Effect of Glycemic Control on High Sensitivity C-Reactive Protein Level in Type 2 Diabetes Mellitus

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ABSTRACT

Objective: To determine with any certainty the association of glycemic control (HbA1c) and high sensitivity C-reactive protein (hs-CRP) in diabetes. Therefore, the present study was carried out to ascertain the relation of glycemic control with hs-CRP levels.

Study Design: Prospective / Longitudinal study

Place and Duration of Study: This study was conducted at the Endocrinology Unit of Hayatabad Medical complex (HMC). Laboratory analyses was done in the laboratories of Rehman Medical Institute (RMI), Peshawar from April 2015 to October 2015.

Materials and Methods: This longitudinal study was conducted on 125 patients who were known type 2 diabetics visiting Endocrinology unit of HMC. A detailed medical history and clinical examination was carried out to exclude co morbidities. At all three visits i.e baseline, first and second follow up HbA1c and hs-CRP were recorded. Statistical analysis of the data was done by spss version 20 using Pearson correlation test to correlate HbA1c levels with hs-CRP levels.

Results: The mean levels of HbA1c reduced from baseline ($9.64\pm2.25\%$) to ($8.56\pm1.99\%$) till second follow up. The correlation between hs-CRP and HbA1c was positive in baseline (r=0.207, p=0.020), the strength of correlation improved in first follow up (r=0.331, p=0.003), in the second follow up the correlation was again positive (r=0.232, p=0.124). The correlation of change in hs-CRP and HbA1c was also positive in all the three data.

Conclusion: The study concluded that there is a significant positive correlation between hs-CRP and HbA1c.

Key Words: HbA1c, glycemic control, , hs-CRP, Type 2 diabetes mellitus

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by increased blood glucose levels due to defective insulin secretion, its action or both. Due to long term hyperglycemia, this disease causes damage and dysfunction of organs including heart and blood vessels[1]. WHO has reported that 30 million people were suffering from diabetes (mainly type 2) worldwide in 1985; the number increased to 217 million in 2005, and is expected to touch the figure of 366 million by the year 2030[2].

WHO survey in 1995 showed that Pakistan was at 8th position in top ten countries having high diabetic prevalence. The same survey has estimated that in year 2025, Pakistan will be on the 4th position with 14.5

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million people having diabetes[3]. About 7.2 million individuals are suffering from this disease in Pakistan in 2012[4]. The prevalence of diabetes has reached to 7.89% in Pakistan in 2015 [5]. In other countries of South East Asia the prevalence of diabetes varied much in 2014, with Mauritius having a prevalence of 14.8%, India had 9.1%, Sri Lanka 7.6%, Bangladesh 6.3%, Bhutan 5.8%, Nepal 4.9% and with Maldives 4.8% [6].

Cardiovascular diseases (CVD) are the most prevalent cause of morbidity & mortality among diabetics[7]. A study has reported that CVD was present in 30% diabetics in Pakistan[8]. Diabetes is an independent risk factor for atherosclerosis, sharing common features of pathophysiology such as endothelial dysfunction, low grade inflammation and oxidative stress[9]. Therefore, it seems that early detection of cardiovascular risk can improve the morbidity status & mortality rate among diabetics.

C-reactive protein (CRP) is a nonspecific marker of inflammation which is a strong independent predictor of cardiovascular risk in future[10,11]. American Heart Association and Centers for Disease Control recommended CRP as biomarker of CVS risk in 2003 [12]. CRP is an acute phase protein produced by liver during inflammation. Atherogenic mechanism of CRP includes impaired production of endothelial nitric oxide, uptake of LDL by macrophages, proinflam-

matory cytokines release, and expression of monocyte chemotactic protein-1, vascular cellular adhesion molecule-1 and intercellular adhesion molecule-1 [13].

Review of the available reports is unable to determine with any certainty the association of HbA1c and hs-CRP in diabetes. The aim of this study was to find out the relationship of glycemic control with elevated hs-CRP level, so that treatment in diabetics can be targeted towards drugs that lower CRP levels along with anti-diabetic medication.

MATERIALS AND METHODS

This longitudinal prospective study was conducted in Endocrinology Unit of Hayatabad Medical complex (HMC). Laboratory analyses of the collected samples were done in the laboratories of Rehman Medical Institute (RMI), Peshawar from April 2015 to October 2015. Type 2 diabetics with age 45-65 years admitted in Endocrinology Unit of HMC were included in this study. All subjects who had type 1 diabetes mellitus, any acute infection or chronic inflammatory disease like infection of upper or lower respiratory tract, urogenital tract, GIT were also not included.. Moreover patients with anemia or taking NSAIDS, lipid lowering drugs or are pregnant or breastfeeding were excluded.

