ORIGINAL RESEARCH PAPER

Dental Science

KEY WORDS: Hormesis, bi-phasic, adaptive response, periodontal disease, intermittent fasting.

"HORMESIS" - INTERPRETING A DOUBLE EDGED SYMBOL IN PERIODONTICS

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ABSTRACT

What does not destroy you fortifies you. A more accurate way to describe hormesis, the paradoxical positive effects of low dose stressors, would be the biphasic dose-response or time- response relationship for any given substances. When compared to continuous exposure, intermittent or pulsatile exposure can have the opposite effects. A first encounter can cause a stress response that is adaptive and provides long-term defense against more exposures. Numerous stressors are a natural part of life and are necessary for homeostasis or healthy growth, a prime example of the adage "illness is the doorway to health." Examples of hormetic stress includes intermittent fasting, hot and cold exposure, hit workouts, dietary restriction etc. The best tactics for addressing the real causes of numerous inflammatory and lifestyle-related conditions are calorie restriction and intermittent fasting. Nature has endowed us with an abundance of dietary tools that, when used in the right way, will improve our longevity, health, and general well-being by regulating the inflammatory environment and lowering our chance of chronic inflammation- related disorders such as periodontal diseases.

INTRODUCTION

Hormesis was initially described as a phenomenon in which little doses of a dangerous material exposed to living organisms result in favorable benefits. One of the first cases that has been documented is the radiation hormesis.[1] Stressor agents such as physical (mechanical, electrical, thermal), chemical or radiobiological.[2] Low-dose ionising radiation, like X-rays, has been demonstrated to inhibit the growth of tumours, even if high-dose radiation encourages mutagenesis and carcinogenesis. When administered at a low dose, certain chemical carcinogens, such DTT or □-benzene hexachloride, can guard against DNA damage and cytotoxic consequences brought on by later exposures at much larger doses. According to the original definition, a substance's "harmfulness" or "stress" is not a fundamental characteristic, toxicology is determined by the dose and the duration of exposure. The body is exposed to a variety of naturally occurring compounds during evolution. Thus, in order to maintain homeostasis and promote healthy growth, our bodies have probably developed defence systems to react to, adjust to, or even depend on the stressors.[1] Ad libitum society that exists in the modern day has made overeating is common for many people and created a number of new difficulties in the diagnosis, treatment, and prevention of illnesses.[4]

According to the Global Nutrition Report published in 2020, one in nine people in the world experiences hunger or is undernourished and one in three is overweight or obese.[5] Dietary restriction raised the maximum and mean life spans substantially. Calorie restriction is one of the most effective experimental strategies to avoid long-term health issues such as asthma, dyslipidemia, type 2 diabetes, cardiovascular disease, as well as cancer. Among the most common inflammatory disorders in humans are periodontal diseases, and their frequency has been increasing over the past decade. As the main preventive method for managing chronic diseases like periodontitis, calorie restriction and intermittent fasting are also expected to be highly cost-effective in healing periodontal inflammation.[4] As a result, the goal of the current review was to summarise the overall notions of hormetic effects on periodontal diseases as well as its clinical consequences and its therapeutic potential for reducing periodontal inflammation.

The Origin of Hormesis

In 1849, Rudolf Virchow took a necropsy specimen of the tracheal mucous membrane of a deceased human being. This membrane is equipped with the lining layer of ciliated epithelia. The ciliae afford a defence mechanism, in that mucus with trapped air pollutants is transported by the beats of the ciliae upward in the respiratory tract. In those days, pathologists were well aware that, after the death of an individual, the ciliae continue beating for many hours, sometimes even for a few days. Observing the fading activity of the ciliae under the microscope, Virchow exposed the layer to gradated concentrations of sodium hydroxide. At low concentrations, he saw a vivid increase in the power and frequency of beating for considerable period of time, whereas higher concentrations and longer exposure times paralyzed the beating activity and finally led to cell death.[2]

The Biphasic Dose Response Concept

The dose response concept is fundamental idea in biology, medicine, and public health. It is the biological integration of responses to endogenous agents, metabolic processes, and externally imposed stressors/threats by living systems at all organisational levels, from the cell to the individual. As a dosage-time response that explains dynamic processes including the induction of toxicity, healing, and recovery, the dose response can capture and offer biological/mechanistic insight to such problems. The dose-time response of biological systems is a reflection of their evolutionary adaptive strategy, making them dynamic entities.[3]

