Matrix Metalloproteinase 2 and Interleukin 29 as Novel Biochemical Markers for Neurovascular Complications among Type 2 Diabetic Elderly Patients

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ABSTRACT

Background: It is still challenging to detect neurovascular disorders in their early phases. This was accomplished by looking at the correlations between microangiopathy rates in adult diabetic patients and serum levels of Matrix Metalloproteinase 2 (MMP-2) and Interleukin-29 (IL-29). **Objective:** This study aimed to assess the relation of MMP-2 and Il-29 with neurovascular complications among diabetic patients and the use of this relation to plan for therapeutic intervention in the future. **Patients and methods:** This case control study included 147 participants who were allocated into 3 groups. Group I control group (non-diabetic), group II included type 2 diabetic patients without neurovascular complications and group III that contained type 2 diabetic patients with neurovascular complications. The MMP-2 and Il-29 were assessed among all participants. **Results:** In terms of MMP2 and IL-29, there was a statistically significant difference between the groups that were examined. Group III had significantly higher levels of MMP2 and IL-29 than groups I and II, according to the post hoc test. Additionally, MMP2 and IL-19 levels were significantly higher in group II than in group I. IL-29 had a sensitivity of 98%, specificity of 89.8%, and accuracy of 93.9% in diagnosing neurovascular complications among DM cases when the cutoff was more than 1945 pg/ml, whereas MMP2 had a sensitivity of 98%, specificity of 91.8%, and accuracy of 94.9% when the cutoff was more than 155 ng/ml. **Conclusion:** Two new biochemical markers that showed promise for the evaluation of neurovascular problems in older patients with type 2 diabetes are Matrix Metalloproteinase 2 and Interleukin-29. Vascular remodeling was linked to elevated MMP-2 levels. Neurovascular problems are more likely and more severe in individuals with type 2 diabetes who had elevated IL-29 levels.

Keywords: Matrix metalloproteinase 2, Interleukin-29.

INTRODUCTION

A malfunction in insulin synthesis, insulin action, or both can lead to hyperglycemia, a symptom shared by a group of metabolic diseases known collectively as diabetes mellitus. Microvascular complications in the long run are associated with diabetes-related chronic hyperglycemia [1]. People who have type 2 diabetes often experience microangiopathic complications [2]. Among the many complications of diabetes include diabetic retinopathy, microangiopathy, diabetic kidney disease, peripheral and autonomic neuropathy, and diabetic neuropathy. It is critical to discover complications in diabetic patients early on so that they can maintain a high quality of life and a life expectancy comparable to the general population. Despite advances in illness prevention and treatment, neurovascular complications do occur from time to time [3].

Varicose vein endothelial growth factor (VEGF) and similar growth factors control this [4]. Nonetheless, its principal use has been called into doubt by other media. Inflammasomes such as tumour necrosis factor and interleukin-6 (IL-6) are released when new blood vessels form or when the endothelium is damaged [5].

Our understanding of glucotoxicity has been enhanced by studies conducted on neurons as well as endothelial cells. Intracellular high glucose concentration induced the same oxidative stress pathways in reaction to hyperglycemia. Both diabetic neuropathy and retinopathy are known to be influenced by the neurodegenerative process. Neurovascular complications are the new nomenclature for microvascular complications [6]. The matrix collagen, elastin, gelatin, and laminin are just a few examples of the extracellular matrix components that can be broken down by metalloproteinases (MMPs). Gelatinase A, or matrix metalloproteinase 2, is another name for this enzyme [7]. Research on the potential benefits of this enzyme for diabetic individuals was conducted. In order to diagnose microvascular disease, MMP-2 levels should be evaluated in patients [8].

The interferon lambda (IFN-) family has gained a new member: interleukin-29 (IL-29, IFN-1). In reaction to autoimmune disorders and viral infections, dendritic cells and macrophages create IL-29. Psoriasis, systemic sclerosis, rheumatoid arthritis, Sjögren syndrome, and other autoimmune illnesses were found to have elevated IL-29 levels. It is still challenging to detect neurovascular disorders in their early phases[10-13].

This work aimed to assess the relationship between Metalloproteinase 2 and Interleukin-29 with Neurovascular complications among diabetic elderly patients and the use of this relationship to plan for therapeutic intervention in the future to determine diagnostic and therapeutic values of the two markers in diabetic elderly patients.

PATIENTS AND METHODS

This case control study was conducted on 147 participants presented to the Zagazig University Internal Medicine Department during the period from February 2022 to October 2022.

