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Original Article

Serum butyrylcholinesterase activity and phenotype associations with lipid profile during various phases of menstrual cycle in young healthy women with regular menses, a preliminary report

Asad Vaisi-Raygani[1,2*], Heidar Tavilani[3], Hadiss Vaisi-Raygani[1], Zohreh Rahimi[2,4], Jamshid Karimi[5], Tayebeh Pourmotabbed[6]

[1]*Fertility and Infertility Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran*
[2]*Molecular Diagnostic Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran*
[3]*Urology & Nephrology Research Center, Hamadan University of Medical Sciences, Hamadan, Iran*
[4]*Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran*
[5]*Department of Biochemistry, Hamadan University of Medical Sciences, Hamadan, Iran*
[6]*Department of Microbiology, Immunology, Biochemistry University of Tennessee Health Science Center, Memphis, TN, USA*

*** CORRESPONDENCE**
Asad Vaisi-Raygani
Tel:+98 8314275494
Fax:+98 8314279919
E-mail:avaisiraygani@gmail.com

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ABSTRACT

Objectives: In this study the association of phenotypes and activity of butyrylcholinesterase (BuChE) with serum level of lipid-lipoprotein and apolipoproteins during various phases of menstrual-cycle was determined.

Methods: The study population consisted of 22 healthy women aged 19–25 years with regular menstrual cycles, 26–30 days in length. The serum levels of lipids, apolipoproteins, and BuChE activity were determined during menses (days 1-2 after the beginning of menstruations), follicular (days 7-8) and luteal (days 21-22) phases of the menstrual cycle.

Results: There were significant differences in the level of serum BuChE activity during three phases of the menstrual cycle (P=0.049). The activity of serum BuChE was the highest during follicular phase (890 ± 292 IU/L), the modest during the menses phase (831 ± 222 IU/L) and the lowest during luteal phase (707 ±211 IU/L). We found a significant positive correlation between BuChE activity with the levels of low density lipoprotein cholesterol (LDL-C, r=0.34, P=0.038) in the follicular and in the menses phase with LDL-C (r=0.4, P =0.025) and triacylglycerol (r=0.47, P=0.033). In addition, carriers of the non-UU phenotypes (*non-wild type* low BuChE activity) had significantly lower levels of serum high density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (APOA1) compared to UU phenotype (usual or wild type) during menstrual cycle.

Conclusion: Our results demonstrate that serum BuChE activity elevates during menstrual cycle. It is low during luteal phase and reaches to a high level in follicular-phase. The lipid profiles are also affected by BuChE activity throughout the menstrual-cycle in reproductive aged, regularly cycling and young healthy women.

Keywords: Butyrylcholinesterase; Lipids; Lipoproteins; Menstrual cycle

Introduction

Human butyrylcholinesterase (BuChE) is predominantly synthesized by the liver as a glycoprotein and is more abundant in the serum [1]. BuChE cleaves hydrophilic and hydrophobic choline esters and hydrolyzes a variety of xenobiotics as a bioscavenger of drugs (succinylcholine) as well as of organophosphate andcarbamate insecticides [2-6].

More than 30 variants of serum cholinesterase have been described. The carriers of some of variants of BuChE (*non-wild type (Non-UU)* such as the atypical (A), the silent (S) and the fluoride-resistant (F) variants are prone to develop pro-

longed apnea following the administration of the muscle relaxant succinylcholine [7-8]. Five phenotypes of nine *non-wild type* of BuChE (BChE-aa/ as/ af/ ss/ sf) are associated with low butyrylcholinesterase activity and hypersensitivity to muscle relaxants succinylcholine and mivacurium [6-13].

The physiologic function of plasma cholinesterase remains unresolved [6]. We have recently shown the association between serum BuChE activity and phenotype with lipid profile in stroke patients [14 18]. BuChE enzymatic activity has been shown to be high in individuals with hypertension, hyperlipidemia and high body weight and low in individuals who had suffered acute myocardial infarction or undergone treatment with beta blockers [15-18, 19-22].

