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European Association of Urology

Letter to the Editor

Re: Timu J. Murtola, Hemo Syvälä, Teemu Tolonen, et al. Atorvastatin Versus Placebo for Prostate Cancer Before Radical Prostatectomy—A Randomized, Double-blind, Placebo-controlled Clinical Trial. Eur Urol 2018;74:697–701

Recently, in a randomized clinical trial (RCT), Murtola et al. [1] reported the effect of statins on prostate cancer in men with prostate cancer. Actually, this study was the first clinical trial that both shows direct evidence and investigates the association between statin therapy and prostate cancer risk or aggressiveness. Although there was no significant association between atorvastatin and prostate cancer proliferation, this study provides crucial information, sheds light on the current limited evidence on this subject, and also suggests essential points that need to be considered in the design of future studies.

Although there is increasing evidence to support the positive role of statins in prostate cancer growth, there has been controversy about the association. While a few RCTs report about the association between statins and prostate cancer risk, they were not originally designed to show this issue as a primary outcome, but rather as a secondary or post hoc outcome. Moreover, their results have a detection bias of prostate cancer because these studies do not consider prostate cancer detection time or screening. In addition to the limits of study design, the controversy is also attributed to inconsistent optimal timing to start of and duration of statin administration, or biological reasons including diversity in regulation of low-density lipoprotein (LDL) receptors, individual sensitivity, and diverse intracellular cholesterol levels.

Low cholesterol has a positive role in the reducing the aggressiveness of prostate cancer, which has been shown in a post hoc analysis of the Prostate Cancer Prevention Trial and REDUCE study [2,3]. However, the association between low cholesterol and low risk of high-grade prostate cancer does not relate to statin use.

Recently, Nordstrom et al. [4] showed in their population-based cohort study including 185 667 individuals that statin had no protective effects on any type of prostate cancer, including high-grade prostate cancer. Kantor et al showed in their community cohort study that there was no strong association between statin use and the overall risk of prostate cancer, and concluded that the protective effect of statin could be modest and cannot be a significant factor as compared with race/ethnicity factor.

For a better understanding of the heterogeneity of the association between statin use and prostate cancer risk or aggressiveness, expected mechanisms have to be thoroughly focused. In in vitro studies, statins have shown anticancer effects using the inhibitory action of the mevalonate pathway and reduction of androgen intake. These actions could act as both cholesterol-mediated and non-cholesterol-mediated effects of statin. Hence, it is logical to focus more on the relationships between statin, androgen, and prostate cancer.

Recently, Baspinar et al. [5] showed that statin treatment reduces the level of total and free testosterone. A meta-analysis showed that statin lowered serum testosterone level by −0.66 nmol/l (95% confidence interval, −0.14 to −1.18) in those placebo-controlled RCTs [6]. Although the level might not be a clinically significant problem, serum testosterone does not directly represent the bioavailable testosterone. Moreover, LDL particles are a potential reservoir of cholesterol in both adrenal and gonadal steroidogenesis. Hsieh and Huang [7] reported that rosuvastatin, which acts on the reduction of both total cholesterol and LDL, lowered free testosterone level significantly.

Regarding the association between testosterone and the risk of prostate cancer, Watts et al. [8] reported, in their analysis of individual participant data from 20 prospective studies including 6933 prostate cancer cases, that there was a significant association between circulating testosterone levels and the risk of prostate cancer: the lower the testosterone level, the lower the risk of prostate cancer. However, there is a controversy regarding the association between testosterone and aggressiveness of prostate cancer. Recently, emerging evidence has shown that testosterone deficiency is independently associated with prostate cancer aggressiveness [9].

Similar to other topics related to testosterone, most studies with testosterone have several limitations, which

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require readers to interpret their findings carefully: small sample sizes, inconsistent assay protocols, not considering bioactive testosterone, and not considering the complexities of the androgen pathway (not measuring or interpreting by chronic basis). Testosterone itself does not reflect the internal prostatic milieu by 100%, considering the complex biological cancer mechanism of prostate cancer. Although more studies are needed to clarify the relationships between statin, testosterone, and prostate cancer, aforementioned evidence shows possible relationships among them.

Conflicts of interest: The authors have nothing to disclose.

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