: GCO1: 16-2619 and Institutional Review Board of the Columbia university medical center, New York; IRB reference NO: AAAA4473) for whom adequate plasma samples were available were included in the study. This tissue bank's purpose was to assess the physiologic, immunologic, and oncologic ramifications of MIS large bowel resection. Patients included in the current study underwent either laparoscopic-assisted (LAP) or hand assisted laparoscopic colorectal resection. Exclusion criteria included perioperative blood transfusion, recent radio- and/or chemotherapy, and immunosuppression (medication-related, HIV+, *etc.*). Demographic, operative, pathologic, and short term outcome data were prospectively collected. Blood samples were collected preoperative (Preop) and at varying Postop time points.

Blood sampling and processing

Blood samples were collected Preop, on post-operative day (POD) 1, 3 and at 1 or more late timepoint (POD 7-34). Only patients for whom sufficient volumes of frozen plasma were available were included in the study. Since most late specimens were obtained post hospital discharge the timing of the samples varied. Consequently, it was necessary to 'bundle' late samples into 7 d time blocks (POD7-13, POD14-20, POD21-27, and POD 28-34) that, collectively, were considered as single time points. Blood was collected in heparin-containing tubes and processed within 5-6 h. After centrifugation, plasma samples were stored at -80 °C until utilized.

Plasma MMP-2 and MMP-7 analysis

Plasma MMP-2 and MMP-7 levels were analyzed in duplicate using commercially available enzyme-linked immunosorbent assays (ELISA) (R and D Systems, Minneapolis, MN, United States) according to the manufacturer's instructions. MMP-2 and MMP-7 concentrations (ng/mL) were calculated using a standard curve made for each ELISA plate and were reported as mean \pm SD.

Statistical analysis

Demographic and clinical data are expressed as the mean \pm SD for continuous variables. As regards analysis of the MMP-2 and MMP-7 data (Preop *vs* Postop comparisons) the Wilcoxon signed rank test was used. Other comparisons (males *vs* females, surgical methods, *etc.*) were carried out using the Mann Whitney test. Correlation between plasma MMP-2/MMP-7 Levels and age, T, N, M stage, incision size and length of surgery were assessed by the Spearman's rank correlation coefficient (rs). Data analysis was performed using SPSS version 15.0 (SPSS, Inc., Chicago, IL, United States).

RESULTS

A total of 88 CRC patients were studied [44 males/44 female; mean age 66.38 ± 12.83 years; colon cancer, 67 patients (76%); rectal cancer, 21 (24%)]. Sixty-two percent underwent laparoscopic assisted resection [mean incision length (IL), 7.3 ± 3.7 cm] whereas 38% had a hand-assisted MIS procedure (mean IL 10.8 ± 4.3 cm) (Table 1). The types of resection performed were; right (37%), sigmoid (24%) and rectal resection (18%). The cancer stage breakdown was: Stage 1, 31%; Stage 2, 30%; stage 3, 34%; and stage 4, 5%. There were no perioperative deaths, anastomotic leaks or intraabdominal abscesses. There was 2 superficial SSI's, 1 pneumonia, 1 pulmonary edema, 1 acute renal failure, 1 seroma, 7 ileus, 4 UTI's, 1 phlebitis, 3 atelectasis, 6 cases urinary retention, and 4 other complications.

The mean Preop MMP-2 level (ng/mL) was 179.3 ± 40.9 ($n = 88$). Significantly elevated mean plasma levels were noted on POD 1 (214.3 ± 51.2 , $n = 87$, $P < 0.001$), POD 3 (258.0 ± 63.9 , $n = 80$, $P < 0.001$), POD 7-13 (229.9 ± 62.3 , $n = 65$, $P < 0.001$), POD 14-20 (234.9 ± 47.5 , $n = 25$, $P < 0.001$), POD 21-27 (237.0 ± 63.5 , $n = 17$, $P < 0.001$) and on POD 28-34 time point (255.4 ± 59.7 , $n = 15$, $P < 0.001$) (Figure 1). The mean Preop MMP-7 level (ng/mL) was 3.9 ± 1.9 ($n = 88$). When compared to Preop levels, no significant differences were noted on POD 1 or 3, however, significantly elevated mean plasma levels were noted on POD 7-13 (5.7 ± 2.5 , $n = 65$, $P < 0.001$), POD 14-20 (5.9 ± 2.5 , $n = 25$, $P < 0.001$), POD 21-27 (6.1 ± 3.6 , $n = 17$, $P = 0.002$) and on POD 28-34 (6.8 ± 3.3 , $n = 15$, $P < 0.001$) when compared to Preop levels (Figure 2).

