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The psychobiological links between chronic stress-related diseases, periodontal/peri-implant diseases, and wound healing

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1 | INTRODUCTION

The first observation of the relationship between stress and oral disease was reported in the 1970s, when mucous membrane lesions from viruses (ie, Coxsackie, Rhinovirus) developed more rapidly and severely under conditions of psychosocial stress. Since these observations, there has been a steadily increased effort to understand the molecular mechanisms involved between psychosocial stress and oral inflammatory diseases such as periodontal/peri-implant diseases and wound healing. Several recent systematic reviews of the current literature have pointed to an increasing platform linking chronic psychosocial stress/disorders with diseases of the periodontium/periosteum[1-3] attributable to dynamics in the immune system, oral microbiome shifts/biofilm formation, enzymatic-mediated protein/collagen turnover ratios, and local/systemic disease progression.[4] Towards this end, there are three possible interactions between the periodontium/periosteum and stress: stress → periodontium/periosteum, periodontium/periosteum ← stress, and stress ↔ periodontium/periosteum.[5] These three interactions will be explored throughout this paper to assess the psychobiologic links between chronic stress-related diseases and periodontal/peri-implant diseases.

2 | PERIODONTAL AND PERI-IMPLANT TISSUES

The gingival tissues and peri-implant mucosa that surround natural teeth and dental implants share many common soft tissue characteristics. Namely, tissue phenotype/thickness, presence of keratinized tissue/mucosa, and bony coverage on the buccal surface are all local factors involved in maintaining a healthy homeostatic and stable situation.[6,7] However, fundamental differences between periodontal and peri-implant tissues lie in the connection of the tooth and/or implant to the alveolus. To this end, natural teeth are suspended in the socket and connected to the alveolar bone in a perpendicular orientation by the periodontal ligament, whereas an endosseous implant is directly connected to the bone through osseointegration.[8]

In the case of disease onset in situations of periodontitis and peri-implantitis, bacterial aggregation in contact with gingival and peri-implant mucosa leads to inflammation and increased probing depth.[9] In both clinical situations, pathology progresses in an apical direction that invades the alveolar bone compartment and subsequently manifests clinically as intraosseous or furcation pockets/defects.[10,11] Histologic evaluations of biopsies from periodontal disease lesions reveal dysbiotic microbiotas with higher numbers of motile organisms and less coccoid/straight rod cells in established gingivitis and advanced periodontal disease samples compared with healthy gingiva controls.[12] From an immunologic perspective, cellular infiltrate of established gingivitis and advanced disease showed increased quantities of plasma cells and a relative decrease in fibroblasts and lymphocytes compared with healthy controls.[12]

Furthermore, like inflammatory lesions in periodontitis, peri-implantitis also progresses apically, invading the alveolar bone compartment and causing intraosseous pockets.[10] However, important nuances have been reported in human biopsy material indicating that the apical extension of inflammatory cell infiltrate

is more pronounced in peri-implantitis compared with periodontitis.[11] In experimental studies, differences between the disease progression of periodontitis and peri-implantitis were also noted. Following ligature removal, a "self-limiting" process may occur in gingival tissues surrounding teeth caused by a reactive connective tissue capsule formation that separated the inflammatory infiltrate from bone, while in peri-implant tissues histologic sections showed significant inflammatory infiltrate extending all the way to the bone crest.[11] Also, histologic data collected from failing implants in humans showed large areas of connective tissue (~64%) containing inflammatory infiltrate consisting of plasma cells, lymphocytes, and leukocytes.[13]

The core principles of periodontal/peri-implant therapeutics remain centered on controlling the microbial challenge and host factors that contribute to microbial dysbiosis, exacerbated inflammatory infiltrate, and subsequent tissue destruction.[14] Some patients present on a more aggressive disease path that does not necessarily correlate with the typical tenets discussed above, suggesting that other contributing factors are present.[15] Recent evidence highlights that diseases related to the periodontium are a positively reinforced and self-sustained loop of inflammation and microbial dysbiosis that drive tissue destruction and disease progression.[16] This loop is further perpetuated and reinforced by systemic contributing/risk factors.[17]

Systemic risk factors for periodontal disease include poorly controlled diabetes, tobacco smoking, and immunodeficiency states such as neutropenia and AIDS/HIV infection, with significant longitudinal evidence of effects on disease progression.[18] However, compounding evidence suggests that there are additional contributing systemic factors in periodontal/peri-implant disease progression and response to therapeutic strategies, including psychologic stress.[18] Psychobiologic connections between stress and systemic health/immunologic dysregulation/microbial dysbiosis are emerging as more evidence is presented. To achieve control of disease progression in aggressively progressing cases, timely assessment of both host- and microbe-centric perspectives must be incorporated to achieve long-term clinical success for these patients.

3 | STRESS AND THE BODY'S BIOLOGIC RESPONSE

Notably, the physiologic stress response is an evolutionarily conserved biologic mechanism that connects an organism to the surrounding environment. Stressor cues can take on both physical and/or psychologic forms in modern times. Physical cues that activate stress include associations with trauma, infection, or tumor. Psychologic or emotional cues include life events, such as financial deficits, caregiving, or the loss of a spouse; or ongoing disorders such as post-traumatic stress disorder or depression. For example, psychologic or emotional stress might interfere with normal immune function and increase certain levels of hormones that could affect the periodontium or peri-implant surrounding tissues. The effects of these factors can be significantly exacerbated to the point of disease presentation in the context of poor coping strategies.

