Glucocorticoid induced osteoporosis – is it relevant in Africa?

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Glucocorticoid Induced Osteoporosis (GIOP) is well recognised as a serious complication of chronic prednisone use for Rheumatic Musculoskeletal Diseases (RMDs). Glucocorticoids (GC) are routinely used in several diverse clinical situations and in varying doses. The mechanisms for bone fragility include increased bone resorption coupled with reduced bone formation. Most reported studies failed to control for important confounding variables such as age, menopause, physical activity, disease activity and treatment of the underlying disease. Studies have been heterogeneous in their selection of patients and controls as well as the method of reporting the bone loss. Some studies have reported on absolute Bone Mineral Density (BMD), and others reported t-scores. The definition of osteoporosis as defined by the World Health Organisation (WHO) may be inappropriate for GIOP; some investigators have recommended a cut-off t-score of -1 rather than -2.5. We were able to identify a few studies on GIOP from Africa. These studies show similar reductions in BMD as in other parts of the globe, affecting both the lumbar spine and hip. There was no information on the treatment of GIOP in the studies from Africa and this is a potential area for future research. Our preliminary findings suggest that a systematic review of the literature may reveal many more publications on GIOP from Africa than is currently appreciated. There is considerable room for further research on GIOP across the African continent, which may contribute to a better understanding of the pathogenesis of this devastating complication of long-term use of GC.

Glucocorticoids (GC) were first used in the treatment of Rheumatoid Arthritis (RA) over 6 decades ago[1]. Their effectiveness was so dramatic that they were subsequently used extensively in the treatment of RA as well as several other Rheumatic Musculoskeletal Diseases (RMDs)[2,3]. Some workers have recommended routine use of these agents in treatment of RA[4-6]. There has been a recommendation that GC would be very useful for RA treatment in Africa, where several synthetic Disease Modifying Anti-Rheumatic Drugs (DMARDs) sDMARDs and bDMARDs (biologic) are not always readily available[7]. The use of glucocorticoids is established in the treatment of RA (usually low-dose), lupus nephritis (usually high-dose) and Polymyalgia Rheumatica (PMR) in intermediate doses. Glucocorticoids are also indicated for the treatment of systemic features of Systemic Lupus Erythematosus (SLE), systemic features of RA, systemic vasculitis, polymyositis and dermatomyositis, to name a few. The overwhelming message from recent reports addresses the adverse effects of these medications, which often make a greater contribution to morbidity and mortality than the underlying diseases[8]. The most concerning long-term side-effect of interest to rheumatologists is the development of Glucocorticoid-Induced Osteoporosis (GIOP) with subsequent bone fragility and fractures.

Bone loss in RMDs is often due to inflammatory mediators such as Tumour Necrosis Factor (TNF), Interleukin 6 (IL6), as well as other osteoclast activators of the TNF class such as RANK-ligand[9-11]. It is possible that these cytokines contribute to localised bone loss described in RA, but their role in trabecular bone loss (bone mineral density (BMD) is often extrapolated from studies of localised osteopaenia. Studies of metacarpal bone density showed that bone loss in RA improves with the use of Disease Modifying Anti-Rheumatic Drugs (DMARDs)[12]. It has also been shown that anti-TNF bDMARD therapy improves BMD in RA subjects over time[9]. Indeed,the bone loss in RA is likely to be multi-factorial and includes the consequences of prolonged uncontrolled inflammation, immobilisation, age, and menopause. GC may reduce inflammation

and limit bone loss due to this mechanism. Overall function and mobility also improve with GC use and may reduce bone loss from other mechanisms, especially in RA. The exact role of GC in studies of GIOP in RMDs is clouded by the inclusion of many of these confounders in the various patient selections. GIOP occurs through several mechanisms, ultimately leading to a synergistic cumulative negative effect of excess bone resorption together with reduced bone formation[13-15]. Some of these postulated mechanisms have been demonstrated in the laboratory[14]. The resorption stimulating pathways are similar to those of post-menopausal osteoporosis[15]. Several studies in RA and SLE have identified a possible relationship between GC use and osteoporosis. However, it is not certain which predictor based on cumulative dose, duration, current dose, ever-user and never-user is the most appropriate method of analysis of data. Some studies used normal controls, while others used matched RA patients not receiving GC[16-20]. The different protocols for the use of GC in the different RMDs also makes comparisons between diseases and across studies difficult.

