SEX STEROID METABOLISM AND BODY COMPOSITION

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg, onsdagen den 20 maj 2009, kl. 9.00.

av

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Avhandlingen baseras på följande delarbeten:

I. **The uridine diphosphate glucuronosyltransferase 2B15 $D^{85}Y$ and the 2B17 deletion polymorphisms predict the glucuronidation pattern of androgens and fat mass in men.**
Swanson C, Mellström D, Lorentzon M, Vandenput L, Jakobsson J, Rane A, Karlsson M, Ljunggren Ö, Smith U, Eriksson AL, Bélanger A, Labrie F, Ohlsson C.
J Clin Endocrinol Metab. 2007 Dec;92(12):4878-82

II. **Sex steroid levels and cortical bone size in young men are associated with a uridine diphosphate glucuronosyltransferase 2B7 polymorphism ($H^{268}Y$).**
Swanson C, Lorentzon M, Vandenput L, Labrie F, Rane A, Jakobsson J, Chouinard S, Bélanger A, Ohlsson C.
J Clin Endocrinol Metab. 2007 Sep;92(9):3697-704

III. **Serum levels of specific glucuronidated androgen metabolites predict BMD and prostate volume in elderly men.**
Vandenput L, Labrie F, Mellström D, Swanson C, Knutsson T, Peeker R, Ljunggren Ö, Orwoll E, Eriksson AL, Damber JE, Ohlsson C.
J Bone Miner Res. 2007 Feb;22(2):220-7

IV. **Androgens and glucuronidated androgen metabolites are associated with metabolic risk factors in men.**
Vandenput L, Mellström D, Lorentzon M, Swanson C, Karlsson MK, Brandberg J, Lönn L, Orwoll E, Smith U, Labrie F, Ljunggren Ö, Tivesten Å, Ohlsson C.
J Clin Endocrinol Metab. 2007 Nov;92(11):4130-7

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ABSTRACT

SEX STEROID METABOLISM AND BODY COMPOSITION

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Background: The bioactive androgens testosterone (T) and dihydrotestosterone (DHT) regulate bone and fat mass in men. The effects of androgens are largely determined by the rate of their synthesis and inactivation. Irreversible conjugation of androgens or androgen metabolites by UDP glucuronosyltransferases (UGTs) into water-soluble glucuronidated androgen metabolites plays an important role in the inactivation of androgens and thereby in the regulation of local intracellular androgen levels.

Aims: To *in vivo* characterize genetic variations associated with substrate-specific glucuronidation of androgens/androgen metabolites and to explore the impact of androgen metabolites and polymorphisms associated with glucuronidation of androgens/androgen metabolites as predictors of bone and fat mass.

Methods: Three candidate polymorphisms in enzymes, proposed from *in vitro* studies to be involved in glucuronidation of androgens (UGT2B7, UGT2B15 and UGT2B17), and androgens/glucuronidated androgen metabolites, measured by mass spectrometry, were analyzed in two well-characterized population-based cohorts of young adult and elderly Swedish subjects.

Results: We demonstrated *in vivo* that the UGT2B7 $H^{268}Y$, UGT2B15 $D^{85}Y$ and UGT2B17 deletion polymorphisms are functional or in linkage with functional polymorphisms. We provided *in vivo* evidence for substrate-specific glucuronidation of androgens by the three UGT2B enzymes. Both UGT2B15 and UGT2B17 were involved in the glucuronidation of the androgen metabolite 5α-androstane-3α,17β-diol (3α-diol) into 3α-diol-17glucuronide (17G), while only UGT2B17 had the capacity to directly glucuronidate T. The urinary T to epiT ratio, commonly used in antidoping test programs, was strongly associated with the UGT2B17 deletion polymorphism. The glucuronidation of DHT was partly dependent on UGT2B17. UGT2B7 was involved in the glucuronidation of 3α-diol into 3α-diol-3glucuronide (3G).

Importantly, the glucuronidated androgen metabolites 3G and 17G associated more strongly with bone mineral density (BMD) than the bioactive androgens. The UGT2B7 $H^{268}Y$ polymorphism associated with cortical bone size. Young adult men homozygous for the UGT2B7 Y-allele had larger cortical bone size than individuals homozygous for the H-allele.

The glucuronidated androgen metabolite 17G, and especially the 17G/DHT ratio, were directly related to fat mass and metabolic risk factors. The 17G/DHT ratio explained a substantial part of the variance of total body fat mass in young adult and elderly men (12% and 15%, respectively). The UGT2B15 $D^{85}Y$ and UGT2B17 deletion polymorphisms associated with fat mass and metabolic risk factors. Subjects homozygous for the UGT2B17 deletion or the UGT2B15 Y-allele had increased amount of fat.

Conclusions: The present findings indicate that analyses of specific glucuronidated androgen metabolites might provide additional information for prediction of the risk of osteoporosis and metabolic diseases. Genetic variations in enzymes responsible for the glucuronidation of androgens result in altered levels of glucuronidated androgen metabolites in serum and probably also of androgen levels in androgen-dependent tissues. Some of these genetic variations associate with bone and/or fat mass.

Keywords: UDP glucuronosyltransferases, polymorphisms, androgens, glucuronidated androgen metabolites, fat mass, bone, metabolic risk factors, population study

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