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POSTMENOPAUSAL OSTEOPOROSIS

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Abstract

Osteoporosis occurs predominantly in women aged 45 to 50 years at the outset of menopause and progresses with age. Most authors support the hypothesis that the cause of postmenopausal bone loss is an increased bone resorption in the presence of a basically normal state of formation. Although sex steroids have been used extensively in the treatment of postmenopausal osteoporosis and other types of osteoporosis, their mechanism of action and therapeutic usefulness are not completely understood and form the subject of this review.

Introduction

The term osteoporosis implies that the skeleton has lost substances, but that the bone which remains is, by conventional histological methods, qualitatively normal. Whether or not osteoporotic bone is biochemically normal is a matter for further investigation. Osteoporotic bone loss occurs predominantly from the endosteal surfaces of the long bones and by resorption of trabecular bone. This review emphasizes the findings concerning the possibility of oestrogen deficiency in development of osteoporosis.

Though a great deal of information on formation and degradation processes of bone matrix is available, little is known about the mechanisms and the detail of calcification and decalcification. New bone formation is controlled by osteoblasts and osteocytes and bone resorption by the osteoclasts. Previously thought as 'dead end' cell, the osteocyte is now believed to be an important component in the cellular response to various hormones and maintenance of plasma calcium homeostasis since its surface area in contact with bone could facilitate rapid calcium mobilization or sequestration.

Hormonal control of skeletal growth and development

The mammalian skeleton serves two different and often imcompatible functions[1-3]. Structurally, the skeleton must be strong, light, mobile and capable of orderly growth, response to stress and repair. Metabolically, it must serve as an ion reservoir of calcium, phosphorus, magnesium, sodium and carbonate. In bone and cartilage, hormones act in a coordinated manner to maintain a balance among these functions. Thus, it is not surprising that skeletal growth and development are under complex hormonal control.

Hormones and factors that influence skeletal development can be classified as calcium regulating hormones, systemic hormones and local factors. It is known that these hormones have important actions on bone and other target organs which may indirectly affect bone metabolism, but only the direct effects on bone growth and development will be dealt with in the present review.

1. Calcium regulating hormones

These hormones have been the subject of a recent review[4]. Briefly, the effect of parathyroid hormone (PTH) on bone growth is controversial[5,6]. High concentrations of PTH were found to inhibit osteoblastic collagen synthesis both *in vivo* and *in vitro*[7]. However, chronic treatment with PTH increase osteoblastic activity and appositional growth rate[8,9]. PTH does stimulate osteoclastic bone resorption.

Vitamin D stimulates bone mineral mobilization to increase the supply of calcium and phosphate in the serum[10]. It is also thought that vitamin D is essential *in vivo* for normal skeletal mineralization. *In vitro,* the active metabolite of vitamin D, 1, 25-dihydroxycholecalciferol (1,25 $(OH)_2D_3$) directly stimulates osteoclastic bone resorption[11]. This catabolic effect of 1,25$(OH)_2D_3$ on bone represents a special adaptation to calcium and phosphate deficiency. For example, when serum calcium and phosphate are normal, the free level of 1,25$(OH)_2D_3$ in plasma is relatively low but at a level enough to permit normal calcium and phosphate absorption in the intestine. When the serum calcium and phosphate are low however, synthesis of 1,25$(OH)_2D_3$ is stimulated. The increased level of 1,25$(OH)_2D_3$ exerts a stimulatory effect on bone resorption to supply the required calcium and phosphate.

Calcitonin (CT) is an antihypercalcaemic hormone that inhibits osteoclastic bone resorption.

2. Systemic hormones

Growth hormone (GH) is essential in the regulation of skeletal growth especially in infants and growing children. Deficiency in GH results in decreased cartilage cell proliferation and matrix synthesis, impaired osteoblastic function and a decline in linear growth. The effect of GH on bone is mediated by somatomedins.

Insulin also has an important role in skeletal development. Juvenile onset diabetes mellitus is associated with diminished bone mass[12-14]. *In vitro,* insulin was found to stimulate growth of bone and cartilage directly[15].

The presence of adequate thyroid hormone is necessary for normal bone development. Hypothyroidism results in impairment of skeletal growth while linear growth in hyperthyroid children is accelerated[16-17]. How thyroid hormone affects the skeletal development is unclear but it is possible that thyroid hormone directly increases osteoclastic bone resorption and thus stimulates bone turn over and remodeling[18].