Stimulus duration is also an important consideration when assessing clinical downstream effects (Figure 1). Acute stressors (infection, surgical procedure) often present with upregulation of innate immune mechanisms but suppression of cellular immunity.[19] Conversely, chronic stress often presents with suppression of both the cellular and innate immune responses.[20,21] The notable paradigm in this field suggests that stressors with the temporal parameters of the acute fight-or-flight situations in their evolutionary roots elicit beneficial changes allowing the body to recover from injury quickly if necessary.[19] For example, following acute trauma experienced in periodontal/peri-implant surgery, the innate surveillance mechanism is heightened to promote clearance of debris and facilitate resolution and healing of wounds. On the other hand, the more these stressors deviate from these biologically preserved parameters (ie, chronic stress), the more the immune system is detrimentally affected.[19] For example, during periodontal/peri-implant surgery under conditions of chronic stress, there might be a decreased debris clearance response with sustained low-grade inflammation that delays wound healing and creates a less favorable regenerative milieu.

The exact point at which stressors move from acute to chronic in nature is currently an intense area of research.[22] However, the guiding mechanisms that create these systemic alterations include the hypothalamic-pituitary-adrenal axis that generates glucocorticoids and the adrenergic nerve signaling axis that generates norepinephrine, adenosine triphosphate, and neuropeptide Y. A myriad of other chemicals are released within the stress response cascade of both the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, but an in-depth discussion of these additional chemokines is beyond the scope of this paper.

3.1 | Glucocorticoids

The effects of hypothalamic-pituitary-adrenal axis glucocorticoids act in catabolic, lipogenic, anti-reproductive, and immunosuppressive circuits resulting in mobilization of energy stores, mild chronic inflammation, intra-abdominal accumulation of visceral fat, increased sodium retention, hypertension, insulin resistance, and an inability to fight bacterial infection.[23-26] Periodontal tissues specifically have glucocorticoid receptors that respond to the chronic release of hypothalamic-pituitary-adrenal axis glucocorticoids. In addition, keratinocytes are unique mediators of the stress cycle and also create an autocrine stress milieu, producing cortisol and neurotrophins.[27] Both systemic and local balance of glucocorticoid levels are needed to achieve soft tissue homeostasis. These excess glucocorticoid levels reduce keratinocyte expression of the growth factors and cytokines necessary for re-epithelialization following injury, delaying wound healing. This may result in poor clinical outcomes caused by open wounds, infection, and abscess formation, which often lead to compromised healing events. In

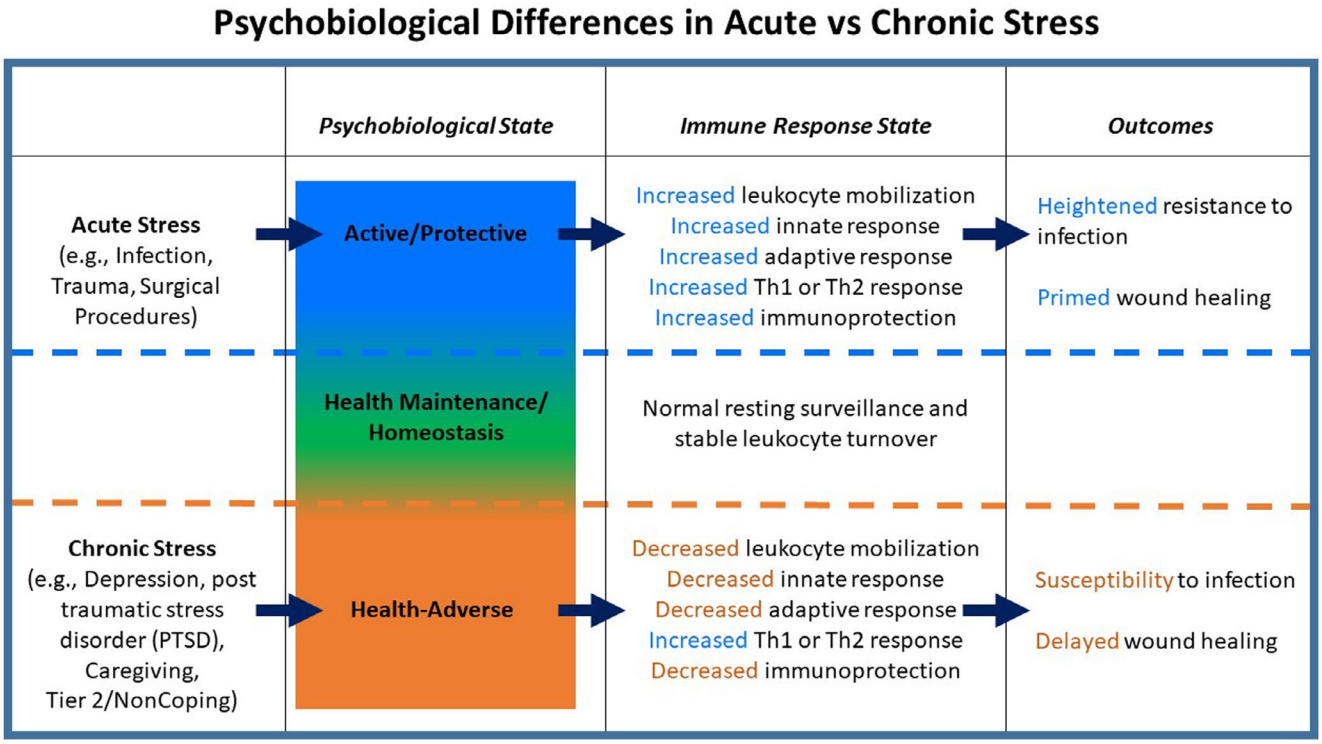

FIGURE 1 Psychobiologic differences in acute vs chronic stress. Acute stressors (infection, trauma, and surgical procedure) frequently present with upregulation of innate immune mechanisms but suppression of cellular immunity. This bodily response is evolutionarily preserved to allow quick recovery if necessary in dire situations. Conversely, chronic stress (depression, post-traumatic stress disorder [PTSD], and caregiving responsibilities) is a phenomenon that has less evolutionary bearing and often presents with suppression of both the cellular and innate immune responses. Th1, type 1 T helper; Th2, type 2 T helper

addition, these excess glucocorticoid levels also lead to anti-inflammatory actions that render the periodontal area susceptible to infection.[28]

