Kontrol Glikemik Pada Diabetes Dan Tingkat Keparahan Periodontitis

(Glycemic Control in Diabetes and The Severity of Periodontitis)

Nuzulul Hikmah[1*], Djoko Wahono Soeatmadji[2], Aulanni'am[3], Mohammad Saifur Rohman[4], Nur Permatasari[5], Hafiedz Maulana[1]

[1] Department of Dentistry-Biomedical Sciences, Oral and Maxillofacial Pathology, Faculty of Dentistry, Universitas Jember, Jember, Indonesia
[2] Division of Endocrinology Metabolic Disease and Diabetes, Department of Internal Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia
[3] Department of Biochemistry, Faculty of Mathematics and Natural Sciences, Universitas Brawijaya, Malang, Indonesia
[4] Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia
[5] Department of Pharmacology, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

Abstrak

Diabetes merupakan penyakit metabolik yang kompleks dengan prevalensi yang semakin meningkat secara global. Diabetes berhubungan dengan peningkatan risiko periodontitis yang dipengaruhi oleh pengendalian indeks glikemik. Pemeriksaan hemoglobin terglikasi (HbA1c) menunjukkan kadar hemoglobin dalam darah yang telah terglikasi (terikat secara kimia dengan glukosa) dan mencerminkan kadar glukosa darah selama tiga bulan terakhir. Tujuan penelitian ini untuk menentukan hubungan antara kontrol glikemik pada penderita diabetes dengan tingkat keparahan periodontitis.
Metode: Studi literatur yang dilakukan menggunakan basis data PubMed dengan kata kunci "HbA1c and periodontitis" dan publikasi antara tahun 2012 hingga Juni 2021. Data dari artikel yang relevan dipilih dan dirangkum dalam tabel serta tinjauan naratif. 20 artikel telah dipilih berdasarkan kesesuaian topik. Pasien dengan kadar HbA1c yang lebih tinggi menunjukkan keterkaitan dengan peningkatan keparahan penyakit periodontal yang ditentukan oleh beberapa parameter yaitu clinical attachment loss (CAL), pocket depth (PD), bleeding on probing (BOP), oral hygiene index (OHI), community periodontal index (CPI), periodontal inflamed surface area (PISA), periodontal screening index (PSI), kolonisasi patogen periodontal, mobilitas gigi, dan jumlah gigi yang hilang. Kadar HbA1c yang tinggi menandakan kontrol glikemik yang buruk dan berhubungan dengan peningkatan keparahan periodontitis.

Kata Kunci: Diabetes, Kontrol Glikemik, Periodontitis

Abstract

Diabetes is a complex metabolic disorder, which has been increasingly prevalent worldwide. Diabetes is related to increasing the risk of periodontitis determined by glycemic index control. The glycated haemoglobin (HbA1c) analysis indicates the haemoglobin rate in the blood has been glycated (chemically bonded with glucose) and determines blood glucose levels over the previous three months. The aim of this study was to determine the relationship between glycemic control in diabetes and the severity of periodontitis. Literature searches were performed using Pubmed with the keyword "HbA1c and periodontitis" and published between 2012 to June 2021. The data from the articles were selected and summarized in tables and a narrative review. A total of 20 articles has been selected based on the relevant topics. Patient with higher HbA1c levels was associated with the severity periodontal diseases determined by several parameters. The parameters were clinical attachment loss (CAL), pocket depth (PD), bleeding on probing (BOP), oral hygiene index (OHI), community periodontal index (CPI), periodontal inflamed surface area (PISA), periodontal screening index (PSI), the periodontal pathogen colonized, tooth mobility, and the number of missing teeth. The higher level of HbA1c, indicated poorly controlled diabetes, associated with the increase of periodontitis severity.

