

## Research Article

**Factors of raised C-reactive protein as a potential determinant of Diabetic patients and Risk factor for Coronary Heart Disease**Sharma Sushil kumar<sup>1</sup>, Rastogi Parag<sup>2\*</sup><sup>1</sup>Assist. Prof, Department of Physiology, VIMS Gajrola (UP) India.<sup>2\*</sup>Assist. Prof, Department of Physiology, VIMS Gajrola (UP) India.**Corresponding author: Dr. Parag Rastogi<sup>2\*</sup>**

Assist. Prof, Department of Physiology, VIMS Gajrola (UP) India

**Abstract:** Elevated C-reactive protein (CRP) levels have previously been described before the onset of type 1 diabetes and gestational diabetes. We hypothesized that inflammation, as reflected by elevated CRP levels, can help predict development of islet autoimmunity or type 1 diabetes. The outcome of this research is to establish potential determinants of raised CRP concentrations in type 1 diabetic patients. Sensitive assay showed 'low-level' CRP concentrations in 147 type 1 patients (83M, 64F, median age 30 years, range 13–67). We have done step by step variant examination to relate these CRP levels to known cardiovascular risk factors and demographic data. Only four patients had established Coronary Heart Disease (median CRP 3.43 mg/l vs. 0.85 mg/l,  $p=0.035$ ). In subjects without overt CHD, multivariate analysis revealed increase in subject age ( $p=0.0027$ ), BMI ( $p=0.001$ ) and HbA1 ( $p=0.013$ ) to be associated with a higher CRP concentration, as was female sex ( $p=0.025$ ) and a history of CHD in a first-degree relative ( $p=0.018$ ,  $n=58$ ). Elevated CRP levels were positively associated with cardiovascular and renal risk factors: age, body mass index, blood pressure, serum cholesterol level, smoking, plasma glucose level and elevated urinary albumin excretion and presence of hypertension were unrelated. This research work advises that certain of the risk factors connected with CHD in type 1 patients are also individually predictive of high CRP concentrations. The reasons for this, and whether intervention would prove valuable, require further analysis

**Key words:** Cardiovascular disease; C-reactive protein; Diabetic patients**Introduction**

Cardiovascular disease is the main cause of morbidity and mortality in patients with diabetes due to atherosclerosis. The reason for this increase in atherosclerosis is multifactorial, but is in excess of that which would be expected when account is taken of traditional coronary heart disease (CHD) risk factors such as smoking, hyperlipidaemia and hypertension. (Kannel et al. 1979; Stamler et al. 1993; Adlerberth et al. 1998; Yudkin et al. 1996). The prevalence of type 2 diabetes has been rapidly rising worldwide, that is a metabolic disease with inappropriate hyperglycemia either due to deficiency of insulin secretion or reduction in the biologic effectiveness of insulin. Elevated inflammatory marker, and altered adipokine concentrations have been observed in obese type 2 diabetes patients (Hansen et al. 2010; Myburgh et al., 2018). Although the main physiological abnormalities in type 2 diabetic are insulin resistance and impaired insulin secretion (Bergman 1989), some studies suggest that inflammation has a crucial intermediary role in pathogenesis of type 2 diabetic, thereby linking diabetes with a number of commonly coexisting conditions thought to originate through inflammatory mechanisms (Festa et al. 2000). Atherosclerosis has been described as an inflammatory disease (Ross 1999).

Measurement of the acute-phase reactant C-reactive protein (CRP) has been routinely used to detect and monitor inflammatory changes in patients with sepsis or connective tissue diseases. Recently, the use of highly sensitive assays has indicated that variations of CRP within the 'normal range' i.e.  $<5$  mg/l, are a potent risk indicator for CHD in non-diabetic subjects. (Kuller et al., 1996; Ridker et al., 1997; Haverkate et al., 1997)

