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# Cholinesterase: Not a robust marker of systemic low-grade inflammation in hypertension

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ChE- Cholinesterase
HTN- Hypertension
DM- Diabetes Mellitus
CAD- Coronary Artery Disease
CVD- Cardiovascular Disease

**A B S T R A C T**

A prospective case-control **s**tudy evaluated the novel risk marker cholinesterase (ChE) in comparison to a well-known marker high sensitivity C reactive protein (hsCRP) to predict the presence of low grade systemic inflammation and to find its applicability for being used in place of hsCRP to predict the risk of CVD. ***Method:*** 285 healthy and 960 hypertensive subjects with/without coexisting cardiac/metabolic diseases were enrolled. Patients were categorized in to three categories: firstly, based on hsCRP levels (<1, 1-3, 3-10mg/l), secondly, based on number of coexisting diseases/risk factors (one, two, three), and thirdly, based on stage of hypertension (pre-, stage 1, stage 2 hypertension), each into three sub-groups, respectively. ***Results:*** Increased serum levels of both hsCRP (mg/l) and ChE (U/L) were found in all three groups and subgroups (based on: hsCRP, risk factors, hypertension stage) of patients (all $p<0.05$) as compared to healthy subjects. Although, ChE was significantly correlated with hsCRP in both healthy and patient groups ($p<0.01$), yet it was affected by more number of variables than hsCRP. ***Conclusion****:* ChE can act as a marker of low grade systemic inflammation but not as robust as hsCRP to predict the risk of CVD.



## Introduction:

Cardio-metabolic syndrome represents a cluster of cardiac/metabolic abnormalities that accounts for a significant burden of cardiovascular disease (CVD) worldwide (Brunzell *et al.*, 2008; Murray *et al.*, 2012). A recent survey performed by Gupta and Gupta, 2013; which reported that South Asian Indians are at highest risk of cardiovascular disease associated morbidity and mortality in the world. Vascular wall inflammation plays a key role in the pathogenesis and progression of various CVDs, like hypertension (HTN) (Boos and Lip, 2005), diabetes mellitus (DM) (Dandona *et al.*, 2005), coronary artery disease (CAD) (Pant *et al.*, 2014), heart failure (Stein and Yang, 1995), stroke (Rodrigues, 2014) and Myocardial infarction (MI) (DeGraba, 2004).

The central nervous system (CNS) interacts dynamically with the immune system to modulate inflammation through humoral and neural pathways. Autonomic regulation of local and systemic inflammation through the 'cholinergic anti-inflammatory pathway' is mediated by the vagus nerve and its major neurotransmitter, acetylcholine (Ach) (Rosas-Ballina and Tracey, 2009). The vagus nerve is the major nerve of the autonomic nervous system (ANS) which regulates organs function like heart rate, gut motility and bronchial constriction (Berthoud and Neuhuber, 2000) and convey message to brain regarding inflammatory processes occurring in the periphery (Goehler *et al.*, 1998). Cholinesterases (ChE) are a group of serine hydrolases, Acetyl-cholinesterase (AChE) and Butyrylcholinesterase (BChE) (Pohanka, 2011), catalyze various metabolic reactions in the body and also act as biomarker of low grade systemic inflammation (Costa *et al.*, 2012; Santarpia *et al.*, 2013). AChE catalyzes the hydrolysis of the neurotransmitter acetylcholine at the cholinergic synapses in the central and peripheral nervous system (CNS/PNS) and at neuromuscular junctions (NMJ), thus leading to inactivation and removal of Ach from