***Keywords**: Diabetes, Glycemic Control, Periodontitis*.

Korespondensi *(Correspondence)*: Nuzulul Hikmah, Department of Dentistry-Biomedical Sciences, Oral and Maxillofacial Pathology, Faculty of Dentistry, Universitas Jember. Kalimantan St, No. 37, Jember, Indonesia, Email: nuzulul@unej.ac.id

Diabetes is a complex metabolic disorder, which has been increasingly prevalent worldwide. Diabetes is characterized by elevated blood glucose levels (hyperglycemia). Diabetes is caused by the body's inability to produce enough insulin, or it cannot use the insulin it produces effectively. Diabetes has become a global problem because the number of people with diabetes is increasing. In 2021, the International Diabetes Federation (IDF) published that the number of people with diabetes aged 20-79 years would reach 537 million and is expected to increase in 2030 to 643 million and in 2045 to 783 million.[1]

The diabetes diagnosis can be made following a random venous plasma glucose test, a fasting plasma glucose test, a two-hour plasma glucose test, or glycated hemoglobin (HbA1c) measurement.[1] HbA1c analysis indicates the hemoglobin rate in the blood has been glycated (chemically bonded with glucose) and determines blood glucose levels over the previous three months.

Diabetes is related to increasing the risk of periodontitis determined by glycemic index control. Periodontitis is an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms, which cause progressive damage to the periodontal ligament and alveolar bone through increased probing depth formation, gingival recession, or both.[2] This study aims to determine the relationship between glycemic control in diabetes and the severity of periodontitis.

METHODS

A literature search of the last ten years was performed using the PubMed database from 2012 to June 2021, with the keyword "HbA1c and periodontitis". The articles were limited to the

English language and human studies. The data from the articles were selected base on the relevant topics. Therefore, the data were summarized in tables and a narrative review.

RESULT

A total of 20 articles have been selected based on the relevant topics. A summary of the review article and the principal findings from literatures is shown in Table 1. Patient with higher HbA1c levels was associated with the severity periodontal diseases determined by several parameters. The periodontal parameters were: clinical attachment loss (CAL), pocket depth (PD), bleeding on probing (BOP), oral hygiene index (OHI), community periodontal index (CPI), periodontal inflamed surface area (PISA), periodontal screening index (PSI), periodontal pathogen colonized, tooth mobility, and the number of missing teeth.

Table 1. Principal findings from works of literatures that investigated factors that potentially associated glycemic control (HbA1c) in diabetes and the severity of periodontitis.

Reference	Study Population	Periodontal Parameter	HbA1c (%)	Main Finding
Haseeb et al., 2012.[3]	40 well controlled and 40 poorly controlled type 2 diabetic subjects having good oral hygiene (scored according to simplified oral hygiene index) were compared with a control group of 40 normal healthy individuals	Mean % of sites with CAL ≥ 4 mm - Mean % of sites with CAL > 6 mm	a. Normal b. ≤7.0 (well controlled) c. > 7.0 (poorly controlled)	a. 19.84 - 3.43 b. 23.51 - 7.13 c. 35.03 - 20.92
Morita et al., 2012.[4]	5,856 people	Community Periodontal Index (%)	a. < 6.5 b. ≥ 6.5	a. Codes 0, 1, 2: 65.1 Codes 3, 4: 34.9 b. Codes 0, 1, 2: 48.7 Codes 3, 4: 51.3
Santos et al., 2012.[5]	91 subjects with type 2 DM and generalized chronic periodontitis	Sites with PD≥5 mm (%) - Sites with CAL≥5 mm (%)	a. ≤ 7.5 b. 7.6–9 c. 9.1–11 d. > 11	a. 22.9 - 44.4 b. 24.4 - 42.0 c. 21.3 - 41.3 d. 24.2 - 38.8 * No statistically significant differences
Susanto et al., 2012.[6]	132 healthy subjects and 101 subjects treated for DM2	Periodontal severity: PISA (mm2) - CAL (mm) - PD (mm)	a. Mean 5.5 (Healthy controls) b. Mean 8.9 (DM2)	a. 83.9 - 1.8 - 1.7 b. 170.4 - 2.4 - 1.9
Weinspach et al., 2013.[7]	111 nondiabetics (ND), 101 type 1 diabetics (T1D), and 236 type 2 diabetics (T2D)	periodontal screening index (PSI)	a. 6.15 (NC) b. 7.21 (T1D) c. 6.84 (T2D)	a. 3.26 b. 2.79 c. 3.52
Poplawska-Kita et al., 2014.[9]	107 patients with type 1 diabetes and 40 healthy controls	Community Periodontal Index (CPI0 – CPI1 – CPI2 – CPI3 – CPI4)	a. Control group b. ≤6.5 (Good metabolic control) c. >6.5 (Poor metabolic control)	a. 2.8–1.7–0.8–0.2–0.0 b. 1.5–2.1–1.5–0.6–0.3 c. 1.3–1.5–1.2–0.9-0.5
Sakalauskiene et al., 2014.[10]	56 subjects divided into 2 groups: healthy subjects (the H group) and diabetic (type 1 diabetes) patients with chronic untreated generalized periodontitis (the DM group)	Clinical: PD (mm) – OHI Microbiological (Frequencies of microbes): FN – EC – PG – PI – CS – AA – SI (%)	a. ≤ 7 (Healthy group) b. >7 (DM group)	a. Clinical: 0.2 – 0.26 Microbiological: 18.5–18.5–81.5–44.4–11.1–100.0–59.3 b. Clinical: 5.33 – 3.04 Microbiological: 96.3–51.9–63.0–70.4–77.8–59.3–33.3

