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Original Article

Routine prescription of calcium in immobile females receiving medroxyprogesterone to prevent osteoporosis/ bone loss

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ABSTRACT

The first objective of this review was to examine updated evidence on the routine prescription of calcium in females receiving medroxyprogesterone acetate (MPA) to prevent bone loss. It is clear from the review that depot MPA (DMPA) users were more likely to experience an increased risk of fracture. Many recent scholarly works have shown an insignificant increase in the risk of fractures linked with DMPA. These studies indicate that exposure to DMPA is associated with more fractures and can have an adverse effect on bone metabolism. Current treatment guidelines recommend providing DMPA users with calcium and vitamin D supplements. The current review shows evidence of positive changes in bone mineral density at the spine among females undergoing hormone replacement therapy combined with calcium supplements. The second objective was to examine physical disability and routine calcium prescription to prevent bone loss. While there are various pharmacologic treatment options for bone loss that improve bone mass and reduce the risk of fracture, the effectiveness of these interventions is dependent on the proper use of calcium supplements as well. Recent research evidence indicates that typical postmenopausal women above 40 years of age have a calcium intake that is less than 50% of the advised amounts. Because of this, calcium supplementation is necessary for immobile women to prevent osteoporosis or bone loss. In the reviewed studies, the recommended prescription of calcium per day ranged from 1,000 to 1,500 mg/d. In sum, calcium supplementation can help prevent bone loss among women on DMPA and those with disabilities. Accordingly, routine prescription of prophylaxis treatment featuring calcium supplements should be encouraged to prevent bone loss among women, instead of carrying out only lab checks.

Keywords: Bone loss, Calcium, Disability, Immobility, Medroxyprogesterone, Osteoporosis, Women.

Introduction

Routine prescription of calcium in females receiving medroxyprogesterone to prevent bone loss

Out of 1.9 billion women of reproductive age (between 15 and 49 years) across the world in 2019, 1.1 billion needed family planning. Among the 1.1 billion, 842 million were using contraceptive methods. Some of the methods of oral contraception may include oral contraceptive pills, injectables, implants, intrauterine devices, vaginal rings, condoms, patches, sterilization, lactational amenorrhea, as well as withdrawal and approaches based on fertility awareness [1]. Among these options put together, hormonal contraceptives are the most popular and efficient method. In the United States, over 11 million women successfully use hormonal contraceptives [2].

In many cases, the use of oral hormone contraception is not linked with bone loss. For instance, a recent systematic review by [3] sought evidence of the relationship between steroidal contraceptives and bone loss among women. According to [3], concerns over potential fractures limits the use of hormonal contraceptives. While there were a few links with the risk of fractures, the systematic review provided evidence from observational studies proving no general link between the use of oral contraceptives and bone loss [3]. Specifically, one case-control study examined by [3] reported no link between hormone

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contraception and bone loss except for women who used these contraceptives for 10 or more years. However, a different case was noted among depot medroxyprogesterone acetate (DMPA) users. DMPA users were more likely to encounter an increased risk of fracture [3]. MPA has two major functions. The first is to treat endometriosis, while the second is as a contraceptive [2]. DMPA users often report an increased risk of fracture, even though oral hormone contraception is less associated with bone loss [2, 3]. DMPA is administered intramuscular or intravenously every three months. The contraceptive works by preventing the secretion of gonadotropin and suppressing ovulation and production of estrogen. The decrease in the production of estrogen causes DMPA to induce bone loss, thereby resulting in a decrease of 2-8% in bone mineral density (BMD) [2].

Fortunately, DMPA-induced bone loss can be treated. Within the first two years of treatment, bone loss reduces quickly before leveling [2]. Many studies provide evidence of this trend, with progress happening faster in the spine compared to the hip. For instance, [4] examined the effectiveness of different forms of treatment on Korean women with DMPA-induced bone loss. The randomized controlled trial enlisted postmenopausal females diagnosed with minimal bone mineral density. The study participants received hormone therapy alone or together with alendronate for a period of 1 year. The authors examined the changes in the BMD and the biochemical markers of bone turnover among the study participants. The findings showed a significant increase in bone mineral density at the lumbar spine and the total hip after a treatment period of 1 year. The increase at the lumbar spine was much more significant in the two treatments used compared to the changes reported at the total hip [4]. These results are consistent with previous research reporting an equivalent bone mineral density response after a treatment period of one year using a combination or hormonal therapy only.

