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Anabolic Effects of Insulin on Bone Suggest a Role for Chromium Picolinate in Preservation of Bone Density

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Abstract — Activation of osteoclasts by parathyroid hormone (PTH) is mediated by PTH stimulation of osteoblasts, and is dependent on a PTH-induced rise in protein kinase C activity. Physiological levels of insulin reduce the ability of PTH to activate protein kinase C in osteoblasts, suggesting that insulin may be a physiological antagonist of bone resorption. In addition, insulin is known to promote collagen production by osteoblasts. These findings imply that efficient insulin activity may exert an anabolic effect on bone, and rationalize the many clinical studies demonstrating reduced bone density in Type I diabetes. Recently, the insulin-sensitizing nutrient chromium picolinate has been found to reduce urinary excretion of hydroxyproline and calcium in postmenopausal women, presumably indicative of a reduced rate of bone resorption. This nutrient also raised serum levels of dehydroepiandrosterone-sulfate, which may play a physiological role in the preservation of postmenopausal bone density. The impact of chromium picolinate (alone or in conjunction with calcium and other micronutrients) on bone metabolism and bone density, merits further evaluation in controlled studies.

Introduction

Primary osteoporosis typically results from an increase in bone resorption rate coupled with an inadequate compensatory increase in new bone formation. Postmenopausal osteoporosis reflects a loss of oestrogen's suppressive effects on osteoclast function (1) and on interleukin-6-mediated induction of osteoclast precursors in bone marrow (2). In senile osteoporosis, an age-related decline in renal 1-α-hydroxylase activity impairs calcitriol production, leading to a decreased efficiency of dietary calcium absorption and secondary hyperparathyroidism (3). In each syndrome, accelerated resorption results in a progressive loss of bone mineral.

Parathyroid hormone (PTH) is the chief hormonal signal that triggers bone resorption. Its physiological role is to increase serum calcium levels in response to a perceived reduction in serum calcium. It accomplishes this by stimulating bone resorption, as well as by promoting renal retention and intestinal absorption of calcium; its effect on intestinal absorption is indirect, mediated by increased renal production of calcitriol.

Although PTH promotes osteoclastic activity, osteoclasts do not appear to express PTH receptors. In tissue culture, PTH only activates osteoclasts if

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osteoblasts are also present (4). Since osteoblasts **do** express functional PTH receptors, it appears that PTH stimulates osteoblasts to send a still-uncharacterized signal to osteoclasts that promotes bone-resorbing activity.

The effects of PTH on osteoblasts are mediated by at least two intracellular second messengers: cAMP, and protein kinase C (PKC) (5). A recent study demonstrates that activation of PKC is crucial to the ability of PTH to promote osteoclastic activity; whereas treatment of fetal mouse calvaria with PTH stimulates calcium release, this effect is blocked by co-incubation with the highly specific PKC inhibitor 1-alkyl-2 methylglycerol (6).

Influence of insulin on bone metabolism

Studies at several labs indicate that osteosarcoma-derived cell lines that behave like osteoblasts in culture, are richly supplied with physiologically active insulin receptors (7–9). When these osteoblast-like cells are pre-incubated with physiological concentrations of insulin, their subsequent response to PTH is severely blunted, as indicated by reduced ability of PTH to elevate intracellular cAMP levels and PKC activity (5,10,11). The ability of insulin to suppress the rise in cAMP appears to be primarily attributable to induction of cAMP phosphodiesterase (10); the suppressive effect on PKC activation may be due, at least in part, to a decreased ability of PTH to activate phospholipase C (5).

Thus, unless insulin has a direct stimulatory effect on osteoclasts (there does not appear to be any evidence for such an effect), it is reasonable to predict that increased insulin activity in bone will inhibit bone resorption by blocking the effect of PTH on osteoblasts, and more particularly, by impeding the PTH-mediated activation of PKC. However, I am unaware of any direct evidence that insulin exerts an anti-resorptive effect on PTH-treated bone explants or bone-derived tissue cultures.

In contrast, the ability of insulin to stimulate collagen production by osteoblasts is well documented (12–15). This effect is seen at physiological insulin concentrations, and thus is not mediated by IGF-1 receptors. Incubation with insulin for 96 hours increases not only the collagen content, but also the calcium content and dry weight of bone explants (14), suggesting that the stimulated collagen production is followed by appropriate mineralization of the new matrix. A beneficial effect of efficient insulin activity on bone formation can thus be anticipated.

