

## Effect of Diabetes Mellitus on Each Phase of Tooth Extraction Socket Healing

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### Abstract

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia that occurs due to abnormalities in insulin secretion, insulin action, or both. The prevalence of DM in Indonesia in 2021 ranked 5th, with a prevalence of 19.5 million cases. <sup>1</sup> Tooth extraction is the act of removing the tooth from the socket, which involves bone and soft tissue in the oral cavity. The phases in the healing process after tooth extraction consist of: the coagulation and hemostasis phase; the inflammation phase; the proliferation phase; and the shaping and remodeling phase. DM affects each phase of wound healing so that the healing process is delayed. <sup>2,3</sup>

To understand the mechanism of DM influence on each phase that plays a role in wound healing after tooth extraction, which is useful in helping to determine the target therapy.

Hyperglycemic conditions in DM produce metabolic products through four pathways that can increase reactive oxygen species (ROS). Increased ROS causes endothelial dysfunction and affects the production of pro-inflammatory cytokines, so that the inflammatory process occurs more frequently and is prolonged. The proliferation phase is impaired because hyperglycemia increases apoptosis in fibroblasts and osteoblasts. In addition, it affects the RANKL/OPG ratio, which can interfere with the bone remodeling process after tooth extraction.

Hyperglycemia-induced intracellular glucose metabolic products affect all stages of the inflammatory phase through various mechanisms.

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### Introduction

Tooth extraction is the act of removing the tooth and tooth root from the socket, involving bone tissue and soft tissue in the oral cavity. The number of tooth extractions at the University of Jember's RSGM in 2014 increased from 1577 cases in 2013 to 1913. <sup>4</sup> Certain systemic conditions need attention when performing tooth extractions, one of which is in diabetic patients. Based on a survey conducted at RSGM UNSRAT, the three largest systemic conditions in

patients for extraction are diabetes mellitus (DM) patients. <sup>5</sup>

Diabetes mellitus (DM) is one of the systemic diseases that can cause the healing process to be delayed and uncoordinated. DM is a group of metabolic diseases characterized by hyperglycemia that occurs due to abnormalities in insulin secretion, insulin action, or both. Common symptoms of DM are polyuria, polyphagia, and polydipsia. The classifications of DM are Type 1 DM, Type 2 DM, Gestational DM, and Other Types of DM. <sup>1</sup>

The International Diabetes Federation (IDF) organization estimates that at least 463 million people aged 20–79 in the world had diabetes in 2019, equivalent to a prevalence rate of 9.3% of the total population of the same age. Indonesia is ranked 5th, with a prevalence of 19.5 million cases in 2021.

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DM has an impact on the healing of dental extractions. As many as 97 people out of a total sample of 147 comorbid people (DM, hypertension, smoking) had complications after extraction. There was a significant difference in post-extraction complications in DM patients. As many as 12.5% of patients with DM complications experienced delayed post-extraction healing.<sup>6</sup> The healing of tooth extractions in diabetics is slower than in groups without DM.<sup>7</sup> The condition of DM is a risk factor for actions that cause tissue injury, such as tooth extraction. There can be post-extraction complications such as dry socket or alveolar osteitis due to infection of the socket and damage to the blood clot.<sup>8,9</sup> These conditions can interfere with the stages of the wound healing phase and interfere with the process of forming new tissue.<sup>10</sup>

Diabetes impairs the delivery of nutrients and the removal of by-products of glucose metabolism, which in turn affects microvascular and macrovascular circulation. Changes in microvascular circulation result in a reduced inflammatory response. Among them are reducing leukocyte migration, tissue perfusion, and hyperemia disorders. This results in increased postoperative risk.<sup>11</sup>

Diabetes leads to an increase in reactive oxygen species.<sup>12</sup> Reactive oxygen species (ROS) are key signaling molecules that play an important role in the development of inflammatory disorders. Increased ROS formation by polymorphonuclear neutrophils (PMN) at sites of inflammation leads to endothelial dysfunction and tissue injury.<sup>13</sup>

