Research Article

Clinical and immunological study of carrageenan on burning mouth syndrome in patients with type 2 diabetes

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Abstract: Background: This study aimed to assess the impact of topical kappa-carrageenan gel on alleviating Burning Mouth Syndrome (BMS) symptoms in type 2 diabetic patients and to assess its impact on salivary immunoglobulin A (IgA) and alpha-amylase levels. Material and methods: 156 participants were included 104 type 2 diabetic patients with BMS (52 males, 52 females) and 52 healthy controls. Diabetes diagnosis was confirmed through fasting blood glucose and HbA1c tests. BMS diagnosis was established clinically, using criteria and laboratory tests to exclude other causes. Kappa carrageenan gel was prepared and applied topically to relieve BMS symptoms. Unstimulated whole saliva samples were collected to measure salivary IgA and alpha-amylase levels using enzyme-linked immunosorbent assay. The collection of saliva was conducted at two different time points for the BMS group and once for the controls. Results: Application of carrageenan gel showed no significant effect on salivary IgA levels in diabetic BMS patients. However, there was a significant reduction in salivary alpha-amylase levels after carrageenan gel application, indicating a possible response to treatment. Conclusions: Kappa carrageenan gel may serve as a potential therapeutic option for relieving the burning sensation and pain associated with BMS in patients with type 2 diabetes. While the gel did not influence IgA levels, the significant reduction in salivary alpha-amylase suggests an impact on stress-related salivary biomarkers, supporting its symptomatic relief potential in managing BMS in diabetic patients.

Keywords: Burning Mouth Syndrome, Diabetes Mellitus Type 2, Carrageenan Gel, Salivary Immunoglobulin A, Salivary Alpha-Amylase.

Introduction

Carrageenan, a sulfated polyglycan, is sourced from a variety of red-type seaweed genera, such as Eucheuma, Chondrus, and Gigartina [1, 2]. It is utilized as an additive for food owing to its thickening, emulsifying, and gelling abilities and is a good substitution for gelatin [3, 4]. Carrageenan is also employed in medications, cosmetics, and oral medication products as inactive ingredients that serve the active substance [1, 4]. The Food and Drug Administration has been authorized Carrageenan usage [5], the European Parliament and Council of Commission Directive, and the Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee, JECFA [6].

Diabetes mellitus (DM) is considered a chronic as well as multisystemic organic disorder recognized by dysregulation in insulin metabolic activity due to inadequate discharge of insulin and/or resistance of body tissues to insulin [7, 8]. Burning mouth syndrome (BMS) can be identified as dysaesthesia involving the oral cavity, with no organic causes that may cause a similar symptom with an apparent cause. BMS is likely an unknown etiopathogenesis condition of multifactorial origin [9, 10]. A complication of chronic DM, peripheral neuropathy, leads to secondary BMS as a consequence of signaling inhibition in the sensory nerve fibers and de-epithelialization from dry mouth as a result of long-standing DM [11]. Salivary immunoglobulin A (IgA) is the main immunoglobulin with a significant specific defense activity in the

oral cavity [12]. Salivary alpha-amylase (SAA) is a stress marker and is considered a very reliable method for measuring physiological stress response [13]. This study aimed to assess the impact of topical kappa-carrageenan gel on alleviating BMS symptoms in type 2 diabetic patients and to assess its impact on salivary IgA and alpha-amylase levels.

Materials and Methods

This clinical study was conducted at Dijlah University College following the ethical principles in compliance with Helsinki and its later amendments. This study had ethical approval (reference no. 4) obtained from the ethical committee of the Department of Dentistry of Dijlah University College on January 16, 2024. Informed consent was obtained from all participants before enrollment in this study.

The study sample comprised 156 subjects and was divided into three groups: 52 diabetic patients with BMS utilizing carrageenan (study group), 52 diabetic patients with BMS not receiving carrageenan (control diabetic group), and 52 healthy individuals (control group). All diabetes patients involved in this study were diagnosed by specialists in endocrinology, with their diagnoses confirmed through two laboratory tests: fasting blood glucose and HbA1c levels. The diagnosis of BMS was established based on established criteria and laboratory examinations aimed at excluding other potential etiological factors.

