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Evaluation of Serum Immunoglobulin M levels in Healthy and Type 2 Diabetes mellitus patients with and without periodontitis: A case control study

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KEYWORDS

Bleeding on Probing, Clinical Attachment Loss, Periodontitis, Serum Immunoglobulin M, Type 2 Diabetes mellitus.

ABSTRACT:

Background/purpose: Advancement of periodontal disease was significantly higher in type II diabetic patients than in non-diabetic. The aim of the study was to assess the level of serum Immunoglobulin M (IgM) in healthy and type 2 diabetes mellitus (T2DM) patients with and without periodontitis.

Materials and methods: A total of 120 patients were selected in this comparative study and they were divided into 4 groups. Periodontitis patients with T2DM, T2DM without periodontitis, systemically healthy periodontitis patients and periodontally healthy controls. Probing depth (PD), Clinical attachment level (CAL), and Bleeding on probing (BOP), HbA1c and IgM level was assessed in all the 4 groups.

Results: The results showed statistically significant difference among the groups for all the clinical parameters except for BOP. It was seen that there was a significant difference in the level of IgM between periodontitis patient with type 2 DM and the healthy group. With the increase in PD and CAL there was a proportionate increase in IgM levels. This shows that increase in the severity of periodontal destruction escalates the level of immunoglobulins.

Conclusion: Summarizing the results we can state that IgM can be considered as an immunological biomarker for periodontitis and type 2 DM independently.

Introduction

Periodontitis is defined as a bacterial inflammatory process with the symptoms of clinical attachment level, formation of periodontal pockets and gingival recessions leading to destruction of alveolar bone.[1] It has been associated with many disease processes in the body like cardiovascular events,[2] respiratory disease,[3] diabetes mellitus (DM),[4] preeclampsia and preterm births,[5] chronic renal disease,[6] and rheumatoid arthritis.[7] Diabetes Mellitus is a risk factor for periodontitis.[8] Evidence by Lamster et al suggests that the periodontal changes could be the first clinical manifestation of Diabetes Mellitus[9] and periodontitis is the 6th major complication of Diabetes Mellitus. Loe et al in 1993 postulated that the frequency of advanced periodontal disease was significantly higher between type 2 diabetic patients than in non-diabetic patients.[10] The degree of

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glycaemic control is a key variable in relationship between Diabetes Mellitus and periodontitis. Evidence provided that type 1 and type 2 Diabetes Mellitus increase the risk and severity of periodontitis, and vice versa, periodontitis has been shown to have impact on diabetic status.[11] Hence, the association between DM and periodontal disease is considered to be bidirectional.

Immune mechanisms play an important role in the initiation and advancement of periodontal disease. Based on antigenic and physicochemical differences, 5 types of Immunoglobulins have been identified IgM, IgA, IgG, IgE and IgD[12]. Immunoglobulin M is the basic antibody produced by the B cells and is dominantly secreted during primary immune response. It is detected mostly in the serum of the host and is noticed as elevated level during acute and chronic infection.[13] By the activation of complement or opsonisation, phagocytosis and killing of oral microorganisms may be enhanced by IgM antibodies.[14] It has been suggested that this may show a response to certain specific Gram-negative microorganism[15] or compensation flora deficient cellular immune response.[16]

Hence, the need of the study is to assess the level of serum Immunoglobulin M in healthy and type 2 diabetes mellitus patients with and without periodontitis as there are contradictory results on this subject matter and this association would further explain immunological parameters in destruction of periodontal tissue in diabetes mellitus patients.

Materials and methods

Ethics approval

A case control study was carried out in the Department of Periodontology and the study was started after Institutional Ethics Committee approval was obtained (SVIEC/ON/Dent/BNPg15/D/6011). All the participants were informed in detail about the study and then informed consent was taken from them before starting the study.

Subject Selection

The Inclusion criteria were as follows: Participants with age group of 20-65 years, Participants should have minimum of 20 natural teeth, Participants should have generalized periodontitis stage II/ III and Grade B/C, Participants already diagnosed with type 2 diabetes mellitus with no other systemic diseases, Participants who are systemically and periodontally healthy for one of the groups.

