Effect of 1-α (OH)D3 on Steroid Induced Bone Loss in Frequently Relapsing Childhood Nephrotic Syndrome

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=Abstract=

Steroid induced bone loss is a serious problem in frequently relapsing nephrotic syndrome especially in growing children.

In order to evaluate whether 1- (OH) D3 (IL Sung Pharma.Co.) is effective in preventing steroid induced bone loss, we gave 0.5μg of 1- (OH)D3 for one year to forty patients with frequently relapsing nephrotic syndrome, receiving longterm prednisolone therapy (mean duration 50.12 ± 29.40 months). We checked the following markers before and after 1- (OH)D3 therapy. i.e. bone mineral density(BMD) using dual energy X-ray absorptiometry(DEXA) at the 2nd to 4th lumbar spine, serum calcium, phosphorus, parathyroid hormone(PTH), osteocalcin and urine pyridinoline(U-PYD). BMD(g/cm^2) was increased even steroid therapy from 0.71±0.0 to 0.73±0.0 ($p < 0.05$).

Lumbar spine BMD is a sensitive marker for evaluating steroid induced bone loss in children receiving longterm corticosteroid therapy and that 1- (OH)D3 appears to be effective in treating and preventing steroid induced bone loss.

Key words : 1-α(OH)D3, Steroid, Bone mineral density, Nephrotic syndrome

Introduction

Steroid induced osteoporosis(SIO) is one of the serious complications of longterm steroid therapy, especially in growing children.[14,15,19] The most vulnerable sites are the trabecular bones such as the vertebrae, ribs & hips.[1,5] Vitamin D preparations, calcitonin, and calcium have been used to treat or prevent corticosteroid induced bone loss, although their efficacy is unproved.[3,6,13,21] Combined therapy with calcium and calcitriol frequently cause hypercalciuria and hypercalcemia; however, 1- (OH)D3, which rapidly converted to 1,25-(OH)D3 and toxic effects is rapidly reversed on stopping treatment.[11] We studied the effects of 1- (OH)D3 on bone mineral density in frequently relapsing childhood minimal change nephrotic syndrome (MCNS) receiving longterm corticosteroid therapy and compared biochemical and endocrinological markers before and after treatment.

Patients and methods

Patients. We studied forty patients with childhood nephrotic syndrome receiving longterm prednisolone therapy. Most patients were frequent relapser or steroid dependent. The mean age of the patients was 9.5 ± 4.2 (years), and the male to female ratio was 7:1 (Table 1).

There was no history of bone, liver or endocrine diseases. All patients had a history of longterm corticosteroids therapy for a minimum of one year due to frequent relapsers with or without steroid dependency. The mean duration of therapy was 50 ± 29 (months). Of the forty patients, twenty two patients were compatible with the diagnostic criteria of international study of kidney diseases in children (ISKDC) and renal biopsy was not performed, however eighteen patients were taking renal biopsies. The following are the indications of renal biopsy: initial nonresponder to corticosteroid therapy associated with hematuria, azotemia, hypertension, and/or hepatitis viral markers, etc.: Two patients were diagnosed as focal segmental glomerulosclerosis, two were mesangial proliferative glomerulonephritis, and the rest of the patients were diagnosed as minimal change nephrotic syndrome(Table 1).

Table 1. Clinical and laboratory data of the patients with nephrotic syndrome at initial diagnosis.

Number (Male/Female)	40 (35/2)
Age(years)	9.5±4.2
Serum Protein/albumin(gm/dl)	4.3±0.8/1.9±0.7
Serum cholesterol(mg/dl)	460.2±131.3
Serum BUN/Creatinine(mg/dl)	11.9±5.8/0.5±0.3
Serum calcium(mg.dl)	7.1±1.0
Serum phosphorus(mg/dl)	5.4±1.3
24 hours urine protein(mg/hr/m^2)	341.6±285.9
Corrected CrCl(ml/min/1.73m^2)	139.0±61.4
Prednisolone therapy duration(months)	50.1±29.4

Methods. The baseline samples, which include serum calcium, serum phosphorus, serum parathyroid hormone, serum osteocalcin, urine pyridinoline, and bone mineral density(BMD), were obtained before the first dose of 1- (OH)D_3 (IL SUNG Pharma.Co, Korea) in forty patients with nephrotic syndrome. Follow-up studies were done after one year of 1- (OH)D_3 therapy. The dosage of 1- (OH)D_3 was 0.5μg/day. Calcium and phosphorus were measured by the automatic analyzer (Hitachi 736-30). PTH levels were measured by PTH-MM II ^{125}I radioimmunoassay(RIA) Kit for the C-terminal/mid region. Urine pyridinoline levels were measured by METRA Biosystems Pyrilinks Kit. Serum osteocalcin levels were measured by INCSTAR Osteocalcin ^{125}I RIA Kit. BMD was measured by DEXA (Lunar, U.S.A.) at the lumbar spine (L2-L4).

Statistical analysis. Data is expressed as mean plus or minus standard deviation Statistical analysis of the data was performed using the student t-test and Wilcoxon's rank sum test. A probability level of less than 0.05 was considered significant.

