SIZE MATTERS: THE CAG REPEAT LENGTH OF THE ANDROGEN RECEPTOR GENE, TESTOSTERONE, AND MALE ADOLESCENT DEPRESSION SEVERITY

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INTRODUCTION

- There is a distinct **increase in the prevalence** of **depression** with the **onset of puberty** (1).
- The **role** of peripubertal **testosterone levels in boys** in this context is **insufficiently understood** and may be **modulated** by a functional **polymorphism** of the **androgen receptor** gene (AR), a variable number of CAG repeats (2).
- Moreover, the relationship between testosterone, CAG repeat length, and the severity of depressive symptoms may **differ** between **subclinical and overt depression** (1, 3).

AIM

Against this background, the present study was conducted to investigate the **relationship** between

- **free testosterone levels,**
- the **CAG repeat length** of the AR,
- **depression status** (subclinical vs. overt),
- and the **severity of depressive symptoms**

in an **adequately powered** study including patients from a **clinical** sample.

METHODS

- Clinical and biochemical data were collected on **155 boys,** treated as in- or daycare patients at a single psychiatric hospital.
- **Testosterone** (and adrenal steroid) levels were determined by **liquid chromatography-tandem mass spectrometry** and free testosterone levels based on Vermeulen (4).
- Data regarding the above outlined relationship (**see AIM**) were subjected to a **higher-order moderation analysis** within the multiple regression framework, considering important covariates (e.g., BMI, smoking, psychotropic medication, adrenal steroids).
- All **analyses** were replicated in a subsample with **confirmed** major depressive disorder (MDD).

RESULTS

Descriptives

Of the 155 adolescent boys, 118 were considered for further analyses, due to either missing information on at least one of the variables of interest or a BMI below the 5th percentile (see **Table 1** for **patient characteristics**).

Multiple Regression

There was a **constant relationship** between **free testosterone** and depression severity irrespective of the number of CAG repeats in adolescents with a **Beck Depression Inventory (BDI-II) score ≤ 13 (subclinical depression;** $b = 0.001$, $t_{101} = 0.36$, $P = .72$).

In adolescents with a **BDI-II score > 13** (**at least mild depression**), there was a significant **negative relationship** between free testosterone and BDI-II score in patients with **less than 19 CAG repeats** and a significant **positive relationship** in those with **more than 28 CAG repeats** ($b = 0.01$, $t_{101} = 2.69$, $P = .008$; $d = 0.33$; see **Figure 1**).

All findings were verified in confirmed MDD.

Table 1
Patient Characteristics

	BDI > 13 (n = 73)	BDI ≤ 13 (n = 45)
age (years)	15.73 (1.76) [11.80 - 18.39]	14.08 (1.98) [11.26 - 18.38]
z-BMI	0.46 (1.20) [-1.54 - 2.76]	0.48 (1.11) [-1.58 - 2.85]
BDI-II	24.97 (8.27) [14 - 48]	6.84 (3.82) [0 - 13]
BDI-II severity category (%)		
mild	30.1	#
moderate	41.1	#
severe	28.8	#
psychotropic medication (%)	21.9	17.0
smoking (%)*	30.1	13.2
FT (pmol/l)	245.74 (120.53) [0.13 - 517.61]	160.65 (118.11) [0.01 - 465.63]
CAG-RL	21.62 (2.77) [11-29]	21.47 (2.84) [15 - 29]
DHEA-S (µmol/l)	6.65 (3.83) [0.08 - 21.84]	5.49 (2.99) [1.46 - 15.77]
androstenedione (nmol/l)	0.09 (0.06) [0.01 - 0.35]	0.06 (0.06) [0.01 - 0.38]
cortisol (nmol/l)	399.36 (133.26) [26.11 - 665.34]	350.16 (142.97) [150.85 - 641.75]
25(OH)-vitamin D (nmol/l)	34.43 (15.94) [11.73 - 86.36]	41.59 (24.41) [15.48 - 141.77]

Mean, standard deviation (in round brackets), and range (in square brackets) for interval scaled variables, percentages otherwise; z-BMI: z-standardized BMI, FT = free testosterone, CAG-RL = CAG repeat length.

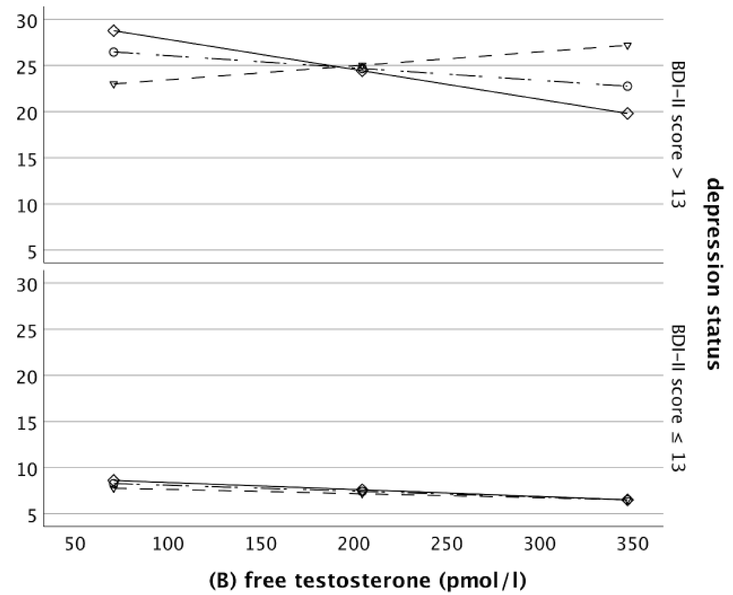

Figure 1 - Free testosterone levels and BDI-II scores separately plotted for exemplary groups of CAG-length (at -1 SD (14. percentile) , the mean , and +1 SD (86. percentile)), considering multiple covariates.

CONCLUSIONS

The results of the present study suggest that the **effects** of **testosterone on mood** in male adolescents with depression **depend on** the **genetic make-up** of the **androgen receptor** gene as well as on **depression status**. This implies that this complex relationship:

- should be **considered** by future **studies addressing mental health** issues in adolescent **boys** and **men** against an endocrine background
- may **contribute to tailored treatment** concepts in psychiatric medicine, especially in adults when testosterone treatment is considered to ameliorate depressive symptoms.

REFERENCES

1. Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. The Lancet. 2012;379(9820):1056-67.
2. Vermeersch H, T'Sjoen G, Kaufman JM, Vincke J, Van Houtte M. Testosterone, androgen receptor gene CAG repeat length, mood and behaviour in adolescent males. Eur J Endocrinol. 2010;163(2):319-28.
3. Colangelo LA, Sharp L, Kopp P, Scholtens D, Chiu BC-H, Liu K, et al. Total testosterone, androgen receptor polymorphism, and depressive symptoms in young black and white men: The CARDIA Male Hormone Study. Psychoneuroendocrinology. 2007;32(8-10):951-8.
4. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab. 1999;84(10):3666-72.

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