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Authors
Aygun Aliyarbayova
Assistant Professor, PhD, Department of Cytology, Embryology and Histology of Azerbaijan Medical University, Baku, https://orcid.org/0000-0003-0887-3132, aeliyarbeyova@amu.edu.az

Vagif Hasanov
Associate Professor, PhD, Department of Therapeutic Dentistry of Azerbaijan Medical University, Baku, https://orcid.org/0009-0004-7447-9875, vhesenov@amu.edu.az

Yegana Shakaraliyeva
Professor, PhD, DSc, Department of Medical Biology and Genetics, Azerbaijan Medical University, Baku, https://orcid.org/0000-0002-0653-7605, ysakaraliyeva@amu.edu.az

Tamilla Sultanova
Associate professor, PhD, Department of Cytology, Embryology and Histology of Azerbaijan Medical University, Baku, https://orcid.org/0009-0001-3461-0881, tsultanova@amu.edu.az

Mehdi Gasimov
Assistant, Dentistry department of Nakhchivan State University, Azerbaijan, https://orcid.org/0009-0004-9808-5571, mehdi.gasimov00@gmail.com

Meleyke Gahramanova
restorative dentistry resident, Center of oral and teeth health of Nakhchivan, Azerbaijan, https://orcid.org/0009-0002-9673-8386, meleykecavadova829@gmail.com

Shahana Gurbanova
Assistant, Department of Cytology, Embryology and Histology of Azerbaijan Medical University, Baku, https://orcid.org/0009-0000-2307-5820, squrbanova@amu.edu.az

Ayten Shukurova
Assistant Professor, PhD, The Department of Pharmacognosy of Azerbaijan Medical University, Baku, https://orcid.org/0000-0002-9485-0932, asukurova@amu.edu.az

***Correspondence to**
Aygun Aliyarbayova
* Assistant Professor, PhD, The Department of Cytology, Embryology and Histology of Azerbaijan Medical University, Baku
https://orcid.org/0000-0003-0887-3132
E-mail: aeliyarbeyova@amu.edu.az

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Influence of Macrophage Migration Inhibitory Factor on Oral Tissue Healing and Its Impact on Prosthodontic Treatment Outcomes

Abstract
Macrophage migration inhibitory factor is a multi-purpose immunoregulatory cytokine, which is involved in the processes of macrophage activation, inflammatory amplification, oxidative stress, angiogenesis, and tissue remodeling. In restorative and prosthodontic dentistry, predictable treatment results are based on the capacity of the oral tissues to heal, adapt, and be biologically stable to microbial, mechanical, surgical, and prosthetic challenges. The review addresses the applicability of macrophage migration inhibitory factor in the healing of the oral tissues and whether it has the potential to affect the outcome of prosthodontics. It may be related to its biological activity, which may be associated with mucosal inflammation, periodontal tissue response, residual ridge remodelling, peri-implant healing, and bone-implant interface stability. The potential effects of altered expression include delayed tissue repair, denture-bearing mucosal discomfort, periodontal breakdown, peri-implant inflammation, marginal bone loss and a decrease in the predictability of the prosthetic. In addition to its mechanistic relevance, macrophage migration inhibitory factor can have a future value in terms of biomarker in saliva, gingival crevicular fluid and peri-implant sulcular fluid to assess the risk of inflammatory risks before and after prosthodontic rehabilitation. Longitudinal studies are required to be able to correlate the level of macrophage migration inhibitory factor with clinically significant outcomes, such as the healing time, mucosal tolerance, periodontal stability, implant survival/prosthesis longevity and patient-reported comfort. Provided it is proven to be correct, this mediator can assist precision prosthodontics by facilitating the earlier detection of risks, personalized planning of treatment, biologically guided implant loading, and personalized maintenance schedules.

1. Introduction

Healing in oral tissues is a biological necessity to be able to predict restorative and prosthodontic dentistry. The success of fixed prostheses, removable partial dentures, complete dentures, implant-supported prostheses and full-mouth rehabilitation does not only depend on the design of the prosthetic and selection of material to be used in the prosthetic, but also on the ability of the oral tissues to heal, adapt, and remain biologically stable in the long term. The structures of the oral mucosa, periodontal tissues, alveolar bone, and peri-implant structures contribute to the comfort, retention, functioning, aesthetics, and longevity of the prostheses. On the other hand, the delayed or disregarded healing may contribute to the mucosal soreness, denture intolerance, gingival inflammation, abutment compromise, peri-implant tissue breakdown, marginal bone loss and prosthetic failure.

Inflammation is a vital early process in wound healing but its severity and occurrence time should be closely monitored. A controlled inflammatory response facilitates microbial defense, recruitment of immune cells, tissue debridement, angiogenesis, fibroblast activity, collagen deposition and

remodeling of the extracellular matrix. Nonetheless, a lot of inflammation or continuous inflammation may slow the healing process and encourage chronic tissue damage. This is critical in particular in the field of prosthodontics since the oral tissues are constantly exposed to saliva, microbial biofilm, masticatory forces, prosthetic pressure, restorative margins, and implant-abutment interfaces. Such local influences can alter the inflammatory signaling and can affect the quality of healing. Macrophage migration inhibitory factor is one of the mediators in the immune regulation process that has drawn attention due to its multifunctional nature (a cytokine). Among the mediators of the immune regulation process, macrophage migration inhibitory factor has attracted attention as a multifunctional cytokine related to the immune regulation process of inflammation, tissue remodeling, and disease progression[1].

Macrophage migration inhibitory factor (also known as MIF) is a cytokine-like, chemokine-like and stress-response pleiotropic inflammatory mediator. It is synthesized by a number of immune and non-immune cells and it plays a role in both innate and adaptive immune regulation. It has a biological significance in that it is capable of affecting the recruitment, survival, migration, inflammation and tissue response of immune cells through complex receptor-mediated signaling pathways. The functional diversity, genetic control and potential applicability of MIF to precision medicine is also reflected in its immunobiology[2]. These characteristics render MIF a pertinent molecule to understand the healing process of oral wounds and tissue adaptation in prosthodontic.

