Evaluation of high sensitive C-reactive protein in development of CVD and stroke among T2 diabetes mellitus.

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Abstract

Aims and objective: To find out the role of hsCRP in development of CVD and Stroke among T2 diabetes mellitus.

Materials and methods: 200 subjects of both males and females are recruited in the study out of 100 subjects are type 2 diabetic patients with no cardiovascular diseases complications (group1) and 100subjects are normal and healthy considered as control group (group2).

Results: The mean levels of LDL was significantly higher in patients with T2DM in higher risk category regarding hsCRP than in risk and normal category ($p<0.05$).In diabetic patients association of family history of stroke, snoring, homocysteine, HbA1c with hsCRP was statistically significant ($P<0.05$).

Conclusion: For T2DM patients, clinicians has to recommend for testing hsCRP at regular intervals as a preventive measures to reduce morbidity and mortality due to complications like CVD and Stroke.

Keywords: T2DM, CVD, Stroke and inflammation markers.

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Introduction

For atherosclerosis, diabetes is considered as important risk factor. In diabetes mellitus patients, atherosclerotic vascular disease is most important cause of morbidity and mortality [1]. In the pathogenesis of Cardiovascular Diseases (CVD) and stroke inflammation plays a key role [2]. Serum concentration of CRP can increase more than 1000 times upon inflammation and with half-life of 19 h, CRP is stable marker of the inflammatory process [3]. In the process of initiation and progression of atherothrombotic, inflammation is the central role in the triggering of CVD events [4].The interaction of innate immune system with atherosclerosis is established in vascular biology [5]. TO envisage cardiovascular risk more perfectly have led to the emergence of a novel risk factor. It believed that C-reactive protein is indicator of inflammation and advance directly every stage of atherosclerosis, as well as plaque ruptures [6]. Among healthy individual, patient with acute coronary syndrome high sensitive C reactive protein(hsCRP) is consider as independent predictor for future risk for cardiovascular event and stroke [7,8]. Individuals with low to average level of low density lipoprotein cholesterol (LDL-C), hsCRP may help in identifying individuals at high risk for a cardiovascular even who may or else be missed by lipid screening; Clearfield [7] may improve global risk prediction among those with low and high cholesterol level. Thus, hsCRP is a potential accessory for global assessment in primary prevention of cardiovascular diseases [8].

Materials and Methods

This study was conducted at GSL Medical College, General hospital Rajahmundry and Adikavi Nannaya University, Rajahmundry. Andhra Pradesh. 100 subjects are type 2 diabetic patients with no cardiovascular diseases complications (group 1) and 100 subjects are normal and healthy considered as control group. Participants will be interviewed to obtain relevant data the following variables were initially will be incorporated into study. Height, weight, age, sex, blood pressure (BP), duration of diabetes, waist circumference, hip circumference, smoking status, alcohol consumption status, physical activity, food habits, family history of diabetes, family history of CVD and stroke are noted, BP will be noted after keeping participant in resting position for 15 min.

Group 1: Inclusion criteria: Patients with known T2DM aged 30-60 years of both males and females. Exclusion criteria: Patients with T2 diabetes insipidus, cardiovascular disorder, stroke, malignancy, liver and thyroid, pulmonary and other debilitating disorder. Group 2: Healthy individuals with aged 30-60 years of both males and females.

10 ml of fasting blood was collected from the subjects. 5 ml of blood sample is collected in container without any anticoagulant, and centrifuged within 30 min to collected serum. 2 ml of blood in EDTA container and immediately used for the HbA1c estimation and blood glucose estimation, 25 ml of spot urine was collected in sterile container for micro albiminuria estimation.

