Indapamine effects on hypercalciuria and bone mineral density

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Abstract

Idiopathic hypercalciuria is associated to urinary stone formation and bone loss and should be treated not only to prevent kidney stone formation but also to prevent fragility fractures. Thiazide diuretics are traditionally used to control hypercalciuria. Indapamine, a sulfonamide thiazide diuretic, with some differences in structure is similar in its mechanisms of action such as its hypocalciuric effect, and bone density protection, with less adverse metabolic consequences than thiazides such as less hypokalemia and hypotension. We evaluated efficacy and adverse effects of Indapamine in 88 idiopathic hypercalciuric consecutive patients and those who reached normal calciuria in the first 9 months, were followed during two years. Changes in bone turn-over markers and bone density were evaluated. Since year one, there was a significant lowering of urine calcium to normal values in 77 patients, with no change in sodium excretion. There were changes in bone turn over markers and gains in bone mineral density according to the groups analyzed. In 25 hypercalciuric osteoporotic patients, there was a significant increment in lumbar spine bone density at year 2 of follow-up, ($p<0.05$). Those hypercalciuric osteoporotic stone former patients had a significant increase in femoral neck bone density since year one. Adverse effects were not significant, no changes found in blood pressure, glycaemia, cholesterol, serum uric acid, sodium and potassium. Two patients needed potassium supplementation for mild hypokalemia and did not stop Indapamine. In conclusion Indapamine is an effective alternative treatment to Idiopathic hypercalciuria, controlling calcium loss and bone density for at least two years.

Introduction

Idiopathic hypercalciuria (IH) is associated to urinary stone formation and bone loss. Our group defines Idiopathic hypercalciuria, as urinary calcium more than 220 mg/day in women and more than 300 mg/day in men or more than 4 mg/Kg [1].

Hypercalciuria should be treated not only to prevent kidney stone formation with its urinary tract complications but also to prevent fragility fractures [2,3,4].

Thiazide diuretics are traditionally used to control hypercalciuria by their known mechanisms of action inducing mild volume depletion, leading to a compensatory rise in the proximal reabsorption of sodium and calcium, and directly increasing calcium reabsorption in the distal tubule. Thiazide diuretics, which inhibit sodium-chloride cotransporter (NCC) in the distal convoluted tubule, are considered as the treatment of choice for idiopathic hypercalciuria due to their hypocalciuric effect [5].

Hye Ryoun et al. have suggested that calcium channel receptor TRPV5 has been directly implicated in the thiazide induced distal calcium reapsorption [6].

It is also well known that thiazides are related to adverse effects such us hypokalemia, fatigue, hypotension and metabolic disadvantages in cholesterol, uric acid and glycemic control, insulin resistance, hypomagnesemia and as a consequence of hypokalemia, reduced urine citrate excretion leading to increase in stone risk formation.

Indapamine, a sulfonamide thiazide diuretic, with some differences in structure is similar in its mechanisms of action such as its hypocalciuric effect, and bone mineral density protection, with less adverse consequences than thiazides such as less hypokalemia [7,8,9,10].

Although mostly used to treat blood hypertension it is becoming useful in the hypercalciuric patients as an alternative to prevent new renal stone events and bone loss.

The aim of our study was to evaluate efficacy and adverse effects of indapamine after one and two years of treatment in idiopathic hypercalciuric patients and changes in their bone mineral density.

Materials And Methods

This is a longitudinal study evaluating indamine fixed dose effects in urine calcium, bone mineral density, bone turn-over markers and adverse events. Idiopathic hypercalciuric consecutive patients, consulting our Metabolic Institution from 2008 to 2020 were included. Idiopathic hypercalciuria was defined as an excretion of urine calcium more than 220mg/day in women and 300mg/day in men. We included 88 hypercalciuric patients most of them women as our Institution is a referring center for bone metabolic diseases such as postmenopausal osteoporosis. To be included they had two samples with hyperalciuria in 24hs with their usual diet and a third sample with hypercalciuria measured after 4 day controlled diet containing per day total sodium 120 mmol, potassium 100 mmol, calcium 800–1000 mg and protein 1 g/kg.