The activity of BuChE has been shown correlatedwith plasma low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and triacylglycerol (TG) concentrations [19-22, 23-26]. Besides cholinesterase, the ability of estrogens and other sex hormones to change plasma lipid and lipoprotein levels have been shown [23-26, 27-30]. Due to importance of sex hormones on lipid metabolism and alteration of these hormones during menstrual-cycle, level of lipid and lipoprotein have been studied during menses, follicular and luteal-phases of menstrual-cycle [23-28, 27-32]. Gevorkian et al. have found that estradiol propionate induces tyrosine transaminase and acetylcholinesterase but has not effect on butyrylcholinesterase [29 33]. Mahmoud et al. have demonstrated that elevated BuChE activity in normal pregnancy may correlate with better ability to clear pregnancy-threatening toxins [30, 31, 34-35].

To our knowledge, there are no published reports related to the effect of menstrual cycle on the activity of BuChE and its phenotypes. Due to the cycling nature of circulating levels of sex hormones in premenopausal women and their possible impact on the activity of BuChE, in this study we evaluated association between the serum BuChE phenotypes and activity and lipids, lipoproteins and hormonal levels during various phases of the menstrual-cycle.

Materials and Methods

The study population consisted of 22 healthy women aged 19-25 years with regular menstrual-cycles of 26-30 days in length (28±2 days). The inclusion criteria for the study were as follow:

1) Regular menstrual-cycles of 26-30 days, with the cycle length not changing by more than two days for the three prior months, 2) not taking any type of oral contraceptives or lowering lipid drugs for at least one year prior to study, 3) not being pregnant or lactating for one year prior to enrolment in the study, 4) body mass index <25 Kg/m^2, 5) no past chronic illness, 6) no liver problem (normal level of alanine aminotransferase, glutamic aminotransferase, alkaline phosphatase and bilirubin), 7) non-smoking and no history of drinking alcohol, and 8) not taking any type of anti-inflammatory or others drugs for the two prior cycle. The subjects fulfilling the inclusion criteria were asked to participate in this research project. Written informed consent was obtained from all those enrolled, according to the criteria of the Ethical Committee of Hamadan University of Medical Sciences.

Sample collection

Blood samples were obtained in menses (days 1-2 after the beginning of menstruations), follicular (days 7-8) and luteal-phases (days 21-22) of the menstrual-cycle. In addition, the length of menstrual-cycle of each participant was noted. The blood samples were collected between 8:30 and 10:30 am after the overnight fasting.

Biochemical analysis

BuChE activity and phenotypes were determined according to the method of Whittaker using benzoylcholine chloride (50 µmol/L) as substrate in the presence or absence of the inhibitor drugs dibucaine hydrochloride (10 µmol/L) and sodium fluoride (50 µmol/L) [for determination of dibucaine (DN) and fluoride (FN) numbers], at 240 nm and at 25ºC. Serum was pre-diluted 1 to 100 with phosphate buffer (pH 7.4, 133 mmol/L) [13].

One unit of BuChE is defined as the amount of enzyme required to hydrolyze 1 µmol of benzoylcholine chloride per minute at standard assay conditions. BuChE activity, DN and FN were calculated as a follow.

Serum BuChE (IU/L) = $\Delta A/\text{ min} \times 30.3\times10^3$

DN or FN = (1– $\Delta A/$ min with inhibitor/$\Delta A/$min without inhibitor) ×100

The serum levels of lipid, lipoproteins, apolipoproteins and LP(a) level were measured

by commercially available enzyme assay kits(Pars Azmon kit, Iran).

Statistical analysis

BuChE activity, levels of lipids, apolipoproteins were compared among the three different phases of the menstrual-cycle using the ANOVA. The correlation values of serum parameters measured, with BuChE activity and phenotypes among the three different phases of the menstrual-cycle were calculated using Pearson correlation, linear regression and an unpaired t-test, ANOVA and post-hoc-Tukey. Statistical significance was assumed at the $P<0.05$ level. The SPSS statistical software package version 16 was used for the statistical analysis.

