ORIGINAL ARTICLE

# Cardioprotective role of insulin: Advantage analogues

**Rituparna Maiti, Jyothirmai Jaida, Pulukuri John Israel Leander[1], Mohammed Irfanuddin, Idris Ahmed, Anuradha Palani**

Department of Pharmacology, [1]Department of General Medicine, Prathima Institute of Medical Sciences, Nagunur Road, Karimnagar, Andhra Pradesh, India

**Aim:** Type II diabetes mellitus (DM) increases the risk of cardiovascular disease. Treatment with insulin substantially reduces C - reactive protein (CRP) because of its anti-atherosclerotic action. This study was designed to explore and compare the cardio protective role of regular human insulin (RHI), aspart and lispro insulin in type II DM. **Materials and Methods:** A randomized, open, parallel group, comparative clinical study was conducted on 90 patients of type II DM. After baseline clinical assessment and investigations, RHI was prescribed to 30 patients, aspart insulin to 30 patients and lispro insulin to another 30 patients for 12 weeks. The efficacy variables were change in blood pressure, glycemic control, lipid profile, serum potassium, high-sensitivity CRP (hsCRP) and UKPDS 10-year CHD risk scoring over 12 weeks. At the end of the study, the patients were followed up and changes in variables from baseline were analyzed by statistical tools. **Results:** Systolic blood pressure decreased significantly in aspart group ($P$ = 0.008) whereas diastolic blood pressure was decreased significantly both in aspart ($P$ < 0.001) and lispro group ($P$ = 0.01). Fasting, postprandial blood glucose and $HbA_{1c}$ were decreased in all three groups significantly but change in aspart group was superior ($P$ = 0.01). Triglyceride was significantly better controlled by lispro ($P$ < 0.01) whereas aspart insulin was superior to decrease total cholesterol and LDL ($P$ < 0.05). The extent of potassium loss was significantly more with RHI ($P$ = 0.004) than others. CRP-lowering effect ($P$ = 0.017) and decrease in UKPDS risk scoring ($P$ = 0.019) in aspart and lispro group was superior to RHI group. **Conclusion:** Short acting insulin analogues, especially aspart insulin have been found to have a better cardio protective role than RHI in type II DM.

**Key words:** hsCRP, insulin analogues, regular human insulin, Type II diabetes mellitus, UKPDS 10-year CHD risk

## INTRODUCTION

Type II diabetes mellitus (DM) is a progressive and complex metabolic disorder characterized by chronic hyperglycemia and disturbances in carbohydrate, lipid, and protein metabolism due to insulin resistance. Insulin resistance is a proinflammatory, hypercoagulable state predisposing patients to develop cardiovascular diseases associated with risk factors for atherosclerosis, including altered hemostasis, dyslipidemia, hypertension, and inflammation.[1,2] The structural and functional abnormalities of vessels along with dyslipidemia and hypertension lead to ischemic heart diseases. Type II DM carries a 2-4-fold increase risk of fatal myocardial infarction. [3,4] hsCRP, an important contributor in endothelial dysfunction and atherosclerosis, has emerged as one of the most powerful independent predictor of cardiovascular disease.[5-10] Patients with type II DM show higher hsCRP concentrations than those without it, suggesting the contribution of inflammation in accelerated atherosclerosis seen in patients with type II DM.[11,12] Positive results in different clinical trials have strengthen the value and acceptance of hsCRP, which is recommended as a predictive laboratory marker for cardiovascular disease risk in patients with diabetes mellitus.[13]

The current therapeutic approach to DM involves intensive blood glucose control, with the aim of reducing the risk of long-term vascular complications. Conclusive evidences are already there in favour of the long-term clinical benefits of maintenance of tight glycemic control in diabetes mellitus.[14,15] The prevalence of diabetes, along with its accompanying long-term micro vascular and macro vascular complications suggests the use of insulin earlier in the treatment process to maintain tight glycemic control.[16] As β -cell function declines, many patients with type II diabetes require insulin therapy on long run. Insulin is the most potent drug available to achieve tight

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**Address for correspondence:** Dr. Rituparna Maiti, Associate Professor, Department of Pharmacology, Prathima Institute of Medical Sciences, Nagunur Road, Karimnagar, Andhra Pradesh, India. E-mail: rituparnamaiti@rediffmail.com

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glycemic control; however, often it is not used early for patients to achieve the glycemic targets needed to prevent chronic complications.

