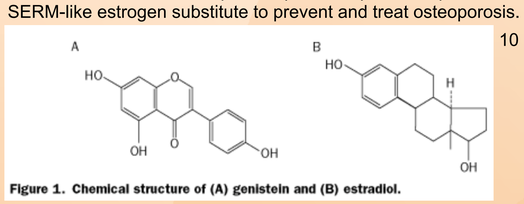
Genistein Aglycone in the Prevention and Treatment of Osteoporosis in Peri- and Postmenopausal Women

Katharine Tjaden, PA-S
The University of Findlay

University of Findlay

INTRODUCTION

The phytoestrogen genistein aglycone (GA) is one of the most researched phytoestrogens. Phytoestrogens like GA behave similarly to selective estrogen receptor modulators (SERMs).[1] SERMs are medications that act on estrogen receptors that selectively inhibit or stimulate different tissues. Hormone replacement therapy (HRT) non-selectively activates estrogen receptors. SERMs, bisphosphonates, and HRT increase bone mineral density (BMD).[2] HRTs or SERMs with bisphosphonates work together and increase BMD more than either alone.[3] HRTs increase risk of cancer and cardiovascular events. Traditional SERMs increase the risk for cardiovascular events.[4] GA could be used as an alternative monotherapy in peri- and postmenopausal women who cannot tolerate the side-effects of bisphosphonates or in a potential combination therapy with a bisphosphonate. Having an effective, safer alternative to traditional HRT and current SERMs would provide peri- and postmenopausal women a SERM-like estrogen substitute to prevent and treat osteoporosis.



10

Figure 1. Chemical structure of (A) genistein and (B) estradiol.

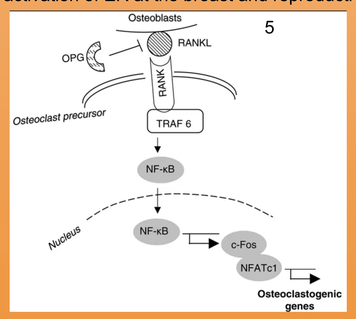
Methods

Google Scholar, Semantic Scholar, and Pubmed were used as databases for searching articles. The phrases “Genistein aglycone” AND “Osteoporosis”, “Hormone replacement therapy”, “Genistein aglycone” AND “Postmenopausal”, “Genistein aglycone” AND “Perimenopause”, “Genistein aglycone” AND “Cancer”, “Genistein aglycone” AND “Cardiovascular disease”, “Genistein aglycone” AND “thyroid”, “Genistein aglycone” AND “Pharmacokinetics”. Inclusion criteria were papers written in English and focusing on humans was preferred over animal research. Exclusion criteria included studies focused exclusively on males, whole soy products, other phytoestrogens, and conflicts of interest.

Mechanism of Action

Genistein aglycone stops bone destruction and also increases new bone formation. Genistein aglycone increases osteoprotegerin (OPG), which is produced by osteoblasts and binds to receptor activator of NF-κB ligand (RANKL).This downregulates the action of osteoclasts. GA also increases the presence of ALP, indicating the upregulation of osteoblastic activity and differentiation.[5,6]

Genistein has a higher affinity for ER-β than ER-α. Mature osteoblasts can express both, but ER-β is more widespread. Mature osteoclasts express only ER-β.[7] Breast, endometrium, and ovarian stroma express ER-α at a much higher rate than ER-β, allowing for targeted activation of ER for bone remineralization with minimal activation of ER at the breast and reproductive organs.[8]



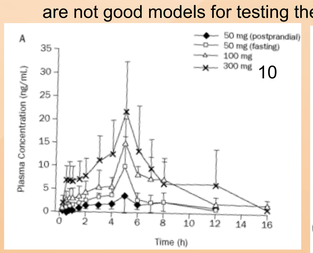
5

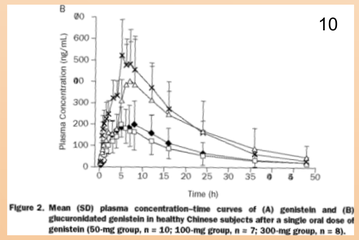
Results

Pharmacokinetics: The pharmacokinetics of GA are nonlinear at high doses; doubling of the dose orally does not result in a doubling of serum concentration of GA. Maximum serum concentration of total GA regardless of dose occurs at an average of 5 hours for men and women.[9, 10]

