Review Article

Desquamative Gingivitis, Oxidative Stress, and 8-Hydroxydeoxyguanosine (8-OH-dG/8-OxodG): Role and Significance: A Review

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ABSTRACT

Desquamative gingivitis is an oral inflammatory disease that leads to tissue damage. Medical and dental research has been largely remains focused on an individual factor in desquamative gingivitis, for example, microbes or host. Nowadays, good clinical outcomes are obtained in gingival disease control, but effective management of desquamative gingivitis is still critical. The oxidative DNA damages may play an important part in pathogenesis of many chronic conditions including gingival conditions. Oxidative stress can result in DNA damage, including the oxidation of nucleoside. 8-Hydroxydeoxyguanosine is an oxidized stress derivative DNA damage of deoxyguanosine and is one of the major products of DNA oxidation. This review has largely focused on the role of reactive oxygen species in desquamative gingivitis; oxidative species play important roles in the development of much pathology.

Key words: 8-Hydroxydeoxyguanosine, deoxyguanosine, DNA, gingivitis, oxidative stress

INTRODUCTION

8-Hydroxydeoxyguanosine (8-OH-dG), it is thought to be that increased levels of 8-OH-dG in a tissue can serve as a biomarker of oxidative stress. With age it increases in both nuclear and mitochondrial DNA. 8-OxodG formation is regulated by local antioxidant capacity and DNA repair enzyme activity. Few authors have also that increased levels of 8-oxo-dG are frequently seen during carcinogenesis.

IUPAC name - 2-amino-9-[(2*R*,4*S*,5*R*)-4-hydroxy-5 (hydroxymethyl)oxolan-2-yl]-3,7 dihydropurine-6,8-dione.

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Other names are:

- 7,8-dihydro-8-oxo-2'-deoxyguanosine
- 7,8-dihydro-8-oxodeoxyguanosine
- 8-hydroxy-2'-deoxyguanosine
- 8-OH-dG
- 8-Oxo-2'-deoxyguanosine
- 8-Oxo-7,8-dihydro-2'-deoxyguanosine
- 8-Oxo-7,8-dihydrodeoxyguanosine
- 8-Oxo-dG; 8-OH-dG.

Reactive oxygen species (ROS) are chemically reactive chemical species and product of normal cellular metabolism despite this it is very well-known for its influence on development of cancer because of its ability to react with DNA. It is detected in almost all types of cancer where they promote many aspects of tumor development and progression.[1] A very old proven concept of ROS is it is formed as a natural byproduct of oxygen and have very important role in homeostasis and cell signaling.

Damage to ROS occurs due to following reasons and leads to formation of oxidative stress are:

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- Ultraviolet (UV) or heat exposure
- Ionizing radiations.

Sova *et al.*[2] in the year 2010 has already done a research and concluded that low serum and tissue levels of 8-oxodG are characteristic of more aggressive cancer, mainly because of its abundance in DNA and also because of its reliable detectability.[1,3]

This review has primarily focused on the role of ROS in desquamative gingivitis and oxidative species which play imperative roles in many biological processes including development of carcinomas and many other ailments. Gingival diseases are inflammatory disorders that are results of the complex interaction between pathogens and host immune response. Desquamative gingivitis is a clinical feature for the variety of conditions. The presence of erythema, ulceration, presence of the vesiculobullous lesion on gingiva, and other oral tissues are some of the characteristic features of the disease.

DESQUAMATIVE GINGIVITIS

First described by Tomes and Tomes in 1894,[4] detailed clinical features were given by Prinz in 1932[5] was that it is synonymous with the presence of erythema, desquamation, erosion and blistering of attached, and marginal gingiva. Desquamative gingivitis is a clinical condition most often characterized by erythematous and desquamative involvement of the free and attached gingiva. The degree, extent, and severity of gingival involvement vary patient to patients. Sometimes erythema predominates with little or no desquamation representing the mild form of the disease, whereas in other cases, the epithelium can be stripped off easily representing the usual form of desquamative gingivitis. Extensive areas of denudation with an exposed connective tissue surface represent the most severe form. Patients may be symptom-free or complain of burning sensation that may or may not be associated with intense pain. It has the higher prevalence in females than in males, but it can appear at any age beginning at puberty, more cases appear in the third decade of life. The duration of desquamated gingivitis disease shows periods of remission and exacerbation with an indefinite period. The gingiva may heal after few months of discomfort, or the condition may linger for several years.

