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IMPACT OF ANTIHYPERGLYCEMIC AGENTS ON WOUND HEALING

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ABSTRACT

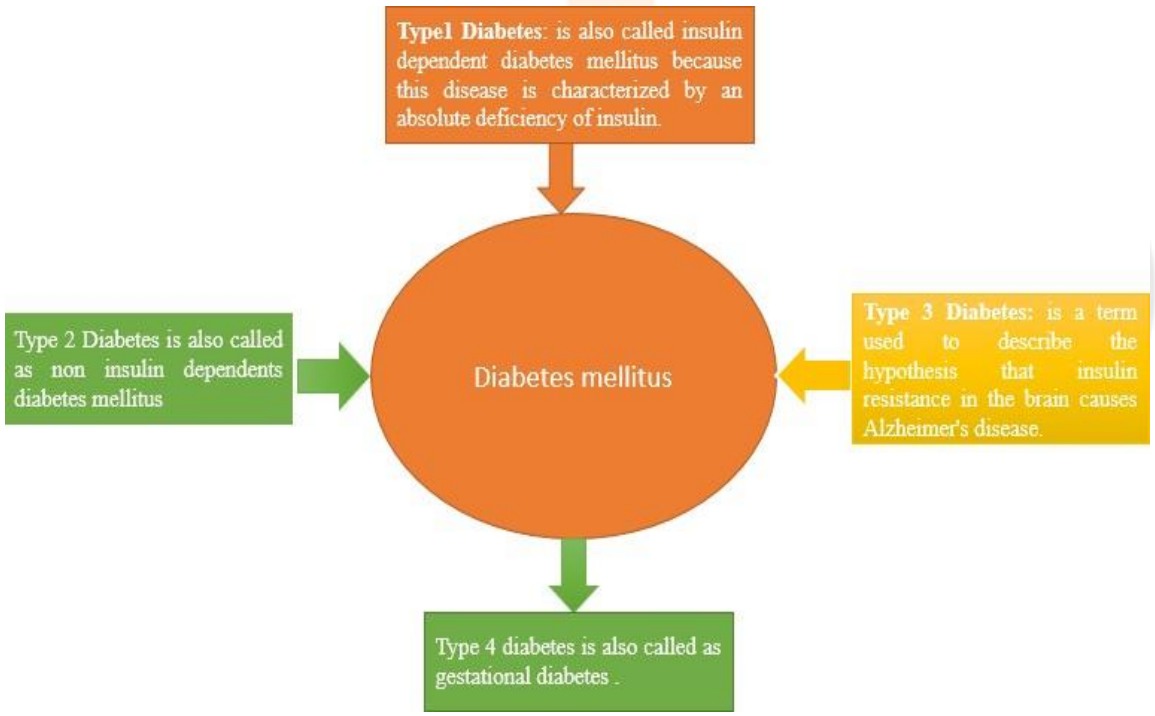
Diabetes is a prevalent metabolic disorder that results in a delayed wound-healing process. Growing evidence proved that impaired glucose homeostasis is an independent risk factor for theoccurrence of various types of diabetes including type 1 diabetes, type 2 diabetes, type 3 diabetes,and type 4 diabetes. Wound healing becomes the most severe complication of diabetic patients. Diabetes mellitus has a strong relationship with the healing process, thus there is a need to look for drugs that can be beneficial in maintaining glycemic levels as well as enhancing the process ofhealing. Therefore, more research is focusing on evaluating the role of antihyperglycemic agents in the wound-healing process. Metformin, sulfonylureas, and Insulin are the drugs that are used toenhance the wound-healing process in diabetics. This review article thus gives a detailed overviewof types of diabetes, its etiology, complications associated with diabetes, the mechanism of diabetes, diagnosis test for diabetes, pathophysiology of diabetes and their relationship with the wound healing process, and the impact of various antihyperglycemic agents on the wound healingprocess.

Introduction:

Diabetes mellitus is a disorder in which there is impaired insulin synthesis and/or functions that result in hyperglycemia. Patients' expectations for survival and quality of life are significantly impacted by DM. Indeed, patients with diabetes are more likely to experience comorbid diseases that impact many organs due to hyperglycemia **[1].** Impairment of the ability to heal oneself is oneof the main effects of diabetes **[2].** Diabetes has a complicated pathophysiology with immunological, neuropathic, vascular, and metabolic components that lead to impaired recover.

Classification of diabetes:

- **Type 1 Diabetes**: It is also called insulin-dependent diabetes mellitus because this disease is characterized by an absolute deficiency of insulin. Beta cells are destructed due to invasion by viruses, the action of chemical toxins, or the action of autoimmune antibodies. The necrosis of β- cells causes insulin deficiency that leads to the development of type 1 diabetes **[3]**.
- **Type 2 Diabetes**: It is also called non-insulin-dependent diabetes mellitus and is frequently accompanied by target organ insulin resistance that limits responsiveness to both endogenous and exogenous insulin **[4].**
- **Type 3 Diabetes:** It is a term used to describe the hypothesis that insulin resistance in the brain causes Alzheimer's disease. It is caused by the dysfunction of insulin resistance and insulin-likegrowth factors that occur specifically in the brain **[5]**.



- **Type 4 Diabetes:** It is also known as gestational diabetes. This type of diabetes is observed in approximately 4-5% of all pregnancies, due to placental hormones that promote insulin resistance**[6].ig 1. Types Of Diabetes Mellitus:**

Etiology Of Diabetes Mellitus:

Insulin resistance: Type 2 diabetes mainly results from insulin resistance. Insulin resistance happens when cells in our muscles, fat, and liver don't respond as they should to insulin. Several factors and conditions contribute to varying degrees of insulin resistance, including obesity, lack of physical activity, diet, hormonal imbalances, genetics, and certain medications.

Autoimmune disease: Type 1 diabetes and Latent Autoimmune Diabetes in Adults happen whenour immune system attacks the insulin-producing cells in our pancreas.

Hormonal imbalances: During pregnancy, the placenta releases hormones that cause insulin resistance. This will result in the development of gestational diabetes. Other hormone-related conditions like acromegaly and Cushing syndrome can also cause Type 2 diabetes.

Pancreatic damage: Physical damage to our pancreas from a condition, surgery or injury can impact its ability to make insulin, resulting in Type 3 diabetes.