Of note regarding the results, because the "n" for each time point varied for both MMP-2 and MMP-7, the Preop mean protein values are different at each time point. Because of this, as regards the bar graph figures, at each time point, in addition to a bar showing the postop result, there is an adjacent bar (on the left) providing the mean preop result.

Of note, when the postop results of the rectal and colon cancer subgroups were compared, no significant differences were noted for either protein. Likewise, the choice of surgical method (laparoscopic *vs* hand-assisted laparoscopic) did not significantly influence the Postop plasma levels of these 2 proteins.

Correlation of MMP-2 and MMP-7 Preop and Postop (POD) time point data *vs* (T), (N) and pathological stage were carried out. Of note, there were only four ($n = 4$) stage 4 patients in the study. No significant correlation was found between preop or Postop time point MMP-2 levels with (T), (N) or pathological stage except at the POD 14-21 time point. MMP-2 levels on POD 14-21 significantly correlated with T stage ($P = 0.002$) N stage ($P = 0.02$) and with final pathological stage ($P = 0.01$). Regarding MMP-7, no significant correlation between Preop and Postop levels and (T), N or pathological stage was found.

Preop and Postop levels of MMP-2 and MMP-7 in node positive and node negative patients were compared. MMP-2 levels of node negative group was significantly higher at POD 14-21 time point compared to node positive group. No other significant difference between the node positive and node negative subgroups were found at any other time points for either MMP-2 or MMP-7.

Table 1 Demographic and clinical characteristics of the study population

Characteristics	
Age, yr (mean \pm SD)	66.3 \pm 12.8
Sex, <i>n</i> (%)	
Male	44 (50.0)
Female	44 (50.0)
Incision length (entire patient population), cm (mean \pm SD)	8.3 \pm 4.2
Incision length (lap procedure group), cm (mean \pm SD)	7.3 \pm 3.7
Incision length (hand procedure group), cm (mean \pm SD)	10.8 \pm 4.3
Operative time, min (mean \pm SD)	306.6 \pm 120.5
Length of stay, d (mean \pm SD)	6.8 \pm 4.1
Type of resection, <i>n</i> (%)	
Right	34 (37.0)
LAR/AR (12/1)	13 (18.0)
Sigmoid/recto-sigmoid (17/6)	23 (24.0)
Total/sub total (5/1)	6 (7.0)
Transverse	7 (8.0)
Left	4 (5.0)
APR	1 (1.0)
Surgical method, <i>n</i> (%)	
Laparoscopic-assisted	58 (62.0)
Hand-assisted/hybrid laparoscopic	30 (38.0)

LAR: Low anterior resection; AR: Anterior resection; APR: Abdominal perineal resection.

DISCUSSION

As mentioned, whereas the vast majority of surgery-related blood protein alterations resolve in 2-5 d, plasma levels of at least 8 proteins have been shown to be persistently elevated for up to 5 wk after MICR[11-15]. Of note, all of these proteins have proangiogenic effects and plasma from the 2nd and 3rd postop weeks has been shown to stimulate EC invasion, migration, and proliferation which are critical steps in neovascularization[16,17]. These findings raise the possibility that the proangiogenic postop plasma might stimulate tumor angiogenesis in residual metastases, thus stimulating tumor growth early Postoply. This study was undertaken to determine the impact of colorectal resection on blood levels of 2 other proteins that, amongst other effects, play a role in angiogenesis.

Plasma MMP-2 and MMP-7 levels were determined Preop and for over one month post-operatively in CRC patients who underwent MICR. Mean MMP-2 levels were found to be significantly elevated during weeks 1 through 5 after surgery (change from mean baseline varied from 22% to 43%). MMP-2, therefore, fits the pattern noted for almost all of the other blood proteins noted to have long duration elevations, namely both early and late postop increases. MMP-7 is unique because although its levels are significantly increased during weeks 2-5 (change from mean baseline varied from 41%-46%), during the first 3 d after surgery plasma levels were not significantly altered. The MMP-7 results support the concept that, perhaps, that the etiology of the early and late protein elevations are different.

