Systematic Revier Article: A Systematic Review of the Effect and Safety of Alendronate on Bone Density in Patients with Chronic Kidney Disease

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ABSTRACT

This study has systematically investigated the effect and safety of alendronate on bone density in patients with chronic kidney disease. In this study, by reviewing more than 75 articles and by searching keywords such as: Safety of alendronate, bone density, chronic kidney disease, the issue has been investigated. Alendronate tablet with the English name Alendronate is one of the well-known drugs for patients with osteoporosis and others who are exposed to this disease. Most of its users are postmenopausal women and people who have been treated with corticosteroids for any reason. The results of the present study showed that this drug slows down the activity of cells that play a role in bone decomposition. Therefore, its consumption can be effective in strengthening bones and reducing the risk of fractures, especially in the elderly. This drug does not help reduce the pain caused by a broken bone, and patients should use other treatment methods to relieve their pain. It is not known whether NSAIDs increase the need for dialysis. Therefore, the available data do not confirm the safety of NSAIDs in patients undergoing surgery. More studies involving patients with other health problems are needed. Patients with chronic kidney disease (CKD) are more at risk of developing osteoporosis (bone weakening), which can often lead to bone fractures. The results of this study showed that this drug may cause ulcers and erosions in the esophagus (the tube that connects the throat to the stomach), which can sometimes be severe.

Introduction

Osteoporosis in English is one of the types of orthopedic diseases that cause bones to become weak and brittle [1]. Pressures that normally do not cause bone damage can be harmful in osteoporosis. Falling and even mild stress such as bending the bone too much or coughing can cause a fracture. Fractures caused by severe osteoporosis may take the form of a fracture (such as a hip fracture) or a compression fracture (such as a vertebral compression fracture) [2-4]. Although fractures related to osteoporosis can occur in any bone, the spine, hip joint, ribs, and wrists are prone

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and common fracture sites [5]. Some of these fractures can have serious consequences.

Causes and factors affecting osteoporosis

Bones are constantly changing and their old tissue is continuously destroyed and replaced by new tissue. The amount of building and formation of bone tissue in youth is more than the amount of their destruction. For this reason, the amount of bone mass reaches its peak at the age of 30 to 35 years. With age due to factors such as menopause, family history, nutrition, etc., the old bone tissue is lost before it is replaced by new tissue. As a result, bone mass gradually decreases (Figure 1).

