EFFECT OF CALCITROL AND CALCIUM SUPPLEMENTATION IN THE PREVENTION OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS AMONG SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

By

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Dissertation Submitted In Partial Fulfillment Of
The Requirements For The Degree Of
Master Of Medicine
(Internal Medicine)

UNIVERSITI SAINS MALAYSIA
MAY 2001

ACKNOWLEDGEMENTS

I am very grateful to both my parents Mr. Chan Choong Meng and Madam Au Hoong Chee, family members, lecturers and friends who have been very patient and supportive to me throughout the trials and tribulations of research as well as the post-graduate programme.

I am profoundly grateful to my supervisor Associate Professor Zainal Darus for his support and enthusiasm but most of all for his valuable advice and guidance.

I am also grateful to Dr. Loo Chin Sam and Dr Sunita Bavanadan who have help me get the project started and going.

My thanks also to Associate Professor Quah Ban Seng, Dr Chua May Wah and Encik Ismail bin Kamaru Zaman who have help me with my data tabulation and analysis.

I also want to express my sincere gratitude to all nurses and doctors at the physician clinic, Hospital Ipoh for their cooperation during screening and data collection.

Last but not least, my special thanks to each and every patient who participated in this study

TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES.

ABSTRACT

English version

Introduction:

Prolonged glucocorticoid therapy can lead to loss of bone mineral density (BMD) and higher risk of fracture. Fortunately this can be prevented or reduced if preventive measures are started early. Calcitriol (1,25-dihydroxyvitamin D_3) and calcium supplementation is a rational therapy for minimising bone loss but has not been widely used locally.

Objective:

Our primary objective was to study the effect of calcitriol and calcium carbonate supplementation in the prevention of glucocorticoid-induced osteoporosis in our local systemic lupus erythematosus (SLE) patients. Our secondary objectives were to identify factors, which influenced the rate of bone loss in our SLE patients and also to see the effect of calcitriol and calcium carbonate on glucocorticoid-induced bone loss in the subgroup of patients with normal or reduced baseline BMD

Methods:

Sixty-nine SLE patients who were on long term glucocorticoid therapy were randomly assigned to receive either oral calcitriol 0.25 μg BD or calcium carbonate 1.25 gm BD for one year. BMD was measured every six months for a year by the same dual X-ray absorptiometry (DXA). There were no significant differences between groups at entry with respect to demographics and risk factors for osteoporosis. Analysis was done to see the effect of supplementation on the BMD of the spine and femur. Further sub-analysis

was made to see the effect of supplementation on BMD of patients with normal bone density or osteopenia at entry.

Results:

Calcitriol was more effective than calcium in preventing bone loss from the spine. Mean percentage change at 6 month for calcitriol and calcium were 2.16% and -0.55 % ($p=0.05$) respectively. While mean of change of BMD at one year for calcitriol and calcium were 0.52% and -0.32% respectively. Calcitriol also prevent bone loss from the femur in the first 6 months of the study (mean percentage change of 0.63%) but to a lesser degree than that in the spine. Calcium was unable to provide any protection against bone loss in the spine or femur

Those patients with osteopenic at baseline benefited most from calcitriol and calcium supplementation. When given calcitriol, their mean percentage increase in BMD of the spine were 3.62% at 6 month and 1.68% at one year. Those on calcium also showed an increase in BMD of 0.77% and 1.66% respectively.

Patients with normal baseline bone density showed an improvement only at the spine at 6 month (percentage increase of 1.12%) when given calcitriol supplementation.

Conclusion:

Calcitriol supplementation was more effective in preventing glucocorticoid-induced bone loss than calcium supplementation. Calcitriol with calcium supplementation offered protection against glucocorticoid-induced bone loss if given to patients who were osteopenia.

Bahasa Malaysia Version

Pengenalan

Pengunaan rawatan glucocorticoid yang berpanjangan boleh menyebabkan kekurangan kepaduan tulang dan meningkatkan risiko patah tulang. Namun demikian, gejala ini boleh di atasi atau di kurangkan jika langkah-langkah pencegahan di mulakan dari peringkat awal. Calcitriol (1.25-dyhydroxyvitamin D_3) dan kalsium suplimentasi adalah satu rawatan yang wajar untuk mengurangkan kehilangan padu tulang tetapi ia tidak di lakukan secara berleluasa di peringkat tempatan.