Glucocorticoids inhibit growth in many tissues including bone[19]. The major mechanism for growth arrest is the inhibition of proliferation of precursor cells[20].

Sex hormones such as adrenal androgens, testosterone and oestrogen are associated with accelerated linear growth and epiphyseal closure at puberty. Even after puberty, they stimulate the increase in bone mass[21]. Bone growth appears to be more dependent on androgen than oestrogen[22]. Controversies arose when another group of investigators found that oestrogen decreased bone growth by inhibiting somatomedin production[23]. At menopause, the lack of oestrogen is also associated with excess loss of bone mass which is thought to be due to accelerated bone resorption[24]. However, the mechanism by which oestrogen affects bone metabolism is not yet understood and is the subject of this review.

3. Local factors

Klein and Raisz in 1970[25] found that prostaglandin E_2 (PGE_2) can inhibit bone collagen synthesis. Moreover, prostacyclin (PGI_2) produced by bone itself can stimulate bone resorption[26]. Another local factor, a potent stimulator of bone resorption and an inhibitor of collagen synthesis is called osteoclast activating factor (OAF) which is produced by lymphocytes[27]. However, the physiological significance of OAF is still doubtful.

Osteoporosis

The term osteoporosis originated in the histological distinction by German pathologists of three disorders of the bone: osteomalacia, in which much of the bone tissue is uncalcified, osteitis fibrosa, in which the bone is eroded by osteoclasts and replaced with fibrous tissues; and osteoporosis, in which the bone tissue is calcified and otherwise normal, except that there is too little of it.

In 1940, Albright and coworkers[28] proposed a general theory of osteoporosis based upon a postulated failure of osteoblasts to deposit normal quantities of new bone matrix. According to their theory, osteoporosis occurred in postmenopausal woman because of decreased secretion of oestrogens; in senile or debilitated subjects or in patients with Cushing's syndrome or hyperthyroidism because of a defect in protein anabolism or because of deficiency in anabolic hormones and/or excess in catabolic hormones. The Albright's theory was seriously challenged when the calcium balance and radiocalcium kinetic studies showed that the bone formation is normal in post-menopausal and senile osteoporosis[29,30] and is even augmented in hyperthyroidism[31]. Moreover, the osteoclastic activity is found to increase in osteoporosis[32,33] and the gonadal hormones suppress bone resorption[34,35].

While these and other studies have made the Albright theory untenable, they have not been able to explain the mechanism of osteoporosis. Albright theory was wrong when it proposed that osteoblastic activity is decreased in osteoporosis. Frost's proposal in 1961[32] was also over-simplified when he suggested that osteoporosis was essentially a disorder of osteoclastic activity. The realization that bone formation and resorption are not independent but are homeostatically linked is of key importance in the understanding of osteoporosis. The degree of parathyroid activity and consequent bone resorption depend on how well intestinal absorption balances excretory loss. If the body intake of calcium balances the loss, then bone resorption will balance bone formation. A change at a single end organ will provide a compensatory shift of parathyroid hormone secretion, but the new equilibrium will be the result of the altered activities of all end organs. Under such circumstances, calcium homeostasis will be maintained but bone mass may well change. The following diagrams whow 3 situations; a normal condition (Fig. 1A) and two osteoporotic conditions, one of which showing disturbance at the level of bone such as excessive resorption (postmenopausal osteoporosis) as a cause of calcium disturbances (Fig. 1B), and the other demonstrating development of osteoporosis as a result of calcium disturbances caused by decrease in intestinal calcium absorption (Fig. 1C).

Diagram A represents the normal condition with a normal level of PTH secretion. The urinary calcium excretion balances the dietary intake and bone accretion balances the resorption resulting in a constant level of plasma calcium.Diagram B illustrates the reciprocal interdependence of end organ effects. Assume that the osteoclasts have somehow acquired an increased sensitivity to circulating PTH or their activities are stimulated by certain factor (eg. as in postmenopausal osteoporosis), the increased resorption will lead to hypercalcaemia and a reduced PTH secretion. The kidney and intestine when exposed to low PTH will conserve calcium less effectively and the new equilibrium will be in a negative balance. On the other hand, as shown in diagram C, dietary calcium deficiency or malabsorption will result in hypocalcaemia. Osteoporosis thus occurs simply as a result of a compensatory increase in PTH secretion. These diagrams show that the observed osteoporosis may develop primarily from disturbances in the bone itself causing the shift in activities of various end organs or it may well be the end result of the readjustment of the calcium regulating system to provide extra calcium.