CRP has recently been introduced in cardiovascular medicine as a predictor of myocardial infarction, stroke and peripheral artery disease in different populations (Ridker et al., 1998; Strandberg et al., 1998). Among pro-inflammatory markers, CRP a sensitive physiological marker of subclinical systemic inflammation, is associated with hyperglycemia, insulin resistance, and overt type 2 diabetic (Frohlich et al. 2000; Yeo et al. 2010). CRP is a main inflammatory factor that is produced by the liver during acute infection or inflammation and its concentration in plasma can increase as much as 1000-fold during injury and infection (Schultz and Arnold 1990). Intervention may also be successful in reducing CRP levels 10 and coronary events (Ridker et al., 1997; Ridker et al., 1998). CRP may be an independent risk factor for chronic kidney

disease in patients with type 2 diabetes (Yeo et al. 2010). CRP, leptin, and triglyceride levels are significantly higher in the obese diabetes patients compared with the healthy normoglycemic controls (Hansen et al. 2010). Elevated levels of CRP and IL-6 predict the development of type 2 diabetic. These data support a possible role for inflammation in diabetogenesis. Experimental evidence and some cross sectional data demonstrated that CRP as a sensitive physiological marker of subclinical systemic inflammation is associated with hyperglycemia, insulin resistance, and overt type 2 diabetic. But Su et al stated that there is no relationship between CRP and insulin resistance in type 2 diabetes (Su et al. 2010; Frohlich et al. 2000). The outcome of this research aimed to determine factors which predispose to high CRP concentrations in patients with type 1 diabetes.

**Material and Methods**

**Blood sampling**

*The present Study was conducted in VIMS & associated hospital Gajrola, Uttar Pradesh India from 2015 - 2016. Blood was collected in the morning after an overnight fast and after a 30-minute rest in a semi-recumbent position. Sampling was done without stasis, using the vacutainer technique*

**BMI and BP measurements**

Height was measured with stadiometer and weight was measured with a digital weighing scale. Only subjects with normal range of BMI (18.50–24.99 kg/m<sup>2</sup>) were included in the study. Hypertension was defined as having a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg. According to a self-administrated questionnaire, patient’s with a history of malignancy, liver disease, untreated hypothyroidism, alcohol abuse, inter current diseases or use of lipid-lowering drugs was excluded from the study. The cut-points of serum total cholesterol (TC), HDL and LDL Cholesterol (LDL-C) and serum triglycerides (TG) distributions used to assign subjects at different levels of risk

were obtained from the NCEP guidelines in the United States (Adult Treatment Panel III).

Patients with type 1 diabetes (n=147, 83M, 64F, median age 35 years) attending the Diabetes Unit, and approval by the local Ethical Committee were studied. None had overt evidence of infection or connective tissue diseases, and all participants had negative urinalysis for nitrite and leukocytes. All patients also had a baseline ECG performed at the time of diagnosis or referral if aged >35 years. Each had low-level CRP measured using a modified latex-enhanced immunoturbimetric assay (Thermo Fisher Scientific, India). Between-batch precision (CV) for the assay was 5.6%, 6.9% and 8.2% at CRP concentrations of 5.3, 2.2 and 1.0 mg/l, respectively. The locally-derived median reference value was 0.73 mg/l (0.95 interfractile reference interval 0.2–6.4 mg/l, n=77). Log<sub>10</sub> CRP in the patients without known CHD was related by univariate regression and by forward stepwise multiple regression to the following variables: age, sex, duration of diabetes, presence of microvascular complications (retinopathy defined as early background diabetic retinopathy or worse when examined by an experienced examiner using direct ophthalmoscopy through dilated pupils; known microalbuminuria defined as a consistent overnight timed urine albumin excretion rate >20 mg/min, neuropathy defined as peripheral neuropathy using DCCT clinical criteria<sup>12</sup>), body mass index (kg/m<sup>2</sup>), current HbA<sub>1c</sub>, current smoking status, current spot early-morning urine micro albumin concentration (mg/l), current non-fasting cholesterol/triglyceride/HDL-cholesterol, hypertension (on treatment or current blood pressure >140/90) and first-degree family history of cardiovascular disease.

**Results**

Table 1 lists the characteristics of the diabetic patients who participated in the study. Figure 1 shows the log-normal distribution of CRP values found in these patients. Only six patients had overt CHD (Table 1).