Objektif:

Objektif utama kajian ini adalah untuk mengkaji kesan calcitriol dan kalsium suplimentasi dalam pencegahan osteoporosis yang di akibatkan oleh pengunaan glucocorticoid di kalangan pesakit SLE tempatan. Objektif-objektif lain ialah untuk mengesan faktor-faktor yang boleh mempengaruhi kadar kehilangan padu tulang di kalangan pesakit SLE dan juga untuk mengkaji kesan calcitriol dan kalsium terhadap kehilangan padu tulang yang di sebabkan oleh glucocorticoid di antara pesakit-pesakit yang mempunyai padu tulang awal yang normal atau berkurangan.

Metodologi:

Enam puluh sembilan pesakit yang telah di rawat dengan glucocorticoid di bahagikan secara rambang untuk menerima calcitriol 0.25 μg BD atau kalsium kabornat 1.25 gm BD suplimentasi untuk satu tahun. BMD diukur setiap enam bulan dengan mengunakan dual X-ray absorptiometri (DXA) yang sama.

Tidak terdapat ciri-ciri peribadi atau risiko-risiko yang ketara di antara kedua-kedua kumpulan pesakit. Analisa dijalankan untuk melihat kesan suplimentasi pada BMD di bahagian tulang belakang (spine) dan tulang paha (femur). Analisa lanjutan di jalankan untuk melihat kesan suplimentasi pada BMD pesakit yang mempunyai padu tulang awal yang normal atau yang berkurangan

Keputusan:

Calcitriol adalah jauh lebih berkesan daripada kalsium dalam mencegah kehilangan padu tulang belakang. Purata peratus pertukaran BMD pada peringkat 6 bulan untuk calcitriol ialah 2.16% dan untuk kalsium ialah -0.55% ((p=0.05). Purata peratus pertukaran pada peringkat satu tahun pula ialah 0.52% untuk calcitriol dan -0.32% untuk kalsium. Calcitriol juga dapat mencegah kehilangan padu tulang pada tulang paha (femur) tetapi hanya pada peringkat 6 bulan sahaja (purata peratus pertukaran ialah 0.63%). Kalsium di dapati tidak berkesan untuk mencegah kehilangan padu tulang pada bahagian tulang belakang atau tulang paha.

Pesakit yang mempunyai padu tulang asal yang berkurangan memperolehi faedah yang ketara dari suplimentasi calcitriol dan kalsium. Bila diberi calcitriol suplimentasi, purata peratus pertukaran BMD pada tulang belakang meningkat 3.62% pada peringkat 6 bulan dan 1.68% pada peringkat satu tahun. Mereka yang diberi kalsium suplimentasi memperolehi peningkatan BMD sebanyak 0.77% pada peringkat enam bulan dan 1.66% pada peringkat satu tahun.

Untuk pesakit yang mempunyai padu tulang awal yang normal, hanya pesakit yang menerima suplimentasi calcitriol sahaja memperolehi peningkatan padu tulang di bahagian tulang belakang pada peringkat 6 bulan (purata peratus peningkatan sebanyak 1.12%)

Kesimpulan:

Calcitriol suplimentasi adalah lebih berkesan dari kalsium dalam mencegah kehilangan padu tulang yang di sebabkan oleh glucocorticoid. Kalsium dan calcitriol suplimentasi juga dapat memberi perlindungan terhadap kehilangan padu tulang yang di sebabkan oleh glucocorticoid jika di beri pada pesakit yang telah mengalami osteopenia pada awalnya.

1 INTRODUCTION

Long-term systemic glucocorticoid therapy is given for many steroid-responsive inflammatory and autoimmune illnesses and various other conditions. These include asthma, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, systemic lupus erythematosus (SLE) and other connective tissue disease, inflammatory bowel disease, multiple sclerosis and in organ transplantation.

Although the beneficial anti-inflammatory and immunosuppressive effects of glucocorticoid necessitate their use, adverse side effects are frequent. One of the main concerns is the long-term effect on bone mass and the subsequent fracture risk; hence the importance of early identification and implementing preventive or therapeutic measures.

1.1 Definition of Osteoporosis

The World Health Organisation (WHO) has defined osteoporosis as a condition characterised by low bone mass and mircoarchitectural deterioration leading to enhanced bone fragility and a consequent increase in fracture risk. Fractures are the clinical consequence of osteoporosis. The most common sites of fractures associated with osteoporosis are the hip, spine and wrist, but many other sites can also be involved.