Glickman and Smulow[6] proposed a classification based on etiological consideration and also stated that it can be clinical features of wide number of disorders.[7,8] The proposed classification as:

A. Dermatological diseases
    - Cicatricial pemphigoid
    - Lichen planus
    - Pemphigus
    - Psoriasis
    - Bullous pemphigoid
    - Epidermolysis bullosa acquisita
    - Contact stomatitis.
B. Endocrine disturbances
    - Estrogen deficiencies following oophorectomy and in postmenopausal stages
    - Testosterone imbalance
    - Hypothyroidism.
C. Aging
D. Abnormal response to bacterial plaque
E. Idiopathic
F. Chronic infections
    - Tuberculosis
    - Chronic candidiasis
    - Histoplasmosis.

DESQUAMATIVE GINGIVITIS AND OXIDATIVE STRESS

Desquamative gingivitis is an oral inflammatory disease that leads to tissue damage and as a result of the complex interaction between pathogenic bacteria and the host's immune response. Medical and dental research have been and largely remains to be focused on an individual factor, for example, microbial or host but one of the main open question regarding desquamative gingivitis is to know all the etiologic and pathogenic processes involved. Nowadays, good clinical outcomes are obtained in gingival disease control, but efficient management of desquamative gingivitis is still critical. It's hard to identify the real etiologic agent, a success rate of 100% is hardly attainable, it's hard to prevent the disease establishment, the identification of the population at risk is also not feasible. Furthermore, in desquamative gingivitis, a plaque is not essential, and in some patients, the disease has a different path depending on the systemic health. Therefore, in the last few years, the significance of the host response has increased markedly.[2] The role of oxidative stress in desquamation is complicated; there is growing documentation for compromised antioxidant capacity in gingival tissues. Oxidation products can lead to increase in chemotaxis, adhesion of neutrophil, and priming in hyperreactive neutrophils, and further, deteriorate damaging effects of the resultant oxidative stress,[1,3,4,9] along with this, there is upregulation of pro-inflammatory transcription factors, for example, nuclear factor κB and activating protein-1, in inflamed tissues lead to a formation of ROS. There may be initial hyperactivity with low-level extracellular ROS release in the absence of any exogenous stimulus in persons with desquamative gingivitis. Desquamative gingivitis also can influence on serum and plasma oxidative markers in humans. Evidence suggest that oxygen-derived free radicals and their products play a key role in the pathogenesis of the chronic inflammatory disorder.[5-8] Many of the studies have shown that gingival periodontal diseases were highly associated with various

inflammation-linked systemic diseases such as cardiovascular disease, chronic respiratory illness, and diabetes mellitus. Oxidative stress plays a significant role in the pathogenesis of these diseases.[1,3-5] It has been well-documented systemic inflammation is the result of oxidative stress arising from periodontal lesions, and their products play a significant role in the pathogenesis of chronic inflammatory disorder such as gingivitis and periodontitis.

MECHANISM LINKING OXIDATIVE STRESS AND FREE RADICALS

Oxidative stress can be defined as a process derived from the failure of body's endogenous antioxidant defenses to scavenge free radical species. The oxidative DNA damages may play a significant role in the pathogenesis of many chronic conditions, including neurodegenerative disease, diabetes, cancer, and chronic inflammatory conditions.[6,7] This evidence suggests that free radicals play a key role in the development of several pathological conditions. Free radicals are highly reactive chemical species, characterized by very short half-life. They are made up of an individual atom or various atoms that form a molecule with a free electron. Free electron present is accountable for the high reactivity of free radicals [Figure 1].[8,10-12]

ROS are partially reduced metabolites of oxygen. They are generated through a variety of processes including ionizing radiation, UV, ultrasound, activation of the mitochondrial respiratory chain, respiratory protein oxidation, and from enzymatic reactions and peroxisomes. They are also produced in a "respiratory burst" from phagocytes. They act through phagosomes as molecules toxic to microorganisms, fungi, parasites, and neoplasmic cells and are thus play a pivotal role in the intracellular killing mechanism.[10] They are naturally occurring molecule that is essential to life but concurrently they are capable of harmful pathophysiology also. Following are some of the ROS that are involved in various intracellular reactions:

- Superoxide anion O_2^-
- Hydrogen peroxide H_2O_2
- Hydroxyl radical $^{\bullet}OH$
- Singlet oxygen $^{\bullet}O_2$
- Hypochlorite anion OCl^-
- Alkoxy radical $RO^{\bullet}$
- Peroxy radical $ROO^{\bullet}$
- Organic hydroperoxides ROOH
- Ozone O_3
- Lipoxyl $LO^{\bullet}$
- Lipid peroxyl $LOO^{\bullet}$