Table: 1 Patient characteristics

Characteristic	Patients without known ischaemic heart disease	Patients with ischaemic heart disease
Sex (male:female)	83:64	1:2
Duration of diabetes (median (IQR)	13 years (6–21)	29 years (16–33)
Age (median (IQR)	32 years (20–38)	45 years (38–55)
Body mass index (mean (SD))	25.1 kg/m <sup>2</sup> (3.6)	27.9 kg/m <sup>2</sup> (2.3)
Family history of cardiovascular disease	53 (32%)	5.5 (83%)
Presence of hypertension (n (%))	7.5 (4%)	3.5 (50%)
Presence of microvascular complications (n (%))	53 (32%)	2 (18%)
Current smoker (n (%))	42 (26%)	1 (18%)
Triglyceride (geometric mean (±SD))	0.93 mmol/l (0.57–1.60)	1.00 mmol/l (0.65–1.59)
Cholesterol (mean (SD))	4.96 mmol/l (1.07)	5.29 mmol/l (0.39)
HbA <sub>1c</sub> (median (IQR))	9.7% (8.8–11.2)	9.9% (8.3–10.4)
C-Reactive protein (median (IQR))	0.85 mg/l (0.46–1.90)	3.44 mg/l (1.91–5.01)

In these patients CRP concentrations were higher than in unaffected patients (median CRP 3.41 mg/l vs. 0.85 mg/l, p=0.035 using Mann-Whitney). While (Table 2 and Table 3) shows those, which remain significantly associated with log<sub>10</sub>CRP when the data is subjected to a forward stepwise multivariate regression

Table 2 Determinants of C-reactive protein concentration in patients without overt CHD analysed by stepwise multiple regression

Variable	Relative increase in C-reactive protein per unit increase in explanatory variable (95% CI)	p
Body mass index (kg/m <sup>2</sup> )	1.09 (1.04–1.13)	0.0011
Family history of cardiovascular disease (yes vs. no)	1.46 (1.08–1.99)	0.019
Female sex (vs. male)	1.39 (1.05–1.87)	0.027
Age (per 10 years)	1.19 (1.09–1.45)	0.0029
HbA1 (%)	1.12 (1.03–1.19)	0.013

Table 3. Joint effects of C-reactive protein and risk factors on the relative risk of diminished filtration

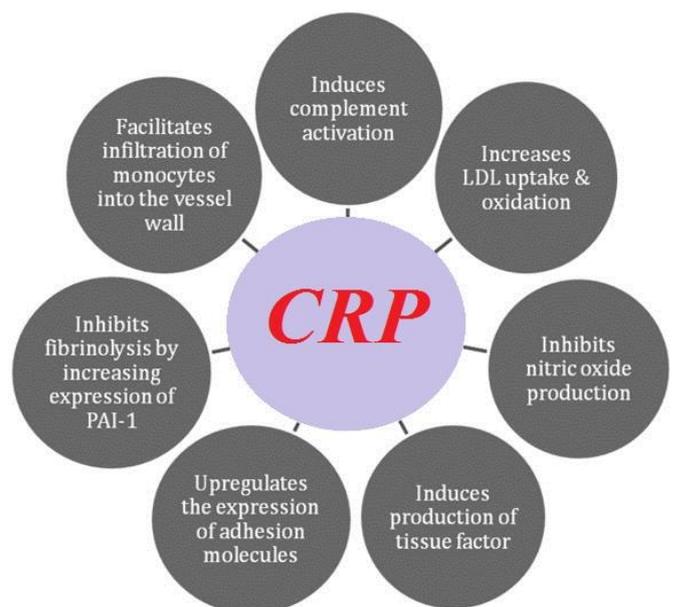
Risk factors	Limits	CRP ,75 <sup>th</sup> percentile	CRP .75th percentile
Obesity	No	1	1.52 (1.11–2.08)
	Yes	1.19 (0.73–1.96)	1.67 (1.04–2.68)
Smoking	No	1	1.49 (0.98–2.27)
	Yes	1.344(0.98–1.83)	1.92 (1.35–2.82)
Hypercholesterolemia	No	1	1.54 (1.12–2.16)
	Yes	1.19(0.82–1.73)	1.72 (1.09–2.72)
Hypertension	No	1	1.58 (1.10–2.23)
	Yes	1.59(1.10–2.28)	2.01 (1.31–3.15)
Albuminuria	0-18 mg/24 h	1	1.73 (1.26–2.37)
	15-32 mg/24 h	0.41 (0.21–0.80)	0.40 (0.13–1.26)
	30-312 mg/24 h	1.33 (0.80–2.15)	1.37 (0.75–2.53)
Glucose	<5.2 mmol/L <sup>a</sup>	1	1.54 (1.11–2.13)
	≥5.2 mmol/L	0.86 (0.57–1.26)	1.27 (0.80–2.03)

