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Original Article

Serum MMP-9 as a Novel Indicator of Complications in Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: As per IDF atlas 2025, India accounts for 1 in 7 of all adults living with diabetes worldwide. Diabetes mellitus is a pro-Inflammatory state predisposing to many complications like atherosclerosis, retinopathy, neuropathy, vasculopathy and nephropathy. General analogy is that hyperglycaemia predisposes to complications. But in practice, a lot of patients with poor glycaemic control still present with minimal or no complications. Multitude of factors, together influence the development of these complications. Matrix Metallo Proteinase 9 (MMP 9) is a type IV collagenase. Metabolic dysregulation results in excessive production of MMP 9, which results in the development of these complications, in Type 2 Diabetes mellitus patients.
Aim: To estimate Serum MMP 9 levels in type 2 diabetes mellitus patients with complications like neuropathy, nephropathy and diabetic foot.
Methods: A case control study was designed. 50 type 2 diabetes Mellitus patients, each, with and without pre-existing complications were selected. Baseline investigations included FBS, PPBS, HbA1c, Urea, Creatinine, FRAP, TBARS, Serum Insulin along with Serum MMP 9.
Results: Serum MMP 9 levels were elevated in Type 2 Diabetes Mellitus patients with complications (15634.40 ± 1067.94) when compared with Type 2 Diabetes Mellitus patients without any complications (7812.61 ± 533.92). P value is less than 0.0001 and is statistically significant.
Conclusion: More than 70 % of diabetes Mellitus patients experience one or other complications in their lifetime. A nexus of hyperglycaemia, oxidative stress and chronic inflammation predisposes to excessive serum MMP 9. This hastens the development of complications. Hence, monitoring Serum MMP 9 levels will help in predicting the development of complications in Type 2 diabetes Mellitus patients.

Keywords: *Type 2 Diabetes Mellitus; Matrix Metalloproteinase-9; Diabetic Complications*

INTRODUCTION

As per IDF atlas 2025, 588.7 million people around the world are diabetics, out of which South east Asia alone has 106.9 million diabetics. India accounts for 1 in 7 of all adults living with diabetes worldwide. Type 2 diabetes is the most common type of diabetes, accounting for over 90% of all diabetes worldwide. It is currently the 8th leading cause of disease burden globally and estimated to become the second leading cause by 2050[2]. Diabetes mellitus is a pro-Inflammatory state predisposing to many complications like atherosclerosis, retinopathy, neuropathy, vasculopathy and nephropathy. Hyperglycaemia is one of the main feature of the disease, and it generates damage to the vascular system, nerves, eyes, kidneys, and heart[3]. General analogy is that hyperglycaemia predisposes to complications. But a fair number of patients with tight glycaemic control, end up with complications.

Matrix Metallo Proteinase 9 (MMP 9) is a type IV collagenase. This is involved in degradation and remodelling of extracellular matrix (ECM)[4]. Recent studies reveal that MMP 9 can regulate chemokines and cytokines synthesis, thus participating in innate immunity processes, inflammation, and angiogenesis[5]. Pathological induction of MMP synthesis is associated with an imbalance between synthesis and degradation of ECM proteins leading to ECM degradation[5].

Past hyperglycemia triggers several **persistent biochemical and molecular changes** that continue to drive tissue damage—even when blood sugar is normalized. **Epigenetic modifications** (e.g., histone methylation/acetylation) in vascular and immune cells persist after glucose normalization[6].

Monocytes and Macrophages exposed to high glucose develop a pro-inflammatory "trained" phenotype[6]. This programming results from epigenetic changes—alterations to DNA and histone markers that do not revert when glucose is normalized. Transient hyperglycemia increases methylation of S100A9/A12 promoters in macrophages, sustaining pro-inflammatory gene expression [7]. These immune cells remain more likely to secrete inflammatory cytokines (like TNF-α, IL-6) in response to triggers, even after achieving normoglycemia[6]. High glucose can induce long-term changes in bone marrow stem and progenitor cells, causing subsequent generations of immune cells to retain a pro-inflammatory, hyperresponsive state. Hence a state of chronic low-grade inflammation exists.

Cytokines such as TNF-α, IL -1β and IL-6 activate transcription factors like **NF-κB** and **AP-1** in target cells (e.g., monocytes, macrophages, fibroblasts, and glial cells). Activation of these transcription factors leads to increased transcription of the MMP-9 gene and higher MMP-9 protein synthesis[8].

Hyperglycemic spikes rapidly increase MMP-9 levels by generating oxidative stress, activating key transcription factors (especially AP-1 via the MAPK/ERK pathway), and enhancing pro-inflammatory signaling[9].

All these factors lead to a state of chronic metabolic dysregulation, results in excessive production of MMP 9, which results in the development of these complications, in Type 2 Diabetes mellitus patients. Hence monitoring inflammatory status is key in predicting the development of complications, in addition to routine blood glucose monitoring.

Earlier studies have observed a positive correlation between serum MMP 9 levels and complications in type 2 diabetes mellitus. Hence in this study we evaluated serum MMP 9 levels in Type 2 Diabetes Mellitus patients with and without complications.