## Discussion

The healing phase after tooth extraction consist of: (1) the coagulation and hemostasis phases, which occur immediately after tooth extraction. (2) The inflammation phase, which begins immediately after hemostasis. The inflammatory response under normal conditions peaks at 48 hours and will disappear after 1 week. (3) The proliferation phase, which begins in the following days and incorporates most of the healing process, occurs between days 3 and 14. The proliferation phase is characterized by the formation of granulation tissue in the wound. (4) The formation and remodeling phases aim to restore form and function. This phase occurs

from 3 weeks to 1 year. Each phase contributes to the success of the next.<sup>3,14</sup>

Metabolic products of diabetes can stimulate Reactive oxygen species through four pathways, namely the polyol pathway, hexosamine, protein kinase C (PKC) activation, and increased advanced glycation end products (AGE).<sup>12</sup>

1. Polyol pathway. Hyperglycemia stimulates aldose reductase (AR) enzyme activity to catalyze glucose into sorbitol via the sorbitol/polyol pathway. This results in an increase in intracellular sorbitol and fructose and a decrease in the ratio of NADPH to NADP. The increase in intracellular sorbitol will activate p38 MAPK and JNK, triggering the production of several inflammatory mediators and the inflammatory process.<sup>15</sup>

2. Hexosamine pathway. Under normal circumstances, intracellular glucose is metabolized through glycolysis to produce glucose-6-phosphate (G6P), assisted by the enzyme hexokinase or glucokinase, resulting in the formation of fructose-6-phosphate (F6P) from glucose-6-phosphate (G6P). Hyperglycemia causes part of the F6P compound to be converted to glucosamine-6-phosphate and UDP (uridine diphosphate) N-acetyl glucosamine (GlcNAc) by the enzyme glucosamine fructose-6-phosphate amidotransferase/GFAT via the hexosamine pathway.<sup>15</sup> The N-acetyl glucosamine formed will bind to transcription factor serine and threonine residues that play a role in activating cofactors so as to induce gene expression such as transforming growth factor- $\beta$ 1 (TGF-1) and plasminogen activator inhibitor-1 (PAI-1). Increased levels of TGF-1 and PAI-1 play an important role in the mechanism of cellular hypoperfusion, which triggers an increase in reactive oxygen compounds.<sup>16</sup>

3. Diacyl glycerol (DAG)/protein kinase C (PKC) pathway. Hyperglycemia increases the synthesis of the diacyl glycerol molecule. This molecule is the classical form of protein kinase-C,  $\beta$ ,  $\alpha$ , and  $\delta$  compounds. Activation of PKC leads to the expression of various genes such as endothelin-1, VEGF, TGF- $\beta$ , PAI-1, NF- $\kappa$ B, NAD(P) oxidase, and decreased levels of endotheline nitric oxide synthetase/eNOS. Increased expression of these genes causes vascular system abnormalities and inflammatory reactions.<sup>16,17</sup> Increased NADPH oxidase enzymes in the PKC pathway will increase

reactive oxygen compounds, while decreased eNOS will reduce nitric oxide and NO production. Low levels of NO cause vasoconstriction of blood vessels, leading to cellular hypoperfusion and ultimately increasing the production of reactive oxygen compounds.<sup>17</sup>

4. Advanced glycation end products (AGEs). It is a product of the non-enzymatic glycation process of heterogeneous proteins, lipids, and nucleic acids in patients with diabetes mellitus through the glyoxylation pathway. In the early stages of hyperglycemia, it is compensated by the reaction of sugar reduction (aldose) with proteins non-enzymatically so that Schiff bases and Amadori products (ketoamine compounds) are formed, which are reversible. Long-term conditions result in the formation of AGEs, which are irreversible. AGEs that are formed will accumulate in various body tissues and blood vessels and cause various complications of diabetes. This glycation product will bind to its receptor (RAGE). RAGE-AGEs binding in diabetes triggers increased production of reactive oxygen species (ROS) and up-regulation of inflammatory processes.<sup>18</sup>

RAGE expressed on the cell surface of monocytes (macrophages) will cause postreceptor signals on these cells, namely activating NF- $\kappa$ B, so that the inflammatory stages occur, namely the formation of pro-inflammatory cytokines such as tumor necrosis factors (TNF- $\alpha$  and TNF- $\beta$ ), interleukins (IL) 1, 6, 8, and 18, and interferon- $\gamma$ , as well as growth factors such as vascular endothelial growth factor (VEGF), increased endothelial permeability, and monocyte chemotaxis.<sup>15</sup>