Importantly, most of the individuals experiencing stress-related adrenal insufficiency may still receive routine dental care or minor surgical procedures, including periodontal surgery, without needing to have supplemental glucocorticoids unless previously diagnosed with primary adrenal insufficiency.[29] If patients have been previously diagnosed with primary adrenal insufficiency, discussion regarding a "stress dose" (an administration of increased hydrocortisone coverage during major stress events to avoid a life-threatening adrenal crisis) is necessary with the patient's endocrinologist for any surgical interventions.[30]

3.2 | Norepinephrine

The effects of the adrenergic nerve signaling cascade molecules norepinephrine, adenosine triphosphate, and neuropeptide Y directly affect the vasculature of postsynaptic smooth muscles. Vascular tension affects many pertinent organ systems in the periodontium. Vascular flow decreases to connective tissue plexuses limiting cellular and nutrient diffusion through adventitia or collagenous fibrils, causing poor adaptive immune responses and restricting repair reactions in periodontal and periosteal (bone) tissues.[31-33] Adrenergic nerve fiber synaptic effects also limit vascular perfusion at primary/secondary lymphoid tissues, resulting in host-wide immunodysregulation.[31,34] Immunodysregulation in any form can have system-wide effects, especially those noted in marginal alveolar bone loss and periodontal disease progression.[35,36]

3.3 | Neurologic alterations affecting behavior

In addition to these hard-wired peripheral and central system responses, stress duration can also initiate physically adaptive changes in the form of cognition and behavior (eg, feeding/hunger, vigilance, alertness). In fact, functional imaging studies have shown that morphologic changes in the brain, in particular in the hippocampus, occur with psychosocial stress and related disorders.[37-39] In a postmortem study of chronically depressed patients, distinct patterns in protein expression changes were noted in scaffolding proteins and ion channels within the hippocampal subregions.[40] These data are also in line with other studies that reported epigenetic changes in hippocampal subregions in rodent chronic stress studies.[41,42] Overall, hippocampal morphology changes might play a role in the behavior modifications (ie, lethargy, anxiety, lack of organization/motivation, difficulty in keeping appointments, hygiene practice, and compliance to treatment) seen in situations of chronic stress and depression.

4 | PSYCHOBIOLOGIC EFFECTS ON PERIODONTAL/PERI-IMPLANT STRUCTURES AND THEIR WOUND-HEALING CAPACITY

Both physical and psychologic stimuli can affect a biologic system at an organ system level, cellular level, and molecular level through mechanisms of the hypothalamic-pituitary-adrenal axis, adrenergic nerve signaling axis, and behavior modification (Figure 2). Periodontal structures, including the mucosal tissues/keratinocytes/periodontal extracellular matrix, periosteum/bony tissue, and the microbiologic/periodontal microenvironment, are most susceptible to stress-related dysbiosis. The following sections discuss periodontium/periosteum-specific responses and adaptations under conditions of chronic stress.

4.1 | Mucosal tissues/keratinocytes/extracellular matrix

Stress-related psychobiologic changes in endocrine, autocrine, and paracrine signaling systems affect oral soft tissue kinetics during homeostasis and during wound-healing responses. Increased glucocorticoid production following a punch biopsy was associated with greater perceived stress and delayed dermal healing.[43] Spatial or temporal summation of these psychobiologic effects also interplay, resulting in the delayed healing phenotype. Congruently, catecholamine production (the other major biochemical player within the biologic stress response, as discussed above) in soft tissue can also delay soft tissue wound-healing responses.[44] Hence, caution is needed when performing periodontal/implant surgery in a highly stressed patient or in an individual in a high stress environment, and special considerations and issues include primary wound closure, a longer healing time, antibiotic coverage, minimizing extensive and long surgical procedures, or even postponing the surgery to a time when there is less stress in the patient's life. Without expedient soft tissue closure, injury or infection of these susceptible oral tissues and underlying structures can be persistently problematic, both in the short and long term.

Oral tissues are constantly under a state of general maintenance and assault from homeostatic forces, microbiome changes, or occlusion.[45] Oral soft tissue wound healing follows a well-established trajectory that consists of four categories: (1) hemostasis/inflammation; (2) migration; (3) proliferation; and (4) remodeling.[46] It appears that the psychobiologic effects of stress may affect all stages of wound healing in some capacity.

During the initial, mid, and late phases of wound-healing phases, a variety of stress models report observations in cytokine/immune crosstalk dysregulation, hypoxia, dysregulation of cellular mobility and metabolomic kinetics, and matrix metalloprotease activity.

4.1.1 | Immunologic effects

A human study that evaluated the association of chronic caregiving stress and distribution of T cell phenotypes reported important changes in the relative proportions of T cell subpopulations consistent with immunologic aging.[47] These T cell subpopulations appear to include those involved in periodontal disease progression; however, more research is needed in this area because of the complexity of subpopulation characterization.[48]

4.1.2 | Cytokine alterations

In multiple human blister study model trials, monitoring of local cytokine production showed that increased levels of perceived stress

