ORIGINAL ARTICLE

Hostile Marital Interactions, Proinflammatory Cytokine Production, and Wound Healing

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Context: A growing epidemiological literature has suggested that marital discord is a risk factor for morbidity and mortality. In addition, depression and stress are associated with enhanced production of proinflammatory cytokines that influence a spectrum of conditions associated with aging.

Objective: To assess how hostile marital behaviors modulate wound healing, as well as local and systemic proinflammatory cytokine production.

Design and Setting: Couples were admitted twice to a hospital research unit for 24 hours in a crossover trial. Wound healing was assessed daily following research unit discharge.

Participants: Volunteer sample of 42 healthy married couples, aged 22 to 77 years (mean [SD], 37.04 [13.05]), married a mean (SD) of 12.55 (11.01) years.

Interventions: During the first research unit admission, couples had a structured social support interaction, and during the second admission, they discussed a marital disagreement.

Main Outcome Measures: Couples' interpersonal behavior, wound healing, and local and systemic changes in proinflammatory cytokine production were assessed during each research unit admission.

Results: Couples' blister wounds healed more slowly and local cytokine production (IL-6, tumor necrosis factor α, and IL-1β) was lower at wound sites following marital conflicts than after social support interactions. Couples who demonstrated consistently higher levels of hostile behaviors across both their interactions healed at 60% of the rate of low-hostile couples. High-hostile couples also produced relatively larger increases in plasma IL-6 and tumor necrosis factor α values the morning after a conflict than after a social support interaction compared with low-hostile couples.

Conclusions: These data provide further mechanistic evidence of the sensitivity of wound healing to everyday stressors. Moreover, more frequent and amplified increases in proinflammatory cytokine levels could accelerate a range of age-related diseases. Thus, these data also provide a window on the pathways through which hostile or abrasive relationships affect physiological functioning and health.

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MARRIAGE IS THE CENtral relationship for the majority of adults, and morbidity and mortality are reliably lower for married individuals than unmarried individuals across such diverse health threats as cancer, heart attacks, and surgery.[1-4] Although loss of a spouse through death or divorce can provoke adverse mental and physical health changes,[1,5-7] the simple presence of a spouse is not necessarily protective; a troubled marriage is itself a prime source of stress, while simultaneously limiting the partner's ability to seek support in other relationships.[8] The impact of a turbulent marriage is substantial; for example, epidemiological data demonstrated that unhappy marriages were a potent risk factor for major depressive disorder, associated with a 25-fold increase relative to untroubled marriages.[9] Similarly, other researchers found a 10-fold increase in risk for depressive symptoms associated with marital discord.[10]

Marital discord also has substantial physiological repercussions. For example, in a population-based, prospective study of women aged 30 to 65 years with coronary heart disease, marital stress worsened the prognosis 2.9-fold for recurrent coronary events.[11] Among patients with congestive heart failure, marital quality predicted 4-year survival as well as the patient's illness severity.[12] Greater marital conflict was associated with a 46% higher relative death risk among female patients undergoing hemodialysis.[13]

Laboratory studies have provided evidence of possible mechanisms. For example, discussion of a marital disagreement produced clinically significant

increases in blood pressure in patients with hypertension, with subjects reaching a mean of 160/100 mm Hg. These blood pressure changes were specifically associated with hostile marital interactions; neither supportive nor neutral behaviors were significantly associated with blood pressure changes.[14] Similarly, newlywed couples who exhibited more hostile behaviors during a marital problem discussion showed greater decrements over 24 hours on a battery of functional immunological assays relative to low-hostile couples.[15] Endocrine data from these same newlyweds also demonstrated the impact of hostile behaviors; more hostile couples showed more persistent elevations in serum epinephrine, norepinephrine, and corticotropin levels during the conflict discussion,[16] as well as greater elevations in stress hormone levels throughout the remainder of the day.[17] Indeed, hostile marital conflicts can have adverse physiological effects even in long-term marriages; endocrine and immunological data were associated with hostile conflict behavior in older couples who had been married an average of 42 years.[18]

Thus, a series of studies have shown that marital conflict alters physiological functioning, and hostile behavior, particularly during conflict, markedly enhances adverse physiological changes; moreover, women appear to be more adversely affected than men.[5] In this study, we extended this line of research to assess how hostile marital behavior modulated an important health outcome, wound healing, as well as local and systemic proinflammatory cytokine production.

