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Dental implications of altered hemostasis in patients with diabetes mellitus: A narrative review

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Abstract

The current study examines the effects of altered hemostasis on various dental issues related to patients with diabetes mellitus (DM). Chronic hyperglycemia causes substantial changes to the hemostatic status, producing a state of platelet hyper-reactivity and reducing the vascular response. The underlying pathophysiology involves the non-enzymatic glycation of the coagulation proteins and the development of microangiopathy, both of which diminish the efficacy of local vasoconstriction during surgical manipulation. Furthermore, the presence of hypo fibrinolysis, caused by increased levels of PAI-1, creates a dense yet fragile clot that does not undergo appropriate remodeling. The result is that these systems expose the patient to increased clinical risk for prolonged postoperative bleeding and inadequate socket healing, thus requiring increased vigilance when performing dental procedures on patients with DM. To effectively manage these patients in the dental setting, it is essential to have a thorough understanding of the relationship between metabolic control and local tissue repair. This study used a literature review approach with a descriptive narrative to synthesized the most current findings on biomarkers and surgical outcomes in dental procedures. Overall, the findings from this study demonstrate that some common postoperative complications, such as osteitis alveolaris and delayed healing of the surgical site, are directly related to the microvascular and hematological impairments that characterized DM. Therefore, in order to provide safe dental care, dentists should develop and implement multidisciplinary treatment strategies, including the use of local hemostatic agents (e.g., tranexamic acid) and perform preoperative glycemic assessments. Finally, the need for customization of dental interventions to meet the unique characteristics of individual patients with DM was also stressed.

Keywords: Diabetes; Hemostasis; Microangiopathy; Hypofibrinolysis

1. Introduction

Diabetes Mellitus (DM) is a chronic metabolic condition that causes elevated blood glucose (hyperglycemia) levels. The metabolic state associated with DM has long-term effects on the body, including damage to the vascular system, which affects how well the body heals when injured [3]. For dental professionals, the impairment of hemostasis in DM patients creates a unique risk for their patients; they are more susceptible to blood clotting and bleeding during and after dental surgery because of impaired microvasculature integrity [4]. One of the reasons DM patients have altered hemostatic function is the biochemical effects of hyperglycemia, which allows proteins involved in the coagulation cascade to undergo non-enzymatic glycation (stick), leading to increased platelet activation and decreased levels of endothelial-derived molecules such as nitric oxide (NO), which are normally responsible for inhibiting platelet aggregation [5]. Therefore, although platelets are more "sticky" in DM patients, the resulting clot may not be structurally stable or able to be integrated into the healing wound as expected [6].

In addition to impaired platelet function, the majority of DM patients also have impaired clot dissolution, due to elevated PAI-1 levels [7]. This means that the fibrin network created by DM patients is usually denser and harder to dissolve than

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that of non-DM patients. This has important implications for the normal healing process following dental surgery, since although an initial clot forms, DM patients may experience delayed healing or incomplete stabilization/crisis of the clot due to the quality of the fibrin network [8].

The principal clinical consequences of diabetes are an increased chance of developing post-surgical bleeding and decreased ability to heal from surgery (for example, with alveolar bone healing). Patients with microangiopathy have stiff and non-responsive blood vessels and do not stop bleeding as well after having a tooth extracted [2]. As a result, dentist owners must take greater care in designing the surgical procedure and the anaesthetic chosen to administer to the patient. In addition to diabetes alone, a number of patients are taking medications to treat heart diseases, such as blood-thinning medications or anti-platelet medications [8]. When these medication combinations are combined with an underlying diabetic condition, they create an even more complex case scenario. When performing oral surgery on patients, dentists will need to be more conscious of the potential for uncontrolled 'blood flow' (uncontrollable post-surgical bleeding) [10]

In order to effectively manage patients with diabetes mellitus, it is necessary to perform a complete risk assessment, which includes assessing levels (i.e., levels of glycemic control) as an important biomarker. As blood glucose control deteriorates, so too does the severity of the patient's hemostatic disturbance, or perturbation hemostatic [7]. Pre-operative strategies often involve the use of hemostatic agents such as collagen sponges or topical agents like tranexamic acid, which provide a stable environment in which the patient will heal post-operatively. The evaluation and comprehension of altered hemostasis is the basis for the safe provision of dental treatment to medically compromised patients. To best reduce the patient's risk for either excessive bleeding or infection, practitioners should incorporate the patient's systemic medical history into their individualized treatment plan [2]. Through collaboration and communication between physicians and dentists, complex dental procedures can be completed in a safe manner and with the patient's overall health and well-being remaining intact.