These considerations are of interest in light of ample evidence that diabetes – in particular, Type I diabetes – is associated with decreased bone density (16–21). Findings with respect to Type II diabetes are more equivocal (16,22,23), perhaps owing to the compensatory hyperinsulinemia typically seen in this syndrome. Assessing the impact of insulin resistance (diabetic or non-diabetic) on bone metabolism is complicated by the fact that obesity, the most common cause of insulin resistance, typically has a **favourable** effect on bone density (24), presumably due in part to the greater bone stress associated with everyday weight-bearing activities (25).

Chromium picolinate may inhibit bone resorption

Could agents which promote efficient insulin function have a beneficial impact on bone metabolism? In an effort to answer this question, Evans and co-workers have recently completed a double-blind crossover study (26) in which postmenopausal women alternately received the insulin-sensitizing nutrient chromium picolinate (27) (400 mcg chromium daily) or matching placebo for 60-day supplementation periods, separated by a three-month wash-out period. As compared to baseline, the urinary hydroxyproline/creatinine and calcium/creatinine ratios dropped 24% and 19%, respectively, after 60 days of supplemental chromium; these changes were statistically significant relative to the negligible changes observed after placebo. After completion of the blinded crossover protocol, all 27 women were given a daily supplement of 400 mcg chromium **plus** 800 mg calcium for 60 days, at the end of which the urinary hydroxyproline/creatinine ratio was reduced by 47% relative to baseline. Since calcium absorption was not measured, the chromium-mediated reduction in urinary calcium may or may not reflect improved calcium balance; however, the marked reduction in urinary hydroxyproline most likely indicates (28,29) that the insulin-sensitizing activity of chromium picolinate (reflected in an improvement of glucose tolerance in these subject) can indeed reduce bone resorption – an effect which is substantially potentiated (not surprisingly) by co-supplementation with calcium. Presumably, supplemental calcium reduces PTH secretion, while chromium diminishes PTH's ability to activate osteoclasts.

Evans also measured total serum alkaline phosphatase during his study, and found no significant change during chromium supplementation. Since only about half of serum alkaline phosphatase derives from bone, this parameter is not a very sensitive marker of bone formation rate. Nevertheless, the absence of a significant decrease in alkaline phosphatase activity suggests that bone formation showed little if any decline despite the substantial reduction in bone

resorption. Since bone resorption and bone formation are typically tightly coupled (by extracellular signals which remain obscure), the data suggest that an anabolic action of chromium on osteoblasts offsets the expected decline in osteoblast activity consequent to reduced bone resorption. Thus, a net increase in bone density is implied. Whether this can be confirmed in longer-term studies that directly measure bone density remains to be seen.

If chromium reduces the rate of bone resorption, a compensatory increase in PTH secretion can be expected. Increased PTH activity in distal renal tubules, perhaps coupled with a slight drop in serum free calcium levels, might then account for the decreased urinary calcium loss observed in the Evans study. It is pertinent to note that insulin exerts a direct calciuretic effect on the kidney (30); the **decline** of calcium excretion during supplemental chromium thus suggests that chromium does not substantially enhance net insulin activity in the kidney.

Potential impact of dehydroepiandrosterone (DHEA)

Several epidemiological studies suggest that the steroid hormone DHEA may play a physiological role in the maintenance of bone density in postmenopausal women (31–35). Although DHEA can serve as a precursor for the peripheral synthesis of oestrogens, there is little evidence that the low oestrogen levels of postmenopausal women (not receiving oestrogen-replacement therapy) have a significant influence on bone density (34,36). Thus, if DHEA does indeed influence postmenopausal bone density, this effect is likely mediated by DHEA itself or its androgenic metabolites. The restoration of normal serum DHEA levels has been shown to reduce cancellous bone loss in ovariectomized rats (37); whether moderate-dose DHEA therapy can exert a comparable benefit in postmenopausal women remains to be determined.

In light of the suggestive evidence for an anabolic effect of DHEA on bone, Evans also measured serum levels of DHEA-sulfate during his chromium study, and noted a statistically significant 24% increase after the 60 days of supplemental chromium.

The mechanism responsible for this intriguing effect is obscure. Several investigators have reported a reduction of serum DHEA-sulfate following an oral glucose tolerance test or after a prolonged insulin clamp using high physiological or supraphysiological insulin levels (38–41); an insulin-mediated inhibition of the rate-limiting enzyme for adrenal DHEA synthesis, 17,20-lyase, is suggested by the data (41). However, other researchers have failed to confirm this effect (42–44). If we presume that insulin can indeed inhibit 17,20-lyase, and if we further presume that chromium picolinate down-regulates insulin secretion but selectively fails to sensitize the adrenal cortex to insulin, then the ability of chromium to promote DHEA production could be anticipated. However, there are no data regarding the impact of chromium on adrenocortical cells.