MATERIALS AND METHODS

This is a case control study conducted in the department of biochemistry, Government Medical college, Nagapattinam between the period of March 2024 and April 2025. Ethical approval was obtained from the institutional human ethical committee. Written informed consent was obtained from all the study subjects.

Study protocol and laboratory analysis

The study comprised of two groups with 50 subjects in each group.

Group A included type 2 diabetic patients with pre-existing complications like neuropathy, nephropathy and diabetic foot (wound culture negative).

Group B included type 2 diabetic patients without any preexisting complications. All the patients were aged between 35 to 65 years. Diabetic patients on insulin treatment, infectious and inflammatory conditions, neoplasia, hypo/hyperthyroidism, pregnancy were excluded from the study.

All the patients had Type 2 Diabetes Mellitus for a duration of 5 to 20 years.

Baseline demographics and clinical data were collected after obtaining informed written consent from each study patients. 5 ml of blood was drawn as the study sample from all subjects in fasting state. 2 ml of blood was drawn in post prandial state (2 hours). Serum separation was done after centrifugation of the blood at room temperature, for 5 minutes, at 3000 rpm. The routine biochemical parameters blood glucose, urea, creatinine were analysed using the auto-analyser (XL640). The remainder of the serum was analysed for MMP-9 (Booster Biotechnology Ltd., USA), and Insulin (DIAsource, Belgium) using commercially available ELISA kits and readings were taken using Biotech ELISA reader.

HOMA-IR was calculated using the formula:

HOMA-IR = [Fasting insulin (μIU/ml) × Fasting glucose (mg/dl)] / 405

FRAP were estimated colorimetrically using Benzie & srain method (1996)

TBARS was estimated using Mahfouz et al method (1986)

Statistical analysis

Statistical analysis was performed using Minitab software for Windows. The distribution of continuous data was calculated and expressed as median with interquartile range. The comparisons of these variables between the groups were done by using Mann Whitney U test. The correlation analysis between variables were done by Spearman's correlation. All statistical tests were two-tailed and $p < 0.05$ were considered statistically significant.

Results

Baseline demographic data of study subjects

The baseline characteristics compared between the study groups are given in **Table 1.**

Biochemical parameters of study subjects
The comparison of biochemical parameters of the cases and controls are given in **Table 2.** Group A has higher serum levels of fasting serum glucose, post prandial glucose, urea, creatinine, HbA1c in comparison to Group B.

Special serum parameters assayed between the study groups
Table 3 shows the results of comparison made between the major study parameters of the case and control groups. FRAP, TBARS, MMP-9, Insulin, and HOMA-IR levels of Group A are higher than that of controls. and show statistically significant difference.

Sub-group analysis of Special serum parameters within cases
Table 4 contains comparison data for special study parameters between the three sub-groups in the Group A with different complications like Neuropathy, Nephropathy and Diabetic Foot.

GROUP A = Type 2 DM patients with complications
GROUP B = Type 2 DM patients without complications

Baseline demographic data of study subjects

PARAMETER	GROUP A (mean ± SD)	GROUP B (Mean ± SD)
Age	50.5 ± 8.10	49.9 ± 7.20
Duration of diabetes(yrs)	12 ± 5	11 ± 2

3.2. Biochemical parameters of study subjects

PARAMETER	GROUP A	GROUP B
FBS(mg/dl)	122.5 ± 14.6	105.37 ± 10.75
PPBS(mg/dl)	152.12 ± 25.23	139.5 ± 11.88
HbA1c %	6.5 ± 0.5	6.1 ± 0.3
Urea(mg/dL)	34 .2 ± 3.8	28 . 02 ± 4.6
Serum Creatinine (mg/dL)	0.94 ± 0.21	0.87 ± 0.11

3.3. Special serum parameters assayed between the study groups

PARAMETER	GROUP A	GROUP B
TBARS(µmoles/L)	4.14 ± 0.61	2.88 ± 0.23
FRAP(µmoles/L)	2046.3 ± 189.8	2208.8 ± 168
Serum Insulin (mIU/L)	38.43 ± 5.05	29.07 ± 2.46
HOMA IR	8.90 ± 1.43	6.65 ± 1.30
Serum MMP 9 (pg/mL)	15634.40 ± 1067.94	7812.61 ± 533.92

3.4. Sub-group analysis of Special serum parameters within cases

Complications	No of patients	Duration of Diabetes (Years)
Diabetic Neuropathy	32	12 ± 3
Diabetic Nephropathy	9	11 ± 4
Diabetic Foot	11	15 ± 2

Complications	Serum MMP 9 (pg/mL)	TBARS (µmoles/L)	FRAP (µmoles/L)
Diabetic Neuropathy	15250.50 ± 949.2	3.76 ± 0.54	2074.20 ± 155.14
Diabetic Nephropathy	11244.89 ± 902.5	3.86 ± 0.62	1940.34 ± 145.17
Diabetic Foot	17486.20 ± 1103.7	4.44 ± 0.61	2055.22 ± 105.13

DISCUSSION
In Type 2 diabetes, presence of insulin resistance prompts an increase in insulin production, which, over time, may result in inadequate insulin production as pancreatic beta cells fail to keep up with demand[1]. The lack of symptoms makes the exact time of the onset of type 2 diabetes difficult or impossible to determine. As a result, there is often a long period before the diabetes is diagnosed. At any given time, as many as one-third to one-half of people with type 2 diabetes in the

population may be undiagnosed[10]. If the diagnosis is delayed for a prolonged time, complications may develop. Many are diagnosed because they already have one or more of the complications associated with the condition[11].