Carrageenan, a substance derived from seaweed, is obtained by subjecting the seaweed to heat in water combined with a dilute alkali, enhancing the gel strength as a final product. All procedures adhered to a consistent protocol [14]. Regarding the preparation of the kappa-carrageenan gel, the pharmaceutical formulation included the following components in specified percentages: 0.9% carrageenan powder, 20% sucrose, 0.35% potassium citrate, and 0.45% citric acid.

Patients were instructed to use the carrageenan gel over one week, applying it after breakfast and before bedtime. Patients utilized the carrageenan gel to alleviate the burning sensation associated with BMS. Unstimulated whole saliva was conducted to analyze the immunological markers, which were quantified using an enzyme-linked immunosorbent assay. All the samples of Saliva were obtained at two different time points for the study groups; on the other hand, Saliva was obtained at one interval for the control group.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics. Categorical data were presented as numbers and percentages. The normality of salivary alpha-amylase and IgA values was examined using the one-sample Kolmogorov–Smirnov test. Pearson's chi-square test was used to compare categorical variables and biomarker cut-off distributions across the study groups, while the contingency coefficient was used to indicate the strength of association. Receiver operating characteristic analysis was applied to assess the discriminatory ability of salivary alpha-amylase and IgA. Results were reported as area under the curve, standard error, 95% confidence interval, and two-sided P-value. Statistical significance was set at $P < 0.05$.

Results

The demographic analysis revealed no statistically significant differences among the three groups regarding age, gender, and material status. The majority of participants are within 40-49 years of age, accounting for 52% of the study, the control diabetic group, and 44% of the healthy control group. Gender distribution was balanced, with males comprising 48% of the studied and control groups and 44% of the healthy control group, while females accounted for 52% and 56%, respectively. Regarding the material status, most were married, with 84% in the study and healthy control, and 68% in the control diabetic. The previously mentioned findings were comparable characteristics, ensuring the validity of the following comparisons.

Regarding the general information variables, the study and control diabetics were similar across most variables, with significant differences observed in the HbA1c level ($P < 0.001$). The study group had a

higher proportion of HbA1c level (50%) compared to the control group (27%). Other variables, including the duration of BMS, onset and duration of pain, family history, and age of onset, showed no statistically significant difference between these findings, demonstrating the overall similarity between the groups with HbA1c as the main distinguishing factor, as illustrated in Table 1.

Table 1: General Information of BMS and HbA1c of the Study and Controlled Diabetic groups

GIv.	Groups	Study		Controled Diabetic		C.S. P-value
		No.	%	No.	%	
Duration	1 - 2	12	23	5	10	C.C.= 0.259
Time of	3 - 4	19	37	22	42	P= 0.058
BMS	5 - 6	12	23	21	40	NS
	7 - 8	9	17	4	8	
	Total	52	100	52	100	
HbA1c	6.5 -	26	50	24	27	C.C.= 0.354
	7.0 -	25	48	19	37	P <0.001
	7.5 - 8.0	1	2	19	37	S
	Total	52	100	52	100	
Pain	15 -	28	54	39	75	C.C 0.311
duration	50 -	12	23	12	23	P= 0.004
	85 - 120	12	23	1	2	S
	Total	52	100	52	100	
Pain onset	Morning	36	69	43	83	C.C.= 0.134
	Afternoon	16	31	9	17	P= 0.169
	Total	52	100	52	100	NS
Family	negative	40	77	40	77	C.C.= 0.000
history	positive	12	23	12	23	P=1.000
	Total	52	100	52	100	NS
The	20 - 29	4	8	6	12	C.C.= 0.203
starting of	30 - 39	16	31	19	37	P= 0.349
age	40 - 49	19	37	22	42	NS
	50 - 59	10	19	4	8	
	60 - 69	3	6	1	2	
	Total	52	100	52	100	

