Osteoporotic Fractures

ii. Summary

General introduction

Osteoporosis is a chronic disease with loss of bone mass and increased risk of osteoporotic (OP) fractures. It is predominantly a disease of elderly or postmenopausal women, with substantial personal and societal impact, mainly because of the associated fractures. Osteoporosis and OP fractures can occur secondary to other morbidities (such as rheumatoid arthritis [RA]) or use of some medications (for instance, glucocorticoids [GCs]). Diagnosis of osteoporosis is based on measurements of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA). Main OP fracture sites include hip, vertebrae, humerus, forearm, pelvis and ribs. Among the OP fractures, vertebral fracture is the most prevalent, and hip is the most problematic with high morbidity, mortality and societal costs.

Absolute number of OP fractures is increasing due to the global increase in life expectancies and the ageing trajectory. On the other hand, awareness about the disease, improved lifestyles and fracture prevention by anti-osteoporotic medications, might have resulted in reduced fracture rates. On that line, previous studies have shown a decrease in incidence rates (IRs) of hip fracture, especially in North European or North American countries in the past decades. However, there is little known about the secular trend in all OP fractures globally, not especially from a Northern European country with traditionally high incidence of OP fractures.

OP fractures are devastating outcomes due to their associated high morbidity and mortality rates. Previous literature has shown that anti-osteoporotic therapies (such as bisphosphonates [BPs]) can prevent a subsequent fracture. There is also evidence that BPs could have some anti-atherosclerotic effects, which might confer a mortality benefit. However, whether BPs would have a beneficial effect against mortality after a fracture is unsolved and highly controversial in the literature.

Oral GCs are one of the most potent anti-inflammatory medications with relatively high frequency of use in many chronic inflammatory diseases. Effects on bone quality and induction of an increased risk of OP fracture is one of the most established side effects of oral GCs. Previous literature has shown a role for daily or cumulative dose of oral GCs in developing an OP fracture. However, the association between various exposure patterns of oral GCs and risk of OP fractures is less clear, particularly in patients with a chronic inflammatory disease who need long-term GC therapy.

RA is a chronic inflammatory musculoskeletal disease, which is characterised by synovitis in the small joints of hands and feet, pain, morning stiffness, and limited range of motion. It is most prevalent among middle-aged and older women. A set of clinical signs and symptoms in physical examination, laboratory tests, and imaging determine the diagnosis of RA. Based on the European Alliance of Associations for Rheumatology (EULAR) recommendations, pharmacotherapy of RA includes conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) with or without short-term low-dose GC therapy in early disease, and biological DMARDs (bDMARD) and targeted synthetic DMARDs (tsDMARDs) in case of failure of csDMARDs. Patients with RA are at an increased risk of OP fractures compared to the general population due to the inflammatory process of the disease and reduced mobility.

Some of the medications that are recommended for use in RA have known and sometimes compound effects on fracture risk. For instance, oral GCs especially in low doses might have some local beneficial effects on bone by supressing the background inflammation and increasing the mobility of patient. But the effect of low-dose oral GCs (≤7.5 mg prednisolone equivalent dose [PED]/day) on OP fracture risk in RA is not yet clear. Furthermore, patients with RA, especially elderly patients, frequently use proton pump inhibitors (PPIs), which have been reported to increase the fracture risk in observational studies, although the exact mechanism has never been established. Thus, it would be of interest to investigate the effect of concomitant use of oral GCs and PPIs on OP fracture risk. Likewise, previous studies have shown that bDMARDs may have protective effects on BMD in patients with RA. But there are few studies who investigated the association between use of bDMARDs and OP fracture risk in RA.

Pharmacoepidemiology is an interdisciplinary field studying the effectiveness of medications and their adverse effects in real-world setting. The pharmacoepidemiological research is observational in essence, and generally uses previously collected anonymised patient data in electronic healthcare databases (EHDs). The randomisation performed in randomised controlled trials (RCTs) is lacking in pharmacoepidemiological studies and hence should be mimicked by means of complicated study designs. This can bring up major limitations, such as confounding and bias, in order to have a fair comparison between the studying groups. We took advantage of pharmacoepidemiological methodologies to investigate the above-mentioned knowledge gaps in the literature.

In this thesis, we aimed to study the OP fractures, and their relation to mortality, medication use and RA. The first section of this thesis evaluated various attributes of OP fractures in the general population, including a recent secular trend of OP fractures,

mortality after fracture with oral BP use, and the association between various exposure patterns of oral GCs and OP fracture risk. The second section focused on the role of medication use in risk of OP fractures among patients with RA, which included low-dose oral GCs, oral GCs and PPIs concomitantly, and bDMARDs.

Section 1, Osteoporotic fractures in the general population

An investigation of recent secular trends in IRs of OP fractures in the general population of Denmark was performed in Chapter 2. We found a general decline in IRs of major OP fractures (MOF) for 50+ adults in Denmark between 1995 and 2010 (from 169.8 to 148.0 per 10,000 person years). All OP fractures were decreasing in women, however, a lower decrease of hip fracture in addition to increasing rates for clinical vertebral and steady rates for humerus fracture were observed in men. Our observed trends were generally in line with previous studies from Denmark, Canada and US. Based on these findings, we recommend appropriate screening for OP fractures (by fracture risk assessment and BMD measurements if needed), in addition to proper use of anti-osteoporotic treatments not only in postmenopausal women, but also in older men.

The association between oral BP use and mortality risk following a MOF was evaluated in Chapter 3, using a cohort of patients with a MOF in the UK Clinical Practice Research Datalink (CPRD) between 2000 and 2018. We found a 7% increased risk of all-cause mortality after non-hip MOF, and a 28% reduced risk after hip fracture with current use of oral BPs versus never use. Both the timing and effect size of an association based on anti-atherosclerotic properties of BPs were not supported by our results. Instead, unknown distortion due to healthy-user bias and selective prescribing, or unknown pleiotropic properties of BPs might explain our findings. Future in vitro and in vivo studies are recommended to elaborate on the alternative mechanisms or pleiotropic properties of BPs, which confer a mortality benefit.

The role of daily and cumulative doses of oral GCs in OP fracture risk in the general population of Denmark was studied in Chapter 4, with a case-control study between 1996 and 2011. The remarkable finding was a distinctive elevated risk of hip and clinical vertebral fracture with heavy use of oral GCs, defined as average daily doses ≥15.0 mg PED/day and a cumulative use ≥1.0 g PED, as in clear contrast to short course users (those with high average daily doses but cumulative use <1.0 g PED). Presumably, the threshold for a marked increased fracture risk in high daily oral GC users is the cumulative use ≥1.0 g PED, which is the hallmark of long-term GC therapy. Therefore, avoiding unnecessary high

doses of oral GCs, adequate fracture assessment and timely anti-osteoporotic therapy are all recommended in patients with a chronic inflammatory disease who need long-term GC therapy, to avoid the catastrophic consequences of an imminent fracture.

Section 2, Osteoporotic fracture risk with medication use in rheumatoid arthritis

The association between low-dose oral GC use (≤7.5 mg PED/day) and OP fracture risk in patients with RA was evaluated in Chapter 5, in a cohort of patients with RA from the CPRD between 1997 and 2017. Current use of low-dose oral GCs was not associated with overall risk of OP fractures compared with past GC use; however, it incurred a 59% increased risk of clinical vertebral fracture. The main results remained unchanged regardless of a short-term (with a cumulative use <1 g PED) or a long-term (≥1 g PED) use. Apparently, the beneficial effect of low-dose GC therapy on suppressing the background inflammation of RA could probably be enough to offset its negative effect on bone synthesis in most fracture sites but not in vertebrae. Thus, clinicians should be aware that even in RA patients who use low daily doses of oral GCs, the risk of clinical vertebral fracture is increased.

The association between concomitant use of oral GCs and PPIs and OP fracture risk in patients with RA was studied in Chapter 6, using the CPRD with all RA patients from 1997 to 2017. We observed a 1.6-fold increased risk of OP fractures with concomitant current use of oral GCs and PPIs in RA patients compared to non-use of both drugs. This was statistically different from a 1.2-fold increased fracture risk associated with single use of oral GCs or PPIs. We did not observe an increasing trend in fracture risk with higher daily doses or longer durations of PPI use, which is in contrast to older observational studies. More attention should be paid to those RA patients who are prescribed both drugs, with routine fracture risk assessment and proper preventative anti-osteoporotic therapies. As we could not match the PPI findings with any of the previously proposed biological mechanisms of action of PPIs on bone or falling, more studies are recommended to investigate the associations that we and others found in real-world data.

The association between use of bDMARDs and OP fracture risk in patients with RA was evaluated in Chapter 7, using nationwide registries in Denmark including all RA patients between 2006 and 2016. We found no reduced risk of OP fractures with bDMARD use in patients with RA compared with no treatment with biologicals. The only known mechanism of action of bDMARDs on bone health is supposed to be through the inflammatory cycle. The negative findings of our study and other observational studies,

could be due to the "treat-to-target" strategy of RA management in a real-world setting, which means comparable control of disease activity in both comparison groups in the study. We believe, this still conforms with the previously reported beneficial effects of bDMARDs on BMD identified in single-arm before-after trials. More investigation is needed to inform on alternative mechanisms or various pleiotropic effects that biologicals might have on different cytokines or bone active molecules.

General discussion and conclusion

The main findings of the studies in this thesis, in addition to putting them into the broader context of the previous literature are presented in Chapter 8. Moreover, the major limitations in pharmacoepidemiological studies, i.e., confounding and bias, have been described with potential examples that we might have encountered in our studies, the strategies embraced to tackle them, and any possible impact on our results. Finally, the clinical implications of our findings and some novel ideas for future research have been presented.

In conclusion, there was an overall decreasing trend in IRs of MOFs in Denmark between 1995 and 2010, while there was an increasing trend in clinical vertebral fracture among men. Oral BPs had apparently no beneficial effect on mortality reduction in patients with a MOF, although our results were probably impacted by healthy-user bias and confounding by selective prescribing. Furthermore, we showed that the threshold for a marked increased risk of hip and clinical vertebral fracture in high daily oral GC users is the cumulative use ≥1.0 g PED, which is a hallmark of long-term GC therapy.

Low-dose oral GC therapy (≤7.5 mg PED/day) in RA patients was associated with an increased risk of clinical vertebral fracture, while there was no association with risk of non-vertebral OP fractures. We also found an increased and additive risk of OP fractures by concomitant use of oral GCs and PPIs in patients with RA, although the risk did not increase with increasing daily doses or longer duration of PPI use. Finally, we found that bDMARDs had no independent beneficial effect on reducing the risk of OP fractures in patients with RA.