Results

There were 200 individuals recruited in this study. In group1, there were 100 individuals with known type 2 diabetes mellitus with mean age of 47 ± 7.8 years ranging from 30 years to 60 years. In group 2, there were 100 healthy individuals with mean age of 44.4 ± 6.9 years ranging from 31 to 60 years. All the clinical characters of 100 individuals with known type 2 diabetes mellitus and 100 healthy control subjects in the present study are listed and compared in Table 1. The means of BMI Body mass index(BMI), cholesterol, Triglycerides (TGL), LDL, very low density lipoprotein (VLDL), fasting blood sugar(FBS), Creatinine, glycated hemoglobin (HbA1c), hsCRP, homocysteine, MDA (Malonaldehyde) and Microalbuminuria were significantly higher in patients with T2DM when compared with healthy control subjects (P<0.05). The mean values high density lipoprotein (HDL), estimated glomerular filtration rate (eGFR) significantly lower in patients with type 2 diabetes mellitus when compared control subjects (P<0.05).

In this study, all T2DM patients are stratified according serum hsCRP level. 84 individuals were in low risk category, 9 were in risk category, 7 were in high risk category From Table 2, the mean value of LDL was significantly higher in patients with T2DM in higher risk category regarding hsCRP than in risk and normal category (p<0.05).

The mean values of age, FBS, TGL, VLDL creatinine and MDA was insignificantly higher in patients with T2DM in risk category regarding hscrp than in higher risk and low risk (P>0.05). The mean values of HDL and eGFR was insignificantly low in patients with T2DM in risk category regarding hscrp than in higher risk and low risk category (P>0.05). The mean values of BMI and microalbuminuria was insignificantly higher in patients with T2DM in risk category regarding hscrp low risk category than in higher risk and risk category (P>0.05).

Table 1. *Morphometric measurements, clinical characteristics and biochemical measurements of type 2 diabetes patients and healthy controls.*

Anthropometric & Biochemical Parameters	T2DM	Healthy control	P value
Age (years)	47 ± 7.8	44.48 ± 6.9	**<0.05**
BMI (kg/m^2)	26.4 ± 4.8	24.6 ± 3.7	**<0.05**
FBS (mg/dl)	188.0 ± 55.0	85.7 ± 8.2	**<0.05**
Cholesterol (mg/dl)	196.9 ± 41.8	179.8 ± 27.1	**<0.05**
TGL (mg/dl)	210.5 ± 112.7	140.1 ± 37.1	**<0.05**
HDL (mg/dl)	45.4 ± 5.2	46.8 ± 6.8	**<0.05**
LDL (mg/dl)	110.01 ± 37.3	105.8 ± 23.9	**<0.05**
VLDL (mg/dl)	42.3 ± 22.5	28.1 ± 7.9	**<0.05**
Creatinine (mg/dl)	0.94 ± 0.22	0.79 ± 0.13	**<0.05**
HbA1C (%)	8.71 ± 1.4	5.16 ± 0.34	**<0.05**
hsCRP (mg/L)	1.1 ± 0.7	0.48 ± 0.3	**<0.05**
Homocysteine (µmol/L)	14.12 ± 7.1	9.71 ± 2.5	**<0.05**
MDA (µmol/L)	7.2 ± 1.9	5.3 ± 1.1	**<0.05**
Microalbuminuria (mg/g of Creatinine)	60.73 ± 69.7	11.9 ± 5.1	**<0.05**
eGFR (ml/min per 1.73m^2)	85.45 ± 15.1	99.2 ± 18.9	**<0.05**

From Table 3, Association of family history of stroke in T2DM subjects with hsCRP was statistically highly significant (P<0.05). Percentage of T2DM patients with family history of stroke in high risk category were more when compared with risk category. Association of snoring in T2DM subjects with hsCRP was statistically significant (P<0.05) Percentage of T2DM patient with snoring habit were more in both risk and high risk category. Association of smoking, alcohol consumption, Physical activity, family history of diabetes, family history of CVD and hypertension with hsCRP was statistically insignificant (P>0.05).