Inclusion criteria: Patients aged ≥ 65 years old, of both sexes, diagnosed with type 2 diabetes mellitus of 5 years or more.

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Exclusion criteria: The estimated glomerular filtration rate (eGFR) is below 30 mL/min/ 1.73 m^2. Alanine transaminase (ALT) or aspartate transaminase (AST) was 1.5 times above the upper limit of normal. Symptoms or a high-sensitivity C-reactive protein (hsCRP) level of more than 10 mg/L indicate acute inflammation. Type 2 diabetes < 5 years, neoplasm, or autoimmune disease-related ketoacidosis or ketonurea. Other conditions that could lead to exclusion include infections, heart failure, hematuria, and excessive physical activity.

Participants were divided into 3 groups: Group I: Control group (non-diabetic), **group II**: Type 2 diabetic patients without neurovascular complications, and **group III**: Type 2 diabetic patients with neurovascular complications.

All patients included in this study were subjected to the following: Every possible detail was recorded. Analysis of the patient's vitals, weight, body mass index, and conduction of a thorough physical examination. A basic physical examination was conducted for each participant, which comprised taking their anthropometric measurements and blood pressure readings. Risk assessment for neurovascular complications.

Patients were separated into two groups based on whether they have microangiopathy or not. For microangiopathy to be diagnosed, a patient must exhibit one or more of the following symptoms: Neuropathy (both peripheral and autonomic), diabetic retinopathy or diabetic kidney disease [3, 14]. An evaluation of 24-hour urine albumin excretion (in mg) or a random albumin/creatinine ratio (in mg/g) was used to diagnosis diabetic kidney disease when no other notable causes of kidney damage were found [15].

When the albumin to creatinine ratio in the urine was less than 30 mg/g over 24 hours, or when the albumin excretion in the urine was less than 30 mg/24 hours, it was considered normoalbuminuric [16]. The patient underwent a comprehensive eye exam with dilated pupils and direct ophthalmoscopy in accordance with standards set by the American Academy of Ophthalmology [17].

In this study, the following categories of results were used: There are three types of retinopathies: No retinopathy, non-proliferative retinopathy, and proliferative retinopathy [18]. Diabetic peripheral neuropathy was diagnosed using diagnostic criteria developed by the American Diabetes Association [19].

Laboratory investigations including:

(A) Routine investigations in the form of: eGFR (We utilised the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) model. This calculation takes into consideration factors including age, sex, and serum creatinine concentration). Glycated haemoglobin (HbA1c) in whole blood. ALT or AST enzyme. HDL, LDL, total cholesterol, and triglycerides. HsCRP stands for high-sensitivity C-reactive protein. Creatinine to albumin ratio in urine.

(B) Special investigations in the form of: **(1) Serum Metalloproteinase 2** (Measured by Human Matrix Metalloproteinase 2 (MMP2) ELISA Kit). **(2) Serum Interleukin 29** (Measured by Human Interleukin 29 (IL29) ELISA Kit). R & D Systems of Minneapolis, MN, USA created the enzyme-linked immunosorbent assay (ELISA) to detect MMP-2 (gelatinase A) concentrations in serum samples. Both active and inactive forms of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) can be detected by monoclonal antibodies.

Ethical approval: The Ethics Committee of Mansoura Faculty of Medicine authorized this study. After receiving all of the information, each participant signed their permission. The Helsinki Declaration was followed throughout the course of the investigation.

Statistical analysis

We used Microsoft Excel 365 to compile and tabulate all of the data before doing any statistical analysis. Research was then conducted using SPSS version 25.0 for Windows, developed by SPSS Inc. of Chicago, IL, USA. To represent quantitative values, the median (range) and mean ± standard deviation were utilised. We used the X^2- test to compare the different types of data. The variables were compared using the non-parametric Mann-Whitney U (M-W) test in two case subgroups and between the case and control groups. We used Kruskall-Wallis's test (K-W) for comparisons with more than two case subgroups. We utilised the Spearman coefficient to determine the relationship between MMP2 and IL-29 and the following laboratory variables: HbA1c, cholesterol, HDL, LDL, TG, ALT, AST, creatinine, and ACR. Statistical significance was determined by the applicable test at a 95% confidence interval and a p-value ≤ 0.05.