Postmenopausal Osteoporosis

The relation between osteoporosis and the menopause was first noted by Albright *et al.* in 1941[36], when they described 42 cases of spinal osteoporosis, all but 2 of them in postmenopausal women, 9 of whom had undergone an artificial menopause. Donaldson and Nassim in 1954[37] found no relation between osteoporosis and an artificial menopause, but radiological observations by workers using different techniques have all

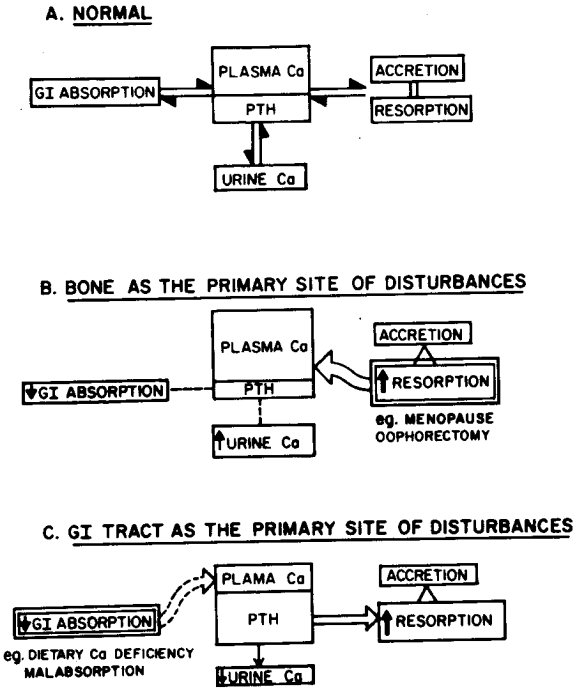

Figure 1: Diagrams showing the difference in the distributions of calcium among four main compartments: the plasma, GI tract, urine and bone in (A) normal condition where the bone accretion equals bone resorption; (B) an osteoporotic condition with bone as the primary site of disturbance ie. bone resorption exceeds bone accretion, and (C) an osteoporotic condition with GI tract as the primary site of disturbance, and the bone resorption again exceeds bone accretion.

suggested that loss of bone density in women starts at or around the menopause[38-40].

A "physiologic" demineralization of bone occurs in women aged 45-50 years at the onset of menopause and progresses with age. In men, this process seems to begin somewhat later, between the age of 60 and 70[41,42]. The obvious suggestion that the earlier onset in women is due to menopause continues to be put forward but awaits proof[38].

Most authors support the hypothesis that the cause of bone loss in osteoporosis is an increased bone resorption in the presence of a basically normal state of formation[29,43-45]. Since then sex hormones have been used extensively in the treatment of osteoporosis although their mechanism of action and therapeutic usefulness have not been completely understood. However, some authors have suggested that the association of osteoporosis with the menopause is largely fortuitous because autopsy studies have demonstrated that maximal bone mass is attained between ages 20 and 40 years in both sexes, and then there is a progressive bone atrophy which begins premenopausally in women and correlates linearly with age[46]. Despite that observation, higher values of calcium in serum, urinary excretion of calcium and urinary hydroxyproline excretion which is taken as an index for resorption, have been observed in postmenopausal woman[47] supporting the theory of an increased bone resorption. If the menopause is associated with a rise in plasma and urine calcium oestrogens might be expected to reverse the process. This is infact the case. Oestrogen substitution has been found to decrease plasma calcium as well as urinary calcium excretion[36,47-49].

Oestrogen Treatment in Postmenopausal Osteoporosis

Many investigators have proposed that the major effect of sex hormones on osteoporosis is an inhibition of bone resorption[34,43,48,51,52]. There is uncertainty concerning the benefit of sex hormone treatment after a long term administration. Although treatment with sex hormones produces calcium retention in the majority of osteoporotic patients studied by metabolic balance method[50], but years of treatment fails to increase the radiodensity of bone. These observations suggest that short term treatment can result in calcium retention which, however, cannot be maintained indefinitely[43-45] by long term treatment.