Odds ratios (95% CI) are adjusted for age and gender in models. The cut-off point of glucose is based on the 75<sup>th</sup> percent

**Discussion**

Independent studies have shown that the measurement of baseline concentrations of CRP as a marker of systemic inflammation can predict the risk of future myocardial infarction in non-diabetic subjects (Kuller et al., 1996; Ridker et al., 1998). It is thought that this theory of low-grade inflammation and atherosclerosis could therefore bring together, in one unifying hypothesis, the apparently disparate cardiovascular risk markers of fibrinogen, ferritin and white blood cell count, since they are all acute-phase reactants. Our study has sought to establish some of the determinants of raised CRP concentrations in type 1 diabetic patients (Ridker et al., 1998; Cleland et al. 2000). The measurements which are predictive of a raised CRP concentration. These findings are in agreement with previous studies involving only non diabetic subjects. (Mendall et al. 1996; Pradhan et al. 2001) Additionally, female sex, a family history of cardiovascular disease and a high current glycated haemoglobin value are also related to rises in CRP. However, when these factors are adjusted for each other by stepwise multiple regression, only the variables in Table 3 (age, sex, family history of CHD, BMI and current HbA1) are found to be independently associated with CRP concentrations. Growing body of evidence implicating low-grade inflammation as a potential dynamic in the pathogenesis of type 2 diabetes. Potential mechanisms for this relationship may be direct or indirect. For example, cytokines such elevated levels of IL-6, which is known to be a main stimulator of the production of most acute-phase proteins, were shown to increase the risk of diabetes (Thorand et al. 2003) Type 1 diabetes is now accepted to be a chronic immune-inflammatory disorder. Because it is a disease of

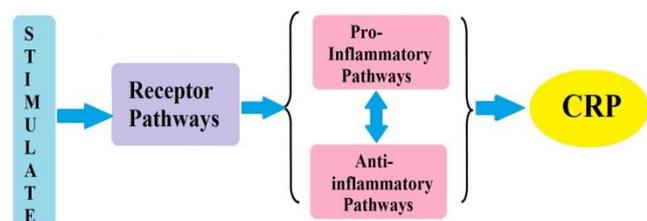
inflammation—both of the innate and adaptive immune systems—it is perhaps not surprising that elevated CRP levels were found. It is important to note that the elevated CRP levels were found before elevated glucose levels, so that this marker of inflammation is not related to hyperglycemia. This observation is impossible to study in people who already have type 1 diabetes (Tooke 1999; Nakanishi et al., 2003; King et al., 2003) (Fig. 1).



**Fig. 1 C-Reactive Protein Attention in Diabetic Patients**

The female/male difference may simply be associated with an increased prevalence of subclinical urinary infection in

