Raised Serum MMP-9 Activity is Associated with Glycemic Control in Type 2 Diabetes Mellitus

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ABSTRACT
Aim: *People with Type 2 Diabetes are at increased risk of developing long term complications. Dysregulation of Matrix Metalloproteinase activity may be an important factor in the onset and progression of these Diabetic complications. In the present study we assessed serum MMP-9 activity and HbA1c levels in Type 2 Diabetes.*
Materials and Methods: *The study included 100 type 2 Diabetic Subjects and 100 age-matched healthy individuals with no history of Diabetes. The Anthropometric measurements, Fasting plasma glucose, Post prandial plasma glucose, HbA1c and serum MMP-9 were all measured in these subjects.*
Results: *Overall an increase in Fasting and Post prandial plasma glucose, serum MMP-9 and HbA1c levels were observed in Type 2 Diabetic Subjects when compared to controls. A highly significant positive correlation was observed between serum MMP-9 with HbA1c levels (r=0.61, p<0.01) in subjects with Type 2 Diabetes.*
Conclusion: *MMP-9 is strongly associated with glycemic control and it could be a useful diagnostic biomarker for assessing long term complications in Diabetes.*
Key words: *Type 2 diabetes mellitus, HbA1c, MMP-9, diagnostic biomarker, long term complications.*

I. INTRODUCTION

Type 2 diabetes Mellitus is a chronic progressive metabolic disorder characterized by hyperglycemia resulting from relative deficiency of insulin [1]. People with diabetes are at increased risk of developing long term complications such as retinopathy, neuropathy, nephropathy and cardiovascular problems [2]. These complications remain the most common cause of the morbidity and mortality in these subjects [3].

The matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases involved in the degradation and hydrolysis of Extracellular Matrix components [4]. In Diabetes the expression of MMP seems to be altered causing abnormal degradation of extracellular matrix, which is supposed to be the initial cause in the pathogenesis of Diabetic complications [5]. MMP-9 (Gelatinase B) belongs to the Gelatinase subgroup of the matrix metalloproteinases family [6]. Available data suggests that MMP-9 through remodeling of the extracellular matrix may contribute to the progression of vascular complications in diabetes [7].

HbA1c (Glycated hemoglobin) is used to assess glycemic control and it reflects the average blood sugar over about three months [8]. It is considered as a reliable marker for assessing the microvascular and macrovascular complications in diabetes [9]. Associating Serum MMP-9 levels with glycemic control could give better insight in to preventing the progression of diabetic complications. The objective of the present study was to assess serum MMP-9 and HbA1c levels in type 2 Diabetic Subjects and healthy controls and then to evaluate relationship between serum MMP-9 and HbA1c levels in Type 2 Diabetic subjects.

II. MATERIALS AND METHODS

This Cross Sectional Study was conducted in the Department of Biochemistry at Rajah Muthiah Medical College & Hospital, Annamalai University. 100 Type 2 Diabetic subjects in the age group of 35–60 years were selected for this study and 100 age-matched healthy individuals were selected as a control group. The study was approved by the institutional ethical committee. Informed consent was obtained from all the subjects. The patients and Controls voluntarily participated in this study. All the Type 2 Diabetic subjects were on oral hypoglycemic drugs. The subjects who were Smokers, on insulin treatment, having complications of Diabetes Mellitus, with history of Type 2 Diabetes Mellitus, liver diseases and lung diseases were all excluded

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from the study. The Anthropometric measurements, Fasting Plasma Glucose, Post Prandial Plasma Glucose, HbA1c and serum MMP-9 were all measured in these subjects.

Statistical Analysis: All statistical analysis was performed using SPSS statistics version 20.0. The results are expressed as mean ± SD. Statistical difference between the control and Type 2 Diabetic Subjects were carried out using Student "t" test and p value of < 0.05 was considered to be statistically significant. Pearsons Correlation analysis was performed for assessing correlation of serum MMP-9 with HbA1c in Type 2 Diabetic Subjects.

III. RESULTS

Table I shows the Anthropometric and Biochemical characteristics of healthy controls and Type 2 Diabetic Subjects.

Table II shows the Correlation Statistics between serum MMP-9 and HbA1c levels in Type 2 Diabetic Subjects.

The controls and Type 2 Diabetic Subjects were of same age group and no significant difference was observed between the groups. Blood pressure and BMI were significantly higher Type 2 Diabetic Subjects than the control group (p<0.01). Fasting plasma glucose, Post prandial plasma glucose, HbA1c & serum MMP-9 were all significantly higher in Type 2 Diabetic Subjects than the control group (p<0.01). In Type 2 Diabetic Subjects the Correlation between serum MMP-9 level and HbA1c revealed a highly significant (p<0.01) positive correlation (r=0.61).