The Exclusion criteria were as follows: Participants undergoing periodontal treatment in the preceding 6 months, Participants who have the habit of smoking and chewing tobacco, Participants who were on any antimicrobial treatment in the previous 6 months, Participants who are pregnant and lactating women.

Data Source

The diagnosis of periodontitis will be determined based on: Interdental Clinical attachment level 3-4 mm, Probing depth (PD) ≥ 5mm at three to four sites for > 4 teeth in each quadrant.[17]

The diagnosis of diabetes mellitus will be based on American Diabetes Association:[18] Fasting plasma glucose ≥ 126mg/dL, Glucose tolerance test ≥ 200mg/dL, HbA1c ≥ 6.5%.

In this research a case-control study was used where a case group and a control group was identified, with and without the concerned outcomes.[19] Cases were considered as Group 1 (Type 2 DM patients with periodontitis) and Group 3 (Systemically healthy patients with periodontitis) and controls were Group 2 (Type 2 DM patients without periodontitis) and Group 4 (Healthy subjects). 200 participants were screened for the study, out of which 80 participants were omitted as they did not match the inclusion and exclusion criteria. Therefore, 120 participants were divided into 4 groups. **(Fig 1)**
Clinical parameters checked includes: Probing depth (PD), Clinical attachment level (CAL), Bleeding on probing (BOP). PD and CAL were measured using a pressure sensitive probe. All clinical parameters were recorded by single examiner. Bleeding on Probing (BOP) is done by walking the probe around the gingival sulcus. BOP is considered positive if bleeding occurs 30 seconds after walking the probe. Six sites per tooth were examined in all teeth in the dentition (disto-buccal, mid-buccal, mesio-buccal, mesio-lingual, mid-lingual, disto-lingual). Lab investigations conducted were IgM immunoassay and HbA1c test.

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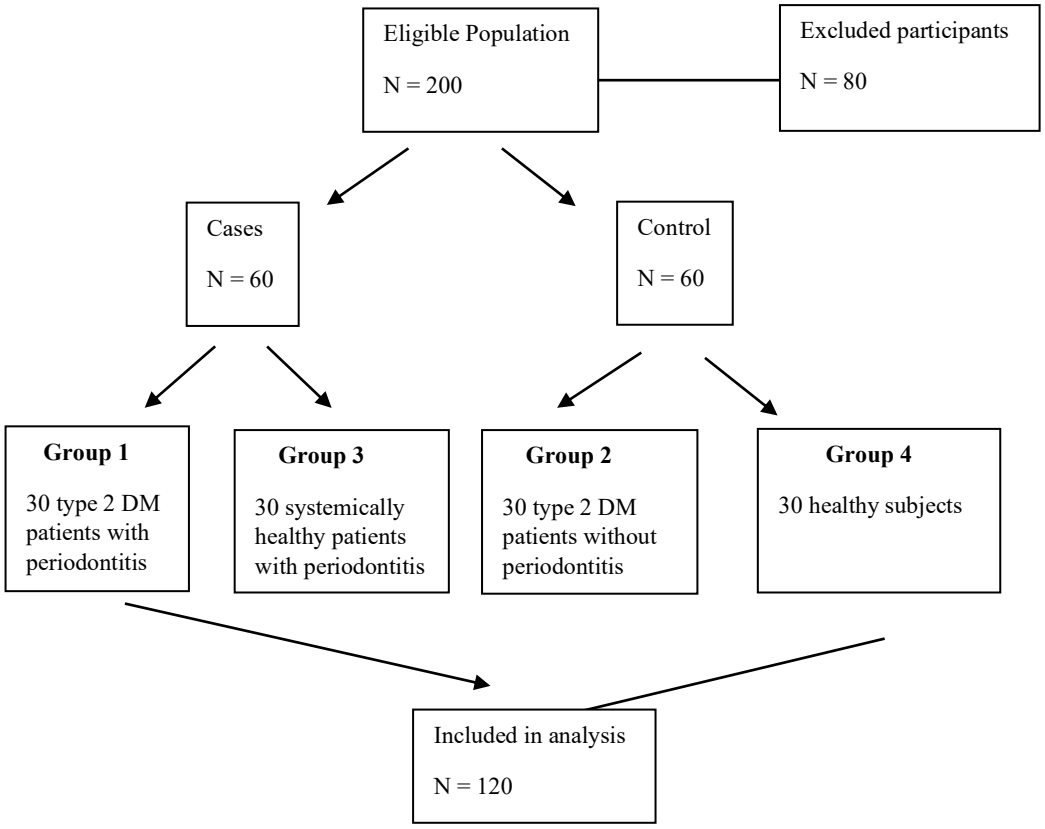

