

Genetic studies of the regulation of bone parameters and serum testosterone

Akademisk avhandling

Som för avläggande av medicine doktorexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentlig försvaras i hörsal Arvid Carlsson, Academicum, Medicinargatan 3, Göteborg, den 14 juni 2018, klockan 13.00

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Avhandlingen baseras på följande delarbeten

- I. Estrada K, Styrkarsdottir U, Evangelou E, Hsu YH, Duncan EL, Ntzani EE, Oei L, Albagha OM, Amin N, Kemp JP, Koller DL, Li G, Liu CT, Minster RL, Moayyeri A, Vandenput L, Willner D, Xiao SM, Yerges-Armstrong LM, Zheng HF, Alonso N, **Eriksson J**, et al. Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture. *Nature Genetics*, 2012; 44(5):491-501.
- II. **Eriksson J**, Evans D, Nielson C, Shen J, Srikanth P, Hochberg M, McWeeney S, Cawthon P, Wilmoth B, Zmuda J, Tranah G, Mirel D, Challa S, Mooney M, Crenshaw A, Karlsson M, Mellström D, Vandenput L, Orwoll E, Ohlsson C. Limited clinical utility of a genetic risk score for the prediction of fracture risk in elderly subjects. *Journal of Bone and Mineral Research*, 2015; 30(1):184-94.
- III. *Paternoster L, *Lorentzon M, *Lehtimäki T, ***Eriksson J**, Kähönen M, Raitakari O, Laaksonen M, Sievänen H, Viikari J, Lyytikäinen LP, Mellström D, Karlsson M, Ljunggren O, Grundberg E, Kemp JP, Sayers A, Nethander M, Evans DM, Vandenput L, Tobias JH, Ohlsson C. Genetic determinants of trabecular and cortical volumetric bone mineral densities and bone microstructure. *PLoS Genetics*, 2013; 9(2):e1003247. (* contributed equally)
- IV. **Eriksson J**, Haring R, Grarup N, Vandenput L, Wallaschofski H, Lorentzen E, Hansen T, Mellström D, Pedersen O, Nauck M, Lorentzon M, Nystrup Husemoen LL, Völzke H, Karlsson M, Baumeister SE, Linneberg A, Ohlsson C. Causal relationship between obesity and serum testosterone status in men: A bidirectional mendelian randomization analysis. *PLoS One*, 2017; 12(4):e0176277.

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Abstract

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. The clinical utility of these genetic variants for fracture prediction in elderly subjects was, however, 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.

Keywords: osteoporosis, bone mineral density, genetics, genome-wide association study, testosterone, body mass index, Mendelian randomization