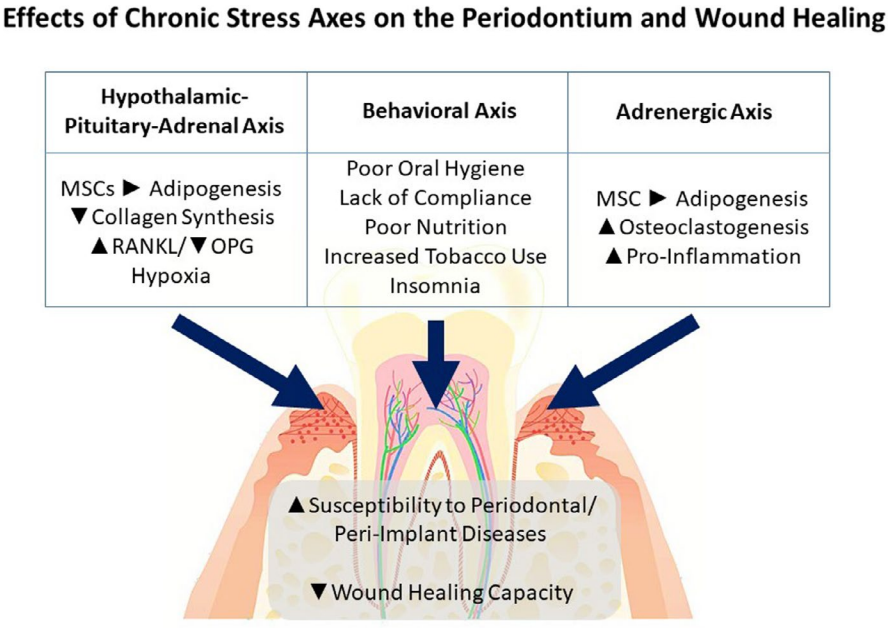

FIGURE 2 The effects of chronic stress axes on the periodontium and wound healing. The three axes involved in chronic stress include the hypothalamic-pituitary-adrenal axis, behavioral axis, and adrenergic axis (neurovascular). Concomitant aberrance to homeostasis via these three mechanisms results in diminished wound-healing capacity and susceptibility to progressive periodontal/peri-implant disease. MSC, Mesenchymal Stem Cell; OPG, osteoprotegerin

were associated with a delay in the initial phase of wound healing with lower interleukin-1-alpha, interleukin-8, interleukin-1-beta, interleukin-6, and tumor necrosis factor-alpha cytokine levels.[49,50] Additionally, exogenous glucocorticoid administration can also transiently depress skin and mucosal cytokine signaling through suppression of interleukin-1-beta, tumor necrosis factor-alpha, and platelet-derived growth factor production.[49] Furthermore, in an animal model of experimental periodontitis that applied chronic stress conditions, the authors reported elevated inflammatory mediators, interleukin-1-beta, and tumor necrosis factor-alpha, and decreased expression of regenerative factors such as basic fibroblast growth factor.[51] These data suggest that in situations of chronic stress, the local periodontal environment appears to be in a pro-inflammatory and anti-regenerative state. Care should be taken to avoid these consequences; it is often recommended to prescribe antibiotics to prevent potential infection.

4.1.3 | Hypoxia

A well-oxygenated environment is essential to maintain homeostasis and achieve regeneration or repair following injury in the periodontal apparatus. Through use of a stress-induced animal model, several studies reported that chronic stress could increase wound hypoxia measured via nitric oxide synthase levels (a common indicator of wound hypoxia).[52-55] Furthermore, some studies also reported reversal of these stress-induced impairments and nitric oxide synthase levels by implementing hyperbaric oxygen therapy.[54]

Mechanisms of hypoxia in chronic stress are currently an intense area of investigation. In a series of studies, osteoblasts exposed to chronic glucocorticoid dosing downregulated hypoxia-inducible factor 1-alpha and vascular endothelial growth factor.[56,57] These hypoxic effects of chronic glucocorticoid exposure could contribute to a local clinical state that is unprepared for periodontal regeneration or repair.

4.1.4 | Cellular migration and proliferation

Chronic stress-associated delays in soft tissue wound repair have also previously been mechanistically ascribed to early/mid-phase wound-healing delays in cellular migration and proliferation.[58-61] Elevated cortisol levels mimicked results with the administration of corticosteroids showing delayed epithelial wound healing via diminished cellular migration and proliferation. Furthermore, inhibition of glucocorticoid synthesis can reverse stress-induced skin abnormalities in healing or barrier function.[58-61] In addition, glucocorticoids inhibit proliferation and suppress essential Wingless-related integration site (Wnt) signaling pathways (a group of signal transduction pathways that begin with proteins that pass signals into a cell through cell surface receptors) in periodontal ligament stem cells, suggesting that their regenerative capacity becomes limited under conditions of chronic stress.[62] These deleterious observations could be further compounded by the addition of concomitant stress-related catecholamine production locally in the periodontal tissues, which express an abundance of adrenergic signaling receptors.[63] Furthermore, catecholamine production in soft tissue impairs initial stages of wound healing through reduction of keratinocyte motility and migration.[44]

4.1.5 | Matrix metalloprotease activity

Mid and later stages of oral wound healing also appear to be affected by the psychobiologic changes induced in conditions of chronic stress by alterations in matrix metalloprotease activity. Matrix metalloproteases are essential enzymatic proteins that break down damaged protein/collagen or turn over existing protein/collagen at a periodontal injury site.[64,65] Specifically, the activity of the collagenases matrix metalloprotease-1 and matrix metalloprotease-13, as well as the gelatinases matrix metalloprotease-2 and matrix metalloprotease-9, appear to be important in wounded oral tissue healing.[66] In human surveys of stress and surgical outcomes, there was a negative correlation between increased stress levels and the amounts of local matrix metalloprotease-9.[64] When hydrocortisone was applied to gingival fibroblasts, increased production of matrix metalloprotease-1, matrix metalloprotease−2, matrix metalloprotease−7, and matrix metalloprotease−11 was noted.[67] This implies that under conditions of chronic stress or increased cortisol concentrations, periodontal destruction might occur at a higher rate.[67]

Interestingly, a negative correlation between plasma cortisol levels and matrix metalloprotease-2 protein levels was reported in human blister wounds.[65] These findings were confirmed in a murine stress model, indicating that stress can also downregulate matrix metalloprotease production at the wound site in both human and murine models.[68]

4.2 | Periosteum/bone homeostasis and hard tissue wound healing

Stress-related psychobiologic changes in endocrine, autocrine, and paracrine signaling systems affect oral bony tissue kinetics during homeostasis and during wound-healing responses. Chronic stress disorders, including post-traumatic stress disorder and depression, and stress-related adrenergic signaling, are associated with poor alveolar bone growth,[69] osteoporosis,[70-73] and short stature if affected as a child.[74,75] The underlying mechanisms for these stress-induced, bone-associated phenotypes include poor maintenance of osteoid competence. Care should be taken to minimize the risk of adverse outcomes in these patients.