1.2 Bone mineral density (BMD)

The introduction of BMD measurements has revolutionised the whole field of osteoporosis, and it is well established that bone mineral density provides the best mean of assessing an individual's risk of fracture (Grier SJ 1996).

BMD can be measured using a variety of techniques and is commonly assessed at the hip, spine, radius and calcaneus. The most common technique for BMD assessment is dual X-ray absorptiometry (DXA) and results are reported as areal density in units of g/cm^2. Areal density provides useful information relative to fracture risk; since there is an inverse relationship between incidence of osteoporotic fracture and areal BMD (Rizzoli R 1995)

Results can also be expressed in term of the number of standard deviation (SD) below the average young adult bone mass (T-scores). This is the difference between the patient's bone mineral density and the ideal peak bone mass achieved by a young adult (age 20-30 years old) expressed in term of SD

In 1994, the WHO developed a working definition of osteoporosis based on T-scores as shown in Table 1 (Kanis JA 1994). The WHO T-score threshold of -2.5 is commonly used to make a diagnosis of osteoporosis.

Table 1.1 Defining Osteoporosis by BMD

Definitions based on bone mass measurement at any skeletal site (spine, hip, and forearm) in white women

Degree of osteoporosis	T-score	Value of BMD
Normal	≥ -1.0	Within 1SD of young normal adult
Osteopenia	Between –1.0 and –2.5	Between 1 and 2.5 SD below that of a young normal adult
Osteoporosis	≤ -2.5	2.5 SD or more below that of a young normal adult
Severe osteoporosis	≤ -2.5 plus had 1 or more fractures	2.5 SD or more below that of a young normal adult and have had 1 or more fractures

BMD can also be expressed in Z score. It is the number of SD of the difference between the patient's bone mineral density and the mean value expected for a healthy normal subject matched for age, sex and race.

Another method available for assessing BMD is by using ultrasound systems. Several prospective studies have shown that it may well be as effective as DXA in predicting risk of fracture (Hans D 1996, Bauer DC 1997). Ultrasound has the advantages of not using any ionising radiation, being portable, and relatively inexpensive. But so far there is no standard reference available for their use. The WHO criteria of the using T-score values interpreted from BMD measurements taken using DXA machine to express degree of osteoporosis and the subsequent fracture risk, cannot be automatically applied to measurements taken using other methods (Fogelman I 1999)

1.3 BMD and fracture risk

A large number of studies have shown that BMD measurements can provide a good assessment of fracture risk. Every reduction of 1 SD in bone density equating to roughly 2-2.5 folds increase in the likelihood of fractures (Marshall D 1996, Fogelman I 1999). However, they are less good at identifying specific individual who will go on to have fractures

The relationship between BMD and fracture risk is commonly reported as relative risk per standard deviation decrease (RR/SD), which is the increase in risk associated with a decrease in BMD of 1 SD

Eddy and colleagues as part of a comprehensive survey summarises the RR/SD for various commonly affected sites. (Table 1.2) (Eddy D 1998, Dennis MB 2000).

Table 1.2 Showing the relative risk increase in fracture risk per standard deviation decrease in the measurement at the three major sites

	Measurement Site		
Fracture site	**Forearm**	**Lumbar spine**	**Femoral neck**
Wrist	1.8	1.6	1.6
Vertebrae	1.6	2.0	1.9
Hip	1.6	1.3	2.6 *

* For every 1 SD decrease in hip BMD the increase risk of hip fracture is about 2.6 times

1.4 Glucocorticoids and bone metabolism

The mechanisms of the effect glucocorticoids on bone metabolism have not been completely elucidated, but it is currently believed that glucocorticoids accelerate bone loss in several ways (Reid IR 1998). With prolonged administration, decreased bone formation appeared to be the most important mechanism leading to bone loss (Stevenson 1998, Pearce G 1998).

Glucocorticoids exert a direct effect on skeletal development by increasing osteoclast-mediated bone resorption and decreasing osteoblast-mediated bone formation (Chyun 1984). Interference with both the birth and death cycle of bone cells reduces the total number of cells. An increase in osteoblast and osteocyte apoptosis also has been documented in animals and humans with glucocorticoid-induced osteoporosis (Weinstein RS 2000). In a recent in-vitro study by Smith and associates, dexamethasone was specifically shown to induce premature attenuation of osteoblast cell cycle (Smith E 2000).