From Table 4, Association of LDL, HbA1c, and Homocysteine was statistically significant with hsCRP (P<0.05). Higher percentage of T2DM patients under high level LDL category was present in normal category of hsCRP. Higher percentage of T2DM patients under >10% HbA1c category were present

Table 2. *Morphometric measurements and CVD risk factors mean values as a function of serum hsCRP category in T2 diabetes mellitus.*

Characteristics	Low risk n=84	Average Risk n=9	High risk n=7	P value
Age (years)	46.8 ± 7.9	49.6 ± 5.5	45.1 ± 9.5	>0.05
BMI (Kg/m^2)	26.5 ± 5.1	26.0 ± 1.8	24.8 ± 1.8	>0.05
FBS (mg/dl)	189.5 ± 57.8	200.7 ± 32.0	153 ± 25.9	>0.05
Cholesterol (mg/dl)	194.6 ± 42.1	190 ± 40.6	232 ± 21.2	>0.05
TGL (mg/dl)	210.9 ± 118.8	218.8 ± 78.6	195.4 ± 77	>0.05
HDL (mg/dl)	45.4 ± 4.9	43.8 ± 9.0	47.2 ± 2.4	>0.05
LDL (mg/dl)	106.6 ± 37.2	112.8 ± 38.5	146.2 ± 11.9	<0.05
VLDL (mg/dl)	42.4 ± 23.7	43.7 ± 16.4	39.1 ± 15.4	>0.05
Creatinine (mg/dl)	0.93 ± 0.21	1.03 ± 0.25	0.84 ± 0.19	>0.05
MDA (µmol/L)	7.2 ± 1.8	8.2 ± 2.4	7.0 ± 2.2	>0.05
Microalbuminuria (mg/g of Creatinine)	62.01 ± 74.4	51.22 ± 32.06	57.57 ± 45.4	>0.05
eGFR (ml/min per 1.73m^2)	85.5 ± 14.8	79.2 ± 20.0	92.5 ± 14.8	>0.05

P value by one way Anova; P value<0.05 is statistically significant

Table 3. *Demographic characters of type 2 diabetes patients according to stratification of serum hsCRP.*

	Status	Low risk n=84	Average Risk n=9	High risk n=7	P value
Smoking	No (n=86)	73 (84.9%)	8 (9.3%)	5 (5.8%)	>0.05
	Yes (n=14)	11 (78.6%)	1 (7.1%)	2 (14.2%)	
Alcohol consumption	No (80)	70 (87.5%)	5 (6.3%)	5 (6.3%)	>0.05
	Yes(20)	14 (70%)	4 (20%)	2 (10%)	
Physical activity	No (79)	67 (84.4%)	6 (7.6%)	6 (7.6%)	>0.05
	Yes (21)	17 (81%)	3 (14.3%)	1 (4.8%)	
Sleep	Interrupted (n=41)	38 (92.7%)	1 (2.4%)	2 (4.9%)	>0.05
	Uninterrupted (n=59)	46 (78%)	8 (13.6%)	5 (8.5%)	
Family History of diabetes	No (47)	37 (78.7%)	7 (14.9%)	3 (6.4%)	>0.05
	Yes (53)	47 (88.7%)	2 (3.8%)	4 (7.5%)	
Family History of stroke	No (83)	74 (89.2%)	7 (8.4%)	2 (2.4%)	*<0.05*
	Yes (17)	10 (58.8%)	2 (11.8%)	5 (29.4%)	
Family History of CVD	No (87)	72 (82.8%)	9 (10.3%)	6 (6.9%)	>0.05
	Yes (13)	12 (92.3%)	0	1 (7.7%)	
Hypertension	No (67)	57 (85.1%)	6 (9.0%)	4 (6%)	>0.05
	Yes (33)	27 (81.8%)	3 (9.1%)	3 (9.1%)	
Snoring	No (62)	58 (93.5%)	3 (4.8%)	1 (%)	<0.05
	Yes (32)	26 (68.4%)	6 (15.8%)	6 (15.8%)	

