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SHORT COMMUNICATION

Efficiency of Estrogen Replacement Therapy in Osteoporosis

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ABSTRACT

Estrogen therapy has been taken as a settled approach for both prevention and treatment of osteoporosis, especially in post-menopausal women as well as for the treatment of symptoms associated with menopause. Recent studies suggest that nuclear factor kappa-B ligand/receptor activator of nuclear factor kappa-B/osteoprotegerin system plays a significant role in osteoclastic activity regulation, with receptor activator of nuclear factor kappa-B ligand signaling in the presence of macrophage colony stimulating factor leading to increase in osteoclastic differentiation and functioning while osteoprotegerin neutralizing receptor activator of nuclear factor kappa-B ligand. Estrogen acts by increasing osteoprotegerin levels, and decreasing macrophage colony stimulating factor and receptor activator of nuclear factor kappa-B, thereby reducing bone resorption. Furthermore, estrogen is also known to be causing increased calcium absorption. The use of estrogen therapy in patients of osteoporosis is also considered to be highly cost effective. On the negative side, studies have shown that oral estrogen therapy can lead to complications like cholelithiasis, thrombophlebitis and pulmonary embolism, the most detrimental being endometrial cancer. But studies have shown that it can be virtually eliminated with the addition of progesterone in the cyclic combined regimen. Majority of beneficial effects occur with long term use of estrogen therapy, but the compliance by most of women appears to be poor. Additional studies should therefore be conducted to evaluate in detail the causes of non-compliance and strategies to improve compliance. The benefit of quality of life improvement with estrogen therapy should be taken into account and further evaluated via studies.

MAIN BODY

Osteoporosis is defined as a skeletal disruption with decreased bone mineral density (BMD), ideally recorded by dual-energy X-ray absorptiometry (DXA) as 2.5 standard deviation (SD) below the mean BMD reference (1). Due to its prevalence globally, osteoporosis is considered as a serious public health concern and currently it is estimated that greater than 200 million people world-wide bear the disease (2). However, the prevalence of osteoporosis is differed by race, gender, ethnicity and it rises with age (3). It can be further branched out as primary or secondary osteoporosis. Primary osteoporosis can occur in both men and women at any age, though particularly affecting postmenopausal women, elderly men and in children with conditions such as Juvenile Idiopathic Osteoporosis and Osteogenesis Imperfecta (1, 4). Secondary osteoporosis can be due to numerous causes including drug therapy (glucocorticoids), endocrine disorders, hematological diseases, gastrointestinal disorders, nutritional insufficiencies, alcohol intake and organ transplant (1, 4, 5). As a result of compromised bone strength, patients of osteoporosis are prone to fractures, and the risk grows with age (1). Studies have shown increased incidence of vertebral, hip, and wrist fractures in these patients (6), consequently affecting the quality of life (1). Furthermore, patients with osteoporosis are reported to have psychological impacts, including depression and anxiety (1, 7). Overall osteoporosis with its widespread results not only affects the individual, but also the family and ultimately the community. Early diagnosis of bone loss and fracture risk are important because of the availability of therapies that can prevent or reverse the progression of osteoporosis (1).

Diverse treatment options have been considered for osteoporosis and numerous studies have shown evidence based conclusion on various modalities. The modalities commonly used for the treatment of osteoporosis include exercise, calcium, vitamin D, bisphosphonates (4), selective estrogen receptor modulators (SERMS) and estrogen replacement therapy (1, 8, 9). Estrogen therapy has been taken as a settled approach for both prevention and treatment of osteoporosis, especially in post-menopausal women (1, 8-10) as well as for the treatment of symptoms associated with menopause (9, 11). The mechanism of action of estrogen is unknown, consisting

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of several theories. Early studies on estrogen have shown that it is known to act on pro inflammatory factors (that increase bone resorption) by down regulating them. Recent studies suggest that nuclear factor kappa-B ligand (NF-KappaB Ligand)/receptor activator of nuclear factor kappa-B (RANK)/ osteoprotegerin (OPG) system plays a significant role in osteoclastic activity regulation, with RANKL signaling in the presence of Macrophage Colony Stimulating Factor (MCSF) leading to increase in osteoclastic differentiation and functioning while OPG neutralizing receptor activator of nuclear factor kappa-B ligand (RANKL). Estrogen acts by increasing OPG levels, and decreasing MCSF and RANK, thereby reducing bone resorption (9, 12). Furthermore, estrogen is also known to be affecting calcium regulation at gut and kidney, leading to increased calcium absorption (9). Studies have shown that estrogen causes a decrease in the levels of urinary calcium, hydroxyprolene, causes calcitonin stimulation and affects parathyroid hormone (PTH) (10). However, more data is required to evaluate the more definitive mechanism of estrogen action.