- Community Periodontal Index: Code 0, Healthy gingivae; Code 1, Gingival bleeding after probing; Code 2, Calculus detected; Code 3, Pocket 4 to 5 mm; Code 4, Pocket 6 mm or more.[4]
- Periodontal inflamed surface area (PISA) quantifies the amount of inflamed periodontal tissue and is supposed to quantify the inflammatory and infectious burden resulting from periodontitis. Clinical attachment loss (AL) was defined as the distance from the cementoenamel junction to the bottom of the pocket/sulcus and calculated as the mathematical sum of the PD and gingival recession measurements.[5]
- The periodontal screening index (PSI) provides information about the severity and treatment needs of periodontal diseases. It is subdivided into five codes. Code 0 represents healthy periodontal conditions, codes 1 and 2 indicate gingivitis, and codes 3 and 4 indicate periodontitis.[7]
- Tooth mobility Grade 3: severe mobility faciolingually & mesiodistally combined with the vertical displacement.[8]
- The community periodontal index (CPI) code was recorded in each segment (code 0: no signs of periodontal disease, code 1: gingival bleeding after gentle probing, code 2: supragingival or subgingival calculus, code 3: 4–5 mm deep pathologic pockets, code 4: 6 mm or deeper pathologic pockets).[9]
- Oral hygiene status was evaluated by the Simplified Oral Hygiene Index (OHI-S; Green-Vermillion simplified). The OHI-S index consists of 2 components: plaque index (DI), and calculus index (CI). OHI-S = DI + CI. Frequencies of microbes to F. nucleatum (F.n.), E. corrodens (E.c.), P. gingivalis (P.g.), P. intermedia (P.i.), Capnocytophaga spp. (C.s.), A. actinomycetemcomitans (A.a.), S. intermedius (S.i.).[10]

Continued Table 1. Principal findings from works of literatures that investigated factors that potentially associated glycemic control (HbA1c) in diabetes and the severity of periodontitis.

