Detrimental effects of endogenous oestrogens on primary acute myocardial infarction among postmenopausal women

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Abstract

Objective Traditionally, oestrogens were considered to be protective for the cardiovascular system for premenopausal women. Therefore, we conducted a retrospective case–control study to examine the association between endogenous oestrogens and acute myocardial infarction (AMI) risk among postmenopausal women.

Methods A case–control study was performed among 30 primary AMI patients and 60 control subjects. Baseline characteristics data was collected and endogenous sex hormones levels were determined using chemoluminescence and radioimmunoassay methods. Conditional logistic regression models were developed with adjustment for confounders.

Results Compared with controls, the circulating oestrone, oestradiol, androstenedione and testosterone levels were significantly higher in AMI patients ($P<0.05$) while the sex hormone binding globulin (SHBG) level was lower ($P<0.05$). Spearman correlation coefficients showed oestradiol was positively correlated with body mass index (BMI) and waist-to-hip ratio (WHR) in

cases, but not in controls. In univariable conditional logistic regression models, oestrone, oestradiol, testosterone, WHR, BMI, diabetes and hypertension were all found to be positively associated with AMI ($P<0.05$). After adjusting for these factors, oestradiol (odds ratio (OR)=4.75; 95 % confidence interval (CI)=1.07–21.10; $P=0.04$) and WHR (OR=6.46; 95 % CI=1.09–38.39; $P=0.04$) continued to demonstrate strong positive associations with AMI.

Conclusions A higher level of oestradiol was potentially associated with primary AMI risk among postmenopausal women.

Keywords Oestrogens · Acute myocardial infarction · Acute stress · Adipose tissue · Postmenopausal

Introduction

Coronary heart disease (CHD) develops 7 to 10 years later in women than in men [1]. Percutaneous coronary intervention (PCI) has been shown to be beneficial to the patients with CHD [2], whereas the rate of atherothrombotic events, including cardiovascular death, in women has increased during the last decade [3]. Oestrogens are considered to be protective for the cardiovascular system, and oestrogen deficiency contributes to the development of CHD. However, a number of studies have challenged this traditional concept and suggested that there was no significant association between endogenous oestrogens and CHD risk [4–8]. On the other hand, the limitations of these studies impaired the correctness of their conclusions. For example, the participants in one study were all diabetics, limiting the generalisability of the findings [5]. Another study in which CHD and stroke were analysed together as a combined endpoint and did not differentiate risk factors of CHD from those of

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stroke [6]. Therefore, the association between endogenous oestrogens and CHD risk remains to be further explored.

In this study, we conducted a retrospective case–control study including 30 cases and 60 controls to determine the association between endogenous oestrogens and acute myocardial infarction (AMI) risk among postmenopausal women.

Methods

Selection of cases and controls

After being approved by the local ethics committee of the Second Hospital of Tianjin Medical University, 30 postmenopausal women with primary AMI (cases) and 60 postmenopausal women without AMI history (controls) were chosen to participate in our study. All cases were hospitalised for incident AMI within a 1-year period from 2010 to 2011. All the participants gave written consent for our investigation.

The diagnostic criteria for AMI were adapted from the Joint ESC/ACCF/AHA/WHF Task Force [9], including detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following: (1) Symptoms of ischaemia; (2) ECG changes indicative of new ischaemia (new ST-T changes or new left bundle branch block [LBBB]); (3) Development of pathological Q waves in the ECG; (4) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Within 6 h from the onset of symptoms, all cases were treated with primary PCI with a loading dose of 300 mg of aspirin and 300 mg of clopidogrel before the procedure followed by aspirin (100 mg/day) and clopidogrel (75 mg/day). Among these AMI patients, 73.5 % had an anterior AMI, while the other 26.5 % were inferior AMIs. Stent implantation was successfully performed in all patients. No dissection was observed during the procedure. Left ventricular ejection fraction (LVEF) was measured using standard transthoracic echocardiography within 48 h following admission and the mean EF value was 50.62 %. Women were considered postmenopausal when they reported not having had any menses over the past 12 months or had undergone a bilateral ovariectomy. Diagnostic criteria of diabetes and hypertension were based on self-report. All participants in our study were non-users of hormone medications and had no history of AMI prior to blood sample collection. Each case was randomly matched with two controls according to age (5-year age group). Controls were recruited from the general population for routine physical examinations in the same hospital. Controls were excluded if they had

endocrine-related diseases or took any medications known to affect endogenous sex hormone levels.