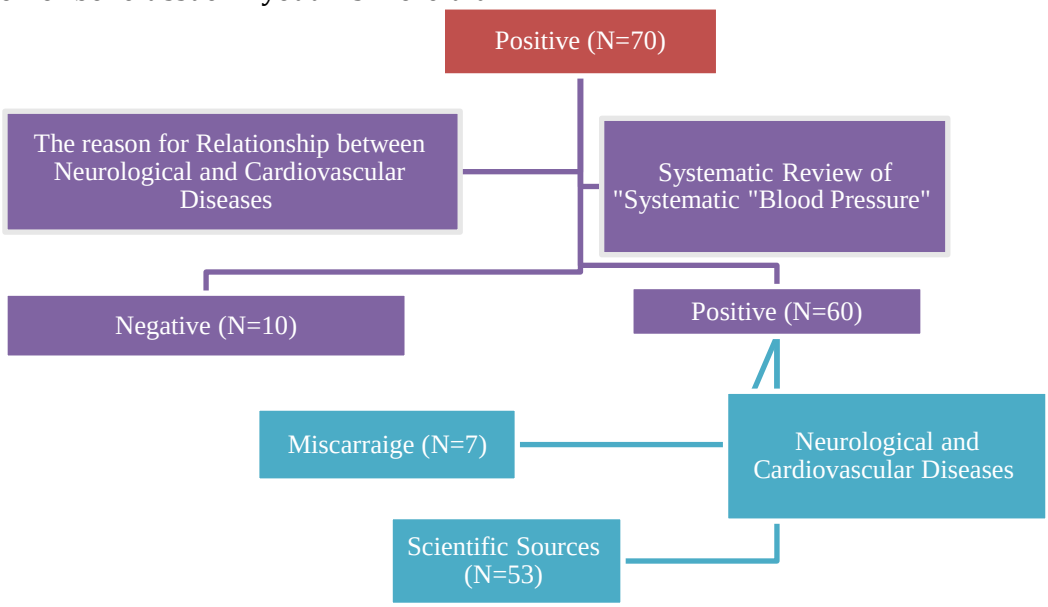

Figure 1. Flow chart of included subjects

Lack of bone mass is the main cause of osteoporosis in old age. Therefore, if during adolescence and youth, sufficient amount of bone is not made or the bone is destroyed faster due to other factors, the amount of bone mass will be less than the required amount and the person will suffer from osteoporosis in the future. If this amount is enough, even with the loss of bone in old age, menopause and other factors, the amount of remaining bone will be enough and the possibility of osteoporosis will decrease. Estrogen, testosterone and raloxifene drugs are in the category of hormonal drugs and are used to treat osteoporosis. Estrogen therapy, if started soon after menopause, is likely to help maintain bone density. Raloxifene's effects on bones are similar to estrogen, but without some of the risks. In men, with increasing age and the gradual decrease of testosterone, the possibility of osteoporosis increases. Therefore, testosterone replacement drugs can help improve the symptoms of low testosterone. These types of drugs are used to treat acute osteoporosis and when other treatments have failed. Romosuzumab is one of the newest bone building drugs and simultaneously causes new bone formation and decreases bone breakdown. Triparatide and abaloparatide are also similar to parathyroid hormone and their use will cause new bone formation. Drug interactions may change the action and effect of drugs or increase the risk of their side effects. Therefore, to take this medicine, share with your doctor the list of all the medicines you are taking, both prescription and non-prescription drugs (herbal, supplements, etc.). If you need to take medication during treatment with alendronate.

What is chronic kidney failure?

Chronic kidney disease occurs when the kidneys are damaged in such a way that they cannot return to their normal function. To diagnose chronic kidney failure, a person must have this disease for at least three months. There are many reasons for chronic kidney disease, including genetics, infection, immune disorders, diabetes and high blood pressure. With chronic kidney disease, you can live a normal life for years. However, many people experience a steady decline in their kidney's ability to filter blood and will eventually need kidney replacement therapy. Alternative treatment may include dialysis or kidney transplantation.

How to take alendronate tablets?

Alendronate tablets are available in doses of 5, 10, 35, 40 and 70 mg. According to the patient's condition [6-8], the doctor prescribes the appropriate dose of this medicine for daily or weekly use. Regardless of the prescribed dose, it should be taken in the morning on an empty stomach with only a glass of water [9]. You should take your pill immediately after getting out of bed and before eating or drinking anything else [10-12]. Never take it before going to bed and never lie down for thirty minutes after taking the pill. It is forbidden to eat and drink anything, especially vitamins and antacids, up to thirty minutes after taking this medicine [13]; Because any other substance will have a negative effect on the amount of drug absorption by the body [14-16]. You should sit or stand completely straight until at least half an hour has passed after taking the medicine and you have eaten your first meal of the day [17]. Chronic kidney disease is more common in blacks, the elderly, smokers, obese people, and people with a history of kidney disease. Considering the increasing use of kidney transplant in the treatment of chronic kidney failure and increasing the life expectancy of these patients, it is necessary to know the important complications of kidney transplant [18-20]. Decreased bone mineral density is one of these complications that can be minimized with timely diagnosis and treatment [21]. Chronic kidney diseases are growing rapidly in countries like the United States. In the year 2000, about 400,000 patients underwent kidney transplant or dialysis in this country [22-24]. It is believed that this figure will reach 2 million people by 2030 AD. Osteoporosis is another problem that has a prevalence of 6% in men and 7.2% in women in people over 50 years old [25-27]. In that group of osteoporosis sufferers who also suffer from kidney diseases, bisphosphonates - which are excreted by the kidneys - cause kidney poisoning. Several reports of acute kidney toxicity following treatment with bisphosphonates have been recorded. So far [28-30], 7 bisphosphonates have been approved by the US Food and Drug Administration [31]. Other extensive studies have been conducted to find the most appropriate bisphosphonates in patients with chronic kidney problems or patients who have undergone transplant surgery [32-34].

Risdronate

Risedronate is prescribed for the treatment of osteoporosis caused by the use of glucocorticoids, osteoporosis in men [35-37], Paget's disease and osteoporosis during menopause. Risedronate is not recommended in patients whose creatinine clearance is less than 30 milliliters per minute [38-40]. In some studies, the use of risedronate has been associated with kidney toxicity [41]. Another group of findings have considered risdronate safe in patients suffering from moderate to severe kidney problems [42]. On the other hand, transplant patients who have received glucocorticoids for a long time are at risk of losing bone mass due to pre-existing renal dysfunction [43-45]. Studies have shown that the administration of risedronate is well tolerated in these patients. Therefore, it can be concluded that risedronate does not have an adverse effect on kidney function in transplant patients [46-48].