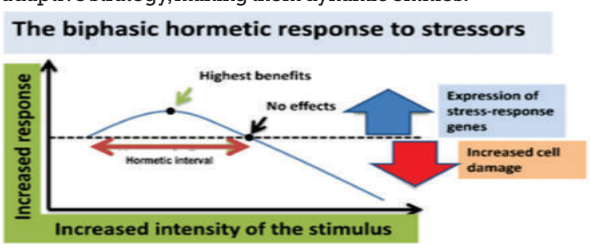
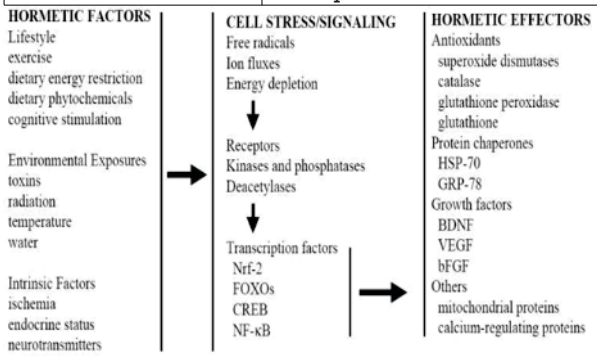


Figure 1: Biphasic Hormetic Effects

Hormesis In Health and Disease

HORMETIC EFFECTS	HEALTH	DISEASE
Reactive oxygen species (ROS)	Low-level ROS act as signal molecules to start biological activities without having the negative effects. The production of ROS by neutrophils is essential for liver healing. When tissue is wounded, neutrophils are drawn and repair the liver by changing the phenotype of macrophages from pro-inflammatory to pro-regenerative.1	Excessive concentration of ROS that ruins DNA, proteins, or other cellular constituents.1
Hypoxia	Exposure to a daily IH cycle lasting four days, consisting of two minutes at 6–8% oxygen and three minutes of re-oxygenation five times, can prevent ischemia reperfusion injury in the heart.1	Obstructive sleep apnea (OSA) is a risk factor for cardiovascular and liver diseases. One of the main causes of OSA is intermittent hypoxia.1
Nitric oxide (NO)	NO at low concentrations modulates glutamatergic neurotransmission. NO stimulates the creation of new blood vessels, reduces constriction of existing vessels, reduces inflammation, and increases blood flow in the cardiovascular system.1	NO can cause mutagenesis and cell death by preventing DNA synthesis, rupturing cell membrane integrity, stopping the cell cycle, breaking DNA strands, and inducing apoptosis.1
Parathyroid hormone (PTH)	Once daily exposure to PTH or its paralogue at an intermittent rate improves bone mass. Such intermittent exposure strategy has been approved as a therapy for osteoporosis.6	Parathyroid hormone (PTH) induces bone loss at a persistently high level.6
Glucocorticoid	Pulsatile weekly glucocorticoid therapy - improving muscular performance recovery.1	Chronic daily exposure worsen muscle performance.1
Thyroid hormone	Thyroid hormone stimulates neo- angiogenesis, lowers fibrosis, activates mitochondrial metabolism, and suppresses apoptosis and have cardioprotective effects.7	Hyperthyroidism - Causes Atrial fibrillation, pulmonary hypertension, and coronary heart disease.7
Estrogen	At low dosages - Encourages tumour cell proliferation.1	At large concentrations, it promotes cell death.1
Progesterone	Progesterone has biphasic time-effects on estrogen-dependent regulation of memory. Progesterone treatment six hours before to extinction training can enhance the facilitation of extinction recall by estradiol.1	
In Cancer Therapy	In chemotherapy, switching from the maximum tolerated dose concept to low dose, intermittent therapy, or "metronomic" therapy. In the case of radiation therapy, highly precise stereotactic targeting makes it possible to deliver ablative, immuneogenic doses of radiation to the tumour while sparing the surrounding normal tissues. Future cancer treatments may involve more localised debulking surgery, repositioning chemotherapy, and radiation therapy in addition to developing immunotherapeutic techniques.8	



