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Association of hs-CRP with Diabetic and Non-diabetic individuals

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Abstract

الملخص

Association of hs-CRP in diabetic and non – diabetic subjects were studied epidemiologically. The analysis was done with 400 diabetic and 400 non-diabetic individuals. Anthropometric and biochemical parameters were studied to assess the association of hs-CRP with in diabetes mellitus. Type II diabetes Mellitus encompasses -90 % of the diabetic subjects, and it is characterized by insulin resistance often accompanied by obesity and dyslipidemia. hs- CRP, the golden marker of inflammation was analyzed in diabetic and non- diabetic subjects. Anthropometric parameters were found to be high in diabetic subjects compared with non-diabetic subjects. The high hs-CRP levels in diabetic subjects were observed.
The hs- CRP levels were seen in diabetes with insulin resistance. Serum hs- CRP levels were positively related to anthropometric parameters. The relationship of hs-CRP with glycaemic control was studied with HbA1c, and it was positively correlated with hs-CRP. The results concluded that hs-CRP has strong association with diabetic individuals. The significance of hs-CRP in diabetic and non diabetic individuals was discussed.

Keywords: hs-CRP, -Insulin resistance, Diabetes mellitus , biochemical parameters,HbA1C..

1. Introduction

Diabetes is a metabolic -disorder with inappropriate hyperglycemia either due to an absolute or relative deficiency of insulin secretion or reduction in the biologic effectiveness of insulin or both. It is also associated with disturbances concerned with protein, carbohydrate and lipid metabolism. The decreased uptake of glucose into muscle and adipose tissue leads to chronic extra cellular hyperglycemia which results in tissue damage and chronic vascular complications in both type I and II Diabetes Mellitus (Brownlee et al. 1981; Luscher et al. 2003).

Among several markers of inflammation, hs –CRP is found to be significant in people with diabetes. CRP, a pentameric protein produced by the liver has emerged as the ‘ golden marker for inflammation’ . It is a non-immunoglobin protein having five identical sub units. It is a member of pentraxin family proteins. The C-reactive protein derives from the fact that it reacts with capsule polysaccharide of *streptococcus pneumoniae*. It is an acute phase response protein markedly increased in both inflammatory and infectious diseases. It plays an important role in innate immunity. It assists in complement binding to foreign and damaged cells and enhances phagocytosis. It was also noticed that the elevated levels of IL18/IL18BP in plasma during active stages of disease suggest a possible role in the pathogenesis and course of idiopathic thrombocytopenia (ITP) (Shan et al.2009). Hyper glycemia is an associated factor to the increase of serum CRP levels, non-controlled type II diabetic subjects (Martha and Fernando , 1999). Several studies demonstrate that hs-CRP remained a significant predictor of diabetes risk even after adjusting with body mass index, family history of diabetes mellitus, smoking and other factors (Pradhan et al. 2005). In people with diabetes , CRP levels is highest tertile (> 0.28 mg/dl) were associated with a 2 fold increase in CV mortality after adjusting for age , sex and glucose tolerance tests (Chiriboga et al. 2009 ; Jager et al. 1999; Pfutzner and Forst, 2006) . Hypertensive patients with DM2 had higher levels of hs-CRP, a circulating inflammatory marker, than normal subjects. This finding suggests that patients with two associated diseases have a more active inflammatory state (Luciana etal.2007).

Though we have several studies on hs-CRP and diabetes mellitus association with different age groups is limited . So current study focus on association of hs-CRP and diabetes mellitus with different age groups.

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2. Materials and methods

The significance of the hs-CRP levels in different age groups of diabetics, analysis were carried out on various metabolic and biochemical parameters for the 400 healthy non-diabetic subjects and 400 diabetic individuals.

2.1. Anhtropometric measurements:

Weight and height measurements were obtained, using standardized technique as detailed elsewere. (Deepa *et.al.* 2003). BMI was calculated as the weight in kilograms divided by the square of height in meters. Blood pressure was recorded in the sitting position by using the right arm to the nearest 2mm Hg with a mercury Sphygmomano meter.

