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Effects of Non-Thermal Dielectric Barrier Discharge Plasma on Human Fibroblasts: A Narrative Review

Sara Pourshahidi, Kimia Hafezi Motlagh*

Department of Oral and Maxillofacial Medicine, School of Dentistry, Tehran University of Medical Sciences, Tehran, Iran

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**** Corresponding author:***

Department of Oral and Maxillofacial Medicine, School of Dentistry, Tehran University of Medical Sciences, Tehran, Iran

Email: hafezikimia18@yahoo.com

ABSTRACT

Objectives: Fibroblasts are among the most critical connective tissue cells in almost all tissues and organs. Enhancement of fibroblast differentiation, proliferation, and morphogenesis is of paramount importance in tissue regeneration and wound healing. The non-thermal dielectric barrier discharge (DBD) plasma technology has recently gained interest due to its extensive applications and multiple biological effects. This review article outlines the applications of DBD plasma in dentistry, and its biological effects on human fibroblasts.

Materials and Methods: Relevant keywords were searched in PubMed, Ovid, and Google Scholar online databases. The search strategy resulted in selection of 7 studies according to the eligibility criteria.

Results: Most studies reported increased cell proliferation and viability after the application of DBD plasma. Four studies that focused on the development of adhesion-related appendages examined the morphology of fibroblast cells, including the creation of vinculin, protrusion, and actin cytoskeleton. Expression of cyclin D1/P27 genes and genes associated with adhesion and cell attachments was also reported in two studies.

Conclusion: This narrative review discussed the effects of DBD plasma technology on proliferation and behavior of human fibroblasts, and reviewed the available articles in this regard. More in vivo studies are required to understand the exact effects of this emerging technology on human mesenchymal tissues.

Keywords: Fibroblasts; Plasma Gases; Narrative Review

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INTRODUCTION

Fibroblasts are among the most important connective tissue cells present in almost all tissues and organs. The head and neck fibroblasts have a different origin than other fibroblasts since they arise from the neural crest-derived ectomesenchyme, while fibroblasts in other tissues arise from the primary mesoderm [1]. The importance of fibroblasts in oral tissues is related to their secretory properties. They secrete collagen, proteoglycans, glycosaminoglycans, glycoproteins, prostaglandins, matrix metalloproteinases, some cytokines, and growth factors [2]. Collagen, the main secretory protein of fibroblasts, is an important component of the extracellular matrix of oral tissues such as dentin, cementum, bone, oral mucosa, and salivary glands [3] Fibroblasts are involved in several biological processes including wound healing, osteointegration, tooth movements, inflammatory responses, and tissue angiogenesis [4]. Wound healing is a complex and multicellular process that occurs due to the coordinated effects of different cell types including keratinocytes, fibroblasts, and endothelial cells. Migration, infiltration, proliferation, and differentiation of these cells play important roles in processes such as inflammatory response, new tissue formation, and wound healing [5]. Fibroblasts are the main source of extracellular matrix, especially collagen and fibronectin, and are involved in subsequent

formation of granulation tissue, playing a key role in wound healing [6]. The wound healing process in the oral cavity is influenced by a number of internal and external factors, including systemic diseases or environmental toxins such as nicotine or alcohol [7]. Growth factors and cytokines, including interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor-α secreted by fibroblasts regulate the production of matrix metalloproteinases (MMPs) such as MMP1 that affect the soft and hard tissue remodeling process [8]. Fibroblasts also have an important role in the long-term success of dental implants. Although the long-term success of dental implants highly depends on osteointegration, it is also influenced by the quality of connective tissue attachments and epithelial seal. A proper epithelial seal ensures optimal attachment of fibroblasts to the implant surfacee and their subsequent proliferation [9].