(*) S = Significant at P < 0.05; NS = Non-Significant at P > 0.05; C.C.: Contingency Coefficient

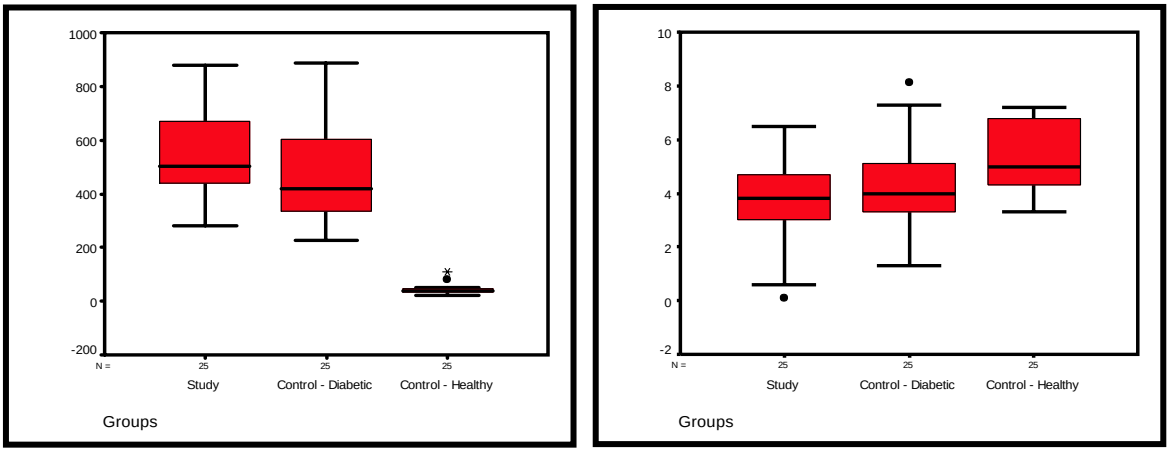

Figure 1: The Stem-Leaf plots for the studied parameters for illustrating a cutoff point

The normal distribution function fitness of salivary alpha-amylase and IgA levels were assessed across all the groups using a one-sample Kolmogorov-Smirnov test. For the study group, pre- and post-treatment measurements of both parameters (S. alpha and IgA) showed no significant deviation from normal distribution at P >0.05. Similarly, in the control diabetic and control healthy groups, the pre-treatment measures of both parameters showed no significant deviation at P >0.05. These results demonstrate that both parameters followed a normal distribution, confirming the validity of subsequent analysis.

The analysis of the measured biomarkers revealed a significant variation among the groups for the analyzed parameters, as shown in Figure 1. The first boxplot (left) shows that the study group exhibited a higher median value than the control diabetic, while the control healthy presented significantly lower values, including one outlier observed. This finding indicates a significant disparity in the biomarker levels across the groups. In the second boxplot (right), IgA levels were relatively comparable among the groups, with the healthy control group showing a slightly higher median compared to the study and control diabetic groups. These results highlight a distinct variation in the biomarker profiles that is primarily attributed to the health status of the individuals (Table 2).

Table 2: Under and upper redistribution of the cutoff point for (Salivary Alpha amylase) in pre-treatment parameters amongst the studied groups

Groups	No. and %	S. Alpha-Amylase (Pre-treatment)		Total	P-value *
		Under	Upper		
Study	No.	0	52	52	CC = 0.245
	%	0.0%	100%	100.0%	P= 0.01
Control - Diabetic	No.	8	44	52	HS
	%	16%	84%	100.0%	
Study	No.	0	52	52	CC= 0.700
	%	0.0%	100%	100.0%	P <0.001
Control - Healthy	No.	52	0	52	HS
	%	100%	0.0%	100.0%	
Control - Diabetic	No.	8	44	52	CC= 0.642
	%	16%	84%	100.0%	P <0.001
Control - Healthy	No.	52	0	52	HS
	%	100%	0.0%	100.0%	