Several studies have revealed large and reliable relationships between stress and wound healing.[19,20] Stress slows the local production of proinflammatory cytokines at wound sites, providing evidence of 1 key mechanism[21]; cytokines play important roles in the early stage of wound healing, acting as chemoattractants for the migration of phagocytes and other cells to wound sites, starting the proliferative phase, which involves the recruitment and replication of cells necessary for tissue regeneration and capillary regrowth.[22] Thus, stress-related delays are important because early events in wound healing, particularly in the first 24 hours, represent a critical period, and dysregulation during this interval potentiates later problems.[23]

Although greater early local production of proinflammatory cytokines at wound sites is beneficial because it is associated with enhanced healing, greater systemic production of proinflammatory cytokines can represent a maladaptive response.[24] Both physical and psychological stressors can provoke transient increases in plasma levels of proinflammatory cytokines, particularly IL-6,[25] as can negative emotions like depression and anxiety.[26-28] More frequent or persistent stress-related changes have broad implications for physical and mental health; sustained elevated levels of proinflammatory cytokines have been linked to a variety of age-related diseases, including cardiovascular disease, osteoporosis, arthritis, type 2 diabetes mellitus, certain cancers, and frailty and functional decline.[29-31]

To separate the effects of the short-term stress of a marital conflict from the long-term strains of marital discord on local and systemic proinflammatory cytokine production as well as wound healing, couples were recruited for two 24-hour admissions to our General Clinical Research Center (GCRC). On each admission, a suction blister protocol provided a mechanism for studying the local inflammatory responses in vivo[22]; healing at the blister sites was assessed daily following GCRC discharge. During the first GCRC admission, spouses had a structured social support interaction; during the second admission, couples discussed an area of disagreement. Thus, the present study assessed production of proinflammatory cytokines in peripheral blood and wound sites following socially supportive and conflictual interactions.

We expected that higher levels of hostile marital behavior would be associated with slower healing of wounds, lower production of proinflammatory cytokines in blister chamber fluid, and higher cytokine production in peripheral blood; however, short-term marital strife would magnify these relationships such that more hostile couples would show relatively greater deficits on these dimensions relative to low-hostile couples during and following the conflict visit. Women were expected to show greater psychological and physiological responsiveness to conflict than men.

METHODS

PARTICIPANTS

Couples were recruited through newspaper and radio ads, notices posted on campus and in the community, and referrals from other participants. Exclusion criteria included health problems (or related medications) that had an immunological or endocrinological component or obvious consequences for these systems or for wound healing (eg, cancer, recent surgeries, strokes, diabetes mellitus, peripheral vascular disease, conditions such as asthma or arthritis that required regular use of antiinflammatories, etc). We excluded couples if either spouse took blood pressure medication, smoked, or used excessive alcohol or caffeine; 224 couples were excluded because at least one spouse did not meet our stringent health criteria. The Ohio State University Biomedical Research Review Committee (Columbus) approved the project; all subjects gave written informed consent prior to participation.

OVERVIEW, GCRC ADMISSIONS

The procedures and timetable were similar across couples' two 24-hour admissions to the GCRC, a hospital research unit. We asked couples not to drink or eat anything after midnight before admission; all couples were served the same meals in the GCRC, controlling for dietary factors such as sodium. To assure consistent physical activity across dyads and admissions, couples remained together in the same room.

At 7 AM, couples were admitted to the GCRC, fed a standard breakfast, and given questionnaires to complete. A heparin well was inserted in each subject's arm, and a baseline blood sample was drawn for immunological assays. At 9:15 AM, nurses attached the vacuum pump and template to raise blisters on the arm[21] (see "Suction Blister Studies" subsection of the "Methods" section). At roughly 10:45 AM, couples were positioned in chairs facing each other in front of a curtain. The couples completed several questionnaires, then sat quietly for 10 minutes.

During the first GCRC admission, two 10-minute discussions assessed couples' behavior toward each other when so-

liciting and offering social support.[32] The first spouse, selected randomly, was asked to "talk about something you would like to change about yourself," while the partner was instructed to "be involved in the discussion and respond in whatever way you wish." Roles were reversed after 10 minutes so that each spouse played the role of helper or helpee. Prior to the discussions, each spouse was asked to identify an important personal characteristic, problem, or issue that he or she wished to change, with the explicit restriction that the issue could not be a source of marital dissension.[32] Next, using the Relationship History Interview,[33] couples were asked to tell the story of their relationship for 30 minutes.