In the studies of osteoporotic patients receiving androgen or oestrogens for less than 3 months, Lafferty *et al.*[43] found the skeletal ^{47}Ca accretion to be unchanged, but found a reduction of ^{47}Ca accretion in 3 of 4 osteoporotic patients receiving sex hormones for more than 9 months. Riggs and his group[45,53] observed similar results and proposed that a sustained inhibition of bone resorption with a secondary decrease in bone formation would provide a basis for the commonly held belief that treatment with sex hormones can arrest but cannot cure osteoporosis. It also would explain the apparent inability to maintain a positive calcium balance throughout long periods of treatment. Similar results were observed in experimental animals[54].

Although the etiology of osteoporosis has not yet been clarified it is impossible to disregard the importance of lack of oestrogen for the development of osteoporosis. Evidence supporting the lack of oestrogen as a possible cause of postmenopausal osteoporosis is gathered mostly from observations in natural and artificial menopause. In addition, observations in other types of osteoporosis also lend support to this hypothesis. The following part will give some details of the finding under various conditions (Fig. 2). The premature occurrance of osteoporosis in Turner's syndrome and in young oophorectomized women indicates such an association[55]. Most of the patients with Turner's syndrome in this study had evidence of increased bone resorption with normal formation. The patients had no historical evidence to suggest significant dietary deficiencies of calcium or vitamin D, the oestrogen deficiency remaining the most likely explanation.

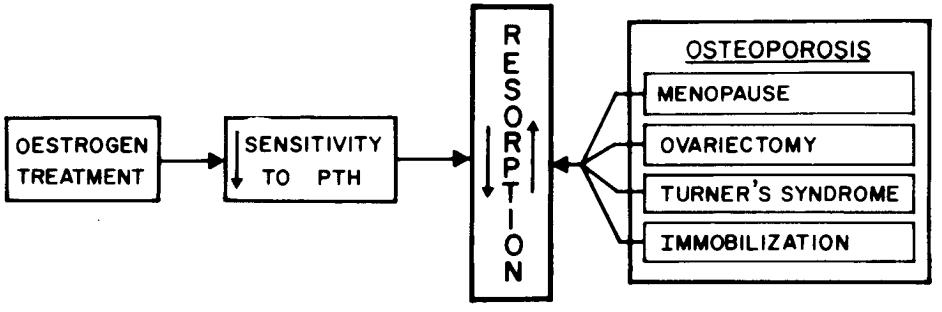

Figure 2: Possible mechanism of oestrogen treatment in preventing excessive resorption of bone which may occur in various conditions.

Oestrogenic hormones have also been shown to have dramatic, acute inhibitory actions on bone resorption in experimental animals[56]. For instance, administration of oestrogen to young rats caused a general reduction in the rate of growth of the skeleton and of the total body[57,58]. This may be explained by the fact that oestrogen may interfere with resorption and thus slows down the general bone turnover rate. In another study, oestrogen treatment for 2 to 6 weeks increased density, breaking strength and ash percentage of the femur[59] but was without effect on the calcium and fluoride content of the femur ash. Fluride intake seemed to offset the action of oestrogen in rats[59], but the mechanism by which it did so is unclear. Another example of the

protecting effect of oestrogens against the development of osteoporosis is described by Orimo[60]. Immobilization of limbs is commonly known to result in osteoporosis; oestrogen administration can prevent this in rats[60]. However, the failure of the development of immobilization osteoporosis in dogs after the removal of the parathyroid gland as shown by Burkhart *et al.*[61] strongly suggests the importance of PTH-induced bone resorption as the etiology factor of this type of osteoporosis. Oestrogen might diminish the severity of immobilization osteoporosis, possibly through the inhibition of PTH-induced bone resorption[60].

There seems to be slight species difference in the effect of oestrogen on bone resorption. A short term[62] and long term[63] decrease in serum calcium concentration after oophorectomy has been noted. The serum calcium changes in the oophorectomized rat differ from these reported in the postmenopausal female[64-66], in whom an increase in serum calcium is found which is reversed by the administration of oestrogen.