Maintenance of bony tissue requires a balance between resorption and formation that is mediated by osteoclastic and osteoblastic mechanics, respectively. Resorptive phases are characterized by higher levels of RANKL, whereas formative phases are characterized by

higher levels of osteoprotegerin. Healing of alveolar bone following periodontal disease, injury, or surgical intervention, including implant placement, requires a shift in the balance of the osteoid cycle towards increased bony lineage commitment and concomitant decreased bone resorptive activity. Interestingly, chronic stress can cause a shift in this ever-important osteoid cycle, affecting osteoid competence through alterations in the balance between additive or resorptive lineage committing cells within the bone.

4.2.1 | Osteoid metabolomics cycle

Accumulating evidence suggests that chronic stress is associated with alterations in skeletal status/fragility.[76,77] However, specific dysregulated bone metabolic mechanisms have recently been investigated. Chronic elevated exposure to glucocorticoids can reduce bone mass altogether by shunting mesenchymal stem cell differentiation from an osteoblastic lineage towards an adipogenic lineage, thereby increasing expression of Wnt signaling inhibitors.[78,79] Furthermore, osteoblasts and osteocytes respond to increased RANKL/osteoprotegerin ratios with higher rates of apoptosis and autophagy.[80,81] Interestingly, one group reported that chronic stress from social isolation in rats did not affect sclerostin expression, a marker of bone formation, but bone resorption markers were significantly altered, showing a decrease in cathepsin K and an increase in C-terminal telopeptide-I.[82] These data suggest that while alterations in bony phenotypes are observed as a result of chronic stress, the complex nature of psychologic and biologic mechanisms involved require more in vivo and in vitro studies to determine pharmaceutical target adjuncts that would be effective in a circumferential way in the local periodontal space.

In an attempt to isolate the effects of the sympathetic arm of chronic stress on alveolar bone metabolic regulation, investigators have also used systemic adrenergic receptor blockers. In an animal ligature model of periodontal disease, an adrenergic signaling blocker, propranolol, was delivered at three different concentrations. At low doses of propranolol, alveolar bone resorption was suppressed through inhibition of RANKL-mediated osteoclastogenesis. In addition, propranolol also reduced osteoclastic activity through depressed tartrate-resistant acid phosphate, cathepsin K, and matrix metalloprotease-9 expression.[83] These data suggest that the destructive effects of chronic stress seen in periodontitis or peri-implant diseases might be targeted through one arm of the chronic stress pathway via administration of sympathetic receptor-blocking pharmaceuticals. However, in discussing the use of sympathetic receptor-blocking pharmaceuticals, it is important to acknowledge that their significant systemic effects require research in coordination with cardiovascular experts to ensure that these drugs are thoroughly tested before moving forward.

4.3 | Microbial-periodontal microenvironment

Research in the field of chronic stress pertaining to the microbial-periodontal interface is limited; however, insights from other studies provide helpful directions for the field of periodontology. Multiple human and animal studies highlight the role of stress in shaping microbial profiles and colonization in favor of microbial dysbiosis, disease, and related immunologic changes.[84] For example, prenatal and postnatal stress impact neonatal microbial colonization.[85,86] Additionally, mice subjected to social-related stressors demonstrate microbial dysbiosis in the gut and a concomitant increase in levels of circulating cytokines.[87] Acute and chronic stress can affect intestinal secretory IgG.[88] Chronic caregiver-related stress in humans has additionally been shown to affect the distribution of T cell phenotypes, changes that are consistent with periodontal disease progression.[47,78] Increased perceived stress levels are also accompanied by delayed initial phase wound healing in humans, with lower interleukin-1-alpha, interleukin-8, interleukin-1-beta, interleukin-6, and tumor necrosis factor-alpha cytokine levels.[50,59] In humans, prolonged stressors result in changes in glucocorticoid physiology that, in turn, interfere with appropriate regulation of inflammation, implicating the role of stress in health and disease.[26]

Furthermore, in the context of periodontitis, chronic stress elevates inflammatory mediators, such as interleukin-1-beta and tumor necrosis factor-alpha, and decreases expression of regenerative factors, including basic fibroblast growth factor.[51] Such data cumulatively suggest that, in situations of chronic stress, the local periodontal environment shifts toward a state of pro-inflammation and anti-regeneration. Importantly, the stress hormone cortisol directly induces shifts in the oral microbiome and its gene expression profiles in vitro, which reproduces results found in the expression profiles of periodontal disease and its progression.[89] These studies and others have important implications for understanding stress-mediated oral dysbiosis, periodontal disease pathogenesis, and related oral immune responses.

Stress additionally has major implications for periodontal disease pathogenesis in the context of increased susceptibility to wound infection and delayed wound healing. For example, increased levels of the opportunistic pathogen *Staphylococcus aureus* were observed in a murine model subjected to stress conditions by two to five logs compared with control conditions, and stressed mice moreover demonstrated bacterial counts predictive of infection (87.5%) compared with controls (27.4%).[90] Furthermore, mice subjected to insomnia or crowding-related stress revealed more severe infection outcomes following intradermal injection of *Streptococcus pyogenes* compared with control conditions.[90] Notably, this effect was mimicked with glucocorticoid administration and reversed with a glucocorticoid receptor antagonist.[91] Infections/inflammation also trigger stress[92]; stress and the immune response have a bidirectional relationship that may include microbial dysbiosis. Chronic stress-associated delays in soft tissue wound repair are mechanistically ascribed to delays in cellular migration and proliferation.[58-61] Furthermore, gingival fibroblasts subjected to hydrocortisone treatment display increased production of tissue-destructive matrix metalloprotease-1, matrix metalloprotease−2, matrix metalloprotease−7, and matrix metalloprotease−11,[67] suggesting that chronic stress or increased

cortisol concentrations may compromise periodontal wound healing by promoting a tissue-destructive phenotype.[67] Stress-related changes in endocrine, autocrine, and paracrine signaling systems also affect oral bone tissue kinetics during homeostatic conditions and during wound-healing responses. Chronic stress disorders, including post-traumatic stress disorder and depression, and stress-related adrenergic signaling, are associated with poor alveolar bone growth[69] and osteoporosis.[70-73] These studies highlight that the underlying mechanisms for these stress-induced, bone-associated phenotypes include poor maintenance of osteoid competence, which may be exacerbated in the context of oral dysbiosis, periodontal disease, and bone healing around dental implants. Although the effects of stress on the oral microbiome and periodontal wound healing have not been specifically identified, such supporting studies suggest a mechanistic relationship.