At the molecular scale, MIF helps to activate immune cells, amplify cytokines and recruitment of inflammatory cells. It has been characterized as a multifaceted cytokine that is controlled by genetic and physiological processes, and is involved in a variety of inflammatory and disease-related processes[3]. Its biological activity is also determined by the interaction with receptor systems including CD74 and chemokine receptor systems which trigger the downstream pathways associated with inflammatory amplification, cellular survival and tissue response. It has been demonstrated that soluble CD74 can modify the effects of MIF/CXCR4/AKT on cellular outcomes and modulate their response to changing environments[4]. Furthermore, MIF is capable of promoting the JNK signaling by CXCR4-dependent and CD74-dependent routes, which supports the involvement of MIF in the inflammatory signal transduction[5].

Macrophages are key regulators of inflammation and tissue repair and MIF is mainly associated with the immune response mediated by macrophages. When it comes to wound repair, the macrophages are involved in pathogen clearance, release of cytokines, regulation of fibroblasts, angiogenesis, and the switching of inflammation to tissue remodelling. This duality is applicable to the case of prosthodontics since oral rehabilitation relies on the predictable healing of the mucosal tissues, gingiva, periodontal structures, extraction sockets and peri-implant sites. The balance in the macrophage regulation will be able to control excessive inflammation and facilitate tissue repair, which is important to note regarding the need to control the immune system during the healing process. Because MIF is involved in macrophage activation and inflammatory persistence, changes in MIF expression could be one of the biological pathways by which oral healing is slowed, excessively or clinically unpredictably.

The greater inflammatory interest of MIF is signified by its role in systemic inflammatory and immune-mediated diseases. The relationship between MIF family cytokines and cardiovascular inflammation and precision-based therapeutic strategies have been discussed, with hints at wider translational applicability to MIF-related pathways[6]. The MIF superfamily also exhibits a functional diversity of immune regulation and inflammatory biology[7]. Additionally, the belief that molecules like MIF can mediate tissue pathology through many overlapping mechanisms supports the notion that inflammatory mediators, including alarmins and atypical chemokines, are inflammatory mediators[8].

In oral rehabilitation, the applicability of MIF is in that it may be associated with mucosal inflammation, periodontal breakdown, residual ridge remodelling, post-extraction healing process, peri-implant tissue response, and bone-implant interface stability. Both the biological and mechanical stressors are presented to the prosthodontic tissues and their healing process may differ depending upon the systemic disease, age, smoking, oral hygiene, microbial load, prosthetic design and the local tissue condition. Inflammatory profiling associated with MIF could thus be potentially valuable in the future in identifying at-risk patients that would otherwise delay in healing, develop mucosal complications, develop peri-implant disease or experience prosthetic failure.

The purpose of the review is to synthesize the existing knowledge about MIF and to relate it to the healing of oral tissues and the outcomes of the oral tissue after the application of MIF. Connecting the clinical issues of rehabilitation in personalized prosthodontic therapy with the molecular inflammatory processes, the review demonstrates the possibility of MIF usage as a translational biomarker and future therapeutic target in personalized prosthodontic therapy.

2. Biological and Molecular Profile of Macrophage Migration Inhibitory Factor

Migration inhibitory factor (MIF) is a structurally unique inflammatory mediator that is involved in immune regulation, tissue injury and repair. First identified in connection with the migration of macrophages, it now has been seen to be a cytokine-like molecule, which is involved in the activation of inflammatory responses, in cellular stress responses and in host defense. This profile renders MIF pertinent to oral tissues which is subjected to microbial biofilm, mechanical irritation, mucosal injury, and inflammatory challenge. These responses are significant in the context of prosthodontic dentistry, where the predictability of the healing of mucosa, gingiva, periodontal tissues, bone and peri-implant structures are important.

MIF is a small, evolutionarily conserved protein which has cytokine-like and chemokine-like activity. It has the capability of acting via extracellular signaling and intracellular stress-related pathways unlike many of the traditional cytokines. It is produced by immune, resident tissue cells, such as macrophages, fibroblasts, epithelial cells, endothelial cells and inflammatory cells. The cells are the key to oral wound healing: macrophages control the pathogen clearance and cytokines activity, fibroblasts regulate the synthesis of the matrix, epithelial cells restore the integrity of the mucosal barrier, and endothelial cells promote angiogenesis. The expression of MIF can be involved in the overlapping events in oral tissue repair. Periodontal-associated mediators in saliva and gingival crevicular fluid are reflective of local immune activity, and support the use of oral fluids in the assessment of inflammation[9]. As illustrated in Figure 1, MIF activates the signaling pathways that are mediated by CD74- and chemokine receptor-mediated signaling pathways which are involved in inflammation, angiogenesis, apoptosis resistance and immune cell recruitment.

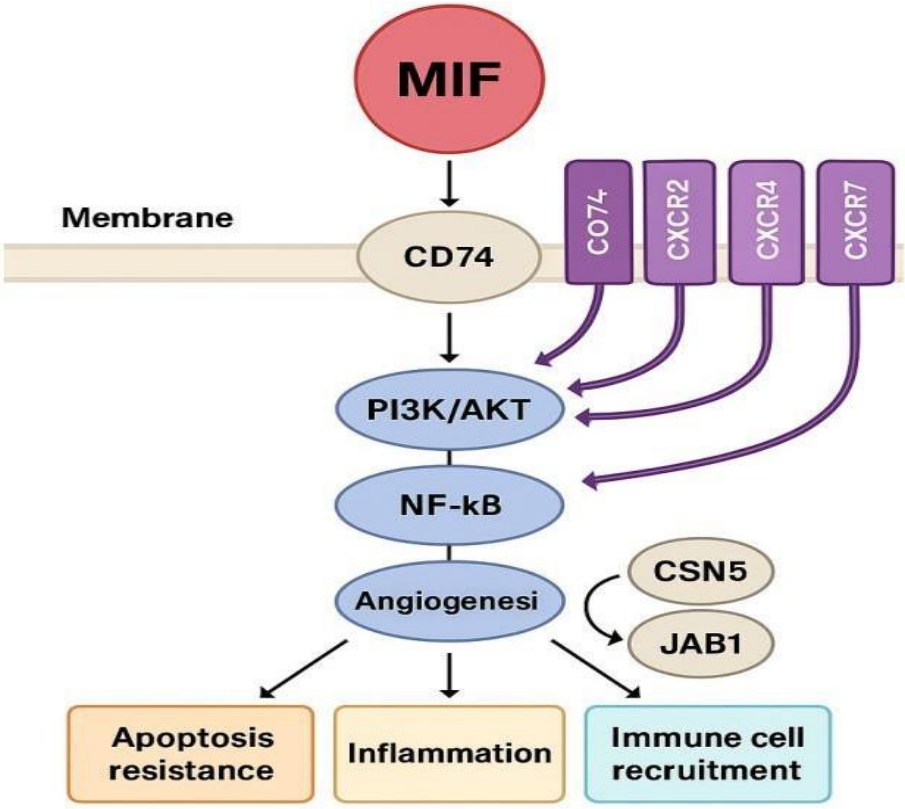

Figure 1. MIF signaling through CD74 and chemokine receptors. Source: Adapted from[10]