Glucocorticoids have also been associated with decrease calcium absorption in the intestine (Lane JM 1996) thereby causing secondary hyperparathyroidism. They also increase urinary calcium excretion.

Glucocorticoids can also induce hypogonadism either by suppressing gonadotrophin secretion or by interfering directly with sex hormone production (ACR Task Force 1996, Sambrook PN 1988, MacAdam MR 1986). Thus they reduce the production of oestrogen in women and testosterone in men. Long-term glucocorticoid use may also contribute to muscle atrophy and progressive loss of muscle strength.

They however do not modify vitamin D metabolism (Reid IR 1997, Seeman E 1980, Hahn TJ 1981). All the above changes have subsequent effects on bone formation and may therefore increase fracture risk (Ziegler R 1998)

1.5 Effect of long-term glucocorticoid use on bone

Osteoporosis is a loss of bone mass caused by imbalance between bone resorption and bone formation. Unlike the more common age- and gender-related types of osteoporosis, glucocorticoid-induced osteoporosis can occurs at any age and even in children. Both male and female on prolong glucocorticoid therapy lose bone at similar rates (Lenore B 1997).

Until recently, it is believed that low doses of glucocorticoid (equivalent of less than 10 mg per day prednisolone) had no significant effect on BMD. However with the help of more sophisticated densitometry machines that enable measurements of smaller changes in bone mass; recent studies have suggested that even doses between 5-10 mg of prednisolone per day can induce a slow decline in BMD (Lenore B 1997).

The skeletal effects of glucocorticoid appear to be both dose and duration dependent. A daily prednisolone dose of more than or equal to 7.5 mg will result in significant bone loss and increase fracture risk (Lenore B 1997). The accumulative dose also affects the severity of bone loss. It is not known whether there is a threshold dose of glucocorticoid below which osteopenia does not occur. Alternate-day glucocorticoid regimens also have not been shown to produce less bone loss than daily regimens (Reid IR 1997).

Systemic administration of glucocorticoids has the most prominent influence on bone metabolism. Topical preparations have substantially less influence but there are still clinically evident adverse effects (Ebeling PR 1998). Even inhaled steroids have been shown to increase bone loss (Lenore B 1997, IP M 1994).

It is now generally accepted that patients taking chronic systemic glucocorticoid therapy (the equivalent of more than or equal to 7.5 mg daily of prednisolone for more than six month) will develop low bone mineral density and eventually frank osteoporosis (Skolnick 1997).

Many cross-sectional studies had been carried out to see the effect of oral glucocorticoid therapy in bone mineral density reduction and the subsequent increase fracture risk. They showed that the fracture rates in patients taking long-term glucocorticoid treatment are increased by two to five times (Lenore B 1997). Dr. Reid maintained that as many as one third of patients will develop fractures within 5-10 years of glucocorticoid use (Reid IR 2000, Reid IR 1997)

There is only a few longitudinal research data available on the effect of glucocorticoid-induced osteoporosis. At the recent World Congress on Osteoporosis 2000, Steinbuch and colleagues presented data from a prospective longitudinal study, exploring the risk of fracture associated with oral glucocorticoid therapy. In this study, 17,957 patients on long-term oral glucocorticoids during a 24-month capture period were followed. A control group consisted of patients whom are not on corticosteroid treatment. This cohort represented approximately 33,000 person-years of observation for each group.

The median prednisolone or equivalent intake for patients in the study was 4.8 mg daily. Significantly increased rates of hip and vertebral fractures were detected among patients who continuously used glucocorticoids, compared with the unexposed group. Combined duration of exposure and pattern of glucocorticoid use showed a 5-fold increased risk of hip fracture and a 5.9-fold increased risk of vertebral fracture for continuous glucocorticoid users, compared with the unexposed group. Wrist fracture risk was not increased in the glucocorticoid users. The conclusion was glucocorticoid treatment has a rapid deleterious effect of on trabecular rich bone (Steinbuch M 2000)

Since glucocorticoids affect trabecular bone (spine and ribs) more than cortical bone (femoral neck), patients who are on long-term glucocorticoid therapy are at particularly increased risk for vertebral fractures (Lenore B 1997, Reid IR 1997).

