Review Article

Epidermal growth factor and diabetes mellitus; friends or faux?

Al-Ankily MM[1], Shamel M[2], Bakr MM[3]

[1]Dr Mahmoud M Al-Ankily
Assistant Lecturer, Oral Biology
Department, Faculty of Dentistry
The British University
Cairo, Egypt
mahmoud.ankily@bue.edu.eg
[2]Dr Mohamed Shamel
Assistant Lecturer, Oral Biology Department
Faculty of Dentistry, October University for Modern Sciences and Arts
Cairo, Egypt
mshamel@msa.eun.eg
[3]Dr Mahmoud M Bakr
Lecturer in General Dental Practice
School of Dentistry and Oral Health
Griffith University, Queensland, 4222, Australia.
m.bakr@griffith.edu.au

Received: 25-01-2016
Revised: 12-02-2016
Accepted:25-02-2016

Correspondence to:
Dr. Mahmoud Bakr
m.bakr@griffith.edu.au

ABSTRACT

Diabetes being the most common chronic metabolic disorder has a number of complications that affect various parts of the body. Epidermal growth factor (EGF) is well known for its healing capacity. In this article we review the two way relationship between diabetes and EGF, where the former needs to block the latter's secretion and reduce its expression on order to produce its notorious complications. On the contrary, the latter is capable of reversing the former's negative adverse effect on various organs of the body. We also shed some light on different studies in the literature that investigated the role of EGF in the dynamics of diabetes, and gain a deeper insight towards the possible applications of local and systemic treatment with EGF in the management of diabetic complications. We also try to answer some questions: EGF and diabetes; Friends or faux? and will EGF be the future trend in reversing damage caused by diabetes and wound healing?

Key words: *Submandibular salivary gland, epidermal growth factor, diabetes, streptozotocin, wound healing*

Introduction

A number of growth factors that are crucial for wound healing are secreted into saliva. These include vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), transforming growth factor α and β, acidic and basic fibroblast growth factors, and insulin-like growth factors (IGF-1, IGF-2). [1] EGF is found in many human tissues including submandibular gland, parotid gland and is controlled by iodine from dietary intake. [2] It is an important protective agent against bacterial and chemical agents in the oral cavity, oesophagus and gastric tissues. It helps in the process of healing of oral and gastro-oesophageal ulcers through stimulation of DNA synthesis, cell migration and proliferation. [3]

Furthermore, growth factors secreted into saliva can be transported to other distant body tissues through the blood stream after reabsorption by the oral mucosa. It was shown that removal of salivary glands in rodents leads to a reduced EGF levels in plasma. Recently, a novel method was developed to detect epithelial growth factor receptor (EGFR) mutations directly through bodily fluids including saliva in the oral cavity. This confirms that salivary growth factors (including EGF) are

distributed to distant body organs through salivary reabsorption. [4]

Expression and functions of EGF in different organs

EGF is a pivotal factor in the healing mechanism, acting on epithelial cells and fibroblasts and promotes recovery of damaged epithelium. In diabetic mice, these repaired cells can improve blood flow by increasing new vessel formation, which also helps in the healing process. [5]

In adult mice, salivary gland–derived EGF plays an important role in skin and soft tissue healing as well as in maintaining organ homeostasis. Wound healing of the skin is enhanced by licking most likely occurring by deposition of EGF onto the wound area, also local production of EGF at the site of injury is another mechanism. It also has been reported that salivary gland–derived EGF enhances the healing of gastric ulcers and tongue lesions. Removal of submandibular salivary glands 2 weeks before creating a wound in the tongue showed there was a significant delay in wound healing compared with control. Treatment of sialoadenectomized mice with EGF (1 microgram/ml in drinking water) restored the rate of wound healing to normal levels. [6]

The wound healing effect of recombinant human epidermal growth factor (rhEGF) in head and neck cancer and lymphoma patients who had developed severe oral mucositis was studied. All patients showed improvements in their oral mucositis after topical treatment with rhEGF. This finding suggests that rhEGF is effective and safe for the treatment of radiation-induced mucositis. [7]