As mentioned, the vast majority of surgery related blood protein compositional changes resolve in 1-7 d. IL-6, IL-2, tumor necrosis factor, C-reactive protein, fibroblast growth factor, hepatocyte growth factor, angiostatin and endostatin are examples of proteins whose levels are transiently elevated early after surgery[48]. The etiology of these short lived blood protein elevations is likely to include anesthesia, surgical trauma, and the acute inflammatory response. As mentioned, longer duration plasma

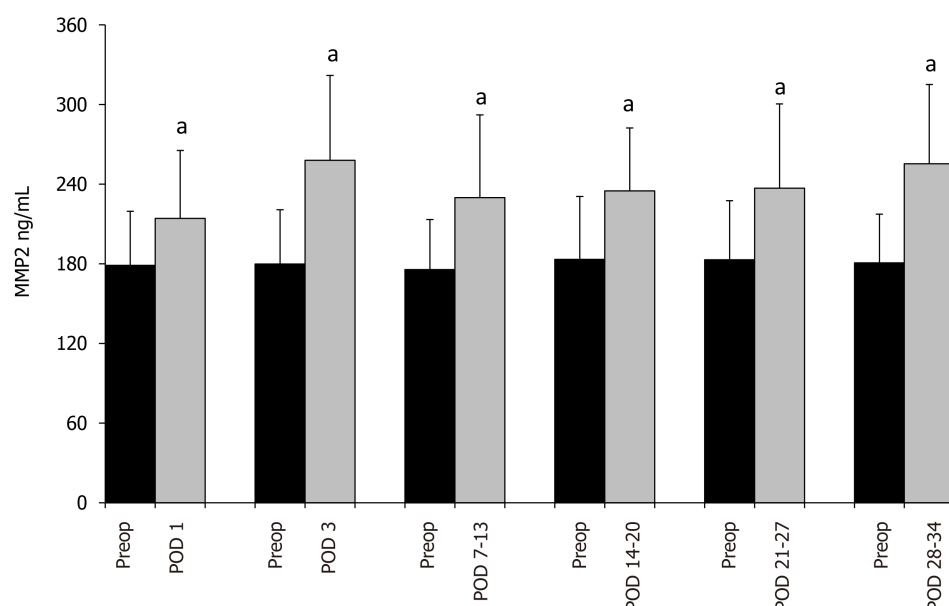


Figure 1 Enzyme-linked immunosorbent assay determined preoperative and postoperative plasma MMP-2 levels of colorectal cancer patients. MMP-2 levels are expressed as mean \pm SD [preoperative (Preop) vs post-operative day (POD) 1 ($n = 87$, $^aP < 0.001$); Preop vs POD 3 ($n = 80$, $^aP < 0.001$); Preop vs POD 7-13 ($n = 65$, $^aP < 0.001$); Preop vs POD 14-20 ($n = 25$, $^aP < 0.001$); Preop vs POD 21-27 ($n = 17$, $^aP < 0.001$); POD 28-34 time point ($n = 15$, $^aP < 0.001$)]. Statistical significance is expressed as $^aP < 0.001$. POD: Post-operative day; Preop: Preoperative.