A number of studies have also shown an insignificant increase in fracture risk associated with DMPA. In [5], the authors evaluated the link between women's use of hormonal contraceptives and the risk of fractures, more so DMPA. The participants in the study were females aged between 20 and 44 years diagnosed with fractures. After controlling for smoking, body mass index, and other possible confounders, the authors noted that the possibility of fractures was highly probably after a longer treatment duration of more than 2 to 3 years. There was no variation in the probability of fractures between participants below and those above 30 years old [5]. The study findings suggested that the use of DMPA was highly associated with an increased risk of fractures. In the same manner, [6] examined the effect of DMPA on the risk of fractures from a study sample drawn from the UK. The study sample consisted of women ranging between 20 and 44 years and experiencing a fracture for the first time. In general, 11% of the fracture cases, as well as 7.7% of the controls, reported the use of DMPA. The greatest risk of fracture was reported among two groups of patients. The first was among young participants below 30 years with a longer period of exposure to DMPA, while the second was among patients in their latter procreative years with previous use of DMPA [6]. These two studies indicate that exposure to DMPA is linked with an increased probability of fractures and can have a negative impact on bone metabolism.

Increased risk of traumatic fractures among women who chose DMPA has also been associated with their baseline characteristics [2, 7]. Some of these characteristics may include the use of alcohol, smoking, as well as patterns of exercise. These confounding characteristics are evident in a current retrospective study by [7]. The authors examined the use of DMPA contraception and the occurrence of bone fracture. Study participants were below 50 years old and the authors classified the DMPA users based on DMPA exposure using prescription records. The research included information on all the incident fractures, incidence rate of fractures, as well as the risk factors. The study findings revealed that DMPA users reported more fractures compared to nonusers [7]. However, this association was largely due to confounding factors. Some of the confounding factors identified by [7] included alcohol abuse or dependence, inflammatory bowel disease, drug abuse, asthma, epilepsy, oral corticosteroid therapy, baseline fall, smoking, estrogen replacement therapy, and pregnancy. Specifically, smoking and the consumption of excessive alcohol were largely linked with more cases of fractures [7]. More continuing research is required to completely tackle the role of baseline characteristics on DMPA exposure and the risk of fractures.

Most cross-sectional and longitudinal studies use dual-energy X-ray absorptiometry (DXA) technology to examine current users of DMPA. An example of this is evident in the study by [8] where the authors examined the predictive value of bone turnover markers among postmenopausal women diagnosed with bone loss. [8] determined the bone mineral density using DXA at baseline as well as at 12 months of treatment. However, the use of DXA to screen bone health among DMPA users is considered contentious [2]. In [8], it was clear that DXA used to measure bone mass had a precision error of between 1-2%. Because of this precision error, it is important to wait at least 1-2 years after the start of therapy before determining whether the treatment of DMPA users is effective [8]. The advice provided by various organizations including the American College of Obstetrics and Gynecology, the World Health Organization, and the Society for Adolescent Health and Medicine does not endorse regular DXA evaluation among premenopausal women using DMPA. Instead, DXA should only be used among adolescent females with a history of minimal amounts of trauma fracture and those with evident triggers of bone loss. Suitable guidelines for assessing bone mineral density among postmenopausal women can be drawn from the International Society for Clinical Densitometry (ISCD) and the International Osteoporosis Foundation (IOF). ISCD advocates the use of BMD Z scores instead of the T scores at the lumbar spine, hip as well as the forearm. A Z score less than or equal to -2.0 is interpreted as being below the anticipated range for age, while one that is greater than -2.0 is considered to

be within the expected range. Alternatively, the IOF promotes the use of Z score less than -2 to define low bone mass among children, adolescents, and those below 20 years [2]. Unlike the ISCD, the IOF promotes the use of T scores among women aged 20-50 years and delineates a T score of less than -2.5 to define osteoporosis, especially in women with identifiable secondary causes [2].

