

A REVIEW ON STATINS FOR THE TREATMENT OF DIABETIC WOUND HEALING

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Abstract

Diabetic wounds, especially foot ulcers, are hard to heal and can lead to severe complications. Statins, drugs usually used to lower cholesterol, are now being studied for their ability to help heal these wounds. This abstract explains how statins might help, what the benefits are, and what challenges exist.

Besides lowering cholesterol, statins have other useful effects. They can reduce inflammation, increase blood flow, and protect tissues from damage, all of which are important for healing wounds. In diabetic patients, wounds often heal slowly due to poor circulation and chronic inflammation. Statins can improve blood vessel function and help new blood vessels grow, which brings more oxygen and nutrients to the damaged areas. They also lower the levels of certain harmful proteins, making the wound environment better for healing.

Statins are a class of drugs that lower cholesterol levels and have additional benefits like reducing inflammation and improving blood vessel function. There are several types of statins, which vary in their potency, effectiveness, and side effects. Studies show that statins can speed up wound healing, shrink the size of ulcers, and reduce the chances of infections and amputations. However, the results may depend on the type of statin, dosage, and individual differences among patients. While statins have shown promise in healing diabetic wounds, we still need to fully understand how they work and be mindful of potential side effects like liver issues or muscle problems.

Keywords:- Statins, diabetic wound healing, foot ulcers, inflammation, diabetic complications

Introduction

Diabetic wounds, especially foot ulcers, are a common and serious problem for people with diabetes. These wounds are hard to heal due to poor blood flow, ongoing inflammation, and slower tissue repair, making infections and amputations more likely. This greatly impacts the lives of people with diabetes. Researchers are now looking into whether statins—medications usually used to lower cholesterol—could also help with healing diabetic wounds. Statins have some surprising benefits beyond managing cholesterol. They can reduce inflammation, protect cells from damage, and help form new blood vessels, all of which can speed up healing. These effects could address the root causes of why diabetic wounds heal so slowly. Statins improve blood flow by helping blood vessels function better and encouraging new ones to grow, which is essential for getting oxygen and nutrients to the wound. They also reduce harmful inflammation by lowering the levels of certain proteins in the body. Because of these combined effects, statins could be a useful extra treatment to help wounds heal faster and reduce the

chances of infections or amputations. Traditionally, treatments for diabetic wounds have focused on managing blood sugar levels, improving circulation, using antibiotics for infections, and employing wound care techniques like debridement and dressings. However, even with these treatments, many diabetic patients continue to experience slow or incomplete wound healing, leading researchers to explore additional therapies that can support and accelerate the healing process. One area of interest is the use of statins, a class of drugs widely prescribed to lower cholesterol and reduce the risk of cardiovascular disease. While statins are primarily known for their ability to reduce cholesterol levels, recent research has shown that they have other beneficial effects, such as reducing inflammation, improving blood vessel function, and promoting tissue repair. These properties make statins a potential option for enhancing the healing of diabetic wounds. Statins help improve wound healing in a few key ways. They reduce the levels of harmful inflammatory proteins in the body, helping to create a more balanced immune response. This is important because chronic inflammation can interfere with wound healing by damaging tissue and slowing the repair process. Additionally, statins help improve the health of blood vessels and encourage the growth of new blood vessels, a process called angiogenesis. This is especially important in diabetic patients, as poor circulation is one of the main reasons why their wounds heal so slowly.

Statins

Statins are drugs that help lower the amount of **bad cholesterol** (LDL cholesterol) in your blood. When you have too much LDL,

it can build up inside your arteries, forming a thick, waxy substance called plaque. Over time, this plaque can clog your arteries, making it harder for blood to flow. This raises your risk for heart problems, like heart attacks or strokes. They block a certain enzyme in your liver that's responsible for making cholesterol. So, your liver produces less cholesterol, and as a result, the amount of bad cholesterol in your blood goes down. If your cholesterol is high, statins lower it to reduce your risk of heart problems. If you have certain conditions like **diabetes**, doctors may prescribe statins to protect your heart, even if your cholesterol isn't super high.

Classification of Statins

1. Atorvastatin (Lipitor)

- **Uses:** One of the most commonly prescribed statins, atorvastatin is known for its high potency in lowering LDL (bad cholesterol) levels.
- **Additional benefits:** Atorvastatin has strong anti-inflammatory effects and improves endothelial function, which can help in promoting wound healing.
- **Common doses:** 10–80 mg daily.