Recent studies already proved that insulin has an anti-inflammatory and anti-atherosclerotic effect. More recently, a study confirmed that insulin infusion reduces hsCRP concentrations by 40% in patients undergoing coronary artery bypass grafting.[17] Because hsCRP values are related to the magnitude of myocardial damage in patients with acute MI, insulin-induced reduction in hsCRP has promising clinical applications. A low-dose infusion of insulin reduced hsCRP concentrations and found to be cardio protective.[18-20]

Other than regular human insulin (RHI), aspart and lispro are two short-acting insulin analogues which are widely prescribed for type II diabetes mellitus by physicians. The pharmacokinetic properties and advantages of aspart and lispro insulin over RHI are known. But there are limited data on their possible cardioprotective role in type II DM. This clinical study was designed to explore and compare the effect of insulin analogues on cardiovascular risk in type II DM.

## MATERIALS AND METHODS

### Patients

The study was conducted on 90 patients of type II DM attending the department of General Medicine, Prathima Institute of Medical Sciences, Karimnagar, Andhrapradesh, India. The study population included patients irrespective of sex, aged more than 30 years suffering from type II DM and not responding to oral hypoglycemic agents. The patients were free from other significant morbidity like infection, infestations, inflammatory or neoplastic diseases. Patients with hsCRP level >10 mg/L (non-specific elevation) were excluded from the study. Those patients already on statins, anti-platelet drugs, angiotensin receptor blockers, glitazones, ACE Inhibitors and gliclazide, were not included in this study. Patients hypersensitive to insulin, pregnant and lactating mothers were also excluded from the study.

### Study design

The present study is a 12 week, randomized, open, parallel group comparative clinical study between RHI, aspart and lispro insulin in patients with type II DM conducted in a single centre. The study was approved by Institute Ethical Committee and procedures followed in this study are in accordance with the ethical standard laid down by ICMR's ethical guidelines for biomedical research on human subjects (2006). A written informed consent was taken from all the patients participated in the study after explaining the patient's diagnosis, the nature and purpose of a proposed treatment, the risks and benefits of a proposed treatment (RHI / aspart / lispro insulin). Randomization (Probability sampling: simple random sample) was done by using computer generated random list. After randomization, the patients were divided into three treatment groups. 30 patients were allocated in RHI group who received regular human insulin, 30 patients in aspart group who received aspart insulin and another 30 patients in lispro group who received lispro insulin twice daily for 12 weeks. The patients received pre-breakfast and pre-supper subcutaneous injection of insulin. Dose was individualized and regularly adjusted based on the results of blood glucose determinations. The patients received the drugs free of cost from our institute pharmacy.

At the first visit, after detailed history was taken on baseline symptomatology, clinical evaluation (including Metabolic syndrome diagnostic scoring, UKPDS 10-year CHD risk %) and laboratory investigations (blood glucose, glycosylated hemoglobin, lipid profile, serum potassium and hsCRP) were done. Every 4 weeks, blood glucose level was checked and at the end of 12 weeks clinical improvement was assessed in terms of change in glycemic control, lipid profile, hsCRP, serum potassium and UKPDS 10-years CHD risk (%).

### Parameter studied

The changes in efficacy variables like blood pressure (both systolic and diastolic), glycemic control (fasting blood glucose, postprandial blood glucose, glycosylated hemoglobin), lipid profile, serum potassium, hsCRP and UKPDS 10-year CHD risk scoring from baseline to day 84 were studied. As hsCRP is strongly predictive of future cardiovascular events, it was considered as primary outcome measure. hsCRP was measured quantitatively by solid phase Enzyme Linked Immunosorbent Assay (ELISA) using UBI MAGIWEL™ CRP-kit. 10-years risk for CHD is calculated by the software UKPDS Risk engine version 2.0 considering the parameters like age, sex, ethnicity, and duration of diabetes, smoking habit, presence of atrial fibrillation, systolic blood pressure, $HbA_{1c}$, and lipid profile. For diagnosis of metabolic syndrome, metabolic syndrome diagnostic scoring ATP III criteria was followed.[21]