Laboratory assays

Blood samples from case patients were collected on the second morning of hospitalisation. The time elapsed between AMI occurrence and blood sampling was 18–24 h, while control patients' blood samples were collected on the morning of the routine physical examination. All subjects were fasted for at least 8 h before blood collection. For each subject, 5 ml of venous blood was collected and transferred to the laboratory immediately for centrifugation. All serum samples were stored at -80°C for future analysis.

The serum samples were assayed in the clinical laboratory of the Second Hospital of Tianjin Medical University. The laboratory staff was blind to the status of case and control samples. Serum oestradiol, testosterone (Siemens Medical Solutions Diagnostics, Massachusetts, USA), C-peptide, and sex hormone binding globulin (SHBG) (Siemens Healthcare Diagnostics Inc, Gwynedd, UK) concentrations were measured using the chemoluminescence method, while the radioimmunoassay method was used to determine serum insulin (Siemens Medical Solutions Diagnostics, Los Angeles, USA), oestrone and androstenedione (Diagnostic Systems Laboratories Inc, Webster Texas, USA) concentrations. Each target was measured within the same batch on the same day. The intra- and inter-batch coefficients of variation (CV) were 4.6 % and 9.0 % for oestrone (at 1.2 pg/ml), 9.3 % and 6.4 % for oestradiol (at 7.0 pg/ml), 3.7 % and 4.8 % for insulin (at 2 $\mu\text{IU/ml}$), 2.4 % and 5.3 % for C-peptide (at 0.09 ng/ml), 4.0 % and 4.5 % for testosterone (at 10 ng/dl), 5.3 % and 9.4 % for androstenedione (at 0.03 ng/ml), and 6.0 % and 7.9 % for SHBG (at 0.2 nmol/l).

Statistical analysis

Data were analysed using the SAS version 9.13 (SAS Institute Inc., Cary, North Carolina, USA). In our analyses, age, body mass index (BMI) and waist-hip ratio (WHR) were analysed as continuous variables whereas diabetes and hypertension were analysed as categorical variables. Serum sex hormones and SHBG levels were natural logarithm transformed to normalise their distributions. Significance of differences in continuous variables was assessed using the paired *T* test while McNemar's test was used to analyse the categorical variables. Spearman's correlation coefficients were calculated to evaluate the correlations between sex hormones and anthropometric data. Univariable and multivariable conditional logistic regression models were then used to assess the correlation between oestrogens and AMI after adjusting for confounding factors. Variables were considered confounding if they were found to be significantly

Table 1 Basic characteristics of acute myocardial infarction patients and control subjects

	Cases (<i>n</i> =30)	Controls (<i>n</i> =60)	<i>P</i> value
Age (years) ^a	70.20 (10.87)	68.73(8.34)	0.40
BMI (kg/m ²) ^a	26.38 (3.60)	23.74 (3.77)	0.11
WHR ^a	0.91 (0.05)	0.84 (0.08)	0.09
Diabetes (%)	60	16.67	0.02
Hypertension (%)	53.33	20	0.00
Oestrone (pg/ml) ^b	51.94 (29.96, 90.02)	29.27 (22.97, 39.35)	0.02
Oestradiol (pg/ml) ^b	30.91(25.64, 57.76)	13.31 (10.25, 22.68)	<0.00
Testosterone (ng/dl) ^b	58.00 (42.00, 72.00)	38.00(27.00, 54.00)	0.00
Androstenedione (ng/ml) ^b	1.09 (0.72, 2.99)	0.89 (0.82, 1.14)	0.01
Insulin (μIU/ml) ^b	8.29 (6.63, 10.31)	9.10 (5.94, 11.79)	0.45
C-peptide (ng/ml) ^b	2.16 (1.05, 2.42)	1.59 (1.03, 2.41)	0.55
SHBG (nmol/l)	41.70 (34.10, 49.10)	49.65 (43.30, 79.40)	0.01
Culprit vessel, <i>n</i> , %			
LAD	73.33 % (22/30)		
LCX	10 % (3/30)		
RCA	16.67 % (5/30)		
Target lesion location, <i>n</i> , %			
Proximal	43.33 % (13/30)		
Mid	50 % (15)		
Distal	6.67 % (2/30)		

Categorical variables are showed as their positive percentages

BMI body mass index; *WHR* waist-to-hip ratio; *SHBG* sex hormone-binding globulin. *LAD* left anterior descending artery; *LCX* left circumflex artery; *RCA* right coronary artery

^aMeans and standard deviations;

^bMedian and inter-quartile ranges

associated with AMI ($P<0.05$) in the univariable analysis, and were further included in the multivariable model. All P values were two-sided with those lower than 0.05 considered statistically significant.