Genetic mutations: Certain genetic mutations can cause maturity-onset diabetes of the young and neonatal diabetes.

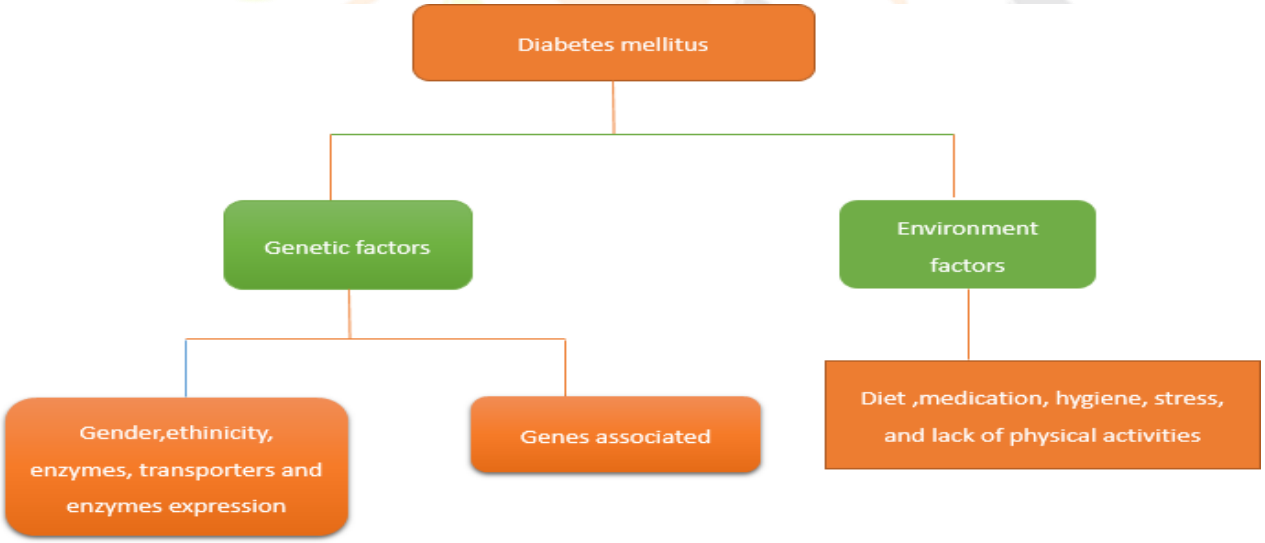


Fig.2 Etiology Of Diabetes Mellitus

Complications of Diabetes Mellitus:

Chronic complications: These are long-term problems that can develop gradually, and can lead to serious damage if they go unchecked and untreated.

Eye problems (retinopathy): Some people with diabetes develop an eye disease called diabetic retinopathy which can affect their eyesight. If retinopathy is picked up – usually from an eye screening test - it can be treated and sight loss prevented.

Foot problems: Diabetes foot problems are serious and can lead to amputation if untreated. Nervedamage can affect the feeling in our feet and raised blood sugar can damage the circulation, makingit slower for sores and cuts to heal.

Heart attack and stroke: Chronic diabetes causes high glucose levels in the blood that result in damaged blood vessels. This can further lead to heart attacks and strokes.

Kidney problems (nephropathy): Diabetes can cause damage to the kidneys over a long period making it harder to clear extra fluid and waste from the body. This is caused by high blood sugar levels and high blood pressure. It is known as diabetic nephropathy or kidney disease.

Nerve damage (neuropathy): People with diabetes may develop nerve damage caused bycomplications of high blood sugar levels. This can make it harder for the nerves to carry messagesbetween the brain and every part of our body so it can affect how we see, hear, feel, and move.

Gum disease and other mouth problems: Too much sugar in your blood can lead to more sugarin your saliva. This brings bacteria which produces acid which attacks your tooth enamel and damages your gums. The blood vessels in the gums can also become damaged, making gums morelikely to get infected.

Related conditions, like cancer: Chronic diabetes causes the risk of developing certain cancers. Some cancer treatments can affect the diabetes and make it harder to control the blood glucose.

Acute complications

These can happen at any time and may lead to chronic, or long-term, complications.

Hypoglycemia: When the blood sugars are too low

Hyperglycemia: when your blood sugars are too high

Hyperosmolar Hyperglycemic State (HHS): a life-threatening emergency that only happens inpeople with type 2 diabetes. It's brought on by severe dehydration and very high blood sugar.

Diabetic ketoacidosis (DKA) – a life-threatening emergency where the lack of insulin and highblood sugar leads to a build-up of ketones.

Factors Affecting Diabetes Mellitus in wound healing process:

1. Intrinsic Factors:

Age: The epidermis becomes thinner with age and has a slower turnover. Collagen, elastin,and hyaluronic acid production also decreases as skin ages. This makes older skin more susceptible to tears and wounds. Human growth hormone plays a significant role in tissuehealing and this decreases with age as well. Once older skin is wounded, it heals slower due to slower turnover of keratinocytes, reduced blood flow to the dermis, and a slowing of the complex healing cascade.

Genetics: The microbiomes of chronic wounds and found that people tend to be susceptibleto infections by certain pathogens depending on their genotype. They also found that the variety of bacteria present is significantly related to wound healing. The more varied a wound microbiome, the faster that wound will close. While a person's microbiome is somewhat modifiable, much of the baseline is related to genotype and to the microbiome you are born with and seeded from during the birthing process.

Sex hormones. The two main sex hormones estrogen and testosterone have wide-rangingeffects in the body. Produced primarily by the ovaries (estrogen) and testes (testosterone),these hormones affect not just your sexual function but also your bones, brain, and blood vessels, the estrogens speed healing and other research is in favour of androgens, dependingon what phase the wound is in. For most patients, this will not be of concern. However, it may need to be considered for patients taking synthetic hormones or going through an abrupt hormonal change, such as menopause.

Systemic diseases. Common medical conditions that may affect healing are Diabetes, vascular diseases, pulmonary diseases, immunocompromised or autoimmune conditions, and conditions that affect the autonomic nervous system. Both sympathetic and parasympathetic divisions play important roles in the wound healing phases.