### Statistical analysis

The statistical calculation for the paired t-test/Wilcoxon signed rank test, one way ANOVA, Turkey-Kramer multiple comparison post test, chi-square test were performed with Instat + version 3.036 statistical software (Statistical Services Centre, University of Reading, Reading, England). $P < 0.05$ was considered statistically significant. The statistician was blinded to the groups during analysis. Considering hsCRP as primary outcome, sample size has been calculated taking level of significance

(a) =0.05, power of the study (1-β) = 0.80 and expected mean difference 0.50.

## RESULTS

### Patient disposition baseline demographics

A total of 90 patients were randomized to three groups to receive either RHI ($n$ = 30) or aspart insulin ($n$ = 30) or lispro insulin ($n$ = 30). Postbaseline values were missing in 16 patients (5 in RHI group and 5 in aspart group and 6 in lispro group) because they were lost to follow-up because of noncompliance. The treatment groups were comparable in demographic features and baseline clinical characteristics [Table 1]. The patients ranged in age from 32 to 78 years (mean age, 51.7 years), and 41% were female and 59% male. The mean duration of type II DM was 4.9 years in RHI group, 5.4 years in aspart group and 4.6 years in lispro group respectively. 83.3% subjects (75/90) were diagnosed as metabolic syndrome patients.

### Change in blood pressure

The systolic blood pressure was found to decrease significantly in aspart group ($P$ = 0.008) whereas change in RHI and lispro group was not statistically significant. The diastolic blood pressure was decreased significantly both in aspart ($P$ < 0.001) and lispro group ($P$ = 0.01). [Table 2] The mean difference of both systolic ($P$ = 0.65) and diastolic blood pressure ($P$ = 0.56) of three groups were compared and found to be non-significant. [Table 3]

### Change in fasting and postprandial blood Glucose

Both fasting and postprandial blood glucose was decreased in all three groups significantly over 12 weeks. [Table 2] Analysis of the mean difference of both fasting and postprandial blood glucose of three groups reveals that change in aspart group ($P$ = 0.01) was superior to RHI and lispro group. [Table 3]

### Change in glycosylated hemoglobin ($HbA_{1c}$ %)

Table 2 shows that $HbA_{1c}$ level was decreased significantly in all three groups. When mean differences were compared, it was found significant ($P$ = 0.01) and the change in aspart group was superior to RHI group ($P$ < 0.05). [Table 3]

### Change in lipid profile

Triglyceride level was found to decrease in aspart ($P$ < 0.001) and lispro ($P$ < 0.001) group significantly but not in RHI group ($P$ = 0.18). The mean difference of triglyceride level of three groups was found to be significant ($P$ = 0.01) and the change in lispro group was superior to RHI groups ($P$ < 0.01). [Table 3]

Table 2 shows that total cholesterol was decreased significantly in all three groups. When mean differences were compared, it was found significant ($P$ = 0.038) and the change in aspart group was superior to RHI group ($P$ < 0.05). [Table 3]

LDL cholesterol was decreased significantly in all three groups. [Table 2] When mean differences were compared,

**Table 1: Baseline demographic data and clinical characteristics of the 90 patients of type II diabetes mellitus who participated in the study in the first visit**

