REVIEW

Downregulated gene expression in diabetic patients and its correlation with oral health: a review

Anasua Debnath[a], Adrita Roy Chowdhury[b]*, Navoneel Debnath[c]

[a]Faculty, Department of Prosthodontics, Dr. R Ahmed Dental College and Hospital, Kolkata, West Bengal, India

[*b]Faculty, Department of Dentistry, Calcutta National Medical College and Hospital, Kolkata, West Bengal, India

[c]Intern, IQ city Medical College, Durgapur, West Bengal, India

***Corresponding author e-mail:** adrita.rc@gmail.com

ABSTRACT

Diabetes mellitus is a growing public health concern and a common chronic endocrinal and metabolic disease worldwide characterized by chronic hyperglycaemia. In healthy subjects, the epithelium of oral mucosa creates a protective barrier against pathogens and carcinogens. Reports document that delayed wound healing is an important manifestation of diabetes. Histological analysis of diabetic animal model showed that the epithelial tissue and collagen functions were affected in diabetics. Quantitative Real-Time Polymerase Chain Reaction (rtPCR) revealed that the expression of genes of growth factors like PDGF, EGF, FGF, IGF, and NGF were significantly altered in diabetic models at the wound site. Increase in inflammatory processes in the gingival epithelium due to suppression of the respective mRNA gene expression was documented in various studies. This strongly suggests that disturbances in the epithelial proliferation, connective tissue growth and delayed wound healing of oral mucosa in diabetes may be associated with altered expression of these regulatory genes. This article reviews oral manifestations in diabetes mellitus to create awareness with specific reference to genetic alterations.

KEYWORDS: Diabetes, Oral Health, Hyperglycemia, Gene Expression

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INTRODUCTION

Diabetes is a chronic hyperglycaemic state of the body, originating from metabolic and endocrinal disorder (American Diabetes Association, 2009). It is characterised by deficiency of insulin secretion caused by dysfunction of the pancreatic β-cell or resistance to insulin by peripheral muscle cells. Diabetes is a risk factor for contracting infections. Oral and periodontal health is susceptible to degradation in hyperglycaemic conditions (Maskari et al, 2011). Wound healing though is well documented at the histological level, but the genes regulating wound repair and their association with diabetes mellitus have only been partially identified. This review article attempts to summarize and discusses the role of various growth factors and cytokines at genetic level, responsible for the delayed wound healing of the oral mucosa in diabetics (Abiko et al, 2010). Experiments and research on animal models like rats/mice provide some idea about the role of genes on growth factors, cytokines, and their fluctuant effects on wound repair in a hyperglycaemic environment.

Method of review

Original research articles investigating growth factor expression in skin and mucosal wounds of non-diabetic and diabetic mice and rats were extracted for this review. Relevant articles were collected from the online database PubMed and search engines like GoogleScholar and Springer. Keywords such as growth factor, cytokines, genetic expression, wound healing, skin, mucosa and diabetes were used. Additional secondary sources of information were included from reference lists of retrieved articles.

Studies that met the following inclusive criteria were considered:

1. Studies involving skin wounds.
2. Research performed on oral mucosa and wound repair.
3. Studies involving the association between oral mucosa and diabetes.
4. Experiments performed on nondiabetic (normal) and/or diabetic mice or rats.
5. Studies scrutinizing the gene expression and/or release of growth factors and cytokines from wounds.
6. At least mention of collagen synthesis or contraction as a variable.

Excluded from these reviews were:

1. Studies performed on animals other than mouse or rat.
2. Studies involving wounds in tissues other than skin or mucosa (e.g., cornea).
3. Meta-analyses.

Factors affecting wound healing of oral mucosa

Wound healing is a dynamic process involving haemostasis, inflammation, wound repair (Indurkar et al, 2016). An injury to the oral mucous membrane triggers a cascade of events including inflammation, new tissue formation, and tissue remodelling with final reconstruction of the wounded area (Devlin et al, 1996; Yamano et al, 2013). Post injury, within a few hours the inflammatory cells like neutrophils, monocytes and lymphocytes invade the wound tissue which are also an enriched niche of growth factors and cytokines, indispensable for the proliferative phase of wound healing. In a sterile wound the repair process incepts almost immediately after cell injury with deposition of extracellular matrix rich in collagen and other proteins like fibrin and elastin (Li et al, 2007, Xue et al, 2015). In diabetic patients the synthesis and secretion of cytokines is minimized and deregulated at a genetic and molecular level interrupting the normal repair process (Werner et al, 2003; Li et al, 2007; Gupta et al, 2015; Ayuk et al, 2016).