Some patients had history of renal stone formation, defined as a stone spontaneously passed by urinary tract or surgically removed or confirmed by X-Ray, ultrasound scan or computed tomography. Other patients had osteoporosis defined in bone mineral density as a T score ≤-2.5 in lumbar spine (LS), femoral neck (FN) or total hip (TH).

Fasting morning venous blood samples were obtained before breakfast and analyzed for creatinine, calcium, phosphorus, 25 OH vitamin D (25 OHD), total alkaline phosphatase (ALP), bone-specific alkaline phosphatase (BAP),osteocalcin (bone GLA protein BGP), serum β crosslaps (CTX), glucose, total cholesterol, uric acid, and serum potassium. Three 24-hour urine samples were obtained from each patient to measure calcium, sodium and creatinine.

Methods

Serum and urine calcium were measured by ion-selective electrode (ISE) method using a Synchron CX3 automated analyzer (Beckman, Beckman Instruments Inc. Brea, California. USA). Normal values for total serum calcium: 8.8-10.5 mg/dl, urinary calcium: < 220 mg/ 24 h in women and <300mg/24h in men. Both blood and urine sodium and potassium were measured with automated analyzer CX3, normal values: serum sodium: 136 – 145 mEq/L, serum potassium: 3.5 – 5.1 mEq/L, urine sodium up to 150 mE/L and urine potassium 25-125 mEq/L. Creatinine (Jaffe kinetic method) and phosphate (UV) were measured using CCX Spectrum automated analyzer (Abbott Labs. USA). Normal values for serum

creatinine: 0.6 – 1.1 mg/dl, and for phosphate: 2.7 - 4.5 mg/dl. Uric acid was analyzed by the uricase method, normal value: 2.5 – 6 mg/dl. Total alkaline phosphatase and its bone isoenzime (Kinetic method, normal value: 90-280 UI/L and 20-48% respectively). Serum β crosslaps (CTX): Electrochemoluminescence, normal value: 556 ± 226 pg/ml. 25 OH vitamin D Radioinmunoanalysis, normal value: 20-40 ng/ml. Osteocalcine (BGP): Electrocheoiluminescence, normal value for women: 11-4 ng/ml, men:14-42 ng/ml.

Bone mineral density (BMD) was assessed by Dual energy X-ray absorptiometry (DXA) using Lunar Prodigy densitometer (Lunar Corporation, General Electric, Madison, WI, USA) measured at the lumbar spine (LS), femoral neck ((FN) and total hip (TH). Bone densitometry was performed at baseline and during two year follow-up under Indapamide treatment, year 1 (Y1) and year 2 (Y2).

All patients were above 18 years of age, had confirmed idiopathic hypercalciuria with normal renal function (Cl Cre > 60 ml/min), parathyroid hormone (PTH) values and serum calcium were normal, and they were free from urinary tract infection. New stone formation or fracture events were not considered.

Exclusion criteria: We excluded patients under 18 years of age, patients with urine tract morphologic abnormalities and those taking drugs or suffering diseases that impair bone metabolism. Those who could not finish at least one year follow-up were also excluded.

All patients received IDP 1.5 mg/day slow release fixed dose. Vitamin D (ergocalciferol or cholecalciferol) was given weekly to correct insufficiency, and there were some osteoporotic patients receiving bisphosphonates.

All patients had blood pressure controls in each visit and were measured with their own medical doctors. Hypertension was present in 30% of the patients and received Losartan or Valsartan besides Indamine.

All the subjects signed an Informed Consent Form. The Informed consent form and the protocol were reviewed and approved by the Institutional Review Board of the Instituto de Diagnostico e Investigaciones Metabolicas

Statistical analysis

Mean and standard deviation were obtained. In all numeric statistical variables tests Kolmogorov-Smirnov or Shapiro Wilk were applied for normal values according to the sample size. Once null hypothesis was confirmed, we applied Factorial analysis of variance, ANOVA for parametric variables and Friedman test for non-parametric variables. We considered as significant change p value < 0.05.

Results

From the total group, (n = 88 patients), there were 11 patients (12.5%) who did not control hypercalciuria within the third and ninth month of evaluation and were prescribed with thiazides. Follow-up was assessed in 77 patients under Indapamine.