2. Rosuvastatin (Crestor)

- **Uses:** Another high-potency statin, rosuvastatin is effective at reducing cholesterol and may also have greater effects on increasing HDL (good cholesterol) compared to other statins.
- **Additional benefits:** Like atorvastatin, rosuvastatin has been studied for its anti-inflammatory

and vascular benefits, making it a candidate for wound healing.

- **Common doses:** 5–40 mg daily.

3. Simvastatin (Zocor)

- **Uses:** One of the older statins, simvastatin is effective at lowering LDL cholesterol and has been widely used for many years.
- **Additional benefits:** Simvastatin is less potent than atorvastatin or rosuvastatin, but still has beneficial effects on blood vessels and inflammation, which may help in wound healing.
- **Common doses:** 10–40 mg daily.

4. Pravastatin (Pravachol)

- **Uses:** Pravastatin is less potent compared to atorvastatin or rosuvastatin but has fewer drug interactions, making it suitable for patients on multiple medications.
- **Additional benefits:** It has a lower risk of muscle-related side effects, making it a safer option for some patients. Pravastatin also has mild anti-inflammatory properties.
- **Common doses:** 10–80 mg daily.

5. Lovastatin (Mevacor)

- **Uses:** Lovastatin is another older statin, often used in patients who need moderate cholesterol reduction.
- **Additional benefits:** It has fewer side effects than some of the stronger statins but may not be as potent in promoting healing due to its lower efficacy in reducing inflammation.

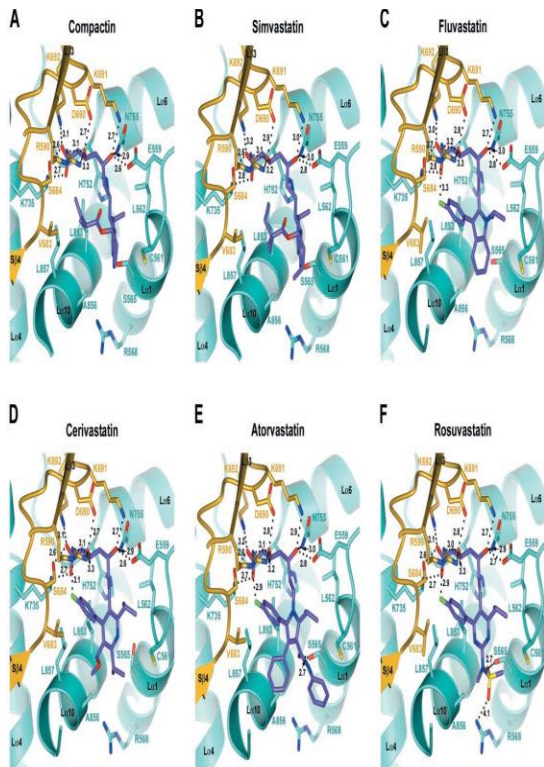
- **Common doses:** 10–80 mg daily.

6. Fluvastatin (Lescol)

- **Uses:** This statin is less potent than the others and is typically used in patients who need mild to moderate cholesterol reduction.
- **Additional benefits:** Fluvastatin has fewer side effects compared to high-potency statins, but its benefits in wound healing are not as well studied.
- **Common doses:** 20–80 mg daily.

7. Pitavastatin (Livalo)

- **Uses:** A newer statin that is moderate in potency but may have fewer side effects in terms of muscle pain and liver problems.
- **Additional benefits:** Pitavastatin shows some promise in improving insulin sensitivity, which may be beneficial for diabetic patients. It may also support wound healing by improving vascular function.
- **Common doses:** 1–4 mg daily



Factors to Consider When Using Statins for Wound Healing

- **Potency:** Higher potency statins, such as atorvastatin and rosuvastatin, may offer greater benefits for wound healing due to their stronger anti-inflammatory and vascular effects.
- **Side Effects:** Muscle pain (myopathy) and liver function issues are common side effects of statins. Lower-potency statins like pravastatin and fluvastatin may be better for patients sensitive to these side effects.
- **Interactions with Diabetes:** Some statins can affect blood sugar control, so monitoring is important when using them in diabetic patients.