Alendronate

Alendronate is prescribed for the treatment and prevention of menopausal osteoporosis, osteoporosis caused by the use of glucocorticoids, osteoporosis in men and Paget's disease [49]. In the case of alendronate, dose adjustment is necessary when the creatinine

clearance reaches less than 35 milliliters per minute [50-52]. In a large study, it was concluded that alendronate is a safe drug in patients undergoing hemodialysis [53-55]. Also, another study found alendronate to be effective and safe in the treatment of osteoporosis in women with reduced kidney function [55].

Etidronate

Etidronate is prescribed for the treatment of Paget's disease, heterotrophic ossification and hypercalcemia caused by malignancy. Etidronate is excreted unchanged by the kidneys. Although the manufacturer of this drug has recommended a lower dosage in patients with renal dysfunction, no specific dosage adjustment has been provided. However, etidronate should be used with caution when the serum creatinine level reaches above 2.5 mg/dL, and this drug is not recommended in patients with serum creatinine more than 5 mg/dL. Scientific evidences regarding the use of oral etidronate in patients with chronic kidney problems are not enough, but intravenous etidronate has been associated with acute renal failure, so currently the evidence is not enough to draw conclusions about the safety of etidronate in patients with chronic kidney diseases [56].

Ibadronate

Ibadronate is prescribed in the treatment and prevention of menopausal osteoporosis. 50 to 60% of consumed ibodronate is excreted unchanged by the kidneys. Therefore, there is no need to adjust the dose of ibadronate in patients with mild to moderate renal impairment. However, ibadervant is not recommended for patients with severe renal impairment and creatinine clearance less than 30 milliliters per minute. Several studies have also been conducted to investigate the effectiveness and safety of ibadronate in kidney patients [57-59].

Tildronate

Tilodronate is prescribed to treat Paget's disease. It is not recommended to prescribe this medicine in patients with creatinine clearance less than 30 milliliters per minute [60]. In addition, its prescription is prohibited in chronic kidney patients [61-63].

Treatment of kidney failure

There are several treatment methods to treat kidney failure; But the type of treatment depends on the cause of kidney failure. Your doctor can help you determine the most appropriate treatment option. Some of these treatment methods include:

Dialysis: In dialysis, the patient's blood is filtered and refined with the help of machine equipment. This device performs the work of the kidney. Depending on the type of dialysis you need, you may be connected to large machines or use portable catheter bags. A low-potassium and low-sodium diet is usually prescribed during dialysis. Dialysis does not cure kidney failure; But if you do it regularly, it will increase your life span.

Kidney transplant: Another treatment option for kidney failure is kidney transplantation; But it usually takes time to find a kidney that is compatible with your body. The advantage of a kidney transplant is that the new kidney will function properly and will not need dialysis. The disadvantage of this method is the need to use drugs that suppress the body's immune system, which must be taken after surgery. These drugs have side effects that can be dangerous. Also, kidney transplant surgery may be fatal if it is not successful.

Prevention of kidney failure

In order not to get involved in this disease, you must do a series of activities continuously and prevent getting infected. These are as follows:

- Regularly check serum creatinine
- Perform urine tests regularly
- Calculation of GFR for all people
- Treatment and control of blood pressure for people with high blood pressure.
- Treatment and control of blood sugar for people with diabetes.
- Treatment and control of blood lipid disorders in people with high blood cholesterol.
- Having proper nutrition
- Adequate physical activity
- Not using tobacco

Discuss

How is osteoporosis diagnosed? The diagnosis stage is even more important than the treatment

of the disease. There are different methods such as blood test to detect osteoporosis, which we will introduce below.

1. Medical history and physical examination

One of the most important steps that the doctor takes to diagnose osteoporosis is to ask the patient questions and examine him. When the patient talks about his bone pains and shares the history of fractures with the doctor. It also talks about his age and background conditions; It becomes easier to diagnose osteoporosis. If necessary, the orthopedic doctor or other doctors you have visited will request further tests and examinations [70].

2. Osteoporosis test

There are many tests to check bone health. After considering your medical history and risk factors, the orthopedic doctor will order a bone mineral density (BMD) scan. A bone densitometry scan uses a low-level X-ray technology known as dual-energy X-ray absorptiometry (DEXA) and bone densitometry. Osteoporosis testing and scanning can determine the probability of fractures caused by osteoporosis and the degree of response to treatment [71]. During this test, which takes 15 minutes and is completely painless, the person lies on a table equipped with a scanner. The DEXA test is very accurate, and patients are exposed to very little radiation (less than 0.1 to 0.01 the amount used in a standard chest X-ray). Two types of devices can perform a DEXA scan:

Central device: This type of scan is based on measuring the density of the bones of the femur, forearm and spine, while the patient is lying on the table [73-75].