Dietary Factors and Hormesis

There is growing recognition of the influence of dietary determinants on longevity and overall health. Energy intake is the main dietary element that influences the risk of many different chronic diseases; consuming too many calories raises the risk. Reducing energy intake by controlled caloric restriction or intermittent fasting increases lifespan and protects various tissues against disease, in part, by hormesis mechanisms that increase cellular stress resistance. Certain dietary ingredients may potentially improve health by triggering cellular stress responses that are adaptive. In fact, recent research indicates that a number of intensively researched phytochemicals may exhibit biphasic dose responses on cells, whereby low doses trigger signalling pathways that enhance the expression of genes encoding cytoprotective proteins such as growth factors, antioxidant enzymes, protein chaperones, and mitochondrial proteins.

Examples include: Broccoli's high isothocyanate content stimulated the production of cytoprotective phase 2 proteins in intestinal, liver, and stomach cells. In animal models of cataract formation, pulmonary toxicity, multiple sclerosis, and Alzheimer's disease. Curcumin, a spice found in curry, has been shown to induce adaptive stress response genes and protect cells. Similarly, resveratrol, a compound found in the skin of red grapes and wine, has been shown to activate stress response pathways and protect cells in models of myocardial infarction and stroke. High concentrations of these phytochemicals, nonetheless, may also be harmful to particular cell types. Because they often exhibit antioxidant activity, it has been widely assumed that the direct free radical scavenging activity of phytochemicals confers their health benefits.[9]

Effects of Calorie Restriction and Fasting and its Hormetic Effects on Periodontium

Periodontal diseases are among the most prevalent of human inflammatory diseases, and their incidence has been increasing over the past decade. The best methods for addressing the proven causes of many inflammatory and lifestyle-related disorders are calorie restriction and intermittent fasting, according to scientific research.[4]

Calorie Restriction

Calorie restriction is defined explicitly as a reduction in energy intake well below the number of calories that would be consumed ad libitum (=10% in human studies and usually =20% in rodent species).[10]

Intermittent Fasting

Intermittent fasting is a dietary approach that requires abstinence from foods or drinks for varying periods; for example, a 16:8 fast (ie, a 16- hour fast with an 8- hour eating window), 24- hour fasts, the 5:2 diet (ie, eating normally for five days per week then restricting calorie intake to 500-600calories on the other 2 days), time- restricted feeding, and alternate- day fasting. Alternate- day fasting is a form of intermittent fasting, in which individuals alternate between not consuming any calories for 1 day and eating without restriction the next day.[11]

Following calorie restriction and intermittent fasting regimens, a decrease in nutrients and calories helps lower the patient's rate of mitochondrial reactive oxygen species production. This lowers the risk of damaging proteins, lipids, and DNA and lessens oxidative damage to the cells. Furthermore, according to this view, a decrease in the rate of DNA damage and mutagenicity is a result of decreased metabolic rates. This probably lowers the rate of neurodegenerative illnesses and cancer while increasing life expectancy through improved genetic health. Limiting calories may lengthen life by slowing down the pace of cell division and encouraging upkeep and repair.[4]

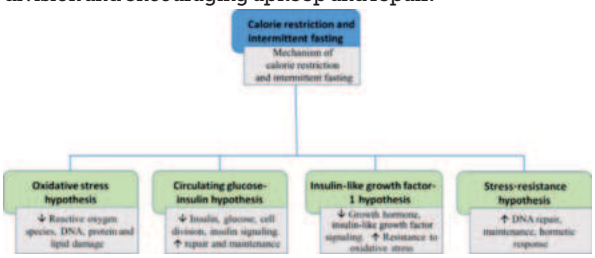


Figure 2: Mechanism of Calorie Restriction and Intermittent Fasting

Numerous dietary guidelines, including vitamin C and D supplements, fiber, antioxidants, omega-3 fatty acids, and lower carbohydrate intake, have been developed to promote periodontal health. Despite ongoing plaque levels, an anti-inflammatory diet has been demonstrated to significantly lower gingival inflammation.[4]