Vascular dysfunction and inflammatory states found in periodontitis can impact wound healing directly. Because of a lack of blood flow due to this condition, Oxygen supply is depleted, which results in inadequate regeneration of periodontal tissue. The inability for immune cells to exit the blood stream and enter the periodontal area because of the inflammatory state increases the risk of secondary infection that would cause enzymatic breakdown of newly formed blood clots.

2. Material and methods

2.1. Material

The initial study was based on existing literature regarding how diabetes affects bleeding as well as how blood clots will be affected by diabetes. The study focused on peer-reviewed scientific journals and university level text books dealing with diabetics and dental treatment as well as how this will affect the clotting ability of the diabetic patient. A comprehensive database search was performed using electronic databases, specifically PubMed, Science Direct and Google Scholar using key words including "diabetes", "coagulation", "surgical extraction" and "microangiopathy". Inclusion of articles was confined to those which were published in the last few years as this ensured up-to-date information regarding blood tests, or biomarkers relating to hemostatic functioning, and the use of local hemostatic measures will be the primary focus of the literature review. The emphasis was on those articles which included a thorough description of how diabetes (a systemic metabolic disorder) affects the vascular response of an individual in his or her mouth.

2.2. Methods

This literature review is considered a descriptive narrative in order to provide a detailed explanation of how hemostatic dysfunction occurs in the dental surgical environment. As part of the analytical process, the researcher collected relevant data, screened for relevance, and systematically organized the information into a manner that followed the biological process from pathophysiology through clinical application. The literature review will evaluate all of the research findings related to platelet activation, coagulation factors, and microvascular response within various clinical settings. Through the narrative approach, a comprehensive description will be provided demonstrating how hypofibrinolysis and delayed healing impact dental treatment success. By integrating and interpreting qualitative data from multiple sources, the researcher was able to develop a coherent understanding of how diabetic patients present with prolonged bleeding post-operatively.

3. Results and discussion

3.1. Pathophysiological Mechanism of Platelet Hyperreactivity

Diabetes mellitus causes a number of alterations to normal hemostasis, the principal factor being the state of chronic hyperglycemia, which has changed the haemostatic status of the patient. The increased concentration of glucose in the patient's blood leads to the non-enzymatic glycation of many proteins including some on the platelet's surface and in the plasma [1]. This change in protein structure alters the physical nature of the membrane of platelets, by increasing its fluidity. Thus, platelets become more sensitive to external stimulation and have a much lower activation threshold, causing them to respond aggressively even to minor injuries to a blood vessel. In a healthy environment within the blood vessel, the endothelium plays an important role as a regulator of blood flow by producing substances that inhibit platelet aggregation, such as NO and PGI2. However, for diabetic patients, the concentration of these substances is greatly decreased because of oxidative damage and AGE [3]. Without these natural "brakes", the platelets remain in a sensitive state and are prone to aggregate with only very little force applied to them. This lack of protection from the endothelium is one of the primary reasons for the prothrombotic state seen in early dental inflammatory disease [9].

Diabetes has an impact on the intracellular signaling pathways in platelets. Increased calcium intracellular concentrations and elevated PKC activity lead to the release of more alpha and dense granule contents. The granules contain several potent pro-coagulant factors such as thromboxane and ADP, which attract and activate platelets to the area of injury. The result of this accelerated recruitment is often a large disorganized plug or clotted mass, which can disrupt the normal socket healing process. Diabetic patients have an increase in the number of surface receptors, particularly the Glycoprotein IIb/IIIa complex, compared to non-diabetic patients. The function of the Glycoprotein IIb/IIIa complex is to bind fibrin, which serves as a bridge that connects platelets together in the formation of a plug. Consequently, increased glycoprotein IIb/IIIa complex expression increases the amount of fibrin that will be available for binding to platelets when the coagulation cascade is initiated; therefore, there is increased likelihood of developing a denser than normal aggregate of platelets. Although some may believe the denser clot provides a greater barrier against bleeding, in reality, the lack of elasticity will reduce the clots ability to support the oral cavity's various mechanical stresses.