The role of EGF in the maintenance of the integrity of the oesophageal mucosa was discussed in literature. Reporting the significant contribution of salivary EGF to the quality of the oesophageal mucosal barrier has been demonstrated in an experimental setting and in a clinical scenario. Patients with low salivary EGF levels are predisposed to severe oesophageal damage if they develop gastro-oesophageal reflux and are a high-risk group for development of Barrett's oesophagus. In addition to the above, the human oesophagus has a profound ability to elaborate and release EGF. EGF receptors are localised on the basolateral and luminal aspect of the mucosal cells playing an important role in fast regeneration of oesophageal epithelium through the high mitotic activity of its proliferative zone. [8] Under normal circumstances, there is an increase in the rate of salivary EGF secretion during mastication, which suggests its potential therapeutic benefit in the treatment of patients with damaged oesophageal mucosa.

In another study, the role of Epidermal Growth Factor on proliferation and restoration after ischemia–reperfusion (I/R) injury in rat small intestine was examined. Compared with the I/R group, administration of EGF presented a significant proliferation effect. Histological destruction was improved and recovery was notably accelerated in all EGF-treated groups. This shows that EGF intraluminal administration is an effective treatment against intestinal I/R injury. [9]

Moreover, epidermal growth factor (EGF) activity during rat liver regeneration was studied. It was found that EGF expression was significantly higher in normal rat liver than in regenerating tissue. [10] In the partial hepatectomy model for liver regeneration, disruption of salivary

EGF production through submandibular gland ablation results in delayed liver cell proliferation and a reduced capacity to regenerate the liver. [11]

Another therapeutical benefit is that the epidermal growth factor receptor inhibitor can improve the regeneration microenvironment and functional recovery in adult rats following spinal cord injury (SCI). The promising future application of EGFR inhibitor as a therapeutic agent after CNS injury was investigated. It was concluded that EGFR inhibitor can ameliorate excessive reactive astrogliosis and facilitate a more favourable environment for axonal regeneration after SCI. [12]

Finally, EGF regulates the major function of the pancreas insulin secretion. It was shown that EGF rapidly increased insulin secretion in mouse pancreatic islets, as well as in a pancreatic beta-cell line. In addition to that, EGF increased plasma insulin levels and mediated glucose lowering in normal and diabetic mice. [13] This provided evidence that EGF is a novel product that regulates plasma glucose levels and a candidate for the development of therapeutics for diabetes.

EGF and diabetes mellitus

The relation between EGF and diabetes has been studied extensively in literature. The general consensus amongst most studies is that although EGF and diabetes have a very close correlation, yet they do not seem to exist together in peace. Therefore we will summarise the findings from different studies investigating the two way relationship between EGF and diabetes.

Streptozotocin (STZ) induced diabetes affects the binding of 125-labeled epidermal growth factor (EGF) to hepatic membranes negatively. Scat chard analysis of the binding data clearly showed that the decrease in EGF binding was due to a decrease in the number of receptors. Treatment of diabetic animals with insulin reversed that negative effect. These results suggest that insulin deficiency in vivo causes a decrease in hepatic EGF receptors. [14]

The above mentioned results are supported by studying the expression of hepatic epidermal growth factor (EGF) receptor gene in genetically diabetic mice and STZ induced diabetic mice. The binding of 125-labelled EGF to hepatic membrane preparations and Levels of EGF receptor messenger RNAs (10 and 6 kb) of both genetically and STZ induced diabetic mice were significantly lower than that of non-diabetic mice. Daily administration of insulin to the STZ induced diabetic mice increased the hepatic levels of EGF receptor messenger RNAs to almost normal levels. [15] The production of epidermal growth factor (EGF) in the submandibular gland and its circulating level were studied in diabetic mice. EGF concentrations in the submandibular gland and plasma were reduced significantly in STZ induced diabetic mice. In addition, histological examination of the submandibular glands indicated that the size of the granular convoluted tubules, which produce EGF, was substantially reduced in the diabetic mice. Insulin administration to STZ-treated mice almost completely reversed the decrease in EGF content in the submandibular gland, and increased the size of the granular convoluted tubules in the gland. Therefore, it was concluded that EGF deficiency occurs in diabetes mellitus and that insulin is important in maintaining the normal level of EGF in the submandibular gland and plasma. [16]