Advantages of Statins

1. Anti-Inflammatory Effects

- Diabetic wounds are often characterized by chronic inflammation, which hinders the healing process. Statins reduce the production of pro-inflammatory cytokines, such as TNF- α and interleukins, which play a key role in sustaining this inflammation.
- By lowering these inflammatory markers, statins create a more favorable environment for wound healing and reduce tissue damage caused by prolonged inflammation.

2. Improved Blood Flow and Circulation

- One of the primary issues in diabetic wound healing is poor circulation, particularly in the extremities. Statins improve endothelial function by increasing the bioavailability of nitric oxide (NO), a molecule essential for vasodilation (widening of blood vessels).
- Better blood flow ensures that oxygen and nutrients reach the wound site more efficiently, promoting tissue regeneration and faster healing.

3. Promotion of Angiogenesis (New Blood Vessel Formation)

- Statins promote angiogenesis, which is the formation of new blood vessels. In diabetic patients, where blood flow is often compromised due to damaged blood vessels, angiogenesis is crucial for supplying oxygen and nutrients to the wound.
- By encouraging new blood vessel growth, statins help improve the

oxygenation of the wound, accelerating the healing process.

4. Reduction of Oxidative Stress

- Diabetic wounds often suffer from high oxidative stress due to an imbalance between the production of free radicals and the body's ability to detoxify them. Oxidative stress can damage cells and tissues, slowing down wound healing.
- Statins have antioxidant properties that reduce the levels of free radicals and oxidative stress in the wound area, protecting tissues and supporting faster recovery.

5. Immune Modulation

- Statins help modulate the immune response by enhancing the activity of beneficial immune cells (such as macrophages) that clean up dead tissue and debris in wounds. This allows for better wound bed preparation, essential for proper healing.
- This immune-regulatory role helps prevent infections, which are common in diabetic wounds and can lead to serious complications like gangrene or amputation.

6. Reduction in Infection Rates

- Statins have been shown to lower the risk of infections in diabetic wounds by improving the immune response and reducing inflammation. Infections can severely hinder wound healing and increase the risk of complications.

- Preventing infections also reduces the need for aggressive treatments such as antibiotics or surgical intervention.

7. Potential to Prevent Amputation

- Diabetic foot ulcers (DFUs) are a major cause of lower-limb amputations. By enhancing wound healing, statins may help reduce the size of ulcers and prevent them from becoming severe enough to require amputation.
- Some studies suggest that patients on statin therapy are less likely to need amputations due to improved wound healing outcomes.

8. Lower Cardiovascular Risk

- Many diabetic patients are also at a higher risk for cardiovascular diseases. Statins, by lowering cholesterol and improving blood vessel function, simultaneously reduce the risk of heart attacks, strokes, and other cardiovascular events.
- This dual benefit is especially valuable for diabetic patients, who often require comprehensive care for both metabolic and vascular health issues.

9. Improved Tissue Repair and Regeneration

- Statins promote the regeneration of damaged tissues by encouraging the proliferation and migration of cells involved in wound healing, such as fibroblasts and keratinocytes. This boosts the overall repair process and

leads to faster closure of diabetic wounds.

10. Reduction in Scar Formation

- By improving the wound healing environment and reducing inflammation, statins may help reduce the amount of scar tissue that forms. This is especially important in diabetic patients, where excessive scarring can lead to long-term complications.

11. Synergy with Other Treatments

- Statins can complement traditional wound care therapies, such as debridement, dressings, and growth factor treatments. Their ability to address underlying inflammatory and circulatory issues can enhance the effectiveness of standard wound care interventions.

12. Potential Cost Savings

- By reducing the risk of infections, amputations, and prolonged hospital stays, statins could potentially lead to cost savings in diabetic wound management. Preventing severe complications can reduce the need for expensive treatments and surgeries, improving patient outcomes and reducing healthcare costs.

Disadvantages of Statins

1. Risk of Muscle-Related Side Effects (Myopathy)

- Statins are known to cause muscle-related side effects, such as muscle

pain, weakness, and in rare cases, a severe condition called **rhabdomyolysis** (muscle breakdown). This can be particularly concerning for diabetic patients, who may already experience muscle weakness due to nerve damage (neuropathy).