Existing treatment guidelines recommend checking vitamin D levels for all DMPA users and providing them with calcium and vitamin D supplements [2]. Past studies have examined the significance of providing calcium and vitamin D supplements to DMPA users. For instance, [9] examined the effects of transdermal hormone replacement therapy combined with calcium and vitamin D supplements administered daily to prevent bone loss. The authors randomized eighteen females to undergo two years of therapy. Each of the groups received supplementation with vitamin D and calcium 1 g every day. The study findings showed substantial increases in bone mineral density at the spine and the femoral neck among females undergoing hormone replacement therapy blended with calcium and vitamin D supplements [9]. Studies have also proposed the need to encourage exercise, putting a stop to smoking, and putting limitations on alcohol intake among all DMPA users. Additionally, low-dose estrogen replacement has also been found to be useful in limiting bone loss among premenopausal women on DMPA [2].

Immobilization and routine calcium prescription to prevent osteoporosis/ bone loss

The number of women with disabilities across the world keeps growing. In 2019, close to 36 million women in the U.S. were diagnosed with disabilities [10]. These women are highly susceptible to osteoporosis and related fractures. Women with disabilities are usually nonambulatory, and frequently take prescriptions that raise the chances of osteoporosis, such as medroxyprogesterone. Many studies have shown how immobility can contribute to immense bone loss. Immobility results in the failure of mechanical stresses on the bones. Studies of bone mineral density among women diagnosed with injuries on their spinal cord show quick bone losses of between 25 and 50% in the lower extremities within the initial years after the injury. These results often develop because of sudden immobility. The first is the increase in osteoclast bone resorption and the second is the slowing down of bone formation driven by osteoblasts. The result is a reduction in bone mineral density and the thinning of the cortical bone. In the end, such changes increase the danger of women developing fractures. In most cases, immobilization osteoporosis can be treated through therapeutic exercise, pharmacological treatments, and electrical therapy to invigorate the muscles. Surgical repair is usually very difficult to fulfill due to the severe vulnerability of the bones [11]. The bones are usually too permeable to the extent that surgical pinning can become unbearable.

Calcium has long been identified as a key nutrient for maintaining bone health. The prescription of calcium in a patient diagnosed with osteoporosis is, therefore, important for ideal care. Sadly, over 90% of women have inadequate levels of vitamin C. While there are various pharmacologic remedies for osteoporosis which improve bone mass and reduce the risk of fracture, the effectiveness of these interventions is dependent on the proper use of calcium as well as vitamin D. Calcium is an important component in the human body and facilitates a number of functions in the cell. It is a key element of bone architecture and is needed for the installation of bone mineral across life. The quantities of plasma calcium determine its balance in the body. A decrease in plasma levels results in an increase in bone resorption to reestablish the plasma levels. The most suitable way to attain the required dietary intake is by the consumption of foods high in calcium, such as dairy products and some green vegetables. However, women who do not obtain adequate amounts of calcium from food should consider taking supplements to meet these guidelines. Research evidence suggests that typical postmenopausal women above 40 years of age have a calcium intake that is less than half the recommended amount. Such outcomes highlight the significance of calcium supplementation in immobile women to prevent osteoporosis or bone loss. The two most popular and widely-explored calcium supplements are calcium citrate and calcium carbonate. Tests on these two supplements show that they absorb well when consumed with food [12].