RESULTS

In terms of age, weight, height, body mass index (BMI), sex distribution, and smoking, no statistically significant differences were found between the studied groups. HbA1c, cholesterol, HDL, LDL, and TG were all significantly different amongst the groups that were evaluated. Group III had significantly higher levels of HbA1c, cholesterol, LDL, and TG than in groups I and II, according to the post hoc test. Additionally, when comparing group I to group III, a statistically significant decline in HDL was noted. When comparing group II to group I, results showed that HbA1c, cholesterol, LDL, and TG levels increased significantly. Comparing the tested groups, we found that ALT, AST, creatinine, ACR, and EGFR levels were significantly different. The results of the post hoc test showed that compared to groups I and II, group III had lower eGFR levels and considerably higher ALT, AST, creatinine, and ACR levels (Table 1).

Table (1): Distribution of the studied groups regarding demographic data, blood sugar, lipid profile results, LFTs & KFTs

Variable		Group I (Control) (*n*=49)		Group II (DM) (*n*=49)		Group III (DM+NVcom.) (*n*=49)		F	P
Age: (years)	*Mean ± SD* *Range*	67.96±2.57 65-75		66.41±1.54 65-70		70.57±3.69 65-81		2.**71**	0.07 NS
Weight: (kg)	*Mean ± SD* *Range*	78.02±2.71 75-82		82.35±4.47 76-90		80.24±5.89 68-90		2.88	0.06 NS
Height: (cm)	*Mean ± SD* *Range*	165.51±4.39 159-170		167.29±3.40 160-175		166.76±4.39 159-185		2.44	0.09 NS
BMI: (Kg/m^2)	*Mean ± SD* *Range*	28.31±1.76 26-30.9		29.52±2.35 26.3-33.2		29.25±2.17 26-33.1		2.50	0.08 NS
Variable		**No**	**%**	**No**	**%**	**No**	**%**	χ^2	**P**
Sex:	*Female* *Male*	24 25	49 51	26 23	53.1 46.9	25 24	51 49	0.16	0.92 NS
Smoking:	*No* *Yes* *Ex-smoker*	30 18 1	61.2 36.7 2	31 18 0	63.3 36.7 0	31 17 1	63.3 34.7 2	1.06	0.90 NS

Variable		Group I (Control) (*n*=49)	Group II (DM) (*n*=49)	Group III (DM+NVcom.) (*n*=49)	F	P	Post Hoc
HbA1c: (%)	*Mean ± SD*	5.74±0.41	7.44±0.41	10.22±0.76	**816.3**	**<0.001****	**<0.001**^{1}** **<0.001**^{2}** **<0.001**^{3}**
Cholesterol: (mg/dl)	*Mean ± SD*	167.14±10.99	249.39±21.69	300.41±14.93	**816.4**	**<0.001****	**<0.001**^{1}** **<0.001**^{2}** **<0.001**^{3}**
HDL: (mg/dl)	*Mean ± SD*	55.41±5.81	53.67±6.87	49.9±8.07	**7.99**	**0.001 ***	0.44 NS^1 **<0.001**^{2}** **0.02*^{3}**
LDL: (mg/dl)	*Mean ± SD*	98.31±10.21	182.24±16.08	220.78±27.27	**521.08**	**<0.001 ****	**<0.001**^{1}** **<0.001**^{2}** **<0.001**^{3}**
Triglyceride: (mg/dl)	*Mean ± SD*	134.08±18.59	178.98±19.87	199.02±39.72	**49.02**	**<0.001****	**<0.001**^{1}** **<0.001**^{2}** **0.009*^{3}**
ALT: (U/L)	*Mean ± SD*	25.14±6.10	25.50±6.11	36.33±8.98	**24.21**	**<0.001 ****	0.92 NS^1 **0.02*^{2}** **0.02*^{3}**
AST: (U/L)	*Mean ± SD*	22.89±5.71	22.91±5.68	26.51±6.61	**4.97**	**0.008***	0.99 NS^1 **0.02*^{2}** **0.02*^{3}**
Creatinine: (mg/dl)	*Mean ± SD*	0.93±0.13	0.94±0.15	1.26±0.21	**62.96**	**<0.001 ****	0.99 NS^1 **<0.001**^{2}** **<0.001**^{3}**
Al/Cr ratio: (mg/g)	*Mean ± SD*	19.44±4.71	18.84±4.43	288.8±71.80	**586.7**	**<0.001****	0.99 NS^1 **<0.001**^{2}** **<0.001**^{3}**
EGFR: (ml/min/1.73 m^2)	*Mean ± SD*	77.53±9.75	78.88±12.88	54.84±10.61	**71.82**	**<0.001****	0.82 NS^1 **<0.001**^{2}** **<0.001**^{3}**
CRP: (mg/dl)	*Mean ± SD*	6.43±1.51	6.29±1.50	6.29±1.52	0.12	0.94 NS	-----