Oral administration of GA is viable due to the high absorption rate in the intestines. However, the liver also rapidly sequesters and metabolizes the GA. The slow release of GA from the liver combined with the nonlinear pharmacokinetics of saturable absorption in the intestines suggests taking multiple smaller doses daily rather than one large or moderately sized dose for maximum steady state concentration.[11]

The pharmacokinetics of GA in men and women are nearly identical. However, male and female rats vary considerably in metabolism to each other and to humans. Male and female mice are similar to each other in regards to the pharmacokinetics of metabolism of GA, however their rate of metabolism is slower than humans.[12] This means that rats and mice are not good models for testing the effects of GA.



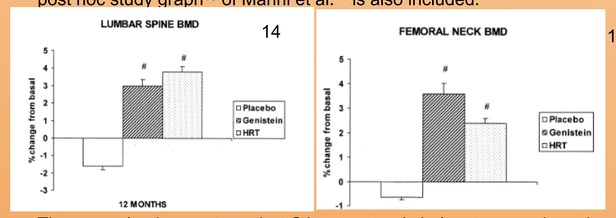


10

Figure 2. Mean (SD) plasma concentration–time curves of (A) genistein and (B) glucuronidated genistein in healthy Chinese subjects after a single oral dose of genistein (50-mg group, n = 10; 100-mg group, n = 7; 300-mg group, n = 8).

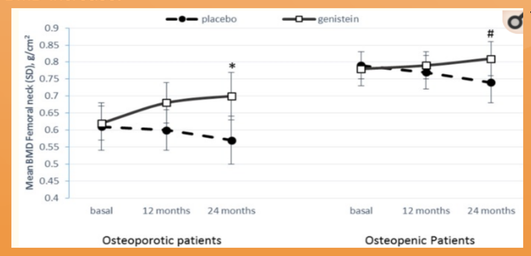
Effectiveness in increasing and preserving BMD: Aglycones are more readily absorbed in the intestines than glycosides, but glycosides are more common in soy than the aglycone form.[6] The meta analysis by Lambert et al.[13] discusses how many commercially available isoflavone supplements do not contain their stated concentrations, and many of the studies evaluating their effectiveness did not independently verify their purity. Studies investigating isoflavone supplementation in regards to their effect on BMD with verification of purity showed moderate effectiveness on BMD.[13]

Marini et al. [14] and Morabito et al.[15] were included as quality studies in the Lambert et al.[13] meta analysis due to verifying their purity. Below are graphs representing their effects on peri- and postmenopausal women. A post hoc study graph[16] of Marini et al.[14] is also included.



14

These results demonstrate that GA can not only halt osteoporosis and osteopenia, but reverse them. The increase in BMD was greater in the osteoporotic women, possibly due to a greater loss of estrogen leading to greater BMD loss. Genistein was also competitive with HRT in overall BMD increase.



16

Results Cont.

Safety:

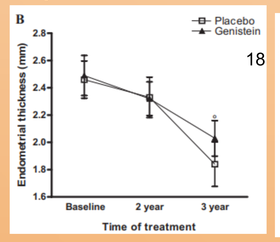
Breast Cancer: Breast cancer (BC) proliferates with the presence of estrogen. ER-α upregulates the gene expression that proliferates BC cells. ER-β upregulates gene expression that limits the proliferation of BC cells. ER-β is usually missing or severely reduced on the surface of BC cells. Low concentrations of GA in vitro when ER-β is present down regulate the proliferation of BC cells.[17] GA used at therapeutic levels for treatment of osteoporosis will not lead to proliferation of BC cells.