2.2. Biochemical parameters:

Fasting plasma glucose (glucose –oxidase peroxidise method) , serum cholesterol (cholesterol oxidase – peroxidase-4-amino phenazone method) , serum triglyceride (glycero phosphate oxidase –peroxidase -4-aminophenazone method), and HDL cholesterol (direct method with polyethylene glycol pre treated enzymes) were measured using Hitachi-912 Auto analyzer (Hitachi , Mannheium , Germany). The intra and inter assay coefficient of variation (CV) for the biochemical assays ranged between 3.1 and 7.6%. LDL cholesterol was calculated using the Friedwald et al. (1972) in subjects with triglyceride <400 mgs/ dl.Hs- CRP is estimated quantitatively by means of particle enhanced immuno nephelometry using BN prospectus (Dade behring, Marburg, Germany). Consistent with recent recommendations from the centres for Disease control and prevention, a CRP cut point of 3 mgs/l was used to differentiate high risk and low risk groups.

2.3. Statistical analysis:

One way ANOVA or student ‘ t ’ test as appropriate was used to compare groups for continuous variables. The Chi-square test or Fisher’s extract test as appropriate was used to compare proportions. Pearson’s correlation analysis was done to determine the relation of hs-CRP with other risk variables. All the analyss were done by using the Windows based SPSS statistical Package (Version 10.0 ; SPSS Inc; Chicago,IL , USA) and P- values <0.05 were taken as the level of significance.

3. Results

The clinical and biochemical characteristics in relation to hs-CRP of the study group were shown on the table 1. In comparison with non-diabetic subjects, the diabetic subjects were older (P < 0.001) and had higher body Mass Index (BMI (P<001). They also had higher systolic blood pressure ((P<0.001) and diastolic pressure . Blood pressure (P<0.001) , fasting plasma glucose (P<0.001) , HbA1C % (P<0.001) , fasting insulin (P<0.001) and insulin resistance (P<0.001). The mean hs-CRP value in the whole study population was 1.87 mgs/ l hs- CRP levels were significantly higher among the diabetic subjects with 4.8 mg/l (P<0.001) for non-diabetic subjects with 2.5 mgs/l.

The clinical and biochemical characteristics in normal and abnormal group of study the subjects were shown in table 2.When the study subjects were characterised as high risk using hs-CRP cut –off >3.0 mgs /l , the subjects with abnormal hs-CRP (hs-CRP>3.0 mgs/l) were older (P<0.001) , and also had higher body mass index (P<0.001) systolic pressure (P<0.001) than the subjects with normal hs-CRP (hs-CRP < 3.0 mgs/l).

Fasting plasma glucose (P<0.001) , total cholesterol (P<0.001) , LDL-cholesterol (P<0.001), HbA1C (P<0.001) and insulin resistance(P<0.001) were also higher in subjects with abnormal hs-CRP than the subjects with normal hs-CRP. Table 3 presents the results of the Pearson’s correlation analysis of hs-CRP with high risk variables. hs-CRP showed a significance positive correlation with age (r=0.168, P<0.001) , BMI (r= 0.238, P<0.001), systolic pressure (r=0.161 , P<0.001),fasting plasma glucose (r=0.274, P<0.001) and HbA1c (r=0.307, P<0.001) .

4. Discussion

Diabetic subjects were older with mean age of 51 years than the normal subjects. Diabetic subjects have higher Body Mass Index (BMI) .This was further confirmed by the study done by Ni Mhurchu et al. (2006). Eric and John (2006) and NHANES (2005) report indicates that most adults with diagnosed diabetes were overweight or obese , prevalence of over weight or obesity was 85.2 % and the prevalence of obesity was 54.8% . Cosin Aguilar et al. (2007) from his study state that the obese patients showed higher prevalence of diabetes.