SD: Stander deviation, F: ANOVA test, χ^2: Chai square test. NS: Non -significant (P>0.05). F: ANOVA test. KW: Kruskal Wallis test. Post-hoc: Tukey test, Post-hoc: P1: Group I versus II, P2: Group I vesrus III P3: Group II versus III

Table (2) showed that the groups that were tested showed a highly significant difference in MMP2 and IL-29. Group III had considerably greater levels of MMP2 and IL-29 than groups I and II. Group II also had much greater levels of MMP2 and IL-19 compared to group I.

Table (2): Matrix metalloproteinase 2 and Interleukin 29 among the studied groups

Variable		Group I (Control) (*n*=49)	Group II (DM) (*n*=49)	Group III (DM+NVcom.) (*n*=49)	KW	P	Post Hoc
MMP2: (ng/ml)	*Median* *Range*	15 2-51	60 25-200	1800 150-3500	**124.9**	**<0.001 ****	**<0.001**[1]** **<0.001**[2]** **<0.001**[3]**
IL-29: (pg/ml)	*Median* *Range*	150 20-755	1200 300-2300	5600 1890-8010	**127**	**<0.001****	**<0.001**[1]** **<0.001**[2]** **<0.001**[3]**

KW: Kruskal Wallis test

Table (3) showed that group III patients who tested positive for MMP2 and IL-29 were also less likely to have renal complications.

Table (3): Relation between MMP2 and IL-29 & complications in group III

Variable		No	MMP2		MW	P
			Median	Range		
Retinopathy:	*Non-proliferative*	16	1950	160-2658	1.02	0.31
	Proliferative retinopathy	33	1800	150-3500		NS
Renal:	*Microalbuminuria*	26	1757	150-2914	**1.98**	**0.04***
	Macroalbuminuria	23	2000	171-3500		
Variable		**No**	**IL-29**		**MW**	**P**
			Median	**Range**		
Retinopathy:	*Non-proliferative*	16	5543.5	1890-80004	1.80	0.07
	Proliferative retinopathy	33	5700	2000-8010		NS
Renal:	*Microalbuminuria*	26	5404	1890-7400	**2.02**	**0.04***
	Macroalbuminuria	23	6001	2000-8010		

MW: Mann Whitney test KW: Kruskal Wallis test

Table (4) showed that MMP2 at cut off more than 155 ng/ml had sensitivity of 98%, specificity of 91.8% and accuracy of 94.9% in diagnosis of neurovascular complications among cases with DM, while IL-29 at cut off more than 1945 pg/ml performed very well in diagnosing neurovascular problems in DM cases, with a sensitivity of 98.2%, specificity of 89.8%, and accuracy of 93.9%.

Table (4): Validity of MMP2 & IL-29 for diagnosing neurovascular complications among the studied cases

Variable	Cut off	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	Accuracy	P
MMP2	>155	0.99 (0.98-1)	98%	91.8%	92.3%	97.8%	94.9%	**<0.001 ****
IL-29	>1945	0.99 (0.98-1)	98%	89.8%	90.6%	97.8%	93.9%	**<0.001 ****

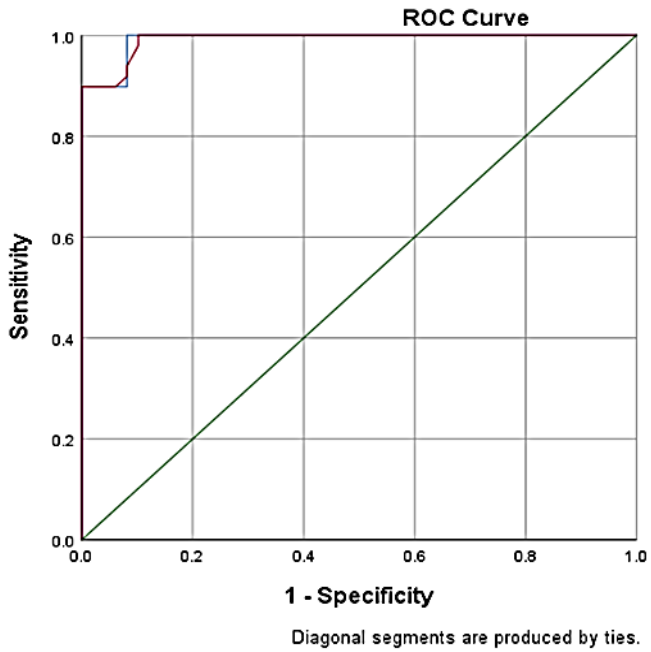

Figure (1): Roc curve for validity of MMP2 & IL-29 in diagnosis of neurovascular complications of DM among the studied cases groups.