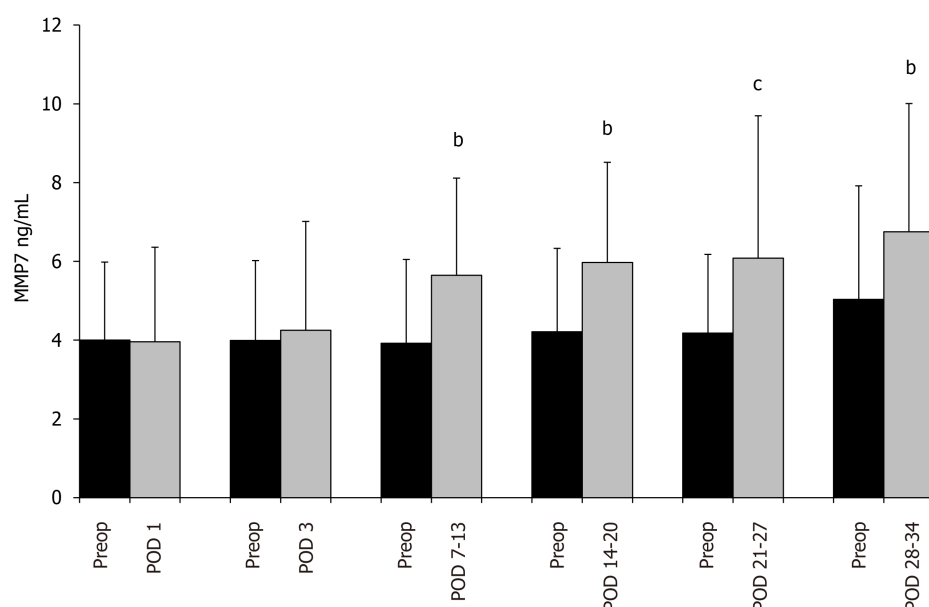


Figure 2 Enzyme-linked immunosorbent assay determined preoperative and postoperative plasma MMP-7 levels of colorectal cancer patients. MMP-7 levels are expressed as mean \pm SD. [preoperative (Preop) vs post-operative day (POD) 1 ($n = 87$); Preop vs POD 3 ($n = 80$); Preop vs POD 7-13 ($n = 65$; $^bP < 0.001$); Preop vs POD 14-20 ($n = 25$, $^bP < 0.001$); Preop vs POD 21-27 ($n = 17$, $^cP = 0.002$); POD 28-34 time point ($n = 15$, $^bP < 0.001$)]. Statistical significance is expressed as $^bP < 0.001$, $^cP < 0.01$. POD: Post-operative day; Preop: Preoperative.

elevations have been noted for VEGF, Ang-2, PIGF, sVCAM-1, MCP-1, CHI3L1, MMP-3 and IL-8[11-15]. The etiology of the later postop plasma changes is unclear, however, there is evidence that at least 1 source of the added proteins are the healing wounds. In a study that simultaneously measured perioperative levels of 8 proangiogenic proteins in both the blood and fluid from surgical wounds for up to 3 wk after MICR, it was noted that wound fluid protein levels were 3-40 times higher than plasma levels which, in turn, were significantly elevated from preop plasma baseline levels[49]. It is postulated that the notably increased levels of these proteins in the wounds are the result of healing related angiogenesis; as a result of diffusion along concentration gradients, blood levels of these proteins subsequently increase. The persistent wound

fluid elevations of these proteins also confirms that angiogenesis plays a prominent role in wound healing. Because both MMP-2 and MMP-7 play roles in neovascularization[50-52], the authors conjecture, without evidence, that the 4-5 wk long plasma elevations of these proteins postop are likely related to the surgical wounds.

Of note, all of the long duration proteins mentioned above are capable of supporting cancer growth and metastasis[11-15,16]; most have also been noted to be overexpressed by a variety of human cancers[50-62]. Further, the mean pre-resection plasma levels of almost all of the long duration proteins have been shown to be significantly higher in cancer patients than in cancer-free patients. MMP-2 and MMP-7 are similar in these regards.

In separate studies from our lab, preop MMP-2 and MMP-7 plasma levels were determined and compared in CRC and benign disease patients (MMP-2, CRC $n = 168$, Benign $n = 128$; MMP-7, CRC and Benign groups, $n = 120$ each). The mean preop levels in the cancer groups were significantly higher for both MMP-2 (24.5% higher than benign group) and MMP-7 (51.1% increase).

Further, increased expression of MMP-2 has been noted in CRC and other cancers [27,28]. Of note, a shortened relapse-free survival has been noted in early stage non-small cell lung cancer patients whose tumor expression of MMP-2 was higher[27]. Further, it has been shown that elevated serum levels of MMP-2 are an independent predictor of overall survival in node positive breast cancer[63].

As regards *in vitro* studies, it has been shown that decreasing MMP-2 expression in CRC cell lines by adding lentiviral-mediated shRNA markedly reduced tumor cell proliferation and invasiveness[22]. The same group showed that protein levels of VEGF and MT1-MMP were markedly reduced in MMP-2-expression suppressed CRC cells *vs* control cells; thus, MMP-2 impacts tumor cell proliferation and invasion[64-66]. MMP-2 also plays a role in wound healing. Using a double knockout mouse model, Hingorani *et al*[67] have shown that MMP-2 and MMP-9 are involved in multiple overlapping activities critical to both epithelial wound healing and tumor progression *in vivo*. Karim *et al*[68] showed that MMP-2 expression is a reliable indicator of clinical wound healing. Thus, MMP-2 plays a role in both cancer development and wound healing.