Effect of DM on coagulation and hemostasis phases

The first step in the healing process of tooth extraction is the formation of blood clotting. Platelets form clots and carry growth factors that further play a role in the inflammatory process.<sup>19</sup> Intrinsic and extrinsic coagulation factors cause hemostasis reactions so that they can fill the wound basin and form a provisional matrix as a scaffold for the migration of inflammatory cells in the inflammatory phase.<sup>20</sup>

Non-enzymatic modification of plasma proteins such as albumin, fibrinogen, and globulin due to hyperglycemia can produce various adverse effects, including platelet activation and impaired fibrinolysis.<sup>18</sup>

Several studies have shown that there is an increase in local thrombin formation and platelet activation, as well as unfavorable changes in the blood clot picture, in diabetic patients.<sup>21,22</sup> The decrease in NO due to ROS will activate NF $\kappa$ B as a transcription factor for the production of VCAM-1, selectin, and ICAM. These proteins play a role in vascular permeability, mediation, and leukocyte aggregation.<sup>23</sup>

AGEs is a Non-enzymatic production of glucose results. AGEs form covalent bonds with active amino groups, then damage blood vessels by increasing oxidative stress and inducing monocytes to produce platelet-derived growth.<sup>24,25</sup> Thus, the blood vessels become pathologically permeable and inelastic, and blockage of blood flow occurs.<sup>18,24</sup> Endothelial dysfunction due to the binding of AGEs and their receptor RAGE can release factor II to initiate extrinsic pathway coagulation and factors XI, VIII, and IX that play a role in the intrinsic pathway.<sup>26,27</sup> Damaged endothelium will release tissue factor, which will then activate factor VII. Then Factor VII, together with calcium ions, will activate Factor X, which, together with Factor V and tissue phospholipids, will form a prothrombin activator complex.<sup>28</sup>

Effect of DM on the Inflammatory Phase

Inflammatory cells, including neutrophils, monocytes, and macrophages, in the fibrin skeleton promote tissue debridement and recruit vital growth factors for wound healing. In this phase, pathogens and dead cells are removed through phagocytosis. The inflammatory process contributes to the release of local growth factors classically associated with bone formation (such as BMPs and TGF- $\beta$ ), as well as the promotion of cell chemotaxis associated with the repair process.<sup>19</sup>

In DM conditions, AGE-RAGE bonding occurs in various cells, including endothelial and neutrophil cells. The bond between AGEs and RAGEs on the surface of endothelial cells can increase the formation of ROS. This bond will activate the enzyme NADPH oxidase, which triggers the formation of intracellular ROS and causes oxidative stress. Furthermore, it can stimulate the activation of NF- $\kappa$ B and affect the expression of pro-inflammatory cytokines, namely IL-1 $\beta$  and TNF- $\alpha$ , growth factors (GF) such as TGF- $\beta$ 1, IGF-1, and metalloproteases (MMP-1, MMP-2, MMP-3, and MMP-13). In

addition, there is increased expression of adhesion molecules such as selectin, vascular adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) on endothelial cells. These molecules are normally required in the process of margination, which is the withdrawal of leukocytes from the blood circulation towards the endothelial surface of blood vessels.<sup>13,17,18</sup> Overexpression of these molecules can interfere with the diapedesis and chemotaxis of inflammatory cells, such as neutrophils. This leads to decreased chemotaxis and phagocytic activity of neutrophils, decreased intracellular bacterial elimination capacity, and increased ROS production in patients with DM.<sup>18</sup> Diabetes suppresses the expression of mitogenic growth factors and increases the expression of pro-inflammatory cytokines, mediated by epigenetic mechanisms. Hyperglycemic conditions can promote M1 macrophage polarization through excess ROS production under inflammatory stimulation in type 1 DM mice.<sup>29</sup> The increased M1 polarization and reduced M2 macrophages are responsible for the delay in healing in DM subjects through aberrant expression of TNF and peroxisome proliferator-activated receptor-g.<sup>30</sup>