The second GCRC admission included the conflict resolution task; the experimenter first conducted a 10- to 20-minute interview to identify the best topics for the problem discussion.[15] Based on their ratings from the Relationship Problem Inventory[34] and this interview, couples were then asked to discuss and try to resolve 1 or 2 marital issues that the interviewer judged to be the most conflict producing (eg, money, communication, or in-laws). The research team remained out of sight during all discussions.

Fluid was removed from blister chambers 4, 7, and 22 hours after raising the blisters. After removal of the blister chamber at 7 AM, participants completed final questionnaires and provided peripheral blood samples for cytokine assays.

OBSERVATIONAL CODING SYSTEM

The Rapid Marital Interaction Coding System (RMICS)[35] provided data on behavior during both the social support and conflict resolution tasks. The RMICS includes 11 communication categories coded in a hierarchy. The RMICS discriminates well between distressed and nondistressed couples. The RMICS has high reliabilities both for the overall system as well as for individual codes.[35] Our tapes were coded by Richard Heyman, PhD, University of New York at Stony Brook.

Most marital communication studies use a positive/negative distinction when assembling summary codes[14,36] because distressed marriages are characterized by negative affect, conflictual communication, and poor listening skills.[37-40] To capture these dimensions in composite indexes, we summed the top 3 RMICS codes in the hierarchy: psychological abuse (eg, disgust, contempt, belligerence, as well as nonverbal behaviors like glowering or talking in a threatening or menacing manner), distress-maintaining attributions (eg, "You're only being nice so I'll have sex with you tonight" or "You were being mean on purpose"), and hostility (eg, criticism, hostile voice tone, or rolling the eyes dramatically). The remaining codes (in order) are dysphoric affect, withdrawal, acceptance, relationship-enhancing attributions, self-disclosure, humor, constructive problem discussion, and "other."

QUESTIONNAIRES

We also assessed emotional responses to the marital discussions, as well as perceptions of marital satisfaction. Couples completed the two 10-item mood scales from the Positive and Negative Affect Schedule (PANAS)[41] before and after their discussions. The widely used Marital Adjustment Test provided data on marital satisfaction, with higher scores indicating greater satisfaction.[42]

Health-related behaviors assessed at screening and/or GCRC admission included medications, exercise, and caffeine and alcohol intake.[43,44] The Pittsburgh Sleep Quality Index[45] assessed sleep quality and disturbances. Plasma albumin levels and body mass data provided information on subjects' nutritional status. Health questions from the Older Adults Resources Survey[46] assessed underlying diseases.

PLASMA AND CHAMBER-FLUID CYTOKINE LEVELS

Plasma IL-6 and tumor necrosis factor α (TNF-α) levels and chamber-fluid IL-6, TNF-α, and IL-1β levels were assayed using Quantikine High Sensitivity Immunoassay kits (R&D Systems, Minneapolis, Minn), per kit instructions, as described elsewhere.[47] Samples were run undiluted in duplicate, and all samples for a couple were run at the same time.

SUCTION BLISTER STUDIES

The suction blister protocol followed the methods described previously[21,22,48,49] and used the same suction blister device (Neuro Probe, Cabin John, Md).[49] To assess the early phase of the inflammatory response to wounding in vivo, a plastic template was taped to the volar surface of the nondominant forearm (shifted slightly laterally for the second GCRC admission); a 350–mm Hg vacuum was applied through a pump attached to a regulator until blisters formed (1-1.5 hours). This gentle suction produced 8 small 8-mm blisters. The blister roof (the epidermis) was removed with sterile scissors, a plastic template with 8 wells was placed over the blister wounds and taped to the arm, the wells were filled with 0.8 to 1 mL of 70% autologous serum in Hank balanced salt solution,[49] and the top was sealed. Chamber fluid from 3 wells was pooled for the 4- and 7-hour samples, and 2 wells were pooled for the 22-hour sample. The pooled samples were analyzed for cytokine levels and cell numbers.[21,22] These procedures produce modest self-rated discomfort, consistent with the small and transient cardiovascular changes observed during blistering.[21]