circulatory system (Colovic, 2013). It regulates cell proliferation, differentiation and cellular response to stress (Wei and Wang, 2012). Although, the biological role of BChE is not clear, yet it hydrolyzes butyrylcholine more quickly than ACh. BChE is associated with neurodegenerative diseases by playing role in scavenging enzymes for the detoxification of naturally occurring compounds (Pezzementi *et al.*, 2011) and might have a role in the altered lipoprotein metabolism in hypertriglyceridaemia associated with insulin insensitivity or insulin deficiency in DM (Abbott and Mackness, 1993). An increased activity of this enzyme has been reported in obesity (Boberg *et al.*, 2010), CVDs (Sato *et al.*, 2014), DM (Rao *et al.*, 2007), and in hyperlipidemic subjects (Abbott and Mackness, 1993). Studies have addressed the association of chronic low grade inflammation and BChE activity with various CVD risk factors, like hyperlipidemia (Sridhar *et al.*, 2005), HTN (Stojanov *et al.*, 2011) and insulin resistance (Ofek *et al.*, 2007).

In clinical prospective, biomarkers cover tools and technologies to interpret the prediction, prognosis/diagnosis, progression/regression, therapeutic response and outcome of the disease (Mayeux, 2004). Of all the biomarkers of vascular inflammation, high sentivity C-reactive protein (hsCRP) has been the most extensively investigated in clinical studies and has shown that baseline levels of hsCRP is a strong independent predictor of risk of future myocardial infarction, stroke, peripheral vascular disease, and vascular death among healthy individuals without knowing vascular disease (Ridker *et al.*, 1997; 1998). Framingham risk score (FRS) is a gender-specific algorithm used to estimate the 10-year risk of developing CAD (Kaur, 2013). The American Heart Association and Center for Disease Control and Prevention have issued a statement recommending that hsCRP be used as a risk marker for CVD in individuals with a FRS between 10% and 20%. In their recommendations, hsCRP levels 1 mg/l were considered low-risk, 1 to 3 mg/l as average risk, and ≥3 mg/l as high-risk for CVD (Jialal *et al.*, 2004).

Although ChE has been designated as a marker of low grade systemic inflammation, yet its place/value in comparison to well-known and robust marker hsCRP has not been established till now. Moreover, India being a developing country, the present scenario reveals high cost of hsCRP as compared to ChE, as laboratory diagnostic biomarker of low grade systemic inflammation to be used in clinical set-up. Objective of the study was to collect the further evidence of altered ChE activity in low grade systemic cardio-metabolic diseases, to compare the serum levels of hsCRP with ChE in patients, to find their correlation and nature/pattern of correlation which may help in uncovering the applicability of ChE for predicting risk of CVD like hsCRP.

## Material and Method:

### Patients:

A prospective case-control study was conducted at the department of Medicine, Rajindra Hospital, Patiala and, at the department of cardiology, Sadhbhavna Medical and Heart Institute, Patiala. The study/protocol was approved by human institutional ethics committee (IEC) of Punjabi university, Patiala (number-ICEC/74/2013, dated 07/02/2013) and was performed in accordance with the declaration of Helsinki and the code of Good Clinical Practice. All patients were assessed for the eligibility of inclusion/exclusion criteria and provided written informed consent to participate after a full explanation of the study. Approximately 1100 patients visiting the OPD (Outdoor Patients) for their routine check-up/ or new diagnosis/ or their ongoing treatment evaluation for HTN and/or diabetes/dyslipidemia/ coronary artery disease (CAD) were recruited for study. 140 patients were excluded from the study at initial screening visit because 90 patients did not meet inclusion/exclusion criteria and 50 patients choose not to participate in the study. 960 patients completed the study. 285 healthy subjects were also considered as control subjects. All patients were on various multiple drug regimens as per their disease conditions. Patients included were men or women of age range 18-65 years; presence of low grade systemic inflammation (hs-CRP level ≥ 1mg/l but ≤ 10 mg/l) (Wei and Wang, 2012); fulfilling the criteria for HTN according to JNC-VII report (Kivimaki *et al.*, 2009) defined as SBP of ≥ 140 to ≤ 160 mm Hg and DBP ≥ 90 to ≤ 110 mm Hg; fulfilling the criteria for diabetes according to WHO/IDF Consultation, 2006 *i.e.* fasting plasma glucose levels ≥ 126 mg/dl (≥7.0 mmol/l) and casual plasma glucose level ≥ 200 mg/dl or (≥11.1 mmol/l) (WHO, 2006); and, CAD patients fulfilling the American College of Cardiology/ American Heart Association (ACC/AHA) 2006 criteria for diagnosis of CAD (Smith *et al.*, 2006). Exclusion criteria were**:** pregnant or lactating women, patients with major surgery/trauma or stroke within last 15 days, history of significant autoimmune or chronic rheumatologic or any other chronic inflammatory disease (including foot ulcers), patients of myasthenia gravis or Alzheimer's disease or on anticholinergic & cholinergic therapies, patients on chronic use of non-steroidal anti-inflammatory agents, cholinesterase inhibitors (donepezil, galantamine & rivastigmine etc), statins, insulin sensitizing agents, patients with abnormal renal and liver function [serum creatinine level ≥2.0 mg/dl; ALT (alanine aminotransaminase) and AST (Asparatate transaminase) levels ≥2 times upper limits of normal)].