N = Number of participants

Figure 1 – STROBE flow diagram for case-control study

Lab investigations

For Immunoglobulin M immunoassay

The blood sample was collected in a sterile vacutainer with no added anticoagulant and was kept at room temperature for 2 hours, hence allowing it to clot than it was centrifuged at 2000 rpm for 5 to 10 minutes, and thus preparing it for serum IgM estimation. For turbidimetric immunoassay, Quantia IgM turbidimetric immunoassay was used. The test specimen was mixed with the R1 and R2 and allowed to react. Presence of IgM in the test specimen results in the formation of an insoluble complex producing a turbidity, which was measured at wavelength 340 nm.[20]

Sample description

Based on the study done by Kranthi J et al[21] minimum sample size required for the study was 108 (27 each group) to detect mean difference 1.9 between 4 groups with standard deviation of 1.65 at 1 % level of risk and 90 % power. Sample size was increased to 30 in each group to prevent follow up. [$N = 2*(Z*SD/d)^2 = 26.82 = 27$, with 95% CI and 80% power (ES effective size = 0.71)].

Statistical analysis

Descriptive analysis and inferential analysis were performed in this study. For intergroup analysis, one way ANOVA, Pearson's Chi-Square and Tukey's Post Hoc Test were performed. For association between clinical and biochemical parameters Pearson correlation test was done.

Results

A total of 120 patients were included in the study. The age of patients included in the study were 22-65 years

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with mean age of 39.49 ± 10.14. The results showed that there was a significant difference seen in age in between the groups with the p value < 0.001 and no difference in the gender. Probing depth and CAL showed significant difference between the type 2 DM patients with periodontitis and type 2 DM patients and healthy patients with the p value < 0.001. There was no statistically significant difference (p = 0.432) in between the groups for BOP. Significant difference was noted in HbA1c and IgM in between the groups with the p value 0.007 and < 0.001 respectively as seen in **Table 1.**

In **Supplementary Table 1** when Tukey's Post Hoc analysis was done the results showed type 2 DM patients with periodontitis exhibited statistically significant difference in the probing depth and CAL than the type 2 DM patients and healthy patients with the p value < 0.001. HbA1c level showed a significant difference in the patients with type 2 DM than the patients with periodontitis and healthy subjects with the p value 0.028 and 0.015 respectively. On comparison of the serum IgM levels periodontitis patients displays significant difference in the diabetes mellitus patients than healthy controls with the p value < 0.001. There is no significant difference of IgM levels between Group 1 and Group 3 which indicates periodontitis is a more influencing variable for the biomarker. Association between the clinical and biochemical parameters were done in which we found out that the probing depth and CAL is positively correlated with Immunoglobulin M level as seen in **Table 2** (p = 0.000).