Table 1 shows the characteristics of the studied population. As mentioned before there is a prevalence of women in the study group, but the proportion of women are similar in those stone formers and those osteoporotic. Body mass index (BMI) is less than 30 in all patients.

Table 1
Population characteristics (n = 77)

Age (years)	**54 ± 11**
BMI (Weight/Height^2)	23,5 ± 4,6
Women (n/%)	71 (92,2)
Men (n/%)	6 (7,8)
Stone formers (n/%)	34 (44,1)
Osteoporosis (n/%)	33 (42,8)
Creat clear (ml/min)	87,5 ± 10,6
Creat clear: creatinine clearance	

Table 2 shows IDP results in the total group at year one and two of follow-up. There was a significant lowering of urine calcium with no change in sodium excretion during follow-up. There was also a decrease in ALP, BGP and CTX in both periods, year one and two.

Table 2
Total group (n = 77) follow-up parameters Year 1 (Y1) and Year 2 (Y2)

Parameters	Mean/SD Basal (n = 77)	Mean/SD Y1 (n = 77)	p	Mean/SD Y2 (n = 69)	p
Calcemia (mg/dl)	9,6 ± 3,2	9,7 ± 0,3	NS	9,7 ± 0,4	NS
Phosphatemia (mg/dl)	4 ± 1	3,6 ± 0,5	NS	3,5 ± 0,4	NS
PTH (pg/ml)	44,1 ± 13,3	42,8 ± 14,6	NS	43,1 ± 18,9	NS
25 OHD (ng/ml)	30 ± 9,4	44,6 ± 14,6*	NS	37,5 ± 18,9	NS
Urine calcium (mg/24hs)	283 ± 63	189 ± 87	< 0.000	182 ± 70	< 0.000
Natriuria (mEq/24hs)	137 ± 58	131 ± 45	NS	128 ± 48,5	NS
ALP (UI/L)	145 ± 61	127 ± 55	< 0.01	121,2 ± 54	< 0.01
bALP (%)	24,7 ± 16,5	21 ± 21,7	NS	17 ± 14,4	0.008
BGP (ng/mL)	24,2 ± 10,2	21,4 ± 12,2	< 0.05	19, 7,2	< 0.01
CTX (pg/mL)	479 ± 262	321 ± 165	< 0.01	322 ± 167	< 0.01
Glycemia (mg/dl)	92,5 ± 10,5	95,3 ± 15,8	NS	96,3 ± 12,9	NS
Uricemia (mg/dl)	4,3 ± 1,0	4,6 ± 1,2	NS	4,6 ± 1	NS
Total Cholesterol (mg/dl)	205 ± 29,5	210 ± 40	NS	214 ± 1	NS
DXA Lumbar Spine	0,960 ± 0,146	0,932 ± 0,126	NS	0,946 ± 0,117	NS
T score Lumbar Spine	-1,8 ± 1,1	-1,9 ± 1,1	NS	-1,97 ± 0,9	NS
DXA Femoral Neck	0,790 ± 0,130	0,770 ± 0,46	NS	0,786 ± 0,09	NS
T score Femoral Neck	-1,5 ± 0,8	-1,6 ± 0,8	NS	-1,6 ± 0,7	NS

ALP: alkaline phosphatase, bALP: bone alkaline phosphatase, BGP: osteocalcin bone gla protein, CTX: Beta Cross laps, 25OHD: 25 vitamin D, Y1: year one of follow–up, Y2: year two of follow–up. DXA: Dual X ray absorptiometry

Table 3 shows results of 34 idiopathic hypercalciuric stone former patients, 28 women (32.6 ± 10.5 years) and 6 men (46.8 ± 12.4 years). After one year 25 patients achieved normal urine calcium and 23 of them continued with normal urine calcium in the second year. This group differs from the total group as no significant changes were found in bone turn-over markers (ALP, BGP, bALP and CTX).