*HS: Highly Sig. at P <0.01; C.C.= Contingency Coefficient; S: Sig. at P<0.05

Moreover, the analysis of IgA levels (pre-treatment) in Table 3 showed variations in distribution across the studied groups, with significant associations observed in specific comparisons. In the study group, 65.4% of participants exhibited upper IgA levels, compared to 63.5% in the control-diabetic group and 96.2% in the control-healthy group. The relation between the study as well as the control-healthy groups was highly significant (C.C. = 0.351, P <0.001), as was the comparison between the control-diabetic and control-healthy groups (C.C. = 0.314, P = 0.001). However, the association between the study and control-diabetic groups was not significant (C.C. = 0.000, P = 1.000). These findings indicate that IgA levels are distinct among groups, particularly healthy individuals and those with diabetes.

The ROC curve analysis for the salivary alpha analysis and IgA of the studied groups, as illustrated in Table 4, revealed a significant diagnostic accuracy among the studied groups. The comparison between the two groups, the study one and the control diabetic group, showed an area under the curve (AUC) of 0.655 for salivary alpha analysis and AUC of 0.548 for IgA, indicating a limited diagnostic differentiation.

In contrast, the comparison between study one and the control healthy group, as well as between the control diabetic one and the control healthy group, both demonstrated perfect diagnostic accuracy with an AUC of 1.000 for salivary alpha analysis, while for IgA study and control healthy groups showed an AUC of 0.240 and 0.304 for the study and control healthy groups, control-diabetic and control healthy groups, respectively, reflecting poor diagnostic accuracy but statistically significant differentiation (P = 0.002 and 0.017), respectively.

These findings suggest that salivary alpha-amylase effectively differentiates between healthy individuals and those with diabetes. With high sensitivity and specificity in specific comparisons and IgA readings offering limited diagnostic utility in some comparisons, they can still distinguish between healthy and diabetic individuals in specific scenarios.

Table 3: Under and upper redistribution of the cutoff point in pre-treatment amongst the studied groups for (IgA)

Groups	No. and %	IgA (Pre-treatment)		Total	P-value *
		Under	Upper		
Study	No.	18	34	52	P= 1.000
	%	34.6%	65.4%	100.0%	CC= 0.000
Control - Diabetic	No.	19	33	52	NS
	%	36.5%	63.5%	100.0%	
Study	No.	12	23	52	P <0.001
	%	34.3%	65.7%	100.0%	CC= 0.351
Control - Healthy	No.	2	50	52	HS
	%	3.8%	96.2%	100.0%	
Control - Diabetic	No.	36	16	52	P= 0.001
	%	69.2%	30.8%	100.0%	CC= 0.314
Control - Healthy	No.	50	2	52	HS
	%	96.2%	3.8%	100.0%	

* HS=Highly Significant at P<0.01; C.C.= Contingency Coefficient; NS=Non-Significant at P>0.05;

Table 4: ROC Curve Statistics for the "Salivary Alpha-amylase and IgA " amongst the Studied Groups

Biomarkers	Parameters	Area Under Curve (AUC)	Std. Error	Asymptotic Sig. (P-value)	Asymptotic 95% C. I.	
					Lower Bound	Upper Bound
S. Alpha-Amylase	**Study vs Diabetic**	0.655	0.079	0.060 NS	0.500	0.810
	Study vsHealthy	1.000	0.000	<0.001 HS	1.000	1.000
	Diabetic vs Healthy	1.000	0.000	<0.001 HS	1.000	1.000
IgA	**Study vs Diabetic**	0.548	0.082	0.561 NS	0.387	0.709
	Study vs Healthy	0.240	0.067	0.002 S	0.109	0.371
	Diabetic vs Healthy	0.304	0.077	0.017 S	0.154	0.454

HS: Highly Significant at P <0.01; C.I. = Confidence Interval; Non-Significant at P >0.05; The positive actual state is Pos.