P value by chi-square; P value<0.05is statistically significant

Table 4. *Association of stratified demographic and biochemical characteristics of diabetes patients according to stratification of hsCRP.*

Characteristics	Classification	n	Low risk n=84	Average Risk n=9	High risk n=7	P value
Age	30-40	25	21 (84%)	0	4 (16%)	
(Years)	41-50	42	36 (85.7%)	5 (11.9%)	1 (2.4%)	>0.05
	51-60	33	27 (81.8%)	4 (12.1%)	2 (6.1%)	
BMI	Normal	22	22 (100%)	0	0	
(Kg/M^2)	Overweight	19	14 (73.7%)	2 (10.5%)	3 (15.8%)	>0.05
	Obese	59	48 (81.4%)	7 (11.9%)	4 (6.8%)	
Cholesterol	Normal	68	59 (86.8%)	6 (8.8%	3 (4.4%)	>0.05
(mg/dl)	Hypercholesterolemia	32	25 (78.1%)	3 (9.4%)	4 (12.5%)	
TGL	Normal	42	36 (85.7%)	3 (7.1%)	3 (7.1%)	
(mg/dl)	Borderline	12	11 (91.7%)	1 (8.3%)	0	>0.05
	High	46	37 (80.4%)	5 (10.9%)	4 (8.7%)	
HDL	Normal	12	10 (83.3%)	2 (16.7%)		>0.05
(mg/dl)	High	88	74 (84%)	7 (8%)	7 (8%)	
LDL	Normal	67	61 (91%)	5 (7.5%)	1 (1.5%)	
(mg/dl)	Borderline	24	16 (66.7%)	2 (8.3%)	6 (25%)	*<0.05*
	High	9	7 (77.8%)	2 (22.2%)	0	
HbA_1C	<8	30	24 (80%)	2 (6.7%)	4 (13.3%)	
(%)	>8-<10	38	29 (76.3%)	7 (18.4%)	2 (5.3%)	*<0.05*
	>10	32	31 (96.9%)	0	-3.10%	
Homocysteine	Desirable	27	26 (96.3%)	1 (3.7%)	0	
(µmol/L)	Intermediate	34	30 (88.2%)	0	4 (11.8%)	*<0.05*
	High	36	25 (69.4%)	8 (22.2%)	3 (8.3%)	
	Very high	3	3 (100%)	0	0	
MDA	<5	11	10 (90.9%)	0	1 (9.1%)	
(µmol/L)	5-<10	80	68 (85%)	7 (8.8%)	5 (6.3%)	>0.05
	>10	9	6 (66.7%)	2 (22.2%)	1 (11.1%)	
Microalbuminuria	Normal	42	36 (85.7%)	3 (7.1%)	3 (7.1%)	
(mg/g of Creatinine)	Microalbiminu-ria	55	45 (81.8%)	6 (10.9%)	4 (7.3%)	>0.05
	Macroalbumin-uria	3	3 (100%)	0	0	
eGFR	Normal	40	35 (87.5%)	2 (5%)	3 (7.5%)	
(ml/min per $1.73m^2$)	Mild decrease	53	43 (81.1%)	6 (11.3%)	4 (7.5%)	>0.05
	Mild moderate	6	6 (100%)	0	0	
	Mild severe	1	0	1 (100%)	0	
Duration (years)	<5	44	35 (79.5%)	5 (11.4%)	4 (9.1%)	
	>5-<10	25	23 (92%)	1 (4%)	1 (4%)	>0.05
	>10	31	26 (83.9%)	3 (9.7%)	2 (6.5%)	

p value<0.05is statistically significant

in low risk category of hsCRP. Higher percentage of T2DM patients under high and very high homocysteine category were present in low risk category of hsCRP. Table 5 shows higher mean levels of HbA1c was noticed in T2DM patients under low risk category and higher level of homocysteine were observed in average risk category of patients with T2DM.