women. However, compared to diabetic men, diabetic women have a higher relative risk of ischaemic heart disease than their non-diabetic counterparts. (King et al., 2003; Yudkin et al., 1996; Abdel-Moneim et al., 2018) Only one previous study of CRP in non-diabetic individuals has included or commented on women, and no difference was found (Kundak et al., 2011). There remains considerable debate as to whether poor glycaemic control can lead to an increase in CHD in diabetic patients. It is thus of interest that this study has found that glycated haemoglobin is an independent predictor of CRP levels, even though it is only the patients' current value. Our data on smoking is consistent with previous studies, in finding no relationship between current smoking and CRP (Tracy et al., 1997; Winocour et al., 1992). Indicating that the effect of smoking on CRP may be long-lasting. The lack of association between CRP and hyper tension may reflect the low prevalence of raised or treated blood pressure (6% of patients) found in this study, presumably because of the young mean age (30 years) of participants. Nevertheless, in studies with non-diabetic subjects, no blood pressure/CRP associations have been noted either. (Adler et al., 1999; Hu et al. 2004). However, it must be regarded as surprising that although the cholesterol, triglyceride and HDL cholesterol of our patients were related to several factors such as HbA1, duration of diabetes and microvascular complications, none of these lipid parameters were independently related to CRP levels (Asegaonkar et al., 2011; Kraemer et al., 2011). Given all the associations found with CRP in this study, the reasons why inflammation is present at all remains speculative. Some authors believe CRP values may reflect the intrinsic inflammation and tissue damage within arterial lesions themselves, with severe atheroma resulting in both raised CRP levels and an increased risk of coronary occlusion. (Haverkate et al., 1997; Spranger et al., 2003). Others believe high levels may be consequent on chronic infection with potentially atherogenic organisms such as *C. pneumoniae* or *H. pylori*. (Lip et al., 1997; Danesh et al., 1991) An attractive alternative possibility is related to the fact that CRP production by hepatocytes is stimulated by inflammatory cytokines (Sheldon et al., 1993) One such cytokine, tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) has also been implicated in the pathogenesis of obesity-associated insulin resistance (Hotamisligil et al., 1994; Vahdat et al., 2007). So they may produce relatively more TNF $\alpha$ , thereby explaining their higher CRP values (Fig.2).



Infections	TLR-4	PRO:	ANTI:	PPAR $\alpha$
Auto-antibodies	CD14	Chemokines	IL-1RA	NF $\kappa$ B
Lipid factors		IL-1 $\alpha$ , $\beta$	IL-10	
Other inflammatory processes		IL-6	TGF- $\beta$	
		TNF- $\alpha$	COX-2	
			Haptoglobin	

Fig. 2 CRP Pathways

Low-level CRP measurements in this situation may thus partly be a surrogate marker for circulating TNF $\alpha$  concentrations. Studies in non-diabetic subjects have shown that aspirin and statin treatment specifically reduce the increased cardiovascular risk associated with high CRP values. (Ridker et al., 1997) If applied to the asymptomatic diabetic patients in our study, it would suggest that it is the older, female, poorly controlled, overweight patient with a bad family history of heart disease who is most likely to benefit from such treatment, since they tend to have the highest CRP levels (O'Sullivan et al., 2013; Keevil et al., 1998)

**Conclusion**

In summary, this study has found that factors already known to be associated with cardiovascular risk in type 1 diabetes are also indicative of raised CRP concentrations. However, the mechanisms involved in these relationships require further investigation

**Conflict of Interest**

None of the authors of this paper have a financial or personal relationship with other people or organization that could inappropriately influence or bias the content of the paper.

**Acknowledgment**

I appreciate the supporting staff of Deptt of Physiology VIMS Gajrola for conducting this study. I am thankful to faculty member and supporting staff of Medicine department for patients information. I am highly grateful to respected Dr. Sudhir Giri ji, our Chairman, VIMS and associated hospital Gajrola (UP) India for given research place for this work.

**References**

- [1] Abdel-Moneim A, El-Senousy W, Abdel-Latif M, Khalil R Association between Antioxidant Enzyme Activities and Enterovirus-Infected Type 1 Diabetic Children. Med Princ Pract. 2018 Jan 10.
- [2] Adler AI, Levy J, Stevens R, Matthews D, Holman RR, Turner RC. Association between insulin resistance at diagnosis of diabetes and macro vascular complications the UKPDS. Diabetologia 1999; 42:A187.
- [3] Adlerberth AM, Rosengren A, Wilhelmsen L. Diabetes and long-term risk of mortality from coronary and other causes in middle-aged Swedish men, a general population study. Diabetes Care 1998; 21:539-45.
- [4] Asegaonkar SB, Marathe A, Tekade ML, Cherekar L, Bavikar J, Bardapurkar J, Ajay R. Rote Ajay. 2011. High-sensitivity C-reactive protein: a novel cardiovascular risk predictor in type 2 diabetics with normal lipid profile. J Diabetes Complications. 2011; 25(6):368-70.
- [5] Bergman R.N. Lilly lecture 1989: toward physiological understanding of glucose tolerance: minimal model approach. Diabetes. 1989; 38:1512-1527.
- [6] Cleland SJ, Sattar N, Petrie JR, Forouhi NG, Elliott HL, Connell JM. Endothelial dysfunction as a possible link