Results

Among thirty subjects who were enrolled, twenty-two women completed the study. Age of participants and length of the menstrual-cycles were 21.7±0.27 years and 28.2±0.25 days, respectively. The BuChE activity and the serum levels of lipids, lipoproteins, and apolipoproteinsat menses, follicular and luteal-phases of the menstrual-cycle are reported in Table 1.

TheBuChE activity was (890±292 IU/L) the highest during the follicular-phase, which was significantly different from the luteal (707±211 IU/L, $P=0.04$) and the menses-phases (831 ± 222 IU/L, $P=0.048$). The levels of serum LDL-C ($P=0.001$), TC ($P=0.005$), TG ($P=0.032$) and APOB ($P=0.012$) were significantly higher and levels of HDL-C ($P<0.001$) and APOA1 ($P=0.004$) were significantly lower in the follicular-phase compared to those in the luteal and menses-phases. We did not observe any significant differences in the concentration of other parameters during menstrual-cycle.

Table 1. Comparison activities and levels of the studied parameters during the menses, follicular and luteal phases of menstrual-cycle in a population from west Iran (n=22)

Parameters	Menses-phase	Follicular-phase	Luteal-phase
BuChE Activity† IU/L	831±222 [a]P=0.1 [b]P=0.048	890±292 [c]P=0.04	707±211
LDL-C (mmol/L)	1.27±0.46 [a]P=0.2 [b]P=0.13	1.51±0.55 [c]P=0.001	1±0.35
HDL-C (mmol/L)	1.26±0.26 [a]P=0.22 [b]P=0.018	1.11±0.28 [c]P=0.001	1.49±0.27
TC (mmol/L)	3.7±1.25 [a]P=0.07 [b]P=0.58	4.51±1.3 [c]P=0.005	3.3±1.16
TG (mmol/L)	0.64±0.29 [a]P=0.02 [b]P=0.98	0.95±0.46 [c]P=0.032	0.67±0.33
ApoA1 (mg/dL)	143±22.2 [a]P=0.85 [b]P=0.017	139±21 [c]P=0.004	163±25
LPO(a) (mg/dL)	21.8±18.5 [a]P=0.86 [b]P=0.4	24.5±18.2 [c]P=0.86	15±14.3
ApoB (mg/dL)	91±17.4 [a]P=0.46 [b]P=0.079	97±16.2 [c]P=0.004	81±11.8

†µmol L−1min−1 at 25°C, substrate (benzoylcholine chloride).

[a]p, [b]p and [c]p parameters compared between menses with follicular, menses with luteal and follicular with luteal-phases, respectively. BuChE, Butyrylcholinesterase ; TC, Total cholesterol; TG, Triglyceride; LDL-C, Low-density lipoprotein cholesterol; HDL-C, High-density lipoproteincholesterol; APoA1, Apolipoprotein A-I; LPO (a), Lipoprotein a; ApoB, Apolipoprotein B.

Correlations between BuChE activity and serum levels of lipids, lipoproteins, and apolipoproteins for each phase of menstrual-cycle and overall in the menstrual-cycle are shown in Table 2. We found a positive correlation between BuChE activity and levels of LDL-C (r=0.49, $P=0.025$)

and TG (r=0.47, *P*=0.033) in the menses-phase. In the follicular-phase, we observed a positive correlation between BuChE activity with LDL-C (r=0.34, *P*=0.038). In the luteal-phase, the BuChE activity on the other hand, was negatively correlated with the levels of Lp(a) (r=-0.53, *P*=0.021). We did not found any significant correlation between BuChE activity and other parameters for each phase of menstrual-cycle and overall in the menstrual-cycle.

