Study on the Effect of Minocycline Adjuvant Therapy on Type 2 Diabetic Periodontitis and its Value in Improving Blood Glucose Levels

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This study aimed to investigate minocycline adjuvant therapy on type 2 diabetic periodontitis and its impact on blood glucose levels. We collected 100 patients with type 2 diabetic periodontitis admitted to our hospital from February 2022 to February 2023 as the study subjects, and then divided them into a control group (50 cases, conventional treatment) and an observation group (50 cases, conventional combined with minocycline treatment) by random number table method, observed and compared the changes in blood glucose, periodontal status and inflammatory indexes in both groups. After treatment, observation group had lower fasting blood glucose, 2 h fasting blood glucose and glycated hemoglobin levels than control group ($p<0.05$); observation group had lower gingival index, sulcus bleeding index, probing depth, plaque index and clinical attachment loss scores than control group ($p<0.05$); the levels of interleukin-6, tumor necrosis factor-alpha and C-reactive protein in the observation group were significantly smaller compared with those in the control group ($p<0.05$). Minocycline adjuvant therapy in the clinical treatment of patients with type 2 diabetic periodontitis can significantly improve the patients' blood glucose, it also improves the patients' periodontal condition and can effectively relieve the patients' inflammatory response, which can effectively improve the prognosis and obtain better treatment effectiveness.

Key words: Type 2 diabetes, periodontitis, minocycline, fasting blood glucose, inflammation

Periodontitis is a chronic infectious disease of the oral cavity with chronic inflammation of periodontal tissue caused by local factors. Currently, periodontitis accounts for 86 % of all periodontal diseases and can lead to loss of clinical attachments, bleeding gums and inflammatory reactions in the early stages, as the condition worsens, teeth may shift and loosen, seriously affecting the patient's daily life[1]. Therefore, the key to the treatment of periodontitis is the inhibition or removal of anaerobic bacteria. Diabetes is a metabolic disorder syndrome caused by progressive impairment of insulin function and is characterized by chronic hyperglycemia[2]. There is a link between the development of periodontal disease and the metabolic disorders in its organism, in patients with severe periodontal disease, dental plaque may contain bacteria that promote the progression of diabetes and produce inflammatory factors and endotoxins, thereby increasing circulating levels of risk factors in diabetic patients[3]. The prevalence of periodontal disease in combination with diabetes is high and topical medication has become the mainstay of treatment, with metronidazole and tetracycline being commonly used[4]. However, antibacterial drugs alone are not effective and combinations are now the main treatment option, especially with newer antibacterial drugs. Minocycline is a new semi-synthetic tetracycline with good penetration, broad-spectrum antibacterial action and the ability to promote periodontal tissue regeneration and inhibit bone tissue resorption. It has been widely used in the treatment of patients with periodontitis and is often placed in periodontal pockets as an adjunctive therapy[5,6]. The value of minocycline in the treatment of periodontitis has been extensively studied, but its use in patients with type 2 diabetic periodontitis has been relatively little reported. Based on this study focuses on studying the effect of minocycline adjuvant therapy on type 2 diabetic periodontitis and its impact on blood glucose