Table 3 Biochemical parameters in idiopathic hypercalciuric and stone former patients, year 1 and year 2 of follow-up

Parameters	Mean/SD basal, n = 34	Mean/SD Y1 (n = 25)	p	Mean/SD Y2 (n = 23)	p
Calcemia (mg/dl)	9,6 ± 0,3	9,6 ± 0,2	NS	9,6 ± 0,4	NS
Phosphatemia (mg/dl)	3,5 ± 0,6	3,5 ± 0,5	NS	3,4 ± 0,5	NS
PTH (pg/ml)	39 ± 9,9	39,7 ± 6,4	NS	43 ± 10,8	NS
25 OHD (ng/ml)	27,1 ± 8,5	28,7 ± 9,3	NS	32 ± 8,4	NS
Urine calcium (mg/24h)	299 ± 65	189 ± 70	< 0.001	168 ± 76	< 0.001
Natriuria (mEq/24h)	166 ± 50	145 ± 52	NS	133 ± 50	NS
ALP (UI/L)	129 ± 58	143 ± 55	NS	140 ± 61	NS
bALP (%)	26,4 ± 17,5	24,5 ± 14,8	NS	24,5 ± 16,4	NS
BGP (ng/mL)	24,2 ± 10,2	24 ± 8,6	NS	19,3 ± 5,2	NS
CTX (pg/mL)	479 ± 277	358 ± 178	NS	333 ± 159	NS
Glycemia (mg/dl)	90,6 ± 7,3	92,2 ± 8	NS	96 ± 9,7	NS
Uricemia (mg/dl)	4,4 ± 1,2	4,8 ± 1,5	NS	4,4 ± 1,1	NS
Total Cholesterol (mg/dl)	198 ± 25	206 ± 31	NS	197 ± 30	NS

ALP: alkaline phosphatase, bALP: bone alkaline phosphatase, BGP: osteocalcin bone gla protein, CTX: Beta Cross laps, 25OHD: 25 vitamin D, Y1: year one of follow−up, Y2: year two of follow−up

Table 4 shows results in IH and osteoporotic patients. There were 33 women (54.9 ± 9.9 years) and 1 man (46.8 years). Urine calcium is in normal range at year one and also at the second year with a small but significant reduction in ALP and CTX with no changes in BGP nor in bALP.

Table 4 Biochemical parameters in idiopathic hypercalciuric and osteporotic patients, year 1 and 2 of follow-up

Parameters	Mean/ SD basal n = 34	Mean/SD Y1 (n = 24)	p	Mean/SD Y2 (n = 19)	p
Calcemia (mg/dl)	9,5 ± 0,2	9,6 ± 0,2	NS	9,6 ± 0,2	NS
Phosphatemia (mg/dl)	3,8 ± 0,5	3,7 ± 0,7	NS	3,7 ± 0,4	NS
PTH (pg/ml)	44,4 ± 14,6	45,3 ± 15,3	NS	41,7 ± 23	NS
25 OHD (ng/ml)	29,8 ± 9,4	32,8 ± 12,9	NS	35,5 ± 10,3	NS
Urine calcium (mg/24h)	264 ± 65,1	180 ± 61	< 0.001	180 ± 74	< 0.001
Natriuria (mEq/24h)	114 ± 62	133 ± 36	NS	107 ± 43	NS
ALP (UI/L)	147 ± 46	129 ± 51	0.03	124 ± 43	0.03
bALP (%)	23,3 ± 14,2	15,1 ± 9,8	NS	15,1 ± 12,3	NS
BGP (ng/mL)	24,2 ± 9	22,7 ± 18	NS	17,4 ± 5,8	< 0.05
CTX (pg/mL)	426 ± 263	311 ± 181	< 0.05	297 ± 145	< 0.05
Glycemia (mg/dl)	90 ± 9,7	94 ± 6,8	NS	97 ± 11	NS
Uricemia (mg/dl)	4,3 ± 0,7	4,3 ± 0,7	NS	4,6 ± 1,3	NS
Total Cholesterol (mg/dl)	201 ± 36	215 ± 23	NS	220 ± 27	NS

ALP: alkaline phosphatase, bALP: bone alkaline phosphatase, BGP: osteocalcin bone gla protein, CTX: Beta Cross laps, 25OHD: 25 vitamin D, Y1: year one of follow–up, Y2: year two of follow–up

Patients with both conditions, stone forming and osteoporosis, (9 patients, 8 of them women, age 60,2 ± 7,2 years), achieved normal urine calcium and a reduction of bone turn-over markers, ALP, bALP and CTX both at year 1 and 2. (Table 5). No differences were seen in BGP.

