TNFα signaling mechanism against cell necrosis due to overextended denture

[1]Imam Safari Azhar, [2]Nabila Qothrunnada
[1]Department of Prosthodontics
[2]Bachelor of Dental Science Program
Faculty of Dental Medicine, Universitas Airlangga
Surabaya, Indonesia
Corresponding author**: Imam Safari Azhar**, E-mail: **imam-safari-azhar@fkg.unair.ac.id**

ABSTRACT
Objective: Not all removable partial dentures are successful or function well. One thing that patients complain about injuries to the oral mucosal tissue. The presence of denture edges that are too long or what is often referred to as overextended can cause necrosis of oral mucosal cells which show a clinical form of ulcers. The purpose of this paper is to explain the process of mechanical injury due dentures overextended against cell necrosis. **Methods**: Conduct a review by covering the keywords mucosal ulceration, overextended denture, TNFα signaling. Various articles that have been obtained were thoroughly reviewed according to the inclusion and exclusion criteria. **Results** and **discussion**: The literatures show that overextended dentures cause discomfort. This is due to pain caused by injury to the mucosal lining of the oral cavity. Injury due to overextended denture causes cells to release death receptors in the form of TNF-R1 receptors. TNFα signals to bind to TNFα trimer with the TNF-R1 receptor. This response then proceeds to various processes that then lead to necrotic cell death. **Conclusion**: Death receptors and TNFα initiate cell death where this necrotic cell death depends on the formation of reactive oxygen species.
Keywords: overextended denture, TNFα signaling, necrosis cells

INTRODUCTION

In the field of prosthodontics, the manufacture of removable dentures (RD) aims to improve aesthetics, masticatory function, speech function and protect the supporting tissues under RD. Not all removable partial dentures (RPD) are successful or function properly, because there are many patient complaints, including loose prostheses, pain due to excessive pressure on the oral mucosal tissue, occlusion errors and the presence of a fractured prosthesis base.

One thing that complained by the patient is the injury to the oral mucosal tissue. The wound is a cell death that causes ulcers of traumatic lesions. Traumatic lesions are tissue discontinuities that extend from the dermis to the subcutis and always occur in pathological conditions. In general, these lesions are caused by mechanical trauma and the relationship between the causes is known.[1]

Traumatic lesions are classified as reactive lesions of cell necrosis with a clinical picture in the form of a single ulcer on the mucosa which can be caused by physical or mechanical trauma, thermal, chemical and radiation changes that cause tissue damage.[2] The lesion is characterized by a yellowish purulent fibrin membrane accompanied by pain.[3] These lesions may be healed within a few days or weeks after the cause of the trauma is removed. The pain will go away within 3 or 4 days, and will heal within 10-14 days. The RPD can cause trauma to the hard and soft tissues beneath the denture. These changes begin to occur as soon as the patient wears the denture and involve a high proportion of mucosal inflammation within one year of the denture being made. In a new complete denture (CD), which is clinically good dexterity. The existence of a denture edge that is too long or what is often referred to as overextended can cause necrosis of oral mucosa cells which shows a clinical form of ulcers.

Thus, this paper is aimed to to explain the process of mechanical injury due to overextended denture to against cell necrosis.

Removable dentures

Dentures are artificial devices that are used to replace part or all of the natural teeth that have been lost and restore changes in tissue structure that occur due to the loss of natural teeth. The purpose of making dentures, both CD and partial dentures, is essentially to improve the function of mastication, taste, aesthetics, maintain tissue health and prevent further damage to the structure of the oral cavity organs. In elderly patients itself the goal is to maintain the health and function of the masticatory system by establishing preventive measures without involving excessive medication.[4] The indications for making CD are loss of all teeth, the condition of the alveolar process is still good, the patient's oral condition is good, the general condition of the patient is good, and the patient is willing to have dentures made.[5] Problems often occur after

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the installation of a full denture include continuous pain under dentures, denture less fixed and comfortable, the mouth feel full and uncomfortable and impaired speech function.[6]

The RD consist of dentures that are attached to the base of the prosthesis; their bases can be made of metal or metal alloys. However, most denture bases are made of polymers, commonly are made of poly (methyl methacrylate) resin. This resin is very stable, does not change color under ultraviolet light, is durable, and is quite stable in heat. Acrylic resin is more often used because of its advantages, that is light weight, cheap, the same color as the gingival color, easy to manufacture and easy to prepare. The disadvantage, acrylic has micropores, make it easier for food debris and bacteria to enter it.[4]

Overextended denture

Denture *overextended* is a term applied to denture plate is longer than the peripheral seal mucosa. The denture will cause injury to the oral mucosa in the form of ulcers. Dentists who have made dentures on a patient often get complaints about the feeling of discomfort or pain due to the use of the denture. Usually, dentists only reduce or remove the parts of the denture that are considered to be the cause. But what is often found is abnormalities or pain that arise because the supporting mucosa is not treated. As a result, it is difficult for patients who have suffered from abnormalities or changes in the oral mucosa to support dentures to be able to accept dentures again if they are not treated properly.[7]

Necrosis cell

Necrosis is the death of cells as a result of damage or trauma (for example: lack of oxygen, extreme temperature changes, and mechanical injury), where cell death occurs uncontrollably which can cause cell damage, an inflammatory response and very potentially cause serious health problems. Stimulus that is too heavy and lasts too long and exceeds the adaptive capacity of cells will cause cell death in which cells are no longer able to compensate for the demands of change. A group of cells that experience death can be recognized by the presence of lysis enzymes that dissolve various cell elements and the emergence of inflammation. Leukocytes will help digest dead cells and then morphological changes begin to occur. Necrosis is usually caused by a pathological stimulus. Apart from pathological stimuli, cell death can also occur through a programmed cell death mechanism; after reaching a certain life span, the cell will die. This mechanism is called apoptosis, that is cells will destroy themselves (suicide).[6,7]

