World Journal of Diabetes

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.4239/wjd.v5.i1.14

World J Diabetes 2014 February 15; 5(1): 14-16
ISSN 1948-9358 (online)

TOPIC HIGHLIGHT

WJD 5th Anniversary Special Issues (1): Insulin

Insulin and bone: Recent developments

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Received: November 24, 2013 Revised: December 4, 2013
Accepted: December 17, 2013
Published online: February 15, 2014

Abstract

While insulin-like growth factor I is a well-known anabolic agent in bone evidence is beginning to accumulate that its homologue, insulin, also has some anabolic properties for bone. There is specific evidence that insulin may work to stimulate osteoblast differentiation, which in turn would enhance production of osteocalcin, the osteoblast-produced peptide that can stimulate pancreatic β cell proliferation and skeletal muscle insulin sensitivity. It is uncertain whether insulin stimulates bone directly or indirectly by increasing muscle work and therefore skeletal loading. We raise the question of the sequence of events that occurs with insulin resistance, such as type 2 diabetes. Evidence to date suggests that these patients have lower serum concentrations of osteocalcin, perhaps reduced skeletal loading, and reduced bone strength as evidenced by microindentation studies.

Key words: Type 2 diabetes; Insulin; Bone; Osteoblasts; Insulin resistance

Core tip: This is a review of recent publications that suggest an anabolic loop among bone, pancreas, and skeletal muscle.

Klein GL. Insulin and bone: Recent developments. *World J Diabetes* 2014; 5(1): 14-16 Available from: URL: http://www.wjgnet.com/1948-9358/full/v5/i1/14.htm DOI: http://dx.doi.org/10.4239/wjd.v5.i1.14

INTRODUCTION

The interactions between insulin and bone would on the surface appear to be an unlikely subject for an article, let alone a review article, but with the advent of the knockout mouse model many relationships that would not have been obvious now require investigation. The aim of this paper is to provide evidence supporting an anabolic loop including the pancreas, skeletal muscle, and bone.

GROWTH FACTOR

We do not want to confound the anabolic effects of insulin with those of insulin-like growth factor (IGF)-1, although the homology of molecular structure of both molecules may in fact account for some of the anabolic effects of insulin on bone. It should be emphasized at this point that insulin is synthesized in the pancreatic β cells while endocrine IGF-1 is synthesized in the liver. The stimuli for insulin production include glucose and, as we will see, osteocalcin, while endocrine IGF-1 is synthesized by liver in response to growth hormone and the paracrine IGF-1 produced by bone cells, including preosteoblasts and osteoblasts, osteocytes and osteoclasts[1,2] is synthesized in response to stimuli that have not yet been clarified.

While there are copious reports of the anabolic effects of IGF-1 on bone there is a growing amount of data suggesting that insulin itself has an anabolic effect on bone. Suggestions of this effect came from studies involving burned children in which a hyperinsulinemic, euglycemic clamp was employed resulting in an increase in both lean body mass, often indicative of muscle mass, and bone mass at time of hospital discharge compared

to controls, usually between 6 wk to 3 mo post-burn[3]. Moreover, both pre-osteoblasts and osteoblasts manifest different isoforms of the insulin receptor (IR), with IRA being expressed in pre-osteoblasts and IRB being expressed in mature osteoblasts[4]. This specificity suggests that insulin is a critical element in osteoblast differentiation from marrow stromal cells. This may have significance in the generation of the osteoblast peptide osteocalcin, which, as we shall see, has major implications for glucose metabolism. Whether the direct effect of insulin on osteoblasts has clinical significance, however, is not entirely clear. This is in part because the abovementioned report on hyperinsulinemia demonstrated increases in both lean body mass and bone mass[3].

INSULIN

The other side of this proposed loop is the effect of bone on insulin. The stimulus for the work that produced these findings is the knockout mouse model. In this model a significant contribution has been made by Wei *et al*[5] who have most recently reported that osteocalcin stimulates β cell replication in the pancreas *via* a cyclin D1-dependent mechanism utilizing the G-protein coupled receptor family C group 6 member A receptor expressed by these cells. This stimulation occurs during both peak β cell proliferation, which occurs in the perinatal period and in adult mice[5]. Moreover, they described the effects of daily osteocalcin injections in obese type 2 diabetic mice reporting an increase in the number of mitochondria in skeletal muscle as well as an increase in energy expenditure[6], indicating that osteocalcin can also increase muscle work by increasing insulin sensitivity.