Reference	Study Population	Periodontal Parameter	HbA1c (%)	Main Finding
Jindal et al., 2015.[11]	50 patients with Type 1 diabetes	PD (mm) –CAL (mm)	a. ≤7 b. 7-8 c. >8	a. 2.93 - 3.33 b. 3.81 - 4.43 c. 5.31 - 6.15
Kiedrowicz et al., 2015.[12]	75 patients with DM2 were grouped according to glycemic control: 40 subjects with HbA1c < 7.0 and 35 subjects with HbA1c ≥ 7.0	PD >7 mm (mm) - CAL (mm) - Tooth mobility grade III (%)	a. < 7.0 b. ≥ 7.0	a. 3.49 - 3.07 - 0.53 b. 6.72 - 2.87 - 1.32
Miranda et al., 2017.[13]	56 subjects with type 2 DM, HbA1c<8 (n=28), HbA1c≥8 (n=28)	Periodontal pathogen colonized in PD≥5 mm (%): TD – PG – TF – ED – PM – EF – PI	a. <8 b. ≥8	a. 87.5 – 80.3 – 83.9 – 82.1 – 83.9 – 83.9 – 83.9 b. 96.4 – 91.0 – 96.4 – 96.4 – 98.2 – 98.2 – 98.2
Yonekura et al., 2017.[14]	108 patients with T2DM hospitalized	BOP – PD>4 mm	a. <9.0 b. ≥9.0	a. 23.21 - 18.33 b. 32.74 - 31.07
Alasqah et al., 2018.[15]	41 Healthy Patients 41 Patients with prediabetes 43 Patients with T2DM	PD (mm) – CAL (mm) - Number of missing teeth	a. 4.5 (4.3–4.8) b. 6.1 (5.8–6.3) c. 8.4 (8.1–9.3)	a. 2.5 - 0.6 - 4.8 b. 5.2 - 3.5 - 10.4 c. 5.8 - 3.8 - 13.2
Dhir et al., 2018.[16]	1235 patients with type 2 DM and 465 nondiabetic patients	Periodontal disease severity	a. <5.6 (no diabetes) b. <7 (well control diabetes) c. >7 (poor control diabetes)	a. No-mild periodontitis: 19.52% b. No-mild periodontitis: 18.78% c. Moderate-severe periodontitis: 61.7%
Panezai et al., 2020.[17]	51 patients with periodontitis and 20 healthy subjects	Correlation (r) and p value of glycated proteins with periodontal parameters (PD - Missing teeth)	a. ≤ 5.7 (Normal glucose tolerance) b. 5.7-6.4 (Prediabetes) c. ≥ 6.5 (Type 2 diabetes)	r = 0.49 - 0.48 p value = <0.0001 - <0.0001
Qureshi et al., 2020.[18]	118 patients with type-2 diabetes mellitus and periodontitis	Correlation (r) and p value between HbA1c and PD - HbA1c and CAL	Range 6.2 - 14.61	r = 0.36 – 0.43 p value = <0.001 – <0.001
Grigoriadis et al., 2021.[19]	150 subjects with undiagnosed diabetes	PD (mm) - CAL (mm)	a. <5.7 b. ≥5.7	a. 2.81 - 3.18 b. 3.20 - 3.54
Kassab et al., 2021.[20]	30 healthy subjects (H group), 30 non-diabetic subjects suffering from chronic periodontitis (CP group). Type 2 diabetic patients were divided according to HbA1c level: 30 adequately controlled type 2 diabetes subjects (HbA1c ≤ 7 percent (AT2D&CP group)) and 30 inadequately controlled type-II diabetes subjects and HbA1c > 7 percent (IT2D&CP group)	PD (mm) - CAL (mm) - Biofilm Species Prevalence (%)	a. H b. CP c. ≤ 7 (AT2D&CP) d. > 7 (IT2D&CP)	a. 2.20 – 0 – 0 b. 4.7 – 4.9 – 75 c. 5.9 – 6.1 – 65 d. 6.3 – 7.36 – 95
Rapone et al., 2021.[21]	Participants with type 2 diabetes and periodontitis	Correlation (r) and p value between HbA1c and PD - HbA1c and CAL	Mean 8.081	r = 0.136 - 0.142 p value = 0.201 - 0.181 *no statistically significant
Romano et al., 2021.[22]	104 T2DM patients	No/Mild – Moderate – Severe Periodontitis (%)	a. < 7 (good) b. ≥ 7 (poor)	a. 21.1 - 39.5 - 39.5 b. 1.5 - 19.7 - 78.8
Stoicescu et al., 2021.[23]	182 patients with type 2 diabetes mellitus and generalized chronic periodontitis	Sites with PD≥5 mm (%) - Sites with CAL≥5 mm (%)	a. < 7 b. ≥ 7	a. 23.4 - 43.7 b. 27.8 - 42.6 *CAL no statistically significan