Being an immunoregulatory mediator, a pro-inflammatory cytokine, MIF is involved in the recruitment of immune cells, the amplification of cytokines, and the maintenance of inflammation. This is applicable as both periodontal and peri-prosthetic tissues are put to test by microbial biofilms and the host immune responses. Defense and repair of the body requires inflammation; however, too much or too long of the inflammation may facilitate the breakdown of the connective tissue, delayed healing, and compromised prosthodontic results. An example of this process is periodontal disease, where dysregulated processes of host responses can transform a microbial challenge into a destructive tissue inflammation with systemic effects[11]. The interactions between biofilms and immune responses, as well as genetic susceptibility and environmental factors also contribute to periodontal diseases and can potentially impact abutments and implants[12].

The activity associated with MIFs can play a role in the shift of protective inflammation to a persistent tissue damage. MIF could be beneficial in early host defense through the activation of macrophages and the amplification of cytokines but may lead to sustained inflammation and hamper recovery. This dual role is significant bearing in mind that oral rehabilitation needs tissues to heal under the functional loading, prosthetic loading, plaque retention, restorative margins, and implant abutment interfaces. The studies on biomarkers have demonstrated that Gingivitis-related salivary chemokines can be used to diagnose gingivitis implying that they are diagnostic[13].

Receptor-associated pathways shown to mediate the biological effects of MIF include inflammation, cell survival, oxidative stress and tissue remodelling. These pathways control the macrophage activation, production of cytokines, the cellular motility and the restoration and inflammatory persistence balance. They could influence the healing of epithelia, the activity of fibroblasts, periodontal remodeling, and peri-implant response in the oral tissues. MIF as a regulator of the inflammatory response in experimental models is suggested by novel

MIF inhibitors that can be used to down-regulate inflammatory activation[14]. This evidence is not oral-specific, but will assist in making therapeutic relevance in excessive inflammation or delayed repair.

Recent periodontal studies stress the need to comprehend inflammation based on molecular and proteomic levels. The development of microscopy to proteomics and next-generation sequencing allowed examining the interactions between the host and the microorganism and between the inflammatory system and cells in greater detail[15]. This perception is significant since MIF operates in networks which include biofilms, immune cells, epithelial barriers, vascular responses, and remodeling.

MIF can also interplay with oral tissue cells which are concerned with healing. It can act on the release of cytokines and resolution of inflammation in macrophages. In fibroblasts it can have an influence on collagen production and turnover of the matrix. The inflammatory activity of epithelial cells can slow the process of restoring the barrier in case of trauma, surgery or even irritation of the prosthetic. The MIF-related pathways can have an impact on the angiogenesis and vascular support in endothelial cells. Among these is the gingivitis healing around fixed restorations, the mucosal adaption under dentures, the extraction socket repair and the peri-implant stability. The oral-systemic inflammatory situation justifies this interpretation, as the mucosal immune interactions are interpreted through the integrated oral and systemic views[16]. Therefore, the patterns associated with MIF can have an effect on the mucosal adaptation, periodontal stability, residual ridge remodelling, peri-implant healing and long-term prosthetic prognosis.

3. Cellular and Molecular Mechanisms of Oral Tissue Healing

Healing of oral tissues is a complex biological process, which includes vascular response, immunotropic, epithelial repair, connective tissue formation, and tissue remodeling. Healing in the oral cavity takes place in a special environment that is constantly exposed to saliva, microorganisms, occlusal forces and prosthetic or restorative mechanical loading. Oral mucosal wounds, as compared to many extraoral wounds, tend to heal faster and with less scarring due to the unique transcriptional and immunological profile of the oral mucosa that supports rapid healing[17]. This is of clinical significance in the field of prosthodontics since the processes of denture and fixed restoration, implantation, and post-extraction prosthetic rehabilitation all demand predictable and stable tissue recovery.

The general stages involved in the healing of oral wounds are homeostasis, inflammation, proliferation, and remodeling. Homeostasis commences shortly after injury, and entails the formation of clots, platelet activation and release of early signaling molecules that prepare the wound bed to repair. This is followed by the inflammatory stage where neutrophils, macrophages and other immune cells are involved in cleaning up the debris, limiting microbial invasion, and the release of cytokines, which control subsequent healing events. This phase is particularly applicable in the context of the prosthodontic care since the ongoing inflammation can delay the mucosal adaptation, impair periodontal support, or disrupt peri-implant tissue stability. The process of inflammation resolution is thus an active biological process as opposed to a passive inhibition of immune activity. Pro-resolving mediators assist in limiting the tissue destruction, restoring a normal immune response, and preventing chronic periodontal inflammation[18].

The proliferative phase involves migration of the epithelial cells to restore continuity of the mucosal barrier, synthesis of collagen and other elements of the extracellular matrix by the fibroblasts and the proliferation of the angiogenic process supported by the endothelial cells. Epithelialization is necessary since the surface of the oral mucosa needs to quickly re-establish the protection against saliva, microorganisms and mechanical irritation. Angiogenesis provides the oxygen and nutrients needed by the cell proliferation, and the fibroblast activity determines the integrity and structure of the newly formed connective tissue. These are directly related to denture-bearing mucosa, gingival tissues around the crown margins, extraction socket and peri-implant soft tissues. When impairments are observed in the epithelial closure, vascular supply, or fibroblast functioning, tissues can be left susceptible to ulceration, inflammation, slow healing, and intolerance of prostheses.

