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Study an association of some oral ulcer types and features with GST null genotyping in systemic lupus erythematosus patients

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Abstract

AIM. Systemic lupus erythematosus (SLE) is an autoimmune disease known by immune response disturbance and imbalanced in oxidative stress status. one of the SLE features is an oral ulcer that is associated with oxidative stress, the present study aims to assess some oral ulcer types and features with GST (GSTT1, GSTM1 and GSTP1) null genotyping in SLE with and without oral ulcer in addition to its types and features.

MATERIALS AND METHODS. Null genotyping PCR was used to detect GSTT1, GSTM1 and GSTP1.

RESULTS. They show significant association of GSTM1 and GSTP1 with SLE ($p = 0.0010$, $p = 0.0024$) respectively, and non-significant changes of GSTT1 ($p = 0.7426$) when compared with the control group. a cross section comparison GST between SLE patients with and without oral ulcer shows a significant association of GSTT1 ($p = 0.0367$) and a non-significant association of GSTM1 ($p = 0.1056$) and GSTP1 ($p = 0.218$). The number of oral ulcers (single and multiple ulcers) shows a non-significant association in all GST genes ($p = 0.882$, 0.959, 0.552) respectively. The painful oral ulcers show non-significant association of GST genes ($p = 0.803$, 0.143, 0.585) respectively, the oral ulcer types included buccal, palatal, labial and tongue, were non-significantly ($p = 0.608$) correlated with GST.

CONCLUSIONS. There was a strong association of GSTM1 and GSTP1 with SLE, a non-significant association of the GST with oral ulcer types and features.

Keywords: oral ulcer, GST null genotyping, systemic lupus erythematosus

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Изучение связи некоторых типов и клинических особенностей язвенных поражений слизистой оболочки полости рта с нулевым генотипом GST у пациентов с системной красной волчанкой

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Резюме

ЦЕЛЬ. Системная красная волчанка представляет собой аутоиммунное заболевание, характеризующееся нарушением иммунного ответа и дисбалансом системы оксидативного стресса. Одним из клинических проявлений волчанки являются язвенные поражения слизистой оболочки полости рта, развитие которых связано с оксидативным стрессом. Настоящее исследование было направлено на оценку взаимосвязи между некоторыми типами и клиническими особенностями язвенных поражений слизистой оболочки полости рта и нулевыми генотипами генов GST (GSTT1, GSTM1 и GSTP1) у пациентов с системной красной волчанкой с наличием и отсутствием язв полости рта, а также на анализ связи с различными типами и характеристиками этих поражений.

МАТЕРИАЛЫ И МЕТОДЫ. Для определения нулевых генотипов генов GSTT1, GSTM1 и GSTP1 применяли метод полимеразной цепной реакции.

РЕЗУЛЬТАТЫ. Выявлена статистически значимая связь генов GSTM1 и GSTP1 с развитием системной красной волчанки ($p = 0{,}0010$ и $p = 0{,}0024$ соответственно), тогда как для гена GSTT1 достоверных различий по сравнению с контрольной группой не установлено ($p = 0{,}7426$). При сравнительном поперечном анализе пациентов с системной красной волчанкой, имеющих язвы слизистой оболочки полости рта и не имеющих их, обнаружена статистически значимая связь с геном GSTT1 ($p = 0{,}0367$), тогда как

для GSTM1 (p = 0,1056) и GSTP1 (p = 0,218) значимых ассоциаций не выявлено. Количество язв (одиночные или множественные) не было статистически значимо связано ни с одним из исследованных генов GST (p = 0,882; p = 0,959; p = 0,552 соответственно). Аналогично болезненность язвенных поражений не продемонстрировала достоверной связи с генами GST (p = 0,803; p = 0,143; p = 0,585 соответственно). Локализация язв (слизистая оболочка щеки, неба, губ и языка) также не была статистически значимо связана с исследуемыми генотипами GST (p = 0,608).
ЗАКЛЮЧЕНИЕ. Установлена выраженная ассоциация генов GSTM1 и GSTP1 с системной красной волчанкой. Вместе с тем статистически значимой связи между генотипами GST и типами или клиническими особенностями язвенных поражений слизистой оболочки полости рта не выявлено.