The role of routine calcium prescription in the deterrence of osteoporosis or bone loss has been evaluated in many recent studies. [13] carried out a randomized clinical trial examining the efficacy as well as the safety of zoledronic acid combined with daily calcium and vitamin D in the treatment of osteoporosis. The study was carried out for a period of two years in the Pittsburgh Pennsylvania area. The authors enrolled the participants and treated them between 2007 and 2012. The study sample featured feeble women above 65 years old staying in a nursing home or an assisted living facility. The women were not receiving bisphosphonate at the time of the study and had a BMD less than -2.0, which was below the treatment cut off for osteoporosis. All the women received a divided dose of 1200 mg/d elemental calcium supplement together with 800 IU/day of vitamin D. The findings showed an increase in total hip BMD in the treatment group compared to the placebo group when measured at 12 and 24 months. The BMD of the spine also increased more in the treatment group compared to the placebo when measured at the same duration [13]. In essence, the study findings suggested that calcium supplementation could help prevent osteoporosis/ bone loss among immobile females.

The health benefits and risks of calcium supplementation in the prevention of bone loss have also been assessed in the existing literature. [14] carried out a clinical trial and cohort study using a sample of postmenopausal women in the U.S. The objective of

the trial was to examine if calcium supplementation together with vitamin D in a population that uses these supplements extensively would reduce hip fracture as well as a total fracture. The study participants received 1,000 mg of elemental calcium carbonate each day, together with 400 IU of vitamin D^3 or a placebo. The average period of the intervention was 7 years. The outcome of the study yielded few clear clinical effects of daily calcium supplementation in the prevention of bone loss. The strongest evidence for this benefit was reported on hip fracture where the supplementation of calcium together with vitamin D resulted in a substantial reduction after a period of 5 years of treatment. A larger BMD was evident in the intervention group in general, as well as among women not taking other personal supplements [14]. Medicines are important in the provision of medical care, and can aid in the treatment of various diseases if used efficiently. [15-22] These findings tend to suggest that the public health implications of supplementation can be substantial.

Conclusion

Bone loss is referred to as a "silent disease" since most of the women at risk are never aware of it. There are usually never any symptoms until a person has a bone fracture. Such breakage, frequently occurring in the hip or the spine areas can cause significant pain as well as proctored or permanent disability. Many factors contribute to the increased likelihood of bone loss among women. A key observation from the review is that there is an insignificant increase in fracture risk associated with DMPA, a medication used in the treatment of endometriosis and as a contraceptive agent. DMPA causes a decrease in the production of estrogen, which eventually induces bone loss and causes a decrease in bone mineral density. In the same way, bone loss can occur as a result of immobility resulting from disability. In most cases, women are subjected to regular lab checks to determine whether they have osteoporosis, low bone mass, and an increased risk of experiencing bone loss. However, this review seeks to encourage the routine prescription of calcium in any treatment procedure to prevent osteoporosis/ bone loss. Calcium is a major component in maintaining bone health, and its prescription among patients with bone loss is critical for optimal care. From the reviewed studies, it was evident that calcium supplementation could help prevent bone loss among women on DMPA and those with disabilities. Hence, the routine prescription of prophylaxis treatment with calcium supplements should be encouraged to prevent bone loss rather than carrying out only lab checks.