As regards MMP-7, it has been shown that upregulation of MMP-7 and other MMPs in tumors as well as increased blood levels of these proteins have an adverse association with cancer survival[69-72]. Decreasing MMP-7 levels *via* antisense RNA mediated knockdown or by knockout in mice reduces tumor incidence, while increased MMP-7 expression leads to increased tumor formation[73-75]. MMP-7 also plays a role in the shedding of cell-surface molecules including EGFR[33], HB-EGF[34], E-cadherin[37] and Fas ligand[35,36] which suggests that MMP-7 plays a role in tumor invasion and metastasis. Also, elevated MMP-7 expression is associated with aggressive CRC tumor cell behavior, *in vitro*[39,75-78]. Recombinant MMP-7 accelerates EC proliferation in a dose dependent manner which confirms its role in angiogenesis which is critical to both wound healing and tumor growth[79].

To summarize, blood levels of MMP-2 and MMP-7, which play roles in both wound healing and tumor growth are elevated after surgery for over 1 mo. There are now a total of 10 proangiogenic proteins shown to be elevated post MICO for up to 5 wk. It is the authors' position that the first month after MICO (or any major operation) may be a dangerous period for cancer patients with residual disease. Of note, a number of investigators have suggested that cancer excision[80] and/or surgical trauma[81] may stimulate the development of recurrences or the growth of residual lesions early postoperatively[3-8,81]. Kaibori *et al*[5] noted, within a short period of time after surgery, new liver lesions in 31% of CRC patients presenting with synchronous liver metastases who underwent resection of the colon primary alone. Similarly, Yoshidome *et al*[6], as regards a similar patient population (CRC patients with synchronous liver lesions), noted new liver lesions on computed tomography in 43% of patients who underwent staged resection (median time between surgery and scan 2.4 mo). Also, Slessor *et al*[3] noted that resection of the colon tumor alone in similar synchronous disease patients was associated with disease progression. A variety of mechanisms for accelerated tumor growth/development have been proposed and include: Immunosuppression, removal of primary tumor generated circulating growth suppression factors, surgery induced spread of viable cancer cells and stimulated tumor angiogenesis[82].

Perhaps, the administration of anti-cancer agents during the first month after surgery would make sense. Presently, adjuvant chemotherapy is usually started 4-8 wk after surgery. The use of standard chemotherapeutic agents is problematic since these agents may interfere with wound and anastomotic healing. Immunotherapies (vaccines, select monoclonal antibodies, immunomodulators) and other anti-cancer

agents that do not interfere with wound healing, however, might be given during the first month after surgery.

Limitations of study

Obtaining post hospital discharge blood samples is a challenge from several perspectives. These specimens are mainly obtained during follow up office visits and since the timing of these visits vary, it was not possible to get late samples on the same postop days. Therefore, by necessity, late samples were grouped into 7 d time blocks that were considered as individual timepoints. Also, because contact between MD and patients wane after the first follow up appointment, there were fewer opportunities to obtain late first month samples. One result is that the “*n*” for weeks 2-5 time is substantially less than the starting number and is ever diminishing. Also, ideally, open (lengthy incision) patients would have been included so that the impact of the abdominal wall trauma element of these operations on plasma MMP2/7 levels could be determined. Lastly, because there is no long term outcome data it is not possible to correlate postop MMP 2/7 levels with recurrence rates or the time to recurrence.

CONCLUSION

Significant and enduring plasma elevations over baseline were noted for 5 wk after MICR for MMP-2 (entire period) and for MMP-7 (weeks 2-5 only). No correlation between postop levels and cancer location (rectal *vs* colon), disease stage, or MIS surgical method used was noted. MMP-2 and MMP-7 join the list of proteins with proangiogenic and tumor promoting effects and associations that are persistently elevated during the first month after MICR. Although unproven, these conditions may stimulate the growth of residual tumor deposits early after surgery. Further studies are warranted to further investigate the postop time period and to determine the clinical importance, if any, of these systemic changes.

ARTICLE HIGHLIGHTS

Research background

Major abdominal surgery is known to results a brief period of immunosuppression and short lived plasma protein alterations. In past decade it has been shown that minimally invasive colorectal cancer resection (MICR) is associated with elevated levels of at least 8 plasma proteins after surgery that play major role in angiogenesis. Angiogenic proteins included on this list are vascular endothelial-derived growth factor (VEGF), angiopoietin-2, placental growth factor, soluble vascular adhesion molecule-1 (sVCAM-1), monocyte chemotactic protein-1 (MCP-1), interleukin 8 (IL-8) and matrix metalloproteinase-3 (MMP-3). The plasma from the second and third postoperative weeks stimulates *in vitro* endothelial cell proliferation, migration and invasions which are critical for angiogenesis suggests that post colorectal surgery plasma bears proangiogenic property. The impact of MICR for colorectal cancer (CRC) on plasma levels of MMP-2 and MMP-7 is unknown.