Results

The mean age at onset was 9.5±4.2 years and the mean duration of prednisolone therapy was 50±29 months. Of the forty patients, two patients were lost to follow up. The mean height before 1-α(OH)D_3 therapy was 133.8±20.9 (cm) and one year later 137.6±19.6 (cm). The mean body weight was increased from 38.6±16.0 (kg) to 41.8±15.8 (kg) during 1-α(OH)D_3 therapy. The changes of serum calcium and phosphorus level between pre-treatment and post-treatment level did not show statistical significance. The serum PTH level at baeline in the samples taken before 1-α(OH)D_3 therapy was 51.2 ±58.4(pmol/L) and after treatment was 43.4± 37.1(pmol/L). The serum osteocalcin(Bone Gla Protein, BGP) level which has been known as a useful marker of osteoblastic bone formation, which showed at baseline in the samples taken before 1-α(OH)D_3 therapy was 7.8 ±3.3(ng/ml) and after therapy was 9.4±5.1(ng/ml). The measurement of pyridinium crosslinks(pyridinoline & deoxy-pyridinoline) is a well known marker of osteoclastic activity, which showed 417.3±251.0(nmol/mmol Cr.) at baseline and 462.6±265.2(nmol/mmol Cr.) after treatment. However the changes of serum osteocalcin and urine pyridinoline levels were not significant statistically in our study. The lumbar bone mineral densities at baseline was 0.71±0.0 and increased to 0.73±0.0 ($P<0.05$) after treatment (Table 2).

Table 2. Biochemical and endocrinological markers before and after treatment with 1-α(OH)D_3 in forty patients with frequently relapsing nephrotic syndrome.

	Pre-treatment (Mean ± S.D.)	Post-treatment (Mean ± S.D.)	P value
Calcium(mg/dl)	9.1 ± 1.3	9.0 ± 0.1	NS
Phosphorus(mg/dl)	4.2 ± 1.1	4.1 ± 0.1	NS
PTH(pmol/L)	51.2 ± 58.4	43.4 ± 37.1	NS
Osteocalcin(ng/ml)	7.8 ± 3.3	9.4 ± 5.1	NS
U-PYD(nmol/mmol Cr.)	417.3 ± 251.0	462.6 ± 265.2	NS
BMD(g/cm^2)	0.71 ± 0.0	0.73 ± 0.0	P <0.05

NS, Not significant

Discussion

As yet corticosteroid is the mainstay therapy in childhood minimal change nephrotic syndrome, although some newer steroids such as cloprednol and deflazacort have been claimed to possess less inhibitory effect of bone as well as glucose metabolism. However the evidence that the use of steroids with different molecular structure might reduce steroid induced osteoporosis is unconvincing.[8,17,19] Several well known side-effects of steroid therapy include cushingoid feature, infection, hypertension, diabetes mellitus, growth failure etc. Next to growth failure osteoporosis is the most important side effect in growing children.[16,19] According to the definition by WHO, a measurement of 1.0 SD to 2.5 SD below the mean value indicates th presence of osteopenia, a measurement of more than 2.5 SD below the mean value indicates osteoporosis, and a measurement of more than 2.5 SD below the mean value in the presence of one or more fragility fractures is severe osteoporosis or established osteoporosis.[10] The pathogenesis of steroid induced osteoporosis(SIO) is still controversial, however suggestions are as follows : direct glucocorticoid suppression of osteoblastic bone forming activity,[4] increased osteoclastic bone resorbing activity caused by increased PTH,[20] reduced intestinal calcium absorption caused by decreased synthesis of the calcium binding protein,[7] increased renal loss of calcium[13], and reduction of insulin like growth factor I (IGF-I)[2] Steroid therapy leads to a loss of trabecular bone especially in the lumbar spine. The reduction in cortical bone is less pronounced. Bone dissolution is greatest during the initiation of steroid therapy and can result in the loss of up to twenty percent of trabecular bone in the first year. Vitamin D preparations, and calcium with or without calcitonin have been used to treat or prevent SIO in adults, although their efficacy is unproved.[3,6,13,21] In our study BMD was increased from $0.71 \pm 0.0(g/cm^2)$ to $0.73 \pm 0.0(g/cm^2)$ even steroid therapy($p < 0.05$). However, other markers such as serum osteocalcin and urine pyridinoline which is known as a sensitive marker for osteoblastic and osteoclastic activity,respectively in adults was not significant in our study, might be related to high bone remodelling rate in children.[14]

In conclusion, lumbar spine BMD is a simple, sensitive marker for detecting bone loss than any other markers which are known sensitive marker in adult. In addition 1-α(OH)$_3$ appears to be effective in treating and preventing steroid induced bone loss especially in children with frequently relapsing nephrotic syndrome requiring longterm steroid therapy.

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빈회재발형 소아 신증후군에서 스테로이드에 의한 골다공증에 미치는 1-α(OH)D_3의 효과

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< 한 글 요 약 >

스테로이드에 의한 골다공증은 특히 성장하는 소아 신증후군에서 심각한 문제이다. 이러한 경우에 활성형 비타민 D원알파, 일성신약)를 1년간 투여하고 그 효과를 보기 위하여 여러가지 골대사 지표를 치료 전후에 검사하여 보았다.

대상 환자는 40명의 빈회재발형 신증후군 환아이며, 본 연구를 시작하기전까지 환자의 스테로이드 치료기간은 50 ±29 개월 이었다.

성인에서 골형성지표로서 잘알려진 혈청 osteocalcin(ng/ml)은 치료전 7,75±3.34, 치료후 9.38±5.06으로 증가 되었고, 골 흡수 지표로 장 알려진 소변 pyridinoline(nmol/mmol Cr)은 치료전 417.26±250.98, 치료후 462.59 ±265.15로 증가되어 소아 에서 골대사 지표로서 유의하지 않았다. 그러나 골밀도는 0.71±0.016에서 0.73± 0.015로 의미 있게 증가하였다($p<0.05$). 스테로이드에 의한 골다공증때 활성형 비타민의 투여로 골다공증을 예방할 수 있을것으로 사료되며, 골 형성 및 골 흡수의 지표로서 성인에서 많이 쓰이는 검사법은 소아의 경우는 예민하지 않았으며, 골밀도 검사만이 유의한 것으로 나타났다.