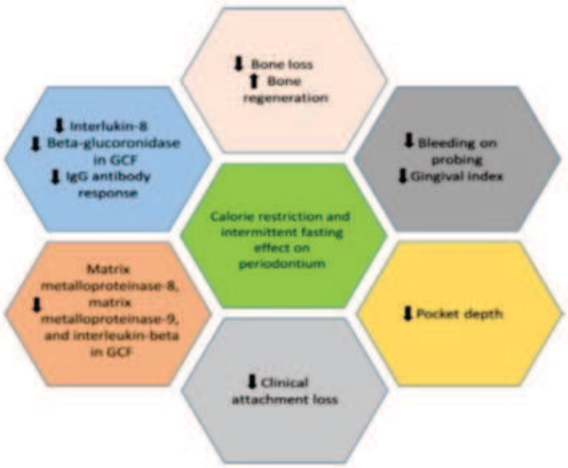


Figure 3: The Effect of Caloric Restriction and Intermittent Fasting on the Periodontium.

HORMETIC EFFECT – FUTURE PROSPECTS IN PERIODONTICS

Human Periodontal Ligament Stem Cells and Hormesis: Enhancing Cell Renewal and Cell Differentiation

Because third molar teeth are frequently extracted from young adults, human periodontal ligament stem cells (hPDLSCs) have found widespread use in therapeutic applications. Seo et al were the first to isolate and cultivate periodontal ligament stem cells from periodontal ligament tissue.

PDLSCs shown a high potential for proliferation and the capacity to differentiate into several cell types both in vitro and in vivo, resulting in a variety of cellular phenotypes such as adipocytes, osteoblasts, cementoblasts, and chondrocytes. hPDLSC renewal and differentiation into functional cell types are enhanced by a variety of substances through a hormetic biphasic dosage response relationship.

A growing body of research based on evaluations of several kinds of stem cells indicates that hormetic dosage responses are common, indicating significant universality and a highly conserved evolutionary characteristic.[12]

Rapamycin – Hormetic Effect

Rapamycin is hormetic in nature, it demonstrates contrasting effects at high and low doses. It is toxic at moderate/high doses, while it can restrain aging and extend lifespan at low doses. Rapamycin, a particular inhibitor of the mTOR (mammalian/mechanistic target of rapamycin) signalling system and the most common autophagy activator, is essential for controlling a variety of cellular functions. The impact of rapamycin on osteoclast (OC) production in vitro and on the rat periodontitis model. Rapamycin prevented OC production in a dose-dependent manner by up- regulating the Nrf2/GCLC signalling pathway, hence reducing intracellular redox state as evaluated by 2',7'-dichlorofluorescein diacetate and MitoSOX. Furthermore, rather than just enhancing autophagosome formation, rapamycin boosted autophagy flux during OC formation.[13] In future rapamycin can be incorporated in the form of local drug delivery for the management of chronic periodontitis.

Effect of CO_2 Laser Irradiation On Hormesis Induction in Cultured Oral Cells

On cultured cells, both drugs (including toxins) and radiation therapy and have been shown to exhibit biphasic hormone effects, but only when both the concentration and treatment time were optimal. The author investigated whether CO2 laser treatment causes hormesis in HGF and oral squamous cell carcinoma (HSC-2) cells. Cells were cultivated for 24, 48, or 72 hours following exposure to various irradiation strengths, and the viable cell number was evaluated using the 3 (4,5dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method.

Cell growth was enhanced by low-power CO 2 laser irradiation and inhibited by high- power irradiation. Super pulse (SP)2 was the most successful of the three dispatch modes in inducing HGF growth stimulation, at an irradiation dose slightly lower than that which induced cytotoxicity. Higher irradiation dosages were equally lethal to both normal (HGF) and tumour (HSC-2) cells, reaching a cytotoxicity plateau within 24 hours. Optimal circumstances for inducing hormesis in HGF cells are critical for clinical use in dentistry due to their limited range and degree of response. Similarly, high-level laser treatment (HLLT) caused cell membrane and DNA damage, while low-level laser treatment (LLLT) spurred cell proliferation and wound healing.[14]

Low-Level Laser Therapy (LLLT)