Chronic oral infections, such as periodontitis, are significant contributors to the pathophysiology of systemic inflammatory mediators, which in turn results in increased platelet production through the stimulation of pro-inflammatory cytokines [10]. The combination of systemic metabolic dysregulation with local inflammatory stress creates a hyperreactive state. In the context of dental medicine, this instability of the microvasculature can result in an inadequate response to wounds of the dental environment and increased potential for clotting failure [7]. A second component of this hyperreactivity is the change in the interaction between platelets and the vascular wall in the setting of diabetes. When subendothelial collagen becomes glycated (which occurs in diabetes), collagen's affinity for platelet receptors increases [1]. Therefore, when a dentist effects an incision or performs an extraction around collagen, the platelets attach to collagen more quickly than normal. This rapid initial attachment depletes localized clotting factors at the site, which may explain why more delayed secondary haemorrhage occurs after the initial fragile plug of platelets fails to hold [2].

Historically, identifying the hyperreactive state in the clinical setting has been problematic; however, today, new analytical tools such as thrombelastography allow for an improved understanding and quantification of the viscoelastic characteristics of blood clots as they form, providing objective documentation for the physician of the elevated "strength" and rate of clot formation in diabetic patients (1). The physician's ability to appreciate these slight variations allows for timely implementation of appropriate site-specific hemostatic agents (5) prior to making the initial incision on the patient. The pathophysiologic mechanisms by which platelets exhibit a hyperreactive behaviour represent a "hemostatic paradox" in that patients have an increased risk for micro-thromboembolic events as well as substantial clinical bleeding due to the compromised structure of the resultant fibrinous meshwork (1). For the dental surgeon, it requires a dual approach on the part of the doctor to manage the potential for excessive bleeding during surgery, as well as to ensure that the resultant blood clot remains intact in order to support wound healing (sanatio vulneris). Appreciating this complex biological landscape represents a vital first step in ultimately arriving at predictable surgical results in diabetic patients (8).

3.2. Microangiopathy and its Impact on Local Vasoconstriction

The development of diabetic microangiopathy is one of the consequences of a diabetes mellitus, particularly in those who have had the condition for an extended period of time. The process of developing microangiopathy begins with a progressive smooth muscle thickening of the walls of small caliber arteries (the capillaries) resulting from an

accumulation of advanced glycation end-products (AGEs) within the vascular walls themselves. The development of diabetic microangiopathy in the oral cavity occurs primarily within the small arterioles and capillaries that supply blood to the gums and jaw bone supporting the teeth. The mechanical loss of elasticity that occurs due to the thickness of the inner and outer walls of the artery leads to the first series of difficulties in controlling bleeding when a dental extraction is performed.

In contrast to healthy individuals, the first physiological response of the body in the event of an injury to a blood vessel (as would be the case with the dental extraction) is to constrict the blood vessels in an effort to reduce the amount of blood flowing from the injured vessel (fluxus sanguinis) and allow the body time to form a plug of platelets that will provide the initial foundation for clotting. In healthy individuals, the contraction of the smooth muscle cells located in the outer layer of the arterial wall causes the diameter of the lumen to decrease, thereby reducing the amount of blood flowing from the injured vessel. However, in the case of patients with diabetes, the outer and inner walls of small blood vessels have experienced the effects of the ongoing process of glycation and, as a result, they are physically incapable of expanding and contracting with the same efficiency as in those without diabetes. This inability to expand and contract provides a serious mechanical deficiency to the ability of the body to control bleeding at the initial time of injury.

The biochemical signal that ordinarily causes blood vessels to contract is significantly disturbed. When hyperglycemia occurs, there is an impairment in the ability to produce endothelin-1, an endogenous potent vasoconstrictor, and, conversely, there is chronic low-grade inflammation [3]. Chronic low-grade inflammation produces an imbalance that promotes continuous dilation of the microvasculature. At the surgical site, due to the lack of neurogenic and chemical stimulation, there is a continuous "sweating" of the site as local blood vessels have no potential means of stopping blood flow [2]. The effect of the autonomic nervous system, which regulates the tone of blood vessels, is frequently lost during a diabetic patient due to a process known as diabetic neuropathy. Thus, diabetic patients have diminished sympathetic responses necessary for rapid vasoconstriction after surgical stimulation [10]. In the dental chair, this results in a situation in which, although the patient may appear calm, the vascular system is unable to mount the "fight or flight" response required in response to trauma. The neurovascular dissociation provides the primary reason that diabetic patients bleed for longer periods of time than do non-diabetic patients [8].