Subjects were divided into two major groups, healthy control group (GP I) and hypertensive patients (GP II). Patients were categorized into three categories: firstly, based on hsCRP levels (<1, 1-3, 3-10mg/l), secondly, based on number of coexisting diseases/risk factors (one, two, three), and thirdly, based on stage of

HTN (pre-hypertension, stage-1, stage-2 hypertension), each into three sub-groups, respectively. Based on hsCRP, hypertensive patients (group II) were further subdivided into 3 categories in accordance with levels that make the basis to describe Framigham risk score (Wei *et al.*, 2012): group IIa- patients with hsCRP < 1mg/l (mild inflammation: less than 10% risk for CHD); group IIb- hsCRP levels 1-3mg/l (moderate inflammation: 10-20% risk for CHD); group IIc: hsCRP levels 3-10mg/l (severe inflammation: more than 20% risk for CHD). Based on number of co-existing diseases, patients were categorized in to three sub-groups as, group IIx: hypertensive patients; group IIy: patients having hypertension plus diabetes; group IIz: patients with hypertension plus diabetes plus CAD. Based on stage of HTN, patients were classified according to JNC VII criteria for diagnosis of HTN (Jialal *et al*, 2004) in to three sub-groups as group IIp: pre-hypertension (SBP, 120–139 mm Hg and DBP, 80-89 mm Hg); group IIq: stage-1 HTN (SBP, 140–159 mm Hg and DBP, 90-99 mm Hg); group IIr: stage-2 HTN (SBP ≥ 160 mm Hg and DBP ≥ 100 mm Hg).

All patients were on various multiple drug regimens as per their disease conditions. Hypertensive patients were on either single dose therapy (ramipril/lisnopril or telmisartan/losartan or amlodipine/ nifedipine) or on multiple drug therapy [amlopidine 5mg plus lisinopril 5mg (once a day) or telmisartan 40mg plus amlodipine 5mg (once a day) or atenolol 25mg plus chlorthalidone 12.5mg (twice a day) or losartan 50 mg plus ramipril 2.5mg (once a day)]. Hypertensive diabetic patients were also on metformin 500mg plus gliclazide 80mg (once a day), or glimipiride 2mg plus pioglitazone 15mg, or metformin 500mg (twice a day). Hypertensive diabetic CAD patients were on multiple drug therapies such as atenolol 5mg plus isoorbide trinitrate 5mg (once a day), or monotrate 10mg plus metoprolol 2.5mg (bed time), and verapamil 5mg plus aspirin 75mg (once a day).

**Assessment of biomarkers:**

Overnight fasting blood samples of all patients & healthy subjects were withdrawn, serum was separated out and stored at -40$^0$C till subjected for further bio-analysis. Estimation of hsCRP and ChE was carried out using diagnostic kits (AGAPPE Diagnostics Ltd., Kerala, India), according to the manufacturer's recommended protocol on Erba Menheim Chem-5 plus v-2 auto analyzer (model: EC-5plus v2). Blood pressure was measured using digital automatic blood pressure monitor (Omron Healthcare Company Ltd. Gurgaon, Haryana, India). Height and weight of the subjects were measured to calculate body mass index (BMI) according to the formulae as [Weight (kg)/Height (meter) (Mei *et al*, 2002). Fasting blood sugar was measured using digital Accucheck Glucometer (Roche Diagnostics, Indianapolis, Indiana).

