A *TNFRS11B* mutation is associated with BMD and risk of hip fracture

Evidence suggests a strong genetic influence on osteoporotic fracture risk, although the basis of the link with fracture, especially hip fracture, is ill-defined. Several studies indicate an association between a Lys3Asn polymorphism of osteoprotegerin (encoded by *TNFRS11B*) and osteoporosis outcome, but the findings are inconsistent. Nevertheless, such an association is feasible since osteoprotegerin inhibits bone resorption. Moffett *et al.* conducted a prospective study in elderly women to investigate the association between the osteoprotegerin Lys3Asn polymorphism, BMD and fracture risk.

Participants were 6,658 white women aged ≥65 years enrolled in a osteoporotic fracture study who provided blood samples for genotyping. The womens' BMD was measured by dual-energy X-ray absorptiometry or single-photon absorptiometry, and all fractures reported during follow-up were validated by a radiographic report; fractures owing to major trauma were excluded.

Women homozygous for the Lys allele had significantly lower BMD at the lumbar spine, intertrochanter region, distal radius and calcaneus than women with the Asn allele. During 13.6 years of follow-up, 701 incident hip fractures were reported (362 femoral-neck and 333 intertrochanter fractures). Compared with women homozygous for the Lys allele, those homozygous for the Asn allele had a 51% and 26% increased risk, respectively, of femoral-neck and hip fracture, independent of BMD.

The authors predict that the ability to identify individuals with a genetic susceptibility to hip fracture could aid early intervention and treatment, and call for confirmation of their findings.

Original article Moffett SP *et al.* (2008) Osteoprotegerin Lys3Asn polymorphism and the risk of fracture in older women. *J Clin Endocrinol Metab* [doi:10.1210/jc.2007-1019]

Low testosterone levels are associated with insulin resistance in men with diabetes

Testosterone deficiency is common in men with type 2 diabetes. Limited evidence suggests that low testosterone is associated with insulin resistance, but the prevalence of low testosterone levels in men with type 1 diabetes is unknown. Grossmann and colleagues, therefore, conducted a cross-sectional study to determine the prevalence of testosterone deficiency and examine the relationship between testosterone levels and insulin resistance in 574 men with type 2 diabetes and 69 with type 1 diabetes.

Fasting blood samples were collected in the morning for determination of total testosterone (TT) levels, indices of insulin resistance and calculated free testosterone (cFT; adjusted for sex-hormone-binding globulin). TT and cFT levels of a randomly selected subgroup of 262 men with type 2 diabetes were retested after a median of 6 months.

Interestingly, 43% of men with type 2 diabetes had low TT levels (<10 nmol/l or <288 ng/dl), whereas the prevalence was only 7% for men with type 1 diabetes. However, one in five men with type 1 diabetes had low cFT levels (<0.23 nmol/l or <6.6 ng/dl), a prevalence similar to that of men with type 2 diabetes after adjustment for age and BMI. After adjustment for confounders including age and BMI, low testosterone levels were independently associated with insulin resistance in both groups. Furthermore, changes in TT level and insulin resistance were inversely correlated in the longitudinal analysis.

The authors caution that testosterone replacement therapy should only be recommended for affected men if randomized trials confirm its overall benefit.

Original article Grossmann M *et al.* (2008) Low testosterone levels are common and associated with insulin resistance in men with diabetes. *J Clin Endocrinol Metab* [doi:10.1210/jc.2007-2177]

Elevated sex-hormone-binding globulin level is an independent risk factor for hip fracture

Previous studies indicated that low serum estradiol levels increase the risk of hip fracture in postmenopausal women. Sex-hormone-binding globulin (SHBG) reduces the levels of bioavailable estradiol and testosterone in circulating blood, which further increases fracture risk. Lee and colleagues investigated the associations and interactions between estradiol, testosterone, SHBG, and the risk of subsequent hip fracture in postmenopausal women.