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Commentary

Impact of oral antidiabetic agents on bone metabolism

There is an exponential increase in the incidence of diabetes the world over, more so in the Indian subcontinent[1]. Recent advances in the screening and therapy of diabetes and its co-morbid disorders such as dyslipidemia and hypertension with potentially novel therapeutic targets are anticipated to decrease the mortality and subsequent increase in longevity. The average life span of the Indian population has increased and by the year 2050 over 75 per cent of the ageing population will live in the developing world[2].

Non-communicable diseases such as osteoporosis are more likely to be seen in these age groups in association with chronic diseases like diabetes. The most durable clinical end point of osteoporosis is a fracture, which has a significant impact on morbidity and mortality as well as on the quality of life[3]. In this issue, Siddhartha Kumar *et al*[4] describes a cross-sectional study involving 41 type 2 diabetes mellitus (T2DM) patients who were on oral antidiabetic drugs for at least three years and 41 age- and BMI-matched controls looking at the bone mineral density. About one third of the patients with 2DM were on thiazolidinediones alone or in combination with other oral antidiabetic drugs. There was no difference in the occurrence of osteoporosis or osteopenia between cases and controls. Moreover, no difference was observed between thiazolidinedione users and other oral antidiabetic drug users. However, owing to small sample size, it may be difficult to draw definitive conclusions from this study.

The impact of diabetes as well as oral antidiabetic drugs (OADs) on bone mineral density (BMD) and fractures has been reported in a few studies over the last couple of decades[5,6]. Both subjects with type 1 and type 2 diabetes have a higher risk of sustaining fractures when compared to normal individuals. Bone quality rather than BMD, is the key factor affected in patients with type 2 diabetes. This has been established in patients with type 2 diabetes who have an increased or normal BMD[7]. Moreover, the propensity for falls secondary to factors such as poor vision- due to cataracts and retinopathy, and postural hypotension- as a result of autonomic neuropathy or medications, may add to the vulnerability of developing a fracture. Some studies have leant more ambiguity by not demonstrating either a beneficial or a deleterious effect of diabetes and OAD on bone[8]. Many interactions between bone and glucose metabolism have been reported which incorporate the role of osteocalcin, Wnt signalling and insulin growth factors[7].

Osteocalcin has been shown to have a favourable effect on glucose metabolism. A reciprocal relation exists between blood osteocalcin level and the presence of diabetes[6]. An increase in oxidative stress has been demonstrated to have a negative effect on Wnt signalling resulting in the insulin resistance and decreased osteoblastic proliferation. A positive correlation appears to exist between insulin-like growth factor (IGF-1) and BMD[6]. In contrast, an increase in advanced glycosylated end products (AGEs) which is a consequence of chronic uncontrolled hyperglycaemia may hamper bone metabolism as their deposition in bone matrix causes an increase in interleukin-6 production which favours bone resorption[5].

Sulphonylureas, the potent insulin secretagogues are used as second line agents in the treatment of type 2 diabetes. The evidence with regards to the detrimental effect of these drugs on bone is limited. However, by improving glycaemic control, these may exert a favourable effect on bone health[8].

The Biguanide derivative metformin, an insulin sensitizer has been shown to increase osteoblast proliferation and differentiation and also augments type 1 collagen formation in cell culture. In addition, it seems to inhibit adipocyte differentiation and promotes osteoblast differentiation[9]. In a large case-control study by Vestergaard *et al*[10], metformin utilization was associated with a reduction in the risk of fractures.

Bone forming osteoblasts and adipocytes have a common progenitor mesenchymal stem cell (MSC). Peroxisome proliferator-activated receptor gamma (PPAR-γ) overexpression stimulates adipogenesis from the MSC rather than bone forming osteoblasts which results in a decrease in bone mass[11]. In a study involving PPAR-γ knock-out mice, an increase in osteoblastogenesis has been shown in both *in vivo* as well as the embryonic stem cell cultures. The thiazolidinediones, when used as antidiabetic drugs (PPAR-γ activators), convert MSCs to adipocytes thereby suppressing osteoblast development[11,12].

Pioglitazone, a thiazolidinedione antidiabetic agent, promotes adipocyte differentiation into smaller and insulin sensitive adipocytes as a trade off for osteoblast formation. In pre-clinical studies, both decreased bone formation and increased resorption have been described with the use of these drugs[7]. In a recent meta-analysis involving 22 randomized control trials (n=29,544), a significantly increased incidence of fracture was found in women on thiazolidinediones (OR=1.94; 95% CI: 1.60-2.35; $P<0.001$)[13].