To date, various techniques have been identified to influence and modulate the biological behavior of mesenchymal cells, including laser irradiation, hyperbaric oxygen, and plasma techniques [10,11]. Plasma is a general term used to describe partially ionized gases, which was introduced by Irvin Langmuir [12] in 1927. Plasma is divided into two groups: thermal plasma and low-temperature plasma. Thermal plasma is a method in which metals and ceramics are sprayed on the surface of other materials. This method is used to improve the biocompatibility of titanium, silver, and hydroxyapatite implants [13]. Low-temperature plasma is used directly for living tissues for the purpose of blood coagulation, sterilization, wound healing, and tissue regeneration, and also indirectly in plasma-treated implants [14]. Plasma treatment can increase the titanium surface wettability and reduce the risk of infection; it can also accelerate the osseointegration process by stimulating early attachment of surface fibroblasts and creating an optimal seal. Increased wettability induced by plasma treatment can greatly promote the biological response of human gingival fibroblasts (HGFs) [15]. Such dramatic changes in hydrophilicity also have significant effects on HGF count [16]. The use of non-thermal plasma devices operating under cold atmospheric pressure enables the treatment of viable tissues with no significant side effect. Evidence shows that non-thermal plasma can destroy or inactivate a wide range of bacteria [17]. Apart from antimicrobial effects, cold atmospheric pressure plasma (CAPP) stimulates microcirculation and shows anti-inflammatory effects, making CAPP an eefficient treatment option of many conditions with possible applications in cariology, endodontics, periodontics, and oral oncology [18]. Laroussi [19] was the first to note the antibacterial effects of CAPP [19]. Subsequent studies confirmed the inhibitory role of CAPP on proliferation of Gram-positive and Gram-negative bacteria, bacterial spores, and fungal species [20]. Borges et al, [21] also reported that CAPP treatment for 5 minutes had anti-biofilm effects on Candida albicans with low toxicity.

Non-thermal plasma discharge is sufficiently homogenous and cold enough for safe application on the living cells and tissues. Its discharge is generated by applying a high voltage time-varying waveform between a dielectric covered electrode and the biological target [22]. Direct dielectric barrier discharge (DBD) occurs when there is a high-voltage electrode and a grounded electrode. The electrodes can both be individually covered by a dielectric layer or the dielectric material placed between their spaces [23]. Plasma contains a mixture of different radical species, UV radiation, and flux of charges that, when applied directly to cells or tissues, can have a variety of biological effects. When plasma works with ambient air, it produces reactive nitrogen and reactive oxygen species (ROS) and hydroxyl radicals; accumulation of nitrite and nitrates can affect the physiology of fibroblast cells [24]. Hydrogen peroxide (H_2O_2) is another product produced by the use of plasma, which acts both as an oxidant and antimicrobial agent, and is involved in signaling and signal transduction pathways in multicellular organisms [25]. Although the bactericidal and bacteriostatic effects of this technology have been previously acknowledged, it has also been reported that non-thermal plasma can affect endothelial cell proliferation and release of growth factors such

as fibroblast growth factor (FGF)-2 [26].
Due to the growing interest of the scientific community in plasma technology applied in dentistry, this study aimed to review the available studies on the effect of non-thermal DBD plasma on human fibroblast cells.

MATERIALS AND METHODS

PubMed, Ovid, and Google Scholar online databases were searched using the following individual keywords: "DBD plasma", "cold atmospheric plasma", "atmospheric plasma" AND "fibroblasts", "human gingival fibroblasts", and "HGF". No time limits were specified. The inclusion criteria for the articles were: (I) originality, (II) English language, and (III) application of DBD plasma on human fibroblasts. The exclusion criterion was (I) full text not written in English.
Both researchers read the selected articles, and a third person was consulted in cases of disagreement.

RESULTS

The search strategy resulted in selection of 50 articles including 7 from PubMed, 41 from Google Scholar, and 2 from Ovid. After duplicate removal, 42 abstracts were reviewed, which resulted in selection of 9 studies according to the eligibility criteria. One study was excluded because the full text was not in English, and another one was excluded due to inaccessibility to its full text. In total, 7 articles were recruited for the present review study (Figure 1).
The present narrative review focused on investigating the impact of plasma treatment on fibroblast cells, specifically in relation to cell proliferation and viability, cell attachment, cell morphology, and expression of attachment-related genes. Five articles were performed on cell culture, and two were on human samples.