DISCUSSION

The current study revealed that differences in age, weight, height, body mass index (BMI), sex distribution, and smoking status were not statistically significant among the groups that were analysed. Age was positively and statistically correlated with MMP2. When it came to age, sex, and body mass index, **Chung *et al.*** [20] also found no statistically significant differences between the groups they analysed. Unlikely, **Lewandowski *et al.*** [21] stated that neither age nor body mass index were associated with MMP concentrations in the control group. There was an inverse relationship between age and MMP-2 in diabetic individuals.

In the present study, we found that group III had a much longer duration of diabetes than group II, while there were no statistically significant changes in the prevalence of hypertension between the groups. The favourable connection between duration, IL-29, and MMP2 was statistically significant. **Falkowski *et al.*** [22] corroborates our findings by showing that groups with microangiopathy had a statistically significant longer duration of diabetes than groups without microangiopathy.

Comparing the groups in this study, we discovered that HbA1c, cholesterol, HDL, LDL, and TG were all significantly different. Group III had significantly higher levels of HbA1c, cholesterol, LDL, and TG than groups I and II according to the post hoc test. Additionally, when comparing group I to group III, a statistically significant decline in HDL was noted. Group II had significantly higher levels of HbA1c, cholesterol, LDL, and TG than group I. Among the groups of patients analysed, a positive association was found between MMP2, IL-29, and HbA1c, cholesterol, and LDL. **Yadav *et al.*** [23] corroborates our findings by stating that WC, FPG, TC, TG, HDL-C, and DBP were significantly correlated with the serum level of MMP2. **Sardarmelli *et al.*** [24] showed that diabetic individuals exhibited favourable correlations between IL-29 and HbA1c as well as FPG. **Chung *et al.*** [20] found no statistically significant change in HbA1c, cholesterol, HDL, LDL, or TG between the control and diabetes groups that were investigated.

Our current findings clearly revealed that in terms of MMP2 and IL-29, there was a highly significant difference between the groups that were examined. When comparing group III to groups I and II, the post hoc test revealed a significantly higher level of MMP2 and IL-29. Additionally, when comparing group II to group I, MMP2 and IL-19 levels were significantly higher in the latter. In group III, renal problems were statistically related to MMP2 and IL-29.

Concerning the validity of MMP2 and IL-29 in the diagnosis of neurovascular complications, we found that MMP2 at a cut-off of more than 155 ng/ml had a sensitivity of 98%, specificity of 91.8%, and accuracy of 94.9% in the diagnosis of neurovascular complications among cases with DM, while IL-29 at a cut-off of more than 1945 pg/ml had a sensitivity of 98%, specificity of 89.8%, and accuracy of 93.9% in the diagnosis of neurovascular complications among DM cases. **Yadav *et al.*** [23] found a much increased blood MMP-2 level in metabolic syndrome cases compared to the control group, which is in agreement with our findings. **Da**

s and Maiti [25] verified that the activities of matrix metalloproteinases were noticeably greater in the blood samples of people with diabetes compared to those without the disease.

Serum levels of matrix metalloproteinase-9 and matrix metalloproteinase-2 were considerably greater in type 2 diabetic participants than in control subjects. Based on these findings, patients with type 2 DM are at increased risk for developing peripheral artery disease, which can lead to cardiovascular complications, due to the elevated activity of MMP-2. **Sardarmelli *et al.*** [24] demonstrated significantly higher levels of IL-29 in patients compared to controls, which is in line with our findings. People with diabetes secrete more IL-29 from their T helper cells than healthy controls [24].