- These side effects can limit the use of statins, especially in high doses, and may lead to treatment discontinuation in some patients.

2. Liver Toxicity

- Statins can sometimes lead to **elevated liver enzyme levels**, indicating liver damage or dysfunction. While this side effect is rare, it can be more concerning for diabetic patients who may already have liver problems related to diabetes or other metabolic conditions.
- Regular monitoring of liver function is required in patients on statin therapy, which can be a burden for both the patient and healthcare provider.

3. Impact on Blood Sugar Levels

- Statins have been shown to **increase blood glucose levels** slightly, which can worsen glycemic control in some diabetic patients. Although this effect is usually mild, it may still be significant for patients struggling to maintain stable blood sugar levels.
- This could potentially increase the risk of complications associated with poor blood sugar control, such

as delayed wound healing or the development of new wounds.

4. Variability in Effectiveness

- The effectiveness of statins in promoting wound healing may vary between different patients. Factors such as the specific type of statin used, the patient's overall health condition, and genetic differences can influence how well statins work.
- Not all patients respond equally to statin therapy, and in some cases, the benefits in wound healing may be limited or not observed at all.

5. Drug Interactions

- Statins can interact with other medications commonly prescribed to diabetic patients, such as anticoagulants, blood pressure medications, and certain antibiotics. These drug interactions can increase the risk of side effects or reduce the effectiveness of the treatments.
- Patients on complex medication regimens may require careful monitoring to avoid harmful interactions, which can complicate the management of their wound care.

6. Potential for Increased Fatigue

- Statins have been associated with **increased fatigue** and low energy in some patients, particularly in those who are older or already dealing with chronic conditions like diabetes. This can further impact the patient's ability to engage in

physical activity, which is important for circulation and overall health in wound healing.

7. Long-Term Safety Concerns

- While short-term studies have shown potential benefits of statins for wound healing, the long-term safety of using statins specifically for this purpose is not well established. Over extended periods, statin use can lead to cumulative side effects, particularly muscle and liver-related issues.
- Diabetic patients, who may require lifelong wound care management, might experience more pronounced side effects if statins are used for extended periods.

8. Limited Direct Evidence for Wound Healing

- Although some studies suggest that statins can help in wound healing through their anti-inflammatory and vascular effects, **direct evidence** on statins specifically improving diabetic wound healing is still limited.
- Much of the research is preliminary, and more clinical trials are needed to conclusively prove that statins are effective and safe for routine use in diabetic wound management.

9. Cost Considerations

- While statins are generally affordable, higher doses or newer statins like **rosuvastatin** can be more expensive, which may be a concern for patients without

comprehensive insurance coverage. For patients already dealing with the high costs of managing diabetes, adding another medication could increase financial stress.

- Moreover, the need for regular monitoring (liver function tests, glucose checks) can also contribute to healthcare costs.

10. Not Suitable for All Patients

- Statins are contraindicated in certain groups of people, such as those with **severe liver disease**, **pregnant women**, and individuals with a history of statin intolerance or allergic reactions to the medication.
- This limits their use in some diabetic patients, particularly those with complex health profiles or coexisting conditions that make statin therapy inappropriate.

11. Insufficient Data on Optimal Dosing for Wound Healing

- While statins have established dosing guidelines for cholesterol management, the **optimal dose** for promoting wound healing is not clearly defined. Using doses too low may not provide the desired healing benefits, while higher doses increase the risk of side effects like muscle pain and liver problems.

Side Effects

1. Muscle Pain and Weakness

- Many people on statins feel muscle pain or weakness. In rare cases, this can be severe and cause muscle breakdown, which can harm the kidneys.

2. Liver Problems

- Statins can sometimes affect the liver, leading to higher liver enzyme levels. This could indicate liver damage, though it's uncommon. Signs of liver issues include yellowing of the skin or eyes and dark urine.

3. Higher Blood Sugar

- Statins may slightly raise blood sugar levels, which could increase the risk of diabetes or make it harder for people with diabetes to control their blood sugar.

4. Digestive Issues

- Some people may experience upset stomach, diarrhea, constipation, or gas while taking statins.

5. Headaches

- Mild headaches are a common side effect, especially when first starting statins.

6. Memory Problems

- A small number of people report memory loss or confusion, though this is rare and usually goes away after stopping the medication.