- TD – PG – TF – ED – PM – EF – PI: Treponema denticola, Porphyromonas gingivalis, Tanerella forsythia, Eubacterium nodatum, Parvimona micra, Fusobacterium nucleatum ssp. and Prevotella intermedia.[13]
- Biofilm species prevalences of the study were Aa: Aggregatibacter actinomycetemcomitans, Pg: Porphyromonas gingivalis, Tf: Tannerella forsythia, Td: Treponema denticola.[20]
- No periodontitis: no evidence of mild, moderate, or severe periodontitis, mild periodontitis: ≥2 interproximal sites with AL ≥3 mm, and ≥2 interproximal sites with PD ≥4 mm (not on same tooth) or one site with PD ≥5 mm, moderate periodontitis: ≥2 interproximal sites with AL ≥4 mm (not on same tooth), or ≥2 interproximal sites with PD ≥5 mm (not on same tooth), severe periodontitis: ≥2 interproximal sites with AL ≥6 mm (not on same tooth) and ≥1 interproximal site with PD ≥5 mm.[24]

DISCUSSION

Diabetes increases the risk for periodontitis, and glycemic control is critical in determining the level of risk. Most of the research on periodontitis and diabetes has focused on type 2 diabetes, but type 1 diabetes has also been associated with increased periodontal destruction. The risk of periodontitis is 3-fold higher among diabetic patients, its prevalence and severity even greater in diabetic patients presenting elevated HbA1c levels.[25] Glycosylated hemoglobin (HbA1c) allows the control of serum glucose levels in an interval of 120 d and is a valuable decision-making tool. According to the International Diabetes Federation (IDF), in 2021, the diagnostic criteria for diabetes are HbA1c 48 mmol/mol (6.5%).[1] HbA1c has traditionally been expressed as a percentage of hemoglobin that has glucose molecules absorbed onto the hemoglobin molecule, that is, the percentage of hemoglobin that is glycated. However, how HbA1c values are reported has now switched from a rate to mmol/mol. For a non-diabetic, HbA1c is typically around 5.5% (37 mmol/ mol). In people with diabetes, HbA1c levels of <7.0% (53 mmol/mol) would typically indicate good glycemic control. 8-9% (64-75 mmol/mol) or higher indicate poor glycemic control.[26]

The results of this study were that patients with higher HbA1c levels were associated with the severity of periodontal diseases. Previous studies have shown that diabetes increases the risk of periodontitis by 86%.[27] Hyperglycemia increases advanced glycation end product (AGE) levels, which can affect the function of normal proteins such as collagen or bind to receptors (RAGE) on different cell membranes.[28] High AGEs can modify the structure of collagen and make periodontal tissue less reparative, making it more susceptible to damage.[29] AGEs influence diabetes complications through the RAGE, mitogen-activated protein kinase (MAPK), and nuclear factor kappa-B (NF-kB) pathways. In diabetes with periodontitis, AGE exacerbates the inflammatory response of periodontal tissues by increasing the expression of interleukin-6 (IL-6) and intercellular adhesion molecule-1 (ICAM-1) via the RAGE, MAPK, and NF-kB pathways in gingival fibroblasts.[30] These factors result in periodontal tissue breakdown and alveolar bone damage.

According to Wang et al. (2021), the susceptibility and severity of periodontal disease in diabetes are due to hyperglycemia triggering cellular senescence (cellular aging) and inflammation in macrophages. Therefore, it changes glycometabolism mediated by glucose transporter 1 (GLUT1) and a senescence-associated secretory phenotype (SASP) response, accelerating periodontal tissue destruction. SASP can ameliorate hyperglycemia-induced inflammation. Macrophages in periodontal inflammation have high transcriptional activity so that hyper-glycometabolism occurs, which is necessary to correct this phenomenon, but this can lead to fatigue and aging of macrophages. Several pathways involved in SASP and regulation of cellular senescence are NF-kB, mammalian target of rapamycin (mTOR), and nucleotide-binding leucine-rich repeat (NLR).[31]

