

## 7. SUMMARY

### **The physiological influence of adrenal androgens and glucocorticoids on forearm bone of healthy children during growth.**

The positive effect of gonadal steroids on bone mass are a well known phenomenon. Supraphysiological adrenal androgen secretion levels in growing children (e.g. premature pubarche) may also exert bone anabolic effects. These beneficial effects of both strong and weak sex steroids are contrary to the osteoporosis-promoting effects of glucocorticoid excesses. The aim of this thesis was to cross-sectionally and longitudinally ascertain whether individually raised endogenous adrenal androgen and glucocorticoid secretion rates within their physiological ranges influence bone mass during normal growth in healthy children.

In the cross-sectional part, 205 (109 prepubertal, 96 pubertal) healthy 6-18 year old participants of the DONALD-Study collected 24h urine samples which were then analysed using GC-MS. Daily excretion rates of cortisol, 5-androstene-3 $\beta$ ,17 $\beta$ -diol (17 $\beta$ -Adiol, also known as hermaphrodiol) and the sums of specific adrenal androgen metabolites (DHEA&M and C19) and the 7 quantitatively most important cortisol metabolites (C21) were determined. These boys (n=100) and girls (n=105) had undergone a densitometric analysis of the non-dominant proximal and ultradistal forearm using peripheral quantitative computer tomography. Cortical density ( $vBMD_{65}$ ), cortical area (CA), bone mineral content ( $BMC_{65}$ ) and strength strain index ( $SSI_{65}$ ) of the radial diaphysis, and muscle area (MA) were determined proximally. Trabecular ( $vBMD_{trab}$ ) and total ( $vBMD_{tot}$ ) bone density, bone mineral content ( $BMC_4$ ) and strength strain index ( $SSI_4$ ) were determined at the ultradistal radial metaphysis. Isometric grip force of the non-dominant hand was additionally measured using a dynamometer. In the longitudinal study urine samples were analysed retrospectively. 54 prepubertal children had collected a 24h urine sample 4 years prior their likewise prepubertal pQCT analysis and in a further group of 55 children, the prepubertal urine sample had been collected 8 years before the pubertal pQCT analysis was performed.

In multiple regression analyses, muscularity and/or age were the primary predictors of prepubertal  $vBMD_{65}$ , CA,  $BMC_{65}$  and  $SSI_{65}$ . Total androgen excretion (C19) also significantly explained a positive portion of the variability of all 4 proximal radial bone parameters. In addition, C19 had a small, but significant, effect on  $SSI_4$ , whereas C21 in no way contributed to the variability of prepubertal bone density and strength. In further regression models, either  $17\beta$ -Adiol or DHEA&M were shown to be predictors of diaphyseal bone.  $17\beta$ -Adiol also had a significant influence on prepubertal female metaphyseal  $vBMD_{trab}$ ,  $vBMD_{tot}$  and  $BMC_4$ . Muscularity and age were two further predictors of the metaphyseal radius. Ultimately, cortisol proved to have a significant negative influence on  $vBMD_{trab}$ ,  $vBMD_{tot}$  and  $BMC_4$  in prepubertal boys.

In pubertal children, muscularity, age, sex and, in part, C19 and  $17\beta$ -Adiol were the predominant predictors which positively influenced proximal radial bone. Pubertal development also contributed significantly to the variability of diaphyseal bone. C19 only predicted a part of  $vBMD_{trab}$ , whereas C21, DHEA&M and  $17\beta$ -Adiol did not contribute to the variability of bone mass and stability. Cortisol had a positive effect on  $vBMD_{trab}$  and  $BMC_4$  in pubertal boys.

Longitudinally, no adrenal androgen or glucocorticoid effect on diaphyseal bone was discernible in the 4 year retrospective analysis. However, a longitudinal influence of C19 and  $17\beta$ -Adiol was seen for metaphyseal  $vBMD_{tot}$  and  $vBMD_{trab}$ , respectively. In the 8 year longitudinal analysis, prepubertal  $17\beta$ -Adiol, as well as muscularity and maternal influences, explained a significant portion of variability of pubertal  $vBMD_{trab}$ ,  $BMC_4$ ,  $SSI_4$ , CA,  $BMC_{65}$  and  $SSI_{65}$ .

Altogether, this thesis shows that the prepubertal increase in adrenal androgen secretion has a clear independent influence on the accretion of radial diaphyseal bone. Apparently, adrenarche has an anabolic effect on bone, which is manifested especially in the shaft of long bones. A clear sex dimorphism exists for the influence of adrenal steroids on metaphyseal bone, whereby cortisol negatively affects prepubertal male bone and androstenedione ( $17\beta$ -Adiol) positively predicts the variability of bone in prepubertal girls.