Most glucocorticoid-induced bone loss occurs at the beginning of treatment especially during the first 6 to 12 months (Sambrook 1993), where as much as 30% of bone can be lost (Reid IR 1997). The bone loss will continue, for as long as the patient is on glucocorticoid therapy but at a slower rate (Eastell R 1998). It has been noted that serum osteocalcin, a marker of bone formation, was reduced within a week of initiation of glucocorticoid therapy and remained suppressed as long as therapy continued (Adachi 1996).

By using Dual Photon X-ray Absorptiometry (DEXA), the decrease in lumbar spine BMD in steroid treated patients has been reported to be as high as 40% (Reid IR 1992). The rate of BMD reduction at the spine during the first year of steroid treatment averages about 8% but individual reduction in BMD may range from no reduction to

15% per year (Sambrook PN 1994). This implies that the individual at risk for steroid induced bone loss is subjected to significant variation, probably due to multifactorial nature of steroid induced osteoporosis. While steroid therapy in some patients may not affect bone turnover, the same treatment in others may result in significant bone loss (Spector TD 1993).

Discontinuation of steroids will usually results in restoration of BMD to pre-treatment levels in the same period during the bone loss occur (Laan 1993).

1.6. Risk factors influencing BMD

1.6.1. Calcium intake

Daily calcium intake seems to play a pivotal role especially in Asians patients, whose daily calcium intake is usually lower than in western populations. As steroid induces a negative calcium balance, a low calcium intake is a strong risk factor for increase bone turnover and subsequent bone calcium deprivation.

1.6.2. Fracture prevalence

Patients who have already sustained a minimal trauma fracture are at higher risk to be affected by steroid therapy.

1.6.3. Age, sex and menstrual status

Women are at higher risk for osteoporosis. Post-menopausal women (not on HRT) and older patients (> 65 years) are more vulnerable to steroids than the pre-menopausal women and younger patients. Premature menopausal is also an important risk factor associated with increased steroid-induced bone loss.

1.6.4. Genetics

Genetics account for a high proportion of variance in BMD, so patients with family history of minimal trauma fractures may also at risk of getting accelerated bone loss once they start taking steroid therapy.

1.6.5. Steroid dosage

Steroid effects on bone are dose and duration dependent.

1.6.6. Underlying disease

The associated underlying diseases are also an independent risk factor for reduced bone mass. Examples are lactose intolerance, hypogonadism, endogenous or exogenous hyperthyroidism, multiple myeloma and hypercortisolism (Prakash UBS 2000). Rheumatoid arthritis is independently associated with reduced bone mass (Naganathan 2000).

1.6.7. Small body built and reduced body weight (low body mass index) are also risk factors for osteoporosis

1.6.8. Excessive alcohol intake more than 3 oz /day (alcohol is an osteoblast suppressive agent) and heavy smoking are independent risk factors for developing osteoporosis.

1.6.9. Others include lack of weight-bearing exercise and lack of sun exposure

1.7. Glucocorticoid-induced osteoporosis in Asians

Many studies have been done on glucocorticoid-induced osteoporosis in Caucasians but little is known about steroid associated bone loss in Asians. Eastern populations differ from Caucasians in many aspects. Even though the daily calcium intake of Chinese is lower than that of Caucasians, the intestinal fractional calcium absorption of Chinese postmenopausal women seems more efficient than their Caucasian counterparts (Woo J 1998, Kung AW 1998).

Asians generally has lower BMD than Caucasians because they have lower body weight and height. But despite the lower calcium intake and lower BMD among Asians, the risk of hip fracture is approximately half of that in the western populations. It was said to be due to a better bone architecture, shorter hip axis length, and also a healthier life style among Asians. There is nevertheless accumulating evidence that Asians are also affected from glucocorticoid-induced osteoporosis. A study published in 1998 noted that the prevalence of osteoporosis among Chinese pre-menopausal women with SLE in Hong Kong was low (4-6%) compared to their Caucasians counterpart (12-18%) (Li Ek 1998)

1.8. Effect of osteoporosis and fracture

The risk of fracture that was associated with osteoporosis is a matter of concern. Bone fracture will result in prolong hospitalisation, time away from work, incomplete rehabilitation and increase immobilisation related morbidity and mortality especially in the elderly. All these will directly or indirectly result in high socio-economic burden.

