



PHARMACOVIGILANCE RESEARCH CENTER

Main supervisor.

Assist. Prof. Maurizio Sessa, MPharm, PhD.

Topic.

Pharmacoepidemiology.

Title of the project.

The relationship between the use of 5 α -Reductase inhibitors, glucose intolerance, and type 2 diabetes mellitus.

Project description.

The 5 α -reductases (5 α Rs) convert testosterone to its more potent metabolite 5 α -dihydrotestosterone (DHT). Investigation of rare cases of 5 α R deficiency, presenting with a 46XY disorder of sexual development, led to the discovery of 2 isozymes: 5 α R type 1 (5 α R1) is expressed in metabolic tissues including liver, adipose, and skeletal muscle, and 5 α R type 2 (5 α R2) is expressed predominantly in the reproductive tract, where deficiency accounts for disordered sexual development, and in human liver. 5 α R inhibitors, which reduce circulating and prostatic DHT levels, are prescribed commonly in patients with benign prostatic hyperplasia (BPH). Finasteride inhibits 5 α R2 selectively, whereas dutasteride inhibits both 5 α R1 and 5 α R2.

In addition to testosterone, 5 α Rs also catalyzes the reduction of a range of steroid hormones, including glucocorticoids. Due to widespread enzyme expression, and lack of substrate specificity, 5 α R inhibition may alter local steroid concentrations in extraprostatic tissues. Targeting of another enzyme, 11 β -hydroxysteroid dehydrogenase type 1, which metabolizes glucocorticoids in the liver and adipose tissue, alters local but not systemic glucocorticoid levels and affects body fat distribution and insulin sensitivity. Increased liver fat and decreased insulin sensitivity are seen in mice with a targeted disruption of 5 α R1, but not 5 α R2. We hypothesized that inhibition of 5 α R1 decreases insulin sensitivity in humans, as it does in rodents. Previous studies of the metabolic effects of 5 α R inhibitors in humans have been limited to simple but insensitive measures such as fasting plasma glucose. In this project, you will use Danish administrative data to investigate the association between the use of 5 α R inhibitors and the occurrence of glucose intolerance and type 2 diabetes mellitus.

Acquired skills: statistical programming in R and SAS; data management; observational study design; scientific writing.

References

1) Upreti R, Hughes KA, Livingstone DE, et al. 5 α -reductase type 1 modulates insulin sensitivity in men. *J Clin Endocrinol Metab.* 2014;99(8):E1397-E1406. doi:10.1210/jc.2014-1395