However, a study comparing metacarpal bone content in RA and SLE against normal controls showed that RA patients suffered greater bone loss than SLE patients, despite larger cumulative doses in the patients with SLE[20,21]. The prevalence of GIOP was extensively reviewed in a global meta-analysis of the published literature[22]. Wang *et al*[23], in a systematic review, reported that there were no studies on GIOP from Africa. In a preliminary search of the literature, we identified at least five publications from Africa on the subject, reported in reputable journals[16-21]. The studies from Africa show similar results[16-21]. The weakness of many of these studies was the inclusion of the confounders mentioned earlier, making it difficult to evaluate the true effects of inflammation, immobilisation, age, menopause, and therapy in the genesis of GIOP in RMDs.

We also found inconsistencies in the definition of GIOP across the various studies, globally. Some studies define GIOP based on a T-score of -1, others use the WHO definition of a T-score of -2.5, and yet others based the diagnosis on vertebral and non-vertebral fractures among patients[15,24,25]. Most studies show that the prevalence is higher in post-menopausal females with RMDs, suggesting that oestrogen deficiency may have a promiscuous effect on bone resorption in the presence of GC therapy[12]. There is clearly a need for further research to better define GIOP in order that we can generalise across studies and cohorts on this subject. This will also allow for the development of suitable guidelines for the detection and treatment of GIOP in these diseases. The treatment of GIOP is addressed in several National guidelines[26,27]. These guidelines are meant to be evidence-based, but the recommended routine use of calcium and vitamin D has not been tested in any Randomized Controlled Clinical Trial (RCT). The anti-resorptive agents such as bisphosphonates are still the mainstay of treatment for GIOP[13]. The therapies used for treating Post-Menopausal Osteoporosis (PMOP) have been used successfully to treat GIOP as well. Newer therapies like teriparatide, an analogue of parathormone, have been successfully used in some patients. Denusomab, a monoclonal antibody directed against RANK-ligand, has been shown to be effective in treating GIOP, and its use is based on the evidence that RANK-ligand may be the major cytokine in the pathogenesis of GIOP[18]. Romosozumab is a monoclonal antibody against sclerostin. It has shown benefits in post-menopausal osteoporosis and men. Some data suggest an important role of sclerostin in mediating the effects of glucocorticoids on bone formation. In addition, treatment with an antibody directed against sclerostin prevented bone loss and reduction of strength in a mouse model. These results highlight the potential beneficial effect of romosozumab on GIOP osteoporosis[28-31]. However, it has not yet been studied in patients on chronic steroids. We were unable to identify studies from Africa which evaluated therapies for the treatment of GIOP, and this is an area requiring further research.

In conclusion, contrary to popular belief, research on GIOP has been undertaken on the African continent. The recent formation of the African Society of Bone and Mineral Research (ASoBMR) provides an ideal forum for research into post-menopausal osteoporosis and GIOP across the African continent. Our current literature search was preliminary, but a systematic review/meta-analysis may reveal more studies being done in Africa than is appreciated. Most of the research has focused on RA, but there are reports in patients with SLE as well. Overall, there is a paucity of GIOP research from Africa, emphasizing the need for more studies from this region of the globe. There is a need for prospective research which will address confounding variables, establish a standard definition and reference point for GIOP, evaluate the effects of treatment and ultimately measure the impact of GIOP on vertebral and non-vertebral fractures in patients with RMDs. All these findings will contribute to improving the quality of life of our patients in Africa (and globally) who suffer from these, often debilitating complications of RMDs and their treatment.

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