Table 5 Biochemical parameters in IH patients with both conditions, stone-formers and osteoporotic patients, year 1 and 2 of follow-up

Parameters	Mean/SD basal	Mean/SD Y1 (n = 9)	p	Mean/SD Y2 (n = 8)	p
Calcemia (mg/dl)	9,37 ± 0,3	9,6 ± 0,5	NS	9,9 ± 0,2	NS
Phosphatemia (mg/dl)	3,9 ± 0,3	3,7 ± 0,4	NS	3,6 ± 0,4	NS
PTH (pg/ml)	55,1 ± 12,8	55,6 ± 12,7	NS	50,6 ± 13,4	NS
25 OHD (ng/ml)	25,8 ± 5,8	29 ± 12,5	NS	33 ± 7,4	NS
Urine calcium (mg/24h)	298 ± 54	167 ± 44	< 0.01	167 ± 42	< 0.01
Urine Sodium (mEq/24h)	127 ± 38	140 ± 40	NS	125 ± 40	NS
ALP (UI/L)	174 ± 72	136 ± 67	< 0.05	112 ± 61	< 0.05
bALP (%)	24,6 ± 16,5	17 ± 11	< 0.05	14,9 ± 11,5	< 0.05
BGP (ng/mL)	28,8 ± 13,1	19,4 ± 4,5	NS	18 ± 2,2	NS
CTX (pg/mL)	550 ± 304	303 ± 126	< 0.05	341 ± 66	< 0.05
Glycemia (mg/dl)	100 ± 2,8	98 ± 2,9	NS	95 ± 6	NS
Serum Uric Acid (mg/dl)	4,8 ± 1,6	5,5 ± 0 7	NS	5 ± 1,1	NS
Total Cholesterol (mg/dl)	192 ± 17	210 ± 22	NS	233 ± 27	NS

ALP: alkaline phosphatase, bALP: bone alkaline phosphatase, BGP: osteocalcin bone gla protein, CTX: Beta Cross laps, 25OHD: 25 vitamin D, Y1: year one of follow–up, Y2: year 2 of follow–up

Figure 1 shows results in BMD lumbar spine (DXA-LS) in IH and the three groups, IH-stone formers, IH-osteoporotic, IH-stone formers and osteoporotic. No significant changes in lumbar spine was found in stone formers (IH-SF), 15 women, (age: 47 ± 11years) and 5 men (age: 48 ± 10 years), and stone formers with osteoporosis (IH-SF-OS), 9 patients, (8 of them women, mean age: 60.2 ± 7.2 years). In IH with only osteoporosis (IH-OS), 24 women (age: 57.8 ± 7.5 years), there was a significant increment in lumbar spine bone mineral density at year 2 of follow-up, ($p<0.05$).

Figure 2 shows changes in BMD femoral neck (DXA-FN) in the three groups. No changes in stone formers, nor in osteoporotic groups. There was an increment in the group presenting both conditions that was significant in the first year and continued stable in year 2 of follow-up.

Many osteoporotic patients received bisphophonates that may account for changes in bone turn-over markers and BMD.

No significant changes in blood pressure nor hypotensive clinical events were reported.

No significant adverse events were seen. There were no changes in glycemia, serum uric acid and total cholesterol. Two patients needed potassium supplementation for serum potassium less than 3.5mEq/L,

but they did not stop the indapamine treatment.

Discussion

Two major concerns of idiopathic hipercalciuria are renal stone formation and its urinary tract complications as the third cause of renal pathology, as well as bone fragility [11-17].

Tannenbaum et al found 9.8% of IH in postmenopausal osteoporosis [18]. Our group found IH in 34.1% of 1000 patients with osteopenia or osteoporosis, (*not published*).

Idiopathic hypercalciuria is present in 40-60% of renal lithiasis [1,19,20] and is considered a risk factor for bone loss throughout life with fragility fractures increased risk [17,21,22]. Giannini and colleagues found that up to19% of postmenopausal women with osteoporosis, referred for the first time to their Metabolic Bone Diseases Unit, had hypercalciuria in their bone metabolic evaluation [23].