| Characteristics | RHI group | Aspart group | Lispro group | *P* value |
|---|---|---|---|---|
| Number of patients recruited | 30 | 30 | 30 | |
| Number of patients at follow-up (%) | 25 (83.3) | 25 (83.3) | 24 (80) | |
| Male sex (%) | 18 (60) | 16 (53.3) | 19 (63.3) | 0.34 |
| Metabolic Syndrome patients (%) | 26 (86.7) | 25 (83.3) | 24 (80) | 0.44 |
| Age (years) | 50.23 ± 10.9 | 53.97 ± 8.7 | 51.03 ± 9.3 | 0.29 |
| Duration of diabetes (years) | 4.93 ± 3.5 | 5.42 ± 4.6 | 4.58 ± 4.7 | 0.75 |
| Waist circumference (inch.) | 34.6 ± 3.8 | 33.4 ± 5.4 | 33.7 ± 4.2 | 0.55 |
| BMI (kg/m$^2$) | 25.22 ± 5.2 | 24.88 ± 5.6 | 23.56 ± 7.4 | 0.54 |
| Systolic Blood Pressure (mm of Hg) | 132.87 ± 12.3 | 139.67 ± 12.3 | 135.67 ± 13.2 | 0.12 |
| Diastolic Blood Pressure (mm of Hg) | 88 ± 7.1 | 92.2 ± 6.2 | 89.2 ± 9.2 | 0.09 |
| Fasting Blood Glucose (mmol/L) | 7.33 ± 1.2 | 7.55 ± 1.9 | 6.95 ± 1.5 | 0.33 |
| Post-prandial Blood Glucose (mmol/L) | 10.54 ± 1.8 | 11.38 ± 2.5 | 11.15 ± 2.3 | 0.33 |
| $HbA_{1c}$ % | 8.11 ± 1.3 | 8.25 ± 1.9 | 8.24 ± 1.6 | 0.93 |
| Total Cholesterol (mmol/L) | 5.70 ± 0.8 | 5.60 ±0.6 | 5.42 ± 0.7 | 0.37 |
| LDL Cholesterol (mmol/L) | 3.85 ± 0.8 | 3.79 ± 0.8 | 3.59 ± 0.6 | 0.39 |
| HDL Cholesterol (mmol/L) | 0.98 ± 0.06 | 0.95 ± 0.07 | 0.99 ± 0.11 | 0.18 |
| VLDL Cholesterol (mmol/L) | 0.87 ± 0.07 | 0.86 ± 0.07 | 0.84 ± 0.07 | 0.15 |
| Triglyceride (mmol/L) | 2.01 ± 0.6 | 1.98 ± 0.7 | 2.24 ± 0.6 | 0.25 |
| Serum Potassium (mEq/L) | 4.31 ± 0.5 | 4.24 ± 0.5 | 4.15 ± 0.5 | 0.50 |
| hs-C-Reactive Protein (mg / L) | 1.43 ± 0.8 | 1.46 ± 0.9 | 1.56 ± 0.6 | 0.80 |
| UKPDS 10-year CHD risk (%) | 17.9 ± 11.6 | 20.6 ± 12.5 | 20.3 ± 13.5 | 0.66 |

Data are in Mean ± SD

it was found significant ($P = 0.039$) and the change in aspart group was superior to RHI group ($P < 0.05$). [Table 3]

HDL level was improved in all three groups over 12 weeks significantly and VLDL level was decreased only in aspart group significantly ($P = 0.02$). [Table 2] The mean difference of both HDL and VLDL cholesterol of three groups were compared and found to be non-significant. [Table 3]

### Change in serum potassium

There was significant decrease in serum potassium with all three types of insulin preparations but it was highly

