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Statins and adrenal androgen levels in prostate cancer: A new twist

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Statins inhibit HMGCoA reductase, the rate-liming step in the mevalonate (MVA) synthesis pathway that generates metabolites essential in multiple metabolic and signaling pathways, including both cholesterol-derived (e.g. steroid hormones, oxysterols, vitamin D, bile acids) and non-sterol derived products (e.g. lipoproteins, dolichol, ubiquinone, isoprenoid intermediates.) Statins are associated with pleiotropic cholesterol-related and unrelated anti-tumour properties including anti-oxidant, anti-inflammatory, immune-modulatory and anti-proliferative effects. Clinical and pre-clinical studies have linked stains with improved outcomes across multiple tumour types, but the specific mechanisms by which statins mediate their anti-tumour effect in each context are not clear. In prostate cancer (PCa), the data are generally consistent in linking statins with the prevention of aggressive disease, a protective effect against lethal PCa in men with localized or advanced disease, and a longer time to progression in men taking a statin at initiation of androgen-deprivation therapy (ADT) [1,2].

Despite a myriad of potential anti-tumour mechanisms, a prevailing hypothesis in PCa is that statins work by blocking accumulation of intratumoural cholesterol esters (whether via a decrease in exogenous cholesterol or by blocking cholesterol production *in situ*), therefore decreasing substrate for *de novo* intra-tumoural androgen synthesis. The clinical relevance of intratumoural androgens in promoting prostate tumour growth is clearly confirmed by the efficacy of potent ligand synthesis and AR inhibitors such as abiraterone and enzalutamide. Moreover, a link between statins, cholesterol and intra-tumour androgen levels has been demonstrated in preclinical and xenograft models of advanced PCa which co-express the suite of enzymes required for *de novo* synthesis of androgens from cholesterol.

However, a potential impact of statins on *de novo* intratumoural steroid synthesis is unlikely in primary prostate tumours or in a substantial subset of castration resistant PCa (CRPC) tumours, in which the key enzymes required for *de novo* androgen synthesis (e.g. CYP11A and CYP17A) are not simultaneously expressed [3]. In contrast, primary and metastatic CRPC tumours largely express the more limited number of downstream enzymes (e.g. AKR1C3, SRD5A1 or 2) required for conversion of circulating adrenal androgens to active metabolites. In these tumours, any impact of statin therapy on intratumoural androgens is more likely to occur via a decrease in the circulating pool of testicular and/or adrenal androgens available for uptake and conversion [3,4]. In this regard, it is notable that statins might even more directly decrease androgen levels via inhibition of testicular 17-ketosteroid-oxidreductase activity, a primary enzymatic function of AKR1C3 [5].

In men, statins have indeed been shown to variably but measurably decrease total serum testosterone (T) levels, by ~4% in a recent meta-analysis (0.66 nmol/l; 95% CI -0.14 to 1.18; ~19 ng/dL) [6,7]. While a majority of studies used less-specific ELISA-based methods, a recent study using mass spectrometry (MS) also showed that statins statistically decreased serum T [8]. However, to place the magnitude of this change in context, a 125% change in serum T levels in hypogonadal men treated with T replacement therapy (baseline 282 ng/dL [9.8 nmol/L]; 6 months, 640 ng/dL [22.2 nmol/L]) was associated with no difference in prostate tissue levels of T and dihydrotestosterone (DHT).

This casts significant doubt as to whether a 4% or 0.66 nmol/L change in serum T associated with statin use could have a meaningful impact on prostate androgen exposure such as that invoked in a primary prevention setting [9]. Likewise, in castrate patients, an impact of statins on testicular androgens is unlikely to be meaningful in context of the 95% suppression of serum T and 75% suppression of prostate tissue T already achieved by ADT [3]. These observations suggest a statin mediated effect on serum T levels, whether sufficient to impact other endpoints such as erectile function not-withstanding, is unlikely to have a meaningful impact on prostate tumour androgens in either the eugonadal or castrate setting.

In contrast, a statin-mediated decrease in adrenal steroids (clearly demonstrated in women but less studied in men) could theoretically be relevant, particularly in men already treated with ADT. Intratumoural uptake and conversion of the adrenal androgen dehydroepiandrosterone sulfate (DHEAS) is a well-recognized mechanism of progression to CRPC. Statins could impact this pathway by decreasing adrenal production of DHEAS, as well as by blocking organic anion transporter protein (OATP)-mediated tumoural uptake of DHEAS [2]. This may explain why a protective effect of statins is seen so

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consistently in context of ADT when the specific contribution of adrenal androgens to disease progression becomes salient.

The work by Raittinen et al makes several novel observations that are consistent with and expand this hypothesis [10]. They performed a pre-planned analysis of androgen levels in serum and prostate tissue from 108 men with localized PCa treated on a randomized study of neoadjuvant atorvastatin (80mg daily) vs placebo for 28 days. Using MS they find no change in serum T or DHT in the statin-treated arm, a borderline significant decrease in canonical adrenal products (pregnenolone, 17-OH pregnenolone, DHEA, androstenedione (AED); $0.05 < p < 0.10$) that was lost after controlling for false discovery, and a significant 35% decrease in the non-canonical adrenal androgen 11-Keto AED (11KAED; $p = 0.001$). In tissue they found a statistically significant 25% decrease in 11-Keto DHT (11KDHT; $p = 0.027$) and an unexpected 28% increase is DHEA ($p = 0.037$).

While requiring confirmation, these data suggest for the first time that statins may indeed modify the intratumour androgen pool, but not by limiting T and DHT. 11 hydroxy AED (11OHAED) is an abundant product of the adrenal gland that undergoes peripheral conversion to 11KAED, 11-Keto T (11KT) and 11-OH T (11OHT) [3]. While 11OHAED and 11KAED are not active at the androgen receptor (AR), recent studies demonstrate that their immediate metabolites 11OHT and 11KT (generated by the activity of AKR1C3) activate wild type AR with potency that is 50% and 100% of T, respectively. Likewise, the SRD5A1 reduced metabolite, 11KDHT, activates wild type AR with potency similar to DHT, with this work being the first publication of its levels in tissue.

It remains to be determined whether a change in tissue 11KDHT of this magnitude, particularly in context of eugonadal levels of T and DHT, materially impacts prostate tumour biology, and further work is needed to assess levels of the 11OH/11K androgens in CRPC serum and tissue. Regardless, this work deserves note both for assessing the impact of statin therapy on androgens in the tumour tissue environment, and for analyzing the largely unrecognized 11OH/11K family of adrenal androgens. The findings suggest a shift in focus from the impact of statins on T is warranted and that the adrenal androgen axis may serve as a potentially more informative indicator of a statin effect on androgen levels in PCa.

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Declaration of Competing Interest

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