**Sample Size and Statistical Analysis:**

Results were expressed as mean ± standard deviation (SD). One way ANOVA followed by Tukey's test was used to assess the difference between continuous variables among different groups. The correlation between various variables was examined by Pearson's Univariate correlation analysis. Simple and multiple linear regression analysis were used to reveal dependency of one variable on the other. The normal distributed data in male (M) and female (F) healthy subjects in two groups was compared by student's t-test. All data were analyzed using Sigma stat 3.5. Statistical significance was accepted at $p \leq 0.05$.

**Results:**

The distribution of demographic, biochemical & clinical characteristics of subjects are presented in table 1. All the hypertensive patients [n=960, Male (M)/Female (F) = 586/374] were in the age range of 18-65 years (mean age, 51.20±11.02 years). 285 healthy (age, sex matched) subjects (M/F =158/127; mean age, 49.36±10.94 years), were taken as control.

As compared to control group age ($p$<0.01), BMI ($p$<0.01), FBS ($p$<0.01), SBP ($p$<0.01), hsCRP ($p$<0.01) and ChE ($p$<0.01) levels were high and significantly different in all the groups, when classified based on hsCRP, no. of risk factors and stage of hypertension, respectively (table 1). hsCRP (M/F= 0.59±0.21 / 0.54±0.22 mg/l) and ChE (M/F = 9271.62 ± 4193.09 / 8347.41 ± 3236.76 U/L) levels were higher in males as compared to female subjects, respectively. The data revealed that as the inflammation increased (hsCRP level) ChE levels increased both parallel and linearly. Similarly, as the severity of disease and number of disease risk factors increased, there was a corresponding rise in both hsCRP and ChE levels.

**Univariate association of variables:**

A significant correlation was found between hsCRP and ChE levels in healthy subjects (GP I: r=0.15, $p$=0.01) (figure 1). Similarly, hsCRP and ChE was significantly and positively correlated in all groups and subgroups. Pearson's Univariate co-relation analysis followed by simple linear regression analysis revealed nature/pattern of fit between these two variables. Results revealed a positive and linear fit/pattern in all the groups (figure 2).

**Multiple associations of variables:**

To find the effect of other variables such as age, BMI, FBS and SBP on serum levels of both hsCRP and ChE, Pearson's correlation analysis (table 2) followed by multiple linear regression analysis was applied. Variable (s) that did not show significant correlation were not entered into the multiple linear regression model. In healthy subjects neither age, nor BMI and FBS showed any association with either hsCRP or ChE, except SBP ($p$<0.05).

**a) Based on severity of inflammation:**

***Mild inflammatory group (group IIa):*** SBP ($p$<0.01) and FBS ($p$<0.01) were independent determinants for hsCRP [hsCRP= -0.673 + (0.00677 *SBP) + (0.00356 *FBS)], but none of the variable showed any association with ChE.

***Severe inflammatory group (group IIc):*** only SBP showed positive association with both hsCRP (p<0.01) and ChE (p<0.01).

**b) Based on number of risk factors:**

***One risk factor (group IIp):*** Only BMI ($p$=0.02) and SBP ($p$<0.01) were found independent determinants of hsCRP [hsCRP= -10.86 + (0.07*SBP) + (0.14*BMI)]; but SBP ($p$<0.01) and age ($p$=0.02) were found independent determinants of ChE [ChE= -22352.39 + (104.98*age) + (180.35*SBP].

***Three risk factors (group IIr):*** only age ($p$=0.04) and BMI (p<0.01) were independent determinants for hsCRP [hsCRP= -11.80 + (0.02*age) + (0.37*BMI)], but, except age, others [(FBS (p<0.01), SBP ($p$<0.01), BMI ($p$<0.01)] were independent determinants for ChE [ChE= -4145.83 + (55.39*SBP) + (227.49*BMI) + (32.79*FBS)].