Role of AGE (Advanced Glycation End Products)

Non enzymatic glycosylation of collagen forms AGE (Rhee et al, 2018). Sustained elevated blood glucose level increases the formation of AGE than at normal blood glucose level and is considered a major contributor to diabetic complications (Huijberts et al, 2008). In normal oral wound healing, collagen is formed from oral fibroblasts. Cross-linking of collagen is aggravated by AGE, rendering it less soluble and highly susceptible to enzymatic degradation by collagenase. This leads to an altered collagen metabolism that inhibits the proper course of remodelling of the wound area (Huijberts et al, 2008; Rhee et al, 2018).

Genetic association of AGE with diabetic wound healing

A study by Adams et al in 2016 documented that single nucleotide polymorphisms (SNPs) occurring in RAGE (Receptor for AGE) is associated with increased AGE levels in diabetics (Adams et al, 2016).

Role of Matrix metalloproteinases (MMPs)

MMPS are the predominant collagenase in a normal wound healing mechanism. The MMPs initiate degradation of collagen, deposition of new extracellular matrix and regeneration of the tissues (Sorsa et al, 2004).

Excessive collagenolytic activity in a normal wound repair is controlled by Tissue Inhibitor Metalloproteinase-1 (TIMP-1) (Armstrong et al, 2002). Abnormal wound healing as in case of Diabetes Mellitus is well documented to be associated with reduced TIMP-level. The imbalance between TIMP and MMP results in excessive MMP activity, thus disrupting the normal wound healing (Lobmann et al, 2002; Argyropoulos et al, 2016).

Role of MMP in diabetics at a genetic level

Diabetic mucosa shows elevated levels of MMPs. Laser capture microdissection (LCM) coupled rtPCR indicated that increased MMPs in diabetic mucosa were related to an increased lysyl oxidase (LOX) expression and higher cross-linked collagens with change in their structural and mechanical properties (Lobmann et al, 2002; Argyropoulos et al, 2016).

Role of Growth factors in wound healing (Table 1)

A growth factor, found anywhere in the body including oral mucosa is directly or indirectly responsible for stimulating fibroblast production, thus enhancing collagen deposition required for wound repair and remodeling (Schultz et al, 2011).

TABLE 1: Role of Growth Factors in Normal Wound Healing and Their Genetic Influence on Diabetic Wounds.

GROTH FACTORS/ CYTOKINES	ROLE IN WOUND REPAIR	GENETIC CHANGES IN DIABETICS WOUNDS
PDGF	Induces chemotaxis for migration of immunocompetent cells and production of ECM though proliferation of fibroblasts.	Decreased PDGF type Receptors

FGFs	Recruitment of fibroblasts, collagen deposition and granulation tissue formation.	Decreased FGF-1 and FGF-2 Receptors
IGF	Proliferation of fibroblasts, collagen deposition, granulation tissue formation, wound contraction.	Decreased IGF-1mRNA and delayed IGF-1 receptor Expression
EGF	Repair tissue differentiation through collagen synthesis, reepithelization of wound.	Decreased EGF mRNA Expression
VEGF	Remodelling of the vasculature through deposition of collagen in the ECM.	Decreased Receptor for VEGF (flt-1) undergoes phosphorylation and decrease in the number
NGF	Influences the production of immunocompetent cells at the site of repair.	Decreased NGF receptors (Tropomysin-related kinase TrkA)
TGF-β	Pivotal role in ECM deposition and prevention of degradation of ECM.	Decreased TGF-b1 gene expression

Platelet-derived Growth Factor on wound healing (PDGF)

Post injury, PDGF is released from degranulating platelets. It induces chemotaxis for migration of neutrophils, monocytes, and fibroblasts at the repair site. It also enhances proliferation of fibroblasts and production of extracellular matrix through the stimulation of fibroblast gene expression (Werner et al, 2003).

Expression of PDGFs and their receptors in Diabetics

Transforming Growth Factor-β (TGF-β) signals the DNA synthesis in human fibroblasts through production of PDGF related proteins. It helps in collagen formation, thus playing an important role in granulation tissue synthesis. Experiments on diabetic mice revealed a significant reduction in PDGF expression. This phenomenon may be linked to the decreased expression of TGF-b mRNA in diabetics (Lynch et al, 1987; Werner et al, 2003).

Fibroblast Growth Factor (FGF)

FGFs are structurally related polypeptide growth factors mainly found extracellularly at the surface of the oral wounds. They recruit fibroblasts accelerating the collagen deposition and granulation tissue formation (Devlin et al, 1996).

Genetic downregulation of FGF in diabetic patients

Werner et al in 2011 determined the mRNA FGF level in full thickness excisional wounds in mice by RNAse proteinase assay (Werner et al, 1994; Werner et al, 2011). Induction of FGFs occurred both in wounds of diabetic and nondiabetic animals, but expression of FGF mRNA were

reduced to basal levels within 3 days in diabetics compared to the non-diabetic wounding where it lasted for 7 days (Peplow et al, 2012).