Table 1: One Way ANOVA between groups

		Sum of Squares	df	Mean Square	F	p-value
Age	Between Groups	7983.15	3	2661.05	72.37	<0.001
	Within Groups	4264.83	116	36.76		
	Total	12247.99	119			
PD	Between Groups	180.18	3	60.06	281.53	<0.001
	Within Groups	24.74	116	0.21		
	Total	204.92	119			
CAL	Between Groups	804.92	3	268.30	1.30	<0.001
	Within Groups	23.77	116	0.20		
	Total	828.69	119			
BOP	Between Groups	187.47	3	62.49	0.92	0.432
	Within Groups	7858.33	116	67.74		
	Total	8045.81	119			
HbA1c	Between Groups	1035.79	3	345.26	4.24	0.007
	Within Groups	9428.71	116	81.28		
	Total	10464.50	119			
IgM	Between Groups	15742.93	3	5247.64	9.59	<0.001
	Within Groups	63446.73	116	546.95		
	Total	79189.66	119			

Note: PD: Probing Depth; CAL: Clinical attachment level; BOP: Bleeding on Probing; HbA1c: glycated hemoglobin; IgM: Serum Immunoglobulin M

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Table 2: Pearson's Correlation between parameters

Parameters		CAL	BOP	HbA1c	IGM
PD	Pearson Correlation	0.966**	-.094	-.054	0.439**
	P-value	0.000	0.308	0.559	0.000
	N	120	120	120	120
CAL	Pearson Correlation		-0.083	-.051	0.460**
	P-value		0.370	0.580	0.000
	N		120	120	120
BOP	Pearson Correlation			-.003	-.097
	P-value			0.977	.291
	N			120	120
HbA1c	Pearson Correlation				-.036
	P-value				0.693
	N				120

Note: PD: Probing Depth; CAL: Clinical attachment level; BOP: Bleeding on Probing; HbA1c: glycated hemoglobin; IgM: Serum Immunoglobulin M; **: Highly Significant

Dependent Variable	Group		Mean Difference	p-value	95% Confidence Interval	
					Lower Bound	Upper Bound
Age	Group-1	Group-2	9.53	<0.001	5.45	13.61
		Group-3	5.33	0.005	1.25	9.41
		Group-4	22.1	<0.001	18.02	26.18
	Group-2	Group-1	-9.53	<0.001	-13.61	-5.45
		Group-3	-4.2	0.041	-8.28	-0.12
		Group-4	12.56	<0.001	8.49	16.65
	Group-3	Group-1	-5.33	0.005	-9.41	-1.25
		Group-2	4.2	0.041	0.12	8.28
		Group-4	16.76	<0.001	12.69	20.85
	Group-4	Group-1	-22.1	<0.001	-26.18	-18.02
		Group-2	-12.56	<0.001	-16.65	-8.49
		Group-3	-16.76	<0.001	-20.85	-12.69
Probing depth	Group-1	Group-2	2.53	<0.001	2.22	2.84
		Group-3	0.07	0.916	-0.23	0.38
		Group-4	2.43	<0.001	2.12	2.74
	Group-2	Group-1	-2.53	<0.001	-2.84	-2.22
		Group-3	-2.46	<0.001	-2.77	-2.15
		Group-4	-0.1	0.825	-0.41	0.2

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	Group-3	Group-1	-0.07	0.916	-0.38	0.23
		Group-2	2.46	<0.001	2.15	2.77
		Group-4	2.35	<0.001	2.04	2.66
	Group-4	Group-1	-2.43	<0.001	-2.74	-2.12
		Group-2	0.1	0.825	-0.2	0.41
		Group-3	-2.35	<0.001	-2.66	-2.04
CAL	Group-1	Group-2	5.17	<0.001	4.86	5.47
		Group-3	-0.01	0.999	-0.32	0.28
		Group-4	5.17	<0.001	4.86	5.47
	Group-2	Group-1	-5.17	<0.001	-5.47	-4.86
		Group-3	-5.18	<0.001	-5.49	-4.88
		Group-4	0	1	-0.3	0.3
	Group-3	Group-1	0.01	0.999	-0.28	0.32
		Group-2	5.18	<0.001	4.88	5.49
		Group-4	5.18	<0.001	4.883	5.49
	Group-4	Group-1	-5.17	<0.001	-5.47	-4.86
		Group-2	0	1	-0.3	0.3
		Group-3	-5.18	<0.001	-5.49	-4.88
BOP	Group-1	Group-2	-2.85	0.537	-8.39	2.68
		Group-3	-0.01	1	-5.55	5.52
		Group-4	0.09	1	-5.44	5.63
	Group-2	Group-1	2.85	0.537	-2.68	8.39
		Group-3	2.84	0.54	-2.69	8.38
		Group-4	2.95	0.508	-2.58	8.49
	Group-3	Group-1	0.01	1	-5.52	5.55
		Group-2	-2.84	0.54	-8.38	2.69
		Group-4	0.1	1	-5.42	5.64
	Group-4	Group-1	-0.09	1	-5.63	5.44
		Group-2	-2.95	0.508	-8.49	2.58
		Group-3	-0.1	1	-5.64	5.42
HbA1c	Group-1	Group-2	-2.48	0.71	-8.55	3.58
		Group-3	4.1	0.296	-1.96	10.17
		Group-4	4.6	0.203	-1.46	10.67
	Group-2	Group-1	2.48	0.71	-3.58	8.55
		Group-3	6.59	0.028	0.52	12.65
		Group-4	7.08	0.015	1.01	13.15
	Group-3	Group-1	-4.1	0.296	-10.17	1.96