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References

1. World Health Organization, Family planning/Contraception Methods, Who.int, 06-2020. [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/family-planning-contraception. [Accessed: 21-Aug-2020].
2. Panday K, Gona A, Humphrey MB. Medication-induced osteoporosis: screening and treatment strategies. Therapeutic advances in musculoskeletal disease. 2014 Oct;6(5):185-202.
3. Lopez LM, Chen M, Mullins S, Curtis KM, Helmerhorst FM. Steroidal contraceptives and bone fractures in women: evidence from observational studies. Cochrane Database of Systematic Reviews. 2012(8).
4. Yoon BK, Lee DY, Park MC, Cho SH, Park HM, Choi YM. Effects of combination therapy of alendronate and hormonal therapy on bone mineral density in postmenopausal korean women: multicenter, randomized controlled clinical trial. Journal of Korean Medical Science. 2017 Jun 1;32(6):992-8.
5. Meier C, Brauchli YB, Jick SS, Kraenzlin ME, Meier CR. Use of depot medroxyprogesterone acetate and fracture risk. The Journal of Clinical Endocrinology & Metabolism. 2010 Nov 1;95(11):4909-16.
6. Kyvernitakis I, Kostev K, Nassour T, Thomasius F, Hadji P. The impact of depot medroxyprogesterone acetate on fracture risk: a case-control study from the UK. Osteoporosis International. 2017 Jan 1;28(1):291-7.
7. Lanza LL, McQuay LJ, Rothman KJ, Bone HG, Kaunitz AM, Harel Z, Ataher Q, Ross D, Arena PL, Wolter KD. Use of depot medroxyprogesterone acetate contraception and incidence of bone fracture. Obstetrics & Gynecology. 2013 Mar 1;121(3):593-600.
8. Kim SW, Park DJ, Park KS, Kim SY, Cho BY, Lee HK, Shin CS. Early changes in biochemical markers of bone turnover predict bone mineral density response to antiresorptive therapy in Korean postmenopausal women with osteoporosis. Endocrine journal. 2005;52(6):667-74.
9. Ormarsdóttir S, Mallmin H, Naessén T, Petrén-Mallmin M, Broome U, Hultcrantz R, Lööf L. An open, randomized, controlled study of transdermal hormone replacement therapy on the rate of bone loss in primary biliary cirrhosis. Journal of internal medicine. 2004 Jul;256(1):63-9.
10. Centers for Disease Control and Prevention, Disability and Health Information for Women with Disabilities, Centers for Disease Control and Prevention, 28-Oct-2019. [Online]. Available: https://www.cdc.gov/ncbddd/disabilityandhealth/women.html. [Accessed: 21-Aug-2020].
11. Schrager S. Osteoporosis in women with disabilities. Journal of women's health. 2004 May 1;13(4):431-7.

12. Sunyecz JA. The use of calcium and vitamin D in the management of osteoporosis. Therapeutics and clinical risk management. 2008 Aug;4(4):827.
13. S. L. Greenspan, S. Perera, M. A. Ferchak, D. A. Nace, and N. M. Resnick, "Efficacy and Safety of Single-Dose Zoledronic Acid for Osteoporosis in Frail Elderly Women," JAMA Internal Medicine, vol. 175, no. 6, p. 913, Jun. 2015.
14. Prentice RL, Pettinger MB, Jackson RD, Wactawski-Wende J, Lacroix AZ, Anderson GL, Chlebowski RT, Manson JE, Van Horn L, Vitolins MZ, Datta M. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. Osteoporosis International. 2013 Feb 1;24(2):567-80.
15. Alshammari E, Alshammari A. Clofarabine-based regimen as useful bridge therapy for stem cell transplantation in refractory or relapsed pediatric leukemia. International Journal of Research in Pharmaceutical Sciences. 2020; 11(2): 2303-2307
16. Alshammari E, Alshammari A. Glucosamine effects on lipids and blood pressure. International Journal of Research in Pharmaceutical Sciences. 2020; 11(1): 431-436.
17. Alshammari E. Levetiracetam and memory loss. International Journal of Research in Pharmaceutical Sciences. 2019; 10(2), 1249-1253.
18. Alshammari E. Irrational prescribing habit of omeprazole. International Journal of Pharmaceutical Quality Assurance. 2019; 10(4): 578-582.
19. Alshammari E. Prescription evaluation practice by final year pharmacy students. J. Adv. Pharm. Edu. Res. 2019; 9(3): 76-79.
20. Alshammari E. Recent updates published about favipiravir in COVID-19. International Journal of Research in Pharmaceutical Sciences. 2020; 11(SPL1): 192-197.
21. Alshammari E, Alshammari A. Review of topiramate effect on weight loss. International Journal of Research in Pharmaceutical Sciences. 2020; 11(1), 507-510.
22. Alshammari E. Role of clinical pharmacist in dose adjustment of renally eliminated drugs in cardiac patients with renal impairment. Int. Res. J. Pharm., 2019; 10(1):70-74.