2. Extrinsic Factors:

Medications. It is important to perform a medication review and investigate any potentialeffects which could delay healing.

Steroids will delay all phases of wound healing. They can also contribute to elevated glucose levels with long-term use, recall how hyperglycaemia can delay healing asdiscussed above.

Anticoagulants: inhibit the coagulation cascade and can result in tissue necrosis. This is especially common in fatty tissue.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) use delays wound healing by,Suppressing the inflammatory response, decreasing collagen synthesis, Reducing tensile strength and Increasing the risk of infection.

Chemotherapy drugs interfere with, cell proliferation, prolong inflammation, inhibit protein synthesis, and decrease collagen synthesis. Chemotherapy-associated nausea and vomiting may also impair nutrition.

Immunosuppressive or anti-rejection medications: impair fibroblast formation, increaserisk of infection and decrease wound tensile strength. The gastrointestinal side effects of these see below for more details on nutrition).

Nutrition. The nutritional requirements for tissue healing are greater than the levels recommended for routine tissue maintenance or the recommended daily allowance (RDA).For example, additional water is needed to help with tissue repair depending on the size ofthe wound and the patient's overall health.

Stress and elevated cortisol levels. Stress results in an increase in the incidence of opportunistic infection, to reduced expression of human growth hormone, and delayed healing.

Smoking. Smoking leads to hypoxia, tissue ischemia, blood vessel inflammation, and interferes with every phase of wound healing. Smoking a single cigarette has been shownto reduce tissue oxygen concentrations, whereas pack-per-day smokers experience tissue hypoxia for a significant portion of each day. It is possible to reverse the damage caused by smoking:

Alcohol. Drinking alcohol delays wound closure, increases the risk of infection, reduces angiogenesis, impairs collagen production, interferes with epithelialization, and induces

tissue hypoxia. Wound healing can be affected after just a few exposures to alcohol drinking above the legal limit.

Infection. Bacterial infection. All skin surfaces, including open wounds, are colonised withbacteria. Some bacteria are harmless and are part of the skin's biome. They are necessary for wound healing. Chronic wounds will have more bacterial colonisation than acute wounds and tend to have more pathogenic bacteria.

Obesity. Obesity is a known risk factor for multiple diseases. It also increases the risk of wound infections, haematomas, surgical complications, venous ulcers, and pressure injuries.

3. Iatrogenic factors are related to how the wound is managed. The rehabilitationprofessional can have the biggest influence over this factor by modifying the treatment planthroughout the healing process after assessing the wound's response to interventions. **Dressing selection and management:**

Compression is essential for venous wounds, and is indicated for edema reduction in otherwounds as well. Care must be taken to apply compression appropriately and monitor patient response regularly. Compression applied over an arterial wound or with an incorrecttechnique can reduce tissue perfusion and or create a tourniquet effect that damages both the wound and the peri-wound tissue.

Incorrect, unnecessary, or too frequent debridement. Excessive debridement is detrimental to healing because it causes a disruption of the wound bed. While maintenancedebridement is often needed, attempts should be made to limit interruption to the healing process.

Oedema management via positioning. Many chronic wounds are associated with oedema, particularly venous ulcers. Dependent positioning of an extremity will increase oedema, reduce the return of blood and lymphatic flow out of the extremity, and increase pain.

Mechanism of inducing diabetes:

Glucose Metabolism

Glucose is the key source of energy and fuel for human cells. It is gotten from the diet consumed,processed within the body, and transferred from the circulation into target cells. The movement of

glucose across the plasma membrane is important (7). Lipids, proteins, and carbohydrates eventually break down to form glucose, which serves as fuel for the metabolic processes of the body. Glycogenesis, glycolysis, gluconeogenesis, and glycogenosis are only a few of the multipleprocesses that make up glucose metabolism. An enzyme-catalyzed metabolic mechanism called glycolysis promotes glucose catabolism in cells and the conversion of glucose to pyruvate (8). In order to maintain steady blood sugar and glucose levels during the fasting state, the cytosol and mitochondria of hepatocytes undergo a series of metabolic activities that result in the synthesis of glucose from non-carbohydrate substrates.

Glucose Transport and Defect In Transport Activity:

Glucose transport is a regulated process conducted by facilitated diffusion with the aid of carrier proteins to cross cell membranes. There are different kinds of glucose transporters, but the most important are glucose transporters. These are sensitive to a range of metabolic stresses, includinggrowth factors, hypoglycemia, stress hormones, and hypoxia. Many signaling pathways participatein transporter regulation. Glucose transport is needed for the supply of energy or fuel to the cells for metabolism (9).

Hormonal Regulation for Glucose Metabolism:

Glucagon and insulin secreted by the pancreas maintain plasma glucose levels. Glucagon is triggered by hypoglycemia via pancreatic α-cells leading to glycogenolysis, gluconeogenesis, andlipolysis, all aiming to restore a normal blood glucose level. Contrarily, insulin is secreted by pancreatic β-cells in response to hyperglycemia, which encourages glucose uptake for metabolism(10). Reduced insulin secretion and the failure of the pancreatic β-cells to equal the demand is oneof the key forces aggravating hyperglycemia in patients with type 2 diabetes mellitus. Continuousβ-cell failure is thought to be caused by continuously increased levels of plasma glucose, whereasvigorous insulin treatment has been shown to improve β-cell sensitivity to insulin, glucagon, and glucose (11).

Diagnostic Tests for Diabetes

Diabetes can be diagnosed using a range of tests listed and discussed below. They are:

1. **Hemoglobin A1C:** The HbA1C test is a diagnostic test used to check a patient's glycemic level.The average of 2-3 month patient's glycemic level is assessed through this test. It is useful and effective in evaluating patients with diabetes or at risk of diabetes complications (12).

2. **Fasting Plasma Glucose:** The fasting plasma glucose (FPG) test calculates blood glucose levels simultaneously. For accuracy, the test is administered in the morning after a fasting period of about8 h. A value

larger than 126 mg/dL infers diabetes (13).

3. **Random Plasma Glucose:** the blood sample is taken and analyzed after food has been ingested.Diabetes is suspected when the value is greater than 200 mg/dL (14).

4. **Oral Glucose Tolerance Test:** It is a medical test conducted when glucose is administered, andthe blood sample is analyzed to measure how fast glucose has been cleared out. It is used to screenfor type 2 diabetes mellitus (15).

