Stress Reduction as a Means to Enhance Oral Immunity in HIV-Infected Individuals

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The primary diseases that currently plague the industrialized world are those resulting from cumulative damage over many years, such as cerebrovascular diseases, heart disease, and cancer. These diseases would have been unrecognizable to past generations of Americans, who dealt with acute conditions related primarily to infectious diseases and malnutrition. Diseases of the late 20th and early 21st century are brought on by decades of wear-and-tear, poor lifestyle choices, and a condition commonly referred to as "stress." In fact, the programmed physiological response to our everyday stressors, the stress response, has allowed animals to survive extreme and dangerous acute conditions. However, overwhelming evidence during the past few decades indicates that chronic activation of this biological stress response to nonlife-threatening situations such as traffic jams and work pressures affects physiological systems like immunity and is believed to cause or exacerbate many contemporary physical and psychological ailments. The study of the relationship among the neural, endocrine, and immune systems, called *psychoneuroimmunology*, is an important piece in understanding and treating the effects of stress (Ader & Cohen, 1993; Solomon, 1969). Understanding this relationship is especially relevant for the immunocompromised population infected with HIV. Stress-related conditions are prominent clinical problems in HIV-infected individuals and are associated with acute as well as chronic conditions. It seems that stress can have a detrimental effect on oral as well as general health. Oral immunity and health becomes an important area of study with regard to the HIV-infected population, because these individuals are disproportionately affected with opportunistic oral and esophageal infections.

Psychoneuroimmunology Theory

Psychoneuroimmunology theory proposes that the reduction of perceived stress (rather than reduction of the stressors themselves) and increased immunity are interrelated. This proposition is based on extensive evidence that there are multidirectional communication pathways among the neural, endocrine, and immune systems. For example, immune cells have receptors that are specific to catecholamines released during sympathetic nervous system (SNS) activation and other receptors that are specific to corticosteroids (primarily cortisol) released by the limbic-hypotha-

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lamic-pituitary-adrenal axis (LHPA) (Borboni et al., 1989; De Souza, Webster, Grigoriadis, & Tracey, 1989). These two pathways, the SNS and LHPA axes, are the primary drivers for the stress response and have a profound inhibitory effect on immune function. Activation of these pathways coincides with reduced proliferation of lymphocytes during administration of immunostimulatory phytohemagglutinen and concanavalin-A, reduced natural killer cell number and activity, reduced number and percentage of circulating B and T lymphocytes, and reduced levels of a number of immunoglobulins.

A number of studies support that there is negative impact of personal and environmental stressors on general health and immune function in HIV-infected individuals (Hillhouse & Adler, 1991; Maier, Watkins, & Fleshner, 1994; O'Leary, 1990). Personal stressors that are typically identified include the HIV infection itself, commonly identified markers of the disease including CD4+ cell count and HIV-RNA viral load, and stage of HIV disease with associated symptoms. In addition to these personal stressors, there are environmental stressors that impact the HIV-infected individual that usually are identified as an increased number of hassles of daily living and social issues associated with HIV infection. These interactions hold importance for the HIV-infected individual dealing with opportunistic oral infections and other oral diseases. Theoretically, a reduction in stress should enhance oral immune function and reduce stress-related oral symptoms of HIV infection. Based on this general psychoneuroimmunology model, the authors of this report and other investigators have hypothesized that various types of stress reduction techniques will reduce the chronic activation of the stress response, reduce the stress-induced progression of HIV-associated oral immunosuppression, and reduce common oral manifestations of compromised immune function in HIV-positive individuals.

Oral Disease Associated With HIV Infection

Several oral conditions are associated with disease state and are used in staging systems for the diagnosis of progression of HIV infection. Further, oral conditions are often used as inclusion criteria and therapeutic endpoints in clinical trials of antiretroviral drug efficacy. These conditions are categorized as (a) oral fungal infections including oropharyngeal candidiasis (OPC), the most common infection of the mouth, (b) bacterial infections such as necrotizing ulcerative gingivitis and necrotizing ulcerative peridontitis (HIV peridontitis), (c) oral viral infections such as *Herpes simplex* and Epstein-Barr viruses, and (d) oral malignancies such as Kaposi's sarcoma.

OPC is the most common oral manifestation of HIV infection, a significant indicator of CD4+ numbers, a marker for seroconversion illness, and a first clinical sign of immunosuppression during the progression of HIV to AIDS (Langlais & Miller, 1998; Reichert, Gelderblow, Becker, & Kuntz, 1987). A number of oral conditions suggest HIV infection in nondiagnosed subjects. These conditions include OPC, hairy leukoplakia, Kaposi's sarcoma, and ulcerative gingivitis.

Oral viral infection figures prominently in acute and chronic oral disease with AIDS. *Herpes simplex* virus infections usually appear on the lips as herpes labialis or in the mouth on keratinized epithelium. Unlike patients with normal immune function, HIV-infected individuals may have herpetic lesions on mucosal surfaces such as the tongue (Langlais & Miller, 1998; Reichert et al., 1987). Recurrent viral infections are more frequent, more persistent, and more severe with HIV immunosuppression. Hairy leukoplakia on the lateral tongue, specific to HIV-infected people, is associated with Epstein-Barr virus and immunosuppression (Langlais & Miller; Reichert et al.).

