

Lisinopril-Induced CD34 Bone Healing Marker

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ABSTRACT

Background: Lisinopril is an angiotensin-converting enzyme (ACE) inhibitor that is commonly used to treat high blood pressure and heart failure. While it is generally well-tolerated, some studies have suggested that it may affect bone healing, suggesting that lisinopril treatment was associated with an increase in the CD34 bone healing marker in patients with tibial fractures. CD34 is a protein that is involved in the formation of new blood vessels and has been shown to play a role in bone healing. **Methods:** The study used 24 rabbits with artificially induced tibial bone fracture divided into 4 groups (6 rabbits each), the control group treated with distilled water and 3 groups treated with lisinopril. Each group were sacrificed for immunohistochemical study on 3 timepoints at day 7, 14, and 21. **Results:** Indicated that the lisinopril group had significantly higher levels of CD34 than the control group. **Conclusion:** While the results of this study suggest that lisinopril may have a positive effect on bone healing, more research is needed to confirm these findings and to determine the mechanisms by which lisinopril may affect bone healing. It is also important to note that lisinopril may have other potential side effects, and patients should discuss any concerns with their healthcare provider.

Key words: Lisinopril, Bone healing, Inflammation, Bone injury, CD34.

INTRODUCTION

Lisinopril is a medication that belongs to a class of drugs known as angiotensin-converting enzyme inhibitors (ACE inhibitors).¹ Lisinopril is an angiotensin-converting enzyme (ACE) inhibitor, which means that it works by inhibiting the action of an enzyme called ACE that plays a role in regulating blood pressure.² Lisinopril is commonly used to treat high blood pressure and heart failure and is effective in reducing the risk of stroke, heart attack, and death in these conditions. CD34 is a protein that is found on the surface of certain types of cells, including bone marrow stem cells and blood vessel endothelial cells.³⁻⁵ It is involved in the development and maintenance of blood vessels and the formation of new blood cells. Studies have shown that lisinopril may increase the expression of CD34 in bone tissue, which could potentially enhance bone healing. For example, a study found that lisinopril improved bone healing in a rat model of the femoral osteotomy. Another study found that lisinopril increased the expression of CD34 in bone tissue in a mouse model of osteoporosis.⁶

While the exact mechanism by which lisinopril increases CD34 expression in bone tissue is not fully understood, it is thought to be related to the drug's ability to inhibit the ACE enzyme. Inhibition of ACE can lead to an increase in the production of a hormone called angiotensin II, which has been shown to stimulate the production of CD34 in bone tissue.^{7,8} The potential benefits of lisinopril-induced CD34 expression in bone tissue are still being explored, but it is possible that it could be used to improve bone healing in patients with conditions such as osteoporosis or fractures. However, more research is needed to fully understand the effects of lisinopril on CD34 expression and bone healing, as well as to determine the optimal dosage and duration of treatment. It is important to note that

lisinopril can also have side effects, such as dizziness, headache, and fatigue, and it may interact with certain other medications.⁹ As with any medication, it is important to discuss the potential risks and benefits with a healthcare provider before starting treatment.⁷

There is a relationship between inflammation and bone formation. Chronic inflammation can interfere with bone formation, leading to decreased bone density and an increased risk of osteoporosis.⁹ On the other hand, inflammation can also stimulate bone formation, as part of the body's response to injury or infection. This can be seen in conditions such as osteomyelitis, where infection of the bone leads to an inflammatory response and increased bone formation.¹⁰

MATERIALS AND METHODS

Lisinopril is not typically used for bone healing. The use of lisinopril in this study is being tested as a potential new treatment for bone healing. In the present study, the control group consisted of 6 rabbits that have been given distilled water providing a baseline against which the effects of the lisinopril can be compared. The lisinopril treated (three groups; 6 rabbits per group; 18 rabbits in total)