The remodeling stage encompasses maturation of collagen, reorganization of the extra-cellular matrix, decrease in vascularity and restoration of tissue architecture. Remodeling is crucial in the context of prosthodontic treatment since healed tissues are required to be long-term functional loaded. Mucosa bearing dentures should be able to adapt to pressure and friction, abutment teeth need to be supported by the periodontal tissue, peri-implant tissues should be in a position to maintain a protective soft tissue seal and stable bone interface. Poor remodeling can result to residual ridge resorption, unstable denture support, gingival recession, marginal tissue breakdown or peri-implant complications. The healing process of oral tissues follows a sequence of steps in homeostasis, inflammation, proliferation and remodeling, including a coordinated recruitment of immune-cells, angiogenesis, fibroblast activity, re-epithelialization, organization of the extracellular matrix and collagen maturation, as illustrated in Figure 2.

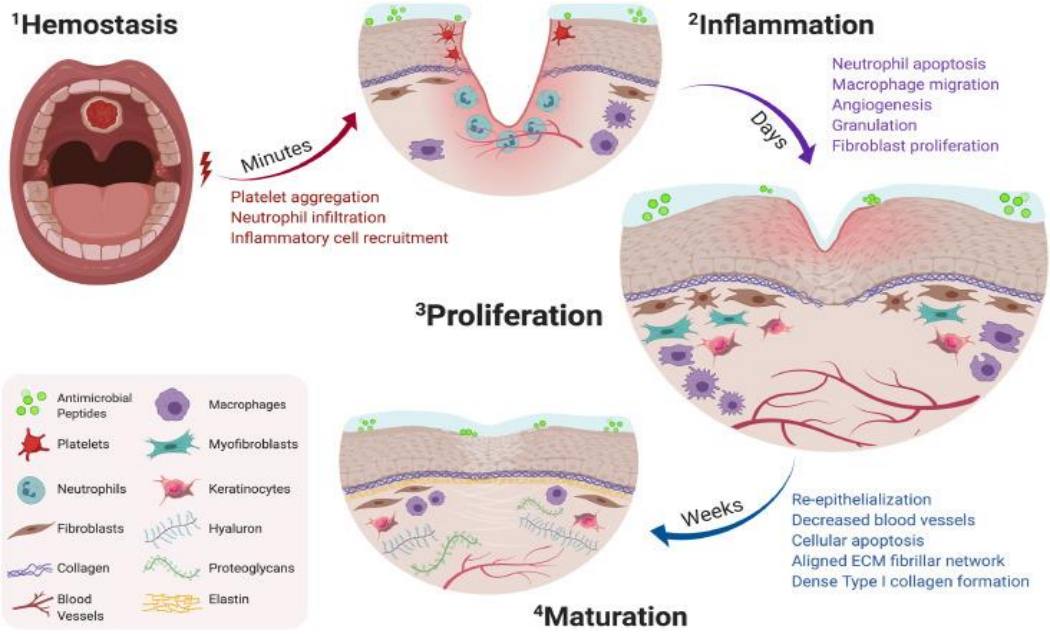

Figure 2. Sequential phases of oral wound healing
Source: Adapted from[19]

There are a number of local and systemic influencing factors on oral healing. Saliva provides defense to tissues by keeping tissues moist, lubricating surfaces, aiding antimicrobial defense, and aiding in repair of the epithelial layer. The evidence supporting the biological relevance of saliva is that the oral cavity and the salivary environment actively engage in host defense and processes related to diseases[20]. A significant impact on healing is also due to the oral microbiota. Harmonious microbial living may be accompanied by healthy tissues, and dysbiosis can exacerbate inflammation and slow down healing. Systemic diseases may change the microbial composition and host-microbe interactions in the oral cavity, increasing the inflammatory load and changing the healing ability[21]. This is especially applicable to the patients of prosthodontics with diabetes, immune dysfunction, cardiovascular disease or chronic inflammatory conditions.

Oral healing is also attached to the extended systemic inflammatory processes. Periodontal disease has now been recognized as local inflammatory condition as well as a cause of systemic inflammatory comorbidities. The pathways that may connect periodontal inflammation with a systemic disease may involve shared pathways involving immune activation, microbial dysbiosis, endothelial dysfunction, and release of inflammatory mediators[22]. In the case of prosthodontics, such a connection is significant since the systemic inflammatory condition can affect periodontal stability, post-surgical restoration, prognosis of implants, and maintenance needs.

The patterns of healing vary around the sites of oral tissues. The healing of the mucosal is generally quick, but periodontal healing is more complex since it involves the gingival epithelium, connective tissue attachment, periodontal ligament, cementum and alveolar bone. The healing of extraction sockets involves clot organization, formation of granulation tissue, deposition of woven bone and subsequent bone remodeling. The microbial challenge, mechanical loading and inflammatory imbalance are sensitive to peri-implant healing where both mucosal sealing and bone integration is required. Therefore, the healing of oral tissues must be considered as site-specific, instead of uniform. These mechanisms are important to understand to enhance mucosal comfort, periodontal support, residual ridge stability, peri-implant integration, and long-term prosthodontic success.

4. MIF in Oral Inflammation and Tissue Repair

Migration inhibitory factor (MIF) is a significant inflammatory mediator which can influence the repair of the oral tissues through its effects on the activation of macrophages, its interaction with cytokines, its influence in regulating immune responses, its role in oxidative stress, in regulating angiogenesis, and in controlling remodelling of the extracellular matrix. The mouth cavity is a distinct healing environment due to the constant exposure of the tissues to saliva, microbial biofilm, mastication, prosthetic pressure and restorative interfaces. Oral tissues usually exhibit a high rate of wound healing, but wound healing may be impaired when there is excessive, prolonged, or unresolved inflammation. Mouth wound healing issues are usually related to local infection, systemic, mechanical irritation, impaired vascularity, and dysregulated inflammation, which may contribute to the results of prosthodontics[23].

Macrophages are the key controllers of the oral inflammatory healing. They are involved in clearing pathogen, cytokine secretion, clearance of debris, and the engagement of repair pathways, following tissue injury or microbial challenge. MIF may contribute to the activation of macrophages, recruitment of inflammatory cells, and hence enhance the responses of the cytokines. This could be a protective activity in early healing as it enhances host defense and conditions the wound environment to facilitate a healing process. But in cases

of prolonged activation of Macrophage, prolongation of inflammation and interference with tissue recovery may occur. This two-fold effect is clinically significant since denture-bearing mucosa, gingival tissue, extraction socket, and peri-implant sites require an inflammatory response which should be resolved with timely effects before the stable prosthetic performance can be achieved. MIF-mediated pathways have been reported to influence oral healing by activation of the macrophage, amplification of cytokines, immune regulation, oxidative stress, angiogenesis, remodeling of the extracellular matrix and peri-implant inflammatory responses, which have been demonstrated to be important to the prosthodontic tissue adaptation and long-term treatment outcomes, as shown in Table 1.

