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Brief communication (Original)

Cross-sex hormone use does not increase cardiovascular risk in young male-to-female transsexuals: a study of self-medication by healthy Thai cabaret dancers

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Background: Cross-sex hormone (CSH) use is widespread among transsexuals in Thailand. CSHs are used by male-to-female (MtF) transsexuals for feminization.
Objectives: To determine effects of self-medication with CSH on cardiovascular risk biomarkers, C-reactive protein (CRP) and fibrinogen (Fb), in Thai MtF transsexuals.
Methods: Data were collected from healthy MtF transsexual cabaret dancers in Pattaya city, Thailand, using a questionnaire and descriptive interview. Blood samples were collected to determine lipid profile, CRP, Fb, and sex hormone levels. ANOVA, Pearson correlation, and logistic regression were analyzed for effects of CSH on biomarkers; comparing CSH users with non-using controls.
Results: We grouped 102 MtF transsexual participants (average age 28 years) as CSH (n = 66) and non-hormone using controls (n = 36). Several female and antimale hormonal products were used in CSH self-medication, with an average 12.5-year exposure. In the CSH group, significantly higher HDL with lower CRP levels and a negative correlation between total cholesterol, LDL, and 17β-estradiol were observed. Risk prevalence analysis exhibited lower prevalence of disease susceptibility in the CSH group. Logistic regression accordingly revealed the effect of CSH on CRP levels with odds ratios of 0.26 (CI 0.1–0.68) and 0.34 (CI 0.13–0.93) in crude and adjusted models, respectively.
Conclusions: Moderate exposure to low doses of CSH use showed no serious risk or health problems in healthy MtF transsexuals in terms of cardiovascular risk biomarkers.

Keywords: C-reactive protein, cardiovascular, estrogen, fibrinogen, male-to-female transsexuals progesterone, testosterone

Cross-sex hormones (CSH) are defined as exogenous steroid sex hormones (namely androgens for female-to-male transsexual men and estrogens for male-to-female (MtF)) transsexual women administered for the purpose of synchronizing a person's secondary sexual characteristics with their gender identity [1, 2]. Previous studies have shown positive health benefits of exogenous female hormones for women's health [3, 4]. When hormone replacement therapy (HRT) was first introduced for clinical use, it was considered "the golden period" of hormone utilization for menopausal women. Several clinical studies, including those reported by the Women Health Initiative (WHI) the Postmenopausal Estrogen/ Progestin Intervention (PEPI) Trial, Heart and estrogen/progestin replacement study follow-up (HER II), indicated harmful adverse effects of estrogen and progesterone and an association with cancer and cardiovascular risks [5-7]. Female hormones have also been used by male patients for various purposes including the use CSH in patients with aromatase insufficiency, prostate cancer, and MtF transsexuals [1, 8, 9]. While the use of CSH including estrogen, progesterone, or antitestosterone in patients with aromatase insufficiency and prostate cancer is intended for hormonal stabilization and bone/lipid improvement, MtF transsexuals are aiming for aesthetic appearance changes from masculine to feminine characteristics. CSH use in MtF transsexuals

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could, therefore, be a tool to study beneficial or adverse effects of female hormones in healthy men. Previous reports did not confirm a decrease of cardiovascular risk factors in these groups [10-12]. However, while C-reactive protein (CRP) and fibrinogen (Fb) have become novel biomarkers and are expected to be the most effective surrogates for cardiovascular disease [13, 14], several studies in MtF transsexuals showed inconsistent outcomes of CSH on CRP and Fb [10, 12, 15, 16].

In Thailand, the number of transsexuals is considered to range from 0.3% to 0.6% of the population [17]. MtF transsexuals have limited access to psychological assessment or surgery in Thailand. Most seek hormones for their gender treatment outside the medical profession or hospitals [18]. This usually represents hormonal self-medication. We found that use of CSH in Thai teen MtF transsexuals was not under the supervision of a physician. Most obtained information from friends (unpublished data by the present authors). Knowledge regarding desired or undesired effects of CSHs in Thai MtF transsexuals has been limited. This cross-sectional study was intended to provide more comprehensive information in assessing utilization of CSHs and their effects on health. We also focused on effects on inflammatory markers (CRP, Fb) among Thai MtF transsexuals.