Thiazide diuretics and their analogs are commonly used for lowering calcium excretion in hypercalciuric, recurrent calcium stone formers [11]. Four randomized controlled trials (RCTs), which evaluated 408 patients over periods of 26 to 36 months, demonstrated significant reductions in recurrent kidney stones with thiazides and the thiazide analog, indapamide [12,13,14]. Thiazide administration along with dietary sodium restriction to maximize the hypocalciuric effect of thiazide is the treatment of choice in hypercalciuric, calcium stone-forming subjects. The incidence of thiazide diuretic adverse effects is about 30%, although adverse effects requiring discontinuation of the drug are rare [15]. Indapamine is a diuretic agent that was developed to be administered alone or combined for the treatment of hypertension [24,25] with similar effect as hydrochlorothiazide that has been reported in many studies to have 50% reduction in hypercalciuria even in patients followed for 3 years [7,26,27].

In our cohort of 88 IH patients we observed 12.5% non-responders that were prescribed other drug to control urine calcium. This lack of response percentage to indamine 1.5 mg fixed dose was also published by Martins et al. that found in a double blind randomized crossover protocol with indapamine 2.5 mg versus hydrochlorothiazide 50 mg a lack of response in the indapamine group of 16.6% after 3 months of treatment [28].

Significant reduction in hypercalciuria and no bone loss with few adverse events along 2 years under indamine 1.5mg/day, resulted in 77 patients participating in our study. We also observed a significant reduction in bone turn-over markers, (CTX, ALP, Bone ALP and BGP) different to Lalande et al. that reported that IDP, decreased bone resorption but increased bone formation without significant variation of PTH level in vivo, as assessed by bone histomorphometry [10].

Urine calcium in IH and stone forming patients was significantly reduced at first and second year of follow-up with no urine sodium changes nor bone turn-over markers changes in this group. Urine calcium had a 36.8% reduction at year one and 44% at year 2, similar to the 48% reported by Alonso et al in 12 IH

stone forming patients followed for 18 months. Kadir et al. [27] reported similar reductions, 43% and 50% in IH patients with and without stone formation respectively [8].

Urine calcium also decreased significantly in 34 IH and osteoporotic patients, 32% reduction at both year 1 and 2 with a small reduction in ALP and CTX.

In a small group of 9 IH patients with both conditions stone formation and osteoporosis, there was a 44% reduction in urine calcium at both years of follow-up.

Bone densitometry showed no changes in lumbar spine and femoral neck in IH stone formers during the two year follow-up while IH osteoporotic patients had a significant increase in lumbar spine at year 2 of follow-up. Those IH with both conditions had an increase in femoral neck since year 1 that stayed stable at year 2.

Our 77 patients showed a significant reduction in urine calcium in all IH groups.

Bone turn-over markers changed with reduction in CTX (resorption) and in ALP and BGP (formation) different as it was observed in the experimental study with spontaneously hypertensive rats supplemented with sodium [29].

These changes were present in all IH and osteoporotic patients with or without renal stones. No changes were present in IH and stone formers.

The lack of changes in bone density in IH and stone formers suggests that IDP keeps stable bone mass by correcting urine calcium and increasing calcium balance [30].

There was a significant increase in lumbar spine at year 2 follow-up in IH and osteoporotic patients with small but not significant increase in femoral neck. In IH with both conditions the increase was seen in femoral neck since year 1 with a tendency of increase not significant in lumbar spine at year 2, but this group included low number of patients to withdraw evidence.

Changes in bone turn-over markers and bone density could be influenced by bisphosphonates. Giusti et al have demonstrated that combination of IDP and alendronate in IH has a superior result in controlling urine calcium and increasing bone density than alendronate alone [31].

Adverse effects were not significant, no changes in blood pressure, glycaemia, cholesterol, serum uric acid, sodium and potassium were found. Only 2 patients needed potassium supplementation for mild hypokalemia and did not stop IDP.