Ovarian Cancer: GA down regulates miR-27a, which is a gene involved in regulating some cancers. This helps prevent the growth and spread of ovarian cancer. The cell signaling molecule vascular endothelial growth factor and its receptor are down regulated, inhibiting angiogenesis. At high levels, GA causes apoptosis among ovarian cancer cells. At low levels, GA displays anti-oxidant properties without causing apoptosis.[17] This generally indicates that genistein is safe for use in women with intact ovaries.

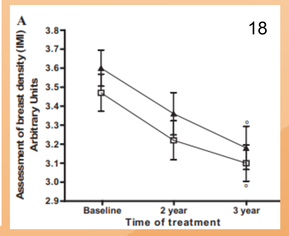
Uterine Cancer: Postmenopausal women experienced no appreciable change in uterine thickness.[18,] GA used at therapeutic levels for treatment of osteoporosis will not lead to endometrial hyperplasia or endometrial cancer in women with a uterus.

Cardiovascular disease: GA raised HDL levels significantly. However, LDL, triglycerides, and cholesterol were not lowered in a statistically significant way when compared to the placebo in the general population of postmenopausal women. Homocysteine levels were also reduced in postmenopausal women taking GA compared to the placebo.[19] These findings indicate that GA will not increase the risk of CVD in postmenopausal women.

Thyroid Health: GA has goitrogenic qualities and can negatively affect thyroid hormone levels in vitro. However, postmenopausal women receiving therapeutic levels of GA had no change in thyroid hormones. Isoflavones consumed at dietary levels in individuals with adequate iodine levels will not lead to thyroid dysfunction.[20]



18



18

DISCUSSION

GA has potential for treatment and prevention of osteoporosis in peri- and postmenopausal women. Much of the research that exists uses various animal models, has not verified the purity of the GA supplements, and has small sample sizes. These factors are also present in the studies evaluating safety. Excessively high dosing, not following the group long enough for proper evaluation, or not investigating the effects of GA in survivors of certain cancers creates opportunities for research.

Research that administered doses within the biphasic model of GA and followed groups for an extended period of time demonstrate a good overall safety profile. Further studies investigating the effectiveness and safety of GA in the treatment and prevention of osteoporosis in peri- and postmenopausal women at this time need to focus on the parameters mentioned here. Administering bisphosphonates with GA could help improve bone strength and increase BMD more than either agent alone. GA could be used as an alternative monotherapy for those who cannot tolerate more traditional medications.

CONCLUSIONS

Genistein aglycone is promising in the future treatment and prevention of osteoporosis in peri- and postmenopausal women in combination with bisphosphonates or as an alternative monotherapy. GA demonstrates effectiveness in increasing BMD in high quality studies using GA with independent verification of purity. The safety profile of GA as a hormonal treatment with the current data is better than standard HRT or SERMS while having SERM-like qualities for increasing BMD. More, higher quality research is needed at this time before a clinical recommendation can be made. However, the available data suggests successful future clinical use of GA pending further research.