Another line of evidence which is relatively new is concerned with the role of peripheral oestrogens. Perspective studies starting 3 years after oophorectomy indicate that not all castrated women continue to lose bone mass during the ensuing years. This prompts the question of whether extraovarian tissues in certain women can produce osteotrophic substances similar or identical to those produced by the ovary and thereby protect the skeleton from further bone loss. This concides with another finding of a later onset of menopause in obese women[67]. The explanation for this may be that these women synthesize oestrogen peripherally. Increasing evidence suggests that fatty tissue may produce oestrogens in sufficient quantity to protect against osteoporosis. De Waard *et al.*[68,69] reported persistent oestrogenic effect in the vaginal smears of obese postmenopausal women that often persisted for decades after menopause. In these subjects, this evidence of oestrogen effect subsided with weight loss. Grodin and his group in 1973[70] as well as Schnider *et al.* in 1972[71] have indicated that adipose tissue is a likely site for the production of oestrone from steroidal precursor androstenedione found in the plasma of postmenopausal women. Therefore, it seems that obesity may help protecting the postmenopausal women from osteoporosis presumably by adipose tissue synthesis of oestrogen.

Mode of Action of Oestrogens

The mean by which oestrogen exerts its effects upon the skeletal system remains unclear. It has been demonstrated that tritiated oestradiol is taken up by the rat femur[72], although it is not known whether this is nonspecific binding or if this binding is to the cell or to other areas of bone. No receptor was demonstrated in osseous tissue, making it unlikely that bone is a primary target organ for the hormone[73]. There are contradictory data on the influence of oestrogen on tissue or organ culture of bone. In some *in vitro* experimental situations, oestrogen fails to inhibit bone resorption[74]. There is a suggestion[75] that the reason for any measurable effect is direct toxicity of oestrogen on cell metabolism. On the other hand, there have been several suggestions that oestrogen

may affect bone metabolism simply by decreasing the sensitivity of bone to parathyroid hormone[45,51,62].

Previous *in vivo*[54,62] and *in vitro* experiments[76,77] have confirmed that oestrogens decrease the sensitivity of bone to the effect of PTH. The increase in serum PTH noted after oestrogen therapy in one report[54] was probably related to the oestrogen-induced decrease in serum calcium. Hossain *et al.* in 1970[78] reported that hyperparathyroid postmenopausal women are more osteoporotic, and hypoparathyroid postmenopausal women less osteoporotic than normal controls. Oestrogen treatment can reduce the fasting plasma calcium, urine calcium and the hydroxyproline content in urine[66] presumably by suppressing PTH induced bone resorption. These results offer a possible explanation of the relatively high incidence of hyperparathyroidism in postmenopausal women. Hyperparathyroidism in postmenopausal women is sometimes due to adenoma of the parathyroid gland. However, it seems unlikely that the menopause or the oestrogen lack gives rise to adenoma formation. More probably, a preexisting adenoma only becomes clinically manifest when oestrogen lack leads to a drop in the plasma calcium which in turn stimulates the secretion of PTH. The markedly increased level of PTH, thus, exerts its full effect on bone and leads to a rise in plasma and urine calcium. This can be looked upon as an exaggerated form of the increase in bone resorption which normally follows the menopause[66].

Treatment with Calcium and Vitamin D

Can osteoporosis be the result of chronic calcium deficiency? Administration of calcium with or without vitamin D rivals sex steroid therapy as the most widely used form of treatment for osteoporosis. Inspite of its long use, there is controversy regarding its value. The use of a high calcium intake in the treatment of osteoporosis has been strongly advocated by Nordin[30,79]. He postulated that osteoporosis is the result of a prolonged negative calcium balance in which mineral is mobilized from the skeleton to maintain the serum calcium. He is supported by the experimental studies of Harrison and Fraser[80] which demonstrated that in rats deprived only of calcium osteoporosis developed, whereas in those deprived of both calcium and vitamin D osteomalacia developed. Although some investigators succeeded in maintaining positive calcium balance in parients with postmenopausal osteoporosis[79–83], no improvement in mineralization was observed. Failure of the skeleton to retain the additional calcium absorbed with the high calcium intake, as evidenced by the significant increase in urinary calcium, is against the concept of osteoporosis resulting from chronic calcium deficiency and points to a pathologic process primary to bone.

There have been few studies on the effect of pharmacologic doses of vitamin D in primary osteoporosis. Riggs and his group[84] in 1976 demonstrated that oral calcium and vitamin D therapy decreased bone turnover in osteoporosis. The suggested mechanism for the observed decrease in bone resorption was a decrease in PTH secretion.