Data Collection: Detailed medical history and physical examination was done on 125 diagnosed cases of type 2 diabetes mellitus. Three fasting blood samples were taken from each patient; one initially on day one, second after three months and third after six months of the initial sample. Whole blood before centrifugation was analyzed for HbA_{1c} on immunoassay method by Architect *i1000*SR machine and expressed as percentage (%). hs- CRP was measured from plasma through automated analyzer architect *ci 8200* machine by Immunoturbidimetric method and it was expressed in mg/dl which was then converted to mg/L.

Data Analysis: Data was analyzed to measure the frequency and percentages for categorical variables while mean and standard deviation were calculated for numerical variables using SPSS version 20. Pearson's correlation coefficients were determined for numerical variables i.e. between HbA1C and hs-CRP.

RESULTS

In this study, 125 patients of type 2 DM were recruited and followed up for 6 months. About 70% of the data was available for the final analysis due to loss of follow up. In current study, HbA1c less than and equal to 7 was taken as good glycemic control whereas HbA1c more than 7 was taken as poor glycemic control.

In Table No. 1, HbA1c0 indicates baseline glycosylated hemoglobin level, HbA1c1 indicates first follow up and HbA1c2 indicates glycosylated hemoglobin levels of second follow up in percentage (%).Mean baseline glycemic control (HbA1c0) was 9.64±2.25 %. The mean glycemic control at 1st follow up (HbA1c1)

decreased to 8.83±2.01 %. The mean glycemic control in 2nd follow up (HbA1c2) further reduced to 8.56±1.99 %. The change of HbA1c level in baseline and first follow up, and that between baseline and second follow up was significant. While the HbA1c change during first and second follow up was not significant.

Table No.2 shows mean high sensitive C - reactive protein at baseline (hs-CRP0) 4.71±2.97mg/l. The mean 1st follow up hs-CRP (hs-CRP1) and hs-CRP in 2nd follow up (hs-CRP2) was 4.35±3.09 mg/l and 4.15±3.09mg/l respectively. The changes in hs-CRP values in baseline, first and second follow up were insignificant.

Table No.1: Baseline, 1st follow up and 2nd follow up HbA1c levels

Sr. No	Variables	Mean (%)	Standard Deviation	95%CI	p value
1	HbA1c0	9.64	2.25	-1.491 to -0.132	0.020
	HbA1c1	8.83	2.01		
2	HbA1c1	8.83	2.01	-0.362 to 0.910	0.396
	HbA1c2	8.56	1.99		
3	HbA1c2	8.56	1.99	0.409 to 1.762	0.002
	HbA1c0	9.64	2.25		

Table No.2: Baseline, 1st and 2nd follow up hs -CRP

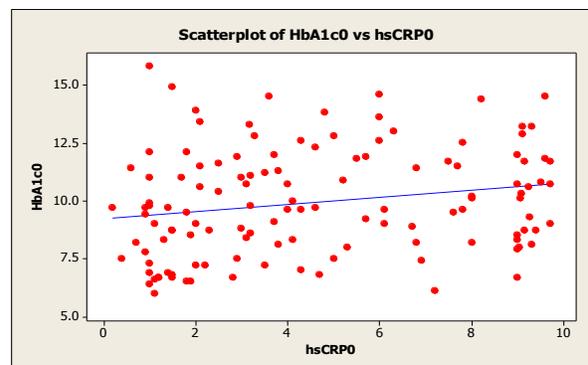| Sr. No	Variables	Mean (mg/l)	Standard Deviation	95%CI	p value
1	hs -CRP 0	4.71	2.97	-0.598 to 1.332	0.453
	hs -CRP 1	4.35	3.09		
2	hs -CRP 1	4.35	3.09	-0.750 to 1.151	0.678
	hs -CRP 2	4.15	2.88		
3	hs -CRP 2	4.15	2.88	-0.365 to 1.500	0.231
	hs -CRP 0	4.71	2.97		

Figure No.1: Correlation of HbA1c0 and hs-CRP0 in baseline data r= 0.207 and p = 0.020).