Cell culture:

The majority of the reviewed studies emphasized on enhancement of fibroblast cell

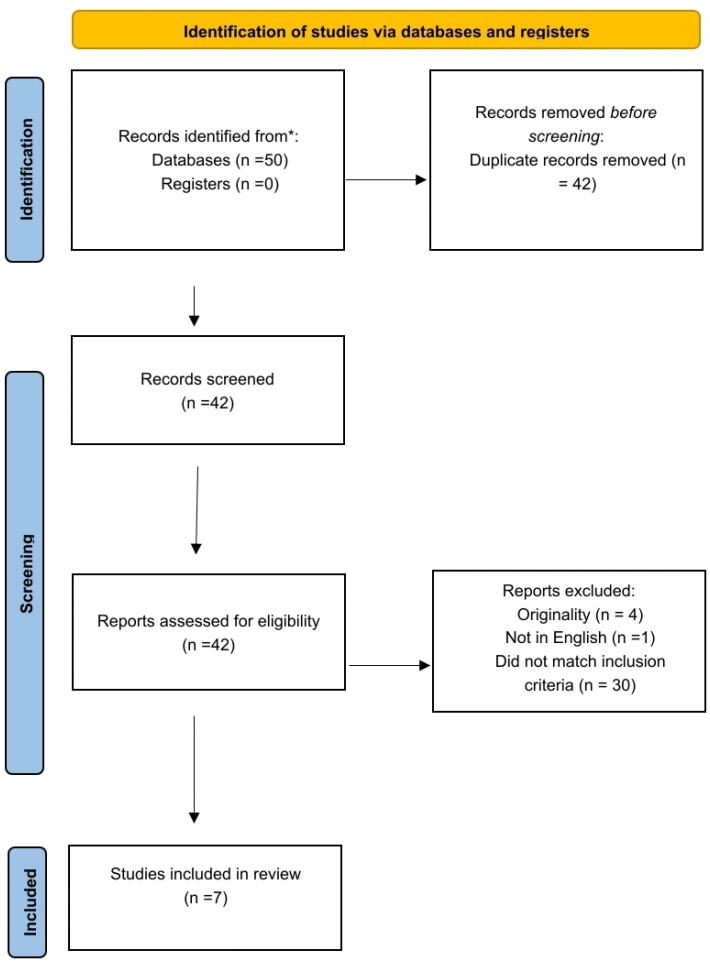

Fig. 1. Flowchart of study selection process

Table 1. Reviewed articles on the effects of DBD plasma on fibroblasts

Author Year	Population	Type of Plasma	Voltage/ Current	Time/ Distance	Cell Attachment	Cell Proliferation	Viability	Cell Morphology	Gene Expression
Jung-Hwan Lee et al. [29] 2015	HGFs on titanium discs	AAPPJ	2.24 kV/ 1.08 mA	10 s/3 mm	Increased	Increased	NM	Vinculin formation	NM
Miao Zheng et al. [28] 2015	HGFs on zirconia discs	DBD	4.6 kV/	30 s, 60 s, 90 s	Increased attachment-related gene expression	Increased	NM	Protrusion formation	Adhesion integrins/ Fibronectin
Balzer et al. [30] 2015	Foreskin fibroblasts of five patient	DBD	14 kV	5 min	NM	Decreased	Significant decrease	NM	NM
Hoffmanns et al. [31] 2015	HDFs from dermal specimens	DBD	14 kV	5 min	NM	NM	Decreased	NM	NM
Shi X et al. [32] 2016	Fibroblast culture	DBD	NM	15 s/25 s	NM	NM	Increased in 15 s Decreased in 25 s	NM	Cyclin D1/ P27
Yan et al. [27] 2021	HGFs on titanium surfaces	DBD	24v/ 1.5A	20s	Increased	Increased	NM	Pseudopodia form	NM
Rabel at al. [33] 2021	HGF culture	Oxygen DBD plasma	NM	NM	NM	No significant change	NM	Vinculin formation	NM