The most pressing issue associated with microangiopathia is the manner in which it affects the use of local anesthetics within dentistry. Local anesthetics are most commonly used in combination with vasoconstrictors, most often epinephrine, to both extend the effect of a local anesthetic and to limit local bleeding [6]. Yet, when blood vessels are glycated and/or thickened in diabetic patients, those vessels often demonstrate diminished sensitivity toward these exogenous catecholamines. This state of "vasoconstrictor resistance" is a part of the reason why, after a dentist administers a standard-dose local anesthetic containing a vasoconstrictor, the dentist is often surprised by the unexpected extent of post-operative bleeding [6]. Additionally, microangiopathia often creates a state of chronic ischemia that results in a dysfunctional form of compensatory angiogenesis. Due to the nature of the microangiopathic environment, blood vessels formed in such an environment will be of a fragile nature; thus, they will likely rupture. This contributes additional complexity to the hemostatic profile of the microangiopathic patient [1]. When performing periodontal surgery and flap procedures, the presence of these "leaky" vessels will facilitate the formation of hematomas beneath the tissue; subsequently, these hematomas increase the possibility of secondary infection and prolong the healing time of the wound [10].

There is a complicated relationship between periodontal tissue and microangiopathia in patients with diabetes. Periodontitis causes an ongoing state of vasodilation through the release of inflammatory mediators such as prostaglandin [4]. In addition, diabetes damages blood vessels; therefore, when combined with vasodilation from periodontitis, patients develop a highly vascularized but a very poorly contracting phase of the periodontal tissues. As a result, even a simple scaling and root planing procedure can cause an enormous amount of bleeding that is difficult for the practitioner to control in a poorly controlled diabetic patient [7].

Since inadequate local vasoconstriction occurs because of microvascular damage, a clinician will have to change his or her clinical approach. Clinicians can no longer rely on the body's natural ability to close cut blood vessels. They must intervene sooner in the procedure by using mechanical and chemical aids, including acidum tranexamicum and pressure packs [5]. A clinician must understand the limitations imposed by microangiopathia on the structure of the periodontal tissues, as this understanding will outline how aggressive a surgical approach will be and how closely a practitioner will need to monitor his or her patient post-operatively. A clinician treating medically compromised patients, such as diabetics with periodontal disease must understand these limitations [9].

3.3. Hypofibrinolysis and Delayed Clot Stability

In people that are diabetic the final stage or ultimate step in the process of hemostatic (blood clotting) has been changed drastically because of diabetes mellitus. The term used to describe this change is hypofibrinolysis. In a diabetic state one will have a systemic inability to break down fibrin or the polymerized form of fibrin. Fibrin is a temporary support as it is broken down by plasmin in a "healthy" individual. The fibrinolytic system is what breaks down fibrin. In a hyperglycemic or insulin resistant state the fibrinolytic system is not working properly; hence, the clot remains as a dense, functionally impaired clot, which resists "normal" lysis. The molecule responsible for the suppression of the fibrinolytic process is PAI-1 (Plasminogen Activator Inhibitor), which is produced in increased amounts in chronic hyperglycemia, and chronic insulin resistance. Both of these pathologies result in PAI-1 being produced in increased amounts from adipose and endothelial tissues. PAI-1 directly inhibits tPA (tissue plasminogen activator), which is responsible for converting plasminogen into plasmin, the enzyme needed for breakdown of fibrin. For dental patients, this means that any blood clot formed after tooth extraction will remain in a saturated, non-functional state and be unable to advance to tissue restoration.