Materials and methods

Study design and participants

We designed a cross-sectional study. The main outcome aimed to investigate effects of CSH on CRP and Fb, which indicate an inflammatory response. They were assessed by inferential statistics using two groups of MtF transsexuals: 102 MtF participants from a cabaret setting in Pattaya, Thailand. They were divided into CSH consumers; subdivided into (1) continuous current users and (2) noncontinuous current users, and a control group who never used CSH. The protocol was approved by the Khon Kaen University Ethics Committee for Human Research (HE532065) before initiation of the study, and written informed consent from study participants was obtained before their inclusion in the study. The recruitment of these MtF transsexual actors was from two cabaret settings. Inclusion criteria in this voluntary study included healthy trans women and normal men over 18 years old. Participants suffering from any severe or chronic diseases were excluded from the study.

Data collection

Personal data were collected by face-to-face interview and physical and gender examination. Data collections comprised three groups of variables; (1) CSH consumption patterns (self-report by self-medication questionnaire), (2) physical examination included determination of age, weight, height, systolic and diastolic blood pressure and pulse, (3) general clinical variables included serum hormone levels (estradiol, progesterone, and testosterone) and lipid profile (total cholesterol, triglyceride, low density cholesterol, and high density cholesterol), and (4) specific inflammatory markers included CRP and Fb.

Blood samples were obtained following a minimum of an 8 h fasting, and after at least 10 min of rest. Samples were stored in vacuum tubes for a maximum of 2 h before delivery to the laboratory unit at Bangkok Pattaya Hospital. Serum sex hormones were analyzed using an electrochemiluminescence immunoassay technique (estradiol and testosterone with an Elecsys 2010 system, Roche Diagnostics, Rotkreuz, Switzerland, and progesterone with an Elecsys E41 system). The most effective estrogenic agent, 17-β estradiol (E2), was chosen for estrogen analysis. Total progesterone was also measured, while total testosterone was measured to provide an indication of androgen action. Sex hormone measurement exhibited a sensitivity range detection for estrogen at 5.00–4,300 pg/mL, progesterone at 0.03–60 ng/mL, and testosterone at 0.025–15.0 ng/mL. Full lipid profile was analyzed using an enzymatic method using a Cobas C501 Analyzer (Roche Diagnostics). CRP was determined by using a particle enhanced immunoturbidimetric assay using a Cobas C501 Analyzer (range 1.00–250 mg/L) and Fb with a Clauss assay using a Sysmex CA-1500 System (Siemens Healthcare, Malvern, PA, USA) (range 50–500 mg/dL).

Statistical analysis

Descriptive statistics with mean, standard deviation, and 95% confidence interval were calculated. Correlations between serum sex hormones and both inflammatory markers CRP and Fb were tested using a Spearman product moment correlation. An analysis of variance (ANOVA) was used for the mean differentiation of all clinical outcomes between the groups. Statistical significance was accepted at the level of $P < 0.05$. Analyses were performed using the Statistical Package for the Social Sciences (SPSS)

statistical analysis software package, version 16 (Chicago, IL, USA). Prevalence of presumptive cardiovascular risk among CSH users and a control group were tested by using a chi-Square test. Logistic regression of the use of CSH and each clinical cardiovascular parameters was determined with age and smoking adjustments.

Results

We prospectively recruited 102 MtF transsexual women to participate in this study. Participants were monitored for the effects of CSHs (estrogen, progesterone, and antitestosterone) on health. Approximately 65% of male subjects (n = 66, average age = 28 years) used CSH for the purpose of changing from masculine to feminine characteristics with the average hormone use period of 12.5 years. All hormone products were used based on self-administration dose and schedule. Hormones used consisted of commercially available contraceptive pills and injectables. Dosages varied arbitrarily. The control group consisted of healthy men without CSH use (n = 36, average age = 29.1 years). The CSH group clearly exhibited a lower level of smoking than the control group (19.6% vs 54.3%). For cardiovascular related parameters, HDL levels were significantly higher in the CSH group than in the control group; while BMI and CRP levels in the CSH group were significantly lower. Meanwhile, other parameters including systolic and diastolic blood pressure, total cholesterol, triglyceride, LDL and Fb were found to be comparable among the two groups (**Table 1**).