AAPPJ: air atmospheric-pressure plasma jet; DBD: dielectric barrier discharge; HGF: human gingival fibroblasts; NM: not mentioned; HDF: human dermal fibroblasts

proliferation subsequent to the application of DBD plasma [27-29]. Two studies reported decreased cell viability and inhibition of fibroblast proliferation subsequent to the application of DBD plasma [30,31]. Two studies precisely examined the expression of Cyclin D1/P27 genes and genes associated with cell adhesion and attachment [28,32]. Four studies focused on development of adhesion-related appendages and examined the morphology of fibroblast cells, including the formation of vinculin, protrusion, and actin cytoskeleton [27-29,33]. The topic of cell attachment was examined in three separate studies [27-29], all of which reported a notable enhancement in cell attachment subsequently to the application of plasma.

Human samples:

Two studies were conducted on patient specimens and reported a decrease in cell viability and inhibition of fibroblast proliferation subsequent to the application of DBD plasma [30,31]. The voltage used in these studies varied from 2.24 kV to 14 kV, and the duration of exposure to plasma was in the range of 10 seconds to 90 seconds.

DISCUSSION

Plasma is the fourth form of matter and includes positively or negatively charged particles, free radicals and ultraviolet photons in a solution or gas. This technology has clinical applications in medicine, dental equipment, and food industry packaging [34]. The role of plasma in medicine is based on its synergistic effects on ROS, reactive nitrogen species, electrons, and ions [35]. DBD plasma was first introduced by Siemens in 1857 for ozone production. There are different types of DBD plasma systems available, with the planar and cylindrical geometries as the most common types [36].

The articles discussed in this review were published from 2015 to 2021, although no date limitation was set in searching, showing that DBD plasma is a new and emerging technology (Table 1). Out of seven articles discussed in this review, five articles were done on cell culture mostly on titanium discs [27-29,30,33], and two were on human samples [31,32]. The voltage used in these studies varied from 2.24 kV to 14 kV, and the duration of exposure to plasma was reported in the range of 10 seconds to 90 seconds. Decreased viability was reported in only two studies, both of which performed exposure to DBD plasma with a voltage of 14 kV. It appears that the effects of plasma are dose-dependent and vary from increased cell proliferation to cell death. Considering such dose-dependent effects and absence of a clinical protocol for exposure to DBD plasma, more studies are required to achieve a specific clinical protocol for this technology. Although the role of ROS in increasing the intracellular signaling molecules has been proven, there are confusing findings regarding the role of ROS in cell differentiation, which is probably due to different methodologies for ROS generation in intracellular processes. Cell viability was evaluated by measuring the expression of cyclinD1 and P27 genes in one of the articles included in this study [32] and cell attachment was measured by measuring the expression of fibronectin and adhesion integrin genes [32].

In recent years, many studies [37,38] have been conducted on the clinical effects of non-thermal atmospheric pressure plasma (NTAPP), and its applications for sterilization, antibacterial effects, and apoptosis of cancer cells have been confirmed. Meanwhile, limited studies are available on the effect of DBD plasma on proliferation, differentiation, and viability of fibroblasts [39,40]. Ma et al. [41] showed that NTAPP selectively induced apoptosis of cancer cells by activating the ROS pathway. However, some degree of proliferation was also observed in normal fibroblasts and adipose tissue-derived stem cells [41]. There are some studies [42-44] that confirmed the stimulating effect of NTAPP on proliferation of mesenchymal cells. It has been reported that using NTAPP accelerates wound healing through the activation of nuclear factor erythroid-related factor 2 signaling pathway in keratinocytes [45]. In another study conducted by Nastuta et al, [46] on wound closure in rat skin, stimulation of re-epithelialization through the activation of keratinocytes was confirmed by helium atmospheric pressure plasma.