The inflammatory response also plays an important role in the pathogenesis of diabetes with periodontitis. The interactions between AGEs and RAGE also result in increased secretion of interleukin-1β (IL-1β), tumour necrosis factor-a (TNF-a), and IL-6, and increased oxidative stress. These interactions also disrupt the receptor activator of the NF-κB ligand/osteoprotegerin (RANKL/OPG) axis to favor bone resorption.[25] The study in a rat model of type 2 diabetes-induced periodontitis using *Porphyromonas gingivalis* showed increased alveolar bone destruction associated with increased expression of various inflammatory proteins. The increase is through increased expression of Janus family kinase 1 (JAK1), signal transducer and activator of transcription 1 (STAT1), and signal transducer and activator of transcription 3 (STAT3); increased serum levels of TNF-α; and decreased expression of nonreceptor type 2 tyrosine phosphatase protein (PTPN2) in the gingival epithelium.[32] Serum TNF-a levels positively correlated with fasting blood glucose levels, destroying pancreatic cells, reducing insulin sensitivity, and activating JAK/STAT-like signalling. PTPN2 is a regulator of the inflammatory response, and the expression of PTPN2 in the gingival epithelium negatively correlates with the severity of periodontal breakdown and hyperglycemia. The JAK/STAT pathway also plays an important role in developing chronic inflammatory diseases, including diabetes and periodontitis.[32-33]

Diabetes affects alveolar bone destruction and imbalanced bone remodelling in periodontal disease through several mechanisms.[34] Diabetes affects osteoblasts and osteoclasts through increased expression of inflammatory mediators, RANKL/OPG ratio, and increased AGEs and ROS.[34,35] Diabetes increases the susceptibility to bacterial infections in the periodontal tissues. Anaerobic bacteria are the pathological bacteria that predominate in periodontitis. Bacterial accumulation can induce apoptosis of bone-lining cells, and diabetes strongly affects the bone-lining cells and matrix-forming cells (MMP8 and MMP 9), resulting in alveolar bone destruction.[36] Therefore, appropriate periodontal therapy and glycemic control are prioritized in managing diabetic patients with periodontitis to avoid the risk of continued severity.

Dental clinicians must know the different measurements of HbA1c as patients report their diabetes control.[25,37] Good glycemic control is essential in preventing diabetic complications. Periodontal screening and treatment of periodontitis are fundamentally important in people with diabetes. Both dental and medical healthcare professionals should inform patients about the links between the two diseases and work towards improved collaboration and interprofessional working. The dental team has an important role to play in the management of patients with diabetes.

