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Review Article

Spironolactone and glucose metabolism, a systematic review and meta-analysis of randomized controlled trials

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Abstract

Diabetes predicts cardiovascular disease (CVD); some drugs are effective for CVD prevention but increase the risk of diabetes. In a systematic review and meta-analysis of placebo-controlled trials, we assessed if spironolactone, a mineralocorticoid receptor antagonist, affected glycemic control. We searched PubMed using (''spironolactone'' or ''aldactone'') and trial and (''glucose'' or ''diabetes'' or ''insulin'' or ''insulin resistance'') until January 4, 2016. In total, 18 eligible trials were identified; 10 on fasting glucose, 8 on hemoglobin A1c (HbA_{1c}), 7 on homeostatic model assessment (HOMA)-insulin resistance (IR), and 8 on insulin. Spironolactone increased HbA_{1c} (0.16%, 95% confidence interval 0.02 to 0.30) but had no clear effect on fasting glucose, HOMA-IR, and insulin. A mechanistic randomized controlled trial in people with and without diabetes might provide insight concerning these pleiotropic effects on diabetes and CVD relevant to prevention of both diseases. J Am Soc Hypertens 2016;10(8):671–682.

Keywords: Anti-androgen; diabetes mellitus; hypertension; placebo-controlled trial.

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality globally.[1] Prevention and treatment of CVD are challenging as several promising drugs have unexpected side effects which could increase the risk of CVD.[2] Specifically, certain classes of CVD drugs are known to prevent CVD effectively, via different targets, while similarly increase the risk of diabetes, such as some diuretics[3] and lipid modulators.[4] Explicating this unusual phenomenon has important implications for treatment and etiology, both in terms of balancing the risks of diabetes and CVD and of generating further understanding of complex and challenging common diseases.

Mineralocorticoid receptor antagonists and potassium-sparing diuretics, such as spironolactone and eplerenone, are effective in the treatment of heart failure[5,6] and hypertension.[7] Spironolactone, widely used in clinical practice, is also by far the most effective drug for resistant hypertension,[8] but concerns have arisen about its effect on glucose metabolism. In animals and *in vitro* experiments, aldosterone stimulates glucose intolerance and insulin resistance,[9,10] so spironolactone might be expected to be beneficial for glucose metabolism via aldosterone antagonism. However, a randomized controlled trial (RCT) suggested it might worsen glycemic control.[11] Moreover, a similar aldosterone antagonist, eplerenone, shows quite different effects on glucose metabolism,[12] suggesting a mechanism beyond aldosterone. Evidence is accumulating for some rather speculative pathways via the endocrine system, based on the well-known trade-off between lifespan and reproduction.[13–15] Spironolactone with structural elements of the progesterone molecule,[7] is unique in being a known anti-androgen,[16,17] used in polycystic ovary syndrome to decrease androgens.[18] Meta-analysis of RCTs suggests that testosterone has beneficial effects on glucose metabolism.[19] We hypothesized that spironolactone might have adverse effects on glucose metabolism as a side effect. Here, we carried out a systematic review and meta-analysis of placebo-controlled randomized trials to examine the effect of spironolactone on glucose metabolism in men and women.

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Methods

We implemented this meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and a published protocol.[20] Two reviewers (J.V.Z. and L.X.) searched independently and compared their selections at the end of the search process. Differences were resolved by consensus or by reference to a third reviewer (C.M.S.). A statistician (S.L.L.) extracted information from the selected trials, with the guidance from a third reviewer (C.M.S.). The extracted information was double checked by one reviewer (J.V.Z.).

Data Source and Searches

We searched PubMed using (''spironolactone'' or ''aldactone'') and trial and (''glucose'' or ''diabetes'' or ''insulin'' or ''insulin resistance'') in any field until January 4, 2016. We first discarded any studies that were irrelevant based on title and metadata, then on abstract, and then read the remaining to identify placebo-controlled randomized trials of spironolactone with any indicators of glucose metabolism reported, such as fasting glucose, hemoglobin A_{1c} (HbA_{1c}), homeostatic model assessment (HOMA)-insulin resistance (IR), and insulin. We then did a bibliographic search of the selected trials and relevant reviews to identify additional studies. We also searched the World Health Organization International Clinical Trials Registry Platform for any additional trials using spironolactone as an intervention.

Study Selection

Given that many of these trials were in older people with chronic diseases, we included trials giving a comparison of spironolactone with placebo against the background of other drug use as long as the groups only differed in their use of spironolactone. We only included trials with duration of at least 2 weeks, because this study concerns the effects of regular rather than of acute spironolactone use. We also limited trials to published studies or registered trials available to track down the results.

We did not exclude trials based on the number of participants, to make use of all available evidence. We did not exclude by participant characteristics, because spironolactone is used for similar purpose in a wide variety of people, and there is no reason to think that spironolactone has different effects by patient subgroup. We did not exclude trials based on date of publication, because there is no reason to think that the effect of spironolactone has changed over years. We excluded trials in children (<18 years), because spironolactone is rarely used in children.

Data Extraction

The extracted information included publication details (author, year of publication, title, and journal); study population, including age, sex, setting, diabetes status, diabetes type, and co-treatment with other medicines, number of participants in each arm (spironolactone and placebo) in the trial; dose and duration of spironolactone treatment; the means and standard deviations (SDs) for all indicators of glucose metabolism (fasting glucose, HbA_{1c}, HOMA-IR, and insulin) at baseline and post-treatment, as well as the changes with treatment and the corresponding standard deviation (SD), if available, by trial arm; funding source or competing interests. For trials not reporting the changes with treatment with SD, we calculated them from means and SDs at baseline and post-treatment, using a well-established formula.[21]

Data Synthesis

The principal summary measure was the mean difference between spironolactone and placebo group in the change in indicators of glucose metabolism (fasting glucose, HbA_{1c}, HOMA-IR, and insulin) during the trial. We combined the results of the selected trials using inverse variance weighting with random effects. We also checked using fixed effects models assuming constant effects across the trials. We used the ''metacont'' function from the ''meta'' package of R for mean differences and the ''forest'' function for the forest plot.

We used I^2 to assess heterogeneity between trials. I^2 is the proportion of total variation observed between the trials attributable to differences between trials rather than to sampling error (chance), with values <30% representing low heterogeneity, <60% moderate heterogeneity, and the ≥60% high heterogeneity. We used funnel plots and ''trim and fill'' to assess publication bias, that is, missing trials, using the ''trimfill'' function from the ''metafor'' package. For outcomes with high heterogeneity, we used meta-regression, with inverse variance weighting, to assess whether the effects of spironolactone varied by age, duration, dosage, setting, sex, or funding source, using the ''rma'' function of the ''metafor'' package in R. In subgroup analysis, if available, we considered men and women separately because of the different hormone milieu by sex. We also conducted the following sensitivity analyses beyond the protocol.[20] Given the difference in cross-over and parallel study designs, a subgroup analysis excluding cross-over RCTs was conducted. Given the potential differences in the effects of spironolactone by diabetes status (diabetes and nondiabetes) and diabetes type (type 1 and type 2 diabetes), sensitivity analyses by diabetes status and diabetes type were conducted. Given HbA_{1c} is a measure of mean glucose level over the previous 2 to 3 months,[22] a sensitivity analysis was conducted in trials