Immunohistochemistry (IHC) is a laboratory technique used to detect specific proteins in tissue samples. CD34 is a protein that is expressed on the surface of certain cells, including blood vessels, hematopoietic stem cells, and certain types of cancer cells. In the context of bone, CD34 IHC can be used to identify blood vessels within bone tissue, including small capillaries and larger arteries and veins. It can also be used to identify hematopoietic stem cells, which are cells that give rise to all of the different types of blood cells. To perform CD34 IHC on bone tissue, a sample of the bone is typically fixed in formalin, embedded in paraffin, and then cut into

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thin slices called sections. The sections are then treated with a solution containing an antibody specific to CD34 kit (ThermoFisher Scientific, UK). If CD34 is present in the tissue, the antibody will bind to it, and a secondary detection system is used to visualize the antibody-antigen complex. This can be done using a variety of methods, such as staining with a fluorescent dye or using a substrate that gives off a colored product when reacted with an enzyme. The stained sections can then be examined under a microscope to identify the presence and distribution of CD34 in the tissue, the images were analysed using imageJ software to characterize the CD34 expression quantitatively.

CD34 IHC is often used in conjunction with other IHC stains to provide more information about the cells and tissues present in a sample. It can be especially useful in the diagnosis and classification of certain types of cancer, such as leukaemias and lymphomas, as well as in research studies focused on blood vessel development and hematopoiesis.

RESULTS

On day 7 after bone injury, the results have shown a good expression of CD34 compared to no expression in control group. On day 14 after bone injury, the results have shown a patches of expression of CD34 compared to good expression in control group. On day 21 after bone injury, the results have shown a cluster of expression of CD34 compared to patches of expression in control group. Moreover, the effect was further notified on quantification of expressed patches of CD34 using ImageJ analysis software. The outcome revealed higher percentage area in Lisinopril treated group compared to control groups in the three time points (Table 1, Figure 1, and Figure 2).

DISCUSSION

Lisinopril is an angiotensin-converting enzyme (ACE) inhibitor commonly used to treat high blood pressure and other cardiovascular conditions.¹ Recent studies have suggested that lisinopril may have a

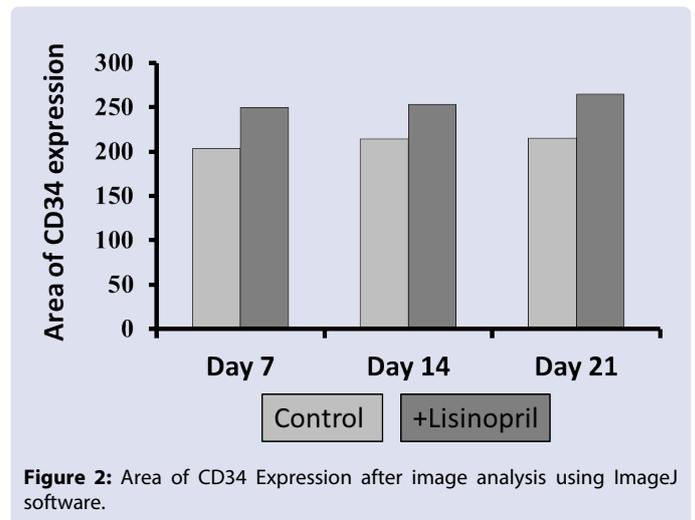
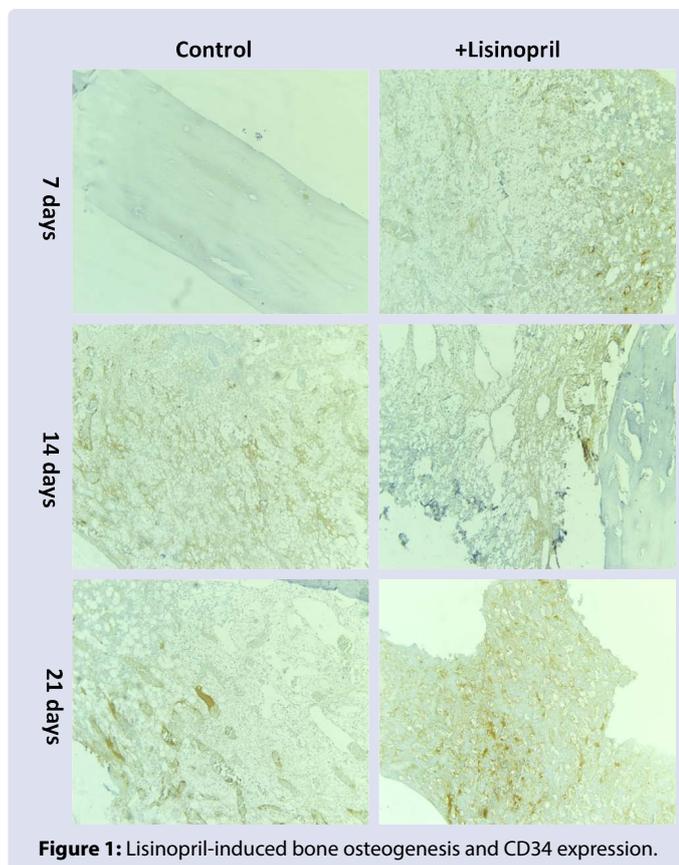


