Study of High sensitive C-reactive protein and Gamma-glutamyl transferase in Type 2 Diabetes Mellitus with Hypertension

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ABSTRACT
C-reactive protein (CRP), produced by the hepatocytes is a primary inflammatory marker of T2DM. Higher levels of gamma-glutamyl transferase enzyme (GGT) and Hs CRP (High sensitive CRP) are associated with the complication of poor glycemic control. This study was aimed to find the association of Hs CRP and GGT for cardiovascular risk factors in Type 2 diabetes mellitus (T2DM) and Hypertension in the suburbs of Chennai. This study includes 57 subjects with T2DM and Hypertension (Group A) and 62 subjects with T2DM (Group B) within the age group of 40-60 years. FBS, HbA1C, Hs CRP, GGT and blood pressure were determined. Statistical analysis was performed using Statistical Package for the SPSS 17 version. Mean values of FBS, blood HbA1C, Hs CRP and GGT were significantly higher among participants of Group A than Group B. Significant difference of FBS, HbA1C were found between the two groups. In contrast, no significant difference of GGT was found between the groups. Differences were considered statistically significant at two-sided \( P < 0.05 \). Within the group, Hs CRP shows the significance and positive correlation with FBS, SBP and DBP. Still, GGT does not show any significance in Group A. In contrast, in Group B, both Hs CRP and GGT shows the importance and positive correlation with FBS and HbA1C. It is concluded that high levels of HsCRP are associated with T2DM and Hypertension, indicating increased cardiovascular risk, and it should be included in regular monitoring of type-2 diabetic patients.

INTRODUCTION
Type 2 diabetes mellitus (T2DM) is a global issue, and it is associated with disturbances in protein, carbohydrate and lipid metabolism due to decreased uptake of glucose into muscle and adipose tissue resulting in tissue damage and chronic vascular complications (Wild et al., 2004; Fowler, 2011). Chronic low-grade inflammation with increased production of inflammatory markers has been attributed to the development of T2DM (van
Various Prevalence studies have shown that Hypertension is common among patients with T2DM and depends on duration, age, sex, race, glycemic control, and the presence of kidney disease. Furthermore, Hypertension is a risk factor for atherosclerotic cardiovascular disease and microvascular complications. It is the leading cause of morbidity and mortality for individuals with T2DM and is the most significant cause for the direct and indirect effects of diabetes. (Arauz-Pacheco et al., 2003; Ettehad et al., 2016) (Thomopoulos et al., 2017).

C-reactive protein (CRP), produced by the hepatocytes, is considered to be a primary inflammatory marker of T2DM. It markedly increased in both inflammatory, infectious diseases and it is a potential marker of cardiovascular risk in patients with Hypertension. (Blake et al., 2003; Cortez et al., 2016). Serum CRP above 3.0 mg/L is regarded as a worse cardiovascular prognosis, and more than 50% of deaths in diabetic patients are attributed to cardiovascular diseases (Sabatine et al., 2007; Group, 1996). Higher CRP can initiate atherosclerosis and clot formation, so, therefore, it will be advantageous to reduce the plasma levels of CRP (Fowler, 2011). This HsCRP is the most evaluated biomarker for cardiovascular disease (CVD) risk prediction and techniques are available that can detect CRP in a sensitivity range of 0.01 to 10 mg/l. (Ridker et al., 2007; Rosen et al., 2001).

Gamma-glutamyl transferase (GGT), an enzyme, produced in many tissues, mainly derived from the liver (Iqbal et al., 2010) and it is needed to maintain the levels of reduced glutathione, a major antioxidant. Increase in the levels of gamma-glutamyl transferase is an indicator for oxidative stress (Pleiner et al., 2003) and this leads to chronic inflammation which enhances inflammatory response and associated with complications of poor glycemic control. Studies have already reported that there is an association of Hs CRP as an inflammatory marker and GGT as an oxidative marker in T2DM and Hypertension (van Woudenbergh et al., 2011; Blake et al., 2003; Pleiner et al., 2003). Our objective was to study the association of Hs CRP and GGT for cardiovascular risk factors in T2DM and Hypertension in the suburbs of Chennai.