Suction blister wounds are an excellent model for studying the effects of early wound healing.[50] Measurement of the rate of transepidermal water loss (TEWL) through human skin provides a noninvasive method to monitor changes in the stratum corneum barrier function of the skin, providing an excellent objective method for evaluation of wound healing.[51] The 8 blister sites were assessed daily for 8 days following removal of the blister chambers[50] and then again on day 12, along with daily control values from adjacent nonwounded skin; after subtracting the average control values from the average daily measurement, the 90% standard for healing was based on reaching 90% of the day 1 measures. A computerized evaporimetry instrument, the DermaLab (CyberDERM, Media, Pa), was used to measure TEWL, following established procedural guidelines.[52]

DATA ANALYSES

High- and Low-Hostile Groups

Husbands' and wives' hostile behaviors on the RMICS were significantly correlated ([Spearman ρ], $r=0.66$ during social support and $r=0.79$ during conflict; $P<.001$ for both). Thus, following methods in other marital research, we summed the hostile behavior percentages within each GCRC admission for each couple.[14,53] Also, we were interested in the couple's aggregate hostile behavior because one partner's behavior clearly affects the other.

Behavioral data were skewed at both GCRC admissions; during the social support interactions, 2 or fewer of the total dyadic behaviors were categorized as hostile in 56.1% of couples (range, 0-27). Indeed, even during conflict discussions, 50% of couples had 7 or fewer hostile behaviors (range, 0-63). Accordingly, because our interest was in the effects of recurring or customary hostility, we categorized couples who were higher than the median on hostile behaviors at both GCRC admissions as high hostile (28.6% of the sample) and the remainder

as low hostile; thus, a couple was not classified as hostile simply because they had 1 bad day.

Wound Healing

Using survival analysis[54] to investigate wound healing, the "event" was defined as the first point that the wound was 90% healed using TEWL data and remained higher than 90%. Participants with a ratio less than 90% at their last observed point, either by day 12 or earlier, were censored at that point.

The Cox proportional hazards model with clustering on couple[55] in Stata 8.0 (Stata Corp, College Station, Tex) compared time to healing between the high- and low-hostile behavior groups at each visit, controlling for sex. Subjects' times to healing were also compared between the 2 visits in a third model. The assumption of proportional hazards across groups was tested after fitting each model. Missing data occurred at varying points because of technical difficulties and missed appointments. Where necessary, time to healing was calculated using last observation carried forward.

Immunological and Psychological Data

To analyze relationships among behavior (high vs low hostile) on the cytokine levels of each subject at each visit (social support or conflict) and each point, mixed models from SAS 9.1 (SAS Institute Inc, Cary, NC) were used with repeated measures across spouse, visit, and time of day. An unstructured covariance matrix was used to allow for the most flexible estimation of covariance parameters between each level of spouse, visit, and time. The mixed models also allowed use of partial data when subjects had occasional missing data.

Prior to analyses, cytokine data were normalized with log transformations. Log transformations did not normalize the data for PANAS negative mood and cell numbers; thus, the ranks of the data were used in a linear mixed model of PANAS negative mood, and cell number data were analyzed using area under the curve across the 3 points. All tests used a 2-sided, $\alpha = .05$ significance level.

RESULTS

The 42 couples ranged in age from 22 to 77 years (mean [SD], 37.04 [13.05]) and had been married a mean (SD) of 12.55 (11.01) years (range, 2-52 years). Couples were well educated: 26.2% had additional postgraduate training, 40.5% were college graduates, 23.8% had some college training, and 9.5% were high school graduates. The majority were white (88.1%). A mean (SD) of 2.37 (1.93) months elapsed between the 2 GCRC admissions. Four additional couples did not return for the second admission because of scheduling or medical problems (eg, a cancer diagnosis) and thus could not be included in these analyses.

The high- and low-hostile behavior groups did not differ on age or education ($F < 1$; $P > .44$ for both). The 2 groups did not differ on the duration of their marriages or the length of time between GCRC admissions ($F < 1.57$; $P > .21$ for both).