The CSH group exhibited significantly higher female sex hormone levels (17β estradiol and progesterone) and lower male sex hormone (testosterone). The average estrogen level in the CSH group was approximately five times the level in the control group (145.3 ± 417.2 vs. 28.2 ± 16.1 pg/mL). There were high variations in the CSH group, presumably because of various estrogen self-consumption regimens. Among those in the CSH group, there was one participant with an extremely high estrogen level (2,567 pg/mL) who had an injection of estrogen before the blood sample collection. Progesterone and testosterone were found within normal levels in both groups despite significantly lower levels in the CSH group. In the control group, all hormone levels were at baseline levels found in normal men (**Table 2**).

Linear correlation analysis (**Table 3**), under the classification of two groups of participants (CSH and control group), showed a negative correlation between total cholesterol and LDL, with 17β-estradiol in the CSH group. Whereas, testosterone and BMI levels were found to be positively correlated. In the control group, only the levels of 17β-estradiol showed a negative correlation with age. It is noted that an increase of female sex hormone level in the control group was found to correlate with an increase of CRP. However, progesterone showed no correlation with any markers in either the CSH or control group.

Table 1. Baseline characteristics

Characteristic	Cross sex hormone use (n = 66)	Control (n = 36)
Age (years old)	28.0 (± 6.3)	29.1 (± 8.4)
Years of exogenous hormone exposure	12.5 (± 6.2)	–
Cigarette smoking, (% Yes)	20%**	54%
Body Mass Index (kg/m^2)	20.4 (± 2.1)*	21.6 (± 2.6)
Systolic Blood Pressure, SBP (mmHg)	114.8 (± 15.4)	117.8 (± 11.8)
Diastolic Blood Pressure, DBP (mmHg)	72.9 (± 11.3)	75.6 (± 9.8)
Pulse (/minute)	76.3 (± 11.8)	79.1 (± 10.6)
Total cholesterol (mg/dL)	189.7 (± 34.8)	189.2 (± 52.1)
Triglyceride (mg/dL)	95.5 (± 40.0)	107.8 (± 56.0)
Low density cholesterol (mg/dL)	108.7 (± 28.4)	114.3 (± 38.9)
High density lipoprotein (mg/dL)	59.8 (± 22.5)*	51.5 (± 16.0)
C-reactive protein, (CRP) (mg/L)	1.4 (±1.7)*	2.1 (±1.8)
Fibrinogen (mg/dL)	246.7 (± 66.9)	264.9 (± 63.0)

*Significantly different from control group (*t* test) ($P < 0.05$).
**Significantly different from control group (Pearson chi-square) ($P < 0.01$).

Table 2. Serum sex hormone levels

Sex hormone	Cross-sex hormone Mean ± SD, (median)	Control Mean ± SD, (median)
17β-estradiol (pg/mL)	145.3 ± 417.2 (21)*	28.2 ± 16.1 (29)
Progesterone (unit)	0.4 ± 0.2 (0.4)**	0.6 ± 0.5 (0.5)
Testosterone (unit)	2.1 ± 3.3 (0.2)**	5.6 ± 3.2 (6)

*Significantly different from control group (*t* test) ($P < 0.05$).
**Significantly different from control group (*t* test) ($P < 0.01$).

Table 3. Correlation of serum sex hormones with cardiovascular risk markers

	Serum 17β estradiol		Serum progesterone		Serum testosterone	
	CSHgrou	Control group	CSHgroup	Control group	CSHgroup	Control group
Age		–0.44**				–0.47**
Body Mass Index					0.4*	
Total cholesterol	–0.47**					
Low density lipoprotein	–0.41**					
C-reactive protein		0.5**				

CSH = Cross-sex hormone. *Significantly different from the control group (*t* test) ($P < 0.05$).
**Significantly different from the control group (*t* test) ($P < 0.01$)

Presumed risk prevalence analysis, shown in **Table 4**, demonstrated standard health risk levels for cardiovascular diseases according to JNC 7 for age, blood pressure, lipid profile, and inflammatory biomarkers comparing between CSH and control groups [19]. Results from this study showed that participants in the control group had a predicted higher prevalence of disease susceptibility than those in the CSH group for all parameters. The only significant difference was found for CRP in which the control group contained 44% of the population proportion who had exceeding the levels of CRP (>1.8 mg%), while only 17% were found in the CSH group ($P < 0.01$).