Discussion

Carrageenan is safe on the mucosal epithelium [15-17]. The presented study and many others confirm this safety, as all patients showed no complaints from the treatment. This lack of complaints is a strong indicator of carrageenan's tolerability. The utilization of carrageenan in this study as a topical gel for relieving pain in BMS has proven its effectiveness, as the majority of patients in the present study experienced profound relief in the burning sensation immediately following carrageenan gel utilization.

Moreover, several studies proved that orally administered carrageenan is not absorbed [18, 19], and the presented study confirms this, as the immunological salivary marker (salivary IgA) in this study remained unaffected. The dramatic change in salivary alpha-amylase in this study can be related to the stress relief associated with burning mouth syndrome.

The patients in the study experienced prolonged relief and an excellent enhancement in lifestyle performance when topical carrageenan gel was utilized. Many studies confirm this prolonged duration of symptom relief. Carrageenan is incorporated in most gel formulations to assist in the prolongation of the

buccal drug delivery. Carrageenan is also used as a part of the composition of extended-release medication, prolonging the medication's release for about twenty-four hours, which improves the effect of the medication as well as prolongs its effect [20].

Dimeric IGA, present in saliva, is produced by plasma cells situated in the stroma of the salivary gland [21]. Immunoglobulin A is considered an essential immunoglobulin that plays a fundamental role in the immunity of the oral cavity [22-24]. This study assessed salivary immunoglobulin A in diabetic and nondiabetic patients. It was found that there is variability in salivary IgA in diabetes, and this was confirmed [25], in which salivary IgA levels were assessed in diabetic and nondiabetic patients, and salivary IgA levels in 54% of diabetic patients were lower than the normal range, and diabetic patients showed higher variability in salivary IgA levels as compared with nondiabetic patients. Another study that matched with this study regarding IgA [26]. So, a scientifically acceptable fact that is offered to explain that carrageenan does not affect the IgA level in saliva is that carrageenan cannot be absorbed by the oral mucosa of the cavity; therefore, it will not act systemically. It is pointed to the critical fact that the mucosa of the oral cavity cannot absorb carrageen, and as a result, it will never act systemically [27].

There are many proteins in saliva, and alpha amylase consists of up to 60% of salivary protein [28]. Amylase, a fundamental salivary protein, has been considered a biomarker of the sympathetic reaction to parasympathetic responses and psychosocial stress. Salivary amylase has been related to the catecholamine level in plasma [29]. An analysis of the ground knowledge that Salivary alpha-amylase can be assessed to indicate the severity of burning when there is a burning, but there is no physical cause for pain, as well as in a situation where the severity of pain reported is not related to visible injuries [30]. It is demonstrated that there is a strong and significant relationship between pain and salivary alpha-amylase levels [31]. This study shows a marked increase in SAA before treatment and a marked reduction after carrageenan use. This may be attributed to pain relief after carrageenan use since almost all the patients report burning relief associated with carrageenan usage. The study of the basic idea about Salivary alpha-amylase is increased in diabetes compared with healthy people [32], which is confirmed by this study, which showed a marked increase in SAA in diabetes compared with healthy people. Salivary alpha-amylase is increased in BMS [33], confirming the present study. It is found that BMS is a stomatological problem that is a psychosomatic condition and can be influenced by symptoms of depression, anxiety, obsession, and somatization, which are strongly associated with the duration of symptoms [34]. This can be related to this study, as almost all patients showed a prolonged duration of the syndrome with a stressful condition and anxiety. Another study confirmed the present study was done by López-Jornet et al. (2014), which proposed that pain in BMS is mainly due to anxiety [35]. A study by Malik et al. (2012) proved that there is moderate to severe depression in burning mouth syndrome patients [36]. SAA in diabetes is less than in healthy people [37].

Salivary α-amylase activity has garnered increasing interest as a sympathetic nervous system stress marker [38,39]. A previous study reported a significant elevation in salivary α-amylase levels in BMS patients and identified a correlation between this high level and increased warm thresholds [40].