**Table 2: Change in different parameters among follow-up patients in individual groups over 12 weeks**

| Parameters | | RHI group ($n = 25$) | | | Aspart group ($n = 25$) | | | Lispro group ($n = 24$) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | First visit | Second visit | *P* value | First visit | Second visit | *P* value | First visit | Second visit | *P* value |
| Blood pressure | Systolic blood pressure (mm of Hg) | 131.9 ± 11.1 | 128.5 ± 6.6 | 0.16 | 137.3 ± 10.2 | 130.9 ± 7.5 | 0.008* | 134 ± 12.9 | 130.2 ± 8.9 | 0.16 |
| | Diastolic blood pressure (mm of Hg) | 87.2 ± 6.7 | 85.2 ± 4.9 | 0.11 | 91.4 ± 6.2 | 87.8 ± 4.9 | <0.001* | 87.9 ± 8.8 | 84.7 ± 7.7 | 0.01* |
| Glycemic profile | Fasting blood glucose (mmol/L) | 7.42 ± 1.2 | 6.96 ± 0.97 | <0.001* | 7.69 ± 1.9 | 6.50 ± 0.8 | <0.001* | 7.25 ± 1.5 | 6.79 ± 0.91 | 0.01* |
| | Post-prandial blood glucose (mmol/L) | 10.58 ± 1.9 | 9.87 ± 1.43 | <0.001* | 11.65 ± 2.7 | 9.98 ± 1.8 | <0.001* | 10.83 ± 2.3 | 10.27 ± 1.9 | 0.025* |
| | $HbA_{1c}$ % | 8.23 ± 1.3 | 7.79 ± 1.1 | <0.001* | 8.44 ± 1.9 | 7.23 ± 1.3 | <0.001* | 7.85 ± 1.7 | 7.19 ± 1.1 | 0.003* |
| Lipid profile | Triglyceride (mmol/L) | 1.99 ± 0.7 | 1.94 ± 0.6 | 0.18 | 2.01 ± 0.7 | 1.78 ± 0.5 | <0.001* | 2.34 ± 0.6 | 2.01 ± 0.3 | <0.001* |
| | Total cholesterol (mmol/L) | 5.57 ± 0.8 | 5.45 ± 0.7 | 0.04* | 5.47 ± 0.7 | 5.07 ± 0.5 | <0.001* | 5.48 ± 0.7 | 5.24 ± 0.5 | 0.01* |
| | LDL cholesterol (mmol/L) | 3.73 ± 0.8 | 3.59 ± 0.7 | 0.02* | 3.65 ± 0.7 | 3.25 ± 0.5 | <0.001* | 3.68 ± 0.7 | 3.42 ± 0.4 | 0.006* |
| | HDL cholesterol (mmol/L) | 0.97 ± 0.06 | 0.99 ± 0.05 | 0.007* | 0.96 ± 0.07 | 0.99 ± 0.05 | 0.001* | 0.98 ± 0.10 | 1.01 ± 0.07 | 0.02* |
| | VLDL cholesterol (mmol/L) | 0.87 ± 0.06 | 0.86 ± 0.05 | 0.43 | 0.86 ± 0.07 | 0.82 ± 0.04 | 0.02* | 0.82 ± 0.07 | 0.80 ± 0.06 | 0.08 |
| Electrolyte profile | Serum potassium (mEq/L) | 4.27 ± 0.5 | 3.8 ± 0.3 | <0.001* | 4.19 ± 0.5 | 4.01 ± 0.4 | 0.03* | 4.21 ± 0.5 | 4.02 ± 0.5 | 0.01* |
| Cardiovascular risk assessment | hs-C-Reactive protein (mg / L) | 1.51 ± 0.8 | 1.45 ± 0.7 | 0.06 | 1.32 ± 0.9 | 1.08 ± 0.6 | 0.001* | 1.64 ± 0.7 | 1.39 ± 0.5 | <0.001* |
| | UKPDS 10-year CHD risk (%) | 18.24 ± 12.1 | 17.27 ± 12.1 | 0.006* | 21.32 ± 12.8 | 18.09 ± 10.9 | <0.001* | 20.98 ± 14.1 | 17.73 ± 11.2 | <0.001* |

Data are in Mean ± SD

**Table 3: Comparison of mean differences in different parameters among follow-up patients in individual groups over 12 weeks**

| Parameters | Mean Difference | | | *P* value (one-way ANOVA) | Turkey-Kramer Multiple comparison post test (q value) | | |
|---|---|---|---|---|---|---|---|
| | RHI group ($n = 25$) | Aspart group ($n = 25$) | Lispro group ($n = 24$) | | RHI vs. Aspart | RHI vs. Lispro | Aspart vs. Lispro |
| Systolic blood pressure (mm of Hg) | 3.44 | 6.32 | 3.83 | 0.65 | Not applicable $ | | |
| Diastolic blood pressure (mm of Hg) | 2.0 | 3.6 | 3.25 | 0.56 | Not applicable $ | | |
| Fasting blood Glucose (mmol/L) | 0.46 | 1.19 | 0.46 | 0.01* | 3.813* | 0.024 | 3.799* |
| Post-prandial Blood Glucose (mmol/L) | 0.71 | 1.67 | 0.56 | 0.006* | 3.765* | 0.588 | 4.315* |
| $HbA_{1c}$ % | 0.43 | 1.21 | 0.86 | 0.01* | 4.224* | 2.269 | 1.911 |
| Triglyceride (mmol/L) | 0.05 | 0.23 | 0.33 | 0.01* | 2.891 | 4.365* | 1.504 |
| Total cholesterol (mmol/L) | 0.12 | 0.40 | 0.24 | 0.038* | 3.684* | 1.652 | 1.995 |
| LDL cholesterol (mmol/L) | 0.13 | 0.40 | 0.26 | 0.039* | 3.683* | 1.692 | 1.953 |
| HDL cholesterol (mmol/L) | -0.02 | -0.03 | -0.03 | 0.38 | Not applicable $ | | |
| VLDL cholesterol (mmol/L) | 0.01 | 0.04 | 0.02 | 0.14 | Not applicable $ | | |
| Serum potassium (mEq/L) | 0.47 | 0.18 | 0.19 | 0.004* | 4.298* | 4.202* | 0.052 |
| hs-C-Reactive protein (mg / L) | 0.06 | 0.24 | 0.25 | 0.017* | 3.623* | 3.549* | 0.036 |
| UKPDS 10-year CHD risk (%) | 0.97 | 3.23 | 3.25 | 0.019* | 3.553* | 3.551* | 0.034 |