Insulin Growth Factor (IGF)

IGF-1 stimulates chemotaxis of endothelial cells and proliferation of fibroblasts, prompting collagen deposition, granulation tissue formation and collagen lattice retraction required for remodelling of a wound (Gillery et al, 1992; Devlin et al, 1996). In a study conducted by Devlin et al, delayed expression of IGF and IGF receptor mRNAs was observed in the wounded site in diabetic mice (Devlin et al, 1996).

IGF downregulation in diabetic mice at a genetic level

A study by Brown et al (Brown et al, 1997) published in 1997 quantified the expression of IGF mRNA during early wound healing in diabetics. RT-PCR and radioimmunoassay revealed expression of IGF-I mRNA in diabetic wounds which was significantly delayed until 14 days compared to non-diabetics at 3 days (Brown et al, 1997; Peplow et al, 2012).

EGF (Epidermal Growth Factor)

EGF is mainly produced by submandibular glands that augments cell growth and collagen differentiation in oral tissues encouraging re-epithelialization of oral tissues (Devlin et al, 1996; Abiko et al, 2010; Zeng et al, 2014).

EGF mRNA expression in diabetic patient

A study by Laato et al in 1986 documented that daily application of 5 µg of EGF resulted in augmented cellular response to injury due to elevated aggregation of DNA for protein synthesis like collagen hydroxyproline (Laato et al, 1987). Less EGF in saliva may be associated with delayed wound healing on oral mucosa in diabetics (Abiko et al, 2010). A study by Zhang et al showed that wound healing in diabetics was affected by the down-regulation of EGF mRNA when compared with the genetic expression in case of therapeutic EGF administration in diabetics (Zhang et al, 2018).

Vascular Endothelial Growth Factor (VEGF)

The VEGFs are a family of growth factors that contribute to remodelling of the vasculature by synthesizing collagen in the ECM (Peplow et al, 2012; Kota et al, 2012; Okonkwo et al, 2017).

VEGF and its relation with Diabetes at the genetic level

RtPCR reaction reveals the presence of VEGF receptors or mRNA (flt-1and KDR) on HMC (Human Mesengial Cells) (Amemiya et al, 1999). In diabetic patients the signalling pathway of VEGF is impaired due to reduced flt-1 phosphorylation as a consequence of reduced activation of serine-threonine protein kinase (AKt-1) and endothelial nitric oxide synthase (Amemiya et al, 1999; Sasso et al, 2005; Kota et al, 2012).

Nerve growth factor (NGF)

NGF regulates inflammatory response by affecting the inflammatory cells (Abiko et al, 2010). Literature shows that cutaneous and oral injury triggers NGF production by the salivary glands (Wener et al, 2003; Sasso et al, 2005). Receptors for NGF, tropomyosin-related kinase (TrkA) is expressed in basal and parabasal oral mucosal and gingival epithelial cells (Graiani et al, 2004; Schenk et al, 2017).

NGF downregulated in diabetic wound healing at a genetic level

The expression of NGF was reported to be decreased in the mucosa of both diabetic patients and rats (Yamano et al, 2013). Recent studies revealed an increase in the levels of proNGF in diabetic patients. While mature NGF mediates neuronal cell survival through binding to TrkA and p75NTR receptors, proNGF can promote neuronal

apoptosis because of its high affinity to p75NTR leading to sustained increase of intracellular ceramide causing cell death (Casaccia-Bonnefil et al, 1996; Abdelsaid et al, 2011).

Transforming Growth Factor, TGF-beta in delayed wound healing

TGF-β promotes chemotaxis of monocytes, neutrophils, lymphocytes and fibroblasts, with production of growth factors from them. They impart a prime role in deposition and inhibition of degradation of extracellular matrices (Werner et al, 2003; Peplow et al 2012).

TGF-β and its genetic downregulation in diabetics

In a normal oral wound, a study by Szpaderska et al, 2003 and Zelles et al, 1995, the expression of TGF-β1 increased in the wound site as well as the saliva confirming the accelerated rate of palatal wound healing (Zelles et al, 1995; Szpaderska et al, 2012). A study by Yamano et al, shows that study conducted on animal models affected with diabetes, TGF-β1gene expression was significantly downregulated compared to the control (Yamano et al, 2013). The gene expressions of TGF-b in the diabetic group were significantly lower at 4 and 7 days ((Yamano et al, 2013).

Keratinocyte Growth Factor (KGF) and its downregulation in diabetic wounds

KGF is produced by mesenchymal cells including fibroblasts, endothelial and smooth muscle cells. It stimulates re-epithelization of wounds (Schultz et al, 1987; Werner et al, 2003). According to a study by Peplow et al in 2012, KGF mRNA expression level was reduced in the wounds of diabetic patients (Devlin et al, 1996; Brown et al, 1997; Peplow et al, 2012).