Table 1. MIF-Mediated Oral Inflammatory Mechanisms and Prosthodontic Significance

MIF-mediated pathway	Effect on oral healing biology	Clinical prosthodontic significance
Macrophage activation	Promotes cytokine release and host defense	Supports repair but may delay healing if prolonged
Cytokine amplification	Intensifies inflammatory signaling	May cause mucosal soreness and gingival inflammation
Immune regulation	Coordinates bacterial and fungal defense	Relevant to denture biofilm and mucosal inflammation
Mucosal repair	Affects epithelialization, fibroblasts, and collagen deposition	Influences denture tolerance and tissue adaptation
Oxidative stress	Damages cells and matrix components	May impair healing and promote chronic inflammation
Angiogenesis	Supports oxygen supply and granulation tissue	Important for socket and peri-implant healing
Matrix remodeling	Regulates collagen turnover and tissue maturation	Supports residual ridge and peri-implant stability
Peri-implant inflammation	Persistent signaling may promote tissue breakdown	Linked to mucositis, peri-implantitis, and bone loss
Biomarker potential	Reflects inflammatory activity in oral fluids	May guide future risk assessment and maintenance

The biological capacity of the oral mucosa to repair has a unique rapid repair capability. The transcriptional priming of human oral mucosa in wound healing is relatively efficient, which may explain its relative efficiency in the epithelial closure and reduced scarring of its wounds compared to many wounds on the skin. Nevertheless, this benefit may be undermined by chronic inflammation, microbial imbalance, irritation of the prosthetic, or the immunity. The amplification of cytokines related to MIF may have an impact on epithelial cells and fibroblasts, endothelial cells and immune cells in the transition process between inflammation and repair. These cellular interactions at equilibrium may facilitate epithelialization, angiogenesis, collagen deposition, and extra-cellular remodelling of the matrix. By being dysregulated, they can be a contribution to mucosal soreness, ulceration, delayed epithelial closure, tissue fragility, and poor adaptation to prosthetic appliances.

MIF can also apply to the innate and adaptive oral tissue immune responses. The surfaces of the oral mucosa should be able to protect against the bacteria and fungi as well as prevent too much inflammatory damage. This balance is especially significant to denture wearers, whereby prosthetic surfaces have the ability to trap biofilm and promote chronic inflammation of the mucosa. Denture stomatitis that is associated with Candida is determined by the presence of fungal colonization, denture biofilm, irritation of the mucosal lining, and host immune response[24]. Candida albicans is particularly important in the case of denture patients since its attachment to acrylic surface and mouth mucosa may help cause chronic inflammation and pain[25]. In this situation, MIF-mediated immune activation could be involved in the initiation of host defense, although the persistent signaling of the MIF could perpetuate mucosal inflammation and decrease tissue tolerance.

In addition to mucosal defense, MIF-related pathways can have an impact on oxidative stress, angiogenesis and extracellular matrix remodeling. Oxidative stress may cause damage to cells and matrix elements whereas angiogenesis facilitates oxygen delivery, nutrient supply and granulation tissue formation. To achieve tissue maturation and strength, fibroblasts and collagen turnover is required. These processes play a particularly crucial role around implants, where a combination of a stable soft tissue seal, and bone-interface integration, is essential to achieve successful healing. Surgical trauma, inflammatory regulation, tissue maturation, and early clinical conditions influence the peri-implant wound healing[26]. In case the inflammatory mediators are not decreased, it can be assumed that the remodelling of tissues will change to repair and to breakdown, making tissues more susceptible to peri-implant mucositis, peri-implantitis, and marginal bone loss.

The increased literature concerning oral fluid biomarker also supports the clinical relevance of peri-implant disease inflammatory mediators. Peri-implant crevicular fluid and saliva can have a reflection of local inflammatory conditions and have been explored to diagnose and monitor peri-implantitis[27]. Despite the fact

that there has been very little in the way of direct evidence on MIF in any of the prosthodontic environment, it is established that it plays a role in inflammation, making it a viable candidate in the future as a biomarker. Overall, MIF can have a positive impact on the economy by providing an initial defense and repair, but a negative impact when it becomes excessively active or prolonged. This duality is very pertinent to the field of prosthodontics because the predictable outcomes rely on the mucosal adaptation, periodontal stability, residual ridge healing and peri-implant tissue integration.

5. MIF in Prosthodontically Relevant Oral Tissues

Macrophage migration inhibitory factor (MIF) could be of great interest to the prosthodontically important oral tissues since the success of prosthetics depends on the biological stability of denture-bearing mucosa, residual ridges, periodontal support and peri-implant interfaces. Though there is limited direct prosthodontic evidence on MIF, its known roles in macrophage activation, inflammatory regulation, angiogenesis, extracellular matrix remodeling and tissue repair provides a solid foundation on which to explore its potential role in oral rehabilitation. Mechanical loading, microbial biofilm, pressure, friction, and restorative interfaces recurrently expose prosthodontic tissues to mechanical, microbial, pressure, friction, and restorative interfaces; hence, the inflammatory mediators such as MIF may determine the success or progression of these tissues to chronic inflammation. The denture-bearing mucosa, residual ridge remodeling, periodontal support, and peri-implant tissue stability could be influenced by MIF-mediated inflammation as shown in Figure 3.

