NON-ALCOHOLIC FATTY LIVER DISEASE IN MEN UNDERGOING ANDROGEN DEPRIVATION THERAPY FOR PROSTATE CANCER

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Abstract

Background: Androgen deprivation therapy (ADT) is associated with the development of diabetes and metabolic syndrome, both of which are independent predictors of cardiovascular disease and mortality. Non-alcoholic fatty liver disease (NAFLD) is similarly associated with these outcomes and a condition frequently co-occuring with metabolic syndrome and diabetes. Moreover, NAFLD can progress to steatohepatitis, cirrhosis, and liver failure. However, while an association of low-serum testosterone levels and NAFLD has been demonstrated in hypogonadal men without prostate cancer, this association has not been studied in men undergoing ADT, who exhibit castrate levels of testosterone. We studied the dose-dependent effect of ADT for localized prostate cancer on the risk of NAFLD, liver cirrhosis, hepatic necrosis, and any liver disease, defined as a combination of either outcome.

Methods: We identified 82,938 men aged 66 and older diagnosed with localized prostate cancer within the Surveillance, Epidemiology and End Results-Medicare (SEER) database between 1992 and 2009. Men with pre-existing NAFLD, liver disease, diabetes, metabolic syndrome, as well as those receiving surgical ADT, were excluded. Using competing-risk regression models, we compared the risk of NAFLD between men who received ADT within 6 months of diagnosis *versus* those who did not. We also explored the influence of cumulative exposure to ADT, calculated as monthly equivalent doses of gonadotropin-releasing hormone (GnRH) agonists or antagonists (<7, 7–11, >11 doses).

Results: Overall, 37.5% of men received ADT within six months of diagnosis. Men who were treated with ADT were more likely to be diagnosed with NAFLD (hazard ratio [HR] 1.54, 95 % confidence interval [CI] 1.40-1.68), liver cirrhosis (HR 1.35, 95 % CI 1.12 -1.60), liver necrosis (HR 1.41, 95% CI 1.15-1.72) and any liver disease (HR 1.47, 95% CI 1.35-1.60). A dose-response relationship was observed between the number of doses of ADT with NAFLD (HR 1.17, 95% CI 1.11-1.24), and any liver disease (HR 1.16, 95% CI 1.11-1.21) (both p-trend<0.001).

Conclusions: We found that in men with localized prostate cancer, the use of ADT was associated with an elevated risk of NAFLD, liver cirrhosis, necrosis, and any liver disease. These findings are subject to the limitations of observational study design, yet, given the independent association of NALFD with metabolic syndrome, as well as cardiovascular disease and mortality, patients should be counseled about the increased risk when undergoing ADT. Further investigation is needed to elucidate the mechanisms that lead to development of NAFLD in men receiving ADT and to characterize the risk in patients exhibiting metabolic risk factors at baseline.

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