Perioperative Collagen Deposition in Elderly and Young Men and Women

Rainer Lenhardt, MD; Harriet W. Hopf, MD; Elvine Marker, MD; Ozan Akça, MD; Andrea Kurz, MD; Heinz Scheuenstuhl, AB; Daniel I. Sessler, MD

Hypothesis: Women deposit more collagen after major abdominal surgery than men.

Design: A post hoc analysis of data obtained from 2 prospective, randomized, double-blind clinical trials.

Setting: University hospital general surgical service.

Patients: One hundred sixteen patients undergoing colon resection.

Main Outcome Measures: Protein and hydroxyproline (collagen) deposition during the first 7 postoperative days in expanded polytetrafluoroethylene implants positioned subcutaneously.

Results: On univariate analysis, men and women deposited comparable amounts of collagen (257 ± 120 vs 281 ± 117 ng/mm, respectively). When potential confounding factors were entered into a generalized mixed-effects model, only the interaction between age and sex was a significant factor (P = .047). Collagen deposition decreased with age in men, being 317 ± 133 ng/mm in men younger than 45 years, but only 238 ± 113 ng/mm in those older than 45 years (P = .03). In contrast, collagen deposition was virtually identical in women younger than 45 years (280 ± 133 ng/mm) and in those older than 45 years (281 ± 110 ng/mm). Only 3 of these women were receiving hormone replacement therapy.

Conclusions: Collagen deposition after surgery decreased significantly with age in men, while remaining unchanged in women. Younger men and women deposited similar amounts of collagen. Therefore, older men made less collagen after surgery than older women, perhaps explaining the consistent observation that wound dehiscence is twice as common in men as in women. Our results differ from previous studies conducted in healthy, nonsurgical volunteers, which showed that (1) young women made significantly more collagen than young men and (2) collagen deposition was reduced in postmenopausal women, but deposition returned to premenopausal values with hormone replacement therapy. Differences between our results and those reported previously likely stem from the populations studied. In particular, multiple perioperative factors decrease collagen deposition, which apparently obscures the differences observed previously in healthy, unstressed volunteers.

Arch Surg. 2000;135:71-74

I NADEQUATE SCAR formation contributes to serious surgical complications, including wound dehiscence and postoperative hernias.1 A recent volunteer study concluded that young women heal significantly better than men (ie, deposit 85% more collagen in test wounds).2 That study simultaneously confirmed a previous finding in men that healing was worse in smokers.3 Ashcroft et al3 similarly demonstrated better healing in healthy premenopausal female volunteers than in postmenopausal volunteers. Improved healing was associated with a higher level of transforming growth factor ß-1 in the wounds of young women. Hormone replacement therapy returned collagen deposition and growth factor concentration to premenopausal levels.

Young subjects tend to heal well, and the controlled nature of volunteer studies makes it relatively easy to identify physiological differences. Surgical patients, though, produce less collagen than healthy volunteers,3 in part because healing is impaired by factors including age, illness, malnutrition, medications, and physiological stress.6 Male sex has been shown to double the risk of wound dehiscence in numerous observational and retrospective studies.1 Male sex also increased the risk of wound infection in one study,7 but not in others.8,9 We therefore tested the hypothesis that women deposit more collagen than men after major abdominal surgery.

RESULTS

Sex, age, and weight were comparable in the patients participating in each study (Table 1). Roughly half of the patients...
PATIENTS AND METHODS

With approval from an ethics committee and written consent, we studied 116 patients. All were aged between 18 and 80 years and were undergoing elective colorectal resection for cancer or inflammatory bowel disease. Patients having abdominal-peritoneal pull-through procedures were included, but not those scheduled for minor colon surgery such as polypectomy or isolated colostomy.

Patients were excluded when the surgeon did not anticipate primary wound closure. That is, patients were excluded when delayed primary closure techniques or healing by secondary intention was likely. Patients were also excluded when they had serious malnutrition (serum albumin <33 g/L, white blood cell count <2.5 × 10^9/L, or >20% weight loss), bowel obstruction, or reported a history of fever and/or infection. All patients were aggressively hydrated during and after surgery to minimize hypovolemia. All participants were given the opioid piritramid via a patient-controlled infusion in the postoperative period.