REFERENCES

1. Chan KKL, Siu MKY, Jiang Y-X, Wang J-J, Leung THY, Ngan HYS. Estrogen receptor modulators genistein, daidzein and ERB-041 inhibit cell migration, invasion, proliferation and sphere formation via modulation of FAK and PI3K/AKT signaling in ovarian cancer. *Cancer Cell Int.* 2018;18(1)
2. Qaseem A, Forciea MA, McLean RM, Denberg TD. Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update From the American College of Physicians. Ann Intern Med. 2017;166(11):818-839.
3. Pinkerton JV, Dalkin AC. Combination therapy for treatment of osteoporosis: A review. Am J Obstet Gynecol. 2007;197(6):559-565.
4. Das S, Crockett JC. Osteoporosis - a current view of pharmacological prevention and treatment. Drug Des Devel Ther. 2013;7:435-48
5. Boyce BF, Xing L. Biology of RANK, RANKL, and osteoprotegerin. Arthritis Res Ther. 2007;9(Suppl 1).
6. Viereck V, Gründker C, Blaschke S, Siggelkow H, Emons G, Hofbauer LC. Phytoestrogen genistein stimulates the production of osteoprotegerin by human trabecular osteoblasts. J Cell Biochem. 2002;84(4):725-735.
7. Braidman IP, Hainey L, Batra G, Selby PL, Saunders PT, Hoyland JA. Localization of Estrogen Receptor β Protein Expression in Adult Human Bone. J Bone Miner Res. 2001;16(2):214-220.
8. Lee J-Y, Kim HS, Song Y-S. Genistein as a Potential Anticancer Agent against Ovarian Cancer. Journal of Traditional and Complementary Medicine. 2012;2(2):96-104.
9. Setchell KD, Faughnan MS, Avades T, et al. Comparing the pharmacokinetics of daidzein and genistein with the use of 13C-labeled tracers in premenopausal women. Am J Clin Nutr. 2003;77(2):411-419.
10. Zeng X, Feng Y, Yang L, et al. Single- and multiple-dose pharmacokinetics of genistein capsules in healthy chinese subjects: A phase I, randomized, open-label study. Curr Ther Res. 2008;69(4):318-333.
11. Yang Z, Zhu W, Gao S, et al. Simultaneous determination of genistein and its four phase II metabolites in blood by a sensitive and robust UPLC-MS/MS method: Application to an oral bioavailability study of genistein in mice. J Pharm Biomed Anal. 2010;53(1):81–89.
12. Soukup ST, Helppi J, Müller DR, et al. Erratum to: Phase II metabolism of the soy isoflavones genistein and daidzein in humans, rats and mice: a cross-species and sex comparison. Archives of Toxicology. 2016;90(6):1349-1349.
13. Lambert MN, Hu LI, Jeppesen PB; A systematic review and meta-analysis of the effects of isoflavone formulations against estrogen-deficient bone resorption in peri- and postmenopausal women, Am J Clin Nutr. 2017; 106(3): 801–811.
14. Marini H, Minutoli L, Polito F, et al. Effects of the Phytoestrogen Genistein on Bone Metabolism in Osteopenic Postmenopausal Women. Ann Intern Med. 2007;146(12):839.
15. Morabito, N., Crisafulli, A., Vergara, C., et al. Effects of Genistein and Hormone-Replacement Therapy on Bone Loss in Early Postmenopausal Women: A Randomized Double-Blind Placebo-Controlled Study. J Bone Miner Res. 2009; 17: 1904-1912.
16. Arcoraci V, Atteritano M, Squadrito F, et al. Antiosteoporotic Activity of Genistein Aglycone in Postmenopausal Women: Evidence from a Post-Hoc Analysis of a Multicenter Randomized Controlled Trial. Nutrients. 2017;9(2):179.
17. Russo M, Russo G, Daglia M, et al. Understanding genistein in cancer: The "good" and the "bad" effects: A Review. Food Chemistry. September 2015:589-600.
18. Marini H, Bitto A, Altavilla D, et al. Breast Safety and Efficacy of Genistein Aglycone for Postmenopausal Bone Loss: A Follow-Up Study. J Clin Endocrinol Metab. December 2008:4787-4796.
19. Li J, Liu Y, Wang T, Zhao L, Feng W. Does genistein lower plasma lipids and homocysteine levels in postmenopausal women? A meta-analysis. Climacteric. 2016;19(5):440-447.
20. Marini H, Polito F, Adamo EB, Bitto A, Squadrito F, Benvenga S. Update on genistein and thyroid: an overall message of safety. Front Endocrinol (Lausanne). 2012;3:94. Published 2012 Jul 31.

Great thanks to Professors Sharon Gentry, PA-C and Abigail Allen, PA-C for providing guidance on this paper and to the Graduate Writing Center of the University of Findlay.