There was statistically insignificant association was observed in Age, BMI, Cholesterol, TGL, LDL, MDA, Microalbuminuria, eGFR and duration of T2DM disease with hsCRP (P>0.05).There were 40% of patients in low risk category of hsCRP were very close to risk category regarding hsCRP (Data not given)

Table 5. *Show Mean ± SD levels of HbA_1C, serum homocysteine according to stratification of hsCRP.*

Characteristics	Low risk n=84	Average Risk n=9	High risk n=7
HbA_1C (%)	8.8 ± 1.4	8.1 ± 0.78 7.1-9.6	8.1 ± 1.3
Homocysteine (µmol/L)	13.7 ± 7.1	19.2 ± 5.8	14.9 ± 3.2

Discussion

CRP has been one of the traditional acute phase reactant and sensitive marker of inflammation and tissue damage [9]. In this present study the CRP level was significantly high in T2DM subjects compared with healthy control. T2DM has been considered as an inflammatory disease and inflammatory process seems to play an important role in the development of diabetes and its late complications [10]. Elevated CRP has been associated with many no communicable diseases such as CHD, ischemic stroke, insulin resistance, hypertension, metabolic syndrome and peripheral artery disease. The most extensively studied area is its role as a marker and a maker of CHD. Several landmark large prospective clinical case control studies on middle-aged men [11]. Monitoring Trends and Determinants in Cardiovascular Disease have identified CRP as a strong, independent risk factor for CHD. In recent

studies by Arroyo et al. and Raposeiras [12,13] concluded that CRP is an independent predictor of adverse cardiac events.

In this current study it was found that patients T2DM patients are having higher levels of hsCRP than healthy controls. Almost similar levels are observed in both males and females. There was no significant difference was observed in levels of hsCRP in both the genders similar findings are also observed in the study done by Bocheva et al. [14].

Steven et al. have shown strong positive correlation between CRP and insulin resistance, this might be the reason for the significantly high level of acute phase inflammatory marker CRP observed in diabetic subjects when compared to control groups. Papageorgiou has reported atherosclerosis as a chronic low-grade inflammatory disease with a continuous low-grade production of proinflammatory mediators by T lymphocytes and macrophages: TNF-α, IL-1 and IL-6. These cytokines escape from the plaque into the circulation. This results in an increased production in the liver of the inflammatory proteins CRP.

Svensson et al. [15] have found a raised level of CRP in association with both the development of type 2 diabetes and an increased risk of CVD and also studies predicted that elevation of CRP concentration has been associated with increasing risk of diabetes [16].

Moreover it has shown the existence of positive correlation between level of CRP and severity of CAD which substantiated the significance of CRP as a predictor of CAD over traditional risk factors [17]. Both population-based and prospective studies support that systemic inflammation marker like CRP may integrate with risk of CVD single, hsCRP measurement is a strong predictor of stroke in individuals without a history of CVD [18,19].

Beamer and his associates have reported that stroke patients without infection have increased levels of CRP. Experimental stroke studies have shown that secretion of inflammatory mediators as a direct response to cerebral injury starts within two hours of focal ischemia and that anti-inflammatory treatment may have a neuroprotective role [2].

In a 20 year follow-up of the Honolulu Heart Study, elevated CRP independently predicted future ischemic stroke in middle-aged Japanese-American men, particularly in nonsmokers and in those ≤ 55 years [20]. Similarly, hs-CRP independently predicted a first stroke or transient ischemic attack in elderly men and women (mean age 70 years) in the original Framingham Study cohort [21].

LDL concentration was higher in DM without complications than DM with CVD and healthy controls same findings are also found in study done by Barbalho [22]. Females had higher of concentration of LDL than males. LDL concentration is higher in T2DM patients in higher risk category. LDL levels are gradually raised form low risk, average risk and high risk levels.