Research motivation

MMP-2 and MMP-7 are two proteins that play a key role in angiogenesis whose postoperative blood levels have not been thoroughly studied investigated. Both proteins are members of the large zinc dependent MMP family that breaks down extracellular matrix (ECM) proteins. Based on their substrate specificities MMP-2 and MMP-7 are grouped in the gelatinase and matrilysin sub families, respectively. MMP-2 degrades gelatin and the following ECM components; collagen (types IV, V, VII and X), decorin, elastin, and fibronectin. MMP-2 ECM degradation releases increase bioavailability of angiogenic VEGF and transforming growth factor β . MMP-2 promotes tumor cell invasion and metastasis because of its high specificity for type IV collagen. MMP-7 is produced in normal large bowel epithelium as well as in cancer cells and is associated with tumor invasion and metastasis by virtue of the damage it incurs to the basement membrane. MMP-7, like MMP-2, has a high affinity for numerous ECM proteins. MMP-7 related vascular basement membrane degradation has been shown to facilitate hematogenous metastasis. Overexpression of MMP-2 and MMP-7 activity has been linked to a poor prognosis in many cancers including CRC has been associated with tumor progression. The impact of MICR for CRC on plasma

levels of MMP-2 and MMP-7 is unknown. Motivation of this study was to assess plasma MMP-2 and MMP-7 levels during first month after MICR for CRC.

Research objectives

The objective of this study was to determine plasma MMP-2 and MMP-7 levels during first month after minimally invasive colorectal resection at various postoperative time points, which include the first blood draw on the day of operation before surgery, the second on post-operative day 1 (POD 1), the third on POD 3, and additional four time points between POD 7 and POD 34. The hypothesis was that if blood levels of proangiogenic MMP-2 and MMP-7, which play major roles in wound healing, remain elevated for month after surgery would confirm that surgery has long lasting systemic manifestations that have the potential to influence growth in residual cancer after surgery and metastasis.

Research methods

This study analyzed colorectal patients who underwent elective surgery for cancer pathology. Plasma was obtained from IRB approved perioperative tissue and data bank. The clinical, demographic and pathologic data was prospectively gathered. Blood samples were obtained preoperative (Preop) and at varying postop time points and were stored at -80 °C. Blood samples were obtained from consented patients Preop and at varying postop time points. Late post op samples were collected during follow-up visits. Because of the fewer specimens taken after POD 3, the 7 d blocks were bundled and considered as single time points (POD 7-13, POD 14-20, POD 21-27, and POD 28-34). Plasma MMP2 and MMP7 protein levels were determined in duplicate *via* highly specific commercially available Enzyme-linked Immunosorbent Assays. Demographic and clinical data are expressed as the mean \pm SD for continuous variables. The Wilcoxon signed rank test was used for MMP-2 and MMP-7 data preop *vs* postop comparisons. Other comparisons (males *vs* females, surgical methods, *etc.*) were carried out using the Mann Whitney test. Correlation between plasma MMP-2/MMP-7 levels and age, incision size and length of surgery were assessed by the Spearman's rank correlation coefficient (rs).