The study population consisted of a subset of patients, participating in 2 large outcome trials, in whom wound collagen deposition was measured. The first study evaluated the effects of maintaining intraoperative normothermia on the incidence of surgical wound infection.8 Exclusion criteria included use of steroids or other immunosuppressive drugs (including cancer chemotherapy) within 4 weeks of surgery. These patients were randomly assigned to normothermia (core temperature 36.6°C ± 0.5°C) or mild intraoperative hypothermia (core temperature 34.7°C ± 0.6°C). No postoperative thermal management was provided. The second study evaluated the effects of 30% and 80% inspired oxygen (Grief et al, unpublished data, 1999). In each protocol were assigned to each randomized treatment (temperature or inspired oxygen concentration). The fraction of patients having colon or rectal surgery was also similar in the 2 study groups. Immunosuppressive drugs were excluded from the temperature trial and only a few patients in the oxygen study were receiving immunosuppressants.

Demographic and morphometric characteristics were comparable in the male and female patients, as were the type and duration of surgery. Univariate analysis similarly indicated that collagen and protein deposition, both measures of scar formation, were comparable in men and women (Table 2).

Potential confounding factors including age, sex, cigarette smoking, and study group were entered into a generalized mixed-effects model. Only the interaction between age and sex was a significant factor (P = .047); however, age alone was nearly statistically significant (P = .051). Collagen deposition decreased with age in men, being 317 ± 133 ng/mm in men younger than 45 years (n = 14), but only 238 ± 113 ng/mm in those older than 45 years (n = 46; P = .03). In contrast, collagen deposition was virtually identical in women younger than 45 years (n = 19; 280 ± 133 ng/mm) and in those older than 45 years (n = 37; 281 ± 110 ng/mm). Only 3 of 37 women older than 45 years (presumed to be postmenopausal) were receiving hormone replacement. On univariate analysis, collagen deposition did not differ significantly in men and women younger than 45 years (P = .42) or in those older than 45 years (P = .08). Neither smoking nor study group were significant predictive factors for collagen deposition.

Previous studies observed greater collagen deposition in healthy premenopausal women than in young men.2 Healthy postmenopausal women make less collagen than premenopausal women, a difference that disappears with hormone replacement therapy.4 In male mice, collagen deposition and the rate of healing decrease significantly with age.16 Our results in patients undergoing colon surgery contrast with previous results in that younger men and women deposited approximately equal amounts of collagen, while older women who were not receiving hormone replacement therapy deposited significantly more collagen than older men. This difference resulted from a decrease in collagen deposition with aging in men, whereas deposition remained largely unchanged in women. On univariate analysis, there was no difference between collagen deposition in men and women younger than 45 years (P = .42) or those older than 45 years.