**STUDY SETTINGS**

**Materials and Methods**

This study was conducted for three months among Type 2 Diabetes mellitus and Hypertensive patients who visited the General Medicine Department, ACS hospital, Chennai, institutional ethics committee approved the study protocol.
Table 1: Gender Distribution

| GROUP                      | MALE | FEMALE | TOTAL |
|----------------------------|------|--------|-------|
| GROUP A - DIABETIC WITH HYPERTENSION | 30   | 27     | 57    |
| % within GROUP             | 52.6%| 47.4%  | 100.0%|
| GROUP B - DIABETIC         | 26   | 36     | 62    |
| % within GROUP             | 41.9%| 58.1%  | 100.0%|
| TOTAL                      | 56   | 63     | 119   |
| % within GROUP             | 100.0%| 100.0%| 100.0%|

Table 2: Mean ± standard deviation of FBS, HbA1C, Hs CRP, and GGT

| GROUP                      | N   | Mean    | Std. Deviation | Sig   |
|----------------------------|-----|---------|----------------|-------|
| FBS GROUP A - DIABETIC WITH HYPERTENSION | 57  | 201.9154| 78.43414       |       |
| FBS GROUP B - DIABETIC     | 62  | 172.1811| 68.38599       | 0.029*|
| HbA1C GROUP A - DIABETIC WITH HYPERTENSION | 57  | 9.000   | 2.1335         |       |
| HbA1C GROUP B - DIABETIC   | 62  | 7.568   | 2.3788         | 0.001*|
| Hs-CRP GROUP A - DIABETIC WITH HYPERTENSION | 57  | 7.347   | 5.5656         |       |
| Hs-CRP GROUP B - DIABETIC  | 62  | 6.145   | 6.1944         | 0.050*|
| GGT GROUP A - DIABETIC WITH HYPERTENSION | 57  | 35.212  | 15.1873        |       |
| GGT GROUP B - DIABETIC     | 62  | 33.095  | 23.9820        | 0.101 |

*p<0.05, *** p<0.001

Table 3: Group A - Hs CRP Correlation with FBS, HbA1C, GGT, SBP, DBP

|            | FBS | HbA1C | GGT | SBP  | DBP  |
|------------|-----|-------|-----|------|------|
| Correlation Coefficient | .179*| .028  | .162| .341***| .325**|
| Sig. (2-tailed)          | .050 | .762  | .078| .000 | .001 |
| N                       | 57  | 57    | 57  | 57   | 57   |

*p<0.05, *** p<0.001

Table 4: Group A - GGT Correlation with Hs CRP, FBS, HbA1C, SBP, DBP

|            | HsCRP | FBS   | HbA1C | SBP  | DBP  |
|------------|-------|-------|-------|------|------|
| Correlation Coefficient | .162  | .118  | .083  | .012 | .074 |
| Sig. (2-tailed)          | .078  | .195  | .367  | .901 | .423 |
| N                       | 57    | 57    | 57    | 57   | 57   |

*p<0.05, *** p<0.001

Table 5: Group B Correlation of Hs CRP with FBS, HbA1C, GGT

|            | FBS   | HbA1C | GGT |
|------------|-------|-------|-----|
| Correlation Coefficient | .247**| .240**| .037|
| Sig. (2-tailed)          | .005  | .006  | .675|
| N                       | 62    | 62    | 62  |

**p<0.01
A) and 62 subjects with T2DM (Group B). All the participants were provided with an information sheet, and informed written consent was obtained. A structured questionnaire including the demographic details, present and past medical history, surgical history, any recent infections, drug history and intake of steroids was obtained.

**Exclusion criteria**

Smokers, alcoholics and patients with chronic liver diseases, renal diseases, recent surgeries were excluded from the study.