Analysis of RMICS positive behaviors (the sum of acceptance, relationship-enhancing attributions, self-disclosure, humor, and constructive problem discussion) indicated theoretically consistent significant differences between high- and low-hostile groups; the sex × group interaction reflected women's larger differences than men's ($F_{1,40} = 5.84$; $P = .02$). That is, while high-hostile men showed only slightly fewer positive behaviors than low-hostile men (mean difference, 3.19), the difference between low- and high-hostile women was much larger (mean, 8.08). Not surprisingly, there were fewer positive behaviors in the conflict visit than in the social support visit ($F_{1,40} = 15.02$; $P < .001$).

In accord with RMICS behavioral data, high-hostile participants reported lower marital satisfaction than low-hostile participants on the Marital Adjustment Test[42] ($F_{1,39} = 4.42$; $P = .04$), with no significant sex differences. The low-hostile group mean (SD) score was 120.13 (18.11), compared with 107.95 (21.60) for high-hostile participants.

High- and low-hostile behavior groups did not differ at baseline at either GCRC admission on either the Positive or Negative Affect scales from the PANAS[56] ($F < 1$; $P > .46$ for both). The absence of any baseline affective group differences is important because affective differences are related to plasma proinflammatory cytokine production,[27,57] as well as wound healing.[19,20] Negative mood ratings at the first GCRC admission started off higher than in the second GCRC admission and decreased after the interaction, while ratings at the GCRC conflict admission increased ($F_{1,40} = 12.12$; $P = .01$). However, high- and low-hostile behavior subjects had a different pattern of response to the spousal interactions as reflected in their PANAS negative mood ratings, after controlling for visit; high-hostile subjects' moods were more negative after each of the interactions, while low-hostile subjects' moods were less negative ($F_{1,40} = 5.24$; $P = .03$).

WOUND HEALING

High-hostile subjects had a median time to healing 1 day later than low-hostile subjects at the social support visit (day 6 vs day 5, respectively) and at the conflict visit (day 7 vs day 6, respectively). Ignoring visit, median time to healing was 2 days later in the high-hostile behavior group (day 7 vs day 5). Ignoring hostile behavior, time to healing was 1 day later following the conflict visit than after the social support visit (day 6 vs day 5).

Comparisons of the Kaplan-Meier survival curves between hostile behavior groups using the log-rank test yielded $P = .02$ at the social support visit, $P = .07$ for the conflict visit, and $P = .004$ for the combined visits (**Figure 1**A). Figure 1B displays a comparison of Kaplan-Meier survival curves for time to healing after each visit ($P = .046$); however, the log-rank tests are limited in comparison to Cox models because they cannot adjust for covariates in the model or for clustering within couple.

Using Cox models, the hazard ratio (HR) for the hostile behavior groups at the social support visit, controlling for sex, was 0.592 ($P = .04$). This means the estimated "risk" of 90% TEWL healing on any given day for the high-hostile subjects was 0.592 times that of low-hostile participants. At the conflict visit, the HR for the hostile groups was 0.618 ($P = .08$). Combining visits, high-hostile group subjects healed slower than those in the low-hostile group (HR, 0.598; $P = .03$), controlling for sex and visit. In the model across both visits, healing was significantly slower after the conflict visit (HR, 0.726; $P = .01$),