Low-Level Laser Therapy (LLLT) is a light source treatment that generates light of a single wavelength. Low-level lasers work by stimulating the photobiostimulation process within the tissues, not by raising the temperature of the tissue itself. Tissue is not sliced or ablated by low- power lasers. Gallium

arsenide, gallium aluminium arsenide infrared semiconductor (gallium- aluminum-arsenide), and helium-neon lasers are examples of LLLT devices. With pulsed or continuous wave emission, the output powers span from 50 to 500 mW at wavelengths in the electromagnetic spectrum that fall within the red and near infrared regions, from 630 to 980 nm. The direct biostimulatory impact of low level laser irradiation increases the synthesis of ATP by acting on the respiratory chain's antenna pigments. This will result in altered intracellular metabolism, increased cell division and proliferation, migration of fibroblasts, and accelerated matrix synthesis. Low-level laser will relieve pain and repairs wound, increased epithelization and wound healing following gingivectomy and gingivoplasty, the application of diode laser 810 nm along with MWF results into pain reduction and post-op edema and heal wound in palatal graft site.[15]

Ozone Therapy

Allotrope of oxygen, ozone, is gaining popularity in the context and administration of medical adjunct treatment; this treatment is sometimes referred to as "ozone therapy". Ozone interacts with aryl hydrocarbon receptors (AhRs) like many other naturally occurring substances, such as plantflavonoids. At low concentrations, ozone functions through the paradoxical process of hormesis, which involves mitochondria (mitohormesis). In the hormetic range, ozone protects cells by activating the antioxidant system through Nrf2 and then causing modest amounts of 4-HNE to be released. This has an anti-inflammatory impact as well. Furthermore, when it interacts with lipids and plasma, it produces lipoperoxides (LPOs), also known as ozonides, and reactive oxygen species (ROS), which control the main molecular functions of ozone in cells.[16]

The use of ozone is well indicated in all stages of gingival and periodontal diseases due to its beneficial biological effects, anti-microbial activity, oxidation of biomolecule precursors and microbial toxins implicated in periodontal diseases, and properties that promote healing and tissue regeneration.[17] Local ozone treatment is a viable nonsurgical option for treating periodontal disease while avoiding surgery. It could be a useful instrument in supportive periodontal therapy. Ozone's potent capacity to render microorganisms inactive makes it a viable alternative management tactic. Subgingival ozone irrigation is therefore a useful addition to periodontal therapy.[18]

Ozone therapy seems to both accelerate the healing processes of periodontal/peri-implant wounds and increase the secondary stability of dental implants.[19]

Periodontal Vaccine as Hormesis

Porphyromonas gingivalis, a gram negative anaerobic bacterium, is the major etiological agent which contributes to chronic periodontitis. Porphyromonas gingivalis though it is a virulence factor, acts as a defense mechanism when it is incorporated as a vaccine. Mice infected with Porphyromonas gingivalis and exhibiting a well-established inflammatory immune response specific to the bacterium were shielded from alveolar bone resorption through therapeutic vaccination specifically targets the gingipain proteinases, the major virulence factors of the bacteria. Th2 cell response and an IgG1 isotype antibody specific to the antigen were indicative of protection. IgG1-mediated protection was validated by adoptive transfer of B cells expressing IgG1 or IgG2 that are specific to KAS2-A1. Moreover, KAS2-A1-specific polyclonal antibodies administered parenterally or orally prevented the onset of P. gingivalis-induced bone resorption. By preventing proteolytic activity, attachment to host cells or proteins, and co-aggregation with other periodontal bacteria, the KAS2-A1-specific antibodies neutralized the gingipains. A vaccination containing essential gingipain sequences was developed as a successful therapeutic intervention to prevent periodontitis caused by P. gingivalis.[20]

CONCLUSION

Our bodies are incredibly versatile. One way that stress reactions are protective against further exposures is when the body anticipates additional stress, which happens when exposed to a stressor. These adaptations are necessary because environmental changes can be erratic and the organism must learn to balance various activities. Because they immediately feel changes in theenvironment and relay that perception to the rest of the body, the immunological, neurological, and endocrine systems are especially receptive to these adaptations.[1]

Nature has endowed us with an abundance of dietary tools that, when used in the right way, will improve our longevity, health, and general well-being by regulating the inflammatory environment and lowering our chance of chronic inflammation-related disorders such as periodontal diseases.

Thus, the hormetic effects of low level laser therapy, ozone therapy, human periodontal ligament stem cell, low dose antibiotics and periodontal vaccine can be incorporated for future periodontal therapy.

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