Figure 1 shows significant small positive correlation of HbA1c0 and hs-CRP0 in baseline data (with r= 0.207 and p = 0.020). Figure 2 shows significant positive correlation of HbA1c1 and hs-CRP1 in first follow up data (with r= 0.331 and p = 0.003). Figure 3 shows positive correlation of HbA1c2 and hs-CRP2 in 2nd follow up (with r= 0.232 and p = 0.124).
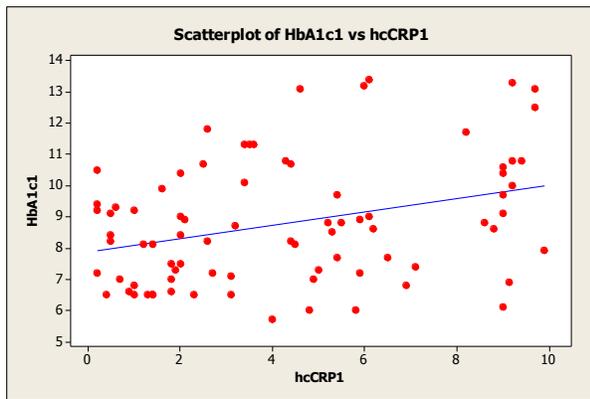
Figure No.2. Correlation of HbA1c1 and hs-CRP1 in first follow up data (r= 0.331 and p = 0.003).
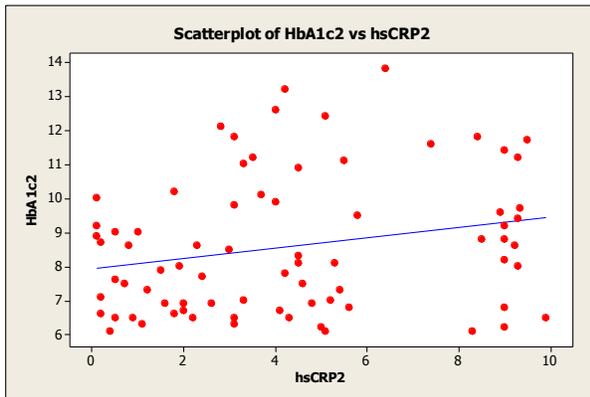

Figure No.3. Correlation of HbA1c2 and hs-CRP2 in 2nd follow up (r= 0.232 and p = 0.124)

DISCUSSION

This study was conducted to determine the hs-CRP levels in type 2 diabetics and to correlate it with HbA1c levels (glycemic control). A significant positive correlation was found between hs-CRP at all three stages of sampling i.e. baseline, first follow up after 3 months and second follow up after 6 month of initial sampling.

The baseline HbA1c in this study was significantly reduced in the first follow up (done after the month of Ramadan). The HbA1c dropped further in second follow up sample, the reduction in HbA1c measured from baseline to second follow up was statically significant. Similar drop in HbA1c level was reported in a study in which type 2 diabetics were followed up for four months [14,15]. In a study done in type 2 diabetics to observe change in HbA1c level in Ramadan, there was a drop of 0.3% in mean HbA1c when measured two weeks after Ramadan[16]. The current study showed a significant positive association of hs-CRP with HbA1c in baseline data, the correlation was stronger in the first follow up. In second follow up the correlation was again positive. All these findings suggest a positive correlation of hs-CRP with HbA1c in type 2 diabetics. Our findings were similar to various studies including a

study conducted in India on newly diagnosed type 2 diabetics in which hs-CRP positively correlated to HbA1c[17]. A prospective study of overweight type 2 diabetic females also found a positive correlation of hs-CRP and HbA1c [18]. A case control study in which hs-CRP levels were measured in Saudi type 2 diabetics and compared with controls, the correlation of hs-CRP with HbA1c was also measured and reported to be positive[19]. In a cross- sectional study of newly diagnosed type 2 diabetics in India showed a positive correlation of hs-CRP and HbA1c[20]. In another study in India in which type 2 diabetics and non-diabetics were investigated, the correlation of hs-CRP with HbA1c was significant and positive[21]. Oxidative stress occurring in diabetes due to poor glycemic control might be a link of correlation between HbA1c and CRP causing increased inflammatory markers level in poorly controlled diabetes.

On the other hand a prospective study in which an intervention was done to reduce HbA1c levels by educating the diabetics about glycemic control and pharmacological interventions for four months, no change in hs-CRP level was observed and no correlation was noticed in the two variables[15]. This might be due to the reason that the duration of follow up was shorter and it could not influence the levels of HbA1c sufficient enough to have an effect on CRP level. The study of CRP in healthy diabetics without complications showed no correlation of CRP and HbA1c because of the study being conducted only in well controlled diabetics[22]. Therefore, it can be deduced from the present study that since the glycemic control improves CRP levels, the inflammatory processes occurring in the body during diabetes can be suppressed by reducing HbA1c levels.

CONCLUSION

The strength of this study was its prospective design which enabled us to draw a few references as far as the relationship of hs-CRP and HbA1c was related. As we proved a positive association of hs-CRP and HbA1c we can recommend that if glycemic control is kept better we have lower chances of getting cardiovascular diseases but we need another cohort study of longer duration and sample size to show that cardiovascular complications develop only in those diabetics who have poor control and high hs-CRP.

Author's Contribution:

Concept & Design of Study:	Zulfania
Drafting:	Zulfania, Soheb Rehman
Data Analysis:	Tahir Gaffar, Mehwish Durrani
Revisiting Critically:	Soheb Rehman, Tahir Gaffar
Final Approval of version:	Zulfania

Conflict of Interest: The study has no conflict of interest to declare by any author.

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