Results

We compared the distribution of conventional risk factors and endogenous sex hormones levels between cases and controls. The demographic characteristics for both cases and controls

were shown in Table 1. There were significant differences in BMI and WHR between cases and controls ($P<0.05$). Both diabetes and hypertension were in a significantly higher percentage in cases than controls ($P<0.01$). Compared with controls, the oestrone, oestradiol, androstenedione and testosterone levels were significantly higher ($P<0.05$) while the SHBG level was lower in cases ($P<0.05$). Spearman correlation coefficients showed oestradiol was positively correlated with BMI and WHR in cases, but not in controls (Table 2). Correlations between sex hormones and SHBG, BMI and WHR were shown in Table 2. In univariable conditional logistic regression

Table 2 Spearman correlation coefficients for associations between oestradiol, oestrone, testosterone, androstenedione, BMI and WHR

	BMI	WHR	Oestrone	Oestradiol	Insulin	C-peptide	Testosterone	Androstenedione	SHBG
BMI (kg/m ²)	–	0.33	0.01	0.17	0.33	0.34	0.07	0.12	–0.06
WHR	0.76**	–	0.15	0.14	0.47**	0.42*	0.10	0.11	–0.27
Oestrone (pg/ml)	0.17	0.25	–	0.50**	0.11	0.28	0.39*	0.49**	–0.21
Oestradiol (pg/ml)	0.83**	0.66 **	0.37	–	0.05	0.18	0.31	0.40*	–0.27
Insulin (μIU/ml)	0.15	0.10	0.63*	0.02	–	0.40*	0.36	0.24	–0.10
C-peptide (ng/ml)	0.21	0.35	0.60*	0.03	0.71 **	–	0.02	0.20	–0.05
Testosterone (ng/dl)	0.35	0.43	0.66 **	0.41	0.13	0.04	–	0.07	–0.16
Androstenedione (ng/ml)	0.30	0.20	0.67 **	0.40	0.38	0.29	0.80 **	–	–0.01
SHBG (nmol/l)	–0.10	–0.01	–0.36	–0.53*	–0.36	–0.21	–0.11	–0.34	–

Boldface presenting control group

SHBG sex hormone-binding globulin; *BMI* body mass index; *WHR* waist-to-hip ratio

* $P<0.05$; ** $P<0.01$ (two-sided test)

Table 3 Odds ratio for acute myocardial infarction using uni-variable logistic regression

Parameters	Odds ratio	95 % Wald confidence limits		P-value
BMI (kg/m ²)	0.83	0.71	0.98	0.02
WHR	3.75	1.23	11.39	0.02
Diabetes	4.57	1.45	14.39	0.01
Hypertension	7.50	2.24	25.06	0.00
Oestrone (pg/ml)	3.90	1.61	9.47	0.00
Oestradiol (pg/ml)	9.44	2.95	30.20	<0.00
Testosterone (ng/dl)	10.83	2.42	48.38	0.00
Androstenedione (ng/dl)	2.20	0.98	4.95	0.06
Insulin (μIU/ml)	1.39	0.52	3.72	0.51
C-peptide (ng/ml)	1.45	0.55	3.82	0.45
SHBG (nmol/L)	0.16	0.04	0.67	0.01

SHBG sex hormone-binding globulin; BMI body mass index; WHR waist-to-hip ratio

models, oestrone, oestradiol, testosterone, WHR, BMI, hypertension and diabetes were all found to be positively associated with AMI risk. On the contrary, SHBG had an inverse association with AMI (Table 3). After adjusting for these factors, oestradiol (odds ratio (OR)=4.75; 95 % confidence interval (CI)=1.07–21.10; $P=0.04$) and WHR (OR=6.46; 95 % CI=1.09–38.39; $P=0.04$) continued to demonstrate strong positive associations with AMI (Table 4).

Discussion

Our study revealed that among postmenopausal women, oestradiol and WHR were positively associated with primary AMI, independent of diabetes, hypertension, BMI and androgens.

Our knowledge concerning oestrogens is that among premenopausal women, oestrogens supply a benefit against hypertension and cardiovascular diseases. On the other hand, the postmenopausal state with profound oestrogen deficiency results in a complex metabolic disorder. These alterations may be regarded as high-risk factors for ischaemic stroke, myocardial infarction (MI) and pulmonary emboli [10]. One study demonstrated that early menopause was significantly associated with increased CHD risk [11] and another study reported that women following bilateral oophorectomy had a higher possibility to have MI [12]. Furthermore, women who initiated hormone therapy closer to

menopause tended to have reduced CHD risk [13]. Thus, based on these studies, it is reasonable to conclude that higher levels of exogenous oestrogens are beneficial to postmenopausal women. However, our findings contrast sharply with these studies.

