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**INFLUENCE OF PSYCHOLOGICAL STRESS ON PERIODONTAL WOUND HEALING AND
POSSIBLE THERAPEUTIC APPROACHES– AN UPDATE**

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ABSTRACT:

The current review aims at narrating the existing knowledge and understanding about psychological stress and periodontal wound healing. Periodontal disease is a complex multifactorial disease. Psychological stress is known to alter at both behaviour and physiological levels, influencing the disease course and the response to treatment. Many animal, in vitro and clinical studies have suggested the role of psychological stress on the periodontal treatment outcome. However the data regarding alternative approaches to manage periodontitis patients with psychological stress are sparse. The evidence is mounting regarding underlying complex pathways, but there is a further need for exploration in the management of stress along with routine mechanical debridement. This article summarises the possible adjunctive approaches to mechanical debridement among these patients.

INFLUENCE OF PSYCHOLOGICAL STRESS ON PERIODONTAL WOUND HEALING AND POSSIBLE THERAPEUTIC APPROACHES– AN UPDATE

Introduction:

Periodontitis is a chronic inflammatory multifactorial disease associated with dysbiotic dental biofilms resulting in an irreversible loss of tooth supporting structures (1). Management of periodontitis involves thorough mechanical debridement along with managing modifiable local and systemic risk factors with tailored oral hygiene advice. There are instances where despite adequate periodontal therapy and dental plaque biofilm control, single or multiple sites continue to remain unresponsive or deteriorate (2)(3). Psychological stress is one among systemic risk factors, which plays a role in the disruption of host and microbial homeostasis and influences periodontal wound healing by either health-impairing behaviours of an individual or by altering cytokine profiles (4). This review article aims to discuss the underlying complex host response to periodontal treatment during psychological stress and attempts to look at the possible therapeutic approaches to improve the host's response to periodontal treatment in patients with psychological stress.

Psychological stress in biological terms refers to the response of the body to the external stimuli, however psychological stress can be either stimuli or response or both. Every individual is different in the way they respond to stress and thus their coping abilities. In the modern society, psychological stress and associated mental and physical health problems are becoming common.

The effects of psychological stress are twofold. On one hand it can initiate maladaptive behaviours and on the other hand can trigger immunomodulatory effects. Maladaptive behaviours can be in the form of poor oral hygiene, poor eating habits, poor sleep, excessive

smoking, alcohol consumption and drug or substance abuse. The immunomodulatory effects can be either suppression or exaggeration of immune response.

HPA axis products: Cortisol, DHEA and catecholamines

It is well established fact that psychological stress activates hypothalamo-pituitary-axis (HPA) and sympatho-adrenal-medullary axis (SAM). The activation of these axes results in complex immune inflammatory responses by elevating cortisol, Dehydroepiandrosterone (DHEA) and other molecules such as adrenaline and alpha- amylase levels in body fluids (Fig 1). Each of these molecules require receptors such as glucocorticoid receptor (GR) mineralocorticoid receptor (MR) and androgen receptors for them to bind within the cytoplasm of the target cells (5). The bound ligand and receptor complex move to the nucleus and binds further to complementary molecule/hormone response element in DNA, such as glucocorticoid response elements (GREs), mineralocorticoid response elements (MREs) This binding initiate specific gene transcription and synthesis of new proteins that enable the effects of hormone (5).

Wound healing:

A wound is a disruption of normal tissue structure and function and can be categorised based on the cause of the wound such as trauma, surgery and pathology. Wound can be classified into acute or chronic based on the healing progression in expected phases. The oral wound healing is quicker compared to cutaneous healing and less scarring; however, the healing course is similar in most of the tissues (6).

Periodontal wound healing:

Periodontium is a unique tissue where epithelium, soft and mineralised connective tissues

together form a dento-gingival junction. During chronic inflammatory periodontal diseases, the integrity of junction is lost. The periodontal non-surgical and surgical periodontal treatment approaches may result in further damage of the already inflamed tissues. Thus, the outcome of such approaches is determined by the cellular and molecular events associated with the wound healing. Many of these events are analogous to those seen elsewhere in the body except for the hard tissue interface at the junction of epithelium and connective tissue.

A typical wound healing process involves the formation of a temporary repair in the form of a clot in the injured tissue, followed by invasion of inflammatory cells and endothelial cells in the clot to form a granulation tissue, with epithelium crawling along the wound margin to cover the denuded surfaces and finally, maturation of the healing matrix and contraction. This process to occur in requires the appropriate recruitment of inflammatory cells to the site and release of the growth factors and cytokines (7). Although it seems oversimplified, it does involve several cytokines such as IL-1, IL-6, IL-8, TNF- α and MMPs (matrix metalloproteinases). These molecules are integral for wound healing process (7).