Association of BuChE-phenotypes with BuChE activity and serum levels of lipids, lipoproteins and apolipoproteinsfor the menses, follicular and luteal-phases of the menstrual- cycle are presented in Table 3. BuChE activity was significantly different between UU and non-UU carriers in the follicular-phase (*P*=0.048), however HDL-C, total cholesterol (TC), TG andAPOA1 levelswere different between UU and non-UU carriers in the follicular-phase but not significant. Overall, we observed higher level of TC and lower levels of HDL-C and APOA1 in non-UU compared to UU carriers in all three-phases of the menstrual-cycle, other parameters showed no significant differences.

Table 2. Correlation between BuChE activity with activities and levels of parameters have been compared various phases of menstrual-cycle and overall menstrual-cycle (n=22)

	BuChE activity of menses-phase	BuChE activity of follicular-phase	BuChE activity of luteal-phase	BuChE activity of overall menstrual-cycle
LDL-C (mmol/L)	r=0.4 P=0.025	r=0.34 P=0.038	NS	r=0.4 P=0.001
HDL-C (mmol/L)	NS	NS	NS	NS
TC (mmol/L)	NS	NS	NS	r=0.304 P=0.015
TG (mmol/L)	r=0.47 P=0.033	NS	NS	r=0.32 P=0.01
ApoA1 (mg/dL)	NS	NS	NS	NS
LPO(a) (mg/dL)	NS	NS	r= -0.53 P=0.021	r= -0.29 P=0.021
ApoB (mg/dL)	NS	NS	NS	NS

BuChE, Butyrylcholinesterase ; TC, Total cholesterol; TG, Triglyceride; LDL-C, Low-density lipoprotein cholesterol; HDL-C, High-density lipoproteincholesterol;APoA1,Apolipoprotein A-I; LPO (a), Lipoprotein a; ApoB, Apolipoprotein B; NS, Non-significant.

Table 3. Association of BuChE-phenotypes (UU (n=17) and None-UU (n=5)) with BuChE activity, activities and levels of parameters compared during various phases of menstrual-cycle and overall menstrual-cycle

BuChE phenotype	Menses-phase (n=22)		Follicular-phase (n=22)		Luteal-phase (n=22)		Overall menstrual-cycle	
	UU	None-UU	UU	None-UU	UU	None-UU	UU	None-UU
BuChE activity (IU/L)	866±320	831±209	1070±475[b]	861±210	756±353	710±193	910±405	801±204
LDL-C (mmol/L)	1.24±0.29	1.3±0.52	1.53±0.47	1.54±0.59	1.01±0.37	1.01±0.32	1.26±0.53	1.27±0.4
HDL-C (mmol/L)	1.4±0.15	1.21±0.28	1.28±0.16	1.07±0.9	1.6±0.3	1.44±0.12	1.4±0.19[d]	1.24±0.32
TC (mmol/L)	3.55±0.21	4.3±1.24	4.3±1.25	5.44±51	3.2±1.01	3.9±63	3.68±1.24[d]	4.56±1.48
TG (mmol/L)	0.64±0.3	0.72±0.32	0.89±0.37	1.29±0.01	0.66±0.34	0.77±0.34	0.71±0.34	0.92±0.5
ApoA1 (mg/dL)	156±13.2	141±24	136±20	155±19.6	180±26.5	159±10.6	145±24.5[d]	164±14
LPO(a) (mg/ dL)	17.2±11.7	22.1±20.5	22.2±19.3	23.7±18.2	11±10.7	15.3±12.6	16.8±14.2	20.6±17.7
ApoB (mg/ dL)	91±20	94±12	95.3±14.9	102±23	79±11.5	86±14.3	89±17	94±17.2

[b] and [d] is significant differences between carrier BuChE U/Uand Non-U/U(U/A,U/F,U/S) phenotypes in the follicular phase and overall of menstrual-cycles, respectively (*P*<0.05). BuChE, Butyrylcholinesterase ; TC, Total cholesterol; TG, Triglyceride; LDL-C, Low-density lipoprotein cholesterol; HDL-C, High-density lipoproteincholesterol; APoA1, Apolipoprotein A-I; LPO (a), Lipoprotein a; ApoB, Apolipoprotein B.

