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# Genetic studies of the regulation of bone parameters and serum testosterone


Osteoporosis is a common disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to increased risk of fracture and represents a huge economic burden on health care systems. The main aim of this thesis was therefore to try to identify new genetic variants associated with different bone parameters that could serve as potential pharmaceutical targets in the future and to evaluate the clinical utility of these variants for fracture prediction.

We used several well-characterized cohorts and performed the largest genome-wide association studies to that date on DXA-derived areal bone mineral density (aBMD), which is used clinically, and trabecular and cortical volumetric BMD, measured by the more specific peripheral quantitative computed tomography. We identified many genetic variants associated with bone parameters and the clinical endpoint fractures. The genetic variants associated with aBMD predicted incident fractures, but the magnitude of these associations was substantially reduced after adjustment for aBMD. Thus, the clinical utility of these genetic variants for fracture prediction is limited when aBMD is known.

Low serum testosterone (T) levels have been linked to an increased risk of osteoporosis in men. Observational studies have also demonstrated that obesity is strongly associated with low serum T, but the direction and causality of this relationship is unclear. The second objective of this thesis was therefore to determine whether low T causes obesity, or vice versa. Hence, using a bi-directional Mendelian randomization analysis, we found evidence of a causal effect of body mass index (BMI) on serum T, whereas no evidence was found supporting a causal effect of serum T on BMI in men.

The studies herein have identified a number of novel loci associated with different bone parameters and, hence, fracture risk. These findings may result in the development of novel pharmaceutical therapies for osteoporosis and the improvement of prediction models with new biomarkers to identify patients at risk. In addition, we demonstrated that there is a causal effect of BMI on serum T in men, suggesting that population-level interventions to reduce BMI are expected to increase serum T in men.



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