#### Effect of DM on the Proliferation Phase

The proliferation phase is known as the fibroplasia phase. This phase has various phases, such as angiogenesis, fibroplasia, granulation of tissue formation, collagen deposition, epithelialization, and wound contraction.<sup>2</sup> In this phase, there is a turnover of granulation tissue into more mature connective tissue. Characterized by increased fibroblast activity synthesizing extracellular matrix, resulting in an increase in collagen fibers.<sup>31</sup>

Growth factors such as TGF $\beta$ 1 and FGF-2 are responsible for promoting the proliferation and activation of fibroblasts, which play an important role in the synthesis of the temporary matrix of tissue granulation.<sup>19</sup> In diabetic conditions, there is a decrease in TGF $\beta$ 1.<sup>32</sup>

Platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and TGF are decreased in diabetic conditions.<sup>32,33</sup> These conditions occur because AGEs cause interference with the biomolecular activity of the wound healing process and trigger cell apoptosis. One of the dominant AGEs found in the serum of patients with DM, CML-collagen, can increase programmed cell death, or apoptosis, in

fibroblasts and osteoblasts. CML-collagen stimulates the expression of p38 and JNK genes involved in the apoptotic pathway through activation of caspase-3 in the cytoplasm and mitochondria of cells. This condition causes many fibroblasts and osteoblasts to undergo apoptosis. Increased apoptosis of these cells will inhibit matrix synthesis activity and disrupt the bone formation process.<sup>34</sup>

The increase in proinflammatory cytokines in DM, for example, is TNF $\alpha$ . TNF $\alpha$  induces the release of arachidonate from diacylglycerol and increases prostaglandin synthesis in osteoblast cultures. These prostaglandins can induce apoptosis and the death of osteoblasts.<sup>35</sup>

Bone formation is the first step of the healing process, characterized by an increase in BMP2, BMP4, and BMP7. RUNX2 expression is a transcription factor involved in osteoblast differentiation. However, in DM conditions, there is a decrease in BMP2 levels and collagen degradation due to increased production of proinflammatory cytokines and NFKB.<sup>32,36</sup>

#### Effect of DM on the Bone Remodeling Phase

Continues in the bone remodeling phase. It is an act of involvement by both osteoclasts and osteoblasts. The increase in the number of osteoclasts parallels the stabilization of osteoblast density observed in the remodeling period.<sup>37,38</sup>

Dysregulation due to decreased insulin causes an increase in osteoclasts, which is thought to be the result of an increase in the RANKL/OPG ratio. The dysregulation also results in decreased bone formation due to decreased BMP, RunX2, and increased PPAR, resulting in decreased osteoblast proliferation and increased apoptosis in osteoblasts through increased TNF $\alpha$ .<sup>39</sup>

In diabetes, there is an increase in inflammatory mediators, such as increased expression of TNF $\alpha$  and IL-1 $\beta$ . TNF- $\alpha$  stimulates osteoclastogenesis by increasing the production of M-CSF and RANKL in marrow stromal cells. TNF $\alpha$  and IL-1 $\beta$  can cause osteoblasts to express RANKL protein, which will further stimulate osteoclast precursors to differentiate and directly result in an imbalance of OPG and RANKL in DM conditions, namely an increase in RANKL and a decrease in OPG.<sup>39,40</sup>

Proinflammatory mediators can regulate receptor activator of NF- $\kappa$ B ligand (RANKL) to bind to receptor activator of NF- $\kappa$ B (RANK), thus leading to increased differentiation of preosteoclasts into osteoclasts and accelerating the osteoclastic process.<sup>41</sup>

Hyperglycemia directly modulates the RANKL/OPG ratio and indirectly through AGE/RAGE, which can trigger inflammation and destruction. AGE-RAGE contributes to osteoclastogenesis through increased expression of RANKL and downregulation of OPG. AGEs can increase RANKL activation and induce osteoblast apoptosis.<sup>42</sup> Increased RANKL/OPG and TNF ratios lead to excessive bone resorption, resulting in disruption of the bone remodeling process in diabetic conditions.<sup>43</sup>

## Conclusions

Intracellular glucose metabolism products due to hyperglycemia can affect all stages of the inflammatory phase. So it is necessary to pay attention to each phase of the healing process after tooth extraction to avoid complications that occur in diabetic patients and prolonged wound healing.

## Declaration of Interest

The authors report no conflict of interest.

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