Ключевые слова: язвы слизистой оболочки полости рта, нулевой генотип GST, системная красная волчанка

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INTRODUCTION

Systemic lupus erythematosus is one of the autoimmune diseases with variable prevalence and incidence in the population. It is a multi-systemic disease with immune system dysregulation, deficient *T* cell responsiveness and hyperactive *B* cells resulting in the production of an array of different autoantibodies which form immune complexes versus different nuclear antigens. The SLE disease may affect some organs [1; 2]. Despite the disadvantage of an unclear SLE pathophysiology, environmental and genetic risk factors are involved in predisposition to this multi-etiologic disease [3].

The Oxidative stress results in lowering the ability of reactive oxygen species (ROS) detoxification that may have a part in the SLE developing and progressing [4]. Physiologically, the free radicals are generated through the reaction of the immune system, repair of tissue, ATP generation [5; 6]. It can also be produced by chronic to ionizing radiation exposure like UV rays and with chemicals such as, pesticides, pollutants and some drugs, cigarette smoking, and prolonged stress considered as a major stimulation of ROS [7; 8].

The harmful impacts of ROS are diverted and contributed in the different diseases, the ROS can destroy cell component and impact in the cellular functions. In the oral cavity the oxidative stress causes dentinogenesis [9] and oral aphthous ulcers in Behçet's disease by elevation ROS titers [10]. Sardaro et al. suggested that the oxidative stress is an influence factor in the most common ulcerative disorder of the oral mucosa [11]. Tugrul et al. described that the oxidative stress index values and total oxidative status were significant elevation in participant with recurrent aphthous stomatitis compared with the control group, while total antioxidant levels were lowered significantly [12].

The antioxidant mechanisms exist in the cell detoxified the ROS effects, in saliva have non-enzymatic antioxidant molecules which produce the bulk of the total antioxidant capacity [13]. Ishita et al. found that the Enzymatic antioxidant system including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) is impaired in recurrent aphthous stomatitis patients and seems to play a critical part in its pathogenesis [14].

Glutathione S-transferase (GST) is contributed in the detoxification of ROS and genetic poymorphisms of genes included (GSTM1, GSTT1 and GSTP1) are related with altered enzyme activity. There was poor information about the relation of GST null genotyping with oral ulcer, thus the present study aims to validate the association GST null genotyping with an oral ulcer in SLE patients.

MATERIALS AND METHODS

Sample collection and study sitting

SLE patients (with and without oral ulcer) have an age range (18–45) years for SLE with oral ulcer, (22–50) years for SLE without oral ulcer and (22–35) years of control group. All patients were attended to a chronic clinic in the Marjan hospital city and diagnosed by a professional physician. Blood samples and data were collected according to ethical approval of the environment and Ministry of Health in Iraq and with written consensus from each contributor (patients and control individuals). The oral ulcer types were depended in the present study that diagnosed by specialist dentist, including (buccal, palatal, labial and tongue) and the oral ulcer features were depended like single or multiple appearances, painful and non-painful.

DNA Extraction and Targeting Genes Amplification

The DNA was isolated from whole blood by Favor-Prep™ Blood kit, then purity and concentration were measured which was 1.7–2.3 and 80–200 ηg/μl. GST null genotyping included (GSTT1, GSTM1 and GSTP1) were targeting using the following primers [15], GSTM1: forward 5' GAACTCCCTGAAAAGCTAAAGC-3', revers 5' GTTGGGCTCAAATATACGGTGG-3' amplified 215 bp and GSTT1: F 5' TTCCTTACTGGTCCTCACATCTC-3', R 5'-TCCCAGGTCACCGGATCAT-3' amplified 312 bp and GSTP1 I105V

F-AATACCATCCTGCGTCACCT R-TGAGGGCACAA-GAAGCCCCTT amplified 308 bp. The amplification programs were (95°C, 59°C, 72°C) for 30 sec to each steps and repeated to 30 cycles in addition to pre-denaturation 95°C for 5 min and final extension 72°C for ten minutes.