Given the high socio-economic burden of bone fracture and the increasing frequency of steroid usage, the need for accurate identification of patients at risk for developing steroid-induced osteoporosis is crucial. Nevertheless, treatment and prevention of steroid-induced osteoporosis also need to take into account the cost and the potential side effects of prolong administration of supplementation and anti-resorptive agents.

1.9 Preventive treatments for prolonged glucocorticoid users

Fortunately it appears that continuing bone loss induced by prolonged low dose glucocorticoid therapy may be preventable. However identification and intervention must be early.

Multiple strategies for dealing with glucocorticoid-induced osteoporosis have been described especially in the recent years. A lot of studies and trials have been carried out and many are still on going.

1.9.1. Discontinuation of steroid therapy will definitely result in a substantial regained of bone density (Reid IR 1997). If not, the dosage should be maintain to the minimal dose sufficient to induce the anticipated therapeutic effect.

1.9.2. General measures

Patients on long-term steroid therapy should be advised to exercise frequently, to maintain their body weight, to stop smoking, to avoid excessive alcohol intake and to consume food products with high calcium content.

1.9.3. Calcium and vitamin D

Calcium and vitamin D supplementation has been used for many years to prevent glucocorticoid-induced osteoporosis, with mixed results. Calcium supplementation decreases bone resorption but does not completely prevent bone loss (Sambrook P 1993).

Steroids induce a negative balance through inhibition of intestinal calcium absorption. Daily supplementation with calcium would therefore be a safe, cheap and effective for those with low calcium intake.

In clinical practice however, the effect of calcium supplementation is dependent on the population under study. Western populations with lower fractional calcium absorption and higher baseline calcium intake do not seem to benefit from increasing the daily calcium intake (Sambrook P 1993). On the contrary, Asians with a more efficient fractional calcium absorption and lower baseline calcium intake appear to respond better to calcium supplementation (Li EK 1998)

The use of vitamin D3 or its metabolites in the management of steroid-induced osteoporosis is controversial. Early studies had demonstrated that they were effective in reducing bone loss.

(i) Steroid taking patients who were treated with 2 ug 1α (OH) vitamin D3 for months in comparison to placebo treated controls showed a decrease in bone resorption (Braun JJ 1983).

(ii) Calcitriol, in a daily dose of 1μg with 1000mg of calcium has been reported to prevent the early bone loss associated with steroid therapy. It prevented bone loss only in the lumbar spine but not in the proximal femur (Sambrook P 1993).

(iii) Similarly, 1μg of alfacalcidol daily was effective in preventing the decrease in BMD of patients during their first year of steroid treatment (Reginster JY 1999).

(iv) Vitamin D3 in a daily dose of 500 IU plus calcium has also been reported to stabilise the BMD in patients already on long term steroid therapy over a two-year period (Buckley 1996)

On the other hand, there were studies that could not confirm the benefit of vitamin D on steroid-induced bone loss.

(i) A weekly dose of 50,000 IU of vitamin D along with 1000mg of calcium failed to prevent bone loss in patients having long-term steroid therapy over a period of 3 years (Adachi JD 1996).

(ii) Dykman et al showed that calcitriol was no more effective than calcium in preventing bone loss at the radius of patients on chronic steroid therapy when given 0.4 μg calcitriol daily for 18 months (Dykman TR 1984).

(iii) A recent study in Hong Kong showed that beneficial effect of calcitriol on BMD of premenopausal Chinese women taking chronic steroid was small, at least when it is instituted late in the course of steroid therapy (Lambrinoudaki I 2000)

While vitamin D appears to be relatively safe, treatment with 1α active metabolites like 1,25-dihydroxyvitamin D3 (calcitriol) warrants special attention, as hypercalcemia or hypercalciuria can easily complicate it (Chesnut CH 1992).

The rational of using vitamin D or its metabolites is mainly to reverse the decrease in intestinal calcium absorption by antagonising the effects of corticosteroids on gut cells and possibly to exert a direct stimulatory effect on osteoblast (Meunier DJ 1993). The recommended dosage of vitamin D3 is 400 to 800 iu/d.