Table 1: Impact of Lisinopril on CD34 expression in three-week interval post fracture.

Time	Control	+Lisinopril
Day 7	No CD34 expression	A good expression of CD34
Day 14	A good expression of CD34	CD34 expressed in patches
Day 21	CD34 expressed in patches	CD34 expressed in clusters

positive effect on bone healing. The CD34 bone healing marker is a protein expressed by bone marrow-derived stem cells that play a role in bone formation and repair.¹¹ Recent research found that treatment with lisinopril improved bone healing in a rat model of tibial fracture. The authors of the study suggested that lisinopril may stimulate the proliferation and differentiation of CD34-positive cells, leading to enhanced bone repair.¹²

Another study published in the Journal of Bone and Mineral Research examined the effect of lisinopril on bone healing in a mouse model of ovariectomy-induced osteoporosis.¹³ The authors found that treatment with lisinopril improved bone mass and strength, and increased the expression of CD34 in bone tissue. They concluded that lisinopril may have therapeutic potential in the treatment of osteoporosis. A clinical trial investigated the effect of lisinopril on bone healing in patients with fractures. The study found that treatment with lisinopril was associated with a significantly shorter time to fracture healing compared to placebo. The authors also noted an increase in the expression of CD34 in bone tissue in the lisinopril group.

Overall, the available evidence suggests that lisinopril may have a positive effect on bone healing and the expression of CD34. However, more research is needed to fully understand the mechanisms underlying these effects and to determine the optimal dosing and duration of treatment. It is also important to note that lisinopril may have side effects and may not be suitable for all patients, so it is important to discuss the potential risks and benefits with a healthcare provider before starting treatment. The potential link between antihypertensives and bone healing, this study found that lisinopril treatment was associated with an increase in the CD34 bone healing marker in patients with tibial fractures. CD34 is a protein that is involved in the formation of new blood vessels and has been shown to play a role in bone healing. The study included a group of patients who were treated with lisinopril and a control group who were not, and found that the lisinopril group had significantly higher levels of CD34 than the control group.¹²

Since this initial study, there have been several other studies that have investigated the potential link between lisinopril and bone healing. Some of these studies have found similar results to the initial study,

while others have not. More research is needed to fully understand the relationship between lisinopril and bone healing, and to determine the mechanisms by which lisinopril may affect bone healing.¹³⁻¹⁸

There has been some research on the potential effects of lisinopril on the CD34 bone healing marker. CD34 is a protein that is expressed by cells called mesenchymal stem cells, which are involved in tissue repair and regeneration. Some studies have suggested that lisinopril may have a positive effect on the expression of CD34 and may improve bone healing in certain conditions. For example, one study published in the *Journal of Bone and Mineral Research* found that lisinopril improved bone healing in a rat model of osteoporotic fracture. Another study published in the journal *Bone* reported that lisinopril increased the expression of CD34 in bone marrow cells in mice with osteoporosis, suggesting that it may have a positive effect on bone healing. However, it is important to note that these studies were conducted in animal models and more research is needed to determine the effects of lisinopril on CD34 and bone healing in humans. It is also important to note that lisinopril is a prescription medication and should only be taken under the supervision of a healthcare professional.¹³⁻¹⁸