$ Post test is done only when *P* value of one-way ANOVA is significant (<0.05), *Statistically significant (<0.05)

significant ($P < 0.001$) with RHI. [Table 2] When mean differences were compared, it was found significant ($P = 0.004$) and degree of potassium loss was significantly more with RHI in comparison to aspart and lispro group. [Table 3]

### Change in hsCRP

hsCRP level was found to decrease in aspart ($P = 0.001$) and lispro ($P < 0.001$) group significantly but not in RHI group ($P = 0.06$). The mean difference of hsCRP level of three groups was found to be significant ($P = 0.017$) and the change in aspart ($P < 0.05$) and lispro group ($P < 0.05$) was superior to RHI group [Table 3].

### Change in UKPDS 10-Years CHD Risk (%)

Table 2 shows that UKPDS 10-years CHD risk was decreased significantly in all three groups. When mean differences were compared, it was found significant ($P = 0.019$) and the change in aspart and lispro group was superior to RHI group [Table 3].

## DISCUSSION

Insulin resistance is a proinflammatory, hypercoagulable state predisposing patients to develop cardiovascular disease, a major cause of morbidity and mortality. The prevalence of diabetes, along with its accompanying long-term micro vascular and macro vascular complications suggests the use of insulin earlier in the treatment process to maintain tight glycemic control. Earlier studies proving anti-inflammatory and anti-atherosclerotic effect of insulin was the impetus behind this comparative study where we found that insulin analogues have a promising cardio protective role and they are superior to RHI.

Though one way ANOVA was statistically insignificant, individual group analysis by paired t test shown in Table 2 reveals systolic blood pressure was better controlled with aspart whereas both insulin analogues controlled diastolic pressure better than RHI. The *in vitro* studies by Ahmad Aljada *et al*. have established that insulin increases the expression of NOS and NO generation.[22] So it is an interesting field to explore whether the effect of insulin analogues on NO generation is more than RHI and this may explain the effect of insulin analogues on diastolic blood pressure.

Control of both fasting and post-prandial blood glucose was best with aspart insulin. Glycosylated hemoglobin, a marker of long term glycemic control was also better controlled with aspart insulin. Glycosylated hemoglobin concentration predicts cardiovascular risk both in diabetic and non-diabetic population, and may help identify individuals at higher risk of cardiovascular disease for targeted interventions, including blood pressure or cholesterol reduction.[23-25] Thus, by decreasing $HbA_{1c}$ level significantly, aspart insulin has established its better cardio protective role when compared to RHI and lispro insulin.

The characteristic features of diabetic dyslipidemia are a high plasma triglyceride concentration, low HDL cholesterol concentration and increased concentration of small dense LDL-cholesterol particles.[26,27] The comparative analysis shows that aspart insulin is distinctly better than RHI and lispro in reducing total cholesterol and LDL cholesterol level whereas lispro insulin showed better effect on reducing triglyceride level. So both the insulin analogues can improve diabetic dyslipidemia better than RHI and reduce cardiovascular risk.