Salivary derived growth factors, including EGF, are important in maintaining levels of oral health and mucosal integrity. Salivary levels of EGF in diabetic versus healthy control patients were studied through collection of salivary samples from patients every 6 hours for 42 hours. Salivary protein concentrations were determined for each sample and EGF concentrations for each sample were quantitated spectrophometrically utilizing an immunoassay. The EGF concentration was significantly lower for the diabetic patients compared to control patients. This study suggested that reduced levels of salivary EGF in diabetic patients may contribute to the development of oral and systemic complications of diabetes, which may have future clinical applications. [17]

Using a mouse model, the reduced concentrations of EGF in the saliva after onset of type 1 diabetes and its effect on oral wound healing was examined. It was found that with diabetes onset and a reduction in saliva-derived growth factor levels, the rate of tongue wound healing was reduced compared with non-diabetic and healthy mice. Addition of exogenous EGF to the drinking water accelerated wound healing in diabetic mice similar to the healthy ones. These results demonstrated that therapeutic treatment with topical delivery may be beneficial to patients with type 1 diabetes and oral wound complications. [11] It opened the horizons for the introduction of EGF supplementations, which may be beneficial to patients with identified complications in situations that require tissue repair associated with dysregulation of salivary sources of EGF.

One of the most common complications of diabetes are diabetic foot ulcers. The healing effect of a topical cream containing recombinant human epidermal growth factor (hEGF) on diabetic foot ulcers was studied. Patients with diabetic foot ulcers were monitored for 24 weeks. After 12 weeks, it was shown that data support the contention that application of hEGF-containing cream, in addition to good foot care from a multidisciplinary team, significantly enhanced diabetic foot ulcer wound healing and reduced the healing time. [18] In another study, the efficacy of topical application of beta recombinant human epidermal growth factor (Urogastrone) in Wagner's Grade 1 and 2 diabetic foot ulcers of patients was also analysed. [19] The results concluded that the application of rhEGF shortens the wound healing time significantly and the mean closure was significantly higher in the EGF group compared with placebo. Also, the Management of diabetic foot ulcers by topical application and intra-lesional injection of EGF was investigated and the authors stated that intra-lesional injection has better availability on the deep wound layers, but pain at the injection site is a common complaint. [5]

In a more detailed study, a total of 89 patients participated in an open-label trial, crossover study related to healing of chronic diabetic foot ulcers. Predetermined criteria were used for diagnosis and classification of ulcer. At the start of the study, the ulcers were debrided and treated with hydrocolloid or composite dressing depending on the condition of the wound. If treatment effect was minimal using this dressing for 3 weeks, patients were crossed over to twice-a-day treatment with 0.005% EGF and advanced dressing. Amongst the patients, 21 patients showed improvement using hydrocolloid or composite dressing

alone and 68 patients were crossed over to treatment with EGF and advanced dressing. In the EGF-treated patients, complete healing was noted in 52 patients within an average of 46 days. [20] A combination of topical treatment with EGF with advanced dressing may have positive effects in promoting healing of chronic diabetic foot ulcers.

The results mentioned above were confirmed through investigating the outcome of dressing a diabetic foot ulcer with epidermal growth factor compared with that of conventional dressing with normal saline. Treatment was given for 8 weeks or until ulcer healed, whichever occurred first. Evaluation of healing response was recorded on 1, 3, 5, and 8 weeks. It was found that duration of hospital stay in the study group was lower as compared with the control group. The study showed that EGF dressing causes early healing up to first 5 weeks as compared with conventional dressing. [21]

The effect of topical external administration of recombinant human epidermal growth factor (rhEGF) when controlling blood sugar on expression of epidermal growth factor receptor (EGFR) and EGFR mRNA of wound in diabetes mellitus (DM) combined with scald was also investigated. The authors found that external application of rhEGF when controlling blood sugar can accelerate the wound healing in DM combined with scald. After controlling blood sugar, external application of rhEGF can boost the expressions of EGFR mRNA, EGFR, and the extending process of signal conduction. [22]

Furthermore, the therapeutic effects of EGF on wound healing were evaluated by wound area measurement, histological analysis, immunohistochemical assessment of proliferating cell nuclear antigen and B-cell lymphoma/leukemia-2, and Western blotting of EGF receptor. It was found that rhEGF-containing hydrogel had an additional effect on induction of EGF receptor expression. Compared with negative controls, protein expression of B-cell lymphoma/leukemia-2 was higher in the rhEGF-containing groups. Proliferating cell nuclear antigen was induced at its highest level on day 7 in the rhEGF-containing hydrogel-treated group. [23] Therefore, the efficacy of hydrogels as a controlled releasing system for topical application of EGFs and therapeutic potential in enhancing diabetic wound healing.