- between C-reactive protein levels and cardiovascular disease. *Clin Science* 2000 98: 531-5. 30
- [7] Danesh J, Koreth J, Youngman L, Collins R, Arnold JR, Balarajan Y, McGee J, Roskell D. Is helicobacter pylori a factor in coronary atherosclerosis? *J Clin Microbiol* 1991; 37:1651.
- [8] Festa A, D'Agostino R Jr, Howard G, Mykkanen L, Tracy RP, Haffner SM. subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation* 2000; 102:42-47.
- [9] Frohlich M, Imhof A, Berg G, Hutchinson WL, Pepys MB, Boeing H, Muche R, Brenner H, Koenig W. Association between C-reactive protein and features of the metabolic syndrome: a population-based study. *Diabetes Care*. 2000; 23:1835-1839.
- [10] Frohlich M, Imhof A, Berg G. Association between C-reactive protein and features of the metabolic syndrome: a population-based study. *Diabetes Care*. 2000; 23:1835-1839.
- [11] Hansen D, Dendale P, Beelen M, Jonkers RA, Mullens A, Corluy L, Meeusen R, van Loon LJ. Plasma adipokine and inflammatory marker concentrations are altered in obese, as opposed to non-obese, type 2 diabetes patients. *Eur J Appl Physiol*. 2010 109(3):397-404.
- [12] Haverkate F, Thompson SG, Pyke SD, Gallimore JR, Pepys MB. Production of C-reactive protein and risk of coronary events in stable and unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. *Lancet*. 1997 15 : 462-6.
- [13] Hotamisligil GS, Spiegelman BM. Tumor necrosis factor- $\alpha$ : a key component of the obesity-diabetes link. *Diabetes* 1994; 3:1271-8.
- [14] Hu FB, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes* 2004; 53: 693-700.
- [15] Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 1979; 241: 2035-8.
- [16] Keevil BG, Nicholls SP, Kilpatrick ES. Evaluation of a latex-enhanced immunoturbidimetric assay for measuring low concentrations of C-reactive protein. *Ann Clin Biochem* 1998; 35:671-3.
- [17] King DE, Mainous AG, Buchanan TA, Pearson WS. C-reactive protein and glycemic control in adults with diabetes. *Diabetes Care* 2003 26: 1535-9.
- [18] Kraemer S, Minarzyk A, Forst T, Kopf D, Hundemer HP. Prevalence of metabolic syndrome in patients with schizophrenia, and metabolic changes after 3 months of treatment with antipsychotics - results from a German observational study. *BMC Psychiatry* 2011; 11:1, 173.
- [19] Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple Risk Factor Intervention Trial. *Am J Epidemiol* 1996; 144:537-47.
- [20] Kundak AA, Tascilar ME, Abaci A, Devrim I, Ozgen IT, Demirtek U, Ozturk O, Olgun A, Kurt I. Serum chitotriosidase activity: is it a new inflammatory marker in obese children? *J Pediatr Endocrinol Metab* 2012; 25 (1-2) 63-7.
- [21] Lip GYH, Beevers DG. Can we treat coronary artery disease with antibiotics? *Lancet* 1997; 350:378-9.
- [22] Mendall MA, Patel P, Ballam L, Strachan D, Northfield TC. C reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. *Br Med J* 1996; 312:1061-5.
- [23] Myburgh PH, Towers GW, Kruger IM, Nienaber-Rousseau C. CRP Genotypes Predict Increased Risk to Co-Present with Low Vitamin D and Elevated CRP in a Group of Healthy Black South African Women. *Int J Environ Res Public Health*. 2018 10;15(1).
- [24] Nakanishi S, Yamane K, Kamei N, Okubo M, Kohno N. Elevated C-reactive protein is a risk factor for the development of type 2 diabetes in Japanese Americans. *Diabetes Care* 2003; 26: 2754-7. 32
- [25] O'Sullivan EP, Ashley DT, Davenport C, Penugonda L, Kelleher G, Devlin N, Crowley R, O'Shea P, Agha A, Thompson CJ, O'Gorman DJ, Smith D. A comparison of osteoprotegerin with adiponectin and high-sensitivity C-reactive protein (hsCRP) as a marker for insulin resistance. *Metabolism* 2013; 62:1, 34-38
- [26] Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001; 286: 327-34. 24.
- [27] Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; 336:973-9.
- [28] Ridker PM, Rifai N, Pfeffer MA, Sacks FM, Moye LA, Goldman S, Flaker GC, Braunwald E. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. *Circulation* 1998; 98:839-44.
- [29] Ross R. Atherosclerosis- an inflammatory disease. *N Engl J Med* 1999; 340:115-26.
- [30] Schultz DR, Arnold PL. Properties of four acute phase proteins: C-reactive protein, serum amyloid A protein,  $\alpha$ 1-acid glycoprotein and fibrinogen. *Semin Arthritis Rheum*. 1990; 20: 129-47.
- [31] Sheldon J, Riches P, Gooding R, Soni N, Hobbs JR. C-reactive protein and its cytokine mediators in intensive care patients. *Clin Chem* 1993; 39:147-50