Research results

A total of 88 CRC patients were studied. Majority of patients (62%) underwent laparoscopic assisted resection whereas 38% had a hand-assisted MIS procedure. The most common resection performed was right colectomy (37%) followed by sigmoid (24%) and rectal resection (18%). The cancer stage breakdown was: Stage 1, 31%; Stage 2, 30%; stage 3, 34%; and stage 4, 5%. The mean Preop MMP-2 level (ng/mL) was 179.3 ± 40.9 . Significantly elevated mean plasma levels were noted on POD 1 (214.3 ± 51.2 , $P < 0.001$), POD 3 (258.0 ± 63.9 , $P < 0.001$), POD 7-13 (229.9 ± 62.3 , $P < 0.001$), POD 14-20 (234.9 ± 47.5 , $P < 0.001$), POD 21-27 (237.0 ± 63.5 , $P < 0.001$) and on POD 28-34 time point (255.4 ± 59.7 , $P < 0.001$). The mean Preop MMP-7 level (ng/mL) was 3.9 ± 1.9 . When compared to Preop levels, no significant differences were noted on POD 1 or 3, however, significantly elevated mean plasma levels were noted on POD 7-13 (5.7 ± 2.5 , $P < 0.001$), POD 14-20 (5.9 ± 2.5 , $P < 0.001$), POD 21-27 (6.1 ± 3.6 , $P = 0.002$) and on POD 28-34 (6.8 ± 3.3 , $P < 0.001$) when compared to Preop levels. Furthermore, when the postop results of the rectal and colon cancer subgroups were compared, no significant differences were noted for either protein. Likewise, the choice of surgical method (laparoscopic *vs* hand-assisted laparoscopic) did not significantly influence the postoperative plasma levels of these 2 proteins.

Research conclusions

This study reports plasma MMP-2 levels are elevated for 5 wk and MMP-7 levels elevated for weeks 2-6 after minimally invasive CRC for cancer pathology. Mean MMP-2 levels were found to be significantly elevated during weeks 1 through 5 after surgery (change from mean baseline varied from 22% to 43%). This study revealed that MMP-2, therefore, fits the pattern noted for almost all of the other blood proteins (such as VEGF, PIGF, ANG2, sVCAM-1, MCP1, CHI3L1, MMP-3, IL-8) noted to have long duration elevations, namely both early and late postop increases. MMP-7 is unique because although its levels are significantly increased during weeks 2-5 (change from mean baseline varied from 41%-46%), during the first 3 d after surgery plasma levels were not significantly altered. The MMP-7 results support the concept that, perhaps, that the etiology of the early and late protein elevations are different. The etiology of these short lived blood protein elevations is likely to include anesthesia, surgical trauma, and the acute inflammatory response. The etiology of the later postop plasma

changes is unclear, however, there is evidence that at least 1 source of the added proteins are the healing wounds. It is postulated that the notably increased levels of these proteins in the wounds are the result of healing related angiogenesis; as a result of diffusion along concentration gradients, blood levels of these proteins subsequently increase. The persistent wound fluid elevations of these proteins also confirms that angiogenesis plays a prominent role in wound healing. It is the authors' position that the first month after MICR (or any major operation) may be a dangerous period for cancer patients with residual disease due to elevated levels blood levels of MMP-2 and MMP-7, which play roles in both wound healing and tumor growth.

Research perspectives

Plasma MMP-2 and MMP-7, which play important roles in both wound healing and tumor growth, are elevated after surgery for over 1 mo. The findings of this study will add 2 more angiogenic proteins to the growing list of proangiogenic proteins which includes VEGF, PlGF, ANG2, sVCAM-1, MCP1, CHI3L1, MMP-3 and IL-8 that shown to be elevated post MICR for up to 5 wk. The results of this study add further evidence and support for the concept that the first month after MICR (or any major operation) may be a dangerous period for cancer patients with residual disease. All of these proteins have proangiogenic effects and plasma from the 2nd and 3rd postop weeks has been shown to stimulate Endothelial Cell invasion, migration, and proliferation which are critical steps in neovascularization. Additionally, previous study showed that simultaneously measured perioperative levels of 8 proangiogenic proteins in both the blood and fluid from surgical wounds for up to 3 wk after MICR, it was noted that wound fluid protein levels were 3-40 times higher than plasma levels which, in turn, were significantly elevated from preop plasma baseline levels. It is postulated that the notably increased levels of these proteins in the wounds are the result of healing related angiogenesis; as a result of diffusion along concentration gradients, blood levels of these proteins subsequently increase. The persistent wound fluid elevations of these proteins also confirms that angiogenesis plays a prominent role in wound healing. These findings raise the possibility that the elevated proangiogenic postop plasma might stimulate tumor angiogenesis in residual metastases, thus stimulating tumor growth early postoperatively. This study further supports the idea of administration of anti-cancer agents during the first month after surgery. Adjuvant chemotherapy is usually started 4-8 wk after surgery. The use of standard chemotherapeutic agents is problematic since these agents may interfere with wound and anastomotic healing. Immunotherapies (vaccines, select monoclonal antibodies, immunomodulators) and other anti-cancer agents that do not interfere with wound healing, however, might be given during the first month after surgery.

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