7. Fatigue

- Some people feel unusually tired or weak, which can impact their daily activities.

8. Skin Reactions

- Occasionally, statins can cause a rash or itching.

9. Nerve Issues

- Rarely, statins can cause tingling, numbness, or burning sensations in the hands and feet.

10. Sleep Problems

- Some people may find it harder to sleep after starting statins, though this isn't very common.

11. Dizziness

- Statins can cause dizziness, particularly when starting the medication or adjusting the dose.

12. Kidney Damage

- In very rare cases, severe muscle breakdown caused by statins can lead to kidney problems.

13. Sexual Issues

- Some men may experience problems with erections, but this is not common.

14. Pancreatitis

- Statins have rarely been linked to inflammation of the pancreas, which can cause severe stomach pain.

15. Allergic Reactions

- Though extremely rare, statins can cause serious allergic reactions, such as swelling of the face or throat, which requires immediate medical help.

Applications

1. Lowering Cholesterol

- **Main Use:** Statins are primarily used to lower "bad" cholesterol (LDL) levels in the blood. This helps prevent heart disease, heart attacks, and strokes.

2. Preventing Heart Problems

- **After a Heart Event:** People who have already had heart problems (like a heart attack or stroke) are often prescribed statins to prevent future issues.
- **Before Heart Issues:** Statins can also be given to those at high risk of heart disease to lower their chances of having a heart attack or stroke.

3. For Diabetic Patients

- **Managing Cholesterol:** Diabetic patients often have higher cholesterol levels, so statins can help keep these levels in check and reduce heart-related risks.
- **Wound Healing:** Some studies suggest that statins might help diabetic wounds heal faster by improving blood flow and reducing inflammation, although more research is needed in this area.

4. Reducing Inflammation

- Statins can help lower inflammation in the body, which may be beneficial for conditions like rheumatoid arthritis and other inflammatory diseases.

5. Protecting Brain Health

- There's some evidence that statins might help protect against brain diseases like Alzheimer's, but more research is needed to confirm this.

6. Protecting Kidneys

- Statins may help slow the progression of chronic kidney disease and protect kidney function in patients at risk.

7. Post-Surgery Care

- Statins might be given to patients after surgery to reduce the risk of complications, like heart attacks or strokes, during recovery.

8. Cancer Treatment Research

- Some studies suggest that statins might improve outcomes in certain cancers, but this is still being researched and is not a standard treatment.

Methods and Material

Methods

□ Study Design

- **Clinical Trials:** These are experiments where researchers test how well statins work and how safe they are for people, including those

with diabetes and wounds. These trials are often designed to be fair and unbiased.

- **Observational Studies:** In these studies, researchers watch how patients who take statins do over time in real-life situations, focusing on the long-term effects and any side effects they may have.

□ Choosing Patients

- **Inclusion Criteria:** Researchers set specific rules about who can participate, such as age, gender, type of diabetes, and whether the person has wounds or high cholesterol.
- **Exclusion Criteria:** Some people, like those with serious liver issues or allergies to statins, are not included in the studies.

□ Dosing

- Different amounts of statins are tested to find the best dose that helps patients without causing too many side effects.

□ Checking Effectiveness

- **Wound Healing Assessment:** Researchers measure how big the wounds are, how quickly they heal, and how healthy the new tissue looks.
- **Cholesterol Levels:** Blood tests are done before and after treatment to see how statins affect cholesterol levels.

□ Monitoring Side Effects

- Patients are regularly checked for side effects, such as muscle pain or changes in liver function and blood sugar levels. This is done through blood tests and doctor visits.
- **Data Analysis**
- Researchers use statistical methods to make sense of the data they collect to see if the results are meaningful.
 - **Materials**
- **Statins**
- **Types of Statins:** Common types include atorvastatin (Lipitor), simvastatin (Zocor), rosuvastatin (Crestor), pravastatin (Pravachol), and lovastatin (Mevacor).
 - **Forms:** Statins usually come in tablet form, and the specific dose can vary based on the patient's needs.
- **Placebo**
- A placebo is often used in studies as a comparison to see how well statins work. It's a non-active treatment that helps researchers understand the effects of the actual medication.
- **Lab Supplies**
- **Blood Collection Kits:** These are used to take blood samples for testing cholesterol and liver function.
 - **Wound Assessment Tools:** This can include measuring devices and cameras to keep track of wound size and healing progress.
- **Monitoring Equipment**
- **Glucose Meters:** Used to check blood sugar levels in diabetic patients during the study.
 - **Liver Function Test Kits:** To monitor liver health while patients are on statins.
- **Data Collection Tools**
- **Electronic Health Records (EHR):** These are used to collect and organize patient information during the study.
 - **Surveys and Questionnaires:** These tools help researchers understand how patients feel about any side effects and their overall quality of life.
- **Data Analysis Software**
- Software like SPSS, R, or SAS helps researchers analyze the collected data and evaluate the effectiveness and safety of statins