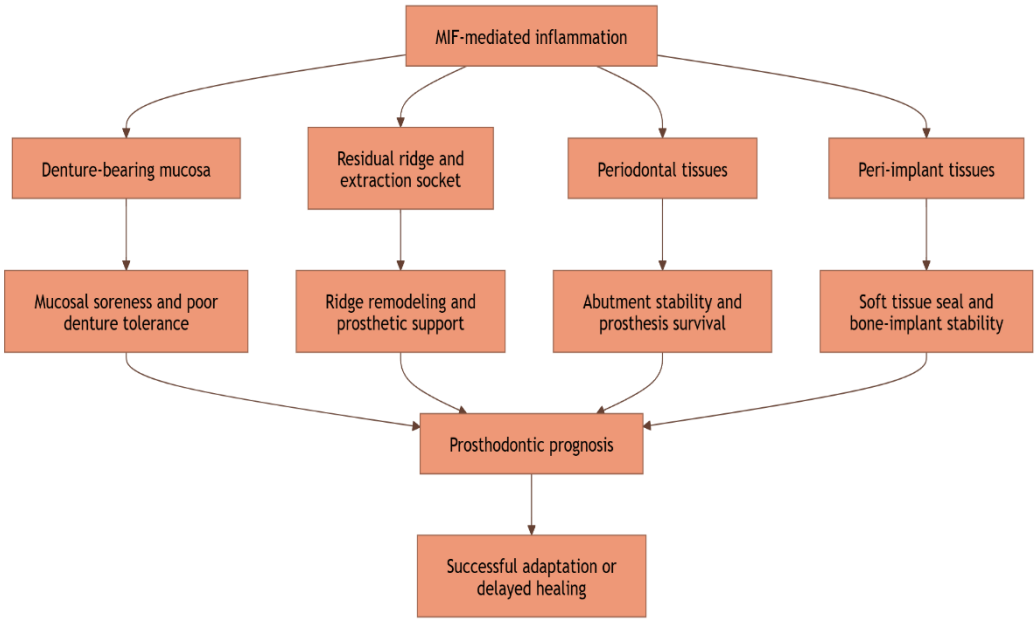

Figure 3. MIF in Prosthodontic Tissue Healing

The most clinically significant site where MIF-related inflammatory activity can be of significant importance is denture-bearing mucosa. The forces of complete dentures and removable partial dentures are sustained in a continuous functional manner on the mucosa, and poorly distributed forces can result in soreness, ulceration, disruption of the epithelial layers, and inflammatory adaptation. When the inflammation, the movement of epithelial cells, the activity of fibroblasts, the vascular support, and the remodeling of the extracellular matrix are well synchronized, oral soft tissues have a high repair potential[28]. Nevertheless, when the inflammation is chronic, it is likely that the mucosa will not be able to adjust to the loading of the prosthesis, thus causing pain, decreased denture tolerance, and poor prosthesis acceptance. MIF may be of interest in this case since sustained cytokine production mediated by macrophages could be a contributing factor to mucosal inflammation and slow wound healing.

Post-extraction remodelling, and residual ridge healing are also the primary considerations in the planning of prosthodontic treatment. The socket goes through the process of clot formation, inflammation, formation of granulation tissue, bone deposition and remodeling after tooth extraction. These processes decide the shape and stability of the residual ridge which directly influences denture support, retention and future development of the implant site. The healing of periodontal and oral wounds involves coordinated efforts of immune cells, fibroblasts, endothelial cells, osteogenic cells, and extracellular matrix components[29]. As MIF is implicated in repair and resorption regulation via inflammatory regulation and macrophage activity, the regulation of repair and resorption during post-extraction remodeling is theoretically changed by the altered MIF expression. This can be clinically significant as too much inflammation might cause ridge resorption, unsteady denture support and low predictability before implant or removable prosthetic rehabilitation.

Another significant area of relevance is periodontal tissues which support both fixed and removable prostheses. Teeth acting as an abutment to a crown, bridge or removable partial denture must have a sound

periodontal attachment, healthy gums and a controlled inflammatory response. The sustained cytokine activity could be a contributor of connective tissue breakdown, collagen turnover impairment and decreased periodontal repair. Periodontal instability can lead to the abutment mobility, gingival recession, loss of attachment and subsequent removal of the prosthesis. So, inflammatory signaling associated with MIFs can be regarded as a potential biological determinant of long-term periodontal support in the area of prosthetic abutments.

Another interface biologically sensitive where MIF can potentially be of clinical significance is the peri-implant tissues. The early soft tissue healing, formation of mucosal seals, angiogenesis, and maintenance of bone-implant contacts are the key factors of successful implant-supported rehabilitation. Dental tissue regeneration is impossible without the process of angiogenesis since vascular support is a source of oxygen, nutrients, and cellular signaling needed to repair[30]. Controlled inflammation facilitates healing in peri-implant sites, whereas prolonged inflammation can disrupt the process of osseointegration, and also predisposes the site to breakdown of the marginal bone or soft tissue. The concept that macrophage-regulated tissue repair studies can be used to influence alveolar regeneration and post-injury tissue outcomes supports the need to investigate mediators such as MIF in oral bone and peri-implant healing[31].

New evidence also indicates that healing of oral wounds has a close association with the dynamics of microbes. The healing of human palatal wounds is accompanied by a change in the associated microbiome, indicating that tissue healing is preconditioned by a host-cell activity and a change in the microbiome associated with the healing process[32]. It applies to prosthodontics since surfaces of dentures, margins of crowns, the location of extraction, and the interfaces of implants can all have a role in retaining microbes and causing inflammation. In general, MIF has the potential to influence prosthodontically relevant tissues through the ability to impact mucosal adaptation, residual ridge remodeling, periodontal support, peri-implant healing and tissue responses to the microbial and mechanical stress. More direct clinical studies are necessary to establish whether MIF can be a useful predictor of risk of prosthodontic tissue, prediction of healing, and prediction of prognosis of long-term treatment.

6. Clinical Relevance in Treatment Planning and Prognosis

The clinical significance of macrophage migration inhibitory factor (MIF) in the planning of prosthodontic treatment has been found to be the possible relationship between MIF and inflammatory risk, capacity of tissue repair and long-term biological stability. The design of the prosthesis, the choice of materials, and the technical accuracy are not the only factors that enable determining the prosthodontic rehabilitation; the ability of the patient to reach controlled healing after the preparation of the tissues, their removal, delivery of dentures, installation of an implant or its functional loading. Since MIF is involved in the activation and repair of inflammation, it can be useful in understanding why some patients experience delayed healing, mucosal discomfort, periodontal breakdown, peri-implant inflammatory, or an inverse relationship between prosthesis tolerance. The MIF/CD74 pathway has been proposed to play a protective role in response to injury and a role in promoting repair, indicating that MIF can be involved in both defense and repair mechanisms of the tissue when properly regulated [33]