**c) Based on stage of hypertension:**

***Pre-hypertension (group IIx):*** age ($p$=0.04), FBS ($p$<0.01), and BMI ($p$<0.01) were found independent determinants of hsCRP [(hsCRP= -8.99 + (0.02*age) + (0.21*BMI) + (0.06*FBS)], but only BMI ($p$<0.01) and SBP ($p$<0.01) for ChE [ChE= 4.15 + (0.14*SBP) + (0.0002 *BMI)].

***Stage-II hypertension group:*** None of the risk factor showed any association with neither hsCRP ($p$>0.05) nor ChE ($p$>0.05) (table 2).

**Discussion:**

A wide range of socio-economical, behavioral, and biological risk factors shapes the distribution and development of cardio-metabolic diseases (Boreham and Cran, 1999). Many studies have indicated that cardiovascular and all-cause mortality rise incrementally as the number of metabolic syndrome components increases (Libby *et al.*, 2002). The last decade has shown an increase in the relevance of inflammation and its mediators in vascular biology, thus, elevated levels of several inflammatory mediators among apparently healthy men and women have proven to have predictive value for future vascular events (Malik *et al.*, 2008). Present findings of high hsCRP (Wei, 2012; Kaur, 2013; Jialal, 2012; Kivimaki, 2009) and ChE (Sato *et al.*, 2014; Rao *et al.*, 2007; Libby *et al.*, 2002) levels in hypertensive, hypertensive diabetic and, hypertensive CAD patients is in support of various previously reported studies suggesting that low-grade systemic inflammation is an integral part of the disease process. Studies have revealed that plasma/serum, red blood cells and leukocyte activities of enzymes AChE and BChE are elevated in patients with Alzheimer's disease (Sridhar *et al.*, 2005), diabetes mellitus (Ofek *et al.*, 2007; Mayeux, 2007) and atherosclerosis (Ridker *et al.*, 1998; Kaur, 2013). Increased serum/plasma and other tissues BChE activity has been proposed as a marker of low grade systemic inflammation (Libby *et al.*, 2002). Assayag *et al*., reported association of lower BChE activity with an adverse outcome in patients suffering from acute ischemic stroke, suggesting that higher BChE activities reflected a better recovery process (Ho *et al.*, 2008). A few studies had reported that the activity of BChE is not only increased in diabetes mellitus, hypertension, insulin resistance, and hyper-lipidemia (Ridker *et al.*, 1997; 1998) but also suggested that as and when the activity of the enzyme is low these subjects are at high-risk of death (Ridker *et al.*, 1997). Assayag *et al*., has observed a significant correlation of BChE activity with different inflammatory markers such as fibrinogen, interlukin-6 and hsCRP in stroke patients (Alcantara *et al.*, 2012). Present study too reported significant positive, parallel, and linear correlation of hsCRP with ChE in all patients as reported in another study (Rao *et al.*, 2007), suggesting role of cholinergic anti-inflammatory pathway in producing systemic low grade inflammation.

We found that BP is the only variable which affects hsCRP and ChE in healthy subjects as supported by Calderon *et al.*, 2006, signifying that BP plays a vital and significant role in producing low grade systemic inflammation (Calderon-Margalit *et al.*, 2006). Present findings of high levels of hsCRP and ChE in healthy male subjects as compared to female subjects may be due to the protective role of estrogen in females. The activated estrogen receptors bind to transcription factor NF-kappa B and prevent its binding to DNA, thus leading to suppression of release of pro-inflammatory markers (Colovic, 2013).

