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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.

Study or Subgroup	Klinefelter patients Mean	SD	Total	Healthy subjects Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Wang C 1975	34	64.32	19	16	38.46	20	1.8%	18.00 [-15.47, 51.47]	1975
Smith DA 1977	25.61	11.74	29	31.87	12.48	84	4.9%	-6.26 [-11.30, -1.22]	1977
Forti G 1978	28	9	15	12.3	5.1	17	4.9%	15.70 [10.54, 20.86]	1978
Barbarino A 1979 (1)	37	11.31	8	20.08	6.6	4	4.4%	16.92 [6.76, 27.08]	1979
Plymate SR 1983	44	6	5	35	6	5	4.7%	9.00 [1.56, 16.44]	1983
Winters SJ 1983	36	0.1	1	32.5	12.86	6	4.4%	3.50 [-6.79, 13.79]	1983
Giagulli VA 1988	22.69	11.5	28	31.6	10.62	20	4.8%	-8.91 [-15.22, -2.60]	1988
Eulry F 1993	23	9	16	33.7	11	16	4.8%	-10.70 [-17.66, -3.74]	1993
Luisetto G 1995	49	27.1	32	39.3	16.4	24	4.2%	9.70 [-1.75, 21.15]	1995
Luboshitzky R 1996	28.87	4.36	6	18.25	1.09	7	5.0%	10.62 [7.04, 14.20]	1996
Luboshitzky R 1997	30.48	4.36	11	18.25	1.09	7	5.1%	12.23 [9.53, 14.93]	1997
Ozata M 2000	70.13	34.92	9	53.42	18.14	22	2.7%	16.71 [-7.33, 40.75]	2000
Kamischke A 2003	21.52	10.05	85	21.79	12.23	244	5.1%	-0.27 [-2.90, 2.36]	2003
Tomasi PA 2003	103	89.79	14	80.8	64.32	39	1.0%	22.20 [-28.98, 73.38]	2003
Wielgos M 2004	58.24	12.1	14	47.62	9.98	12	4.6%	10.62 [2.13, 19.11]	2004
Yesilova Z 2004	68.81	5.32	32	30.55	5.51	20	5.1%	38.26 [35.22, 41.30]	2004
Yesilova Z 2005	69.92	6.55	13	32.56	4.95	9	4.9%	37.36 [32.55, 42.17]	2005
Bojesen A 2006	24.52	39.65	35	34.05	97.83	71	2.4%	-9.53 [-35.80, 16.74]	2006
Host C 2010	24.52	28.2582	19	34.5975	48.3051	20	2.6%	-10.08 [-34.77, 14.61]	2010
Bojesen A 2011	44.945	142.8232	70	34.045	97.8258	71	1.4%	10.90 [-29.56, 51.36]	2011
Ferlin A 2011	27.21	10.02	112	16.83	2.51	51	5.1%	10.38 [8.40, 12.36]	2011
Foresta C 2012	27.62	9.75	92	26.1	9.32	50	5.0%	1.52 [-1.74, 4.78]	2012
Selice R 2013	30.21	9.37	121	25.93	8.99	60	5.1%	4.28 [1.46, 7.10]	2013
Pasquali D 2013	29	33.23	69	33	27.71	48	4.3%	-4.00 [-15.09, 7.09]	2013
Chang S 2014	26.08	60.31	23	29.585	126.8016	73	1.6%	-3.51 [-41.63, 34.62]	2014
Total (95% CI)			**878**			**1000**	**100.0%**	**7.93 [2.24, 13.61]**	

Heterogeneity: $Tau^2 = 164.26$; $Chi^2 = 688.32$, df = 24 ($P < 0.00001$); $I^2 = 97\%$
Test for overall effect: Z = 2.73 (P = 0.006)

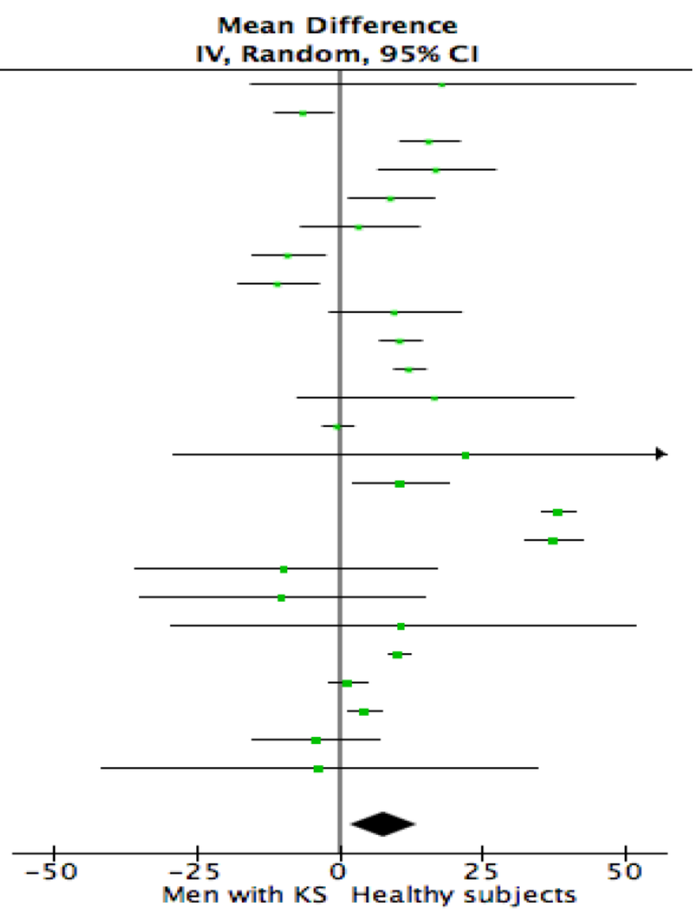

Figure 1. Forest plot for E2 comparison

***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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