The limitations of our study is that women are superior in number, bisphosphonates were not excluded, and new stone or fracture events were not registered. Future prospective studies are needed. The strength is to show the use of an alternative diuretic that controls in the majority of cases urine calcium with very few adverse events.

In conclusion fixed dose of Indamine is an effective alternative treatment to Idiopathic Hypercalciuria, controlling urine calcium loss and bone mineral density for at least two years. Association with bisphosphonates not only controls urine calcium but has a positive effect in bone mass. No significant adverse events were present and only 12.5% of patients were prescribed other thiazide to treat urine calcium loss.

Statements And Declarations

The authors have nothing to disclose, no conflicts of interests.

Acknowledgments

Not applicable.

Authors' contributions

Study concept and design: FRS

Acquisition of data: GS and PR

Results review and data analysis: FRS and PR.

Manuscript writing and review: FRS.

Manuscript style correction: PR.

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Figures

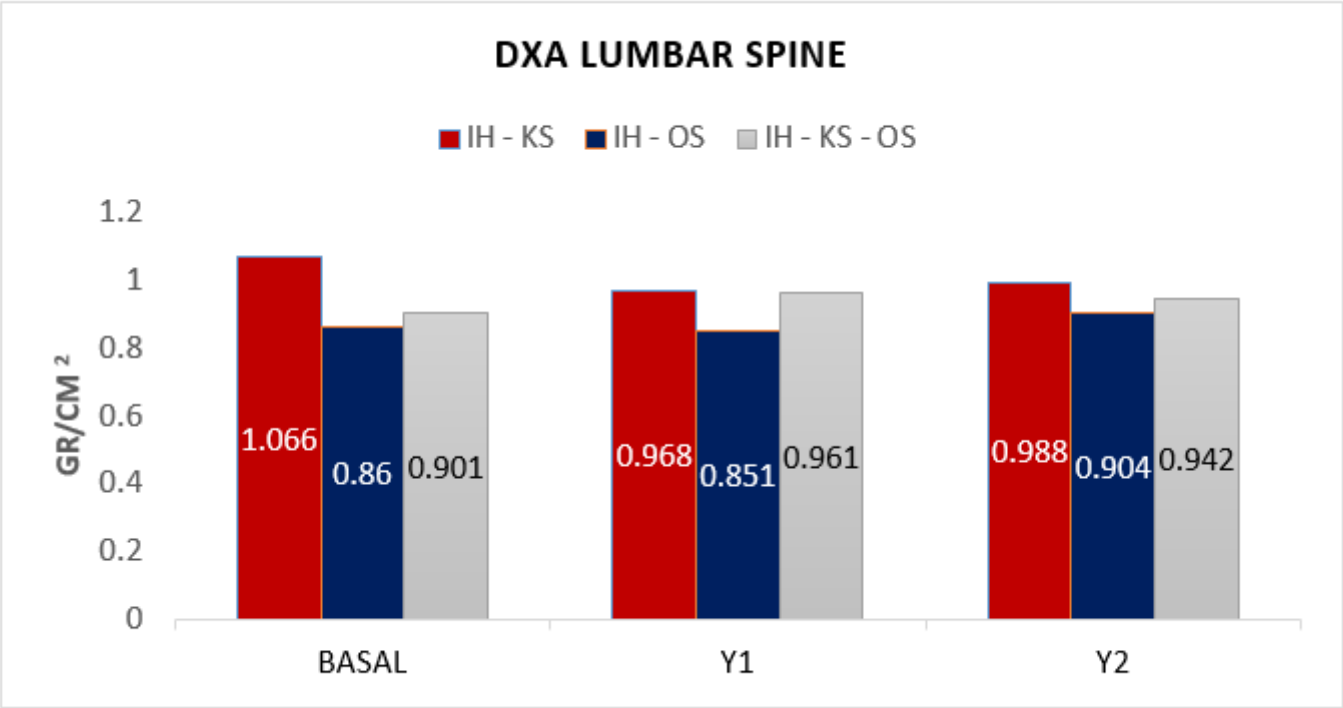

Figure 1

DXA lumbar spine in the three groups: baseline, year 1 and 2

DXA: Dual X Ray Absorptiometry (gr/cm2//Tscore). IH-KS: idiopatic hipercalciuric-stone formers, IH-OS: idiopatic hipercalciuric-osteoporotic patients, IH-KS-OS: idiopatic hipercalciuric with both conditions