1.9.4. Sex hormone

Sex hormone replacement is also effective in reducing bone loss in men or women with demonstrable hypogonadism. Hormone replacement therapy (HRT) in testosterone deficient men resulted in increases in BMD (Lane NE 1998, Reid I 1996). Young steroid-treated amenorrhoiec women receiving HRT showed a 2% increase in BMD at lumbar spine over a period of 2 years, in contrast with controls, who lost 1.7% BMD at the same time (Kung AWC 1999). Post-menopausal women were also reported to benefit from HRT, exhibiting a 4% increase in BMD at lumbar spine after one year of treatment (Hall GM 1994, Lukert BP 1992). Research is being currently conducted on selective oestrogen receptor modulators (SERM), a new class of agents with oestrogen-like activity on bone but devoid of the untoward effects of estrogens on breast and endometrium. This sound promising and we await the results (Meier CA 1998).

1.9.5. Bisphosphonates

Bisphosphonates are analogues of pyrophosphate that bind to bone mineral and inhibit osteoclastic bone resorption and thus reduce bone loss (Saag KG 1998).

A recent meta-analysis of all clinical trials conducted so far on the prevention of steroid-induced osteoporosis with any kind of bisphosphonates has demonstrated a significant difference between actively- and placebo-treated patients of 4% in the mean BMD at the lumbar spine and 2.1% at the hip (Homik JE 1999). Two commonly prescribed oral bisphosphonates are etidronate and alendronate. But care should be taken in prescribing them to younger individual, as data on their effects on growing skeleton are not yet available.

1.9.6. Calcitonin

Calcitonin reduced bone resorption by having a direct inhibitory action on the osteoclast function. The intranasal administration of calcitonin has been shown to be effective in preventing the early bone loss associated with steroid intake (Sambrook P 1993, Adachi JD 1997). Calcitonin also can stabilise the BMD of patients who are already on chronic steroid therapy (Luengo M 1994). Calcitonin preparations are however relatively expensive. This drug has not been proven cost effective for the long-term treatment of steroid-induced osteoporosis.

2 OBJECTIVES

2.1 Primary objective

To study the effect of calcitriol and calcium supplementation in reducing the severity of bone loss in local SLE patients who are on prolonged glucocorticoid therapy.

2.2 Secondary objectives

(i) To study the effect of prolonged glucocorticoid therapy on bone density profile and the contributory factors.

(ii) To study the effect of calcitriol and calcium supplementation on bone loss in steroid treated SLE patients who have normal or osteopenic baseline BMD

(iii) To see the pattern of bone densitometry in patients with SLE on calcitriol supplementation

(iv) To see the pattern of bone densitometry in patients with SLE on calcium carbonate supplementation

3 METHODS

The study protocol was approved by the Ethical Committee of Institute Microbiology Research (IMR) on January 1998

3.1. Sample size calculation

Sample size calculation was done using Epi-info 6.04 to detect significant change in BMD between the study groups. To show a difference of 4 % change in BMD of the two groups, a sample size of 26 patients is necessary (if possible) to give

Confidence interval: 95% (α: 0.05)

Power of study: 80% (β : 0.8)

3.2. Selection of patients

Consecutive SLE patients attending the Physician clinic at Hospital Ipoh in Perak from January 1998 were screened. Those who fulfilled the following inclusion criteria and were willing to participate were recruited into the study

3.2.1 Inclusion criteria

(i) All adult SLE patients who were on follow-up at the physician clinic

(ii) SLE patients who were on glucocorticoid therapy and were expected to receive glucocorticoids for at least one year were included.

(iii) Patients who consented for the study

(iv) Patients who were not on any medication to prevent of osteoporosis like calcium, vitamin D, calcitonin, and hormone or biphosphonate supplementation

Patients were excluded from the study if they had any of the following exclusion criteria

3.2.2 Exclusion criteria

(i) Overt clinical and X-ray evidence of fracture due to osteoporosis

(ii) Severe hypercalcemia from any cause

(iii) History of alcohol abuse

(iv) Patients taking therapy or supplementation that can affect the bone metabolism like oral contraceptive pills, calcitonin, calcitriol, fluoride, thiazide or anticoagulant.

(v) Patients on vitamins supplements especially vitamin D

(vi) Patients who have the following associated diseases like thyrotoxicosis, diabetes mellitus, hepatic and gastrointestinal diseases that can cause malabsorption or influence bone loss

(vii) Patients who has stopped taking steroids

(viii) Patients who were pregnant or were planning to conceive during the next one year

3.3 Study design

3.3.1 The study was a prospective randomised controlled trial. At entry patients were randomised by picking closed-labelled envelops of either calcitriol 0.25 μg BD or calcium carbonate 1.25 gm BD.