Insulin increases cellular potassium uptake and lowers potassium levels in blood. In our study potassium lowering effect was significantly more with RHI in comparison to aspart and lispro insulin. So chances of hypokalemia are less with insulin analogues and it is a very important advantage over RHI.

For cardiovascular risk assessment we relied on two important parameters, hsCRP and UKPDS 10-years CHD risk (%). The UKPDS risk engine is the first coronary risk calculator to be developed from a cohort with type II diabetes. It showed good predictive ability and the risk engine has been externally validated using data from the CARDS study.[28-30] The robust association with future cardiovascular events has provided an analytic opportunity for hsCRP in clinical use. Based on multiple epidemiological and intervention studies, minor hsCRP elevation has been shown to be associated with future major cardiovascular risk (hsCRP: <1 mg/L = low risk; 1-3 mg/L = intermediate risk; 3-10 mg/L = high risk; >10 mg/L = non-specific elevation).[13] 68% patients (61/90) of our study population were found to have intermediate risk whereas rest of the patients had low risk for cardiovascular diseases. The comparative analysis of the changes of hsCRP in the three groups showed that both insulin analogues were superior in CRP-lowering when compared to RHI. [Figure 1] Similarly, UKPDS 10-year CHD

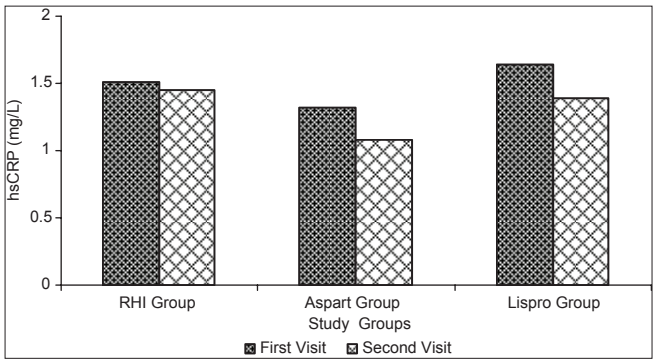


**Figure 1:** Change of hsCRP in study groups over 12 weeks

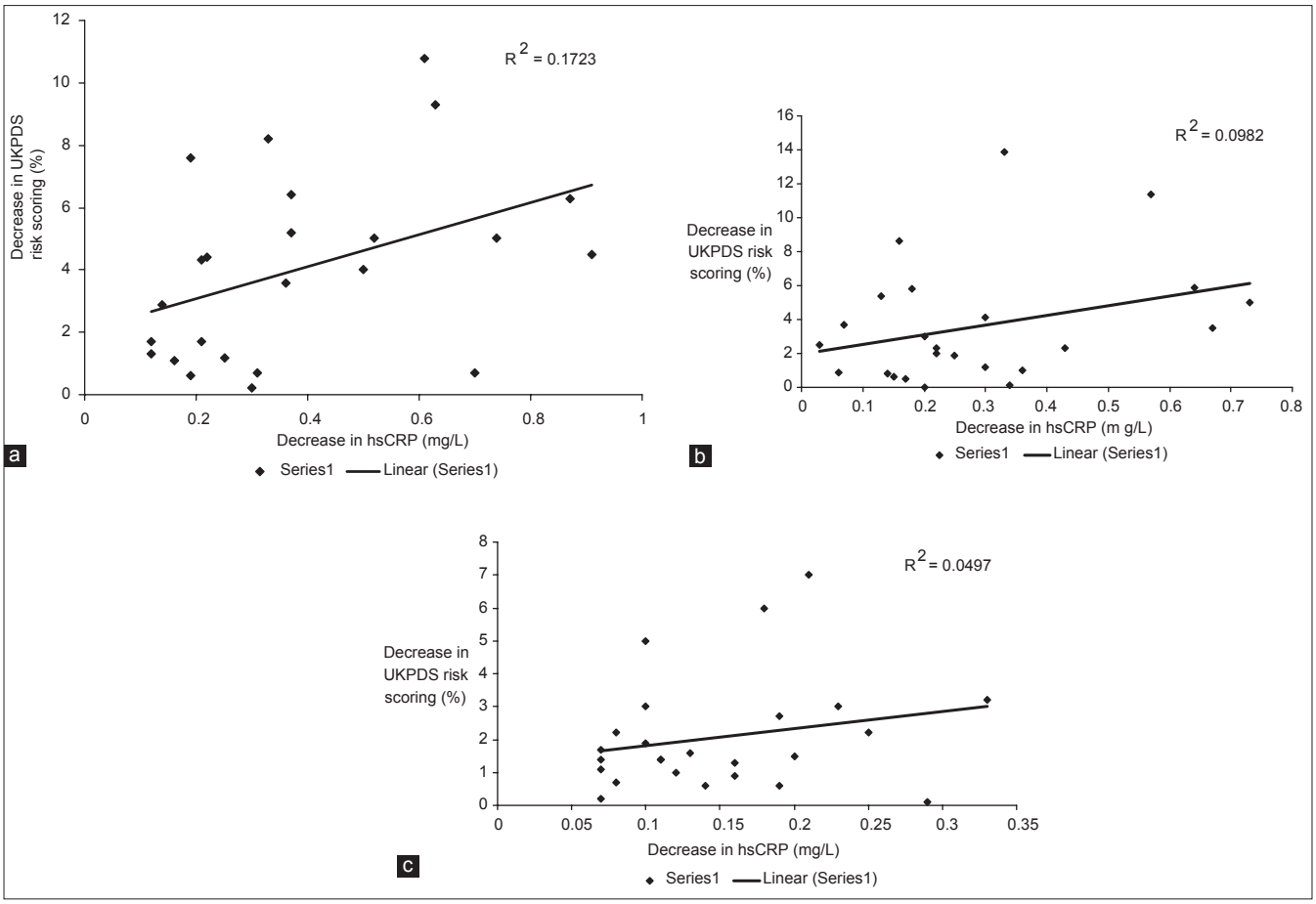


**Figure 2:** Correlation between decrease in hsCRP and decrease in cardiovascular risk in study groups (**a**) Aspart group (**b**) Lispro group (**c**) RHI group

risk was found to decrease significantly more with lispro and aspart insulin as compared to RHI. Positive correlation between decrease in hsCRP and decrease in cardiovascular risk in all three groups have been represented through scattered diagram and the correlation coefficient has been found to be more with aspart and lispro group than with RHI. [Figure 2 a, b, c] Though 12-weeks is relatively short time to assess cardiovascular risk, these findings clearly establishes superior cardio protective role of short acting insulin analogues, aspart and lispro.