4.4 | Health-impairing behaviors

In addition to the biochemical effects of stress that can cause behavioral changes, stress can promote the adoption of health-damaging behaviors, such as tobacco smoking or increased alcohol consumption, inadequate sleep quality, poor diet choices, insufficient hygiene practice, or poor compliance with appointments/postoperative treatment suggestions. Tobacco smoking is well known to slow the healing of surgical wounds[93] and increase the risk of tooth loss,[94] as well as increasing the risk of periodontal disease relapse.[95] Heavy alcohol consumption can delay cell migration and collagen deposition during healing [96] and is an established predictor of tooth loss.[97] Furthermore, sleep disruption and lack of sleep were recently reported as significantly associated with severe periodontal disease[98] and have been previously shown to diminish skin barrier recovery.[99]

Inadequate intake of vitamins and minerals through a balanced diet can also impair the wound-healing process[100,101] and this has been shown to specifically impact the health and regenerative capacity of periodontal tissues.[102] Relevant to this knowledge, uncontrollable stress changes eating patterns and consumption of hyper-palatable foods, including the ingestion of highly processed carbohydrates and/or fatty foods.[103] Unhealthy diets (ie, high carbohydrate, processed, fatty foods) are well recognized in promoting states of microbial dysbiosis and are associated with adverse health outcomes, including obesity, high blood pressure, and inflammation.[84,104-107] However, the role of diet on periodontal disease and peri-implantitis pathogenesis remains minimally explored.

Data from animal models suggest that altered diets mediate changes in oral microbial composition and the local immune response.[45,108,109] Consumption of highly processed or fatty foods in the context of stress can further exacerbate changes in the microbiome towards dysbiosis and disease.[84] In mice, chronic stress in combination with diets high in fat and sugar exacerbates changes in intestinal tight junction proteins and is associated with changes in psychologic behaviors and altered inflammatory markers.[110] A direct link between a high-fat diet, the gut microbiota, and behavior has been demonstrated by microbial transfer from high-fat–fed donor mice to antibiotic-mediated–specific pathogen-free, chow-fed mice.[111] Transfer of the high-fat–related donor microbiota led to increased intestinal permeability and inflammatory markers in the antibiotic-mediated–specific pathogen-free, chow-fed recipient mice and was further accompanied by increased anxiety-like behaviors.[111] Interestingly, probiotic treatment in mice was sufficient to prevent the ability of chronic stress to increase intestinal permeability, and to reduce stress-induced sympathetic outflow and hypothalamic-pituitary-adrenal axis activation.[112]

Fecal microbial transplantation approaches further demonstrate the causal role of the stress-induced microbiota in behavioral changes. For example, investigators have shown that microbial transplants from stress-exposed conventional mice to germ-free mice results in exaggerated inflammatory responses to bacterial infection.[113] A link between disease-related microbiota and behavior has also been demonstrated, in which fecal microbiota transplantation from depressed patients to microbiota-depleted rats increased anxiety-like behaviors.[114]

Lastly, chronic stress diseases can also cause behavioral problems such as those associated with poor periodontal treatment compliance and inconsistent periodontal maintenance appointments, which are historically known contributors to disease progression and tooth loss.[115]

4.5 | Coronavirus disease 19 (COVID-19) pandemic, stress, and implications for diseases of the periodontium

During the current COVID-19 pandemic, levels of stress are heightened more than normal.[116-120] In support, nearly every major health organization has postings on dealing with stress.[121] In a Harvard University-University of North Carolina study of US participants, 55% of individuals reported feeling more stress now during the COVID-19 pandemic than before, and higher rates of stress were reported for racial and ethnic subgroups (61.1% for Hispanic individuals).[122] Stress, in and of itself, is not pathognomonic for disease; however, stress can result in aberrant pathophysiology when it is sustained, uncontrollable, and when individuals do not have access to appropriate coping mechanisms. The conditions of the current COVID-19 pandemic foster this type of chronic stress, providing a perfect storm of circumstances that remain beyond an individual's control, with limited access to appropriate coping strategies (eg, social support).

Additionally, the concept of allostasis (or allostatic load), one of the most prominent frameworks in the stress literature, comes to bear. Allostatic load describes the "wear and tear" on the body as a result of chronic stress, and how this contributes to pathology.[123,124] Thus, allostatic load, especially during the current pandemic and crisis, may contribute to the breakdown of oral tissues and thereby promote or exacerbate oral diseases such as periodontal disease.

Pathophysiologic stress from COVID-19 is unique, as it activates multiple arms of the stressor mechanisms (ie, behavioral, adrenergic, and steroid-based signaling), as well as directly affecting the immunologic infection profile of the respiratory and oral tissues relevant to the periodontal space. These synergistic, positive-feedback, stress-mediated signaling mechanisms have known attributed bacterial coinfections and oral presentations, including necrotizing periodontal disease,[125] which appear to be similar to lesions described in patients with COVID-19.[126,127] When considered in the context of work described by Morens et al,[128] increased disease severity and mortality among individuals with respiratory viral infections are often attributed to subsequent bacterial coinfections, accounting for approximately 95% of deaths during the 1918 Spanish flu pandemic.