Many factors such as age, BP, FBS, and BMI etc. interplay vital role in causing inflammation. Aging is a progressive degenerative process tightly integrated with inflammation and the inflammation progresses due to alterations in cellular redox balance (Boreham and Cran, 1999). High BMI can lead to amplification in insulin resistance and rise in pro-inflammatory cytokines (Sesso *et al.*, 2003). A positive association between FBS and pro-inflammatory markers has also been reported (Pfutzner and Frost, 2006). Inflammation and hypertension may also share some common patho-physiological mechanisms (Pauletto and Rattazzi, 2006). A few studies have reported that levels of hsCRP are affected by many confounding variables such as SBP (Pfutzner and Frost, 2006), fasting glucose levels (Pauletto and Rattazzi, 2006), age (Lukic *et al.*, 2014), sex and BMI (Libby *et al.*, 2002). Similarly, studies have also reported effect of age (Boreham and Cran, 1999), BP (Pfutzner and Frost, 2006), BMI (Lukic *et al.*, 2014) and sex (Randell *et al.*, 2005) on ChE levels. We also reported the individual association of these variables (age, BMI, SBP and FBS) ($p$<0.05), but multiple regression analysis revealed that overall,

**Table 1: Demographic, biochemical and clinical characteristic of subjects**

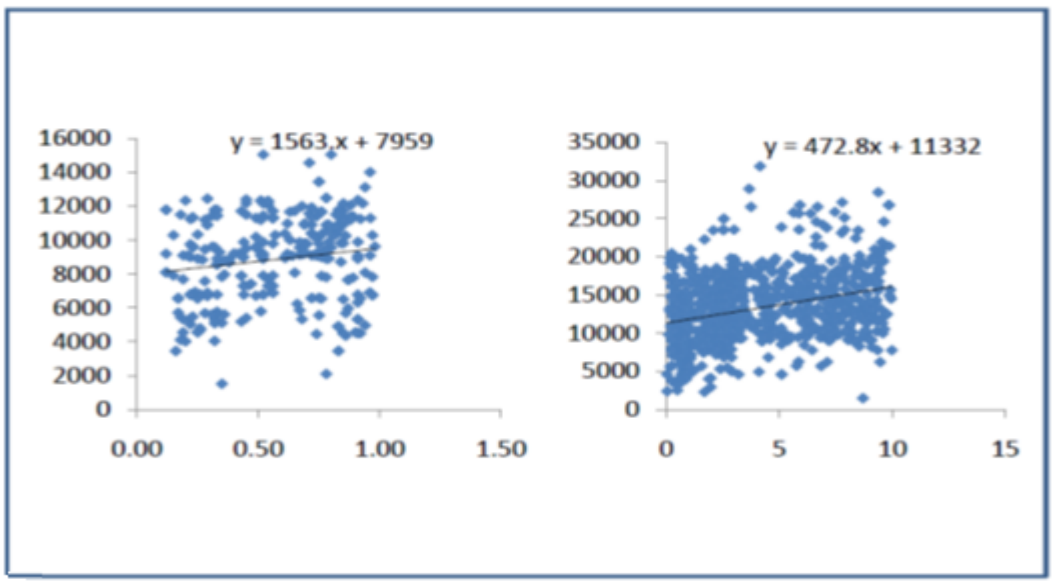
| Parameter / Patients | M/F | Age (years) | BMI ($kg/m^2$) | SBP (mmHg) | FBS (mg/dl) | hsCRP (mg/l) | ChE (U/L) |
|---|---|---|---|---|---|---|---|
| Healthy (GP I) | 158/127 | 36.36±8.94 | 21.83±2.23 | 122.74±6.29 | 93.98±5.98 | 0.57 ± 0.25 | 8859.78 ± 2574.29 |
| **Patients (GP II): Based on hsCRP (mg/l)** | | | | | | | |
| GP IIa (<1) | 147/82 | 50.10±10.85 | 24.99±3.81 | 134.21±8.70 | 113.81±17.96 | 0.64±0.24 | 10605.75 ± 3641.55 |
| GP IIb (1-3) | 176/112 | 49.79±11.02 | 26.79±3.96 | 138.98±8.80 | 124.84±16.71 | 2.22±0.51 | 13107.61 ± 4403.94 |
| GP IIc (>3) | 263/180 | 52.55±10.87 | 28.62±5.16 | 143.23±12.61 | 143.58±15.13 | 6.57±2.06 | 14797.97 ± 6063.67 |
| *p* value | | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| **Patients (GP II): Based on number of disease risk factors** | | | | | | | |
| GP IIx (one) | 126/79 | 43.67±12.12 | 25.07±3.08 | 144.68±12.40 | 131.61±7.75 | 3.63±2.74 | 13504.36±8335.30 |
| GP IIy (two) | 224/153 | 52.03±8.04 | 27.88±5.68 | 142.24±10.26 | 143.40±11.33 | 4.10±3.14 | 14303.78±3932.92 |
| GP IIz (three | 236/142 | 53.68±11.37 | 27.69±4.26 | 135.97±10.52 | 163.40±18.65 | 4.32±3.17 | 14579.46±3932.92 |
| *p* value | | 0.01 | 0.01 | 0.01 | 0.01 | 0.04 | 0.10 |
| **Patients (GP II): Based on stage of hypertension** | | | | | | | |
| GP IIp (pre) | 267/153 | 50.91±10.78 | 26.73±4.34 | 130.62±5.76 | 127.87±9.932 | 3.255±2.83 | 12568.14±3811.08 |
| GP IIq (stage 1) | 194/163 | 51.66±10.97 | 27.92±5.21 | 144.60±4.73 | 137.12±7.91 | 5.076±5.23 | 13285.23±4799.77 |
| GP IIr (stage 2) | 125/58 | 50.07±12.18 | 26.58±2.80 | 166.34±8.28 | 146.04±15.93 | 6.488±2.65 | 16794.87±36340.38 |
| *p* value | | 0.41 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |

**Table 2: Co-relation of hsCRP and ChE with various variables**

| **Co-relation of hsCRP with various variables** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | GP I | GP II (based on hsCRP) | | | GP II (based on risk factors) | | | GP II (based on hypertension) | | |
| Group (GP) | | IIa | IIb | IIc | IIp | IIq | IIr | IIx | IIy | IIz |
| Age | -0.03 | -0.06 | 0.22** | -0.03 | 0.13 | 0.18** | 0.14** | 0.17** | 0.07 | -0.12 |
| BMI | -0.02 | 0.11 | -0.01 | -0.02 | 0.23* | 0.25** | 0.52** | 0.44** | 0.16** | -0.04 |
| SBP | 0.22* | 0.23** | 0.05 | 0.31** | 0.37* | 0.42** | 0.13** | 0.11* | 0.21** | -0.11 |
| FBS | 0.06 | 0.26** | 0.10 | 0.07 | -0.03 | -0.02 | 0.16** | 0.53** | 0.12** | 0.11 |
| **Co-relation of ChE with various variables** | | | | | | | | | | |
| Age | 0.05 | 0.09 | 0.13* | 0.03 | 0.24** | 0.13* | 0.07 | 0.09 | 0.08 | 0.18 |
| BMI | 0.11 | 0.07 | 0.03 | -0.03 | 0.15* | 0.04 | 0.28** | 0.24** | 0.06 | -0.06 |
| SBP | 0.17* | 0.01 | 0.02 | 0.22** | 0.36** | 0.39 | 0.19** | 0.16** | 0.14** | -0.23 |
| FBS | 0.07 | 0.01 | -0.04 | 0.03 | -0.05 | -0.01 | 0.19** | 0.08 | 0.15** | 0.03 |