As for the direct effect of oestrogen on other calcium regulating hormones there is considerable information about the effect of sex steroids on the metabolism of vitamin D. In egg-laying birds, ovariectomy can inhibit *in vitro* renal metabolism of 25 hydroxycholecalciferol[85]. The treatment of female rats with a large dose of oestradiol for 8 days has been claimed to increase the concentration of 1,25-dihydroxycholecalciferol ($1,25(OH)_2D_3$)[86]. Pregnant women and lactating women have markedly raised levels of $1,25(OH)_2D_3$ as have lactating rats[87,88]. But in normal menstruating women, endogenous increase in oestrogen neither directly nor indirectly stimulate $1,25(OH)_2D_3$ production, nor do they affect circulating levels of the hormones known to influence calcium homeostasis in man[89]. However the relatively low $1,25(OH)_2D_3$ levels observed in postmenopausal women are elevated by exogenous oestrogen administration[90]. So from available evidence, it is possible that the regulation of $1,25(OH)_3D_3$ by sex hormones is restricted to the state of calcium stress such as during pregnancy and lactation in mammals.

The hypothesis of the existence of a connection between oestrogen and calcitonin (CT) has received some support by demonstration of a fall in CT levels and a decrease in CT secretion after calcium challenge in ovariectomized rats. The CT levels in postmenopausal osteoporotic patients were lower than in normal age and sex matched subjects[91]. However, the transient fall in CT levels after ovariectomy in rat is not corrected by injecting oestrogens, implying that the fall in CT levels is probably not due to a lack of this steroid[92].

It remains to be shown that the links between ovarian function and CT secretion observed in rats exist in human. The present conclusion on the mode of action of oestrogen is that oestrogen has a direct effect on bone physiology but the manner of this remains obscure.

Other Factors Influencing Postmenopausal Osteoporosis

Factors that are commonly assigned a contributary role in the development of osteoporosis include small constitutional size, female sex, a genetic predisposition including white ancestry, deficiencies of calcium and sex hormones, inactivity, and the aging process. Other less frequent contributory factors include thyrotoxicosis, malabsorption syndromes, the postgastrectomy state, active collagen disease, hyperparathyroidism, chronic uremia and alcoholism. The relative importance of each of these factors has not been determined and the interrelationships between factors remain obscure. One interesting example of factors which may promote development of osteoporosis is cigarette smoking. It has been observed that middle aged men and women with symptomatic osteoporosis were almost exclusively heavy cigarette smokers[93-94]. Several mechanisms by which smoking might contribute to this development have been proposed based on other related findings. For instance, smokers are reported to have earlier menopause[93-95]. However, no conclusive evidence on smoking related early ovarian failure has yet been available. Nevertheless, smoking related phenomena

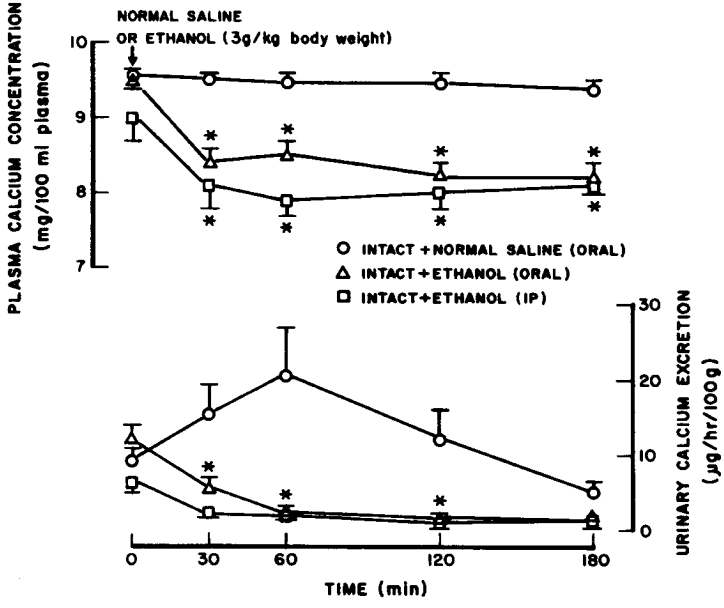

Figure 3: The acute effect of ethanol (3 g/kg body weight) administered orally or intraperitoneally on the plasma calcium concentration and urinary calcium excretion. *denotes a significant difference ($P < 0.05$) from the control value at zero minute.

other than early menopause have drawn considerable attention; and these include change in blood pH (known to affect sensitivity to PTH), the presence of chronic respiratory disease (commonly associated with osteoporosis) and lowered tissue level of vitamin C[96-99] which is essential for bone metabolism.

