Is serum estradiol (E2) really increased in patients with Klinefelter Syndrome (KS)? Results from a meta-analysis study

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**BACKGROUND:** KS has been classically described as characterized by hyperestrogenism and elevated serum E2 together with increased gonadotropins and low-to-normal serum testosterone (T). In literature, data on increased serum E2 are not solid. The aim of this study is to meta-analyse data from studies evaluating serum E2 in both KS and healthy subjects (HS) in order to verify if E2 is increased in KS.

**METHODS:** An extensive MEDLINE was performed using ‘PubMed’ with the following key words: ‘KS’ and ‘E2’ or ‘T’ or ‘sex steroids’ from 1946 to January 2015 (Current Contents-ISI was used for searching oldest studies). All studies (case-control, case-series, case-reports) reporting E2 measurement were considered. Controlled-studies were used for meta-analysis. Only serum E2 at baseline (no ongoing treatments) was included. Meta-analysis was conducted according to the PRISMA statement using RevMan.

**RESULTS:** Out of 956 articles, 26 case-control studies, 15 case-series and 21 case-reports had data on serum E2. A total of 878 KS and 1000 HS were included in the meta-analysis. Serum E2 was significantly higher in HS than in KS, with a mean difference of 7.93 pg/mL (CI: 2.24, 13.61; p=0.006), with a chi-squared=688.32 (I-square=97%) (Figure 1). Serum T was significantly lower in KS than in HS, with a mean difference of -2.79 ng/mL (CI:-3.46, -2.11; p<0.001), with a chi-squared=198.29 (I-square=89%). Data from case-series and case-reports confirmed that E2 is not above the normal range in KS.

**CONCLUSIONS:** Serum E2 is not increased in KS and is significantly lower than in HS in this meta-analysis. The limits of this study are the heterogeneity of methods for steroids measurement and the lack of studies having the comparison of serum E2 between KS and HS as primary endpoint. The traditional belief that KS is associated to elevated E2 should be reconsidered together with some pathophysiological and clinical issues.

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**Figure 1. Forest plot for E2 comparison**