Pathophysiology of Diabetic Wound Healing by Statins

Statins, commonly used for lowering cholesterol, may also have beneficial effects on wound healing in people with diabetes due to their pleiotropic effects—actions beyond their cholesterol-lowering capacity. Below is a detailed outline of how statins may impact the pathophysiology of diabetic wound healing:

1. Anti-Inflammatory Effects

Diabetes is associated with chronic low-grade inflammation, which negatively affects the wound healing process by

prolonging the inflammatory phase. Statins can modulate the inflammatory response by inhibiting the activation of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6). This reduction in inflammation helps to facilitate the transition from the inflammatory to the proliferative phase of wound healing, a step that is often impaired in diabetic patients.

2. Improvement in Endothelial Function and Angiogenesis

Statins enhance endothelial function by increasing the bioavailability of nitric oxide (NO), which plays a crucial role in vascular health. NO promotes vasodilation, improves blood flow, and supports angiogenesis—the formation of new blood vessels. Since diabetes often impairs angiogenesis and reduces blood supply to wound sites, statins can help improve blood flow and oxygen delivery to the wound area, promoting faster healing.

3. Reduction in Oxidative Stress

Diabetic wounds are subject to high levels of oxidative stress, driven by the overproduction of reactive oxygen species (ROS) and reduced antioxidant defenses. Statins have been shown to reduce oxidative stress by inhibiting the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which is responsible for ROS production. This can help reduce cellular damage and enhance tissue repair in diabetic wounds.

4. Promotion of Fibroblast Activity and Collagen Synthesis

Fibroblasts are key cells involved in the synthesis of collagen, a protein essential for wound healing. Diabetic wounds often show impaired fibroblast function and collagen production, which leads to poor tissue regeneration. Statins can stimulate fibroblast migration and increase collagen deposition, thereby improving wound strength and accelerating the closure of diabetic wounds.

5. Reduction in Glycation and Improved ECM Remodeling

Hyperglycemia in diabetes leads to the formation of advanced glycation end products (AGEs), which damage proteins like collagen in the extracellular matrix (ECM). Statins can help reduce the formation of AGEs and promote proper ECM remodeling, allowing for better structural integrity of the wound area and more effective healing.

6. Modulation of Growth Factors

Diabetic wounds often suffer from a deficiency in key growth factors, such as Vascular Endothelial Growth Factor (VEGF) and Platelet-Derived Growth Factor (PDGF), which are crucial for cell proliferation and tissue regeneration. Statins have been shown to enhance the expression of VEGF and other growth factors, promoting tissue repair and vascularization of the wound area.

7. Inhibition of Matrix Metalloproteinases (MMPs)

In diabetes, there is often an overexpression of matrix metalloproteinases, enzymes that degrade collagen and other proteins essential for wound healing. Statins can

reduce MMP activity, preserving the extracellular matrix and allowing for more effective wound closure.

8. Enhanced Immune Function

Diabetes can impair the immune response, delaying the clearing of dead tissue and pathogens from wound sites. Statins may improve immune function by modulating immune cell activity, particularly by enhancing macrophage function. Macrophages play a critical role in clearing debris and orchestrating the transition from inflammation to tissue repair.

Conclusion

Statins, which are mainly used to lower cholesterol, may also help improve wound healing in people with diabetes. They have anti-inflammatory effects and can improve blood flow, which is important for healing wounds that often take longer to heal in diabetic patients. Early studies suggest that statins could be beneficial in treating these wounds, but more research is needed to confirm how well they work and the best ways to use them. It's important for patients to talk to their doctors before adding statins to their treatment plan for wounds

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