The risk of inflammatory risk in patients should be carefully evaluated before the prosthodontic rehabilitation. The tissue response can be changed by local and systemic factors like diabetes, smoking, ageing, periodontal disease, poor oral hygiene, systemic inflammation, and high microbial burden, which can increase the risk of complications. Oral tissues can exhibit slowed mucosal repair, unstable periodontal support, inadequate denture adaptation or increased risk of peri-implant disease in patients with an increased inflammatory susceptibility. The future value of MIF-related inflammatory profiling may therefore have value in the future as an adjunct to standard clinical examination, particularly when the patient is in need of a lot of rehabilitation, in implant therapy or in a patient with compromised periodontal tissues supporting the prosthesis. Nevertheless, MIF is not yet a clinically diagnostic instrument that is routinely practiced but should be thought of as a potential translational marker. Changes in the expression of inflammatory mediators can also be related to the delay of tissue healing and the prosthetic complications. When there is a high inflammatory signaling or prolonged, the repair process can change to controlled healing to chronic inflammation and tissue breakdown. This can be clinically manifested as denture-bearing mucosal soreness, traumatic ulceration, poor soft tissue tolerance, gingivitis surrounding fixed restorations, abutment instability or peri-implant tissue breakdown. The presence of salivary macrophage-related chemokines as potential biomarkers of gingivitis have been investigated in support of the broader idea that inflammatory mediators associated with macrophages in oral fluids may be used as biomarkers of inflammation in the early stages of tissue inflammation. Whilst this does not prove that oral-fluid biomarker measurement can be used as a direct prosthodontic indicator, it does suggest that a measurement of oral-fluid biomarkers may in the future be used as an indicator of direct prosthodontic use. MIF-guided inflammatory risk assessment could be used to predict delayed healing, mucosal discomfort, periodontal breakdown, peri-implant inflammation and decreased prosthesis tolerance, exemplified in Figure 4.

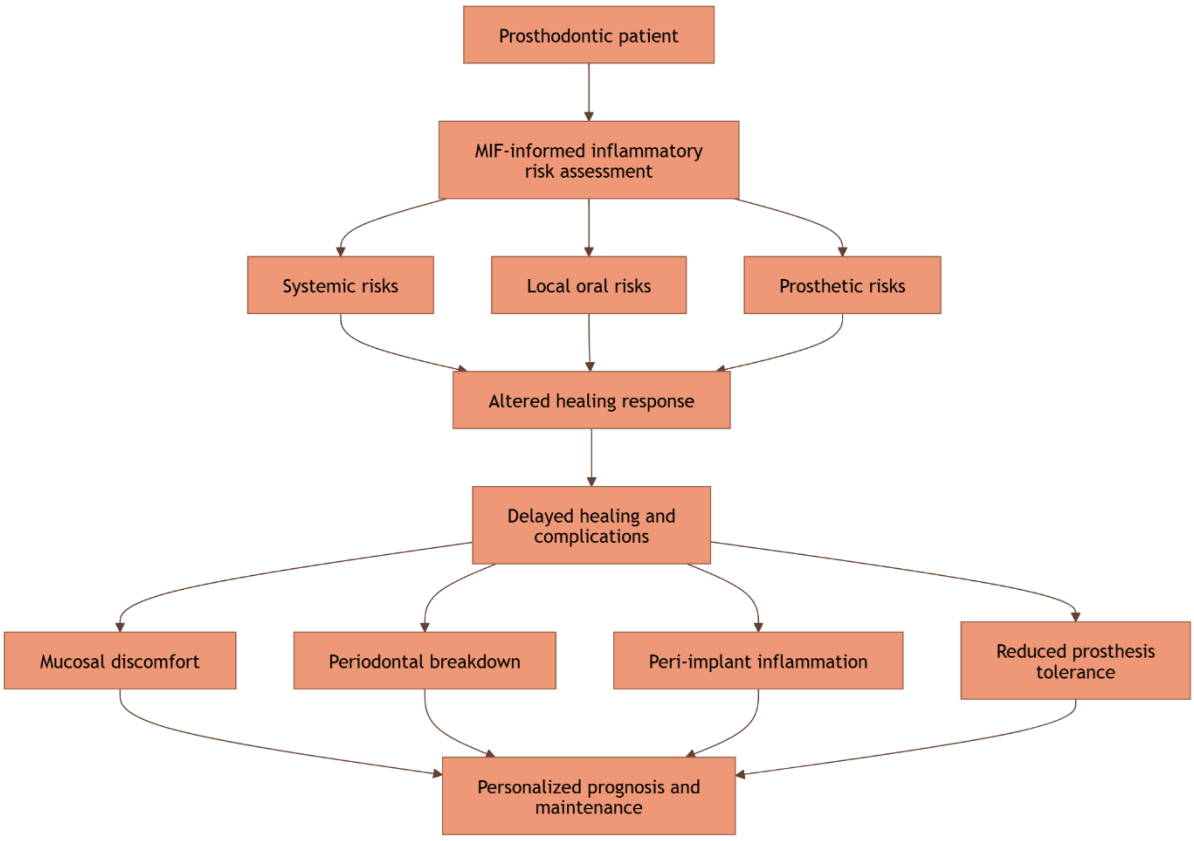

Figure 4. MIF-Guided Inflammatory Risk Assessment for Prosthodontic Prognosis

The clinical applicability of MIF could be applicable to a variety of types of prosthodontic treatments. Long-term inflammatory activity in complete denture patients can affect their mucosal adaptation, their comfort with their dentures, and their tissue tolerance. In removable partial dentures, the inflammation of the abutment teeth and places of denture support could undermine the long-term functionality. Periodontal inflammation at the margins of the crowns and abutments of bridges may influence the stability of the gingiva, as well as its maintenance of attachments, aesthetics and longevity of the prosthesis. In inflammatory-controlled implant-supported prostheses, peri-implant soft tissue healing, bone implant interface stability, as well as maintenance of marginal bone levels are crucial to success in the long term. Peri-implantitis is a common biological complication, and its frequency demonstrates the significance of identifying patients at a higher risk of inflammatory complication, before and after implant rehabilitation[34].

The use of inflammatory status based risk assessment could help enhance predictability of the treatment and long-term maintenance. Prior to the delivery of definitive prosthesis, clinicians ought to strive to stabilize periodontal inflammation, maximize oral hygiene, manage denture-bearing mucosal lesions, control systemic risk factors and allow adequate healing of the aftermath of a surgery or restorative procedure. The MIF-informed assessment may, in the future, help in the individualized sequence of treatment, timing of loading the implants, recall and maintenance. More frequent follow up, increased reinforced hygiene education, periodontal maintenance, denture adjustment, and early monitoring of peri-implant tissues may be beneficial to patients with a high risk of inflammation. However, the evidence needs to be taken with care as there are few direct clinical studies that can be used to relate MIF levels to the results of prosthodontic procedures.