The secretion of DHEA is regulated by mechanisms distinct from those regulating glucocorticoid production. A poorly characterized hypothalamic hormone may stimulate adrenal DHEA secretion (45). The basis for the marked and progressive age-related decline in DHEA production, beginning in the third decade (46), is still unknown. Conceivably, chromium picolinate could influence hypothalamic regulation of adrenal androgens, or partially reverse the age-related factors responsible for the decline in DHEA synthesis.

The physiological role of DHEA remains to be defined. Animal studies employing very high pharmacological doses (which lead to striking increases in sex hormone levels that would not be tolerable clinically) have raised false expectations regarding the clinical potential or physiological role of this hormone. Nevertheless, there is good evidence that physiological concentrations of DHEA promote efficient T cell function by aiding interleukin-2 production, and antagonize immunosuppressive effects of glucocorticoids (47,48). A nuclear receptor specific for DHEA has been demonstrated in murine T cells (49). In ageing mice, replacement doses of DHEA suppress an age-related rise in interleukin-6 (IL-6) production that has also recently been demonstrated in humans (50,51). Since IL-6 is a key mediator of osteoclastogenesis (2), its suppression by youthful levels of DHEA could be expected to reduce bone resorption. IL-6 also stimulates hepatic production of acute phase reactants (50,52), including the important cardiovascular risk factors fibrinogen and plasminogen activator inhibitor (PAI-1) and thus may contribute to their age-related rise (53). The impact of DHEA replacement on plasma levels of IL-6, fibrinogen, and PAI-1 should be assessed in ageing humans. Promotion of youthful cytokine regulation may prove to be the most crucial physiological role of DHEA.

Additionally, a recent study (54) demonstrates that moderate-dose oral DHEA supplementation (50 mg/day, sufficient to raise DHEA-sulfate to youthful levels) has a positive effect on psychological well-being in middle-aged subjects, while modestly increasing serum IGF-1 levels. The putative physiological role of DHEA in promoting postmenopausal bone density remains to be established in long-term supplementation studies. To the extent that the age-related decline in DHEA production contributes to the functional decre-

ments of ageing, the ability of chromium picolinate to enhance DHEA production in middle-aged subjects may be construed as an 'ageing-retardant' effect. The possibility that chromium picolinate may influence ageing mechanisms at a fundamental level is suggested by preliminary animal data (55,56).

Whether the observed increase in DHEA-sulfate plays a role in the apparent reduction of bone resorption during chromium picolinate supplementation, or perhaps promotes bone formation (34), remains to be determined.

Toward future studies

Clearly, further studies are urgently needed to address the impact of chromium picolinate (or other insulin sensitizers), alone or in conjunction with calcium, on calcium balance, bone metabolism, and bone density. Short-term studies can examine efficiency of calcium absorption, urinary calcium loss, and parameters indicative of bone resorption and bone formation. Urinary excretion of the pyridinoline degradation products of cross-linked Type I collagen appears to be a virtually linear function of bone resorption activity (57,58), and thus is superior to urinary hydroxyproline as a measure of bone resorption. (There is considerable 'background' hydroxyproline owing to collagen degradation in other tissues or to dietary gelatin). Currently feasible markers for new bone formation include serum levels of osteocalcin (59) or the bone-specific form of alkaline phosphatase (60) (though it should be noted that insulin may directly suppress osteoblast production of alkaline phosphatase) (7). If short-term studies continue to yield promising results, a long-term study that directly measures bone density would then be indicated.

While dietary calcium and bone health are virtually equated in the minds of the public and indeed most medical professionals, it should be noted that many other nutrients are crucial to proper bone function. In particular, suboptimal intakes or reduced plasma levels of nutrients such as zinc, manganese, copper, boron, and vitamins D and K have been linked to decreased bone density or increased fracture risk (61–68). The foregoing suggests that bioactive chromium may also have a significant role to play in the preservation of bone health. Rather than relying on monotherapy with calcium, chromium, or any other nutrient, it appears likely that well-designed 'nutritional insurance formulas' (69), providing the full spectrum of essential micronutrients in effective forms and dosages, would provide the greatest benefit for bone health, and that lifelong supplementation of this type would have an especially favorable impact on bone density in later life. Indeed, Albanese has reported that an insurance formula (of rather primitive design) was much more effective for promoting bone density than calcium supplements alone (70). Thus, studies should assess the effects of comprehensive nutritional insurance supplementation – featuring ample amounts of bioavailable calcium and chromium picolinate – on bone metabolism and density.

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