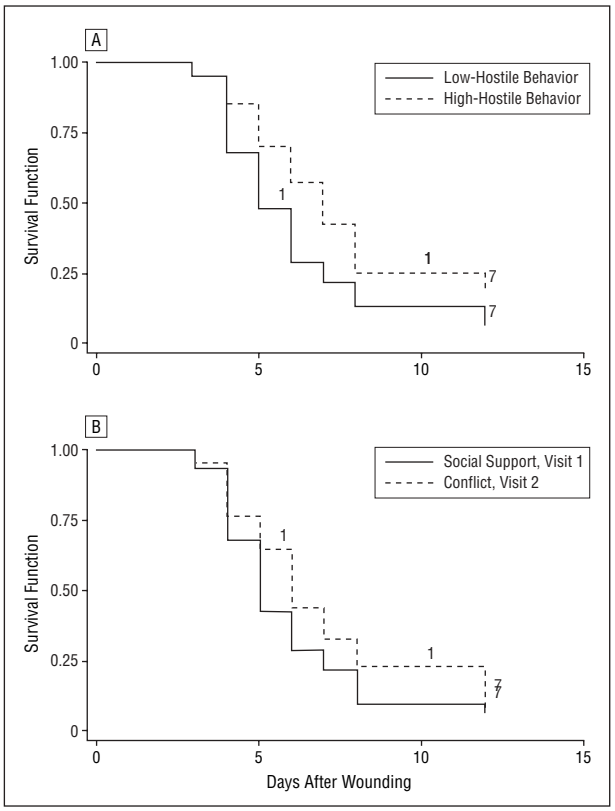

Figure 1. Kaplan-Meier survival curves for time to healing of the standard wound across both visits by high- or low-hostile behavior (A) and for time to healing of the standard wound by visit (B). Couples who demonstrated consistently higher levels of hostile behaviors across both their interactions healed at 60% of the rate of low-hostile couples, and healing during the conflict visit was at 72% of the rate observed following the social support visit. Annotations on the curves show the number of censored observations at each point, indicating patients who were unhealed on their last day of observation.

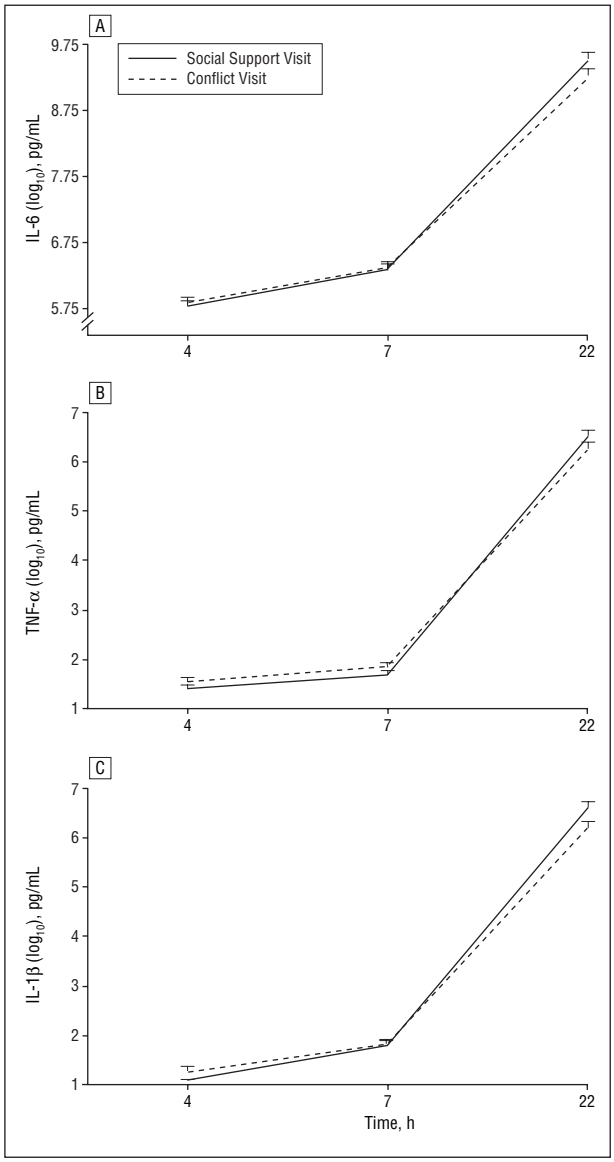

Figure 2. Production of IL-6 (A), tumor necrosis factor α (TNF-α) (B), and IL-1β (C) was lower in the blister chambers at wound sites following the marital conflict task than after the social support task. For all 3 cytokines, the significant time × visit interactions reflect the same or higher baseline values at the second visit (conflict) compared with the first (social support) but lower production at 22 hours.

controlling for sex and hostile behavior group. Although not statistically significant, men healed slightly slower than women at the social support visit (HR, 0.975) but faster than women at the conflict visit (HR, 1.20) and slightly faster across visits (HR, 1.066).