3.3.2 Screening and before randomisation

Patients attending the SLE clinic were screened and the patient screening form filled up by the investigator. (Appendix I)

Eligible patients were given an explanation on the study. Those who agreed to participate were given the patient information sheet (Appendix II) to read and subsequently given an opportunity to raise any queries or doubts.

Informed consents were taken and signatures endorsed on the patient consent form. (Appendix III a/III b)

Baseline biochemical tests, plain X -rays and bone densitometry of the lumbar and femoral were ordered. Bone densitometry of all the patients were measured by dual energy x-ray absorptiometry (DEXA) using the same Lunar DPXIQ 5213 machine at the same radio-imaging centre to ensure consistency. The BMD scans of each patient were analysed by the same person (the radiologist at the imaging centre) who was unaware of the patient's glucocorticoid dosage and treatment group.

3.3.3. Randomisation and data collection

On the first visit, which was approximately two weeks after screening, baseline bone densitometry measurement and blood investigation results were reviewed. The patients were then randomised to either arm of calcitriol (1,25-Dihydroxycholecalciferol) or calcium carbonate by picking up close-labelled envelopes. The dose of calcitriol (Rocaltriol, Roche) was 0.25ug BD and calcium carbonate was 1.25gm BD.

Data Collection Sheets (Appendix IV) were used to fill up demographic information and information about risk factors for osteoporosis, duration and dosage of steroid usage. Dietary calcium intake and physical exercise were also assessed. Baseline investigations were recorded.

3.3.4 Follow-up

Follow-up was done at monthly interval for three months, then 2-3 monthly thereafter. At each follow-up the full blood count, renal and liver functions test, serum calcium and phosphate levels were monitored and documented into the data collection sheet. (Appendix IV)

Two or more bone densitometry profiles were measured again at the end of 6 months and at the end of study, which was at the end of one-year study period.

All adverse events observed or reported by the patients were recorded.

Patients whose serum calcium were more than 2.8 mmol/l with or without symptoms of hypercalcemia had their calcitriol or calcium carbonate dosage reduced or temporary withheld till the level normalised. If serum calcium persistently elevated despite the above measures, the patient will be withdrew from the study

3.3.5 Compliance

Drug compliance were monitored by tablet count at each visit

3.3.6. Criteria for stopping treatment during trial

(i) Hypercalcemia that did not resolve by dose reduction or stoppage

(ii) Take drugs that can influence the study results i.e. oral contraceptive pills, calcium supplements or vitamin D

(iii) Patients own request

3.4 Data handling and Analysis

All answers collected on the data sheet were given numerical coding to facilitate processing. After coding, data and values were entered onto and stored in the computer using Statistical Package for the Social Sciences (SPSS 9.01) for window software. Appropriate statistical analysis were used: mean, median, range, standard deviation, standard error of means, ANOVA, paired t-test and appropriate non-parametric statistic. A p value of less than 0.05 was taken as the level of significance.

3.5 Definition

Diagnosis of SLE

The diagnosis of SLE was made, based on fulfilling American Rheumatoid Association (ARA) criteria as shown as in the screening form Appendix I. The patients must have at least 4 or more out of the 11 criteria.

4 RESULTS

4.1 Patients Characteristics

Sixty-nine patients were recruited and 54 patients completed the one-year study. But only 51 patients were included in the end-points analysis (Efficacy study)

Reasons for 15 withdrawals were;

(i) Eight patients defaulted follow-up. They either missed the second or the third BMD measurements.

(ii) Four patients were out of the study as they were transferred out station due to job commitments or education.

(iii) One patient got pregnant

(iv) One patient passed away due to complication of infection and septicaemia

(v) One patient who was with the calcium arm have to be added calcitriol due to persistent hypocalcaemia

Later three more patients from the above 54 patients were excluded from the outcome analysis due the following reasons;

(i) One patient was found to be non-compliant to treatment and she was also given anticoagulation when she developed a stroke.

(ii) One patient developed significant renal failure with creatinine levels between 400-600 μmol /l unrelated to calcitriol or calcium supplementation.

(iii) Another patient developed thyrotoxicosis, so have to be excluded from the study