Community genomic analysis of patients infected with a similar respiratory virus, severe acute respiratory syndrome coronavirus 2, detected extremely elevated counts of *Prevotella intermedia*, in addition to other periodontal pathogenic species including *Streptococci*, *Fusobacterium*, *Treponema*, and *Veillonella*.[129] A case report was recently published in support of the etiology for necrotizing periodontal disease attributable to COVID-19 infection with pathogenic bacterial oral infection.[130] In this case, oral lesions achieved resolution with the following regimen of 400 mg metronidazole taken three times per day for 5 days and 0.12% chlorhexidine mouthwash twice daily for 10 days.[130] Using case reports and the available literature, the authors predict a spontaneous rise in the prevalence of acute periodontal necrotizing periodontal disease as the number of COVID-19 cases increases.[130] As the pandemic timeline lengthens it is rapidly becoming a long-term, largely uncontrollable stressor, further inciting a need for additional studies on the impact of stress on health and disease outcomes.

5 | CLASSIFICATION OF STRESS FOR TREATMENT OF THE PERIODONTAL/IMPLANT PATIENT

Chronic stress and related diseases affect each individual differently because the body innately has a buffered reserve capacity to maintain a homeostatic equilibrium of the circulating hormones/chemokines. As individuals take on stressors in the context of predisposing conditions and poor biologic/psychologic response, these patients may transition to a state of chronicity, maintaining this state in a continued cycle as resolution and recovery are blocked (Figure 3). One of the drawbacks of current chronic stress classifications is the use of diverse and subjective assessment questionnaires without objective evaluation. In the early 2010s, biophysiologic distinctions were established between chronic and non-chronic psychologic diseases.[131] Moving forward, it may be possible to reliably and objectively stratify the chronic stress population further into a two-tiered system.[132-134] A subclassification of chronic stress disease based on neurologic activity, as determined by an electroencephalogram and novel machine learning algorithms, may be necessary to discern the biologic effects of stress on systemic organ systems. This facilitates better understanding of the chronic stress disease process as well as its impact on the periodontium.[132-134] Based on the current body of literature and considering the current accessibility limitations to this neurologic testing, we propose a two-level classification of chronic psychologic stress as it pertains to periodontal/implant therapeutics, namely, low- and high-tiered categories.

5.1 | Tier 1: low levels of chronic stress

A low level of chronic stress may be defined as a patient exhibiting the clinical diagnosis of chronic stress, but one who has established coping

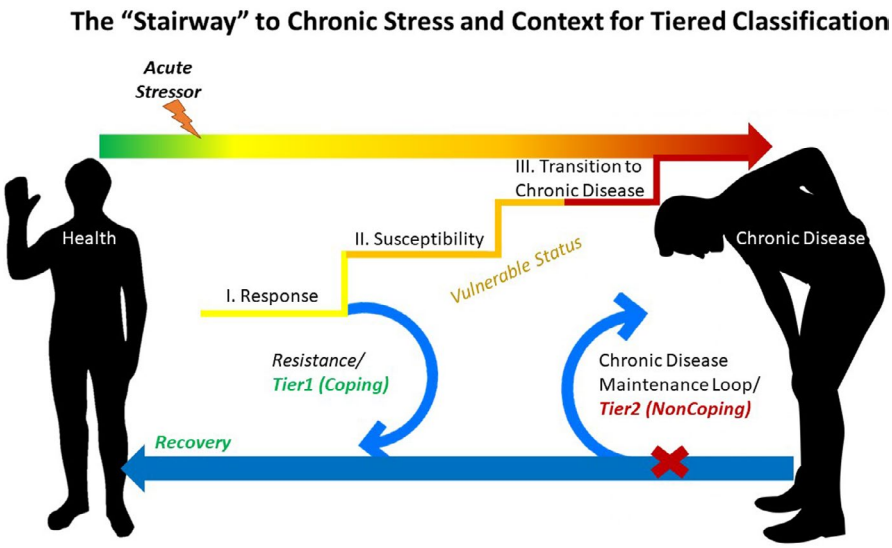

FIGURE 3 The stairway to chronic stress and context for a two-tiered classification. As individuals take on stressors within the context of predisposing conditions and poor biologic/psychologic response, these patients may transition to a state of chronicity. The tier 1 population has excellent coping strategies and positive biologic/psychologic response to stressors with minimal compounding systemic diseases, and large systemic reserve capacity to resolve and restore homeostasis. The tier 2 population falls into a perpetual cycle of relapse and chronic disease with systemic/periodontal complications as resolution and recovery pathways are blocked

mechanisms that minimize the biologic/systemic effects of the disease process. These patients often present with one of the key chronic stress diseases (eg, post-traumatic stress disorder, depression, or psychosis) or life situations (eg, loss of a spouse, caregiver responsibilities, or financial stress), but has identified physical, physiologic, and community-based management strategies that are effective on a daily basis. For these patients, monitoring the availability and consistency of these coping strategies is essential, because over time the needs of the patient, the available time, and access to resources will change. Because periodontal therapy is a lengthy process, continued assessment of these patients is essential and reclassification may be required as their needs change.

5.2 | Tier 2: high levels of chronic stress

A high level of chronic stress may be defined as a patient exhibiting the clinical diagnosis of chronic stress, but one who has not established coping mechanisms. In these patients, the biologic/systemic effects of the disease process (ie, elevated cortisol and adrenergics) are exacerbated. These patients often display one of the key chronic stress diseases (eg, post-traumatic stress disorder, depression, psychosis, chronic pain, or illness) or life situations (eg, loss of a spouse, caregiver responsibilities, or financial stress), but have not identified physical, physiologic, and community-based management strategies that are effective on a daily basis. For these patients, it is essential to use mindful treatment strategies and referral opportunities to provide all-encompassing and effective clinical care.