Osteopenia and increased risk of fracture are well recognized clinical features of chronic alcohol ingestion in man[100-102] and in experimental animals. There have been many hypotheses to explain the effect of alcohol on bone metabolism. Previous reports[103-104] and results from our laboratory showed that acute administration of ethanol induced hypocalcaemia (Fig. 3) which could well cause a defect in bone formation and/or a compensatory increase in PTH secretion resulting in excessive bone

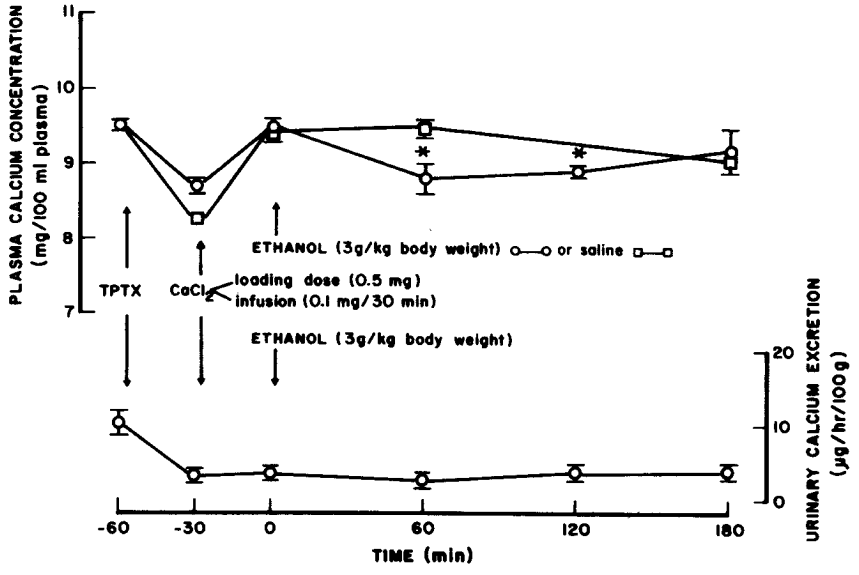

Figure 4: The acute effect of ethanol (3 g/kg body weight) administered orally on the plasma calcium concentration and urinary calcium excretion in thyroparathyroidectomized (TPTX) rats which received a loading dose of 0.5 mg $CaCl_2$ and a continuous infusion of 0.1 mg/30 min $CaCl_2$. *denotes a significant difference ($P < 0.05$) from the control value at zero minute.

resorption. However, alcohol induced hypocalcaemia is present even in thyroparathyroidectomized animals (Fig. 4). Therefore it is unlikely that alcohol acts through either direct or indirect stimulation of PTH secretion. Baran and his group in 1980[105] observed a direct toxic effect of alcohol on bone cells resulting in osteopenia. Other possible explanations are put forward, for instance, defective bone metabolism may be the result of systemic alterations of $25(OH)D_3$[106], testosterone[107-109] or oestrogen[110] which inturn, may promote bone resorption and/or decrease bone accretion.

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บทคัดย่อ

Osteoporosis หรือโรคกระดูกกร่อนพบได้บ่อยในผู้หญิงที่เข้าสู่วัยหมดประจำเดือนคือในช่วงอายุ 45 ถึง 50 ปี อาการกร่อนของกระดูกจะเกิดมากขึ้นตามอายุ มีนักวิจัยเป็นจำนวนมากเชื่อว่าสาเหตุของการเกิดกระดูกกร่อนนี้สืบเนื่องมาจากการที่มี bone resorption มากเกินไป ในขณะที่ bone formation ดำเนินไปอย่างปกติ การใช้ sex steroids รักษาหรือบรรเทาการกร่อนของกระดูกได้มีมานานแล้ว และยังเป็นที่แพร่หลายอยู่ในปัจจุบันนี้ อย่างไรก็ตาม กลไกในการที่ sex steroids มีผลในการป้องกันมิให้กระดูกกร่อนมากขึ้นเป็นอย่างไรก็ยังคลุมเคลืออยู่ และจะพิจารณาในบทความนี้