Earlier studies showed elevated serum levels of MMP-9 as a feature of Type 2 diabetes[12,13]. In our study, the serum MMP 9 levels were significantly elevated in group A when compared with group B. Serum MMP 9 levels showed positive correlation with development of complications. As discussed already, several factors contribute to a state of chronic low-grade inflammation in type 2 diabetes mellitus, apart from blood glucose spikes. This results in elevated serum MMP 9 levels.

MMP-9 facilitates the infiltration of leukocytes into the neuronal cells, degrading the myelin layer, and consequently, generating neuronal damage [14]. Research using rodent models of diabetic neuropathy has demonstrated that increased MMP-9 activity promotes axonal demyelination and neuropathic pain. Spinal inhibition or genetic deletion of MMP-9 significantly alleviates diabetic neuropathic pain, underscoring its pathogenic role[15]. MMP-9 Impairs Vasa Nervorum and Compromises Nerve Blood Supply resulting in neuronal ischaemia and subsequent neuropathy[15].

MMP-9 weakens the blood retinal barrier, by causing breakdown of the endothelial tight junction proteins, mainly, cadherin and occluding[27,28]. It is associated with diabetic vitreous haemorrhage, a feature observed in the later stages of DR[18]. It is a chief effector of neovascularization in the proliferative stage of DR[19]. MMP-9 is thus, an important mediator of retinal ischemia-induced angiogenesis and non-perfusion mediated tissue injury.

The trademark of the pathogenesis of Diabetic Nephropathy is increased extracellular matrix (ECM) accumulation causing thickening of the glomerular and tubular basement membranes, followed by mesangial expansion, sclerosis, and tubulointerstitial fibrosis[20]. The ECM levels are regulated by a homeostatic balance between deposition and degradation of ECM components[21]. MMP-9 has the ability to degrade type IV collagen, the major component of the glomerular basement membrane. concentrations and activity of MMP 9 is increased in urine of type 1 and 2 diabetic patients[22,23,24]. The increase in serum MMP 9 is especially frequent in patients with albuminuria, and has been correlated with an established renal injury.

High MMP-9 breaks down ECM proteins in wound areas, destabilizing tissue structure and preventing the formation of healthy granulation tissue required for wound repair. This catabolic activity leads to chronic wounds by perpetuating tissue destruction instead of healing[25]. Excess MMP-9 disrupts blood vessel integrity by degrading basement membranes, hampering angiogenesis, vital for wound healing. This results in poor oxygen and nutrient delivery to the tissue and promotes ischemia of the foot[26].

Consistent with above studies, our study also showed a positive correlation between elevated Serum MMP 9 and development of complications in Type 2 Diabetes Mellitus patients.

Also, the oxidative stress, as measured by TBARS and FRAP, is high in group A when compared with group B. Recent studies indicate that elevated glucose concentrations can induce dysfunction of several intracellular signal transduction cascades, including modulation of protein kinase C (PKC), activation of mitogen-activated protein kinase, generation of reactive oxygen species (ROS), and accumulation of advanced glycation end products (AGEs)[27,28]. MMPs are highly sensitive to oxidative stress, and they are induced by increase in reactive oxygen species (ROS)[29], possibly via direct oxidation of crucial cysteine residues
contained within the DNA-binding domain[30]. MMPs are also the prime nitric oxide
targets, and peroxynitrite, formed between ROS and nitric oxide can activate pro-MMPs via
interacting with cytosolic glutathione[31,32]. Our study also showed that there is a positive correlation between oxidative stress and serum MMP 9 levels.

Unlike traditional markers, such as HbA1c and fasting glucose, which reflect glycemic control, MMP-9 may capture ongoing pathological changes in the vascular and connective tissue environment independent of blood sugar levels. This supports the notion that tissue remodeling and inflammation are pivotal in the development of complications, and that MMP-9 could potentially serve as a biomarker for risk stratification in T2DM patients.

Conclusion

Chronic inflammation is the root cause of all the complications in diabetes mellitus. Several factors play a vital role in influencing the development of complications. A nexus of hyperglycemia, oxidative stress, advanced glycation end products, Poor Dietary habits, physical inactivity and ageing not only lead to development of inflammation but also sustain it. Hence Serum MMP 9 a marker of inflammation would serve as a novel indicator of development of complications in Type 2 Diabetes Mellitus patients.

Conflict of Interest: Nil

DECLARATION

Conflicts of interests: The authors declare no conflicts of interest.

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