Lastly, Kaposi's sarcoma is the most common cancer associated with HIV infection, presenting as painful tumors usually found on the hard palate (Langlais & Miller, 1998; Reichert et al., 1987).

Although immune suppression is associated with each of these HIV-related oral conditions, altered oral immunity can be divided into changes in the specific immune system (activation of lymphocytes in response to contact with particular antigens) or innate immune system (general protective mechanisms). The physiological mechanisms are quite different for these two immune systems, but both can be suppressed by HIV infection. These impairments of immunity at the oral mucosa can contribute to susceptibility to opportunistic infectious processes. A number of studies have reported significant changes

to specific immunity as it affects oral surfaces. HIV infection commonly alters oral epithelial cell function and can impair mucosal CD4+ T-cell activity. A result of this impairment is a reduced cytokine secretion during infection. For example, one of the best described HIV-associated changes in oral immunity is a decrease in salivary immunoglobulin A (IgA) levels (Muller, Froland, Hvatum, Radl, & Brandtzaeg, 1991). Although most studies report a reduction in salivary IgA levels in HIV-infected individuals, IgA levels rise in serum samples—a seeming dichotomy that has yet to be explained.

Reductions in innate oral immunity seem to result primarily from reductions in saliva secretion (Challacombe & Sweet, 2002). Reduced fluid-producing salivary gland function is a common pathology associated with HIV infection and is reported in 6% to 10% of HIV-infected individuals in the United States. Further, mouth dryness because of reduced saliva production (xerostomia) is a common clinical complaint of HIV infection. Because salivary secretion is the vehicle for many nonspecific immune factors, reduced saliva production may explain the reported net reductions in many of the innate factors that protect the oral mucosal surfaces. Xerostomia often results from a salivary gland disease seen only with HIV infection identified as diffuse infiltrative lymphocytosis syndrome. This syndrome is characterized by parotid gland enlargement, CD8 lymphocytosis, and lymphocytic interstitial pneumonitis. Diffuse infiltrative lymphocytosis syndrome is most prevalent in the United States among HIV-infected African American men, a population that generally has a high level of emotional stress.

Stress as a Mediator of Disease Symptomatology

The oral immunosuppression observed in HIV-infected individuals is representative of a general deteriorating host immunity. One likely mechanism for the decreased immune function is a stress-induced increase in the activity of the LHPA axis. This enhanced activity results in increased serum cortisol levels. A number of studies indicate that stress-induced neuroendocrine activation facilitates the switch from Th1 cytokine production to Th2 cytokine production, which is an important step in the pathogenesis of HIV disease. Therefore, stress through activation of the LHPA axis, and activation of the SNS, may increase viral replication and lead to HIV disease progression. The overall effect of these changes is a reduction in the robustness of immune system communication and a decrease in the number and activity level of immune cells.

The stress-induced inhibition of immune reactivity to viral challenge has been reported in animal and human studies (Mcewen et al., 1997). Normally, infection with an active influenza strain or inactive virus will elicit an immune response as measured by levels of antibodies found in the blood or secreted fluids. However, stress-induced increases in cortisol can suppress the immune system response to viral challenge. For example, Glaser, Pearl, KiecoltGlaser, and Malarkey, (1994) showed that administration of the hepatitis B vaccine produces a greater antibody production in medical students who perceive a better social support network and less overall stress. In addition to a stress-induced decrease in the immune response to viral challenge, the reduced immune function manifests itself in a reduced capacity to inhibit reactivation of latent viruses during times of stress. A common example is the recurrence of fever blisters and other outbreaks in individuals dealing with stressful situations (Jemmott & Magloire, 1988). Several studies examining the effects of stress on medical students indicate an increased outbreak of herpes and high levels of antibody to Epstein-Barr virus during examination periods (Malarkey, Pearl, Demers, KiecoltGlaser, & Glaser, 1995; Glaser et al., 1994). These same responses to stress have been observed in men going through divorce proceedings. Specific to stress-related immune responses in the mouth, several studies have demonstrated a pronounced immunosuppressive effect with corticosteroid administration. Steroid therapy has been shown repeatedly to predispose individuals to OPC and high oral yeast levels (Schechtman, Archard, & Cox, 1986; Odds & Webster, 1988).