Concurrently, **Hao *et al.*** [13] showed that IL-29 is an inflammatory cytokine that promotes osteogenic transformation and calcification in vascular smooth muscle cells (VSMCs) when exposed to a calcification medium. In order to induce calcification and osteogenic transformation in VSMCs, it was demonstrated that IL-29 binding to its receptor IL-28Rα promotes the activation of JAK2/STAT3. This, in turn, upregulates Bone Morphogenetic Protein 2. They hypothesised that a potential method to lessen vascular calcification in patients could be to decrease

IL-29 signaling with synthetic, small-molecule inhibitors. Also, **Qi *et al.*** [26] demonstrated that in two-thirds of patients assessed, exposure to high glucose increased MMP-2 while TIMP-1 was reduced.

Chung *et al.* [20] demonstrated similar results to ours in diabetic arterial vasculature, capillary density is significantly reduced. Angiostatin expression is positively correlated with MMP-2 and -9 activities, VEFG165 levels are decreased, MMP-2 and -9 protein expressions and enzymatic activities are upregulated, and TIMP-1 and -2 are differentially regulated among other things. This supports our findings. These results provide potential molecular pathways by which diabetic vascular tissue perfusion is compromised, leading to vascular disease. Impairment of angiogenesis in diabetes may be a contributing factor. Also, **Death *et al.*** [27] stated that hyperglycemia disrupts MMP/TIMP regulation and enhances MMP-1, MMP-2, and MMP-9 activities in vascular cells, which in turn stimulates ECM degradation and leads to an imbalance in diabetes, suggesting that elevated MMP activity may begin the development of diabetic peripheral arterial disease.

Elevated plasma MMP-2 levels in diabetic patients may indicate aberrant extracellular matrix (ECM) metabolism, as demonstrated by **Derosa *et al.*** [28]**.** Under hyperglycaemic circumstances, diabetes cells and tissue have been found to have higher MMP levels, according to **Kadoglou *et al.*** [29].

Diabetes and hyperglycemia enhance matrix metalloproteinase (MMP) expression and activity via oxidative stress and advanced glycation end products. Plasma levels of matrix metalloproteinases (MMPs)-2 and MMP-1 are considerably increased in the subacute phase of acute coronary syndrome, according to **Hojo *et al.*** [30]. It is possible that these findings suggest that matrix metalloproteinases (MMPs) contribute to the breakdown of extracellular matrix (ECM), leading to ventricular remodeling after myocardial infarction. However, it was established by **Lewandowski *et al.*** [21] that individuals with type 2 diabetes had reduced amounts of MMP-2. Diabetes patients may have lower quantities of MMPs due to a number of variables. Statins, angiotensin-converting enzyme (ACE) inhibitors/AT-II blockers, calcium channel blockers, acetylsalicylic acid, and other drugs frequently taken by people with type 2 diabetes may have an impact on these variables. Macrophage MMP-2 and TIMP-1 secretion is decreased by calcium channel blockers, prostaglandin synthesis is decreased by acetylsalicylic acid, and pathogenic activation of MMPs is controlled by this compound [21].

The results for albumin creatinine ratio, estimated glomerular filtration rate, creatinine, and diabetic nephropathy were significantly different between the groups. Group III had significantly higher creatinine and ACR and significantly lower eGFR when compared to groups I and II, according to the post hoc test. Among the patient groups studied, statistical analysis showed a positive correlation between MMP2, IL-29, and ACR. In addition, the case groups that were analysed showed a statistically significant negative association between EGFR, MMP2, and IL-29. Lastly, microalbuminuria was found in slightly over 50% of group III instances, whereas macroalbuminuria was found in slightly under 50%. Consistent with our findings, **Falkowski *et al.*** [22] showed that 8% of the population has diabetic renal disease.

The pathophysiology of chronic kidney disease has been linked to MMP-2. **Aldemir *et al.*** [31] established that elevated production of MMP-2 causes kidney damage due to ischemia-reperfusion injury. Since MMP-2 alters the tubular basement membrane's structural integrity, it can induce glomerulosclerosis, tubular atrophy, and interstitial fibrosis, all of which are symptoms of kidney disease. Epigenetic regulatory studies have shown a potential association between albuminuria and TIMP-2 gene hypomethylation in patients with early diabetic nephropathy [31]. These findings are in line with those of **Kitsiou *et al.*** [32] who demonstrated that elevated glucose levels in the uremic medium can be associated with the elevated metalloproteinase activity and the reduced serum activity of the tissue inhibitors in diabetic nephropathy. Because it was demonstrated that endothelial cells and macrophages, two important sources of MMPs in peripheral blood, promote discordant MMP expression in response to elevated glucose, it follows that elevated glucose does not affect all types of MMPs evenly [32].