Thus these recent data would suggest that under normal conditions insulin may stimulate osteoblast differentiation in order to produce more osteocalcin, which would then stimulate more insulin production by the pancreas and greater insulin sensitivity of skeletal muscle. There are also some recent clinical correlates of these studies in adults. In a recent study Díaz-López *et al*[7] performed a case-control study of 153 diabetic subjects and 306 individually matched controls and found that both the carboxylated and undercarboxylated forms of osteocalcin were lower than matched controls and that carboxylated osteocalcin concentrations were inversely associated with a model assessment of insulin resistance and fasting glucose concentrations. Another report by Gower *et al*[8] indicated that in obese individuals total osteocalcin was directly associated with skeletal muscle but not hepatic insulin sensitivity while undercarboxylated osteocalcin was associated with β cell function in those with abnormal fasting glucose concentrations.

BONE

A major unanswered question is exactly what happens to bone in cases of peripheral insulin resistance? Are the IRs in pre-osteoblasts and osteoblasts down-regulated? We know that osteocalcin levels are lower in type 2 diabetics[7,8]. In addition, we know that insulin resistance is also caused by factors that cause bone resorption, such as the interleukin-6-mediated chronic low grade inflammation that contributes to non-alcoholic fatty liver disease (NAFLD)[9] and excessive glucocorticoid production, another significant contributor to NAFLD[10]. However, we do not at this point know precisely how peripheral insulin resistance affects bone. One conjecture would be that if muscles expend less energy due to their inability to take up glucose then muscle strength may be reduced and skeletal loading may also be consequently decreased. This scenario could explain abnormalities in bone with type 2 diabetes. Were this to be so then bone loss would result in reduced production of osteocalcin and a perpetuation of the problem of peripheral insulin resistance.

So, why has bone loss with type 2 diabetes been so difficult to determine up to now? As summarized by Ferrari[11] in a review article on diabetes and osteoporosis, bone mineral density (BMD) may not be reduced in this condition inasmuch as weight and fat mass must be factored into the BMD determinations. The probability of fracture as assessed by use of the on-line FRAX tool developed by the World Health Organization may also underestimate fracture risk in this condition. As evidence that this may indeed be the case a recent report by Hothersall *et al*[12] examined the files of all hip fractures in Scotland from 2005-2007 and the prevalence of both type 1 and type 2 diabetes in this population. While there was a significant correlation between hip fractures and type 1 diabetes, in which insulin deficiency is the issue, there was no overall increased risk of hip fracture in type 2 diabetes, according to this review. The investigators do, however, state that these findings do not rule out increased risk in sub-groups of type 2 diabetics. While we have demonstrated that osteocalcin, also a marker of bone formation, is lower in patients with type 2 diabetes, not all markers of bone formation or resorption are consistent. For example, Chen *et al*[13] found that while osteocalcin was lower in diabetics *vs* controls, there was no difference in bone specific alkaline phosphatase. Similarly while Bhattoa *et al*[14] found that urinary cross-laps, a resorption marker, was lower in type 2 diabetics *vs* controls while Chen *et al*[13] found that urinary hydroxyproline was elevated.

A new development, however, has shed some light on this problem. In a study that has been Epublished ahead of print, Farr *et al*[15] have reported the use of *in vivo* microindentation of the tibia as an index of bone strength. In this study of 60 post-menopausal women, half of whom had type 2 diabetes, this technique demonstrated decreased bone strength in the diabetic women.

Much more work needs to be done to follow up on these findings but clearly the greater chance of microcracks in the bones of insulin-resistant diabetics may not be detected by bone density determinations.

Therefore, for those who care for diabetic patients, the complications involving bone have been subtle and difficult to detect but as more attention is being paid to this area the pathogenesis of the bone problem should

be more clearly elucidated and new therapeutic targets identified.

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P- Reviewers: Charoenphandhu N, Tarantino G, Traub M
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