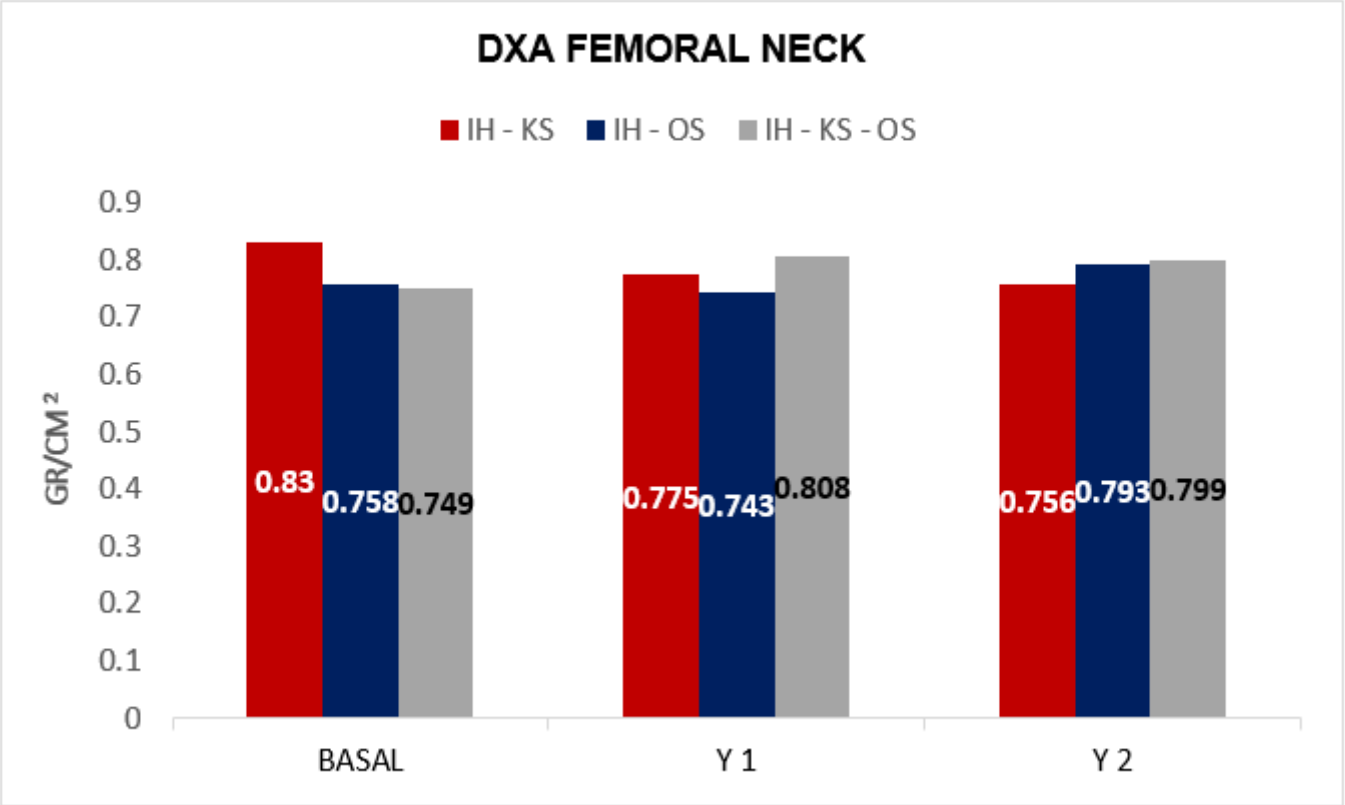

Figure 2

DXA femoral neck in the three groups: baseline, year 1 and 2

DXA: Dual X Ray Absorptiometry (gr/cm2//Tscore). IH-KS: idiopatic hipercalciuric-stone formers, IH-OS: idiopatic hipercalciuric-osteoporotic patients, IH-KS-OS: idiopatic hipercalciuric with both conditions