PRODUCTION OF CHAMBER-FLUID CYTOKINES AND CELLS

As expected, cytokine production in blister chamber fluid increased over time at both GCRC admissions (**Figure 2**). However, consistent with the differences between visits in wound healing, production of IL-6, IL-1β, and TNF-α increased more steeply between 4 and 22 hours following the social support interaction than after the conflict interaction, ending up higher at 22 hours at the first visit for all 3 cytokines (IL-6, $F_{2,81}=3.55$; $P=.03$; IL-1β, $F_{2,81}=9.12$; $P<.001$; TNF-α, $F_{2,81}=3.56$; $P=.03$). At the social support visit, subjects with high-hostile behaviors had lower TNF-α levels than subjects with low-hostile behaviors (overall mean [SD], 3.08 [0.11] vs 3.32 [0.07], respectively), but at the conflict visit, subjects with high-hostile behaviors had higher TNF-α levels (overall mean [SD], 3.25 [0.11] vs 3.19 [0.07], respectively) ($F_{1,81}=4.99$; $P=.03$). High-hostile subjects also had significantly fewer cells in the blister chamber fluid than low-hostile subjects during both GCRC admissions, reflected in area under the curve differences across time ($F_{1,78}=10.5$; $P=.002$).

The substantial increases in local cytokine production over time (Figure 2) have been assumed to be primarily a function of their local synthesis at the site by the cells that are migrating to the chamber.[22,58] In our data, correlations between cell numbers and cytokine levels at 22 hours after the social support interaction were $r=0.29$ and $P<.01$ for IL-6; $r=0.08$ and $P=.45$ for TNF-α; and $r=0.13$ for IL-1β and after the conflict interaction, $r=0.52$ and $P<.001$ for IL-6 and $r=0.38$ and $P<.001$ for both TNF-α and IL-1β. Consistent with other investigators,[22,58] there were not reliable relationships between the local production of cytokines at inflammatory sites and levels in systemic circulation (data not shown); thus, local production is the primary presumptive pathway.[22,58]

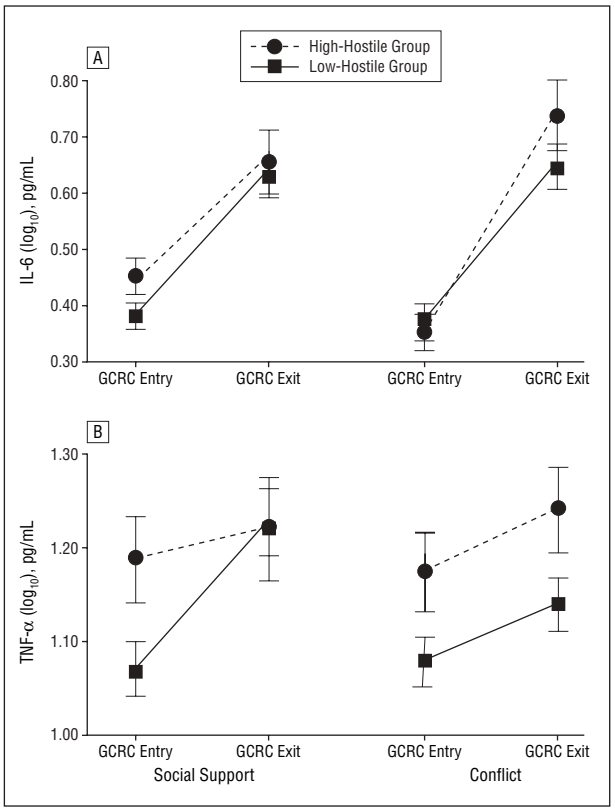

Figure 3. Changes in plasma IL-6 (A) and tumor necrosis factor α (TNF-α) (B) levels in couples high or low in hostile behavior. The respective cytokines are shown at the beginning and end of each the two 24-hour social support and conflict interaction admissions. Low-hostile participants showed roughly the same increase in IL-6 levels over 24 hours following either a social support or conflict interaction (65% vs 70%), while IL-6 production for high-hostile individuals jumped from 45% following the social support task to 113% following the conflict task. High-hostile participants had higher TNF-α values before and after the conflict task than low-hostile participants. GCRC indicates General Clinical Research Center.

PLASMA PROINFLAMMATORY CYTOKINE LEVELS

High-hostile couples produced larger increases in plasma IL-6 and TNF-α levels the morning after a conflict than a social support interaction (**Figure 3**), while low-hostile couples showed 24-hour increases in IL-6 levels that were similar at each visit and a smaller 24-hour increase in TNF-α levels at the conflict visit compared with the social support visit as reflected in the significant 3-way GCRC admission × time × hostile behavior interactions for both IL-6 ($F_{1,40}$=4.75; P=.04) and TNF-α ($F_{1,40}$=7.81; P=.008). Both groups displayed the expected increases in IL-6 and TNF-α levels over 24 hours at each visit.[59] Women had significantly higher IL-6 levels than men ($F_{1,40}$=5.28; P<.001), and men had significantly higher TNF-α levels than women ($F_{1,40}$=5.28; P=.03).