Role of cytokines in wound healing (Table-2)

Cytokines also play important roles in wound repair. They are small, secreted proteins that affect the behaviour of immune cells. They include the interleukins, lymphokines, tumour necrosis factor-α (TNF-α) and interferons (Werner et al, 2003; Yamano et al, 2013). According to recent studies the presence of chemokine receptors on resident cells suggests their role in re-epithelialisation, tissue remodelling and angiogenesis (Peplow et al, 2012).

Role of Inflammatory cytokines in diabetes

Literatures regarding the expression levels of IL-6 in diabetic wounds are contradictory. Few experimental results reveal a decreased IL-6 mRNA level whereas the most recent literature focuses on increased mRNA expression after injury (Fahey et al, 1991; Nishikai-Yan Shen et al, 2017). Type II diabetes increases the blood concentration of inflammatory cytokines such as IL-6 and TNF-α (Brown et al, 1997; Bando et al, 2010). The inflammatory cascade is inhibited by TNF-α in the diabetics, implying abnormal regulation of inflammatory cytokines. Increased level of TNF-α is also induced by the high level of AGE, suggesting its role in the abnormal adaptive immunity. Certain concentration of AGE inhibits production of type I and III collagens, inducing cell apoptosis (Devlin et al, 1996).

TABLE 2: Role of Growth Factors in Normal Wound Healing and Their Genetic Influence on Diabetic Wounds.

Cytokines	Effect of diabetics on the increased/decreased expression of cytokines at the site of wound healing
TNF-α	Decreased level of TNF-α
Interleukins (IL)	
IL-6	Increased/Decreased level of IL-6

IL-1b	Decreased level of IL-1b

Genetics of inflammatory cytokines in diabetic wounds

A study by Nishikai-Yan Shen in 2017 asserts that aberrant IL-6 mRNA expression and macrophage accumulation results in delayed wound healing in diabetics (Bando et al, 2010). A study by Yamano et al reported the IL-1b and their mRNA level in the diabetic group were significantly lower than controls (Yamano et al, 2013).

Psychological stresses in diabetes

Psychological factors like stress and stress related habits such as smoking, stress, alcohol consumption though not an absolutely proven fact, often play an important role in the progress of wound repair especially in case of comorbidities like diabetes mellitus. The role of epigenetics i.e. their influence of long standing environmental factors on DNA methylation, histone acetylation and mRNA expressions may be considered as one of the probable reasons explaining the relation between delayed oral wound healing, comorbidity and psychological stress (Dick et al, 2011; Alegría-Torres et al, 2011).

Discussion

We have attempted to critically analyse the research and review articles published from 1987 to 2019 regarding the genetic influence of various growth factors and cytokines in mucosal wound repair of diabetic patients. It focuses on experimental studies that have investigated the gene expression and release of growth factors and cytokines in the saliva and mucosal wounds of nondiabetic and diabetic animals, mostly mice and rats. This article aims at recognising the abnormal expressions of growth factors in the wounds of diabetics so that a curable process can be researched and administered to the patients. Growth factors initiate intracellular and intercellular interactions that synchronize the sequence of cell migration, proliferation and differentiation in the process of wound healing. Essential part of wound healing is epithelisation and extracellular matrix deposition. Growth factors and cytokines responsible for collagen formation, deposition and remodelling have been methodically scrutinized to establish any correlation of these factors with delayed wound healing from a genetic and molecular viewpoint. Although extensive studies related to this topic have discussed the mechanism of wound healing on different body parts, literatures support the fact that all wound repair mechanisms including oral tissues are closely similar with localized disturbed expression of selective growth factors. Further evidence however are necessary to derive a definitive conclusion between the disrupted expression of various growth factors and delayed wound healing in diabetics.

Conclusion

Wound healing of oral mucosa in diabetes is in itself, a dynamic and multifaceted occurrence. Various growth factors and cytokines influence the extent of repair capacity of a wound. Comorbidities like diabetes alter the expression and level of these inflammatory mediators. The clinical and experimental evidence based on research are yet not enough to explain the differences in the degree of wound repair among diabetic individuals and the cause for genetic deregulation of growth factors and cytokines. A need for further clinical investigations must be encouraged as diabetes is one of the prevailing and persisting comorbidity affecting a very high number of individuals in a community.

Author's Contribution

AD: Topic selection, data collection, assembling, processing and organizing the review write-up.
AR: Second Author: Contributed towards relevance of the parameters associated with the topic, guiding and discussing the review. She also proof-read and edited the manuscript.

ND: Third Author: Contributed towards knowledge on systemic disease (diabetes), proof reading and approving the procedural steps.

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Declaration of originality

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