5. **C-Peptide:** The beta cell function of the pancreas is measured. The measurement and analysis of urine and serum samples are carried out and the value helps diagnose and treat diabetes (16).

6. **Autoantibody:** The presence of autoantibodies, such as insulin autoantibody and islet autoantibody anti-glutamic acid decarboxylase (GAD) autoantibodies suggests auto-immuneresponse also noticed in type 1 diabetes. The presence of autoantibodies for diabetes in the blood confirms type 1 diabetes (17).

	HbA1c Test Score	Mean Blood Glucose (mg/ dL)	Glucose (mmol/ L)
Excellent	4.0	50	**2.6**
	5.0	80	**4.7**
	6.0	115	6.3
Good	7.0	150	8.2
	8.0	180	10.0
Poor	9.0	215	11.9
	10.0	250	13.7
	11.0	280	15.6
	12.0	315	17.4

3. Pathophysiology

The pathophysiology of diabetes is largely based on insulin resistance.

The pathophysiology of type 2 diabetes mellitus is distinguished by insulin deficiency and insulinresistance, which have been linked to inflammatory cytokines in the plasma and high levels of fatty acids, leading deficient glucose transport into target cells, elevated breakdown of fat, and increased hepatic glucose production (18).

Consequent hyperglycemia is caused by the over secretion of glucagon and a deficiency of insulinby the glucagon-secreting alpha cell and the insulin-secreting beta cell, respectively. In the case oftype 2 diabetes mellitus, the disease is diagnosed because patients cannot increase insulin secretionto make up for their insulin resistance, thereby causing a high level of glycemic value (19).

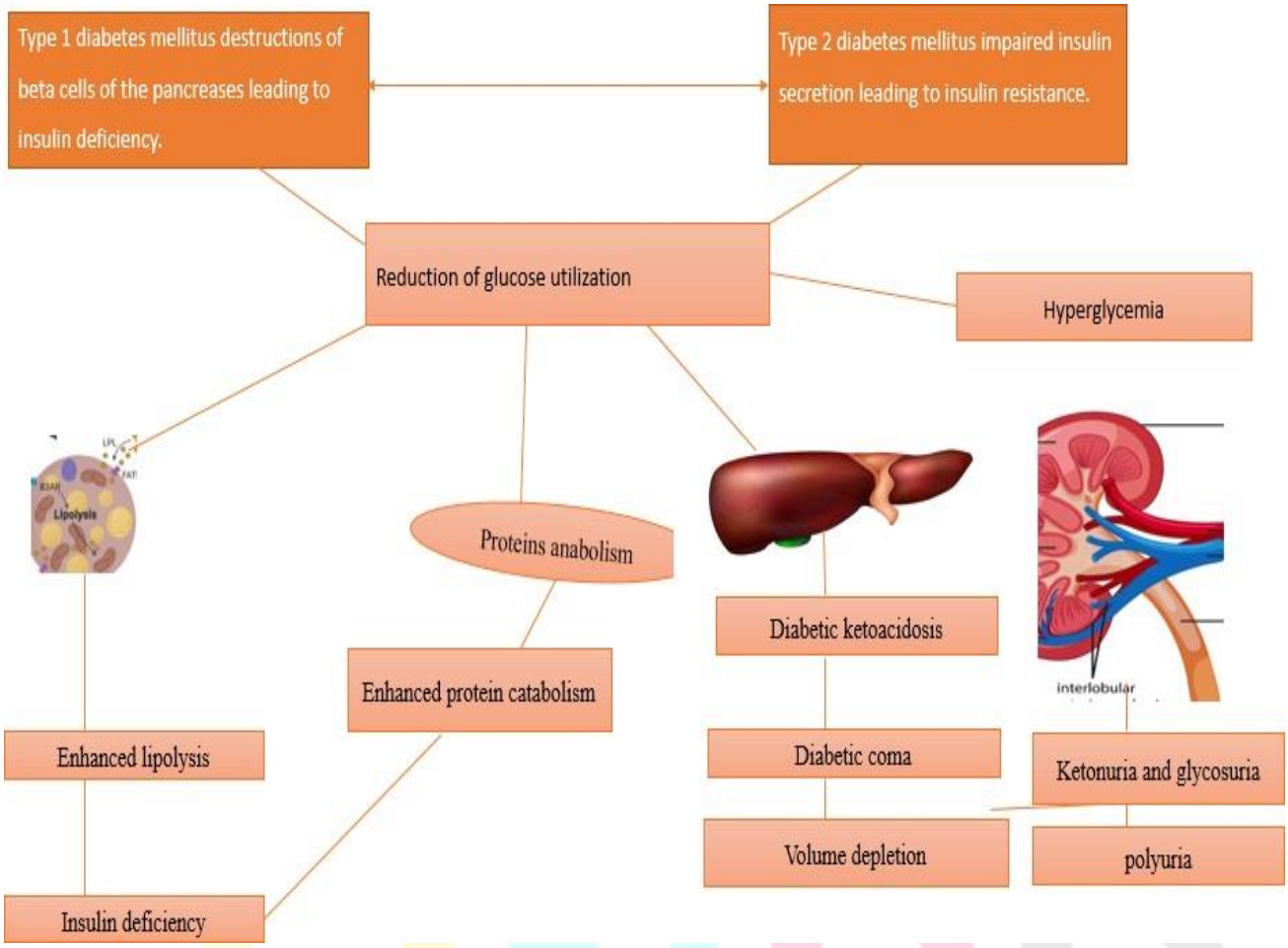
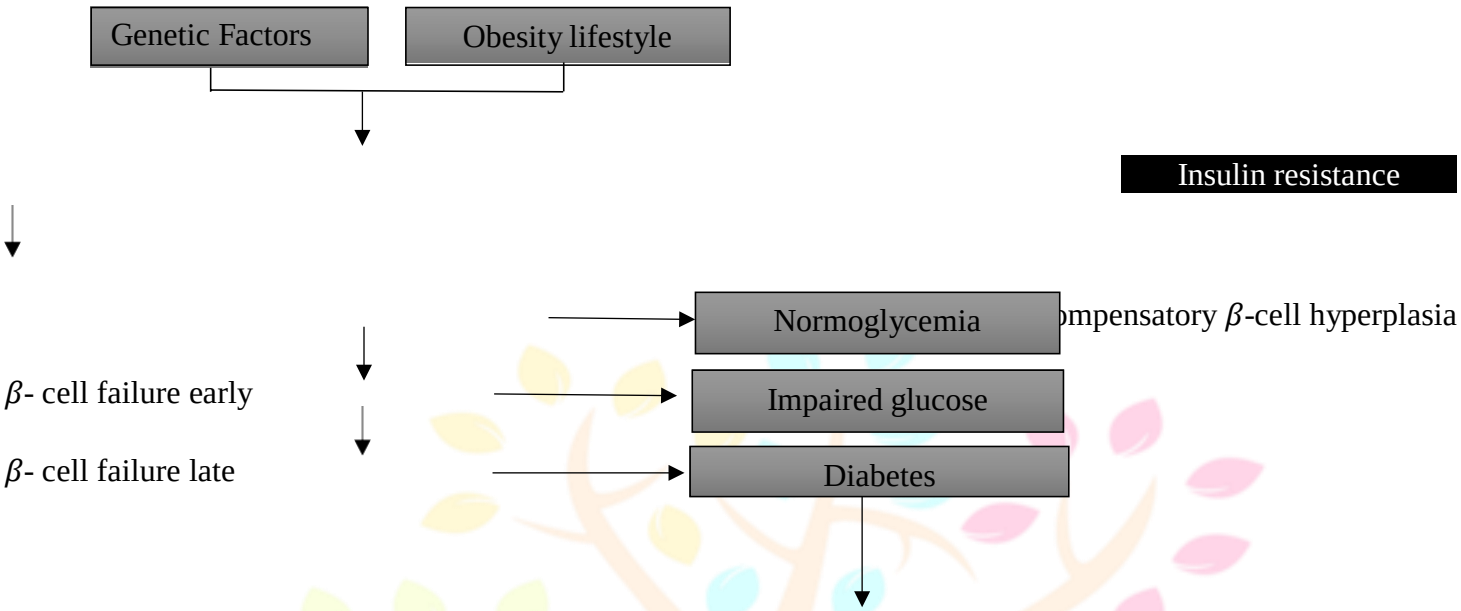


