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Loneliness predicts pain, depression, and fatigue: Understanding the role of immune dysregulation

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Summary
Objective: The pain, depression, and fatigue symptom cluster is an important health concern. Loneliness is a common risk factor for these symptoms. Little is known about the physiological mechanisms linking loneliness to the symptom cluster; immune dysregulation is a promising candidate. Latent herpesvirus reactivation, which is reflected by elevated herpesvirus antibody titers, provides a window into immune dysregulation. Cytomegalovirus (CMV) and Epstein—Barr virus (EBV) are two common herpesviruses.
Methods: Participants were 200 breast cancer survivors who were 2 months to 3 years post-treatment at the time of the study. They completed questionnaires and provided a blood sample that was assayed for CMV and EBV antibody titers.
Results: Lonelier participants experienced more pain, depression, and fatigue than those who felt more socially connected. Lonelier participants also had higher CMV antibody titers which, in turn, were associated with higher levels of the pain, depression, and fatigue symptom cluster. Contrary to expectations, EBV antibody titers were not associated with either loneliness or the symptom cluster.
Conclusions: The pain, depression, and fatigue symptom cluster is a notable clinical problem, especially among cancer survivors. Accordingly, understanding the risk factors for these symptoms is important. The current study suggests that loneliness enhances risk for immune dysregulation and the pain, depression, and fatigue symptom cluster. The present data also provide a glimpse into the pathways through which loneliness may impact health.

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Pain, depression, and fatigue function as a symptom cluster within an array of populations, such as multiple sclerosis patients, cancer survivors, and community dwelling adults (Walker et al., 1993; Bower et al., 2000; Nicassio et al., 2002; Bair et al., 2003; Ohayon and Schatzberg, 2003; Reyes-Gibby et al., 2003; Fleishman, 2004; Motl and McAuley, 2009, 2010; Thornton et al., 2010; Laird et al., 2011). For example, cancer survivors were 2—4 times more likely to simultaneously experience pain, depression, and fatigue than the probability of simultaneously experiencing these symptoms by chance alone (Laird et al., 2011). Loneliness, a socially painful state of perceived social isolation, may be a common risk factor for pain, depression, and fatigue. For example, people who felt socially disconnected were able to tolerate less physical pain than those who felt more socially connected, suggesting that feeling unconnected to those around you may increase pain sensitivity (Oishi et al., 2012). In addition, lonelier people became more depressed and fatigued over time than people who felt more socially connected (Cacioppo et al., 2010; Hawkley et al., 2010a).

Little is known about the physiological mechanisms linking loneliness to the pain, depression, and fatigue symptom cluster. Immune dysregulation is one promising candidate; growing evidence suggests loneliness and immune dysregulation are closely related. For example, lonelier medical students and lonelier psychiatric inpatients had lower natural killer cell activity, an important anti-tumor and anti-viral defense, than those who felt more socially connected (Kiecolt-Glaser et al., 1984a,b). People who were lonelier had smaller antibody responses to an influenza virus vaccine than those who were less lonely, reflecting a poorer vaccine-related immune response (Pressman et al., 2005). Compared with people who felt more socially connected, lonelier people had higher monocyte chemotactic protein-1 (MCP-1; Hackett et al., 2012), a cytokine implicated in inflammatory diseases such as rheumatoid arthritis and atherosclerosis (Deshmane et al., 2009). Interleukin-6 (IL-6), a proinflammatory cytokine that is linked to increased risk for age-related diseases (Ershler and Keller, 2000), was higher after acute stress among those experiencing greater loneliness compared with those who were less lonely (Jaremka et al., in press; Hackett et al., 2012). In addition, proinflammatory genes were over-expressed and anti-inflammatory genes were under-expressed in lonelier individuals compared with less lonely individuals (Cole et al., 2007). Lonelier medical students had higher Epstein—Barr virus (EBV) antibody titers than medical students who felt more socially connected (Glaser et al., 1985a). Similarly, lonelier HIV-infected men had higher human herpesvirus 6 (HHV-6) antibody titers than those who were less lonely (Dixon et al., 2006). Because elevated herpesvirus antibody titers reflect poor cellular immune system control over the latent virus, the EBV and HHV-6 data suggest that lonely people may have dysregulated cellular immunity.

Immune dysregulation has also been associated with each of the symptoms in the cluster: pain, depression, and fatigue (Marchand et al., 2005; Collado-Hidalgo et al., 2006; Dowlati et al., 2010). The experience of pain is partially mediated by elevated inflammation (Marchand et al., 2005). Compared to people with fewer depressive symptoms, those with more depressive symptoms had higher cytomegalovirus (CMV) antibody titers and more persistent inflammation following an influenza virus vaccine (Glaser et al., 2003; Phillips et al., 2008). Elevated CMV antibody titers were also associated with greater fatigue (Fagundes et al., 2012). Because pain, depression, and fatigue behave as a symptom cluster, it is useful to investigate their immunological correlates simultaneously.

Latent herpesvirus reactivation provides a window into immune dysregulation and may be one common immunological correlate of loneliness and the symptom cluster. Herpesviruses are ubiquitous; around 95% of adults are infected with EBV (Fagundes et al., 2012; WHO, 2012) and 60% of adults are infected with CMV (Staras et al., 2006). After the initial infection, herpesviruses create life-long, latent infections. When the cellular immune system is compromised, the virus may reactivate and replicate in latently infected cells, which is reflected by elevated herpesvirus antibody titers. Accordingly, higher antibody titers are thought to reflect poorer cellular immune system control over viral latency (Glaser and Jones, 1994).

1. Overview of current research

The goal of the current research was to examine the links among loneliness, latent herpesvirus reactivation (which reflects immune dysregulation), and the full pain, depression, and fatigue symptom cluster. We assessed antibody titers to two common herpesviruses, EBV and CMV (Staras et al., 2006; Fagundes et al., 2012; WHO, 2012). We hypothesized that, compared to those who felt more socially connected, lonelier people would have higher EBV and CMV antibody titers and greater pain, depression, and fatigue.

Cancer survivors are more at risk for developing pain, depression, and fatigue than people without a history of cancer (Bower et al., 2000; Reyes-Gibby et al., 2006). Accordingly, our sample of breast cancer survivors provided an opportune way to understand the factors that promote the symptom cluster among a particularly vulnerable group.

2. Methods

2.1. Participants

Participants were female stage 0—IIIA breast cancer survivors (N = 200) from the baseline pre-randomization sample of an ongoing clinical trial addressing the use of yoga for cancer-related fatigue. Survivors were recruited through cancer clinics and media announcements if they had completed cancer treatment (except for selective estrogen receptor modulators/aromatase inhibitors) between 2 months and 3 years prior to enrollment in the study. Individuals were ineligible if they engaged in over 5 h of vigorous physical activity per week, or if they had a BMI over 44, symptomatic ischemic heart disease, uncontrolled hypertension, liver or kidney failure, or a prior history of cancer (except basal or squamous cell). The average age of women in our sample was 51.58 (SD = 9.24, range 27—76) and the majority of women were White (89%). Herpesvirus data were available for 161 women; of these participants, 156 (97%) were EBV seropositive and 84 (52%) were CMV seropositive, which is consistent with prior data (Staras et al., 2006; Fagundes et al., 2012; WHO, 2012). Additional sample characteristics are listed in