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levels. We collected 100 patients with type 2 diabetic periodontitis admitted to our hospital from February 2022 to February 2023 as the study subjects, and then divided them into two groups by random number table method with 50 cases, respectively. In control group, 26 males and 24 females; 30 y to 70 y old, mean (51.69±5.36) y old; Body Mass Index (BMI): 24-28 kg/m^2, mean (26.26±1.26) kg/m^2; course of diabetes was 2 y to 8 y, mean (5.36±0.52) y; in observation group, 25 males and 25 females; 30 y to 69 y old, mean (51.55±5.85) y old; BMI: 24-27 kg/m^2, mean (26.85±1.26) kg/m^2; course of diabetes was 2 y to 9 y, mean (5.87±0.74) y. No statistically significant difference when comparing patient's baseline information ($p>0.05$). The study was reviewed and approved by the ethics committee of our hospital. Informed consent was signed by the patients and their families. Inclusion criteria including the meeting the clinical diagnostic criteria for type 2 diabetes[7]; meeting the diagnostic criteria for periodontitis[8]; those with relatively stable blood glucose levels; those with more than 20 retained teeth in the mouth; those who have not taken antibiotics in the last 3 mo; those who have not received periodontal treatment in the last 6 mo. Exclusion criteria including the patients with malignant neoplasm; patients with severe organ insufficiency; allergic patients with hypersensitivity to the drugs used in the study; patients with cognitive impairment and poor compliance with treatment; patients with severe metabolic disorders; pregnant or lactating women; other types of diabetes and patients with periodontal disease caused by other reasons. Control group was given conventional treatment; after admission, they were instructed to undergo various examinations and were advised to take their hypoglycemic drugs normally; they were instructed on diet and oral hygiene, and were guided to use hydrogen peroxide to clean their mouths; they were also given tinidazole treatment (2 ml of tinidazole diluted in 50 ml of warm water and gargled for 1 min) for 3 times/day. After receiving the same treatment as control group, minocycline hydrochloride was added to the observation group; 0.5 g of minocycline hydrochloride was injected into the periodontal pocket, and the patient was instructed to rinse his mouth after the injection. A course of treatment was given for 7 d. Patients in both groups were adapted to the above treatment modalities for 1 mo, followed by assessment of relevant indicators. Glucose index including the 6 ml of venous blood was collected from patients in the morning fasting state before and after treatment, respectively, and the upper layer of serum was centrifuged for 15 min and tested by Shanghai Abbott Yuejia type blood glucose monitor, using glucose oxidase coupling colorimetric method to detect the levels of Fasting Blood Glucose (FBG) and 2 h Postprandial Glucose (2hPG), and the levels of Glycated Hemoglobin (HbA1c) were measured using a Beckman Coulter AU5800 automatic biochemical analyzer and immunoturbidimetric method. Periodontal status was evaluated before and after treatment respectively[9]. Gingival Index (GI) observe the gingival texture, color change and bleeding tendency, score 3 points for severe gingival inflammation, 2 points for moderate gingival inflammation, 1 point for mild gingival inflammation and 0 point for healthy gingiva; Sulcus Bleeding Index (SBI); probe the gingival sulcus lightly with a blunt-tipped periodontal probe, observe the shape and color of the gingiva and record the bleeding conditions, score was from 0 to 3 points. If there is no obvious sign of bleeding at present, score 0 point; severe bleeding gums, score 3 points; in periodontal pocket Probing Depth (PD); use the periodontal probe to probe the depth of the periodontal pocket or gingival pocket; in Plaque Index (PLI), take the probe and gently slide the tooth surface, based on the thickness and area of plaque on the tooth surface, score from 0 to 3 points, a higher score indicates more serious plaque; in Clinical Attachment Loss (CAL); use the electronic periodontal probe to clarify the position of the enamel bone, and observe the distance between the gingival margin and the enamel tooth, determined the degree of attachment loss. Inflammatory indexes including the 6 ml of venous blood was collected from patients in the morning fasting state before and after treatment, respectively, and the supernatant was centrifuged for 15 min, and the levels of Interleukin-6 (IL-6) and blood Tumor Necrosis Factor-Alpha (TNF-α) were detected by Enzyme-Linked Immunosorbent Assay (ELISA) and using a BK-1200 fully automatic biochemical analyzer manufactured by Shandong Boke Biological Industry Co., Ltd. The levels of C-Reactive Protein (CRP) were measured by immunoturbidimetric assay, the kits used are provided by Shanghai Kanglang Biotechnology Co., Ltd. The statistical analysis of the data was completed by Statistical Package for the Social Sciences (SPSS) 22.0 software, and the statistical significance of the difference between the

comparisons was expressed as $p<0.05$. Count data were described as percentages and compared by Chi-square (χ^2) test; measurement data were described as standard deviations ($\bar{x}\pm s$) and compared by t-test. It possessed no remarkable difference in FBG level, 2hFBG level and HbA1c level before treatment ($p>0.05$); after treatment, FBG level, 2hFBG level and HbA1c level in both groups showed significant improvement and the observation group was remarkably lower than the control group ($p<0.05$) as shown in Table 1. Before treatment, it possessed no remarkable difference in the periodontal status related indexes between both groups ($p>0.05$); after treatment, the levels of GI, SBI, PD, PLI and CAL were remarkably improved in both groups, and observation group had significantly higher improvement effect than control group ($p<0.05$) as shown in Table 2. Before treatment, it possessed no remarkable difference in inflammatory factors levels between both groups ($p>0.05$); after corresponding treatment, IL-6, TNF-α and CRP levels were remarkably lower in both groups and were remarkably lower in observation group ($p<0.05$) as shown in Table 3. Periodontitis is a chronic inflammatory disease of the oral cavity caused by pathogenic microbial infections and is one of the leading causes of tooth loss in our adult population[10]. Periodontal disease is associated with a high prevalence of periodontal plaque, local irritation and a variety of anaerobic bacterial infections. As the disease worsens, it can lead to loss of chewing function, which can have a serious impact on daily life. If the patient also has diabetes, the healing time is not only prolonged, but the inflammatory response of the organism is also increased. Periodontal disease in patients with type 2 diabetes is a common clinical condition which, if left untreated, can pose a serious threat to health and life. In the treatment of this disease, conventional measures are taken to stop the progression of periodontal disease through antibiotic drugs in addition to blood glucose control. Tinidazole is one of the most typical drugs that penetrates cells and binds to the Deoxyribonucleic Acid (DNA) of pathogenic bacteria, inhibiting their multiplication. However, tinidazole alone has obvious limitations, so a combination of other drugs is required. Minocycline is a semi-synthetic tetracycline antibiotic with a wide range of anti-inflammatory and antibacterial effects, it has long-lasting, high-efficiency and rapid-acting characteristics and can be used in the treatment of periodontitis with significant efficacy[11].