Peripheral device: Mobile scanning device, which measures the density of the bones of the thigh, heel or toes [76].

If the amount of calcium taken from the bones increases, the bones become porous and the person suffers from osteoporosis. In this case, the bones gradually lose their mass and density and become very sensitive and fragile [77]. Osteoporosis is more common in women [78]; Although it is also seen in men. Recent studies by researchers at the Garvan Medical Research Institute in Australia show that some osteoporosis treatment drugs significantly reduce premature death rates [77-79]. This study, by examining the medical information of 6,120 people over the age of 50, shows that drugs such as alendronate [80-82], which belongs to the bisphosphonate group and is prescribed for the treatment of osteoporosis, reduces the risk of premature death by 34%. For these patients, the drug risedronate is usually prescribed, which does not have such an effect [83]. Bisphosphonates are a group of drugs that prevent the loss of bone mass [84]. This study states that although these drugs have a significant effect in the treatment of osteoporosis and they prevent the loss of bone density, most patients ignore it and do not take the drugs regularly [85-87].

Table 2. Forest plot showed the Effect and Safety of Alendronate on Bone Density in Patients with Chronic Kidney Disease

Raw	Study	Year		Proportion	Wight 98%	Weight %
1	Zhang et al.	**2023**		0.92	**[0.39 – 1.06]**	5.03
2	Yasrebinia et al.	**2024**		0.87	**[0.54 – 1.02]**	6.02
3	Yahaghi et al.	**2014**		0.88	**[0.63 – 1.01]**	5.57
4	Visseren et al.	**2021**		0.60	**[0.25 – 1.08]**	6.13
Heterogeneity t^2=0.02, I^2= 0.00, H^2=1.02				0.95	**[0.22 – 1.07]**	
Test of θ= θ, Q (4) =5.55, P= 0.74						

1	Tahmasebi et al.	**2020**		0.84	**[0.27 – 1.08]**	6.08
2	Taban et al.	**2023**		0.76	**[0.52 – 0.22]**	5.82
3	Sharifi et al.	**2012**		0.11	**[0.54 – 0.89]**	5.85
Heterogeneity t^2=0.14, I^2= 0.11, H^2=0.42				0.77	**[0.19 – 1.00]**	
Test of Θ= Θ, Q (4) =3.35, P= 0.34						
1	Sharifi et al.	**2024**		0.92	**[0.39 – 1.06]**	3.03
2	Shahsavarinia et al.	**2022**		0.87	**[0.54 – 1.02]**	8.33
3	Saedi et al.	**2022**		0.99	**[0.63 – 1.01]**	7.50
Heterogeneity t^2=0.14, I^2= 0.00, H^2=1.02				0.87	**[0.22 – 1.07]**	
Test of Θ= Θ, Q (4) =3.55, P= 0.12						
1	Rostami et al.	**2020**		0.84	**[0.27 – 1.08]**	6.08
2	Pourhanifeh et al.	**2020**		0.76	**[0.52 – 0.22]**	5.82
3	Motamedi et al.	**2023**		0.11	**[0.54 – 0.89]**	5.85
Heterogeneity t^2=0.19, I^2= 0.09, H^2=0.16				0.77	**[0.19 – 1.00]**	
Test of Θ= Θ, Q (4) =3.11, P= 0.04						

Conclusion

People with chronic kidney disease are at high risk of premature death, cardiovascular disease (heart disease and stroke), or kidney failure (dialysis or kidney transplant). Antioxidants, such as vitamin supplements, may be an easily accessible intervention to reduce these elevated risks. When NSAIDs are used in patients with normal renal function after surgery, they have unclear effects on AKI rates. It is not known whether NSAIDs increase the need for dialysis. Therefore, the available data do not confirm the safety of NSAIDs in patients undergoing surgery. More studies involving patients with other health problems are needed. Patients with chronic kidney disease (CKD) are more at risk of developing osteoporosis (bone weakening), which can often lead to bone fractures. There are several drugs to treat osteoporosis; However, it is not clear whether these drugs are equally effective and safe in patients with CKD, because the impairment of bone strength in these patients occurs through a different mechanism.

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