HIV infection is associated with psychological and social stresses. Changes in medical status or personal and work relationships can trigger psychological distress. Psychosocial factors such as life stressors, social support, and coping styles have been associated with reduced immune system measures, increased physical symptoms, and accelerated HIV disease progression to AIDS (Leserman, 2000). For

example, Leserman et al. (2000) and Evans et al. (1997) demonstrated that stressful life events for HIV-infected individuals are associated with greater reductions in killer lymphocytes and faster progression to AIDS. Further, a longitudinal cohort study found that low CD4+ cell counts were related to high self-reported life stressors and poor coping styles (Goodkin, Blaney, & Feaster, 1993). In a study of HIV-infected men (Caumartin, Joseph, & Gillespie, 1993), a longer survival time was associated with greater social participation. It has been hypothesized that elevated cortisol levels mediate the effects of stress on the immune system and hasten disease progression. Membrenon, Irony, & Dere (1987) showed an increased basal cortisol level in individuals hospitalized with HIV compared with non-HIV patients. Recently, it has been demonstrated that cortisol works in synergy with gp120 (a membrane protein that allows binding of the virus with CD4+ lymphocytes) and leads to apoptosis of CD4+ lymphocytes, thus contributing to the immunosuppression associated with HIV infection (Nair, Mahajan, Hou, Sweet, & Schwartz, 2000).

Although not studied extensively, there is some information available concerning the effect of stress and mood on saliva secretion and oral dryness. It has been estimated that 29% of HIV-infected individuals receiving medical care in the United States have reported subjective oral dryness (Younai et al., 2001). As discussed earlier, salivary secretion plays a significant role in oral mucosa immunity. Experiencing a stressful life change or taking prescribed medications that mimic SNS activation significantly reduces salivary flow and increases subjective oral dryness (Bergdahl, Bergdahl, & Johansson, 1997; Locker, 1993). In addition, studies suggest that xerostomia resulting from prescribed medications may result in part from psychological factors (Locker, 1993). It seems that affect such as depression or anxiety can also reduce salivary flow and increase subjective oral dryness (Bergdahl et al., 1997; Mathew, Weinman, & Claghorn, 1979). One study examining oral dryness in clinically depressed individuals showed an increase in saliva production following electroconvulsive therapy (Bolwig, 1972). So it is fairly clear that stress and affect can play a significant role in saliva production and subjective oral dryness and in the resultant reduction in immune function.

Stress Management and Immune Function

Whereas it seems that the industrialized world is destined biologically to suffer from stress and its associated problems, there is good news in that we have the capacity to control our responses to stress. Remember, it is the perceived stress rather than the stressor itself that controls our physiological stress response. It is generally accepted that managing stress levels is an important aspect in the treatment of HIV. A number of studies have shown beneficial physiological and psychological effects of stress management therapy in HIV disease (Auberbach, Oleson, & Soloman, 1992; Eller, 1999b; LaPerriere et al., 1990). Stress management has been shown to decrease HIV-related symptoms, increase vigor and hardiness, and increase CD4+ cell number (Auberbach et al., 1992; Eller, 1999a; Eller, 1999b). Antoni et al. (2002) have shown repeatedly the effectiveness of cognitive behavioral stress management techniques in improving outcomes in HIV-infected individuals (Ironson et al., 1990; LaPerriere et al.; Antoni et al.). For example, these investigators showed reduced self-reported depressed affect and anxiety in conjunction with reduced salivary and urinary cortisol and increases in natural killer cell and CD4+ cell number. Further, the reduction in salivary cortisol correlated with the number of relaxation sessions during the study.

A stress reduction technique that is growing in popularity and is of interest to the authors is acupuncture. A number of studies indicate that acupuncture can enhance immune function or reduce the immunosuppression associated with trauma, stress, and infection. Recent studies of acupuncture in asthma patients showed increased levels of CD3+/CD4+ cells, decreased interleukin 6 and interleukin 10, increased in vitro lymphocyte proliferation rate, and enhanced immunoglobulin levels, compared with controls (Joos, Schott, Zou, Daniel, & Martin, 2000). Berman and Lundberg (2002) showed that a 9-month regimen of acupuncture reduced plasma cortisol levels in prison psychiatric patients. In addition, the patients reported increased perceived auton-

omy, improved inner harmony, and increased calmness.

A number of studies suggest that acupuncture can regulate oral immunological functions and relieve oral symptoms that are common with HIV infection. Blom et al. (1992) reported that 12 weeks of acupuncture on subjects with severe xerostomia increased salivary flow rates as compared with controls. Further, acupuncture has been shown to enhance salivary and gingival fluid immunoglobulin levels in healthy individuals (Yang, Ng, Zeng, & Kwok, 1989), and reduce salivary IgA in patients with allergic asthma (Yang, Chen, Zhao, & Wang, 1995). These studies are supported by results from the authors' laboratory that indicate a regimen of stress-reduction acupuncture in HIV-infected individuals reduces perceived stress levels, increases salivary IgA levels, reduces salivary cortisol levels, and reduces the number and size of HIV-related fungal and bacterial mouth infections.

In summary, it is well established that personal and environmental stressors can take a serious toll on the health of HIV-infected individuals. When added to the immunosuppression associated with infection, chronic biological stress responses not only affect general health but also predispose the infected individual to opportunistic infections of the mouth and pharynx at a rate much greater than in the general population. It stands to reason that stress management techniques for the HIV-infected population would reduce the high incidence of oral morbidity that causes so much discomfort and exacerbates serious disease conditions. Whether through Westernized or traditional Eastern techniques, it is important for professional caregivers involved with the HIV-infected population to promote stress management as a component of a holistic health care approach.

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