EGF's positive effect on diabetes were also studied in different organs other than the foot, including but not limited to the cornea of the eye and the heart. The role of epidermal growth factor receptor (EGFR) signalling on the organization and remodelling of collagen fibrils (CFs) and proteoglycans (PGs) in the stroma of diabetic rat cornea was examined. Daily treatment with a selective inhibitor of EGFR tyrosine kinase, AG1478, for 4 weeks started on the same time of diabetes induction using STZ. It was found that the distribution of corneal stroma CFs and PGs were altered after 4 weeks of diabetes and that treatment with an EGFR signalling inhibitor reversed these abnormalities. [24]

EGFR family is known to have an essential role in cardiac development during embryogenesis and seems to represent a critical survival pathway in cardiac preconditioning and in mediating recovery of cardiac function following ischemic injury in normal and diabetic hearts. It is a double edged sword as on the other hand, EGFR seems to mediate other

detrimental pathways leading to diabetic cardiac myopathy. Thus any therapeutic strategies involving targeting of this important signalling receptor will require a careful assessment of its full effects in the diabetic heart as well as other organs and tissues, where its differential effects are also observed. [25]

EGF and diabetes; friends or faux?

In this article we provide an overwhelming evidence regards the relationship between EGF and diabetes. It is well established that many of the complications of diabetes arise due to reduction of EGF levels in the body. A number of studies showed that local or systemic treatment with EGF in presence of diabetes had positive effects related to healing of different tissues and counteracting diabetic complications in different organs. Despite the fact that the results seem promising, careful assessment of the dose, duration, mode of administration, ease of use and cost should be carefully assessed before clinical application.

To conclude EGF and diabetes friends or faux? A question that time will answer. However, EGF, diabetes and insulin is a complex and ongoing love triangle where none of the involved parties can claim to be a sole winner.

References

1. Keswani SG, Balaji S, Le LD, Leung A, Parvadia JK, Frischer J, et al. Role of salivary vascular endothelial growth factor (VEGF) in palatal mucosal wound healing. Wound Repair Regen 2013;21(4):554-62.
2. Venturi S, Venturi M. Iodine in evolution of salivary glands and in oral health. Nutrition and Health 2009;20(2):119-134.
3. Herbst RS. Review of epidermal growth factor receptor biology. International Journal of Radiation Oncology, Biology, Physics 2004;59(2):21-26.
4. Wei F, Lin CC, Joon A, Feng Z, Troche G, Lira ME, et al. Non-invasive saliva-based EGFR gene mutation detection in patients with lung cancer. Am J Respir Crit Care Med 2014; 190(10):1117-26.
5. Tiaka EK, Papanas N, Manolakis AC, Georgiadis GS. Epidermal growth factor in the treatment of diabetic foot ulcers: an update. Perspect Vasc Surg Endovasc Ther 2012; 24(1):37-44.
6. Noguchi S, Ohba Y, Oka T. Effect of salivary epidermal growth factor on wound healing of tongue in mice. Am J Physiol 1991;260(4):E620-625.
7. Hong JP, Lee SW, Song SY, Ahn SD, Shin SS, Choi EK, et al. Recombinant human epidermal growth factor treatment of radiation-induced severe oral mucositis in patients with head and neck malignancies. Eur J Cancer Care (Engl) 2009;18(6):636-641.
8. Marcinkiewicz M, Grabowska SZ, Czyzewska E. Role of epidermal growth factor (EGF) in oesophageal mucosal integrity.Curr Med Res Opin 1998;14(3):145-153.
9. Geng Y, Li J, Wang F, Li Q, Wang X, Sun L, et al. Epidermal Growth Factor Promotes Proliferation and Improves Restoration After Intestinal Ischemia–Reperfusion Injury in Rats. Inflammation 2013;36:670-679.
10. Adamek B, Zalewska-Ziob M, Strzelczyk J, Spausta G, Kasperczyk J, Wiczkowski A, et al. Does epidermal growth factor effect on late stages of rat liver regeneration upon interferon a2b influence? E&C Hepatology 2011;7(1):29-33.
11. Nagy A, Nagashima H, Cha S, Oxford GE, Zelles T, Peck AB, et al. Reduced Oral Wound Healing in the NOD Mouse Model

