Hyperglycaemia and reduced risk of prostate cancer

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To the Editor: The most comprehensive meta-analysis published to date has demonstrated that the risk of developing prostate cancer may be reduced in men with diabetes mellitus, but the mechanisms responsible for this association remain poorly understood [1]. In their recent Commentary, Frayling et al. summarise currently available data suggesting that this inverse relationship could in part be explained by genetic factors [2]. Of note, it has been shown that the same variation in the *HNF1B* (also known as *TCF2*) gene, which is associated with increased prostate cancer risk, confers protection against type 2 diabetes mellitus [3].

Androgens play a key role in the pathogenesis of prostate cancer [4, 5]. The enzyme 5 α -reductase is able to convert testosterone to the more active androgen, dihydrotestosterone [4, 5]. Inhibition with finasteride of the type II isoform of 5 α -reductase, which is most abundant in prostate tissue [4], is effective in the treatment of benign prostatic hypertrophy [6], and reduces the risk of prostate cancer development [5].

Based on the importance of 5 α -reductase inhibition for prostate cancer prevention, we propose a biologically plausible hypothesis that might explain a lower risk of

prostate cancer in men with diabetes mellitus. This hypothesis is complementary to effects of genetic factors involving both diseases, as discussed by Frayling et al. [2]. 5 α -Reduction of androgens (C19 steroids) to androsterone is dependent on NADPH as a cofactor (reviewed in [7]). Importantly, under hyperglycaemic circumstances cellular NADPH is likely to be decreased in many tissues, consequent to increased aldose reductase-mediated conversion of glucose to sorbitol [8]. We have previously shown that the urinary ratio of androsterone to etiocholanolone (reflecting the proportion of 5 α - to 5 β -reduced C19 steroids) is lower in type 1 diabetes patients; this ratio is inversely related to the HbA_{1c} level [7]. It thus seems plausible that chronic hyperglycaemia could result in a lower relative 5 α -reductase activity via lower cellular NADPH. Hence, hyperglycaemia could contribute to diminished dihydrotestosterone availability in prostate tissue from men with diabetes mellitus.

Obviously, it will be necessary to directly test whether hyperglycaemia decreases 5 α -reductase activity in prostate tissue. In view of the proposed hypothesis, it is also relevant to take account of the degree of metabolic control when evaluating the association of diabetes mellitus with prostate cancer in epidemiological studies, which was not done in any of the studies included in the meta-analysis [1].

Duality of interest The author declares that there is no duality of interest associated with this manuscript.

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