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Invited Perspective

Effects of tibolone on fibrinogen and antithrombin III: A systematic review and meta-analysis of controlled trials

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ABSTRACT

Tibolone is a synthetic steroid with estrogenic, androgenic and progestogenic activity, but the evidence regarding its effects on fibrinogen and antithrombin III (ATIII) has not been conclusive. We assessed the impact of tibolone on fibrinogen and ATIII through a systematic review and meta-analysis of available randomized controlled trials (RCTs). The search included PUBMED, Web of Science, Scopus, and Google Scholar (up to January 31st, 2016) to identify controlled clinical studies investigating the effects of oral tibolone treatment on fibrinogen and ATIII. Overall, the impact of tibolone on plasma fibrinogen concentrations was reported in 10 trials comprising 11 treatment arms. Meta-analysis did not suggest a significant reduction of fibrinogen levels following treatment with tibolone (WMD: −5.38%, 95% CI: −11.92, +1.16, $p = 0.107$). This result was robust in the sensitivity analysis and not influenced after omitting each of the included studies from meta-analysis. When the studies were categorized according to the duration of treatment, there was no effect in the subsets of trials lasting either <12 months (WMD: −7.64%, 95% CI: −16.58, +1.29, $p = 0.094$) or ≥12 months (WMD: −0.62%, 95% CI: −8.40, +7.17, $p = 0.876$). With regard to ATIII, there was no change following treatment with tibolone (WMD: +0.74%, 95% CI: −1.44, +2.93, $p = 0.505$) and this effect was robust in sensitivity analysis. There was no differential effect of tibolone on plasma ATIII concentrations in trials with either <12 months (WMD: +2.26%, 95% CI: −3.14, +7.66, $p = 0.411$) or ≥ 12 months (WMD: +0.06%, 95% CI: −1.16, +1.28, $p = 0.926$) duration. Consistent with the results of subgroup analysis, *meta*-regression did not suggest any significant association between the changes in plasma concentrations of fibrinogen (slope: +0.40; 95% CI: −0.39, +1.19; $p = 0.317$) and ATIII (slope: −0.17; 95% CI: −0.54, +0.20; $p = 0.374$) with duration of treatment. In conclusion, meta-analysis did not suggest a significant reduction of fibrinogen and ATIII levels following treatment with tibolone.

1. Introduction

Several studies found association between elevated plasma fibrinogen levels and cardiovascular disease (CVD) [1–3]. Fibrinogen is one of the most important nontraditional CV risk factors [3–8]. Associations of fibrinogen levels and coronary artery disease (CAD)

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or stroke were not dependent on sex, smoking, blood pressure or blood lipid levels [2]. However, measurement of plasma fibrinogen to improve the prediction of CV risk is not recommended [7]. antithrombin III (ATIII) represents a major physiological inhibitor of thrombin activity in circulating blood [9]. Low ATIII activity levels have been linked to elevated CV risk [10–12], and its deficiency, a genetically determined severe thrombophilic state, is associated with markedly increased risk of venous thromboembolism [13,14], however this abnormality may also predispose to arterial thromboembolic events, including stroke, at young age [15].

The incidence of CVD increases in women after menopause being a leading cause of mortality in postmenopausal women [16,17]. Menopause is associated with sex hormone deficiency and pro-atherogenic lipid profile changes including increase in total cholesterol and low density lipoprotein cholesterol (LDL-C) [18]. Although observational studies had suggested some benefits with hormone replacement therapy (HRT) [19–21], randomized controlled trials (RCTs) failed to confirm it in terms of CV and thromboembolic risks [22,23].