Fig.5 Pathophysiology of type 2 Diabetes.



Primary Q – ***cell failure rare***

Relationship with wounds healing process and impacts of various antihyperglycemic agents or wound healing process.

Impaired healing in diabetes is the result of a complex pathophysiology involving vascular,neuropathic, immune, and biochemical components. Hyperglycemia correlates with stifferblood vessels which cause slower circulation and microvascular dysfunction, causing reduced tissue oxygenation.

Blood vessel alterations observed in diabetic patients also account for reduced leukocyte migration into the wound, which becomes more vulnerable to infections.

The hyperglycemic environment itself can compromise leucocyte function. In addition, peripheral neuropathy can lead to numbness of the area and reduced ability to feel pain, which can lead to chronicization of wounds that are not immediately noticed and properlytreated.

The First Phase: Inflammatory Response

The inflammatory phase is preceded by a coagulation step in which the first response of the injured skin is activation of the clotting cascade with recruitment of platelets and the formation of a fibrin plug. Its significance resides in hemostasis as well as wound coverageand protection. Aggregated platelets within the clot form also the basic structure for the recruitment of inflammatory cells and, through the release of several cytokines and growth factors, including platelet-derived growth factor (PDGF) and transforming growth factor β(TGFβ), they attract different cell types.

The Second and Third Phases: Proliferation and Remodeling;

These phases are aimed at driving wound closure. In this regard, granulation tissue, together with keratinocyte migration, formation of extracellular matrix (ECM) proteins, and the appearance of myofibroblasts cause contraction, one of the first events leading to wound closure. Fibroblasts are then the main cell type in this phase and, through the releaseof collagen, they start to rebuild the wounded area. The early phases of wound healing are characterized by hypoxia that plays a role in promoting migration and proliferation of each cell type as well as release of growth factors. Hypoxia induces in fact activation of hypoxiainducible factor (HIF)-1α and stimulation of vascular endothelial growth factor (VEGF- A), one of HIF-1α principal target genes, is induced

Impaired wound healing in the diabetic patients

Normal wound healing	Impairment in diabetes
Haemostasis	Poor vascular supply Increased risk of infection entering
Inflammation	Slow recruitment of neutrophils Neutrophils remain after 72 hours Persistent inflammation
Infection	Hyperglycaemia allows bacterial growth Slow/ineffective neutrophil & macrophage activity
Proliferation	Reduced tensile strength Reduced collagen deposition Reduced fibroblast activity
Maturation	Reduced tensile strength

Fiq.6: wounds healing process and impacts of various antihyperglycemia agents or wound healingprocess.

Molecular Pathways and Cytokine Levels by Diabetes Medications in Wound Healing process.

INSULIN: Decreased insulin action is a hallmark of diabetes. Systemic insulin treatmentis used for glycemic control and according to the CDC, over 6 million across the world useinsulin as daily diabetes treatment (Centers for Disease Control and Prevention Insulin serves an important role in glucose metabolism, protein synthesis, and proliferation and differentiation of different cell types suggesting that the hormone is capable of affecting different processes involved in wound healing Additionally, insulin has been shown to induce an anti-inflammatory effect in monocytes from obese patients via reduction of NFkβsignaling and ROS generation.

METFORMIN: Metformin, a biguanide, is currently the first line medication for initial treatment of type 2 diabetes and works by suppressing glucose production by the liver viaactivation of AMP activated protein kinase (AMPK) Despite being one of oldest medications prescribed to patients with type 2 diabetes, few studies have investigated its influence on wound healing. Unfortunately, a review of the literature revealed no studies on the effects of metformin on wound healing in diabetic patients. However, some clinicalstudies indicate that oral metformin may induce modest amelioration of systemic inflammation. An outpatient clinic follow-up study of 110 patients with type 2 diabetes taking only metformin or the sulfonylurea glyburide for 4 years indicated that metformin users had lower levels of the inflammatory marker CRP (5.56 ± 1.5 mg/L) than patients taking the glyburide (8.3 ± 1.4 mg/L) (Akbar 2003). Metformin has also been shown to decrease the pro-inflammatory cytokine macrophage migration inhibitor factor (MIF) in the plasma and monocytes from obese patients when compared to untreated patients). Furthermore, a meta-analysis of 33 human studies looking at the effects of metformin on CRP levels of patients with type 2 diabetes indicated decreases on serum levels of CRP Inlaboratory experiments, metformin treatment of isolated human monocytes stimulated withlipopolysaccharide (LPS) showed that the drug inhibits production of TNF-α via inhibitionof the extracellular signal-regulated protein kinase (ERK) pathway.