for Type 1 Autoimmune Diabetes and Its Reversal by Epidermal Growth Factor Supplementation. Diabetes 2001;50(9):2100-2104.
12. Li ZW, Li JJ, Wang L, Zhang JP, Wu JJ, Mao XQ, et al. Epidermal growth factor receptor inhibitor ameliorates excessive astrogliosis and improves the regeneration microenvironment and functional recovery in adult rats following spinal cord injury. J Neuroinflammation 2014;5(11):71.
13. Lee HY, Yea K, Kim J, Lee BD, Chae YC, Kim HS, et al. Epidermal growth factor increases insulin secretion and lowers blood glucose in diabetic mice. J Cell Mol Med 2008; 12(5A):1593-1604.
14. Kashimata M, Hiramatsu M, Minami N, Sato A, Minami N. Effect of experimental diabetes on epidermal growth factor (EGF) receptors in the rat liver. Nihon Yakurigaku Zasshi 1987;89:253-259.
15. Kasayama S, Yoshimura M, Oka T. Decreased expression of hepatic epidermal growth factor receptor gene in diabetic mice. J Mol Endocrinol 1989;3(1):49-56.
16. Kasayama S, Ohba Y, Oka T. Epidermal growth factor deficiency associated with diabetes mellitus. Proc Natl Acad Sci USA 1989;86(19):7644-7648.
17. Oxford GE, Tayari L, Barfoot MD, Peck AB, Tanaka Y, Humphreys-Beher MG. Salivary EGF levels reduced in diabetic patients. J Diabetes Complications 2000;14(3):140-145.
18. Tsang MW, Wong WK, Hung CS, Lai KM, Tang W, Cheung EY, et al. Human epidermal growth factor enhances healing of diabetic foot ulcers. Diabetes Care 2003;26(6):1856-1861.
19. Singla S, Garg R, Kumar A, Gill C. Efficacy of topical application of beta urogastrone (recombinant human epidermal growth factor) in Wagner's Grade 1 and 2 diabetic foot ulcers: Comparative analysis of 50 patients. J Nat Sci Biol Med 2014;5:273-277.
20. Hong JP, Jung HD, Kim YW. Recombinant human epidermal growth factor (EGF) to enhance healing for diabetic foot ulcers. Ann Plast Surg.2006;56(4):394-398.
21. Singla S, Singla S, Kumar A, Singla M. Role of epidermal growth factor in healing of diabetic foot ulcers. Indian J Surg 2012;74(6):451-455.
22. Zong S, Liang S, Ou B. Effect of topical external administration of recombinant human epidermal growth factor on expression of epidermal growth factor receptor and its mRNA in scald wound of diabetes mellitus rat. Chinese Journal of Reparative and Reconstructive Surgery 2010;24(2):150-155.
23. Lao G, Yan L, Yang C, Zhang L, Zhang S, Zhou Y. Controlled Release of Epidermal Growth Factor from Hydrogels Accelerates Wound Healing in Diabetic Rats. J Am Podiatr Med Assoc 2012;102(2):89-98.
24. Akhtar S, Almubrad T, Bron AJ, Yousif MHM, Benter IF, Akhtar S. Role of epidermal growth factor receptor (EGFR) in corneal remodelling in diabetes. Acta Ophthalmol 2009;87(8):881-889.
25. Akhtar S, Benter IF. The Role of Epidermal Growth Factor Receptor in Diabetes-Induced Cardiac Dysfunction. BioImpacts 2013;3(1):5-9.

Cite this article as: Al-Ankily MM, Shamel M, Bakr MM. Epidermal growth factor and diabetes mellitus; friends or faux? Int J Med and Dent Sci 2016;5(2):1290-1296.
Source of Support: Nil
Conflict of Interest: No