Evaluation of MicroRNA-503 among diabetic foot patients

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Abstract

Diabetes mellitus is one of the universal and complex metabolic diseases characterized by dysfunctional glucose control and othersyndromes of metabolism disturbance. Diabetes is accompaniedby various types of side effects, which can affect the metabolism,immunity, urinary system, nervous system, vision and restorativefunction of patients during their whole lifetime.

KeyWords: MicroRNA-503,diabetic foot.

DOINumber: 10.48047/NQ.2022.20.20.NQ109082 **NeuroQuantology2022;20(20):819-821**

Introduction:

Diabetes mellitus is one of the universal and complex metabolic diseases characterized by dysfunctional glucose control and other syndromes of metabolism disturbance. Diabetes is accompanied by various types of side effects, which can affect the metabolism, immunity, urinary system, nervous system, vision and restorative function of patients during their whole lifetime**(Satterfieldetal,2016).**Recently, the significant increase in the prevalence of diabetes mellitus leads to reduction in quality of life, serious financial burden and heavy social pressure of patients all over the world. Among the collective comorbidities, diabetic foot ulcers (DFUs) are the most prevalent and painful complications of patients afflicted with diabetes mellitus. In particular, DFU eventually leads to huge pain, chronic wound and repeated infection, even non traumatic amputation and considerable mortality, which is devastating and fearful **(Paggiaro etal,2018).**

It is estimated that of those patients who are suffering from diabetes mellitus, about 25% are prone to develop DFU which is regarded as a severe worldwide problem and challenge Current clinical therapies of DFU contain conventional medicine, physiatrists and operative treatments, which need a long period of hospitalization, high expense and considerable easy for the wound to recover thoroughly care, but it is not **(Nelson etal,2018).**

The etiology for diabetic foot ulcer is multifactorial. The common underlying causes are poor glycemic control, calluses, foot deformities, improper foot care, ill-fitting footwear, underlying peripheral neuropathy and poor circulation, dry skin. About 60% of diabetics will develop neuropathy, eventually leading to a foot ulcer. The risk of a foot ulcer is increased in individuals with a flat foot as they have disproportionate stress across the foot, leading to tissue inflammation in high risk areas of the foot **(Bekele et al., 2020).**

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Relevant conflicts of interest/financial disclosures:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Age more than 50; rural residence, low socioeconomic standard, hyperlipdemia, obesity, hypertension and neuropathy were identified as risk factors for diabetic foot in Egyptian diabetes patients **(Salama &Zorin, 2018).**

Diabetic neuropathy and peripheral artery disease (PAD) are the major causes of diabetic foot ulcers (DFU), with trauma acting as a starting trigger. At various points in the healing process, both of these factors contribute to the development of ulcers **(Baig et al., 2022).**

The immune system of individuals with diabetes is characterized by a reduced healing response in DFUs. There are many examples, including T-lymphocyte apoptosis; proinflammatory cytokines; degradation of polymorphonuclear cell functions such as chemotaxis, adhesion, and intracellular killing; inhibition of fibrocyte proliferation; and impaired basal layer of keratinocytes with reduced migration of epidermal cells **(Alsanawi et al., 2018).**

Bacteria, particularly aerobic Gram-positive cocci, such as Staphylococcus aureus (S. aureus) and hemolytic streptococci, flourish at high blood glucose levels. Carbohydrates, fibroblasts, and collagen synthesis are all affected by diabetes' metabolic insufficiency as well as other structural inadequacies. Serum glucose concentrations more than or equal to 150 mL/dL were also considered indicative of immune system dysfunction. These traits are likely to lead to a long-term inflammatory disease (Ibrahim, 2018).The term "biofilm" refers to an assemblage of bacterial populations that is well organized and encased in a polysaccharide matrix. Chronic diabetic foot sores are made worse by the formation of biofilms. Wound healing is slow and infection resistance is difficult to overcome because biofilm prevents the host's immune system from accessing antimicrobial medications. S. aureus accounted for the bulk of biofilms, and bacteria that caused chronic DFUs were typically multidrug-resistant, according to a study **(Pouget et al., 2020).**