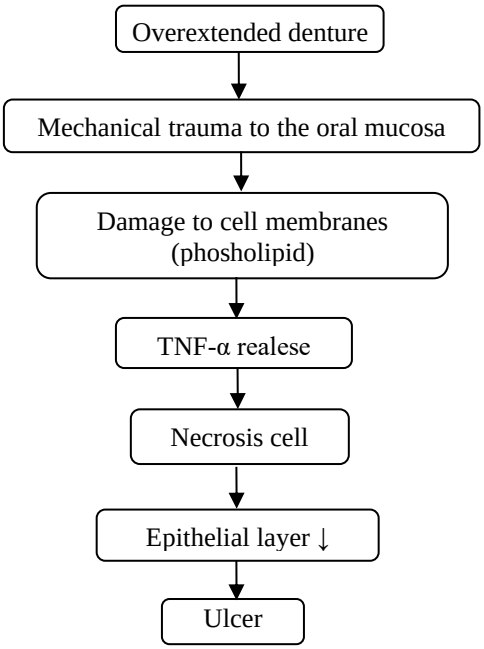

Figure 1 Conceptual mapping

METHODS

This literature review was compiled by searching articles through *databases* literature search *Google Scholar* and *PubMed*. The review was carried out by covering the keywords mucosal ulceration, overextended denture, TNFα signaling. Various articles that have been obtained were thoroughly reviewed according to the inclusion criteria and exclusion criteria. The inclusion criteria used were articles on the mechanism of signaling TNFα on cell necrosis due to *overextended dentures*. The exclusion criteria used were articles that did not have a complete structure, so they were taken for information only.

RESULTS

A good denture is able to improve the function of mastication, taste, aesthetics, maintain tissue health and prevent further damage to the structure of the oral cavity organs. Sometimes it is difficult for dentists to determine the boundaries of movable and immovable mucosa in the oral cavity, resulting in an overextended denture.

The overextended denture causes discomfort to the patient. The discomfort is due to pain in the oral mucosa of the oral cavity. The pain is caused by injury to the mucosal layer by a denture base that is too long. The oral mucosa of the injured oral cavity is in the form of ulceration. Ulceration is a

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lesion formed by local damage from the epithelial tissue to the lamina propria.[8] Cells are damaged and experience the death of cells that exfoliate constantly until the release of stratum basalis even to the lamina propria.

DISCUSSION

The basic function of the mucosa is a barrier, continuing sensation from the external environment, regulating heat and as a medium for the secretion of saliva. The mucosal surface epithelium forms a barrier major to various physical and chemical conditions. Keratinization is a form of protection against adjustment of function from stimulation or irritation. The mucosa in the oral cavity can be either keratinized or non-keratinized.[9] Gingival mucosa is a masticatory mucosa that had epithel as keratinized epithelium, with moderate vascularization. Collagen connective tissue in the mucosa is denser, thicker and more regular than the collagen connective tissue in the covering mucosa. The mucosa of the cheeks, lips and ventral tongue is a flexible covering mucosa. The epithelium of this mucosa is non-keratinized stratified squamous epithelium, while the lamina propria is composed of elastic and reticular collagen fibers.[9-11]

Mucosa which has a small amount of keratin is relatively more prone to injury due to pressure. In other studies; it is said that this pressure causes the mucosa to atrophy. Atrophy is an adaptive response that can lead to reduced blood supply, inadequate nutrition, hypoxia and pressure. Associated with these effects, cell atrophy may increase to the point where cells are injured and die.[12]

Initially, injury occurs because the overextended denture causes the cells to secrete death receptors, namely TNF-1 receptors (TNF-R1). The TNF-1 receptor then activates the caspase. TNFα signals the TNFα trimer that binds to the TNF-R1 receptor. This triggers a change in the receptor that binds the adapter proteins TRADD and RIP1 to the death domain receptor. The adapter protein then recruits TRAF2 and IKK in a complex manner. Recruitment of TRADD, RIP1, and TRAF2 leads to degradation of protein IκBα and activation of MAP kinase (MAP3K). The proteolytic degradation of IκBα that normally maintains NF-B in the cytoplasm allows the translocation of NF-κB to the nucleus, where it acts as a transcription factor. The MAP3K phosphorylates and activates downstream kinases, thereby activating MAP kinases, JNK, p38 and ERK. Activation of this kinase is combined with activation of NF-kB. When NF-B activation is reduced or prevented, TNFα signaling causes FADD and caspase-8 to recruit a secondary complex that triggers caspase-8 activation, leading to cell apoptosis. One of the caspase-8 substrates is RIP1. The continued increase in RIP1 lysis leads to apoptosis. When caspases are inhibited, apoptosis is prevented and the RIP$_1$ protein is stabilized. The RIP$_1$ and TRADD form a complex with NOXO1, and NOXO1 recruits Nox1 and Rac1 to form superoxide to produce the active complex. The RIP1 is an important factor in NOXO1 recruitment, and TRADD is important in complex activation by interacting with the SH3 domain of NOXO1. The presence of NOXA1 as a driving factor is predicted, but has not been demonstrated. The presence of p22 in the complex is unknown. Superoxide production was proposed to promote continuous activation of JNK, leading to cell necrosis.[13]

It is concluded that the injury due to the overextended denture causes cells to release the death receptors in the form of TNF-R1 receptors. The TNFα signals to bind to the TNFα trimer with the TNF-R1 receptor. This response then proceeds to various processes that then lead to the necrotic cell death.

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