A higher level of HbA1c reflects poorly controlled diabetes, which may predict an increased risk and severity of periodontitis. Future studies should explore the longitudinal relationship between HbA1c levels and periodontal disease progression to establish causal links and identify critical thresholds of glycemic control affecting periodontal outcomes. Investigations integrating molecular biomarkers, inflammatory mediators, and imaging of periodontal tissues could clarify the underlying mechanisms. Moreover, interventional studies assessing whether improved glycemic control through medication or lifestyle modification can reduce periodontal inflammation and alveolar bone loss would provide valuable clinical insights for both dental and medical management of diabetic patients.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels, Belgium: International Diabetes Federation; 2021.\
2. Hinrichs JE, Kotsakis GA. Modern concepts in the diagnosis and treatment of chronic periodontitis. J Dent Hyg. 2015; 89(Suppl 1): 6–12.
3. Haseeb M, Khawaja KI, Ataullah K, Munir MB, Fatima A. Periodontal disease in type 2 diabetes mellitus. J Coll Physicians Surg Pak. 2012; 22(8): 514–8.
4. Morita I, Inagaki K, Nakamura F, Noguchi T, Matsubara T, Yoshii S, Nakagaki H, Mizuno K, Ito H, Hirano H, Yamamoto T. Relationship between periodontal status and levels of glycated hemoglobin. J Dent Res. 2012; 91(2): 161–6.
5. Santos VR, Lima JA, Miranda TS, Feres M, Zimmermann GS, Nogueira-Filho GDR, Duarte PM. Relationship between glycemic subsets and generalized chronic periodontitis in type 2 diabetic Brazilian subjects. Arch Oral Biol. 2012; 57: 293–9.
6. Susanto S, Nesse W, Dijkstra PU, Hoedemaker E, van Reenen YH, Agustina D, Vissink A, Abbas F. Periodontal inflamed surface area and C-reactive protein as predictors of HbA1c: a study in Indonesia. Clin Oral Investig. 2012; 16: 1237–42.
7. Weinspach K, Staufenbiel I, Memenga-Nicksch S, Ernst S, Geurtsen W, Günay H. Level of information about the relationship between diabetes mellitus and periodontitis: results from a nationwide diabetes information program. Eur J Med Res. 2013;18(6):1–8.
8. Sindhuja S, Balaji A. Tooth mobility. Eur J Mol Clin Med. 2020;7(2):6713–6.
9. Popławska-Kita A, Siewko K, Szpak P, Król B, Telejko B, Klimiuk PA, Górska M, Szelachowska M. Association between type 1 diabetes and periodontal health. Adv Med Sci. 2014; 59: 126–31.
10. Sakalauskiene J, Kubilius R, Gleiznys A, Vitkauskiene A, Ivanauskiene E, Šaferis V. Relationship of clinical and microbiological variables in patients with type 1 diabetes mellitus and periodontitis. Med Sci Monit. 2014; 20: 1871–7.
11. Jindal A, Parihar AS, Sood M, Singh P, Singh N. Relationship between severity of periodontal disease and control of diabetes (glycated hemoglobin) in patients with type 1 diabetes mellitus. J Int Oral Health. 2015; 7(Suppl 2): 17–20.
12. Kiedrowicz M, Dembowska E, Banach J, Safranow K, Pynka S. A comparison of the periodontal status in patients with type 2 diabetes based on glycated haemoglobin levels and other risk factors. Adv Med Sci. 2015; 60: 156–61.
13. Miranda TS, Feres M, Retamal-Valdes B, Perez-Chaparro PJ, Maciel SS, Duarte PM. Influence of glycemic control on the levels of subgingival periodontal pathogens in patients with generalized chronic periodontitis and type 2 diabetes. J Appl Oral Sci. 2017; 25(1): 82–9.
14. Yonekura S, Usui M, Murano S. Association between numbers of decayed teeth and HbA1c in Japanese patients with type 2 diabetes mellitus. Ups J Med Sci. 2017; 122(2): 108–13.
15. Alasqah M, Mokeem S, Alrahlah A, Al-Hamoudi N, Abduljabbar T, Akram Z, Vohra F, Javed F. Periodontal parameters in prediabetes, type 2 diabetes mellitus, and non-diabetic patients. Braz Oral Res. 2018; 32: e64.
16. Dhir S, Wangnoo S, Kumar V. Impact of glycemic levels in type 2 diabetes on periodontitis. Indian J Endocrinol Metab. 2018; 22(5): 672–7
17. Panezai J, Altamash M, Engström P, Larsson A. Association of glycated proteins with inflammatory proteins and periodontal disease parameters. J Diabetes Res. 2020; 2020: 1–10.
18. Qureshi A, Haque Z, Bokhari SAH, Baloch AA. Evaluation of HbA1c in type-2 diabetes mellitus patients with periodontitis: preliminary findings of three-arm clinical trial. J Pak Med Assoc. 2020; 70(8): 1350–6.
19. Grigoriadis A, Raisanen IT, Pamanen P, Tervahartiala T, Sorsa T, Sakellari D. Prediabetes/diabetes screening strategy at the periodontal clinic. Clin Exp Dent Res. 2021; 7: 85–92.
20. Kassab A, Ayed Y, Elsayed SA, Alqadi SF, Abdelgawad N, Mrag M, Amor FB. Glycated hemoglobin influence on periodontal status, pathogens and salivary interleukins in type II diabetic Tunisian subjects with chronic periodontitis. J Dent Sci. 2021; 16: 614–20.
21. Rapone B, Ferrara E, Corsalini M, Qorri E, Converti I, Lorusso F, Gnoni A, Scacco S, Dipalma G, Grassi FR. Inflammatory status and glycemic control level of patients with type 2 diabetes and periodontitis: a randomized clinical trial. Int J Environ Res Public Health. 2021; 18(6): 3018.
22. Romano F, Perotto S, Mohamed SEO, Bernardi S, Giraudi M, Caropreso P, Aimetti M. Bidirectional association between metabolic control in type-2 diabetes mellitus and periodontitis inflammatory burden: a cross-sectional study in an Italian population. J Clin Med. 2021; 10(7): 1787.
23. Stoicescu M, Calniceanu H, Țig I, Nemeth S, Țent A, Popa A, Bungau S. Significant aspects and correlation between glycemic control and generalized chronic periodontitis in type 2 diabetes mellitus patients. Exp Ther Med. 2021; 22(2): 671.
24. Eke PI, Page RC, Wei L, Thornton-Evans G, Genco RJ. Update of the case definitions for population-