In a murine model, a genetic disruption of glucagon-like peptide-1 (GLP-1) receptor signalling resulted in cortical osteopenia and an increase in bone fragility as a result of greater bone resorption by the osteoclasts which was associated with a reduction in thyroid calcitonin expression[14]. A GLP-1 agonist, exendin-4 has been shown to decrease the urinary deoxypyridinoline (DPD)/creatinine ratio and serum C-terminal cross-linked telopeptides of type I collagen (CTX-I) and increase serum alkaline phosphatase (ALP), osteocalcin, and N-terminal propeptide of type 1 procollagen (P1NP) levels in ovariectomized Sprague-Dawley rats[15]. In a meta-analysis by Monami *et al*[16] which included 28 trials that enrolled 11,880 and 9, 175 patients for dipeptidyl peptidase-4 (DPP-4) inhibitors and comparators, respectively, showed a reduced risk of fractures. However, extended longitudinal studies are required to establish the beneficial effects of DPP-4 inhibitors on bone.

In conclusion, although diabetes and oral anti-diabetic drugs seem to influence the bone health, more research is required to know the overall impact of these medications on skeleton on a long term .

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References

1. Anjana RM, Pradeepa R, Deepa M, Datta M, Sudha V, Unnikrishnan R, *et al*; ICMR-INDIA B Collaborative Study Group. Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: phase I results of the Indian Council of Medical Research-INdia DIABetes (ICMR-INDIAB) study. *Diabetologia* 2011; *54* : 3022-7.
2. Goel A. Emergency care for older people in India. *Natl Med J India* 2013; *26* : 295-6.
3. Nazrun AS, Tzar MN, Mokhtar SA, Mohamed IN. A systematic review of the outcomes of osteoporotic fracture patients after hospital discharge: morbidity, subsequent fractures, and mortality. *Ther Clin Risk Manag* 2014; *10* : 937-48.
4. Siddhartha Kumar B, Ravisankar A, Mohan A, Prabath Kumar D, Katyarmal DT, Sachan A, *et al*. Effect of oral hypoglycaemic agents on bone metabolism in patients with type 2 diabetes mellitus & occurrence of osteoporosis. *Indian J Med Res* 2015; *141* : 431-7.
5. Gilbert MP, Pratley RE. The impact of diabetes and diabetes medications on bone health. *Endocr Rev* 2015; *36* : 194-213.
6. Veldhuis-Vlug AG, Fliers E, Bisschop PH. Bone as a regulator of glucose metabolism. *Neth J Med* 2013; *71* : 396-400.
7. Montagnani A, Gonnelli S. Antidiabetic therapy effects on bone metabolism and fracture risk. *Diabetes Obes Metab* 2013; *15* : 784-91.
8. Lapane KL, Yang S, Brown MJ, Jawahar R, Pagliasotti C, Rajpathak S. Sulfonylureas and risk of falls and fractures: a systematic review. *Drugs Aging* 2013; *30* : 527-47.
9. Molinuevo MS, Schurman L, McCarthy AD, Cortizo AM, Tolosa MJ, Gangoiti MV, *et al*. Effect of metformin on bone marrow progenitor cell differentiation: *in vivo* and *in vitro* studies. *J Bone Miner Res* 2010; *25* : 211-21.
10. Vestergaard P, Rejnmark L, Mosekilde L. Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. *Diabetologia* 2005; *48* : 1292-9.
11. Mieczkowska A, Baslé MF, Chappard D, Mabilleau G. Thiazolidinediones induce osteocyte apoptosis by a G protein-

coupled receptor 40-dependent mechanism. *J Biol Chem* 2012; *287* : 23517-26.

12. Ali AA, Weinstein RS, Stewart SA, Parfitt AM, Manolagas SC, Jilka RL. Rosiglitazone causes bone loss in mice by suppressing osteoblast differentiation and bone formation. *Endocrinology* 2005; *146* : 1226-35.
13. Zhu Z-N, Jiang Y-F, Ding T. Risk of fracture with thiazolidinediones: an updated meta-analysis of randomized clinical trials. *Bone* 2014; *68* : 115-23.
14. Yamada C, Yamada Y, Tsukiyama K, Yamada K, Udagawa N, Takahashi N, *et al*. The murine glucagon-like peptide-1 receptor is essential for control of bone resorption. *Endocrinology* 2008; *149* : 574-9.
15. Ma X, Meng J, Jia M, Bi L, Zhou Y, Wang Y, *et al*. Exendin-4, a glucagon-like peptide-1 receptor agonist, prevents osteopenia by promoting bone formation and suppressing bone resorption in aged ovariectomized rats. *J Bone Miner Res* 2013; *28* : 1641-52.
16. Monami M, Dicembrini I, Antenore A, Mannucci E. Dipeptidyl peptidase-4 inhibitors and bone fractures: a meta-analysis of randomized clinical trials. *Diabetes Care* 2011; *34* : 2474-6.