Logistic regression was used to evaluate the effects of CSH on cardiovascular risk factors in MtF transsexuals (**Table 5**). Both a crude model, to reflect the effect of CSH alone, and an adjusted model for the additional effects of age and smoking with CSH use were considered in this study. Results accordingly showed the effect of CSH on CRP, but no other cardiovascular risk parameters. Odd ratios (OR) for the effect of CSH on CRP levels using a crude model and an adjusted model were found to be 0.26 (CI 0.1–0.68) ($P < 0.01$) and 0.34 (CI 0.13–0.93) ($P < 0.05$), respectively.

Discussion

Results from this cross-sectional study demonstrated favorable effects of CSH use on the results of BMI, HDL, and CRP when comparing men who were constantly exposed to CSH and a non-using control group. Data showed that mean values of all three sex hormones and all clinical markers were within normal reference range, perhaps because of criteria that had excluded severe and/or chronic diseases, and the young age of participants. In addition, participants were actors in a cabaret setting where they constantly exercised and had a normal lifestyle. Despite the higher proportion of smoking in the control group, smoking exhibited no predicted effect on cardiovascular markers when analyzed with logistic regression and adjustment.

Changes in cardiovascular markers because of long-term use of CSH in MtF transsexuals have been reported in previous studies [10, 16, 20]. They reported no significant hazardous effects from long-term use of CSH except for ethinyl estradiol, which may relate to cardiovascular death [20]. The increase of HDL by 10%–24% (approximately 6 mg/dL from baseline) was described in CSH using subjects. This was consistent with our findings. We report an increase of

Table 4. Prevalence comparison of cardiovascular risk factors between cross-sex hormone (CSH) using group and control group

Clinical outcomes	Value cut point of risk for clinical outcomes	CSH group		Control group		Pearson chi-square
		No of CSH	MtF transsexuals in CSH group who had risk (% of risk for CSH users)	No of control	MtF transsexuals in control group who had risk (% of risk for nonusers)	
Age (years)	>30	56	19 (34%)	46	19 (41%)	0.44
C-reactive protein	>1.8	52	9 (17%)	43	19 (44%)	0.004**
Fibrinogen	Out of range of 200–400	45	12 (27%)	40	7 (18%)	0.31
Systolic blood pressure	>120 mmHg	47	12 (26%)	41	17 (41%)	0.13
Diastolic blood pressure	>80 mmHg	36	0 (0%)	30	0 (0%)	–
Pulse (/min)	>80	44	12 (27%)	36	17 (47%)	0.67
Body Mass Index	>25kg/m□	40	3 (8%)	40	9 (23%)	0.06
Total cholesterol	>200 mg/dL	52	19 (37%)	43	16 (37%)	0.95
Triglyceride	>150 mg/dL	52	4 (8%)	43	8 (19%)	0.11
Low density lipoprotein	>100 mg/dL	51	32 (63%)	43	28 (65%)	0.81
High density lipoprotein	<40, >60 mg/dL	52	3 (6%)	43	7 (16%)	0.10

*Significantly different from control group (*t* test) ($P < 0.05$)
**Significantly different from control group (*t* test) ($P < 0.01$)

Table 5. Odds ratio (95% CI) of effects of CSH use on various outcomes

Outcomes	Effect of CSH (odds ratio (95% CI))	
	Crude model	Adjusted model (age, smoking)
Fibrinogen	2.73 (0.27–27.29)	2.14 (0.66–6.92)
C-reactive protein	**0.26 (0.10–0.68)****	**0.34 (0.13–0.93)***
Body Mass Index	0.27 (0.69–1.12)	0.55 (0.11–2.67)
Systolic blood pressure	0.50 (0.21–1.24)	0.63 (0.23–1.72)
Diastolic blood pressure		
Pulse	0.42 (0.17–1.06)	0.60 (0.21–1.74)
Total cholesterol	0.97 (0.42–2.24)	0.91 (0.35–2.40)
Triglyceride	0.37 (0.10–1.31)	0.47 (0.12–1.86)
Low density lipoprotein	0.90 (0.39–2.10)	3.10 (1.17–8.19)
High density lipoprotein	0.32 (0.76–1.32)	0.50 (0.11–2.30)

