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UGT2B17 genotype and pharmacokinetic profile of testosterone during substitution therapy

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Introduction

- Testosterone is mainly excreted in the urine as testosterone glucuronide. Glucuronidation is partly dependent on the *UGT2B17* genotype (1) and testosterone glucuronide excretion is lower in men having the *UGT2B17* deletion polymorphism (2-4).
- We investigated if *UGT2B17* genotypes were associated with serum levels of reproductive hormones in hypogonadal men receiving testosterone substitution.

Material & Methods

- 207 hypogonadal men treated with Testosterone undecanoate (TU, Nebido®) retrospectively included, and genotyped for the *UGT2B17* deletion polymorphism.
- All men had been given 1000 mg TU per injection at start, at 6 and 18 weeks. Subsequent dosage intervals were individualised.
- Reproductive hormone levels were determined in blood samples taken 2 and 6 weeks after the 1st and 2nd injection as well as prior to the 3rd injection and at controls 2-3 years after initiation of treatment.

Table 1. Primary diagnoses stratified according to the *UGT2B17* genotype.

Diagnoses	ins/ins n=87 (42%)	ins/del n=91 (44%)	del/del n=29 (14%)	Total n=207(100%)
Klinefelter Syndrome and 46XX,male	16 (39)	20 (48.8)	5 (12.2)	41 (100)
Primary testicular disease, exl 47XXY	46 (42.6)	49 (45.4)	13 (12)	108 (100)
Kallmann Syndrome	10 (45.5)	6 (27.3)	6 (27.3)	22 (100)
Hypogonadotropic hypog., other reasons	4 (40)	5 (50)	1 (10)	10 (100)
Irradiation induced hypogonadism	3 (50)	3 (50)	0	6 (100)
Others*	8 (40)	8 (40)	4 (20)	20 (100)

*Others: Injury/torsio/aplasia of the testis (n=7), Fragile X syndrome (n= 1), Charge syndrome (n=1), Kennedy syndrome (n=1), Partial Androgen insensitivity syndrome (n=3), Y-microdeletion (n=1), Liver transplant (n=1), Heart transplant (n=1), HIV (n=3) and Hypogonadism induced by opiods (n=1)

Results

- The overall frequency of the *UGT2B17* genotypes was ins/ins: 42.0%, ins/del: 44.0% and del/del: 14.0% (Table 1).
- Testosterone levels did not differ between the 3 genotypes 18 weeks after initiation of TU treatment (Figure 1A).
- LH levels were significantly lower in the del/del group after 18 weeks of TU treatment (Figure 1B). At the same time Estradiol levels tended to be higher in the same group compared to the two other genotype-groups (ins/del and ins/ins) though non-significantly (Figure 1C). SHBG, Free testosterone, total cholesterol or haemoglobin levels did not differ between groups.
- The del/del group had a significantly lower delta testosterone value (8 weeks to 18 weeks) (p=0.044).
- At follow-up 2-3 years after initiation of the treatment, all patients had individual treatment regimes, which were not associated to their UGT2B17 genotype.

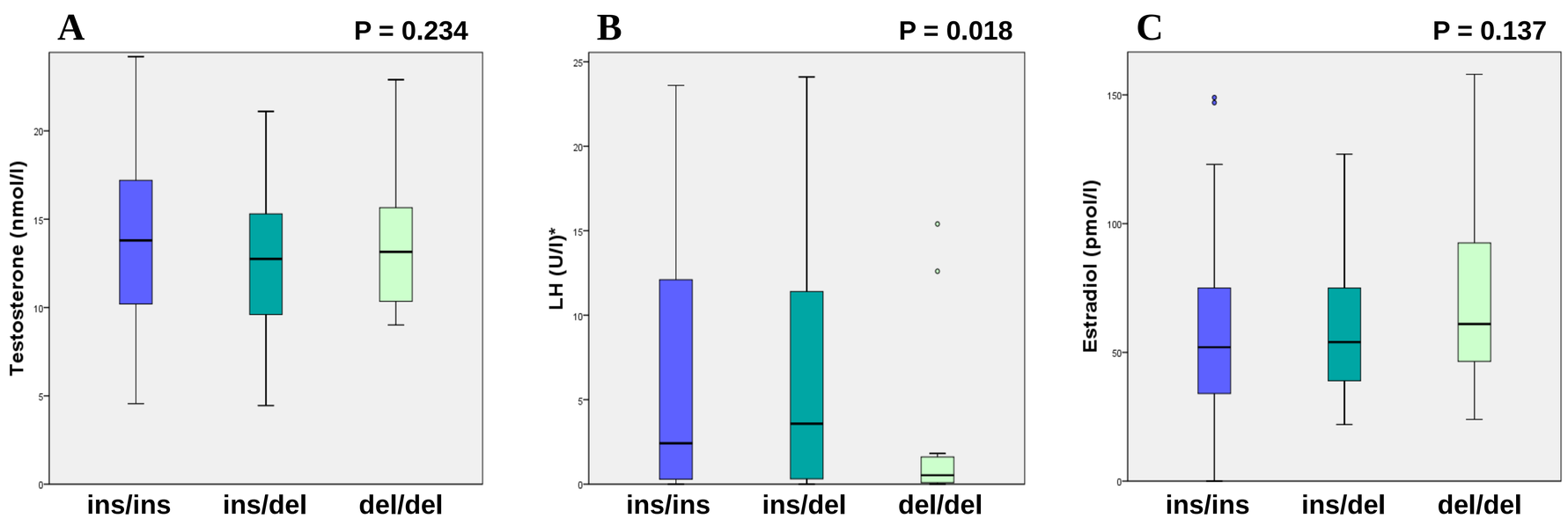

Figure 1.
- Hormone levels in blood samples taken prior to the 3rd injection and stratified according to *UGT2B17* genotypes.
- P-values are based on regression analysis adjusted for confounders (n = 166).

* LH levels from patients with Hypogonadotropic hypogonadism were not included.

Conclusion

Serum testosterone levels at 18 weeks did not depend on *UGT2B17* genotype in hypogonadal men given standard treatment with TU. However the del/del group had a slower fall in testosterone levels in the period between the two last injections as well as lower levels of LH at 18 weeks. This could indicate a lower testosterone excretion rate, and maybe a possible need of a reduction in testosterone dosage. These findings remain to be investigated further.

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