*In vitro* studies, insulin, at physiologic levels, inhibits the expression of Inter-Cellular Adhesion Molecule-1 (ICAM-1), Monocyte Chemotactic Protein-1 (MCP-1), and Nuclear Factor kB (NF-kB), a proinflammatory transcription factor. [22,31] A study by Cecilia C. Low Wang has proved that insulin's ability to maintain VSMC (vascular smooth muscle cell) quiescence and reverse the dedifferentiating influence of PDGF (Platelet Derived Growth Factor) is mediated via the PI3K pathway, whereas insulin promotes VSMC migration via the MAPK pathway. Thus, with impaired PI 3-kinase signaling and intact MAPK signaling, as seen in insulin resistance, insulin may lose its ability to maintain VSMC quiescence and instead promote VSMC migration. [32]

These *in vitro* studies are in support of anti-inflammatory and anti-atherosclerotic properties of insulin but there is lack of data regarding comparative efficacy of different insulin's. So this is an interesting field to explore to explain the superior cardio protective role of insulin analogues.

The major limitation of this study is its non-blinded design. The main aim of our study was to examine the potentiality of short acting insulin analogues as cardiovascular protective agent and to compare its efficacy with human RHI. So a multicentric, randomized, double-blind, large population clinical study is necessary to confirm its cardiovascular protective role.

## CONCLUSION

RHI and two short acting insulin analogues, aspart and lispro can reduce risk of cardiovascular diseases but short acting insulin analogues (especially aspart insulin) have been found to have a promising cardio protective role due to their favorable effect on long term glycemic control, diabetic dyslipidemia, and inflammatory/pro-atherosclerotic biomarker. This is a preliminary clinical study in this domain and it renders support to future prospective clinical

studies of insulin analogues to demonstrate net control of diabetic atherosclerosis and its sequelae.

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