Regarding the tier 2 population, we must also place additional emphasis on effective coping strategies. Effective stress coping requires the patient to adjust reactionary emotions and maintain a neutral/positive disposition in response to stress-inducing events. Generally, there are many coping strategies that include, but are not limited to, asking others/friends for aid, lowering expectations, engaging in problem solving, seeking a professional counseling service, maintaining a positive attitude, seeking/maintaining emotionally supportive relationships, distancing oneself from the source of stress, and attempting to change the source of stress. Some stress coping may be acute, such as a change in residence or the onset of marital problems. Prolonged stressful environments can lead to elevated levels of stress-related hormones and can cause physical breakdown and illness. Some lifestyle changes can be a helpful overall approach for coping with stressors; these include taking regular exercise,a adequate sleep, quality nutrition, the inclusion of a daily meditation routine, and avoiding enabling substances such as caffeine and alcohol.

6 | TREATMENT STRATEGIES FOR CHRONIC STRESS PERIODONTAL/PERI-IMPLANT PATIENTS

6.1 | Preventative measures

For all patients with chronic stress, prevention strategies are the ideal way with which to treat periodontal/implant-related diseases. Short periodontal maintenance recalls (both periodontal and peri-implant) have been reported as good strategies to maintain good periodontal/implant health over time.[135,136] In addition, oral hygiene instruction with an emphasis on positive behavior modifications (eg, consistently keeping appointments, motivation for complete daily plaque removal). Furthermore, psychosocial factors (eg, anxiety, depression, stress, and well-being) can affect patients' quality of life on the day of periodontal treatment and the pain experience and medications used after surgical and nonsurgical periodontal therapy (4-week period).[137] Patient-provider communication and informed consent should address the role of these factors in the treatment process.[137]

Stress-management suggestions are imperative for patients with high chronic stress, as they may be unable to properly identify or manage it effectively without aid. Importantly, coping strategies might be unique to each individual, but as medical providers we can remind patients to continue searching for stress-management solutions that fit their needs. The effects of yoga/meditation in the management of periodontal disease with reference to stress have been examined.[138] While both groups (with and without yoga) exhibited improved periodontal pocket depths and bleeding scores, the group that utilized this stress-management strategy showed accelerated treatment outcomes by combating stress concomitantly with periodontal therapy.[138] Furthermore, the group that utilized the stress-management strategy of yoga exhibited stress scale scores that were significantly reduced.[138]

In addition to suggestions of stress-management options, providers must also understand that chronic stress can negatively influence decision-making by individuals,[139-141] resulting in negative coping behaviors. In these situations, clinicians should consistently update records pertaining to lapses in destructive behavior (eg, depression, smoking, unhealthy diets), continue communication with the primary physician regarding systemic areas of decline/concern, and refer patients to counseling/medical services (eg, smoking cessation, nutritional counseling, sleep specialists) when detrimental behavior modifications surface. While all detrimental behaviors need to be fastidiously managed, one example with well-established importance to the success of periodontal treatment is smoking cessation. Smoking cessation remains a significant factor in tooth retention for periodontal/implant patients and should be discussed and considered in all periodontal treatment plans, especially in the context of periodontal patients with chronic stress.[142]

6.2 | Therapeutic measures

If a patient with chronic psychosocial stress presents for periodontal treatment it is important to identify and remove the etiology, be resourceful in strategies to manage the patient, and utilize conservative treatment techniques. The most important therapeutic strategy is to identify and remove the etiology of the disease to address the onset and progression of the disease. Once

the treatment plan is established, adjunctive therapies can help to cultivate success and maintain therapeutic outcomes in patients with chronic psychosocial stress. Some adjunctive considerations include scheduling early morning appointments to help minimize waiting anxiety that might build up with additional interactions throughout the day.

In addition, prophylactic antibiotics might be considered in immunocompromised individuals. Administration of low-dose doxycycline might also be an adjunct to consider during initial phases of treatment to help mitigate tissue-destruction processes during the inflammatory phases of healing. Lastly, during therapeutic phases of treatment, conservative surgical techniques are important to minimize the inflammatory phases of healing. As such, flap management strategies remain essential.[143,144] Furthermore, the use of antimicrobial oral rinses, such as chlorohexidine 0.2% mouthwash postoperatively, should be considered to manage site healing during periods when oral hygiene cannot be maintained.[145]

7 | DRAWBACKS OF CURRENT MODELS

The classification of psychosocial stress can be very heterogeneous. Some classification systems include major life events, chronic stressors (eg, financial, taking care of individuals with chronic diseases), post-traumatic stress disorder, or even depression. Heterogeneity in classification can contribute to differences in reported values of serum/salivary concentrations of biomarkers and skew correlations with disease presentation. Furthermore, individual coping strategies can modify the outcomes of reported biomarkers. Among individuals in similar stressor groups, coping strategies could lend different physiologic responses to the stressor stimulus. Importantly in chronic situations, coping strategies could inherently improve or deteriorate over time. Controlling these factors may be imperative to evaluating the psychobiologic mechanisms affecting the interplay between psychosocial stress and periodontal-related diseases.

Questionnaires are often used in these studies to address these shortcomings, but there is not a consensus on this tool either. Use of more or less variables on "stress scales" to homogenize stress-inducing life events can also result in different outcomes.[43,64,146] It appears that detailed questions that allow investigators to discern between types of stressors, demographic information, acute vs chronic stress, and coping effectiveness may all be necessary.[17,147,148] Towards this point, one investigation that used a six-point questionnaire found no significant differences in measured periodontal parameters.[17] Conversely, another investigation used a more comprehensive questionnaire and reported significantly impaired healing of chronic wounds.[149]

8 | CONCLUSIONS

Chronic stress is a relevant disease to the periodontal/implant practice, encompassing 25%-28% of the US population.[150] Ideal solutions for these patients include de-escalation of chronic stress conditions, but sometimes this is not possible (eg, caring for a family member with Alzheimer's disease if unable to receive external help). As such, as clinicians we must take measures to incorporate knowledge of this systemic factor and how it contributes to disease so that we can adjust our therapeutic approaches to ensure that periodontal or peri-implant diseases can be effectively mitigated or predictably treated.

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CONFLICTS OF INTEREST

The authors reported no conflicts of interest related to this work.

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