Psychological stress and Periodontal wound healing:

During wound healing in the oral cavity the granulation tissue matrix is continuously remodelled by matrix metalloproteinases such as MMP-2 and MMP-9. It has been established in earlier reports that dexamethasone, a glucocorticoid drug reduces the expression of mRNAs of MMP-1 & 2 along with tissue inhibitors of metalloproteinases 1 & 2, in gingival and periodontal ligament fibroblasts (8).

Cury PR et al, evaluated the effect of 2 different hydrocortisone concentrations on mRNA expression of MMPs and TIMP and suggested that higher dexamethasone concentration significantly increased the production of MMP-1, -2, -7 & -11 and TIMP-1 in gingival

fibroblasts, thus they implied higher psychological stress and increases cortisol levels in the human body and consequently there is an increased periodontal destruction (9). Another study in an animal experimental periodontitis model suggested an elevated level of pro-inflammatory markers such as IL-1 β and TNF- α during healing phase under stressed conditions, along with down regulation of growth factors such as bFGF (basic fibroblast factor) which is crucial factor in periodontal regeneration by enhancing fibroblast proliferation. It appears under psychological stress conditions there is a disturbance in the homeostasis of inflammation and repair process of wound healing as evidenced by the altered ratio of pro-inflammatory cytokines and bFGF (10).

Bakri I et al reported in their study poorer clinical outcome following non-surgical periodontal treatment based on clinical and biological marker such as elastase. Thus the authors concluded that stress management must be part of overall periodontal management (11).

Few studies have explored the psychological factors such as anxiety and psychological distress and their correlation to pain. The reports suggest that patients undergoing surgical treatment had lesser distress compared to patients who were undergoing surgical treatment. This could be due to patients who were undergoing surgical therapy may have had more time spent with the clinician and surrounding and were accustomed to the clinical environment (12). Another study reported anxiety to be a significant predictor of pain perception in four visit conventional staged debridement as opposed to single stage debridement, authors speculated this could be because of the cognitive learning of feeling of anxiety in 4 visit debridement and thus consequent pain perception (13).

Another factor to consider here psychological stress related bruxism or excessive grinding of teeth.

The influence of stress on enamel matrix derivative (EMD) treatment and healing capacity of periodontal tissues in the presence of chronic stress has been reported in an animal study. EMD is known to enhance wound healing by differentiating and encouraging mineralisation of bone marrow stem cells. Further EMD is shown to improve defect fill and bone density in the presence of chronic stress. Chronic stress is thought to affect new cement formation in those sites treated with EMD and enhance osteoclastic activity as demonstrated by increase in Tartrate-Resistant Acid Phosphatase (TRAP)- positive osteoclasts (12).

Kamin and Kertes suggested the estimation of the ratio of cortisol and DHEA is valuable rather than estimating independently, as both are secretory signalling molecules released as a product of HPA axis. These two molecules are interconnected and exert opposing actions in response to stress. Cortisol has been extensively studied independent of DHEA and the reports on DHEA research are sparse (5). Ansai et al conducted a study with an objective of assessing the cortisol and DHEA association with periodontitis in non-smokers and suggested that these hormones can be indicators of the risk for periodontal diseases, as they demonstrated reasonable planes of sensitivity and specificity for periodontitis (13).

Adrenergic receptors and healing

Adrenergic receptors (AR) are G- protein-coupled transmembrane receptors for stress hormone ligands such as epinephrine and nor-epinephrine. These receptors are expressed throughout the body and has been suggested to play a role in slowing down the migration of oral epithelium and thus consequent poor healing. Steenhuis et al reported in their study that activation of β_2 - AR resulted in decreased migratory speed of cultured human oral keratinocytes (HOK) in vitro. Further they demonstrated that β -AR antagonist timolol increased the speed of HOK and their capacity to heal a scratch wound (14).

Timolol is a non-selective β 1- and β 2 adrenergic receptor blocker commonly called as non-selective β -blockers originally used as an ophthalmic preparation has been introduced as a topical drug for the management of dermatological lesions such as pyogenic granulomas and topical haemangiomas (15),(16).