Discussion

This study is unique in that it provides important data for the effect of menstrual-cycle on the activity of BuChE. We found significant differences between activities of BuChE during three-phases of menstrual-cycle. The BuChE activity in the luteal phase was significantly lower than that in menses and follicular phases.

We analyzed the lipid profiles during menstrual-cycle, it was observed that the levels of serum LDL-C, TC, TG and ApoB at follicular-phase were significantly higher than those at the menses and luteal-phases (follicular-phase>menses-phase>luteal-phase). However, the levels of HDL-C and APoA1 were significantly higher at luteal-phase compared to the follicular-phase (luteal-phase>menses phase>follicular-phase). These results are consistent with the results of previous studies [32,33,36,37] demonstrating a significant increase in the level of HDL-C during the luteal-phase compared with the follicular-phase of the menstrual-cycle. These findings together are in accord with Barnett et al. [23, 27] hypothesis of association between lipid and lipoprotein profile with decreased risk of CHD during the luteal-phase compared with the follicular-phase of the menstrual-cycle.

Interestingly, we found a positive and significant correlation between BuChE activity with the levels of LDL-C and TG in the menses and LDL-C in follicular-phase and negative correlation with Lp(a) concentrations in luteal-phase. In addition, a positive and significant correlation was found between BuChE activity with LDL-C, TC and TG levels and inverse significant correlation with LP(a) level in all three-phases of the menstrual cycle. These findings are consistent with the results of other studies indicated a positive association between BuChE activity and serum cholesterol and triglyceride concentrations [14,17,18, 20-22, 24, 26] and the reports of an inverse association between BuChE activity with HDL-cholesterol [14,17, 18, 21]. These results together suggest that significant fluctuations observed in lipid profiles levels. We suggest further work to confirm these results.

The results of this study indicated that BuChE activity in the follicular-phase is significantly different between UU and non-UU carriers. During menstrual cycle TC and TG levels were significantly higher in carriers of non-UU compared to UU-phenotypes carriers. In addition, HDL-C and APoA1 level was significantly higher in UU-phenotype carriers compared to non-UU-phenotype carriers.

The importance of increased BuChE activity in follicular-phase is not clear. Mahmouda et al. [30,31] have demonstrated an elevated BuChE activity in normal pregnancy and reported a positive correlation between BuChE activities with recurrent spontaneous abortion (RSA). The toxic metabolites released upon T-cell activation in RSA may be responsible for the observed elevated BuChE activity in RSA patients. The positive correlation of BuChE activity with total antioxidant capacity was reported in gestational diabetes, healthy pregnancies and non-pregnant healthy controls [30-31, 34-35, 37]. Thus, the homeostasis of BuChE activity in the human female reproductive tract may be of importance.

Conclusion

Our results demonstrate that serum BuChE activity elevates during menstrual cycle. It is low during luteal phase and reaches to a high level in follicular-phase. The lipid profiles are also affected by BuChE activity throughout the menstrual-cycle in reproductive aged, regularly cycling and young healthy women**.** In addition, carriers of the non-UU-phenotypes had higher levels of serum TC and TG and lower levels of HDL-C compared to UU-phenotype carriers. Furthermore, we have two speculates based on our results in this study: 1) in carriers of the non-UU-phenotypes the risk of prolonged apnea may be more increases after receiving a muscle relaxant such as succinylcholine or mivacurium might during the luteal-phase than that of the follicular and menses-phase of menstrual-cycle. We suggest further work to confirm this speculate 2) BuChE activity may play a role in the regulation of menstrual-cycle. Further works is necessary to confirm this hypothesis.

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Conflict of interest

The authors report no conflict of interest.

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