Conclusion

This study demonstrates that carrageenan gel can provide reliable treatment for both immediate and sustained relief from BMS. The gel was safe for patients and had no adverse effects. The gel's stability on the mucosal epithelium shows its compatibility with living tissues and no effect on salivary IgA levels indicates low absorption through the oral mucosa. A decrease in salivary alpha-amylase levels after treatment indicates a reduced stress-related response. Carrageenan gel can help lessen the psychological discomfort caused by BMS. Based on the previously mentioned findings, carrageenan has the potential to develop a sustained-release formulation that can increase therapeutic activity and is suitable for prolonged management in BMS. As a result, using carrageenan may enhance the quality of life of individuals with diabetes suffering from BMS, warranting further exploration and integration into clinical practice.

Conflict of interest

The authors have no conflicts of interest to declare.

Author contributions

MM and FDA; study conception and design. MM; data collection. MM and FDA; methodology. MM; statistical analysis and interpretation of results. MM; original draft manuscript preparation. MM, FDA and MN; writing & editing. FDA and MN; Supervision. All authors reviewed the results and approved the final version of the manuscript to be published.

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Informed consent

Informed consent was obtained from all individuals who participated in this study.

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دراسة سريرية ومناعية لتأثير الكاراجينان على متلازمة الفم الحارق لدى مرضى السكري من النوع الثاني

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المستخلص:

يُعتبر الكار جينان كبريتات عديد السكريات، ويتواجد بثلاثة أنواع مختلفة (إيوتا، لامبدا، وكابا)، وتختلف هذه الأنواع في درجة الكبريتات. تؤثر الإصابة بمرض السكري على جميع الأعضاء الحيوية في الجسم من خلال تغيير النشاط الأيضي للجسم. قد يعاني بعض مرضى السكري من متلازمة الفم الحارق، التي تنتج عن عدة عوامل ويمكن تشخيصها سريريًا من خلال شعور حار ومؤلم في الفم، دون ظهور آفة واضحة .يهدف هذا البحث إلى تقييم تأثير جل الكاراجينان (نوع كابا) الموضوعي على تخفيف أعراض متلازمة الفم الحارق لدى مرضى السكري من النوع الثاني، كما يهدف إلى قياس تأثيره على مستويات الغلوبولين المناعي A (IgA) والأميلاز اللعابي. شملت الدراسة 75 مشاركاً، منهم 50 مريض سكري من النوع الثاني مصاب بمتلازمة الفم الحارق (25 ذكرًا و25 أنثى) و25 شخصًا سليمًا كمجموعة ضابطة. تم تأكيد تشخيص السكري من خلال فحوصات السكر الصائم والتراكمي، وتم تشخيص متلازمة الفم الحارق سريريًا واستبعاد الأسباب الأخرى باستخدام معايير محددة وفحوصات مخبرية. تم تحضير جل الكاراجينان وتطبيقه موضعيًا لتخفيف أعراض المتلازمة، كما تم جمع عينات لعابية غير محفزة لقياس مستويات IgA والأميلاز باستخدام تقنية ELISA.تم جمع اللعاب في فترتين زمنيتين للمجموعة المصابة بالمتلازمة ومرة واحدة للمجموعة الضابطة .لم يُظهر تطبيق جل الكاراجينان تأثيرًا كبيرًا على مستويات IgAاللعابية لدى مرضى السكري المصابين بمتلازمة الفم الحارق، إلا أنه لوحظ انخفاض ملحوظ في مستويات الأميلاز اللعابي بعد استخدام الكاراجينان، مما قد يشير إلى استجابة إيجابية للعلاج .قد يُعتبر جل الكاراجينان (نوع كابا) خيارًا علاجيًا محتملاً لتخفيف الألم والإحساس بالحرقان المرتبط بمتلازمة الفم الحارق لدى مرضى السكري من النوع الثاني. ورغم عدم تأثيره على مستوياتIgA ، فإن الانخفاض الملحوظ في الأميلاز اللعابي يشير إلى تأثيره على مؤشرات الإجهاد اللعابية، مما يدعم فعاليته في تقديم الراحة العرضية لدى إدارة المتلازمة في مرضى السكري