HEALTH-RELATED BEHAVIORS

Further analyses assessed the possibility that the relationships between hostile behavior and cytokine levels and wound healing might simply reflect the contribution of health habits and/or chronic health problems. However, none of the health-related behaviors accounted for differences between hostile behavior groups (F <1 for all).

COMMENT

Blister wounds healed more slowly following couples' conflict discussions than after more supportive interchanges, and couples who were more hostile toward each other during both discussions had wounds that healed more slowly than couples whose interactions were less hostile. The overall differences related to hostility were substantial; small blister wounds in high-hostile couples healed at only 60% of the rate of low-hostile couples. Thus, wound healing appeared to be responsive to both the short-term stress of a conflict, as well as hostile behaviors.

Compared with low-hostile behavior couples, high-hostile couples had relatively greater increases in circulating levels of plasma IL-6 and TNF-α following a conflict discussion than a social support interaction. Indeed, low-hostile participants produced roughly the same increment in IL-6 production over 24 hours following either a social support or conflict interaction (65% vs 70%), while IL-6 production for high-hostile individuals jumped from 45% to 113%.

These changes are important because both stressors and depression can sensitize the inflammatory response in such a way that they produce heightened responsiveness to stressful events as well as antigen challenge.[25,27,28,60] Furthermore, more frequent or persistent stress-related changes in plasma levels of these key cytokines have broad implications for health; elevated levels of proinflammatory cytokines have been linked to a variety of age-related disease, including cardiovascular disease, osteoporosis, arthritis, type 2 diabetes mellitus, certain cancers, and frailty and functional decline.[29] Moreover, inflammatory activation can enhance development of depressive symptoms.[30,31] Thus, relationships characterized by hostility, repeated conflicts, and heightened IL-6 levels could have negative consequences for both physical and mental health. Indeed, our data are consistent with the growing epidemiological evidence that marital stress is a risk factor for mental and physical health.

The 2 GCRC admissions allowed us to separate the effects of the short-term stress of a marital conflict from the long-term strains of marital dissatisfaction. Couples were understandably apprehensive when they came for the first GCRC admission, and their higher negative affect on the first GCRC admission compared with the second reflected this initial concern. Prior work with the blister-chamber model showed that even modest levels of stress prior to wounding were reflected in lower production of proinflammatory cytokines at the wound site.[21] Thus, the fact that the social support interaction always occurred at the first GCRC admission and yet wound healing and local IL-6, TNF-α, and IL-1β production were all poorer following conflict suggests that the effects of the disagreement were larger than our data suggest.

Furthermore, couples' fights at home are more negative and last longer than those studied in the laboratory.[37] Unhappy couples are less likely to volunteer for marital research than those who are more satisfied with

their spouse.[38] Accordingly, the present data are likely to underestimate the health impact of marital strife.

Limitations of the study include the relatively small sample of couples and the number of analyses conducted on the data. Although our hypotheses were largely supported, women did not show greater physiological responsiveness to conflict than men. Moreover, even though the pattern for high- vs low-hostile participants was generally consistent, high-hostile individuals did produce more TNF-α at the wound sites during the conflict admission than during the social support admission, while low-hostile individuals showed a sharper increase in plasma TNF-α levels during the social support admission than high-hostile individuals.

Compared with the low-hostile behavior group, high-hostile participants had fewer positive behaviors, lower marital satisfaction, and reported more negative affect after interacting with their spouse. If abrasive relationships provoke larger and more frequent adverse immunological changes, then individuals in troubled relationships could be at greater risk for a variety of health problems over time. Distressed families experience roughly twice as many tensions per day as nondistressed families.[61,62] There is also greater spillover of conflict from one topic to another and greater "contagion" between marital and child-related tensions among unhappy couples than those who are more satisfied.[62] Moreover, distressed couples are more likely to have continuing conflicts that recur in well-established patterns at the same time on subsequent days.[62]

Accordingly, these data provide a window on the pathways through which close personal relationships may affect physiological functioning and health. If chronically hostile or abrasive relationships produce more frequent and more pronounced proinflammatory cytokine changes, then individuals in troubled relationships could be at greater risk over time.

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