Considering the differences between our study and previous studies, it is mandatory to explore the effects of acute stress on the secretion of oestrogens. One may question whether a high oestradiol level in AMI patients is the possible intermediate variable on the pathway from stress to disease or just acute stress response. As we know, short-term increases in adrenaline and noradrenaline in response to acute stressors are well documented. It has been reported that stress can result in a reduction of oestrogens in the female and testosterone in the male [14, 15]. Two studies demonstrated that a significantly low level of testosterone immediately following MI would subsequently return to normal in men [16, 17]. As in the case of trauma, it may be an acute response [18, 19]. Moreover, the high ratio of cortisol to testosterone (C/T) has recently been reported to increase CHD risk in men [20, 21]. Taken together, in our study a high oestradiol level promotes the occurrence of AMI among postmenopausal women instead of being acute stress response.

Moreover, we found that the oestradiol level was positively correlated with BMI and WHR in AMI patients. Epidemiological studies showed that obese women had high oestradiol and testosterone levels and low SHBG levels

Table 4 Odds ratio for acute myocardial infarction using multivariable logistic regression

Parameters	Odds ratio	95 % Wald confidence limits		P-value
BMI(kg/m ²)	0.84	0.63	1.12	0.23
WHR	6.46	1.09	38.39	0.04
Estrone(pg/ml)	1.76	0.43	7.21	0.43
Estradiol(pg/ml)	4.75	1.07	21.10	0.04
Testosterone(ng/dl)	3.56	0.35	36.71	0.29
SHBG(ng/dl)	0.39	0.07	2.23	0.29

SHBG sex hormone-binding globulin; BMI body mass index; WHR waist-to-hip ratio

[22]. It appears that obesity is primarily responsible for the increased circulating oestradiol levels. After menopause, the ovaries cease to produce oestrogen making peripheral oestrogen conversion in the adipose tissue the main source of oestrogen in the circulation [23]. In adipose tissue aromatase, which was reported to have the ability to convert androgens to oestrogens [24], induced this conversion by hydroxylation at the 19-methyl group, cleavage of the C10–C19 bond and aromatisation of the A ring of androgen [25] resulting in increased levels of oestrogen. Furthermore, a number of inflammatory cytokines are produced during AMI. Among these cytokines, monocyte chemoattractant protein (MCP)-1 can recruit macrophages to adipose tissue [26, 27]. Purohit et al. found that tumour necrosis factor- α (TNF- α) and interleukin-6 (IL-6) produced by macrophages increased the production of oestrogens in both normal and malignant breast tissues [28]. All the evidence suggests that the higher level of oestradiol may originate from adipose tissue.

As expected, BMI, hypertension and diabetes were also demonstrated to be positively associated with AMI (OR range 0.83–8.50). Surprisingly, oestradiol was found to have stronger associations with AMI. In fact, even though oestradiol protected premenopausal women from the cardiovascular system, the protective effects of oestradiol among postmenopausal women were not conclusive. The Women's Health Initiative (WHI) study, a randomised controlled primary prevention trial in which 16,608 postmenopausal women aged 50–79 years were recruited, reported that postmenopausal hormone therapy resulted in a risk of increased cardiac and thromboembolic events [29]. This study indirectly supports our finding that a high oestradiol level promotes incident CHD. Although the underlying mechanisms of the detrimental effects remain to be determined, it appears that the high oestradiol level is associated with perturbations in other factors that mediate acute thrombotic events.

Undoubtedly, there are some potential limitations in our study. First, because the diagnosis of diabetes and hypertension are based on self-report, some degree of recall bias is probable. Second, given the incomplete clinical data including interval between postmenopausal and AMI, interval between the diagnosis of hypertension or diabetes and AMI, the type and length of treatment for these comorbid conditions, and the baseline levels of lipid levels, we were unable to collect accurate information regarding factors that may affect the AMI risk. Third, due to the limited sample size, we were not able to detect small effects which may have underpowered our conclusion. Fourth, since we did not test oestrogen levels at different time points from admission to discharge, we cannot completely exclude the possibility that stress response through adipose tissue effects oestrogen levels in the development of AMI. Finally, since there are no follow-up data in our study, so the long-term hard endpoints need to be further evaluated.

Conclusions

In conclusion, our study indicated that a higher level of oestradiol was potentially associated with primary AMI risk among postmenopausal women. However, due to the limited sample size and inherent limitations of all case–control studies, the results of our study should not be considered conclusive. Further prospective studies are necessary to determine the association between oestrogens and AMI among postmenopausal women.

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