All in all the clinical relevance of MIF in the prognosis of the prosthodontic tooth has potential clinical relevance due to its relationship with inflammatory control, tissue injury response and repair mechanisms. The conceptual and translational is its greatest present value: it may serve to explain the biological variability in healing; it may lead to future biomarker-based research. Further research to determine whether MIF levels in saliva, gingival crevicular fluid, or peri-implant sulcular fluid may predict delayed healing, mucosal inflammation, peri-implant disease, and prosthesis maintenance requirements or long-term failure in treatment should be considered.

7. Biomarker Potential and Therapeutic Modulation in Prosthodontics

Macrophage migration inhibitory factor (MIF) may have a potential part in the biomarker of prosthodontics since the success of the prosthetic is highly dependent on the inflammatory condition and the capacity to heal of the oral tissues. The effective approach of rehabilitation needs to rely on the stable mucosal, periodontal, and peri-implant conditions; thus, molecular signs of inflammation might contribute to identifying the patients at risk of slow healing, peri-prosthetic inflammation, peri-implant disease, and the long-term maintenance complications. Even though

MIF is not yet an established clinical biomarker in the field of prosthodontics, its ability to activate the immune system and elicit a response by the tissues it affects justify its use as a future diagnostic and prognostic tool in the field of prosthodontics.

Oral fluids are an easily accessible, less invasive fluid in which inflammation can be evaluated. The local tissue status can be reflected by saliva, gingival crevicular fluid and peri-implant sulcrate or crevicular fluid and may be of use in monitoring of the inflammatory activity. Assessment using biomarkers is also becoming significant in implant dentistry since traditional clinical manifestations may not be effective in detecting early changes in the biomarker. A systematic review of peri-implantitis diagnosis and prognosis has found that biomarkers could help in the assessment of peri-implant tissue condition, disease activity and prognosis when used in conjunction with clinical and radiographic assessment[35]. This directly relates to implant-supported prostheses where the early detection of inflammation of the soft tissues, marginal bone alterations and the retention of plaque in the prostheses helps to ensure long-term success.

Evidence in peri-implant research of the biomarker of oral fluids further supports its diagnostic usefulness. The sources of host-response biomarkers of peri-implantitis, which are indicators of the inflammatory nature of the environment around the implants, have been investigated in saliva and peri-implant crevicular fluid. Here, a candidate marker to consider peri-implant mucositis, peri-implantitis, delayed healing, marginal bone loss, and implant maintenance risk is MIF. Other applications of biomarker approaches similar in implants dentistry may be applicable to gingival inflammation at abutment teeth margins, mucosal inflammation beneath dentures, and periodontal risk at the abutment teeth margins. But the findings of biomarkers should be used complementary to, rather than instead of, clinical signs like bleeding on probing, probing depth, radiographic bone levels, mobility, occlusal assessment and mucosal examination.

MIF can also predict the occurrence of the complications of the prosthodontics. The changed expression of MIF can be an indication of an increased inflammatory load, which may be related to the delayed repair, sore mucosa, periodontal instability, peri-implant inflammation, decreased tolerance to the prosthesis, or higher maintenance requirements. The applicability of MIF to oral squamous cell carcinoma is supported by the fact that MIF is a promising serological biomarker in oral squamous cell carcinoma[36]. Though the results of oral cancer cannot be directly translated into the field of prosthodontics, it proves that MIF can be measured and has a biological meaning in the process of oral pathology.

A potential future treatment is therapeutic modulation of MIF but is still experimental in providing treatment to the prosthodontic patient. Since MIF is involved in inflammatory signaling, a hypothesis would be to regulate MIF-related pathways to reduce excessive inflammation and aid in tissue repair. These measures may be useful in patients who have recurrent denture-related inflammation or delayed mucosal healing, poor periodontal response, or peri-implant disease predisposition. Currently however, clinical management still needs to be based on established measures which have been included as, plaque control, periodontal stabilization, denture hygiene, prosthesis adjustment, occlusal correction and peri-implant maintenance.

Molecular inflammatory profiling may be useful in the future in modifying the protocols that are currently used in prosthodontics. Assessment of MIF-based, should they prove to be valid, could be used to stratify patient risk, aid in timing of the delivery of the prosthesis or loading of the implant, and support the use of individualized recall schedules. Patients who have high levels of inflammatory activity might need to optimize their tissues, load them slower, follow-up more closely, and increase their preventive care. On the whole, MIF has a promising translational potential as a diagnostic, prognostic and therapeutic target, but its routine application in the context of prosthodontics needs to be supported by longitudinal studies that would be able to correlate levels of MIF with successful outcomes of the healing process, the survival of a prosthesis, its peri-implant stability, and patient-reported comfort.

8. Conclusion

Migration inhibitory factor- MIF is a biologically significant mediator, the linkage between inflammation, immunity and tissue repair. Its applicability to prosthodontics is that it has the potential to explain why oral tissues exhibit varying healing behaviors to similar prosthetic, surgical, microbial and mechanical challenges. Stable biological environment that is able to fix inflammation, support repair and tolerate long-term functional loading is the key to predictable outcomes of prosthodontics. The interest in MIF suggests that eventually the provision of prosthodontic care might shift towards biologically wise decision-making, as opposed to traditional tissue assessment. Signs that are commonly identified only when tissue imbalance has set in are clinical signs like mucosal soreness, bleeding of the gums, residual ridge instability and peri-implant inflammation. Molecular markers like MIF could aid in detecting inflammatory vulnerability at an earlier age, and make more individualized choices on when to treat, what kind of prosthesis, the implant loading, how often to recall, and how to maintain. But this possibility should be taken with a grain of salt. Biological plausibility is currently supported by current evidence, and has yet to be directly clinically validated in populations of prosthodontic patients. Later research needs to correlate the MIF levels of saliva, gingival crevicular fluid, and surrounding the implant sulcular fluid with clinically relevant results, such as healing period, mucosal tolerance, periodontal stability, marginal bone loss, implant survival, prosthesis longevity, and patient comfort. The real worth of MIF will be subject to whether it will be able to enhance clinical decision-making beyond the available examination and radiographic techniques.

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