Cortisol and Melatonin interaction

There is an emerging evidence that disruption of circadian rhythm is a causative factor for several conditions including metabolic syndrome and cancer. The markers for this circadian rhythm in the human body are cortisol and melatonin. Melatonin is released by pineal gland which was initially considered to be a vestigial organ and is a metabolite of tryptophan-serotonin pathway. Cortisol has been shown to peak during early morning, which is the product of hypothalamo-pituitary-adrenal axis and is involved in mobilising energy and hinders sleep or any non-emergency activity. Melatonin chemically is N-acetyl-5-methoxy tryptamine is also known to be released by multiple organs in vertebrates (17). Van Fassen et al reported in their study that the melatonin production was higher in saliva compared to free plasma sample, suggesting the possible local production of melatonin from salivary glands in the oral cavity (18). Melatonin is also known to have properties of antioxidant by reducing levels of reactive oxygen species (ROS), reactive nitrate species (RNS) and thus consequent anti-inflammatory properties and anti-oncotic properties. In addition, melatonin is known for its regulatory effect on circadian rhythm (17).

Maladaptive behaviours and wound healing:

Psychological stress and nutrition:

The earlier reports suggest that psychological stress enhances the nutritional demands from

the body, including greater demand for energy, oxygen, circulation and more metabolic co factors (19). Ironically, individuals suffering from stress crave for comfort foods which lack in nutrition. Thus, psychological stress not only makes a person to indulge in unhealthy eating habits but also causes nutritional depletion, because of mobilisation of energy stores via the cortisol mediated action. These events can cause compromise in the metabolic systems eventually the system becoming susceptible to chronic problems such as diabetes (20).

Kitraki et al 2004 conducted an animal study with an objective of investigating the impact of high fat/low protein/low-carbohydrate diet. They found that the high fat diet impacted the balance of stress hormones by lowering the availability of glucocorticoid receptors in hypothalamus which are essential to mediate the effects of cortisol (21).

Brown and Philips in 2010 suggested that nutritional deficiency, either macro or micro-nutrients deficiency can result in impaired wound healing. Proteins, carbohydrates and fats all play a role in different phases of wound healing. Similarly, micronutrients such as vitamins, copper, iron, selenium, zinc and water influence wound healing or repair process (22). Based on the above evidence it is apparent there is significant influence of psychological stress on nutrition intake and stores and consequently negatively affecting wound healing. Is it reasonable to assume therapeutic supplements could help in enhancing the treatment outcome?

Psychological stress, Insomnia and wound healing: Acute or chronic stress can have multiple consequences depending on the coping ability of an individual. It has been reported the skill of coping has an impact on mental well-being and quality of life. Insomnia or sleeplessness is known to be associated with psychological stress (23). Insomnia is also said to be a consequence of PTSD and depression, (24) and there has been serious interest in exploring

the relationship between sleep and immune system. One study reported reduced mucosal healing in inflammatory bowel disease patients and suggested this could be attributed to tissue hypoxia, oxidative stress and activation of pro-inflammatory cytokines and continued inflammatory state (25)(26). This raises the question of, is this only true in gastric mucosal healing or other mucosa as well in the body including oral cavity and periodontium?

Traditionally, benzodiazepine receptor agonists have been used in the management of insomnia disorder, however due to its rebound insomnia and withdrawal symptoms more non-pharmacological interventions such as cognitive behavioural therapy have been preferred. Nevertheless, due lack of access to trained practitioners, patients start exploring the possibility of alternative therapies. Chinese herbal medicine has been popular in Chinese population for the management of sleep disorders. Zao Ren An Shen (ZRAS) is a CHM formula containing herbs such as ziziphi spinosae semen, schisandrae chinensis fructus and salviae miltiorrhizae radix et rhizome which all known to have sedative effects and is effective in calming and soothing mind. However, the clinical trial is underway to prove the efficacy and safety of ZRAS (27). There are reports to suggest using exogenous melatonin in the management of delayed sleep phase disorders, by keeping the low dose as much as possible and to administer as early as tolerable (28). Moreover, mulberry juice has been shown to demonstrate anti-stress activity by scavenging the oxygen free radicals generated because of psychological stress or restraint stress in mice models (29).

Role of yoga in periodontal wound healing:

Yoga is an ancient Indian practice to enhance healthy attitudes and reconditioning of the neuromuscular systems in an individual. The effect of yoga on the outcome of periodontal treatment has been studied and the results indicate that, yoga could be a possible approach

in the holistic management of periodontal patients with chronic stress to enhance the treatment outcome (30). However underlying mechanism of yoga is yet to be explored to enhance understanding.

Anxiety, stress and depression is thought to affect patient's pain perception, use of analgesics and wound healing. Thus, it is best to adopt treatment strategies that takes the psychological factors into consideration in the management of periodontal patients with chronic stress to bring about positive change in their psychological status. Kloostra et al suggested to educate Periodontists with respect to impact of psychological stress on poorer wound healing. Further there is a necessity to provide knowledge and skills to the graduating students about the management of patients with psychological stress. However so far, there is no single evidence based effective method to assess psychological stress in dental clinics and their management. Further research must focus on developing effective tools to assess psychological stress levels on dental clinics and consider developing targeted interventions in the management of psychological stress as a part of holistic management (31).