Electrophoresis Pattern

The null genotyping was detected by the presence and absence of the amplification targeted sites for GSTT1, GSTM1 and GSTP1 genes. Electrophoresis implemented by 1% agarose, TBE 0.5X, 100 V for 30 minutes with red safe staining and (100 bp – 1.5kb) DNA ladder.

Statistical Analysis

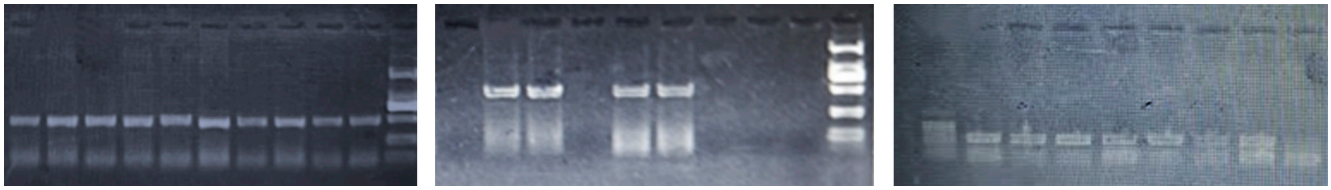
The results represented as percentages, the significant detected by odd ratio and CI 95% and chi square at *p* less than 0.05.

RESULTS

The current study aims to assess the association of GST (GSTT1, GSTM1 and GSTP1) with oral ulcers in the SLE patients, electrophoresis patterns of GST null genotyping clarified in Fig. 1. First of all, the GST (GSTT1, GSTM1 and GSTP1) shows significant association of GSTM1 and GSTP1 with SLE ($p = 0.0010$, $p = 0.0024$) respectively, and non-significant changes of GSTT1 ($p = 0.7426$) in comparison with control group.

A cross-section when compared the GST (GSTT1, GSTM1 and GSTP1) of SLE patients with and without oral ulcer shows significant association of GSTT1 and the presence of oral ulcer ($p = 0.0367$), and high percentages of GSTM1 null genotyping in patients with oral ulcer in non-significant association of GSTM1 ($p = 0.1056$), and GSTP1 ($p = 0.218$) (Table 2).

The number of oral ulcer was depended in present study. Single and multiple ulcers were observed in SLE patients. The results show a non-significant association in all GST genes that investigated in the current study ($p = 0.882$, $p = 0.959$, $p = 0.552$) (Table 3). Although of absent of GSTT1 null genotyping, high percentages of GSTM1 null genotyping and low percentages of GSTP1 null genotyping (Table 3).



A **B** **C**

Fig. 1. Electrophoresis pattern of GST null genotyping in SLE patients: *A* – GSTM1, *B* – GSTT1, *C* – GSTP1
Note. 1% agaros, 30 minutes, red safe staining, 0.5 TBE, DNA marker (100–1000 bp). The PCR products: GSTM1 – 215 bp, GSTT1 – 312 bp, GSTP1 – 308 bp

Рис. 1. Электрофореграмма результатов генотипирования делеций (нулевых генотипов) генов GST у пациентов с системной красной волчанкой: *A* – GSTM1, *B* – GSTT1, *C* – GSTP1
Примечание. 1% агарозный гель, 30 минут, окрашивание красителем RedSafe, буфер 0,5× TBE, маркер длин фрагментов ДНК (100–1000 п.н.). Размеры полимеразной цепной реакции продуктов: GSTM1 – 215 п.н., GSTT1 – 312 п.н., GSTP1 – 308 п.н.

