Study the Influence of Captopril on Bone Metabolism in Elderly Hypertensive Women

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Abstract

Widespread use of antihypertensive agents in clinical practice necessitates the knowledge of their pleiotropic effects. At the present time there are no sufficient evidences of positive effect of these medications on bone coming from randomized controlled trials; knowledge of additional effects of those drugs on the bone metabolism will allow doctors to choose optimal treatment of hypertension, taking into account the state of bone tissue. At the same time it will also allow to prevent osteoporosis in patients having osteoporosis risk factors or initial signs of bone loss.

Ten elderly hypertensive women age > 60 years old (64.2±3.6) treated with captopril for a 5-6 years ago while they attending Al Yarmouk Teaching Hospital in Baghdad; in addition, newly-diagnosed hypertensives, and normotensive of the aged-matched women were participated in this study that were conducted during the period (January- May 2014). Measurement of serum calcium, magnesium, inorganic phosphorus, total alkaline phosphatase activity, and parathyroid hormone were done, in addition to spine mineral density and t-score of such bone density by dual energy x-ray absorptiometry. The results of this study showed that there were no significant differences in the serum levels of calcium, magnesium, inorganic phosphorus, total alkaline phosphatase activity, and parathyroid hormone in postmenopausal hypertensive women treated for 5-6 years with captopril compared to newly-diagnosed and to aged-matched normotensive women. In addition, non-significant differences were observed in the level of bone mineral density and t score of bone mineral density in all groups of the study. In conclusion, the present study provides additional knowledge concerning the influence of captopril treatment on some selected parameters of bone metabolism in elderly hypertensive women.

Keywords: Captopril, Bone metabolism, Elderly women, Hypertension, Dual energy x-ray absorptiometry.

دراسة تأثيرعقار الكابتوبريل على استقلاب العظم في النساء الكبيرات في السن واللاتي يعانين من ارتفاع ضغط الدم

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الخلاصة

الاستخدام السريري الواسع للادوية الخافضة لضغط الدم يتطلب معرفة التأثيرات الاخرى الغير متعارف عليها. في الوقت الحاضر ليس هناك دلائل واضحة حول التأثيرات الأيجابية لتلك الأدوية على العظم كما ان المعرفة الاضافية لتأثيراتها على استقلاب العظم تسمح للاطباء باختيار افضل دواء لعلاج ارتفاع ضغط الدم مع الاخذ بنظر الاعتبار حالة النسيج العظمي. وفي نفس الوقت يمنع ذلك تخلخل العظام في المرضى الذين لديهم عوامل خطورة تسبب تخلخل العظم أو لديهم أعراض أولية من خسارة العظم لذلك صممت هذه الدراسة لاستقصاء تأثيرالكابتوبريل على استقلاب العظم في النساء اللواتي يعانين من ارتفاع ضغط الدم، ولأضافة اراء الى تلك التي تمت من قبل باحثين بهذا الخصوص. تم مشاركة عشر نساء اعمارهن أكثر من ٦٠ سنة ويعانين من ارتفاع ضغط الدم عولجن من قبل أطباء أختصاص بعقار الكابتوبريل لمدة ٥-٦ سنوات خلال زيارتهن لمستشفى اليرموك التعليمي في بغداد، بالاضافة الى عشر نساء لديهن ارتفاع في ضغط الدم شخصن حديثا، وعشر نساء لديهن ضغط دم طبيعي وبنفس العمر. تم قياس معدلات الكالسيوم، المغنيسيوم، الفوسفور اللاعضوي، فعالية انزيم ال Alkaline phosphatase وهرمون الباراثايروويد في مصل الدم لكل النساء المشاركات في الدراسة، كما تم قياس كثافة معادن العمود الفقري و t-score باستخدام الجهاز الممتص للاشعة السينية.

أظهرت نتائج الدراسة بان ليس هناك اختلافات معنوية في معدلات الكالسيوم، المغنيسيوم، الفوسفور اللاعضوي، فعالية انزيم الـ Alkaline phosphatase وهرمون الباراثايروويد لدى النساء في سن اليأس اللاتي يستخدمن الكابتوبريل لمدة ٥-٦ سنوات لعلاج ارتفاع ضغط الدم بالمقارنة مع اللواتي لديهن ارتفاع في ضغط الدم تم تشخيصه حديثا عند زيارتهن الى المستشفى والنساء

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اللاتي لديهن ضغط دم طبيعي وبنفس العمر. بالاضافة الى ذلك، ليس هناك اختلافات معنوية في معدل كثافة معادن العظم و في t-score لكثافة معادن العظم في النساء اللاتي يعانين من ارتفاع ضغط الدم ويستخدمن الدواء بالمقارنة مع معدلاته في النساء اللاتي لديهن ارتفاع في ضغط الدم عند زيارتهن الى المستشفى، والنساء اللاتي لديهن ضغط دم طبيعي.