COMMENT

©2000 American Medical Association. All rights reserved.
ing is an acute reduction in tissue oxygen partial pres-
This is a critical factor because a major effect of smok-
not permitted to smoke in their rooms (and most had lim-
previous studies in normal volunteers3,20 and older sur-
continuing operative stress and underlying illness, over-
dated. Severely malnourished patients were excluded
Factors known to impair collagen deposition in-
clude malnutrition,17 preoperative illness,18 hypovole-
mia,23 hypothermia,3 smoking,20 tissue hypoxia,9 and
corticosteroids and other immunosuppressants.21,22
These factors are common in surgical patients; it is there-
fore hardly surprising that surgery reduces collagen
deposition.5
To the extent possible, we minimized potential con-
founding factors. All patients were aggressively hy-
drated. Severely malnourished patients were excluded
from the study, although mild malnutrition is common
in surgical patients. This is an important issue since col-
lagen deposition is profoundly influenced by recent
nutritional history and even a few days of preoperative
calorie restriction may significantly reduce scar forma-
tion.18,23,24 Nonetheless, it seems most likely that our data
contrast with previous reports because the study popu-
lations differed. Taken together, previous studies and
our current report suggest that perioperative factors, in-
cluding operative stress and underlying illness, over-
whelm sex differences observed in healthy nonsurgical
volunteers.
Interestingly, smoking status was not a significant
predictor of collagen deposition. This result contrasts with
previous studies in normal volunteers3,20 and older sur-
gical studies.25-27 In contrast to normal volunteers who
continued to smoke during the study, our patients were
not permitted to smoke in their rooms (and most had lim-
ited mobility at least for the first few postoperative days).
This is a critical factor because a major effect of smoking
is an acute reduction in tissue oxygen partial pres-
sure lasting roughly 1 hour.20 The older surgical studies
may similarly differ in that patients in those days were
frequently allowed to smoke in their rooms.
Expanded polytetrafluoroethylene implants as a mea-
sure of collagen deposition and scar formation have been
validated in rats,19 where they predict ultimate wound ten-
sile strength. They have been widely and successfully used
in human volunteers3,20,29,30 and patients.5,13,23,24 The im-
plants were placed at the time of surgery and removed af-
ter 7 days to reflect the early postoperative environment.
Although high rates of collagen deposition are not found
until 5 days after injury,31,32 collagen is measurable within
wound implants by 24 to 48 hours after injury.33,34 Peak
collagen deposition rates are found 7 to 14 days after in-
jury.35 These early rates of collagen deposition reflect
the early course of the wound as well as ultimate wound ten-
sile strength, and thus are a useful surrogate measure for
healing.
In the current study, we used the same type of im-
plant as Jorgensen et al.7 (Ashcroft et al4 used wound bi-
opies.) However, the site of subcutaneous implanta-
tion differed. Jorgensen et al inserted the implants in the
lateral upper arm,2 whereas we inserted them in the ab-
domen as in previous studies.35 This is unlikely to have
affected the results; but to the extent that site is a con-
founding factor, implants only a few centimeters from
the surgical incision may better reflect wound condi-
tions than implants at a remote site.
An insufficient number of patients were enrolled in
our study to correlate collagen deposition with wound
dehiscence or hernia. However, it is well established that
wound dehiscence is about twice as common in men than
women. Similarly, men have a greater incidence of anas-
tomotic leak.36 This observation is consistent with the rela-
tively low level of postoperative collagen deposition (a
predictor of low wound tensile strength) we observed in
the older men.

CONCLUSIONS
Collagen deposition after surgery decreased signifi-
cantly with age in men, while remaining unchanged in
women (who for the most part did not use hormone re-
placement therapy). Younger men and women depos-
it similar amounts of collagen. Older men therefore de-
posited less postoperative collagen than older women.
These data are consistent with the observation that men
have about twice the risk of wound dehiscence as women.
Our results differ from previous studies conducted in
healthy, nonsurgical volunteers, which showed that (1)
young women made significantly more collagen than
young men and (2) collagen deposition was reduced in
postmenopausal women, but that deposition returned to
premenopausal values with hormone replacement. Dif-
fences between our results and those reported previ-
ously likely stem from the populations studied. In par-

Table 1. Demographic and Morphometric Characteristics of the Volunteers Participating in Each Protocol*<sup>⁷</sup>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Temperature Study</th>
<th>Inspired Oxygen Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>23/24</td>
<td>37/32</td>
</tr>
<tr>
<td>Age, y</td>
<td>57 ± 13</td>
<td>56 ± 19</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72 ± 16</td>
<td>72 ± 18</td>
</tr>
</tbody>
</table>

* There were no statistically significant or clinically important differences between the groups. Data are presented as mean ± SDs unless otherwise indicated.

Table 2. Collagen and Protein Deposition in Men and Women and Potential Confounding Factors*<sup>⁷</sup>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>60</td>
<td>56</td>
</tr>
<tr>
<td>Age, y</td>
<td>58 ± 17</td>
<td>54 ± 17</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77 ± 15</td>
<td>67 ± 15</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>Collagen, ng/mm</td>
<td>257 ± 120</td>
<td>281 ± 117</td>
</tr>
<tr>
<td>Protein, µg/mm</td>
<td>168 ± 86</td>
<td>165 ± 74</td>
</tr>
</tbody>
</table>

* Data are presented as mean ± SDs unless otherwise indicated. Only weight differed significantly. Ellipses indicate not applicable.

This study was supported by grants GM49670, GM58273,
REFERENCES