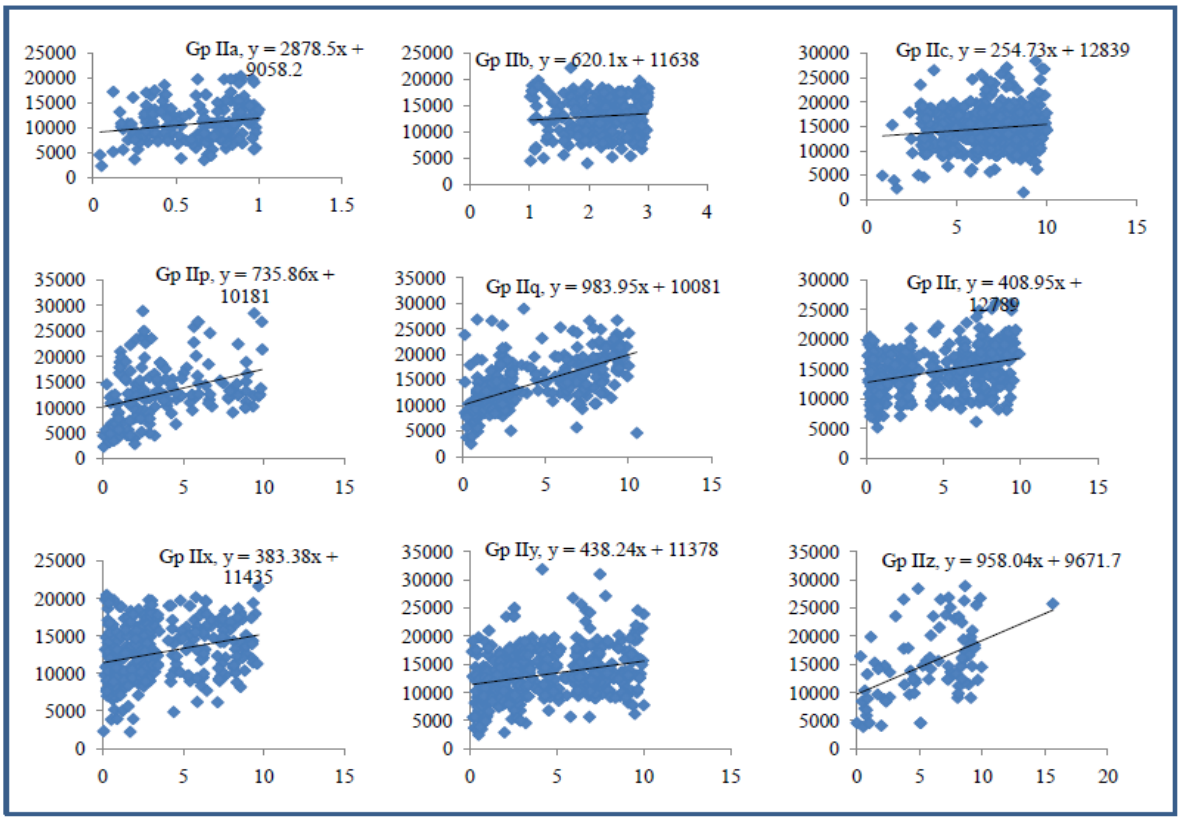
*p<0.05, **p<0.01

**Figure 1:** Regression plots of hsCRP and ChE in healthy subjects and overall patients




x-axis: hsCRP (mg/l), y-axis: ChE (U/L). Regression plot healthy subjects (left) and patients (right)

**Figure 2:** Regression plots of hsCRP and ChE in various groups




x-Axis: hsCRP (mg/l), y-axis: ChE (U/L)

hsCRP was affected by less number of variables (age, BMI) as compared to ChE (SBP, BMI and FBS) in hypertensive diabetic and atherosclerotic patients suggesting that in severe cases hsCRP levels will provide more accurate measure of systemic inflammation than ChE. But, this interpretation is based on just four confounding variables considered in present study. The major limitation of study was that other variables such as gender, lipid profile, central obesity, uric acid etc. were not considered for assessing any effect on hsCRP or ChE levels.

**Conclusion:**

Although majority of studies have demonstrated that ChE has strong association with low grade systemic inflammation, yet, it needs further evaluation to improve risk prediction for cardio-vascular and cardio-metabolic disorders. Framingham risk score predicts the risk of CVD based on hsCRP levels, but, based on finding of present study the same cannot be implemented for ChE.

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