Prior to starting dialysis, patients with diabetic nephropathy had higher serum MMP-2 levels, as pointed out by **Rysz *et al.*** [33]. According to **Lobmann *et al.*** [34], a rise in MMP-2 levels may be associated with diabetic acute microangiopathic consequences.

CONCLUSION

Two new biochemical markers that show promise for evaluating neurovascular problems in older patients with type 2 diabetes are matrix metalloproteinase 2 (MMP-2) and interleukin-29 (IL-29). In type 2 diabetes, neurovascular problems can develop and worsen due to vascular remodeling, disruption of the blood-brain barrier, and neuroinflammation, all of which are linked to elevated levels of matrix metalloproteinase-2. Neurovascular problems, such as neuronal injury, neuroinflammation, and endothelial dysfunction may include IL-29 as a key player. Neurovascular problems are more common and more severe in individuals with type 2 diabetes who have elevated IL-29 levels.

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REFERENCES

1. **American Diabetes Association (2014):** Standards of Medical Care in Diabetes—2014. Diabetes Care, 37 (1): 14-80.

2. **American Diabetes Association (2014):** Diagnosis and Classification of Diabetes Mellitus. Diabetes Care, 37 (1): 81–90.
3. **Falkowski B, Rogowicz-Frontczak A, Szczepanek-Parulska E *et al.* (2020):** Novel Biochemical Markers of Neurovascular Complications in Type 1 Diabetes Patients. J Clin Med., 9 (1): 198. doi: 10.3390/jcm9010198
4. **Wegner M, Araszkiewicz A, Piorunska-Stolzmann M *et al.* (2013):** Association between IL-6 concentration and diabetes-related variables in DM1 patients with and without microvascular complications. Inflammation, 36 (3): 723–728.
5. **Araszkiewicz A, Zozulinska-Ziolkiewicz D (2016):** Retinal Neurodegeneration in the Course of Diabetes-Pathogenesis and Clinical Perspective. Curr Neuropharmacol., 14: 805–809.
6. **Chung A, Hsiang Y, Matzke L *et al.* (2006):** Reduced expression of vascular endothelial growth factor paralleled with the increased angiostatin expression resulting from the upregulated activities of matrix metalloproteinase-2 and-9 in human type 2 diabetic arterial vasculature. Circulation Research, 99 (2): 140-148.
7. **Cabral-Pacheco G, Garza-Veloz I, Castruita-De la Rosa C *et al.* (2020):** The roles of matrix metalloproteinases and their inhibitors in human diseases. Int J Mol Sci., 21 (24): 9739.
8. **Chung A, Rauniyar P, Luo H *et al.* (2005):** Pressure distention compared with pharmacological relaxation in vein grafting upregulates matrix metalloproteinase-2 and -9. J Vas Surg., 42: 747–756.
9. **Lazear H, Nice T, Diamond M (2015):** Interferon-lambda: Immune Functions at Barrier Surfaces and Beyond. Immunity, 43: 15–28.
10. **Dantas A, Gonçalves S, Pereira M *et al.* (2015):** Interferons and systemic sclerosis: Correlation between interferon gamma and interferon-lambda 1 (IL-29). Autoimmunity, 48: 429–433.
11. **Chang Q, Lv C, Zhao F *et al.* (2017):** Elevated Serum Levels of Interleukin-29 Are Associated with Disease Activity in Rheumatoid Arthritis Patients with Anti-Cyclic Citrullinated Peptide Antibodies. Tohoku J Exp Med., 241: 89–95.
12. **Ha Y, Choi Y, Kang E *et al.* (2018):** Increased expression of interferon-lambda in minor salivary glands of patients with primary Sjogren's syndrome and its synergic effect with interferon-alpha on salivary gland epithelial cells. Clin Exp Rheumatol., 36: 31–40.
13. **Hao N, Zhou Z, Zhang F *et al.* (2023):** Interleukin- 29 Accelerates Vascular Calcification via JAK2/STAT3/BMP2 Signaling. J Am Heart Assoc., 12 (1): e027222. doi: 10.1161/JAHA.122. 027222.
14. **American Diabetes Association (2020):** Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes—2020. Diabetes Care, 43: 135–151.
15. **Yang X, Feng S, Yu Y *et al.* (2018):** Study on the relationship between the methylation of the MMP-9 gene promoter region and diabetic nephropathy. Endokrynol Pol., 69: 269–275.