Biofilms do not cause foot ulcers; rather, they are precipitating factors such as peripheral neuropathy (the loss of defensive sensitivity), altered foot architecture, trauma, and Patch. This causes the skin's protective layer to break down in both cases. When pathogenic biofilms have developed in DFUs, they may be a cause of recurrent and reoccurring infections, prolonging the healing of the ulcer **(Afonso et al., 2021).**

microRNA-503

microRNAs (miRNAs) are short (20-24 nt) non-coding RNAs that are involved in post-transcriptional regulation of gene expression in multicellular organisms by affecting both the stability and translation of mRNAs. miRNAs are transcribed by RNA polymerase II as part of capped and polyadenylated primary transcripts (pri-miRNAs) that can be either protein-coding or non-coding. The primary transcript is cleaved by the Drosharibonuclease III enzyme to produce an approximately 70-nt stem-loop precursor miRNA (pre-miRNA), which is further cleaved by the cytoplasmic Dicer ribonuclease to generate the mature miRNA and antisense miRNA star (miRNA*) products**(Kotowska-Zimmer et al., 2021).** The mature miRNA is incorporated into a RNA-induced silencing complex (RISC), which recognizes target mRNAs through imperfect base pairing with the miRNA and most commonly results in translational inhibition or destabilization of the target mRNA**(Zhang et al., 2018).**

microRNA-503 (miR-503) is an intragenic miR located on the chromosomal location Xq26.3 and clustered with miR-424 in human **(Kozomara et al., 2019).** It belongs to the miR-16 family and was first identified in human retinoblastoma tissues by microRNA microarray analysis **(Tian et al., 2020).**

To assess the role of miR-503 in regulating the functions of pancreatic β cells, bioinformatics tools were used to search for potential targets of miR-503. According to the results of these analyses, mTOR, an atypical serine/threonine kinase has recently been found to be involved in sustaining compensatory insulin secretion of pancreatic β cells in response to metabolic stress **(Xie et al., 2017).**

On testing whether miR-503 could directly target 3′-UTR of mTOR, a luciferase reporter assay was conducted. The results showed that overexpression of miR-503 significantly decreased the luciferase activity of mTOR with wt 3′-UTR, whereas miR-503 inhibition increased the luciferase activity of mTOR with wt 3′-UTR. **Zha et al.**demonstrated that miR-503 expression was negatively correlated with mTOR expression in peripheral blood from GDM patients, indicating that miR-503 regulates the expression of mTOR in GDM**(Zha et al., 2019).**

miRNAs as primary biomarkers for the diagnosis and treatment of diabetic foot ulcer

An ideal biomarker for the diagnosis of any disease is the molecule that can be produced at an early stage of that particular disease, and the amount of this molecule in one particular disease condition is not similar to other conditions Such biomarkers should be easily collected by non-invasive methods, preferably obtained from blood and urine samples, and stabilized in the laboratory environment. Although there is still no such biomarker with these specifications for diabetes, there are several conventional biomarkers for diabetes that are not specific to this disease. These include cholesterol, creatinine, free fatty acids, lipoproteins, C-reactive proteins, and adipokines. There are also several biomarkers that are not identifiable in the early stages of the disease. Cases in point include hyperglycaemia; insulin; glutamate decarboxylase; islet-cell dysfunction; and auto-antibodies in type 1 diabetes, phosphatosestyrosine, and in cretin levels. In addition, we are still unable to diagnose people who are susceptible to diabetes and its complications. Ideally, a biomarker must be shaped and adapted according to the progression of the disease and therapeutic interventions. None of the mentioned biomarkers, and even those that are used routinely by physicians, are entirely consistent with the specifications of an ideal biomarker. That is why miRNAs have a promising potential as a biomarker **(Goodarzi et al., 2019).**

miRNAs: Biomarkers for chronic diabetic ulcers

The idea of using miRNAs as a biomarker for diabetes and its complications began with the cohort study of microarray profiling in a large group of diabetic patients, in whom the amount of miRNAs in the blood, whole blood, or part of it was altered, and this was confirmed by qPCR. Such studies allowed the differentiation of miRNA profiles in type 1 and type 2 diabetes and the results of these studies showed that these miRNAs have the potential of becoming biomarkers for the early detection of diabetes **(Takahashi et al., 2014).**

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