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		Group-2	-6.59	0.028	-12.65	-0.52
		Group-4	0.49	0.997	-5.57	6.56
	Group-4	Group-1	-4.6	0.203	-10.67	1.46
		Group-2	-7.08	0.015	-13.15	-1.01
		Group-3	-0.49	0.997	-6.56	5.57
IGM	Group-1	Group-2	19.56	0.008	3.82	35.3
		Group-3	-5.95	0.758	-21.69	9.78
		Group-4	19.51	0.009	3.77	35.25
	Group-2	Group-1	-19.56	0.008	-35.3	-3.82
		Group-3	-25.52	<0.001	-41.26	-9.77
		Group-4	-0.05	1	-15.79	15.69
	Group-3	Group-1	5.95	0.758	-9.78	21.69
		Group-2	25.52	<0.001	9.77	41.26
		Group-4	25.47	<0.001	9.72	41.21
	Group-4	Group-1	-19.51	0.009	-35.25	-3.77
		Group-2	0.05	1	-15.69	15.79
		Group-3	-25.47	<0.001	-41.21	-9.72

Note: PD: Probing Depth; CAL: Clinical Attachment Loss; BOP: Bleeding on Probing; HbA1c: glycated hemoglobin; IgM: Serum Immunoglobulin M

Discussion

Periodontitis plays a key role in inducing impaired blood glucose control, there are evidences showing that periodontitis may induce insulin resistance.[22] It is well known that the prevalence, severity and extent of periodontal disease are greater in patients with DM than in the non-diabetic. All blood cells play an important role in the maintenance of a healthy periodontium but the circulating oral bacteria and lipopolysaccharides are able to stimulate hepatocytes to secrete Immunoglobulins and its isotype. Increased levels of immunoglobulins associated with periodontitis maybe due to inflammatory and infectious burden resulting from periodontitis. Immunoglobulin M is the basic antibody which is produced by B cell and it is secreted during primary immune response. Mainly it is found in serum of the host and level of IgM seem to be elevated during acute and chronic infection. The evidence for serum IgM to be used as a diagnostic tool is limited, hence this study was aimed to find the association between IgM, periodontitis and diabetes.

HbA1c was used as a diagnostic criterion for Type 2 Diabetes Mellitus as it has several advantages compared with Fasting Plasma Glucose and Oral Glucose Tolerance Test, including greater convenience (fasting not required), greater pre-analytical stability, and less day-to-day changes during stress, fluctuations in diet, or illness.[18]

A systematic review with meta-analysis was done by López-Valverde N et al[23] in the year 2024 where the aim was to determine the evidence of periodontal treatment on periodontitis and diabetes mellitus. Eighteen studies were screened that met the inclusion criteria and evaluated 16,247 subjects. The outcomes studied were glycated haemoglobin, bleeding on probing, clinical attachment level and probing pocket depth. The meta-analyses evaluated patients with periodontitis and type 2 diabetes mellitus (T2DM). Periodontal treatment reduces immune cells and inflammatory cytokines that exacerbate T2DM, and hypoglycaemic treatments lessen elevated-sugar condition that support the advancement of certain dysbiosis-causing periodontal pathogens and

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hence this study also concluded that periodontal treatment and DM treatment contribute to improved clinical outcomes in a bidirectional manner.