The diabetic individuals' original structural quality of their fibrin network is also radically different when compared to other non-diabetic individuals. Diabetic patients have very high concentrations of glucose, which causes fibrinogen to undergo glycosylation, thereby changing the structural architecture of the fibrin fibers that form from fibrinogen [14]. These fibers become thinner, with much tighter ganglia of fibrogen, which results in a more tightly packed structure of fibrin, resulting in a fibrous structure that has much higher mechanical rigidity but lower biological function. This "Densely packed Fibrin Phenotype" creates an effective barrier to help prevent plasmin penetrability and continues to prolong the hypo-fibriniloid state of their body and delay natural clean-up of the wound site.[16]

In the context of dental medicine, this prolonged clot stability has a significant impact on the healing time for the alveolar socket. A normal healing process allows fibroblast cells to migrate into the clots and be replaced with granulation tissue as new blood vessels develop; however, a hypofibrinolytic clot continues to act as an external source of attraction, rather than a matrix or scaffold for regeneration.[8] Therefore, when a hypofibrinolytic clot is maintained in place during healing, this will lead to failure of stabilitas cruoris, and the clot will eventually be removed, thereby creating a necrotic state and leading to premature death of the clot. This phenomenon is one of the most common causes of alveolar osteitis, which is an extremely painful complication associated with dental patients who are diabetic.[9]

In addition, because of the continued presence of an unremodeled clot, bacteria can colonize it (the clot) with ease. As the clot is not being incorporated into the surrounding tissue, it is broken down by enzymes produced by the oral cavity (i.e., oral bacteria) instead of by the own body's enzymes [5]. When the bacteria break down a clot in an uncontrolled manner, it produces a period of time (e.g., 5 to 12 days) during which the patient continues to bleed from his/her socket even though there was perfect hemostasis at the time of the surgical procedure. It is common for a patient to return to the dentist after 72 hours to report spontaneous bleeding from a socket that was previously "perfectly healed" [10]. The relationship of hypofibrinolysis with the chronic inflammation of the periodontium is also important. Pro-inflammatory cytokines (e.g., IL-1, IL-6, and IL-8) are elevated in patients with both diabetes and periodontitis and further stimulate PAI-1 production [7]. As a result, there is a continual disruption of the local environment necessary for the sanatio vulneris. The inability of the body to clear out the old fibrin from the wound hinders the transition to the proliferative phase of healing, causing the "slow healing" that many diabetic patients experience [8].

Clots that persist longer than normal are caused by increased blood levels of the protein PAI-1 and abnormal formation of fibrin. Studies show that clots formed in this manner have very little possibility of being able to support normal healing processes. To overcome the difficulties presented by this situation, dentist must select surgical methods which allow for primary closure, and utilize local agents (i.e., acidum tranexamicum) to stabilize the initial fibrin matrix until the host can successfully begin to regenerate its own tissue.

4. Conclusion

In summary, the effects of diabetes mellitus on hemostasis are multifactorial and are created by a combination of factors, including chronic hyperglycemia, microangiopathy, and disturbance in platelet function. As a result of these combined effects, patients with diabetes mellitus can exist in a systemic prothrombotic state and experience unpredictable postoperative hemorrhage. The latter is largely the result of the inability to effectively vasoconstrict and the poor quality of the initial blood clot. In addition, the process of hypofibrinolysis results in the formation of structurally deficient and resistant blood clots to lysis. These two processes delay the number of phases of tissue repair occurring within the oral cavity. From a clinical standpoint, these changes in hemostasis warrant greater emphasis on preventive approaches to dental medicine. Clinicians must understand that complications such as osteitis alveolaris and

delayed healing of surgical wounds are not simply local complications, but instead represent the continuum of systemic damage from microvascular disease and non-enzymatic glycation of coagulation proteins. Risk assessment through the use of biomarkers and an understanding of their effects on the use of antiaggregating agents should become the standard of care whenever dentists perform surgical procedures that could potentially lead to uncontrolled bleeding, such as tooth extractions. Additionally, understanding what biological deficits exist creates the basis for managing a patient's surgical expectations and postoperative recovery.

Ultimately, the coordination of a team approach and a carefully planned application of local hemostatic agents determine the effectiveness of dental service for individuals with diabetes. Use of agents like acidum tranexamicum, as well as accurate suturing techniques, compensates for the underlying patient- specific vascular and platelet insufficiencies. A thorough understanding of the pathophysiology of thrombus activation and impaired wound healing allows dental health providers to reduce the risk of secondary infection and to preserve the health of the patient's salus systemica and orosystemic health at its highest possible level.

Compliance with ethical standards

Disclosure of conflict of interest

There is no conflict of interest declared by authors in this article.

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