Periodontal wound healing biomarkers following regenerative procedures: Evidence indicate that MMP-1 and BMP-7 can be used as predictive biomarkers for regenerative clinical outcome. MMP-1 is shown to decrease in the areas of regeneration. This molecule is involved the degradation of type 1 collagenase and turnover of extracellular matrix and the decrease in the levels of this molecule suggests promotion of proliferative phase and thus facilitating regeneration. Further BMP-7 is possible indicator of osteogenesis and cementogenesis and thus better periodontal regeneration (32). Conceivably, these biomarkers could be used in future studies to investigate the periodontal regeneration outcome in periodontal patients with appropriate psychological stress management.

Pearl powder is another material used in Chinese medicine for insomnia and palpitations. Pearl powder contains primarily calcium carbonate in the form of aragonite and contains about 18 amino acids and over 20 microelements such as Zinc, calcium, magnesium and iron and so on. This material in micro and nanosized is known to accelerate healing. Xi Chen et al demonstrated in their in vitro scratch wound model and animal in vivo models, that the nano sized pearl particles provides greater surface area per unit of dissolution, thus providing increased amount of proteins in the local wound matrix, by increasing the adherence, and by enhancing the endocytosis in the cells when it is delivered topically. Besides it is also known for its antioxidant effects. This is another potential material can be tested in psychologically stressed individuals to enhance wound healing (33).

Probiotics are live microorganisms with positive health benefits. There are several reports in the literature about the benefits of probiotics with microorganisms such as Bifidobacterium, lactobacillus, enterococcus and bacillus. Foureaux et al explored in their animal study the effects of probiotics on periodontal disease in the presence of stress and they reported minimized beneficial effects. The authors suggested that since the immune-inflammatory reactions in the intestinal mucosa are similar to oral mucosa, the actions of probiotics in the oral mucosa is parallel to the intestinal mucosa (34). This needs to be explored further.

Discussion:

Wimmer et al demonstrated in their study that individuals with defensive and passive coping style were associated with advanced periodontal disease and inadequate healing response to non-surgical periodontal treatment. The authors suggested passive and defensive coping styles led to maladaptive behaviours such as smoking, excessive alcohol consumption and substance abuse (35). An animal study reported the influence of alcohol on EMD treated sites

wound healing, and authors suggested excessive alcohol intake can increase TRAP positive cells and decrease bone density (36).

Management of periodontal patients with chronic psychological stress require tailored treatment strategies such as behavioural interventions with the help of medical practitioner's support who can either signpost patients to appropriate support facilities and/or possible systemic and topical pharmacological interventions.

Smoking has been recognised as a risk factor for periodontal disease and there are good support systems to help patients to quit smoking. Perhaps it is best for health care workers to establish support system for managing psychological stress at every possible health care establishments including dental clinics and hospitals.

Considering the above evidence, the periodontitis patients with psychological stress may benefit with exercise, yoga, music therapy, mindfulness based cognitive behavioural therapy along with periodontal treatment (6) (30) (37) (38). In addition, EMDs, vitamin supplements, mulberry juice or powder, pearl powder, Chinese herbal medicine and Timolol may be of some value.

Well-designed controlled clinical studies with the above alternative approaches must be explored. Besides the adjunct pharmacological agents either topically or systemically could be possible therapeutic adjuncts to enhance wound healing in periodontitis patients with psychological stress. So far EMDs have shown some benefit in wound healing in presence of chronic stress in animal studies.

Previous studies have provided evidence about the influence of psychological stress and its influence of periodontal disease and response to periodontal treatment. However, till date

there is no well-established and clear underlying pathway unravelled to understand the influence of psychological stress on periodontal disease and treatment.

The literature evidence so far indicates psychological stress can influence an individual's habits by triggering maladaptive health behaviours such as poor eating, sleeping, smoking, alcohol and substance abuse. Further psychological stress can also have an impact on host's immune system. Hence is it time to look at the root of all the above problems; psychological stress and adopt psychological assessment and management strategies on dental clinics as a part of holistic management of patient? Or should we be aiming at enhancing wound healing by providing pharmacological adjuncts either as systemic or local drug delivery? Or perhaps combination of both?

Future directions:

Evidence with respect to psychological stress and its influence on periodontal diseases and non-surgical and surgical treatment is conflicting and unclear. Hence further research with robust study design in humans must be encouraged to enhance wound healing in non-responsive psychologically stressed individuals.

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Fig 1. Influence of psychological stress on wound healing:



