Summary of the 9th Annual NOREPOS Workshop

18-19 June 2014

written by Kristin Holvik

Thirty participants were gathered at Solstrand Hotel og Bad, Os, for two days of presentations and discussions. We were joined by Prof. Karl Michaëlsson from Uppsala University and Prof. Claes Ohlsson from the Sahlgrenska Academy in Gothenburg.

Wednesday, 18 June

The workshop was opened by Professor **Grethe Tell**, leader of the NOREPOS steering committee, who gave an overview of the history of NOREPOS, its areas of research, data sources, and examples of scientific publications from our research network. This included the study of geographic variations in bone mineral density, studies of precision and methodological comparisons of densitometers, studies of trends in fracture incidence and mortality after fracture, and the study of a wide range of potential risk factors such as drinking water quality and nutritional factors.

Professor **Claes Ohlsson** gave an invited lecture about genetic epidemiology. His research interests and activities cover a wide range from experimental animal research, genetic studies and clinical studies. He collaborates with the Womens' Health Initiative and the Umeå Fracture and Osteoporosis cohort. Genome-wide association studies (GWAS) may be performed on various phenotypes of bone including areal BMD (requiring DXA), trabecular and cortical volume BMD (requiring pQCT), bone microstructure (requiring high-resolution pQCT), and fracture. Polymorphisms identified in GWAS to be highly significantly associated with the phenotype are studied further in functional studies, and need to be replicated in independent cohorts. THE GEFOS consortium (Nat Genet 2012;44:491-501) is the largest GWAS meta-analysis to date, identifying 56 causal SNPs for BMD. Fourteen loci were also associated with fracture risk. His suggestion was that the large hip and forearm fracture cohorts with DNA information in NOREPOS may contribute to identify mechanisms that may lead to development of target treatment for fall prevention.

Grethe Tell presented the DEMAB (Denosumab global safety assessment study among women with postmenopausal osteoporosis) study. This is an ongoing post-marketing study for monitoring the safety of Denosumab (Prolia) compared to other osteoporosis medications in postmenopausal women. It is an open cohort including all women in Norway aged 55 each year, and will continue until 2020. Monitoring of potential long-term adverse side effects of medication on the market is required by the FDA and EMA. Nine selected adverse events of special interest are monitored. Use of Prolia is identified through the Norwegian Prescription Database. Comorbidity diagnoses in all hospitalizations including a diagnosis code for osteoporosis are retrieved from the Norwegian Patient Register (NPR). Validation studies have been performed by reviewing medical records. Thus far, 300 postmenopausal women have used Prolia in the study period. A new validation study of hypocalcaemia and other conditions will be conducted shortly.

Post Doc **Tone Omsland** presented her analyses on future projections of hip fracture incidence in Norway.

Researcher **Ann Kristin Knudsen** presented the Norwegian Burden of Disease project and opened for suggestions for how to best integrate osteoporosis and hip fracture data. The Global Burden of Disease (GBD) project was initiated by the World Bank in 1990 and is now administered by the Institute for Health Metrics and Evaluation at the University of Washington, Seattle. As of 2013 it is updated annually. Its purpose is to provide a comparable overview of cause-specific mortality and morbidity for all countries. Years of potential life lost (YPLL) and Disability Adjusted Life Years (DALYs) are the main measures of

disease burden. Norwegian data in GBD are retrieved from scientific publications and central health registers (NPR and the Cause of Death Registry). When Norwegian data are not available, numbers are estimated preferably from other Scandinavian or European countries. The NOREPOS network may contribute to the quality of GBD by communicating estimates of BMD, falls and fracture incidence to the project. There are three categories of disease in GBD: 1) Communicable, maternal, neonatal, and nutritional disorders; 2) Non-communicable diseases; 3) Injuries. Fractures are categorized as a secondary level (sequela) to the category *fall injuries*, while low BMD is categorized as a risk factor. Thus, a concern is that the contribution of hip fracture to loss of function and mortality will be underestimated in GBD, as a minor proportion of sufferers are expected to have fall injury diagnosis codes recorded in the central registers. An appeal from the audience was that hip fracture should be categorized as a non-communicable disease rather than a sequela to falls. There may be a possibility to establish an advisory group.

Professor **Karl Michaëlsson** summarized his work on identifying the risk of atypical fractures of the femoral shaft in bisphosphonate users (N Engl J Med 2012;367:582). Based on the Swedish prescription database, the Swedish patient register, and review of all X-rays in women with a subtrohcanteric or femoral shaft fracture in 2008, a relative risk of 47.3 (95% CI 5.6 - 87.3) for atypical fractures in bisphosphonate users was estimated. However, the absolute risk is small. He proposed that the conflicting results regarding the possible excess risk of atypical fractures associated with bisphosphonate use stem from differences in definitions of atypical fractures, i.e. interpretations of radiographs.

Research fellow **Cecilie Dahl** who defended her PhD thesis two weeks ago, gave an overview of her thesis, entitled: «Quality of municipal drinking water and the risk of osteoporotic fractures in Norway». The dissertation consisted of three sub-studies where Cecilie studied differences in fracture risk according to drinking water quality in nationwide data. Results from the first sub-study showed that the drinking water that was slightly acidic often was less hygienic, and it was also associated with a higher incidence of forearm fractures. In the second sub-study, higher magnesium content in drinking water could be protective against hip fracture, whereas a higher level of calcium was not associated with hip fractures. In the third sub-study, the concentrations of metals such as lead, cadmium and aluminum in drinking water were examined. A higher concentration of cadmium in drinking water was associated with an increased rate of hip fracture in men. Also, among the oldest participants (66-85 years), a higher concentration of lead in the water was associated with more hip fractures in both men and women.

The day was rounded off with some spare time for spa, bathing and relaxation, and conference dinner.

Thursday, 19 June

The morning session included two invited lectures providing an overview in topics concerning inflammation, oxidative stress, obesity and metabolic syndrome.

Chief physician and Associate Professor **Jørn V Sagen** talked about inflammatory pathways in metabolic syndrome and obesity. His introduction touched upon the development and prevalence of obesity in society, indications for bariatric surgery, and the definitions of metabolic syndrome in WHO and the International Diabetes Federation. He presented the roles of hormones and cytokines expressed by adipocytes which play a role in appetite regulation and insulin sensitivity, including leptin, adiponectin, inflammatory factors and thrombotic factors. Obesity is a combination of subcutaneous and visceral fat. The subcutaneous adipose tissue may play an important role in the regulation of fat storage in adipose tissue. About one in five obese persons are insulin sensitive and thus metabolically healthy. This is associated with a well-functioning remodeling of adipose tissue, with a higher proportion of anti-inflammatory M2 macrophages, in contrast to the majority of pro-inflammatory M1 macrophages in those with poor insulin sensitivity. There is a wide range of immune cells in adipose tissue, including CD4+ and

CD8+ cells, Treg cells, and mast cells. Acute minor inflammations in the adipocytes following meals are necessary and important for normal and healthy expansion of the adipose tissue. Inflammation is thus not only harmful.

Karl Michaëlsson talked about oxidative stress and inflammation in relation to osteoporosis and fractures. He presented evidence of a relationship between risk of cardiovascular disease and hip fracture from the Swedish Twin register. The mechanisms for the link between osteoporosis and cardiovascular disease are not established. Relationships have been found between oxidative stress and bone outcomes. A recently published study from the Swedish Mammography cohort and the Uppsala Longitudinal Cohort in Adult men showed an inverse association between intakes and serum concentrations of alpha-tocopherol, a potent antioxidant, and risk of hip fracture. He also showed some preliminary results on associations between milk intake and fracture risk.

In the following session, results from research projects within the studies in NOREPOS were presented.

Ellen M Apalset presented findings from her doctoral work about C-reactive protein (CRP), neopterin, kynurenines (tryptophane metabolites) and osteoporosis and hip fracture. Concerning CRP, most population studies have found a positive association between CRP and fracture risk, but some have not. BMD data are more conflicting. Ellen will defend her thesis 23 September, 2014.

Anne Johanne Søgaard presented her recently published findings of body mass index, waist-hip ratio and hip fracture based on data from the Cohort of Norway and the NOREPOS hip fracture database. (J Intern Med 2014 Mar 5.)

Researcher **Kristin Holvik** and PhD student **Trine E Finnes** presented findings from a case-cohort-study in NOREPOS on serum measurements of vitamins A, D, E, and K and risk of hip fracture.

The final 1 ½ hours were devoted to initiate discussions about plans and ideas for potential future projects. These include:

- Genetic studies in NOREPOS, by Anil Jugessur
- Inflammation, by Clara Gjesdal
- Vitamins and fatty acid composition, by Kristin Holvik
- Social inequalities in hip fracture incidence and mortality after hip fracture, by Tone Omsland
- A simple prediction model for hip fracture, by Anne Johanne Søgaard
- An application in preparation for the EU programme Horizon 2020, by Karl Michaëlsson and Haakon Meyer

At the end of the workshop, **Siri Forsmo** invited to the 10th Annual NOREPOS workshop in Trondheim in 2015, provided that financing resources are available.

The seminar was rounded off with lunch and bus transport back to Flesland airport.