SULFONYLUREAS: Sulfonylureas such as glyburide (glibenclamide) and glimepiride are some of the most commonly used medications for the treatment of type 2 diabetes. Sulfonylureas work by binding to a receptor on the ATP-dependent potassium channel in the pancreatic beta cells. The binding inhibits the potassium channels which changes the resting potential of the beta cells allowing higher sensitivity to glucose which induces greater insulin secretion Again, although no studies were found on the effects of sulfonylureas on wound healing in diabetic patients, a few studies have investigated effectson inflammation. To investigate the potential influence of different

sulfonylurea drugs on inflammation, a small number of type 2 diabetes patients were switched from glyburide to glimepiride for 28 weeks and titrated up to 6 mg/day.

THIAZOLIDINEDIONES: Thiazolidinedione (TZD) medications improve insulin resistance in patients with type 2 diabetes mellitus by targeting the peroxisome proliferator-activated gamma receptor (PPARγ), which is thought to increase insulin sensitivity by retention of fatty acids in adipose tissue and regulation of adipocyte secreted hormones thatimpact glucose homeostasis Early studies evaluating anti-inflammatory properties by rosiglitazone showed its ability to lower MCP-1 and CRP in plasma and NFkβ-binding activity in mononuclear cell extract from a group of non-diabetic and diabetic obese patients treated for 6 weeks . A single-centre, randomized, open-label study in type 2 diabetes patients showed that 12 weeks of rosiglitazone treatment leads to greater reductions in inflammatory biomarkers compared to metformin/glyburide treatment including greater decreases in hs-CRP (58% vs. 26% non-significant reduction in metformin/glyburide group.

Medications	Reported Molecular Pathways Affected	Reported Effects on Growth Factors and Cytokines Involved in Wound Healing		FDA Reported Clinical Side Effects
		Pro-Inflammatory	Pro-Healing	
Insulin	AKT ERK	MCP-1 ROS	VEGF SDF1α	
Metformin	AMP-Activated Protein Kinase (AMPK) ERK	TNFα IL-6 INF-γ ROS		Lactic Acidosis (Black Label Warning)
Sulfonylureas (Glyburide)	Inhibit Nod-Like Receptor NLRP-3 Inflammasome	IL-1β IL-18	IGF-1 TGF-β IL-10	Hypoglycemia
TZD	PPARγ Activation NFkβ P38 MAPK	TNFα IL-6 Resistin	VEGF IL-8 Adiponectin	Congestive Heart Failure (Black Label Warning)

DIPEPTIDYL PEPTIDASE 4 INHIBITORS: The incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are reported toaccount for 50% to 70% of postprandial insulin secretion from pancreatic beta cells The hormones are secreted after a meal from the small intestine but have a circulating half-lifeof less than 2 minutes from its rapid degradation by dipeptidyl peptidase 4 (DPP-4) Dipeptidyl peptidase 4 inhibitors (DPP-4i) are diabetes medications that work by blockingDPP-4 inactivation of the incretin hormones to allow extended stimulation of pancreatic insulin secretion and inhibition of glucagon release in a glucose-dependent manner). SincePP-4 and GLP-1 receptors are widely expressed throughout the human body including monocyte/ macrophages; it has been proposed that incretin based therapies may exert pleiotropic effects that extend beyond pancreatic islet stimulation Studies on diabetic humans and mice have indicated that DPP-4i improve postprandial lipemia, reduce inflammatory markers, improve endothelial function, reduce platelet aggregation, and are weight neutral.Diabetes Medications Associated Mechanisms of Action Involved in Wound Healing:

Wound healing is a complex process involving highly regulated steps of biological events,consisting a set of coordinated interactions between cells in the dermis and epidermis. Diabetes is associated with abnormalities in connective tissue, and this contributes to impair wound healing, leading to the formation of chronic ulcer. Briefly, the key four inter-related processes involved in wound healing are described below.

Hemostatic phase: The Following injury, platelets adhere to exposed type 1 collagen andbecome activated, secreting glycoproteins leading to platelet aggregation. The complex secretes factors that interact with each other to stimulate intrinsic clotting cascade throughthe production of thrombin; thrombin, in turn, stimulates the formation of fibrin from fibrinogen. The fibrin mesh coupled with platelet, aggregate into a stable hemostatic plug. It is known that within minutes of injury, blood vessels constrict, and reducing the degreeof hemorrhage through different steps which allow hemostasis to be achieved

Inflammation phase: There is an overlapping role between the hemostatic phase and theinflammation phase. The inflammatory phase seems to launch the hemostatic mechanismsto urgently stop blood loss from the wound or injury site. This phase may last for up to 2 weeks. The inflammatory phase is marked by vasoconstriction and platelet aggregation toinduce blood clotting followed by vasodilation and phagocytosis to produce inflammation at the wound site.

Proliferative phase: This phase which follows the inflammatory phase, lasting from 2 days to 3 weeks, consists of key steps which include granulation, contraction, and epithelialization. During granulation, fibroblasts form a bed of collagen with the productionof new capillaries. In the past two steps, wound edges pull together to reduce the defects contraction while fresh epithelial and scar tissues are formed over the wound site epithelialization.

Remodeling phase: During this phase, new collagen is synthesized, accompanied by increased tissue tensile strength due to intermolecular cross-linking of collagen through Vitamin C dependent hydroxylation. It is believed that this phase lasts from 3 weeks to 2 years.