TABLE 1: COMPARISON OF PATIENTS' BLOOD GLUCOSE INDICATORS ($\bar{x}\pm s$)

Group	Cases	FBG (mmol/l)		2hFBG (mmol/l)		HbA1c (%)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control	50	9.98±1.25	7.12±0.15*	15.63±2.33	8.92±1.25*	9.02±2.99	8.11±1.84*
Observation	50	9.95±1.84	6.79±0.36*	15.58±2.14	7.89±1.93*	9.07±2.78	6.86±1.69*
t		0.095	5.983	0.111	3.167	0.086	3.537
p		0.924	0.000	0.911	0.002	0.931	0.000

Note: (*) indicates that within this group compared to pre-treatment, $p<0.05$

TABLE 2: COMPARISON OF PERIODONTAL STATUS BETWEEN BOTH GROUPS ($\bar{x}\pm s$)

Group	Time	GI (points)	SBI (points)	PD (mm)	PLI (points)	CAL (mm)
Control	Before treatment (n=50)	2.86±0.21	2.89±0.52	4.92±0.31	2.85±0.10	5.85±1.42
Observation		2.84±0.28	2.91±0.46	4.91±0.42	2.83±0.12	5.82±1.24
Test value	t	0.404	0.203	0.135	0.905	0.162
	p	0.687	0.839	0.892	0.367	0.871
Control	After treatment (n=50)	1.25±0.63*	2.23±0.34*	3.95±0.21*	1.58±0.31*	4.05±0.23*
Observation		0.52±0.02*	1.16±0.52*	2.22±0.18*	0.38±0.03*	3.75±0.33*
Test value	t	8.189	12.177	44.228	27.244	5.273
	p	0.000	0.000	0.000	0.000	0.000

Note: (*) indicates that within this group compared to pre-treatment, $p<0.05$

TABLE 3: COMPARISON OF INFLAMMATORY FACTOR LEVELS BETWEEN BOTH GROUPS (x̄±s)

Group	Cases	IL-6 (ng/l)		TNF-α (ng/l)		CRP (mg/l)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control	50	13.20±2.35	6.01±1.17*	9.40±2.13	7.38±1.34*	12.70±2.21	7.35±2.41*
Observation	50	13.22±2.30	4.01±1.10*	9.38±2.24	5.37±1.30*	12.68±2.30	4.58±1.37*
t		0.043	8.806	0.045	7.612	0.044	7.065
p		0.965	0.000	0.963	0.000	0.964	0.000