approximately 20% (mean difference 8.3 mg/dL (CI 0.2–16.4) in HDL in the CSH group. These findings are similar in several previous studies with constant reports of increased HDL levels in males who used CSH, including those who had aromatase deficiency and MtF transsexuals despite various outcomes on other lipid profiles (total cholesterol, triglyceride, and LDL) [21-23]. An increase of HDL with sex hormone use was also observed in women [24]. BMI and CRP, by contrast, were previously reported to be increased in CSH groups, but were not significantly different [16]. We hypothesized that the differences between previous studies and the current study were likely to be a consequence of participant selection criteria. The current study was conducted in subjects who were homogeneous in terms of young age and regular exercise; whereas the earlier studies contained higher heterogeneous confounders including age, health status, type, and period of hormone use of the subjects.

Another long-term study of hormone use in MtF transsexuals showed an increased risk of cardiovascular-related death in CSH users of approximately threefold compared with normal men (4.1% in CSH group and 1.3% in never or former use) following the use of CSH for 18.6 years [20]. Interestingly, when analyzed by age, the cardiovascular risk was greater in the older group (older than 40 years) and no risk was found at younger ages despite a similar duration of CSH use. Therefore, age is likely to be the key distributing factor for the effects of CSH. This might explain the lack of negative health impact from CSH use found in the present study.

A study in women found that high-dose sex steroid hormones increases CRP inflammatory marker levels [25], whereas studies in MtF transsexuals and men with prostate cancer showed both increases and decreases in CRP [16, 26]. Studies on the effects of oral ethinyl estradiol (100 μg/d) in 15 MtF transsexuals on CRP [27] and in patients with prostate cancer [26] showed an association of estrogen treatment with increased CRP. Because these two studies studied men with estrogen interventions, the conflicting results on CRP levels may be accounted for by several factors. First, the previous study was conducted in MtF transsexuals who administered much higher doses of estrogen than those in our study. Second, cancer patients frequently had high CRP levels up to 100 μg/mL [28], which may contribute to the increase of CRP found by Lurer et al.

Fibrinogen levels in MtF transsexuals were also investigated in this study as a surrogate marker for the development of venous thromboembolisms (VTE), possibly related to CSHs. Despite a previous report of approximately 2% increased risk of VTE in MtF transsexuals who used CSHs [29], we did not observe this risk from measurement of fibrinogen. This avoidance of risk was likely because participants in this study were healthy and maintained a normal lifestyle. Furthermore, overall levels of sex hormones in our CSH using participants were relatively low, particularly progesterone, which ranged between low and normal. This is in accordance with studies that demonstrated correlation of VTE and progesterone levels rather than estrogen [30].

No records or actual written diaries of hormonal use were retrieved from our participants. Only memory of hormonal use was used and there may be recall bias in this study. CSH studies in developed countries had been performed in only sex change clinics and under the control of expert clinicians. The present study of self-medication with CSH by Thai men was conducted in a real-life field setting. The levels novel cardiovascular outcome markers, CRP and Fb were assessed in these MtF transsexuals. When compared with previous studies, the present study consisted of a larger number of transsexual participants, as distinct from other studies. However, weaknesses could be overcome with a stronger methodological design and more clinical measurements. A larger sample size, hormone utilization diaries, multiple clinical measurements (for average level), serum hormone-binding globulin (SHBG) measurement, more focus on outcomes, and longitudinal follow-up are needed in future field studies. To our knowledge, this study is the first report regarding cardiovascular risk factors in CSH using MtF transsexuals in Thailand. We were able to include a larger group of participants than in previous reports. The smaller MtF transsexual population in most studies included only from 10 to 30 participants per study.

Conclusions

Our findings were consistent with other studies that showed no serious risk or health problems with CSH use at a young age. Studies with longer follow ups and a stronger design would help to clarify this issue further.

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Conflict of interest statement

Authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. There was no pharmaceutical entertainment industry involvement in this study.

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