The route of administration of estrogen can be oral as well as transdermal, both associated with increased bone density (10, 12). Estrogen replacement therapy as different oral regimens, transdermal patches as well as suppositories have a key role in the prevention of osteoporosis by slowing down the bone loss phase. Studies have shown that those patients who had bilateral oophorectomy, if were started on estrogen replacement therapy within 6 weeks, showed total halt of bone loss. Those who were given the therapy a few years after oophorectomy also showed signs of improvement, though the effects were less striking as compared to early treatment (starting within six weeks of the onset of menopause) (10, 13). Along with the rise in bone density, estrogen via its effect on collagen also has favorable effects on intervertebral disc as well as bone matrix. This effect is superior to bisphosphonates as they don't carry this effect (14). In addition to a decrease in bone loss and increase in bone density, there is strong evidence which shows that estrogen therapy decreases the overall incidence of osteoporosis-related fractures (10, 15). The results of epidemiological and observational studies are now supported by clinical randomized trials which shows that oral combinations of HRT is associated with a 30% reduction in vertebral and non-vertebral fractures (15, 16). A meta-analysis also revealed 27% incidence of non-vertebral fractures in patients undergoing hormone replacement therapy (HRT) therapy (15, 17). Women's health initiative (WHI) randomized control trial (15, 18) revealed that hip and clinical vertebral fracture were reduced by 34% and total osteoporotic fractures by 24%. Another study supports that estrogen is very effective in the prevention of wrist and hip fractures in older women (19). Studies have also shown the importance of estrogen's role in the development and maintenance of male skeleton as well. Hence, estrogen therapy can be considered as a beneficial treatment option for osteoporosis in men (20). Added advantages of estrogen replacement therapy includes reduction of vasomotor symptoms, mood disturbance, pelvic atrophy, lability, the risk of Alzheimer's disease and improving quality of life (14, 21). Estrogen replacement therapy is also known to minimize the risk of cardiovascular diseases (21). Estrogen therapy (oral form) helps to reduce levels of low density lipoprotein (LDL) and increase levels of high density lipoprotein (HDL), thereby decreasing the risk of myocardial infarction as well (22). Additionally, the use of estrogen therapy in patients of osteoporosis is also considered to be highly cost effective (21, 23).

On the negative side, studies have shown that oral estrogen therapy can lead to hepatic production of estrogen dependent proteins and bile changes that can cause complications like cholelithiasis, thrombophlebitis and pulmonary embolism. However, these complications can be prevented by administering transdermal estrogen (22). There is a known risk of abnormal uterine bleeding, endometrial hyperplasia and endometrial carcinoma with estrogen therapy (21, 22, 24). Addition of progestin to the regimen can protect against these side effects (21, 24, 25). Additionally, there is a mild risk for breast cancer but this appears to be controversial and more related to the progestogen component of hormone replacement therapy than estrogen. (14, 21). A review on the effect of progestin and progesterone in development of breast cancer however suggests that the increased risk is due to the use of synthetic progestin and continuous combined regimen and hence the risk can be avoided by using progesterone (and not synthetic progestin) in sequential or cyclic combined regimen (25). In this way the net effect is decrease in endometrial hyperplasia and cancer risk without the increase in the risk of breast cancer. Hypertension is also found to be associated with oral estrogen use, but the change in form, administration route and dose can help alleviate this side effect (21). In addition, there is some risk of thrombosis as well with oral estrogen but studies have shown that the risk only increased in those who have a positive family history for thrombosis or had a thrombotic event earlier in life. In such individuals, non-oral forms (transdermal patch/suppositories) are preferable (21). A study demonstrates that transdermal estrogen as compared to oral estrogen, does not decrease anti-thrombin III, low levels of which are considered to be associated with the development of thrombosis (26).

Conclusively, estrogen therapy has a major role in the management and prevention of osteoporosis in post-menopausal women. Based on the data evaluated, it has efficiency in the reducing fractures in post-menopausal osteoporosis as well as osteoporosis in men (15, 20). Overall, the side effects attributed to the estrogen therapy can be reduced with changes in the dose regimens (low/ultra-low) and nature of preparation (oral/transdermal). The most detrimental being endometrial cancer, but studies have shown that it can be virtually eliminated with the addition of progesterone in the cyclic combined regimen (21, 24, 25). Majority of beneficial effects occur with long term use of estrogen therapy, however poor compliance has been reported as a major hindrance in achieving the desirable effects of this therapy (21, 27). The common reasons for non-compliance include lack of awareness about risks and benefits, misconceptions, advice of physician and phobia of side effects (27, 28). Additional studies should therefore be conducted to evaluate in detail

the causes of non -compliance with therapy so as to help determine strategies for improving compliance. The potential risk of estrogen replacement therapy must be weighed against the lifetime risks of developing cardiovascular diseases (CVD), stroke, and bone fractures. The overall reduction in mortality and morbidity rates with estrogen use is generally viewed to be substantial and cost-effective. The benefit of quality of life improvement with estrogen therapy should be taken into account in decision making and should be further evaluated via studies. Lastly, the health care professionals have an important role in shaping their patient's attitudes and both the health care providers and patients must be fully informed and aware about the benefits and risks of estrogen therapy to make a better and beneficial decision.

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AUTHER CONTRIBUTIONS

This article was prepared in collaboration between all authors. Authors Syed Mohammad Mazhar Uddin and Aatera Haq did conception and design, acquisition of data, analysis and interpretation of data. Authors Haris sheikh, Uzair Yaqoob and Bushra zafar sayeed drafted the article and did critical revision. Author Uzair Yaqoob gave final approval of the version to be published. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

None.

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