There are some valuable studies on the anti-inflammatory and tissue repair effects induced

by CAPP. Brun et al. [47] reported increased migration and proliferation of fibroblasts in response to ROS production due to exposure to CAPP. In a similar study, enhancement of wound healing in mice was observed by increasing the collagen type I production in keratinocytes induced by CAPP [48]. Küçük et al. [49] were the first to use CAPP in a clinical trial with a single-session protocol as a non-surgical treatment and observed significant clinical attachment gain after 3 months. Kwon et al, [50] also reported that treatment with CAPP for 1 and 2 minutes improved the morphology of HGFs and increased transforming growth factor-β and vascular endothelial growth factor mRNA expression. Increasing the treatment time to 4 minutes decreased the morphological changes and expression of growth factors in the study groups compared to the control group. Yan et al. [27] reported that 20 seconds of implant surface preparation with DBD plasma increased the number of fibroblasts after 1 day compared to the control group, and resulted in a significantly higher cell viability. The authors concluded that activation of titanium implants with DBD plasma had promoting effects on adhesion and proliferation of fibroblasts with no adverse effects on cytocompatibility [27]. In a similar study, Zheng et al. [28] reported an increase in fibroblast density and attachment-related genes after using DBD plasma for 30, 60, and 90 seconds for surface treatment of zirconia discs. Finally, they concluded that treatment with DBD plasma improved the biological behavior of fibroblasts within 24 hours and increased cell density over longer culture times. On the contrary, Balzer et al, [30] in their study on the effect of DBD plasma on differentiation of human fibroblasts reported a reduction in fibroblast viability by single session DBD treatment, accompanied by prolonged inhibition of proliferation of the remaining cells, suggesting that besides highly reactive radicals such as superoxide and hydroxyl, there are more reactive species including H_2O_2 that may be responsible for the observed effects. A previous study also demonstrated that generation of H_2O_2 plays an important role in plasma-induced cell death [51]. In a similar study, Hoffmanns et al. [31] reported that DBD treatment led to an increase in osmolality, acidification, and accumulation of nitrite and nitrate in cell culture media, which led to a reduction in cell viability of human dermal fibroblasts.

Regarding the morphological changes of fibroblasts due to DBD plasma treatment, Rabel et al. [33] reported that plasma-functionalized implant biomaterials induced distinct cell morphologies compared with untreated surfaces. In a study conducted by Lee et al, [29] an increase in actin cytoskeleton and vinculin localization was observed after implant surface preparation with pressure plasma. Vinculin serves as a connection between cell adhesion molecules and actin filaments, and plays a critical role in cell adhesion and cytoskeleton development [52].

In all the reviewed studies, the control group was without treatment. Since treatments such as low-level laser therapy are known to be effective for proliferation and viability of fibroblasts, further studies are required to compare the effects of low-level laser therapy and DBD plasma. In addition to comparing this developing technology with the existing therapeutic modalities effective on mesenchymal cells, more in vivo studies are required to fully comprehend the precise impact of this emerging technology on human mesenchymal tissues.

CONCLUSION

This narrative review discussed the effects of DBD plasma technology on human fibroblasts, and reviewed the available articles in this regard. The majority of the reviewed studies focused on how applying DBD plasma increased fibroblast cell proliferation while according to some others, the final result was a reduction in cell viability and inhibition of fibroblast proliferation. Others precisely analyzed the expression of genes involved in cell adhesion and attachments. Studies on the morphology of fibroblasts, including the formation of vinculin, protrusion, and actin cytoskeleton focused on development of adhesion-related appendages. Several studies on cell attachment confirmed that plasma treatment significantly improved cell attachment.

CONFLICT OF INTEREST STATEMENT

None declared

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