### Methodology

The recruited subjects were asked to visit the hospital after an overnight fast of 10 – 12 hours, 5ml of the Blood sample was collected in EDTA tube. It was used to estimate the fasting blood glucose by glucose oxidase peroxidase enzymatic endpoint method, HbA1c by resin exchange method, Hs CRP by immunoturbidimetry (Rifai et al., 1999) and GGT by modified IFCC method (Schumann et al., 2002). Liver enzymes, lipid profile, renal function test and blood parameters were also determined by using standard laboratory procedures.

Systolic pressure and diastolic pressure were determined by using digital sphygmomanometer in the sitting position on the left arm. Three recordings were taken after at least 10–15 min of rest. Then, the average of the three readings was obtained.

### RESULTS

A total of 119 subjects between the ages of 40 – 60 years, and it includes 56 males and 63 female Table 1. Data were presented as mean ± standard deviation, differences among groups were calculated using t-test or Mann-Whitney test for parametric and nonparametric variables, respectively. Chi-square test was used. Mean values of FBS, blood HbA1C, Hs CRP and GGT were significantly higher among participants of Group A than Group B (Figure 1, Figure 2, Figure 3 and Figure 4). A significant difference of FBS, HbA1C were found between the two groups, whereas no significant difference of GGT was found between the groups Table 2. Differences were considered statistically significant at two-sided $P < 0.05$. Statistical analysis was performed using Statistical Package for the SPSS 17 version.

The correlation analysis was performed by Kendall’s tau method for nonparametric variables respectively. Hs CRP shows significance and positively correlated with FBS, SBP and DBP but GGT does not show any significance in Group A, whereas in Group B both Hs CRP and GGT shows significance and positive correlation with FBS and HbA1C. (Table 3, Table 4, Table 5 and Table 6).

### DISCUSSION

In our study serum, Hs CRP Levels are significantly associated with T2DM in both Group A (T2DM and Hypertension) and Group B (T2DM) and shows a positive correlation with FBS, HbA1C, SBP and DBP. It was found that diabetic patients had a significantly elevated median of HbA1c, HsCRP and GGT as compared to controls (Khan and Qayyum, 2009; Sharma et al., 2010). Suhadbahijri (2018) shows that high levels of Hs-CRP and GGT are associated with Hypertension and poor glycemic control, indicating increased cardiovascular risk. There was an elevated and significantly higher Hs CRP among hypertensive when compared with Normotensive, and a similar correlation was found in HsCRP with age-matched groups (Sinha et al., 2014). Elevated HsCRP and Hypertension leads to Increased cardiovascular risk. The combination of greatly increases the (Jiménez et al., 2015; Hui-Liu et al., 2019). Similar results were found in Group A of our study where Hs CRP shows the significance and positively correlated with SBP and DBP.

On analysis of GGT values, there was a mean difference of GGT between the groups (Group A 35.2U/I and Group B 33U/I), but it does not show any significant differences in-between the Groups. Low-grade hepatic inflammation induced by hepatic steatosis results in increased production of GGT; this could cause oxidative stress. This increase in GGT synthesis can lead to over utilization of glutathione. (Kunutsor et al., 2015). Similarly, in this study also Hs CRP and GGT were significant and shows a positive correlation with FBS and HbA1C.
in Group B. Elevated serum GGT could be a cardiometabolic risk factor either as a mediator of low-grade systemic inflammation and oxidative stress results from elevated serum GGT could be a cardiometabolic risk factor due to transport of glutathione into the cells. (Alissa, 2018). Statistical significance and correlation were not found for GGT within the various variables of T2DM and Hypertension.

CONCLUSION

It is concluded that increased levels of hs-CRP are associated in T2DM with Hypertension, which could lead to increased cardiovascular risk, and it should be included in the regular monitoring of diabetic patients. Further studies are needed to find the effect of GGT in diabetic and hypertension subjects using a bigger sample size.

ABBREVIATIONS

T2DM- Type 2 Diabetes Mellitus, FBS-Fasting blood sugar HbA1C –Glycated haemoglobin, Hs CRP-High sensitive C-Reactive protein, GGT-Gamma-glutamyl Transferase, SBP-Systolic Blood Pressure, DBP-Diastolic blood pressure.

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Conflict of Interest

There is no conflict of interest among authors.

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