Systolic and diastolic pressure was higher in diabetic subjects. Some studies show that the blood pressure and blood pressure progression were strong and independent predictors of incident Type 2 diabetes among initially healthy women (David and Paul , 2004) .The Third National Health and Nutrition Evaluation Survey (1988-1994) [NHANES] disclosed that 71% of diabetic individuals were found to have hypertension. ((Geiss , et al. 2002). Previous study showed that hypertensive patients have strong association with diabetes mellitus (

Table 1: Clinical and Biochemical characteristics of study subjects

Parameters	Healthy normal subjects n = 400	Type 2 diabetic subjects n = 400	P value
Age (Yrs.)	42 ± 12	51 ± 10	<0.001
Body mass Index (kgs/m²)	23.4 ± 4.5	24.8 ± 4.2	<0.001
Systolic BP(mm Hg)	118 .4 ± 16	129.7 ± 21	<0.001
Diastolic BP (mm Hg)	74.2 ± 10	75.7 ± 11	<0.001
Fasting plasma glucose (mgs/dl)	87 ± 8.1	163 ± 72	<0.001
HbA1c (%)	5.5 ± 0.50	8.7 ± 2.3	<0.001
Insulin reistance (HOMA IR)	1.8 ± 1.27	4.2 ± 2.78	<0.001
Hs-CRP (mgs/l)	2.5 ± 2.9	4.8 ± 3.4	<0.001

Table.2 Clinical and Biochemical characteristics in normal and abnormal hs-CRP levels.

Parameters	Normal hs-CRP (hs-CRP <3.0) (n = 440)	Abnormal hs-CRP (hs-CRP > 3.0) (n = 350)	P value
Age (Yrs.)	45 ± 12.97	49 ± 11.2	<0.001
Body mass Index (kgs/m²)	23.1 ± 4.18	25.3 ± 4.48	<0.001
Systolic BP(mm Hg)	120 .9 ± 18.54	127.9 ± 20.04	<0.001
Diastolic BP (mm Hg)	74.9 ± 10.73	76.9 ± 11.08	0.1
Fasting plasma glucose (mgs/dl)	108 ± 51.68	145 ± 71.68	<0.001
HbA1c (%)	6.4 ± 1.98	7.9 ± 2.39	<0.001
Insulin reistance (HOMA IR)	2.4 ± 2.12	3.6 ± 2.60	<0.001

Table.3 Pearsons correlation analysis of hs-CRP and other risk variables in total subjects.

Parameters	r	P value
Age (Yrs.)	0.168	**<0.001**
Body mass Index (kgs/m²)	0.238	**<0.001**
Systolic BP(mm Hg)	0.161	**<0.001**
Diastolic BP (mm Hg)	0.050	0.055
Fasting plasma glucose (mgs/dl)	0.274	**<0.001**
HbA1c (%)	0.307	**<0.001**
Insulin reistance (HOMA IR)	0.234	<0.001

Coisin Aguilar et al. (2007) ; Eric and John (2006) which support the present study.

Hb1Ac was higher in the diabetic subjects than normal subjects

The present study showed the significance increase of hs-CRP in subjects with Type 2 diabetes. Studies on western populations have shown low grade systemic inflammation to be one of the mechanisms by which known risk factors such as obesity, smoking and Hypertension promote the development of diabetes mellitus (Pradhan et al. 2001; Pfutzner and Forst, 2006). However, there are few studies of hs-CRP in Asian Indians, a very high- risk group for diabetes. (Mohan et al. 2003 ; Mohan et al. 2001 ; Wild et al. 2004). The hs-CRP seems to be strongly associated with diabetes mellitus and insulin resistance. The hs-CRP levels were elevated in diabetic subjects compared with non-diabetic subjects. Several studies have earlier shown that hs-CRP predicts diabetes in western populations (Pradhan et al. (2001), Haffeiner (2003) ; Hanley et al. (2004) as a biomarker of inflammation . The result obtained in this study is comparatively similar to the earlier work that emphasises the prediction of incident Type 2 diabetes by hs-CRP level. (David and Paul (2007) .The present study which showed increased of hs-CRP in diabetes was supported by the previous study results (Li CZ et al.(2004). The hs-CRP levels significantly associated with age in the present study .This was supported by earlier studies (Fransisco et al. 2005; Taniguchi et al. 2002; Chiriboga et al. 2009).