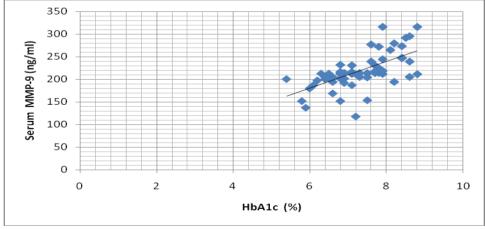**Table I: Comparison of Anthropometric and Biochemical charecteristics between Type 2 Diabetic Subjects & Controls.**

Parameters	Controls (n=100) Mean±SD	Type 2 Diabetic Subjects (n=100) Mean±SD	p-Value
Age (years)	53.08±6.55	53.14±6.50	0.951
Systolic Blood pressure (mm/Hg)	124.25±10.74	129.03±14.4	p<0.01
Diastolic Blood pressure (mm/Hg)	79.8±4.8	86.5±5.7	p<0.01
BMI	22.26±3.84	23.73±3.65	P<0.01
Fasting Plasma Glucose (mg/dl)	90.84±12.77	138.33±45.36	p<0.01
Post Prandial Plasma Glucose (mg/dl)	129.11±13.53	189.92±53.93	p<0.01
HbA1c (%)	5.42±0.85	7.47±1.01	p<0.01
Serum MMP-9 (ng/ml)	144.75±47.32	223.60±56.61	p<0.01

Table II: Correlation between Serum MMP-9 and HbA1c levels in Type 2 Diabetic Subjects

Variables	Type 2 Diabetic Subjects (r Value)	p-Value
Serum MMP-9 and HbA1c	0.61	p<0.01

Fig.1 Correlation between Serum MMP-9 and HbA1c levels in Type 2 Diabetic Subjects.

IV.Discussion:

The present study was carried out to assess serum MMP-9 and HbA1c levels in Type 2 Diabetic Subjects and to explore the possible association between them. The participants in both study groups were of same age group (53.08±6.55 and 53.14±6.50) and no significant difference was observed between the groups (p>0.05). All the Type 2 Diabetic subjects were on Oral hypoglycemic drug therapy. In the present study we observed a significantly higher level of BMI in Type 2 Diabetic Subjects when compared to controls. This might

be due to the presence of decreased insulin sensitivity in diabetes [9]. While both the study groups were found to be normotensive, a significant increase was reported in Systolic Blood Pressure and Diastolic Blood Pressure in Type 2 Diabetic Subjects when compared to controls. Elevated blood pressure is a common finding in type 2 Diabetes Mellitus and this reflects the impact of the insulin resistance over the vasculature and kidney [10]. The mean fasting and post prandial plasma glucose levels and HbA1c were all significantly higher in Type 2 Diabetics when compared to healthy controls. This indicates the poor control of blood sugar in Diabetic population.

In the present study, serum MMP-9 level was significantly higher in Type 2 Diabetic Subjects on comparison with the control group. Similar observation was done by Ebihara *et al* (1998) in their study [11], however Lee et al (2005) in their study showed that serum MMP-9 levels were significantly lower in Diabetic Subjects than in control group. This discrepancy might be due to the fact that most of the Diabetic subjects enrolled in that study were having the Diabetic history of less than three years and had mild Diabetic complications if present [12]. Increased serum MMP-9 activity in our study reflects abnormal ECM metabolism in Type 2 Diabetes, causing increased production of   ECM proteins. These ECM proteins get deposited in all tissues affected by Diabetic complications, ultimately leading to organ damage and dysfunction [13].

The possible mechanisms by which serum MMP-9 level is increased in Diabetes may be due to the presence of chronic hyperglycemia which may cause up regulation of MMP-9 promoter region and mRNA thereby leading to increased levels of matrix metallo proteinase-9 in circulation [14]. Hyperinsulinemia which is observed in Type 2 Diabetic subjects can also act as a potential inducer by increasing the production of MMP-9 activity [15]. Oxidative stress generated in vascular endothelial cells could also increase the expression and activity of MMP-9 in Diabetes [14]. Additionally factors associated with Diabetes such as obesity or hypertriglyceridemia may also increase MMP-9 activity in Type 2 Diabetes [16].

A statistically highly significant ($p<0.01$) positive correlation was observed between serum MMP-9 and HbA1c levels in our study ($r=0.61$). This was consistent with the findings of Lewandowski et al (2011) [17]. Our study supports the possibility that hyperglycemia-induced up regulation of MMP-9 to be the reason for increased MMP-9 activity in Type 2 Diabetes. Hence tight glycemic control should be considered as a goal to prevent chronic complications in Diabetes Mellitus. In conclusion, serum MMP-9 is strongly associated with glycemic control and it could be a useful diagnostic biomarker for assessing long term complications in Diabetes.

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