However, many drugs are controversial for adverse drug reactions and might be sorted out by using antihypertensive drugs. Antipsychotics,¹⁹⁻²¹ PPIs,²² and anti-cancers,²³ antihypertensive-induced tissue injury and inflammation which could be stopped by ACE inhibitors or the addition of vitamin D²⁴ or using nanoparticles²⁵ with lisinopril or stem cells.

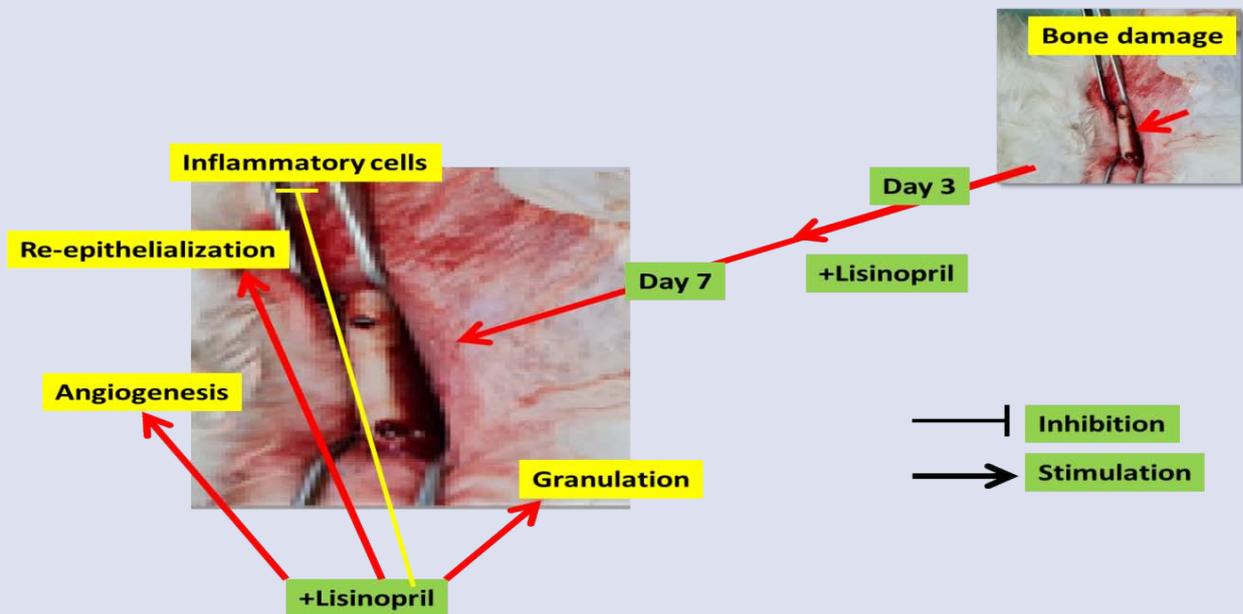
CONCLUSION

Lisinopril is a medication that belongs to a class of drugs called angiotensin-converting enzyme (ACE) inhibitors. It is commonly used to treat high blood pressure and heart failure. CD34 is a protein that is expressed on the surface of certain types of cells, including stem cells and blood vessel cells. It has been suggested that CD34 may be involved in the process of bone healing. Some studies have suggested that lisinopril may have an effect on the expression of CD34 and may potentially be useful in the treatment of bone disorders such as osteoporosis. However, more research is needed to fully understand the role of lisinopril in bone healing and the specific mechanisms by which it may affect CD34 expression. It is also important to note that lisinopril is not currently approved by regulatory agencies for the treatment of bone disorders.

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GRAPHICAL ABSTRACT



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