Table 1. A case-control distribution of GST (GSTT1, GSTM1 and GSTP1) null genotyping in SLE patients and control groups

Таблица 1. Распределение генотипов с делецией генов GST (GSTT1, GSTM1 и GSTP1) у пациентов с системной красной волчанкой и в контрольных группах

GST genes	SLE patients (%)	Control group (%)	Odd ratio	*p*
GSTT1	38 (79.16)	24 (82.75)	0.7895 0.1926 to 3.2357	0.7426
GSTT1 null genotyping	10 (20.3)	5 (17.24)		
GSTM1	24 (50)	27 (93.10)	13.5000 2.8833 to 63.2096	0.0010*
GSTM1 null genotyping	24 (50)	2 (6.89)		
GSTP1	34 (70.83)	10 (34.48)	0.2167 0.0808 to 0.5814	0.0024*
GSTP1 null genotyping	14 (29.16)	19 (65.5)		

Note. * Significant differences
Примечание. * статистически значимые различия

Table 2. A cross-section distribution of GST (GSTT1, GSTM1 and GSTP1) in SLE patients and without oral ulcer

Таблица 2. Распределение вариантов генов GST (GSTT1, GSTM1 и GSTP1) у пациентов с системной красной волчанкой при наличии и отсутствии язв в полости рта

GST genes	With oral ulcer (%)	Without oral ulcer (%)	Odd ratio	*p*
GSTT1	19 (100)	16 (64)	0.0445 0.0024 to 0.8245	0.0367*
GSTT1 null genotyping	0 (0)	10 (36)		
GSTM1	7 (36.84)	16 (64)	2.7429 0.8082 to 9.3088	0.1056
GSTM1 null genotyping	12 (63.15)	10 (36)		
GSTP1	15 (78.94)	16 (64)	0.4267 0.1099 to 1.6570	0.2185
GSTP1 null genotyping	4 (21.05)	10 (36)		

Note. * Significant differences
Примечание. * статистически значимые различия

Table 3. A cross-section distribution of GST (GSTT1, GSTM1 and GSTP1) between SLE patients with single and multiple oral ulcer

Таблица 3. Поперечное распределение GST (GSTT1, GSTM1 и GSTP1) между пациентами с системной красной волчанкой с одиночными и множественными язвами полости рта

GST genes	Single ulcer	Multiple ulcer	Odd ratio	p
GSTT1	8 (100)	11 (100)	0.7391 0.0133 to 41.1295	0.8828
GSTT1 null genotyping	0 (0)	0 (0)		
GSTM1	3 (37.5)	4 (36.36)	1.0500 0.1592 to 6.9245	0.9596
GSTM1 null genotyping	5 (62.5)	7 (63.63)		
GSTP1	5 (62.5)	9 (81.81)	0.5556 0.0800 to 3.8586	0.5522
GSTP1 null genotyping	3 (37.5)	3 (18.18)		

Table 4. A cross-section distribution of GST (GSTT1, GSTM1 and GSTP1) between SLE patients with painful and non-painful oral ulcer

Таблица 4. Поперечное распределение GST (GSTT1, GSTM1 и GSTP1) между пациентами с системной красной волчанкой с болезненной и безболезненной язвой полости рта

GST genes	Painful	Non-painful	Odd ratio	p
GSTT1	7 (100)	12 (100)	1.6667 0.0298 to 93.1304	0.8035
GSTT1 null genotyping	0 (0)	0 (0)		
GSTM1	1 (14.28)	6 (50)	6.0000 0.5440 to 66.1721	0.1435
GSTM1 null genotyping	6 (85.71)	6 (50)		
GSTP1	6 (85.71)	9 (75)	0.5000 0.0415 to 6.0175	0.5850
GSTP1 null genotyping	1 (14.28)	3 (25)		

Table 5. A cross-section distribution of GST (GSTT1, GSTM1 and GSTP1) among SLE patients with different types of oral ulcer

Таблица 5. Поперечное распределение GST (GSTT1, GSTM1 и GSTP1) среди пациентов с системной красной волчанкой с различными типами язв полости рта

GST genes	Types of oral ulcer				Chi-Square	p
	buccal	palatal	labial	tongue		
GSTT1	8	4	7	6	10.0813	0.6088
GSTT1 null genotyping	0	0	0	0		
GSTM1	2	0	3	2		
GSTM1 null genotyping	6	4	4	4		
GSTP1	8	2	7	5		
GSTP1 null genotyping	0	2	0	1		

The painful oral ulcers show a non-significant association of GST (GSTT1, GSTM1 and GSTP1) ($p = 0.803$, $p = 0.143$, $p = 0.585$). The null genotyping was not observed in GSTT1 and in low percentages in GSTP1 and high percentages in GSTM1 in painful oral ulcer SLE (Table 4).