وفقا للنتائج التي تم الحصول عليها يمكن الاستنتاج بأن هذه الدراسة اضافت معرفة حول تأثير عقار الكابتوبريل على معدلات المعايير التي اختيرت في الدراسة والخاصة باستقلاب العظم في النساء المسنات اللاتي لديهن ارتفاع في ضغط الدم.

الكلمات المفتاحية: عقار الكابتوبريل ،استقلاب العظم ،النساء الكبيرات في السن ، ارتفاع ضغط الدم ، الجهاز الممتص للأشعة السينية .

Introduction

Hypertension and osteoporosis are two major age-related disorders that together account for significant morbidity and mortality in the elderly. As 50% of the hypertensive population comprises postmenopausal women at high risk of osteoporosis, hypertension represents a considerable health problem in this population. Several studies suggested that high blood pressure is associated with abnormalities of calcium metabolism, leading to an increase in calcium movement from bone, thereby increasing the risk of osteoporosis [1-3] while, others did not show such association [4-6].

It has been also demonstrated that bone metabolism is closely regulated by hormones and cytokines, which have effects on both bone resorption and deposition. Because the vasculature plays an important role in bone remodeling, the effect of the renin angiotensin system on bone metabolism may be partially related to the regulation of blood flow. Although, the receptors for angiotensin II is expressed in osteoblasts and osteoclasts but, the effects of such peptide hormone are controversial; however, several investigators indicated that angiotensin II is a potent stimulator of osteoclastic bone resorption; on the contrary, others showed that angiotensin II stimulated the proliferation of osteoblast - rich populations of cells [7-8].

In vivo study demonstrated that captopril may improve osteopenia in ovariectomised rats and may promote bone formation in osteoblasts [9]. Conflicting data were demonstrated by several clinical studies concerning the influence of angiotensin converting enzyme inhibitors and abnormalities of bone metabolism [10-11].

Thus, this study was designed to investigate the influence of captopril on bone metabolism in elderly hypertensive women; and to add suggestions to that performed by other researchers concerning this respect.

Women, Materials and Methods

Ten hypertensive women on captopril therapy (daily dose range 12.5-100mg; Midochemie LTD, Limassol-Cyprus), treated by specialist physicians while attending Al Yarmouk Teaching Hospital in Baghdad (Group C); ten newly-diagnosed hypertensives (Group B); and ten apparently healthy (Group A) were participated in this study. The study was approved by the Scientific Committee of the College of Pharmacy-Baghdad University; in addition, an ethical sheet was obtained and approved by the Ministry of Health, Baghdad-Iraq. Verbal consent was obtained from each woman participated in this study. The inclusion and exclusion criteria of all women in this study are summarized in table 1, and their demographic data are showed in table 2.

Table (1) : Inclusion and exclusion criteria of women enrolled in this study

Inclusion criteria	Exclusion criteria	
- Over sixty years old normotensive women. - Over sixty years old patients' women with hypertension.	Disease	Rheumatoid disease Diabetic mellitus Cardiovascular diseases Hepatic and renal dysfunctions Smoking
	Drugs, and supplements	Thyroxin Corticosteroids Estrogen and its derivative Bisphosphonates Nutritional supplements Diuretics

Table (2): Groups of women who participated in the present study

Group	Number of women	Age	Systolic/Diastolic blood pressures mm Hg	Body mass index (BMI)
Group A	10	66.4±4.6	130/86±3.1[a]	28.3±4.4[a]
Group B	10	66.1±5.8 NS	140/95±2.9 [b]	32.0±5.1[b]
Group C	10	64.2±3.6 NS	130/85±3.8 [a]	33.2±5.2[b]

- **Group A**: normotensive elderly control women; **Group B**: elderly women newly diagnosed with hypertension; **Group C:** elderly hypertensive women treated with therapeutic dose of captopril [Midochemie LTD, Limassol-Cyprus; (dosage range 12.5-100mg)].
- Values of age, systolic/diastolic blood pressures, and body mass index (BMI) are presented as mean ±standard error of mean.
- Values with non-identical superscripts (a, and b) are considered significant.
- NS: non-significant difference compared to normotensive controls (Group A).