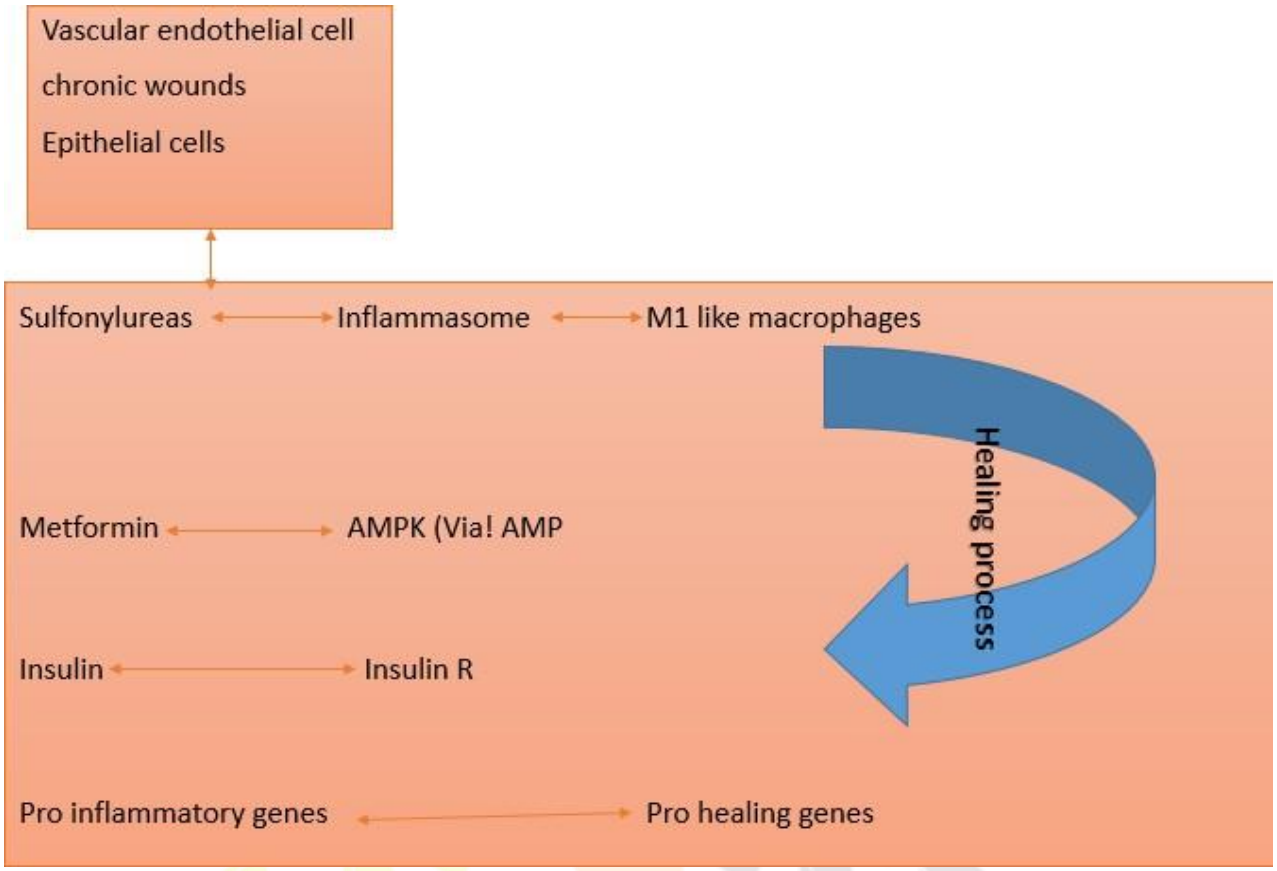


Fig.7 Medications Associated Mechanisms of Action Involved in Wound Healing**:Pharmacological Treatments of Diabetes:**

1. **Sulfonylureas** are insulin secretagogues that have been used extensively in the treatment of patients with diabetes. They are mostly metabolized in the liver and sometimes excreted by the kidneys (20). Irrespective of blood glucose levels, sulfonylureas trigger insulin secretion from thepancreas (21). Also, sulfonylureas inhibit glucagon secretion, enhance insulin sensitivity in peripheral tissues, and reduce hepatic insulin clearance (22).

2. **Meglitinides** are drugs that increase insulin secretion from the pancreas, and they are dependenton glucose levels, which reduces the risk of hypoglycemia. It has a short duration of action and can be administered to match the postprandial increase in glucose (23).

3. **Metformin (Glucophage)** improves hepatic insulin sensitivity and reduces hepatic glucose production. It also reduces insulin resistance in the peripheral tissues by reducing free fatty acids,triglycerides, and

high blood glucose levels (24). It carries out its ant hyperglycemic action withoutinfluencing insulin secretion (26). Also, it elevates gut glucose utilization and triggers GLP-1 secretion. Metformin is commonly administered as the first pharmacological agent in the treatmentof diabetes because of its affordable price, efficiency, and few side effects (27).

4. **Sodium-glucose transport protein 2 (SGLT2) inhibitors** They are a class of oral antidiabeticagents administered to lower blood glucose levels in adult patients with type 2 diabetes mellitus. Its action is not affected by insulin resistance or the insulin levels in the body (28).

5. **Glucagon-like peptide-1 (GLP-1) GLP**-1 is produced and stored in the L cells of the ileum and colon. Neural and hormonal mechanisms coupled with the presence of food in the gastrointestinal tract trigger its release. GLP-1 enhances insulin secretion by the beta cells and inhibits glucagon secretion by the alpha cells when blood glucose levels are elevated above normal(29).

6. **Thiazolidinedione's (TZDS)** Thiazolidinediones are medications used to manage and treat type 2 diabetes mellitus. These medications may be acting as a nuclear transcription regulator andan insulin sensitizer. This activity illustrates the indications, mechanism of action, and contraindications for thiazolidinediones as valuable agents for managing type 2 diabetes(30).