A bio-informative analysis was done by Xindi Wei et al[24] in 2024 where genetically predicted periodontitis was associated with a higher risk of Type 2 DM (OR, 1.469; 95% CI, 1.117 - 1.930; P = 0.006) and insulin resistance (OR 1.034; 95%CI 1.001–1.068; P = 0.041). This study explored causality and revealed that periodontitis was associated with a higher risk of Type 2 DM, 2 risk genes (*RAP2A*, *MCUR1*) and 4 protective genes (*WNK1, NFIX, FOS, PANX1*) and this may play important role in the pathogenesis of periodontitis-related Type 2 DM, shedding light on the development of potential drug targets.

Kranthi J et al (2013)[21] in a comparative study showed that there was increase in the IgM level in diabetic and non-diabetic subjects than the healthy controls this was similar to the results of our study regarding IgM. The distribution of the patient in each group was similar keeping the total sample size 120 into consideration with 30 patients in each group. The unit of measurement taken for IgM in this study was mg/dl; evidence shows that change in the unit of measurement of IgM to g/l did not change the results of the studies [Alabandar JM[25] (2002), Awartani F[26] (2010) and Khan KH[27] (2013)] The result showed that the probing depth is positively correlated with the level of IgM, as probing depth increased so did the level of IgM which showed escalation in the severity of the disease.

Kranthi J et al[21] in 2013 showed that a comparison between periodontitis patient with type 2 DM, type 2 DM patients without periodontitis, periodontitis patient without type 2 DM patients and periodontally and systemically healthy patients was statistically significant in test and control group which was similar to our study.

A study conducted by Oksana et al[28] in 2023 where he studied the nature of changes in innate humoral immunity in oral fluid and blood serum in patients with generalized periodontitis with type 2 diabetes mellitus and were divided into 4 groups which is comparable to our study. The level of IgM in the 2nd group was statistically significantly lower by 1.2 times, while in the 3rd and 4th groups it was probably higher by 1.7 and 1.2 times, respectively. The outcome of this study was similar to what we found in our research. This indicates that type 2 diabetes complicates the course of periodontitis, as evidenced by changes in the concentrations of the main classes of immunoglobulins. A study was conducted by Zhang et al[29] in 2024 where he studied the link between type 2 diabetes mellitus and serum immunoglobulin concentration and the findings are contradictory to our research.

A Prospective Clinical Study was done in the year 2022 by Palwankar et al[30] where she estimated gingival crevicular immunoglobulin A (IgA) using enzyme-linked immunosorbent assay (ELISA) among type II diabetic patients with periodontitis. The clinical parameters that is probing pocket depth, clinical attachment level, sulcus bleeding index, gingival index and plaque index were recorded at baseline, 1 and 3 months. Difference in IgA levels and clinical parameters was seen between diabetic and non-diabetic groups, which was statistically significant. The studies on correlation between immunoglobulin A and type 2 DM with periodontitis are available but there are limited studies available on the correlation between immunoglobulin M and type 2 DM with periodontitis. Limitations of this research was that there is no follow up period for this study and limited sample size. For future investigations randomized control trials can be undertaken with the same mentioned groups and parameters before and after non – surgical periodontal treatment.

Conclusion

The present investigation was done to evaluate the serum IgM in healthy and type 2 DM patients with and without periodontitis and find correlation between clinical parameters and biomarkers. The result of this study showed that there is an increased level of Immunoglobulin M in the type 2 DM patients with periodontitis, as compared to the other groups. Finding an association between periodontitis, type 2 DM and serum IgM has provided us the basis for further research for serum IgM as a biomarker for periodontal diseases.

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