Note: (*) indicates that within this group compared to pre-treatment, p<0.05

The results of this study indicated that observation group had significantly better glucose index, periodontal condition and inflammatory index levels than control group after treatment, indicating that minocycline adjunctive therapy in the treatment of type 2 diabetic periodontitis patients can enhance the therapeutic effect of patients, reduce their inflammatory response and have less impact on their glucose metabolism index. A study has shown that the total therapeutic efficiency of applying minocycline hydrochloride in combination with tinidazole in the treatment of patients with periodontal disease was remarkably higher than metronidazole alone and the application value of the combined treatment regimen was confirmed[12]. There is a close association between type 2 diabetes and periodontitis. Periodontitis is an inflammatory response due to plaque, and there is a close association between plaque and type 2 diabetes, which can further exacerbate the condition. Type 2 diabetes can affect the immune system and inflammatory response, thereby increasing the risk of periodontitis caused by oral bacteria[13]. IL-6 promotes the secretion of other inflammatory mediators, leading to the production of acute response proteins, which in turn increase the periodontal inflammatory response and damage the alveolar bone. TNF-α is associated with the degree of periodontal tissue destruction and in the pathogenesis of periodontitis, it promotes collagen secretion by gingival fibroblasts, which in turn damages gingival tissue and inhibits bone resorption. TNF-α reflects the severity of inflammation and recovery from periodontitis and also promotes the synthesis of inflammatory mediators such as IL-6, which in turn triggers an inflammatory cascade reaction that affects the restorative power of periodontal tissues and aggravates the condition. Chronic hyperglycemia stimulates the local release of TNF-α in organs, which in turn causes damage to tissue cells and overexpression of TNF-α is also involved in changes in local permeability of micro vessels, CRP is a sensitive marker of inflammatory response. Studies have proved that serum CRP concentrations are remarkably higher in patients with type 2 diabetes and are positively correlated with the severity of vascular disease[14]. It has also been shown that endothelial dysfunction is the initiating factor in diabetic atherosclerosis and that micro inflammation is the basis of endothelial dysfunction[15]. Inflammatory factors such as CRP and TNF-α can play an important role in metabolic aspects such as glucolipid metabolism and insulin sensitivity in the body. The long-term presence of these microorganisms can stimulate the body's liver cells and adipose tissue to produce various inflammatory substances, causing insulin resistance. Minocycline is a new and highly effective semi-synthetic tetracycline, whose antibacterial effect is much higher than that of tetracycline. Some scholars have pointed out that the antibacterial effect of minocycline hydrochloride is two to four times that of tetracycline and is stronger than that of metacycline, doxycycline and oxytetracycline, and is effective against tetracycline-sensitive or resistant Staphylococcus aureus. Minocycline specifically inhibits the growth of Gram-negative and Gram-positive bacteria, its specificity comes from the molecular structure of minocycline, i.e. it prevents the synthesis of proteins located in the cell membrane inside Gram-positive and Gram-negative bacteria, preventing the strain from multiplying and spreading, reducing the number and type of oral bacteria, thus inhibiting the production of inflammatory responses and reducing local inflammation levels, which in turn may promote insulin sensitivity, contributing to lower blood glucose levels. Minocycline also inhibits the inflammatory response of the immune system, reducing the cytokines release and the inflammatory mediator's formation, thereby reducing the symptoms and inflammatory response of periodontitis, which further helps to lower blood glucose levels. In addition, minocycline has a collagenase inhibiting effect, thus reducing the rate of enzyme-catalyzed

reactions, alleviating the inflammatory response and mitigating the effects of the inflammatory response, further contributing to lowering the patient's blood glucose levels. Minocycline has a strong tissue penetrating effect and can therefore be rapidly distributed to the liver, kidneys and brain, thus quickly and effectively exerting an antibacterial effect, which in turn can effectively remove pathogenic bacteria and reduce the severity of inflammation, thereby reducing the inflammatory response of the patient's body and lowering blood glucose levels. PLI reflects oral hygiene and periodontal disease status; GI reflects gingival status; SBI can assess the patient's gingival and gingivitis activity status The PLI reflects oral hygiene and periodontal disease; the GI reflects gingival status; the SBI assesses the patient's gingival and gingivitis activity; the CAL reflects gingival pockets and the PPD reflects the degree of alveolar bone resorption, observation of these 5 periodontal function indices provides a good overview of the patient's periodontal function. Minocycline is highly lipophilic in the oral environment and can promote the recovery of periodontal tissues. Minocycline can also effectively promote the formation of new periodontal attachment tissue, inhibit bacteria and plaque under the gingiva, prevent tissue destruction, promote the transformation of ligamentous tissue into osteoblasts within the periodontal tissue, promote the effective proliferation of periodontal membrane fibroblasts, prevent the resorption of the alveolar bone against them, facilitate the stability of the affected teeth, accelerate the regeneration of periodontal tissue, and thus effectively improve GI, SBI, PD, PLI and CAL levels. In addition, minocycline can further promote the clearance and degradation of inflammatory factors by regulating the immune response, which in turn can improve the capillary permeability of periodontal tissues and reduce connective tissue edema, helping to promote the recovery of periodontal symptoms and improve GI, SBI, PD, PLI and CAL levels. Tinidazole is a new bio adhesive agent with a different antibacterial mechanism to minocycline, so the combination of the two drugs can synergies their efficacy and increase the antibacterial effect. In summary, minocycline can be used in the clinical treatment of patients with type 2 diabetic periodontitis, not only to control their blood glucose levels, but also to effectively improve their inflammatory response and enhance their periodontal recovery, which can achieve more significant clinical efficacy.

Funding:

This work was supported by The State Key Laboratory Pathogenesis, Prevention and Treatment of High Incidence Diseases in Asia Fund (SKL-HIDCA-2021-17).

Author's contributions:

Nulipa Abulai and Mayire Nuermaimaiti have contributed equally to this work.

Conflict of interests:

The authors declared no conflict of interests.

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This article was originally published in a special issue, "Drug Development in Biomedical and Pharmaceutical Sciences" Indian J Pharm Sci 2023:85(5) Spl Issue "227-232"