The body mass index (BMI) was calculated using the following formula:
BMI = weight (in kilogram)/height^2 (in meter) [(12)]; while systolic/diastolic blood pressures were measured utilizing sphygmomanometer and stethoscope [(13).]

Blood sampled were collected from each women participated in the study for laboratory analysis to measure serum calcium (Ca^{++}) (Roche/Hitachi, Germany) [(14)] magnesium (Mg^{++}) (Roche/Hitachi, Germany) [(15)], inorganic phosphorus (Pi) (Roche/Hitachi, Germany) [(16)], alkaline phosphatase (ALP) (Roche/Hitachi, Germany) [17], and parathyroid hormone (PTH) (Roche/Hitachi, Germany) [18] by utilizing kits for this purpose. Besides, all women were examined by x-ray to measure spine mineral density utilizing dual X-ray absorptiometry (DEXA) [(19)], and (t) score of such bone mineral density [(20)].

Statistical Analysis

Analysis of data was carried out using the Statistical Packages for Social Sciences-version 22 (SPSS-22). The significance of difference among groups of women concerning their age, weight, height and mean arterial blood pressure was tested using Pearson Chi-square test (χ^2test) with application of Yate's correction or Fisher Exact test whenever applicable. Besides, the significance of difference of different means was tested using Student-t-test for difference between two independent means. Statistical significance was considered whenever the P value was equal or less than 0.05 in all data presented in this study.

Results

Hypertensive elderly women treated with therapeutic doses of captopril, for 5-6 years showed non-significant differences (P>0.05) in the levels of serum calcium, magnesium, and inorganic phosphorus compared to normotensive elderly controls and to newly-diagnosed hypertensive women of the aged-matched as shown in table 3.

Table (3): Influence of captopril on serum calcium, magnesium, and inorganic phosphorus compared to normotensive elderly controls, and to newly-diagnosed elderly women.

Group	Serum Calcium mg/dl	Serum Magnesium mg/dl	Serum Inorganic Phosphorus mg/dl
Group A	9.00±1.05	2.13±0.11	3.01±0.63
Group B	8.96±0.95	2.11±0.24	3.59±0.78
Group C	8.62±0.84	2.24±0.19	3.46±0.54

Group A: normotensive elderly control women; **Group B**: elderly women newly diagnosed with hypertension; **Group C:** elderly hypertensive women treated for 5-6 years with therapeutic dose of captopril.
- Values are presented as mean± standard error of mean.
- Number of women in each group is 10.

The data presented in table 4 showed non-significant differences (P>0.05) in the serum activity of ALP , and the level of serum PTH levels in elderly hypertensive women treated for 5-6 years with captopril compared to the corresponding levels in newly-diagnosed and to normotensive control women.

Table (4): Influences of captopril on serum alkaline phosphatase (ALP) activity and serum parathyroid hormone compared to normotensive elderly controls, and to newly-diagnosed elderly women.

Group	Alkaline phosphatase(U/L)	Parathyroid Hormone pg/ml
Group A	90.00±34.55	44.24±16.89
Group B	90.50±23.11	54.77±43.74
Group C	71.82±20.49	47.34±15.56

Group A: normotensive elderly control women; Group B: elderly women newly diagnosed with hypertension; Group C: elderly hypertensive women treated for 5-6 years with therapeutic dose of captopril.
- Values are presented as mean± standard error of mean.
- Number of women in each group is 10.

The data presented in table 5 showed non-significant (P>0.05) differences in the levels of spine mineral density, and (t) score in elderly hypertensive women treated for 5-6 years with therapeutic dose of captopril compared to those levels in normotensive elderly controls and to newly-diagnosed hypertensive of the aged-matched women.

Table(5): Influence of captopril on spine, and (t) score of such bone mineral density (BMD).

Group	Spine Mineral Density (mg. cm $^{-2}$)	Spine Mineral Density (t) Score
Group A	777.60±113.52	2.74±0.92
Group B	803.40±153.37	2.41±0.95
Group C	841.90±169.65	2.44±1.34

Group A: normotensive elderly control women; Group B: elderly women newly diagnosed with hypertension; Group C**:** elderly hypertensive women treated for 5-6 years with therapeutic dose of captopril.
- Values are presented as mean± standard error of mean.
- Number of women in each group is 10.

Discussion

It has been reported that Ang II may influence calcium metabolism by decreasing ionized calcium and increasing the PTH level [(21)].