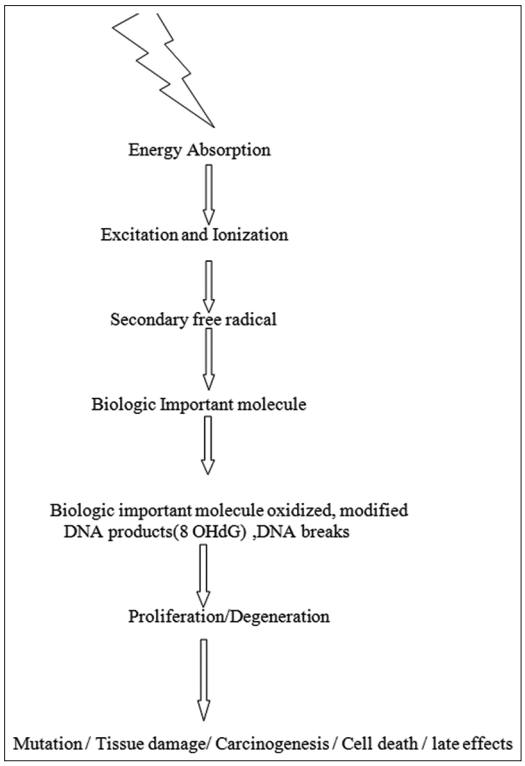

Figure 1: Mechanism of free radical formation and oxidative stress in the body

Normal cells protect themselves from oxidative stress using:

- Enzymatic antioxidants
- Non-enzymatic antioxidants.

Enzymatic antioxidants including superoxide dismutase (SOD), glutathione peroxidase, myeloperoxidase, and catalase (CAT) and non-enzymatic antioxidants include vitamins, minerals, and thiols. While most ROS are short lived, they can cause considerable damage to tissue and cellular components, e.g. cellular phospholipids, nucleic acids, proteins, carbohydrates, and enzymes. Lipid peroxidation is by the hydroxyl radical, which affects polyunsaturated fatty acids or membrane phospholipids.[13-15] Lipid hydro peroxides and aldehydes are formed in this way; as second messengers they lead to protein and DNA damage. There is decrease in respiratory chain activity as well as physical properties of cellular membrane. The hydroxyl radical in association with metal ions bound to the DNA chain, causing DNA damage and cracking and mutations. In addition to this excess ROS cause the activation of specific metabolic systems, e.g., calcium-dependent endonucleases, which split the DNA chain. Damaged DNA becomes cause autoantibody production and become more immunogenic. There is continuous oxidative damage occurring to biomolecules by a variety of free radicals and other +and repair systems. DNA is probably the most important and biologically significant target of oxidative attack and it is extensively accepted that constant oxidative damage to DNA is a sound contributor to the age-related development of the major diseases.[16-18]

BIOMARKERS FOR OXIDATIVE STRESS

Oxidative stress can result in DNA damage, including the oxidation of nucleosides. Damaged DNA becomes more

immunogenic, causing autoantibody production. Studies on hypoxanthine/xanthine oxidase-dependent damage to DNA structure in the presence of calcium ions identified products which may be used as oxidative DNA damage markers. These are 5,6-dihydrocytozine,4,6-diamino-5-formamidopirymidine,2,6-diamino-4-hydoxy-5-form amidopirymidine, 8-hydroxyadenine,8-hydroxyguanine, and 8-hydroxy-2'-deoxyguanosine.

Among various types of oxidative DNA damage, 8-OH-dG is an important biomarker of oxidative stress. ROS are removed or checked by the endogenous antioxidant enzymes such as SOD, GSH, CAT, and other peroxidases. The 8-OHdG is a compound formed as a result of reaction between ROS and DNA. It decreases the link between intracellular ROS accumulation and genotoxicity. Accumulated 8-OHdG can penetrate through the DNA replication process and can hamper DNA repair mechanism. Oxidative stress can lead to DNA damage, including the oxidation of nucleosides. 8-OHdG is an oxidized nucleoside that is excreted in the bodily fluids with DNA repair.[19,20]

CONCLUSION

Serum 8-OHdG is formed as a result of reaction between ROS and DNA. It is a connecting link between intracellular ROS accumulation and genotoxicity. The role of oxidative stress in diseases of oral cavity especially those having multifactorial etiology such as gingival and periodontal diseases cannot be denied. In view of this regular biomonitoring studies in target human populations are utmost necessary to pause their further prevalence in the society. In addition, several life style factors may influence the serum concentrations of 8-OHdG but still this it is an important biomarker that should be studied in detail.

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