Chemical Causes of Diabetes:Alloxan:

Alloxan	**Chemical Properties**	**Phases of diabetes induction**	**Mechanism of action**

lloxan: is most prominent chemical compound used in diabetogenic research.In research it is used for induction of Type 1diabetes.	The chemical name ofalloxan is 2,4,5,6 tetraoxypyrimidine; 2, 4, 5, 6-pyrimidinetetrone, which is an oxygenated pyrimidine derivative which is present as alloxan hydrate in aqueous solution.	Alloxan induces triphasic blood glucose response when injected into experimental animals. The first phase that comes within the first minutes after allo xan administration is transient hypoglycemic phase that lasts maximally for 30 minutes.	Alloxan treatment evokes a sudden rise in insulin secretion in the presence or absence of glucose and this insulin release occurs for short duration followed bythe complete suppression of the islet response to glucose even when high concentrations of glucose were used.
Alloxan is a urea derivative which causes selective necrosis of theβ- cells of pancreatic islets.	Alloxan was prepared by the oxidation of uricacid by nitric acid and the monohydrate form is simultaneo usly prepared by oxidation of barbituric acid by chromium trioxide.	The hypoglyce mic response has been noted to be result of stimulation of insulin secretion that increases the concentration of insulin in plasma.	Alloxan reacts with two SH groups in the sugar binding site of glucokinase and results in inactivation of the enzyme.
It has been widely used to induce experimental diabetes in animals such as rabbits, rats, mice and dogs with different grades of disease severity by varying	Alloxan has been demonstrated to be non- toxic to the human beta- cells, even in very high doses, because humans have different glucose	The mechanism behind the first phase of this hyperinsulinemia may bea temporary increase inATP availability due toinhibition of glucose phosphorylation through	The superoxide radicals liberate ferric ions from ferritin and reduce them toferrous and ferric ions and also undergo dismutation to yield hydrogen peroxide (H2O2).

the dose of alloxan used.	uptake mechanisms as compared to rodents.	glucokinase inhibition.	

Streptozotocin:

Streptozotocin	**Chemical Properties**	**Mechanism of Action**
Streptozotocin is naturally occurring chemical used to produce Type- 1 diabetes in animal model and Type- 2 diabetes with multiple low doses.	Streptozotocin is a nonfunctionalnitrosourea derivative. First isolated from Streptomycesachromogenes.	Streptozotocin prevents DNA (Deoxyribonucleic acid) synthesis in mammalian and bacterial cells, in the bacterial cells; it renders special reaction with cytosine groups, resulting in degeneration and destruction of DNA.

It is also used in medicine for treating metastatic cancer of islets of Langerhans.	It has been used alone or in combination with other chemotherapeutic drugs (vincristine, 5-fluorouracil, methyl-CCNU, procarbazine and 6-thioguanine) for the treatment of colorectal carcinomas and other gastrointestinal cancers, butsevere toxicity and myelosuppression have observed in most of the patients. **Streptozotocin has broad spectrum antibiotic activity.**	The streptozotocin enters the pancreatic cell via a glucose transporter-GLUT2 (Glucose transporter 2) and causes alkylation of DNA. Further STZ induces activation of poly adenosine diphosphate ribosylation and nitric oxide release, as a result of STZ action, pancreatic -cells are destroyed by necrosis and finally induce insulin dependent diabetes.

Dithizone:

Dithizone	**Chemical Properties**	**Mechanism of actions.**
Dithizone induced the symptomsof diabetes in cats, rabbits, golden hamsters and in mice. In	Chemical name of dithizoneis 8-(p- toluene-sulfonyl	Dithizone bind zinc ions present inthe islets beta cells, and therefore stains the islets red.

dithizonised diabetic animals, the levels of serum zinc, iron, and potassium were found to be higher than normal but copper and magnesium levels were unchanged.	amino) – quinolone (8-TSQ). Dithizone is an organosulfur compound that acts as a chelating agent and forms complexes with lead, zinc and mercury.	
After treatment with insulin, most of these serum levels were normal, except for serum potassium and magnesium.	It is used to assess the purity of human pancreatic islet preparations used for transplantation in to patients with types 1 diabetes.	Exocrine tissue also present in the preparations does not bind dithizone and is therefore not stained.

Gold thioglucose:

Gold thioglucose	**Chemical Properties**	**Mechanism of Action**
Gold thioglucose is diabetogenic compound, which is induced hyperplasia and severe obesity induced Type -2 diabetes.	It is derivative of sugar glucose.	Gold thioglucose developed obesity induces diabetes in genetically normal mouse strains.
	Gold thioglucose is precipitated with methanol and recrystallized with water and methanol.	Gold thioglucose treated DBA/2 (Dilute Brown Non- Agouti), C57BLKs, and BDF1 mice gained weight rapidly and significantly increase non fasting plasma glucose level within 812 weeks.

		These mice showed impaired insulin secretion, mainly in earlyphase after glucose load and
		reduced insulin content in pancreatic islets.

Monosodium glutamate:

Monosodium glutamate	**Chemical properties**	**Mechanism of actions**
Monosodium glutamate induces Type -2 diabetes without polyphagia.	It is most abundant naturally occurring non-essential amino acid. Freely soluble in water.	Monosodium glutamate causes avery large insulin response afteringestion. It is developed glycosuria in both male and femalemice but not induced polyphagia. Within 29 weeks level of glucoseconcentration in blood, totalcholesterol and triglyceride were higher.

Methodology:

The review literature has been done by searching different models used to induce diabetes by PubMed. This article is purely based on the published non-clinical and clinical data obtained fromvarious pharmacological studies. This review article thus gives insights into the types of diabetes,etiology of diabetes, the complications of diabetes, the

mechanism of diabetes, diagnosis test for diabetes, the pathophysiology of diabetes, pharmacological treatment of diabetes, and chemical causes of diabetes.

CONCLUSION:

he population suffers from diabetes throughout the world. To reduce this data, many antidiabeticdrugs are used and research is going on for more effective anti-diabetic drugs. For study on diabetes, many diabetic models, chemicals and diabetogenic hormones are used at research level.In this we give an overview of models used to induce diabetes, their chemical properties and mechanism of action. Conclusively many animal models are used to induce diabetes, which furtherhelp in the study of development and screening of new anti- diabetic drugs. Therefore, more research is focusing on evaluating the role of antihyperglycemic agents in the wound healing process. Metformin, sulfonylureas, Insulin are the drugs that used to enhanced diabetes in woundhealing process. This review article thus gives insights on the types of diabetes, etiology of diabetes, complication of diabetes, mechanism of diabetes, diagnosis test for diabetes, pathophysiology of diabetes and their relationship with wound healing process and impact of various antihyperglycemic agents on wound healing process.

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