Conflicting results were obtained concerning the effects of angiotensin converting enzyme inhibitors on bone metabolism; where, patients with risk of fractures who have used angiotensin converting enzyme inhibitor (ACEI), no significant difference in BMD were recorded [(22)]; while other study reported that patients treated with an ACEI showed an increased BMD and more importantly reduced fracture risks [(10,11)]. However, ACEIs also regulate the bradykinin-nitric oxide (NO) pathway as well as block Ang II production, different from angiotensin receptor blockers (ARBs). It was well known that the NO pathway regulates local blood flow in bone marrow capillaries, which might enhance bone marrow formation. Thus , the contribution of the NO pathway might have a role in the prevention of osteoporosis by ACE inhibition [(23)].

An *in vitro* study performed by Liu *et al* in 2011demonstrated that captopril had potential effects of improving lumbar vertebral bone strength in aged ovariectomised (OVX) rats and promoted osteoblast bone formation [(9)]. Moreover, the same study showed that the administration of an ACE inhibitor, enalapril, did not cause significant changes in bone density, mineral content or morphometric parameters of the femur in 14-week-old ovariectomised female Wistar rats.

Captopril acts by inhibiting the conversion of angiotensin I to Ang II; thus inhibits the synthesis and secretion of aldosterone and

reduces blood pressure. The drug also reduces the bradykinin degradation thus, inhibiting the generation of prostaglandins that were considered as local factors that may stimulate bone resorption [24].

It has been demonstrated that in vasculature, estrogen antagonized Ang II signaling and Ang II induced atherosclerosis, which suggest that OVX might accelerate Ang II-induced signaling. Of importance, several reports suggest that estrogen may enhance the ACE inhibition-mediated improvement of vascular remodeling in hypertension in female {(spontaneously hypertensive rats (SHR)} with OVX through the inhibition of extracellular signal-regulated kinase 1/2. It supports the impact of a cross talk between estrogen and Ang II signaling in SHRs females [25,26].

Concerning magnesium (Mg), the result of the present study revealed that no significant differences in the level of serum Mg were observed in all elderly women groups participated in this study.

Such electrolyte works in concert with calcium to regulate electrical impulses in the cells; also it is largely responsible for the bone health and strong teeth. Without *adequate* amounts of the Mg, calcium will not be deposited in these hard tissues, where, Mg has the ability to activate thyrocalcitonin, a hormone that under normal circumstances would send calcium to bones. Furthermore, many authors demonstrated that there was a functional link between Mg and calciotropic hormones such as parathyroid hormone (PTH) and 1, 25$(OH)_2$ vitamin D_3 that all responsible for the regulation of calcium homeostasis [27,28].

Regarding inorganic phosphorus, the intended element is present in every cell of the body, and 85% of the body's phosphorus is found in bones and teeth. Thus, it is vital to the formation of bones and teeth, and healthy bones and soft tissues require calcium and phosphorus to grow and develop throughout life [29]. The tight controlled balance of calcium and phosphorus is maintained by hormonal control of transport in the intestine, bone, and kidney; where, the latter organ acts by modulating calcium and phosphate reabsorption from the glomerular filtrate according to the body needs that is mediated by ion transporters. In addition to the classical endocrine factors (such as PTH and vitamin D) that are involved in maintaining calcium and phosphate balance, other factors have been identified viz, fibroblast growth factor-23 (FGF23), which regulates urinary phosphate excretion by interacting with FGF receptors; and Klotho, a transmembrane protein, facilitates this interaction, with the result of reducing phosphate reabsorption by the kidney. Furthermore, dental matrix protein-1, an osteocyte product, has been shown to participate in FGF23-mediated regulation of phosphorus homeostasis [30] .

Furthermore, the impacts of ACEIs have been studied in stable ischemic heart disease; in such study, the intended group of drugs showed a beneficial effect on FGF-23 regardless of renal function [31].

The effects of captopril utilized in the present study on serum inorganic phosphorus (Pi) were non-significantly different among all elderly women participated in this work which could be attributed to the above regulatory processes. Thus, further works are needed to emphasize the findings of the investigators.

The present study provides additional knowledge concerning the influence of captopril treatment on some selected parameters of bone metabolism in postmenopausal hypertensive women.

Conclusion

According to the results obtained from this study, one can conclude that, there were no significant differences in the serum levels of electrolytes (calcium, magnesium, and inorganic phosphorus); parathyroid hormone,; alkaline phosphatase activity, in addition to bone mineral density in hypertensive elderly women treated with therapeutic doses of captopril, for 5-6 years compared to normotensive elderly controls and to newly-diagnosed hypertensive women of the aged-matched.

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