Tibolone (Livial©, Tibofem©) is a synthetic steroid exhibiting estrogenic, progestogenic and androgenic activity. Its two major active metabolites – 3α- and 3β-hydroxytibolone – act as potent, fully activating agonists of the estrogen receptor, and its metabolite Δ^4-tibolone act as agonist of the progesterone and androgen receptors (3α- and 3β hydroxytibolone conversely, act as antagonists of the same receptors). Moreover, tibolone acts as an antagonist of the glucocorticoid and mineralocorticoid receptors [24–27]. Tibolone represents an attractive treatment option in postmenopausal women [24,25] that effectively can reduce menopausal symptoms [24,26,27]. At present tibolone is recommended as an alternative to menopausal hormone therapy in women with climacteric symptoms and no history of breast cancer and no other contraindications [28] especially in women with mood disorders and sexual dysfunction [29] and those with a history of endometriosis [30]. A systematic review by Formoso et al. did not yield conclusive results regarding effect of tibolone on CV events [26]. In the analyses of surrogate endpoints tibolone was reported to have various CV effects, including favourable effect on acute myocardial infarction and thromboembolism [24,31,32]. Available data on tibolone-induced alterations to coagulation parameters were inconsistent [27,31,33]. Previous studies reported reductions of fibrinogen level [8] or increase in ATIII level [27], while other investigators suggested procoagulant effects through lower ATIII levels [8,34] or no change [31,35]. Therefore the aim of the present study was to assess the impact of tibolone on fibrinogen and ATIII levels.

2. Methods

2.1. Search strategy

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [36]. SCOPUS (http://www.scopus.com), Medline (http://www.ncbi.nlm.nih.gov/pubmed) AND Google Scholar (http://www.scholar.google.com) databases were searched using the following search terms in titles and abstracts (also in combination with MESH terms): (tibolone OR OrgOD14 OR "Org OD14" OR livial OR livial®) AND (fibrinogen OR antithrombin OR antithrombin III or "antithrombin III" OR ATIII OR "AT III")). The wild-card term "*" was used to increase the sensitivity of the search strategy. No language restriction was used in the literature search. The search was limited to studies in human. The literature was searched from inception to January 31st, 2016.

2.2. Study selection

Original studies were included if they met the following inclusion criteria: (i) being a controlled clinical trial with either parallel or cross-over design, (ii) investigating the impact of tibolone on plasma concentrations of fibrinogen and/or ATIII, (iii) presentation of sufficient data on fibrinogen and/or ATIII concentrations at baseline and at the end of follow-up in each group or providing the net change values. Exclusion criteria were (i) lack of a an appropriate control group in the study design, (ii)observational studies with case-control, cross-sectional or cohort design, and (iii) lack of sufficient information on baseline or follow-up fibrinogen and/or ATIII concentrations.

2.3. Data extraction

Eligible studies were reviewed and the following data were abstracted: 1) first author's name; 2) year of publication; 3) study location; 4) study design; 5) number of participants in the tibolone and control groups; 5) age and body mass index (BMI) of study participants; 6) prevalence of diabetes mellitus; and 7) baseline and follow-up plasma concentrations of fibrinogen and/or ATIII.

2.4. Quality assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria [37]. The items used for the assessment of each study were as follows: adequacy of sequence generation, allocation concealment, blinding of subjects and personnel, blinding of outcome assessment, addressing of dropouts (incomplete outcome data), selective outcome reporting, and other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of "yes" indicated low risk of bias, while "no" indicated high risk of bias. Labeling an item as "unclear" indicated an unclear or unknown risk of bias.

2.5. Quantitative data synthesis

Meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [38]. Net changes in measurements (change scores) were calculated as follows: measure at end of follow-up−measure at baseline. For cross-over trials, net change in plasma concentrations of fibrinogen and/or ATIII were calculated by subtracting the value after control intervention from that reported after treatment. All values were collated in percentage changes from baseline levels. Standard deviations (SDs) of the mean difference were calculated using the following formula: $SD = \text{square root } [(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, assuming a correlation coefficient (R) = 0.5. If the outcome measures were reported in median and inter-quartile range, mean and standard SD values were estimated using the method described by Hozo et al. [39]. Where standard error of the mean (SEM) was only reported, standard deviation (SD) was estimated using the following formula: $SD = SEM \times \text{sqrt}(n)$, where n is the number of subjects. When the results were presented in multiple time points, only data relating to the longest duration of treatment were considered.

A random-effects model (using DerSimonian-Laird method) and the generic inverse variance method were used to compensate for the heterogeneity of studies in terms of demographic characteristics of populations being studied and also differences in study design. Heterogeneity was quantitatively assessed using I^2 index. Effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI). In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was con-