- [32] Spranger J, Kroke A, Mohlig M, Hoffmann K, Bergmann MM, Ristow M, Boeing H, Pfeiffer AF. Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Diabetes* 2003; 52: 812-17.
- [33] Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993; 16:434-44.
- [34] Strandberg TE, Vanhanen H, Tikkanen MJ. Effect of statins in C-reactive protein in patients with coronary artery disease. *Lancet* 1999; 353:118-19.
- [35] Su SC, Pei D, Hsieh CH, Hsiao FC, Wu CZ, Hung YJ. Circulating pro-inflammatory cytokines and adiponectin in young men with type 2 diabetes. *Acta Diabetol* 2011 8 (2):113-9.
- [36] Third Report of the Expert Panel on Detection, Evaluation, and Treatment of high blood cholesterol in Adults (2004) Adult treatment Panel III. <http://www.nhlbi.nih.gov/guidelines/cholesterol>.
- [37] Thorand B, Lowel H, Schneider A, Kolb H, Meisinger C, Frohlich M, Koenig W (2003) C-reactive protein as a predictor for incident diabetes mellitus among middle-aged men: results from the MONICA Augsburg Cohort study, 1984-1998. *Arch Intern Med* 163: 93-99.
- [38] Tooke J (1999) The association between insulin resistance and endotheliopathy. *Diabetes Obes Metab* 1 (Suppl. 1) : S17-S22
- [39] Tracy RP, Psaty BM, Macy E, Bovill EG, Cushman M, Cornell ES, Kuller LH. Lifetime smoking exposure affects the association of C-reactive protein with cardiovascular disease risk factors and subclinical disease in healthy elderly subjects. *Arterioscler Thromb Vasc Biol* 1997; 17:2167-76.
- [40] Vahdat K, Jafari SM, Pazoki R, Nabipour I. Concurrent increased high sensitivity C-reactive protein and chronic infections are associated with coronary artery disease: a population-based study. *Indian J Med Sci* 2007; 61: 135-43
- [41] Winocour PH, Durrington PN, Bhatnagar D, Mbewu AD, Ishola M, Mackness M, Arrol S. A cross sectional evaluation of cardiovascular risk factors in coronary heart disease associated with type 1 (insulin-dependent) diabetes mellitus. *Diabetes Res Clin Pract* 1992; 18:173-84.
- [42] Yeo ES, Hwang JY, Park JE, Choi YJ, Huh KB, Kim WY. Tumor necrosis factor (TNF-alpha) and C-reactive protein (CRP) are positively associated with the risk of chronic kidney disease in patients with type 2 diabetes. *Yonsei Med J*. 2010 51(4):519-25.
- [43] Yeo ES, Hwang JY, Park JE, Choi YJ, Huh KB, Kim WY. Tumor necrosis factor (TNF-alpha) and C-reactive protein (CRP) are positively associated with the risk of chronic kidney disease in patients with type 2 diabetes. *Yonsei Med J*. 2010 51(4): 519-25.
- [44] Yudkin JS, Blauth C, Drury P, Fuller J, Henley J, Lancaster T, et al. Prevention and management of cardiovascular disease in patients with diabetes mellitus: an evidence base. *Diabetic Med* 1996; 13: 101-21.