based surveillance of periodontitis. J Periodontol. 2012; 83(12): 1449–54.

25. Preshaw PM, Bissett SM. Periodontitis and diabetes. Br Dent J. 2019; 227(7): 577–84.

26. Casanova L, Hughes FJ, Preshaw PM. Diabetes and periodontal disease: a two-way relationship. Br Dent J. 2014; 217(8): 433–7.

27. Nascimento GG, Leite FRM, Vestergaard P, Scheutz F, López R. Does diabetes increase the risk of periodontitis? A systematic review and meta-regression analysis of longitudinal prospective studies. Acta Diabetol. 2018; 55(7): 653-67.

28. Chen Y, Yu L, Wang Y, Chen Z. Advanced glycation end products induce apoptosis in human periodontal ligament fibroblasts through RAGE–NF-κB signaling pathway. Cytokine. 2012; 60(3): 646–53.

29. Portes J, Bullón B, Quiles JL, Battino M, Bullón P. Diabetes mellitus and periodontitis share intracellular disorders as the main meeting point. Cells. 2021; 10(9): 2411.

30. Nonaka K, Kajiura Y, Bando M, Sakamoto E, Inagaki Y, Lew JH, Kayal RA, Matsuda S, Uemura H, Kato H, Noguchi K. Advanced glycation end-products increase IL-6 and ICAM-1 expression via RAGE, MAPK and NF-κB pathways in human gingival fibroblasts. J Periodont Res. 2017; 52(5): 880–8.

31. Wang Q, Nie L, Zhao P, Zhou X, Ding Y, Chen Q, Yuan Q, Guo Y, Fan J, Meng H, Xu H, Wang Q, Liu G, Wang S. Diabetes fuels periodontal lesions via GLUT1-driven macrophage inflammaging. Int J Oral Sci. 2021; 13(1): 11

32. Wang Q, Li H, Chen Y, Wang S, Wei J, Zou Y, Zhang T, Huang X, Chen X, Zhao L. JAK/STAT signaling pathway plays a key role in Porphyromonas gingivalis–induced periodontitis in rats with type 2 diabetes mellitus. PLoS One. 2016; 11(11): e0166801

33. Colli ML, Moore F, Gurzov EN, Ortis F, Barbieri G, Mogensen CE, Eizirik DL. The role of PTPN2 in cytokine-induced apoptosis in pancreatic β-cells. Diabetes. 2010; 59(11): 3117–25.

34. Kim JH, Lee DE, Choi SH, Cha JH, Bak EJ, Yoo YJ. Diabetic characteristics and alveolar bone loss in streptozotocin- and streptozotocin-nicotinamide-treated rats with periodontitis. J Periodontal Res. 2014; 49(6): 792–800.

35. Wu YY, Xiao E, Graves DT. Diabetes mellitus related bone metabolism and periodontal disease. Int J Oral Sci. 2015; 7(2): 63–72.

36. Chen TL, Xu EL, Lu HJ, Xu H, Wang SF, Zhao HJ, Liu Y. The influence of diabetes enhanced inflammation on cell apoptosis and periodontitis. Advances in Bioscience and Biotechnology. 2012; 3: 712–19.

37. Llambés F, Arias-Herrera S, Caffesse R. Relationship between diabetes and periodontal infection. World J Diabetes. 2015; 6(7): 927-35.