There were four oral ulcer types according to the site of ulcer included buccal, palatal, labial and tongue. The association of these types with GST was non-significant ($p = 0.608$), the GSTT1 null genotyping didn't appear, the GSTM1 null genotyping observed in high percentages and low percentages of GSTP1 null genotyping (Table 5).

DISCUSSION

The role of GST gene family in oxidative stress have been well documented in different disease, thus the lack of GST enzymes can be increased damage inducing by ROS [16; 17], the null mutation of the GST genes could have pathologic and prognostic importance. GSTT1, GSTM1 and GSTP1 genes are three main phase II xenobiotic bio-transforming enzymes which contributed in the ROS generation and metabolic activation. There were poor investigations about the relation between SLE and GSTs polymorphisms and this relation didn't clearly established [4; 18–20]. Current study observed association between GSTM1 and GSTP1 with SLE patients and this agree with investigations observed an association between GSTs polymorphisms and SLE clinical manifestations, but not with SLE susceptibility [21–24].

Salimi et al. found that GSTT1 only void genotype and in aggregate with GSTM1 and as well aggregation of GSTM1, GSTT1 no mutation with GSTP1 genotype can has a significant association with lupus arthrematous and may be related to high risk in Iranian patients [25]. Fraser et al. didn't find a relation between GSTs polymorphisms and SLE, but they found to be three-time higher risk of SLE in patients with more than twenty-four months' job-related sun exposure and GSTM1 void genotype in Caucasians [19].

Regarding the oral ulcer, the role of oxidative stress in oral ulcer has been documented. Ishita et al. concluded that the system of the Enzymatic was declined in pa-

tient with the recurrent aphthous stomatitis and seems to have a critical role in its pathogenesis [14]. The present study showed a significant association of GSTT1 with oral ulcer and non-significant of GSTM1, GSTP, further more null genotyping were observed in different types of oral ulcer types and features in non-significant. Investigations found one way of the pathogenesis of the ulcerative lesions is the system of the antioxidant decline, for example recurrent aphthous stomatitis and establish the oxidant-antioxidant disturbance have major function in the inflammatory reactions seen in recurrent aphthous stomatitis. Moreover, the increment of antioxidant molecules in recurrent aphthous stomatitis patients is among the potential determinants of susceptibility to this disorder [14; 26; 27]. Jesija et al. studied an assessment of antioxidant levels in plasma and saliva of recurrent aphthous and found the comparison of antioxidant concentration between the single and multiple ulcers and among is higher in the major ulcer and have a significant function because of its feature as powerful enzymatic antioxidants against ROS [28].

The association between GST null genotyping and the oral ulcer didn't studied, but the role of antioxidant molecules and the ROS level have been well established, thus the role of antioxidant enzyme gene polymorphisms may have a crucial role in oral ulceration due to the imbalance in oxidative stress status, although of non-significant association of GST null genotyping with types and features of oral ulcer but can be though that it has a role in the oral ulceration with other factors contributed in the free radical generation, immune responses and antioxidant in oral cavity. On the other hand, the types of disease that stimulate the oral ulceration as well as autoimmune disease like Behçet's disease [10], SLE [4] and in different oral cancers [11; 29] may also impact in the types and features of oral ulceration.

CONCLUSION

A strong association was observed between GSTM1 and GSTP1 with SLE, whereas no association of the GST with oral ulcer types and features was reported.

There were several limitations in the current study like the restricted prevalence of oral ulcer in SLE patients, and interaction of other factors with SLE that excluded from the current study. Further investigations are required to confirm the role of oxidative stress in SLE oral ulcer.

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