Although hs-CRP predicts vascular events independent of LDL cholesterol, these two risk factors enhance each other as prognosticators. In the Women's Health Study, who were assessed for the occurrence of MI, ischemic stroke, coronary revascularization, or cardiovascular death over a mean of 8 years, hsCRP surpassed LDL cholesterol in predicting the risk of all study endpoints, even after adjustments for age, smoking status, diabetes, blood pressure, and use of hormone replacement therapy which is associated with increased CRP [23].The analyses also showed that hs-CRP and LDL cholesterol correlated minimally each had a strong linear relationship with cardiovascular risk. However, the two factors together were superior to either factor alone in predicting risk. Survival was bad for women with high levels of both markers and best for women with low levels of note; women with high hsCRP and low LDL cholesterol were at greater risk than women with low hsCRP and high LDL cholesterol. In the absence of hsCRP measurement, risk in this intermediate category would have been greatly underestimated. It can be hypothesized that CRP and LDL cholesterol represent separate but equally critical aspects of the atherosclerotic process, and that both markers must be assessed to obtain a complete profile of vascular risk [6].

LDL will modified by oxidation, glycation (in diabetes) and aggregation, association with proteoglycans or incorporation into immune complexes is major cause of injury to the endothelium and underlying smooth muscle. When LDL particles become trapped in an artery, they can undergo oxidation and be internalized by macrophages by means of the scavenger receptors on the surfaces of these cells. The internalization leads to a development of lipid peroxides and facilitates the accretion of cholesterol esters follow-on in the formation of foam cells [2]. In a study done by Lin [24], concluded that LDL-C might be moderator of the contribution of hsCRP to CHD.

Inflammation plays important role in the development of atherosclerosis and it is associated with increased prevalence of CVD including stroke [5,11]. In this present study there was a significant association between hsCRP and homocysteine similar findings was also observed in the study done by Yan and Bocheva [14,25]. In a small sample study by Youssef et al. [26], observed that high levels of plasma homocysteine were associated with high levels of hsCRP. However its clinical significance especially in predictive value in the prognosis of stroke remains unknown. Yoldas et al. [27] found there was no significant association between hsCRP and homocysteine.

In this present study it was found that there was a significant association between hsCRP and family history of stroke in diabetes. This was supported by the study done by Jisun et al. As far as my knowledge this is the first study in this place, noticed the association between hsCRP and family history of stroke in diabetes, this may be due to influence of genetic factors. A further study has to conduct in genetically approach manner to know the effect of genetic influence of family history of stroke in diabetes on association with hsCRP.

Sleep-disordered breathing (SDB) such as snoring or obstructive sleep apnea and metabolic syndrome are both related to cardiovascular diseases. Being a surrogate marker of high risk for cardiovascular disorder, the high-sensitivity C-reactive protein (hs-CRP) level is thought to be elevated in patients with both SDB and metabolic syndrome. Authors showed that elevated hs-CRP is common in patients with SDB but is not independently associated with the severity of SDB, suggesting that metabolic parameters are important contributors to cardiovascular diseases and should be corrected in patients with SDB.

hsCRP has been reported to be associated with SDB in other studies Larkin et.al; Punjabi [28,29] while others did not observe such an association Taheri et al.; Kaditis et al. [30,31].

In a study done by the Lao et al. [32] stated that increased concentration of hsCRP and habitual snoring had been associated with much more risk of CVD. It remains unclear that what is the mechanism for behind the association of snoring and vascular diseases. Metabolic abnormalities like obesity, hypertension and insulin resistance are having high prevalence in snorers [33]. Previous studies reported there was a conflict between the association of high-sensitivity C-reactive protein (hs-CRP) and snoring [28,29].

Conclusion

It is now an established fact that raised CRP levels are associated with a better prognosis for CVD and stroke. It is important to differentiate between a role as a marker and a factor that directly causes a biological effect because this will determine the best possible therapeutic involvement.

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