In the present study, Serum hs-CRP levels were positively related to anthropometric variables such as Body Mass Index (BMI) and Systolic and Diastolic blood pressure which is supporting earlier study (Li CZ *et al*. 2004;Francisco *et al.* 2005; Taniguchi *et al.* 2002; Wu *et al*. 2006; Earl and Wayene , 2004) .The correlation of hs-CRP with fasting plasma glucose and HbA1c observed is similar to the previous study (Li CZ , et al. 2004; Pradhan et al. 2001). In the current study, hs- CRP was positively correlated to insulin resistance (HOMA-IR) . Some study have explored the relation of hs-CRP with insulin resistance , which precedes diabetes(Nakanishi et al. ;Wu et al. 2006 ; Taniguchi et al. 2002 ; Chambers et al. 2001 ; Visser et al. 2000).Though the hs-CRP was identified as one of the most sensitive marker of inflammation, there are very studies which have looked at the association of insulin resistance with hs-CRP and none in a high risk Asian Indian population. Another interesting observation was the relationship of hs-CRP with glycemic control could influence inflammation. A prospective study on the Type 2 diabetic subjects suggested a decrease in hs-CRP levels with a decrease in HbA1c (Rodriguez and Guerrero, 1993). In diabetic subjects hs –CRP was positively correlated with HbA1c (Li *et al.* 2004) . hs- CRP was also associated with fasting plasma glucose. A recent population based study showed hs-CRP to be independently associated with fasting plasma glucose. (Aronson *et al*. 2004)

In the present study, subjects with abnormal hs-CRP had higher proportion of Hypertension, obesity, hyper cholesterolemia, (Table 5). Previous reports show that hyper trigyceridemia and Diabetes mellitus are positively associated with CRP levels ((Pick up *et al*. 1997). Previous analysis found high concentration of hs- CRP was significantly associated with Obesity. (Visser *et al*. 2000; Chambers *et al.* 2001; Pradhan *et al*. 2001; Forouchi et al. 2001).This is in contrast to median values in other population based studies of 2.1 mgs/l[(National health and Nutrition Examination Survey , 2. 67 mg/l Cardio Vascular Health Study and 1- 2 mg/l (depending upon age) in Europe (Hutchison et al. 2000). The only population based median (3.49 mg/l) to approach that of the present cohort is for the sub group of 230 women taking unopposed estrogens replacement therapy in the Cardiovascular Health study. (Chushma et al. 1999) .

Possible reasons for the higher CRP values in this population include a very high prevalence of Diabetes Mellitus and obesity since Diabetes and high body mass index are associated with elevated CRP. Similar results are found in earlier study (Barinas *et. al*.2001 ; Frohlich *et al.* 2000). In conclusion , the present study showed that hs-CRP has a strong association with diabetes in Chennai Urban Rural population. It is also concluded that age , body mass index , hyper sensitivity and body weight has strong association with diabetic individuals and high levels of hs-CRP groups predicts the high risk of diabetes mellitus type 2. It is very well understand that the levels of hs-CRP significantly associated with age and positively related to insulin resistance, BMI, systolic and diastolic pressure. Similarly, low HbA1c strongly related to negative hs-CRP levels. It is also observed that hs-CRP levels are the ensitive marker forinflammation. Moreover this study also concludes that elevated hs-CRP level significantly different with different age groups of diabetes mellitus individuals.

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