16. **Yang Q, Zhang Y, Yin H *et al.* (2020):** Topical recombinant human epidermal growth factor for diabetic foot ulcers: A meta-analysis of randomized controlled clinical trials. Ann Vasc Surg., 62: 442-451.
17. **Mrozikiewicz-Rakowska B, Łukawska M, Nehring P *et al.* (2018):** Genetic predictors associated with diabetic retinopathy in patients with diabetic foot. Pol Arch Intern Med., 128: 35–42.
18. **Pawlinski L, Gastol J, *et al.* (2019):** Is our treatment in type 1 diabetes mellitus (insulin therapy models, metabolic control) optimal for preventing cardiovascular autonomic neuropathy? Endokrynol Pol., 70: 323–329.
19. **American Diabetes Association (2020):** Standards of Medical Care in Diabetes—2020. Diabetes Care, 43 (1): 135–151.
20. **Chung A, Yang H, Sigrist M *et al.* (2009):** Matrix metalloproteinase-2 and-9 exacerbate arterial stiffening and angiogenesis in diabetes and chronic kidney disease. Cardiovasc Res., 84 (3): 494-504.
21. **Lewandowski K, Banach E, Bieńkiewicz M *et al.* (2011):** Matrix metalloproteinases in type 2 diabetes and non-diabetic controls: effects of short-term and chronic hyperglycaemia. Arch Med Sci., 7 (2): 294-303.
22. **Falkowski B, Rogowicz-Frontczak A, Grzelka A *et al.* (2018):** Higher free triiodothyronine concentration is associated with lower prevalence of microangiopathic complications and better metabolic control in adult euthyroid people with type 1 diabetes. Endocrine, 60 (3): 458–465.
23. **Yadav S, Mandal R, Singh M *et al.* (2016):** Cumulative risk of metabolic syndrome correlated with the coexistence of (-1306C/T) and altered circulating MMP2 level. Exp Clin Endocrinol Diabetes, 124: 380-384.
24. **Sardarmelli Z, Sheikh V, Solgi G *et al.* (2023):** Enhanced production of interleukin-29 and related genes are associated with T helper 1 cell parameters in patients with type 2 diabetes mellitus. Hum Immunol., 84 (3): 235-240.
25. **Das S, Maiti A (2013):** Matrix metalloproteinases in subjects with type 2 diabetes mellitus: pattern of MMP-2 and MMP-9 profile in diabetes mellitus Type-2 patients. Am Int J Res Formal Appl Nat Sci., 3 (1): 57-60.
26. **Qi W, Poronnik P, Young B *et al.* (2004):** Human cortical fibroblast responses to high glucose and hypoxia. Nephron Physiol., 96 (4): 121-129.
27. **Death A, Fisher E, McGrath K *et al.* (2003):** High glucose alters matrix metalloproteinase expression in two key vascular cells: potential impact on atherosclerosis in diabetes. Atherosclerosis, 168 (2): 263-269.
28. **Derosa G, D'Angelo A, Tinelli C *et al.* (2007):** Evaluation of metalloproteinase 2 and 9 levels and their inhibitors in diabetic and healthy subjects. Diabetes Metab., 33 (2): 129-134.
29. **Kadoglou N, Daskalopoulou S, Perrea D *et al.* (2005):** Matrix metalloproteinases and diabetic vascular complications. Angiology, 56 (2): 173-189.
30. **Hojo Y, Ikeda U, Ueno S *et al.* (2001):** Expression of matrix metalloproteinases in patients with acute myocardial infarction. Jpn Circ J., 65 (2): 71-75.
31. **Aldemir O, Turgut F, Gokce C *et al.* (2017):** The association between methylation levels of targeted genes and albuminuria in patients with early diabetic kidney disease. Renal Failure, 39 (1): 597-601.
32. **Kitsiou P, Tzinia A, Stetler-Stevenson W *et al.* (2003):** Glucose-induced changes in integrins and matrix-related functions in cultured human glomerular epithelial cells. Am J Physiol Renal Physiol., 284 (4): 671-679.
33. **Rysz J, Banach M, Stolarek R *et al.* (2007):** Serum matrix metalloproteinases MMP-2 and MMP-9 and metalloproteinase tissue inhibitors TIMP-1 and TIMP-2 in diabetic nephropathy. J Nephrol., 20 (4): 444-452.
34. **Lobmann R, Ambrosch A, Schultz G *et al.* (2002):** Expression of matrix-metalloproteinases and their inhibitors in the wounds of diabetic and non-diabetic patients. Diabetologia, 45: 1011-1016.