

Original research-Orijinal araştırma

Serum immunoglobulin levels in the course of post-burn hypertrophic scar development with specific reference to immunoglobulin E

Yanık sonrası hipertrofik skar gelişiminde serum immunglobulin E ile diğer immunglobulin düzeylerinin incelenmesi

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Abstract

Aim. The relation between the occurrence of the hypertrophic scar and serum immunoglobulin levels with specific reference to IgE was investigated in burn patients. **Methods.** This study included 20 burn patients hospitalized in our clinic. Serum levels of immunoglobulin A, G, M and E were measured in the first 48 hours, on the 10th day and on the 90th day during the treatment. Evaluation of the hypertrophic scar was made using Vankouwer scar scale. The relation between the hypertrophic scar and serum levels of each immunoglobulins were analyzed. **Results.** Serum levels of immunoglobulin A, G and M decreased in the early postburn period, and they returned to normal in the following period. There were serious variations in the levels of IgE. In some patients the levels stayed within normal ranges, in some of them increased and in some of them decreased. **Conclusion.** There were no relation among the hypertrophic scar formation and levels of immunoglobulins A, G and M. We were unable to find a significant relation between the IgE levels and formation of hypertrophic scars; however, there were some peculiarities which we discussed.

Keywords: Burn, immunoglobulin, immunoglobulin E, hypertrophic scar.

Özet

Amaç. Yanıklı hastalarda hipertrofik skar gelişimi ile immunoglobulin düzeyleri arasındaki ilişkinin IgE düzeyleri ön planda dikkate alınarak incelenmesi. **Yöntemler.** Bu çalışma yanık nedeni ile kliniğimize yatırılmış 20 hastayı kapsamaktadır. İmmunglobulin A, G, M, E düzeyleri için kan örnekleri hastalardan ilk 48 saatte, 10. günde ve 90. günde alınmıştır. Hipertrofik skar değerlendirmesi Vankouwer skar skalası esas alınarak yapılmıştır. Hipertrofik skar ve serum immunoglobulin düzeyleri ilişki incelenmiştir. **Bulgular.** Erken dönemde serum IgA, M ve G düzeyleri düşmüş ve daha sonra tekrar normale dönmüştür. Serum IgE düzeylerinde ise ciddi farklılıklar söz konusudur. Serum IgE düzeyleri bazı hastalarda normal düzeylerde seyrederken, bazılarında yükselmiş, bazılarında da düşmüştür. **Sonuç.** Hipertrofik skar gelişimi ile IgA, G ve M arasında herhangi bir ilişki saptanmamıştır. Aynı durum IgE ile hipertrofik skar gelişimi arasında da söz konusu olmakla birlikte IgE düzeylerindeki farklılıklar ilginç olup yazıda tartışma konusu yapılmıştır.

Anahtar sözcükler: Yanık, immunglobulin, immunglobulin E, hipertrofik skar

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Introduction

Hypertrophic scar is a clinical entity emerges both as an increase of collagen production and decrease of collagen degradation in a healing wound [1]. Development of hypertrophic scars generally occurs in burn wounds when the epithelization period exceeds three weeks [2]. The precise etiology of hypertrophic scar is unknown; however, cellular, systemic and local immunologic factors are thought to be responsible. According to the immunologic theory, it was defined as an autoimmune reaction against skin antigens. In patients with keloids, antinuclear antibodies against dermal fibroblasts were detected along with a generalized increase in tissue immunoglobulin levels [3, 4].

Studies performed in patients with keloids and hypertrophic scars revealed IgG deposition among collagen fibers along with the increased levels of blood IgG, suggesting a localized immune response [4-6]. There are some studies suggesting the role of IgE in the development of hypertrophic scarring. Polacek et al. [7] suggested an increase in the levels of Ig E after burn injury especially in patients with burns over 20 % of total body surface area. In another study, Smith et al. [8] suggested an increase in the serum IgE levels along with an increase in anti-collagen antibodies. Considering the fact that thermal injury is a strong predisposing factor for the development of hypertrophic scars, we planned to determine the serum immunoglobulin levels in burn patients. Blood samples were taken in the acute period and this task was repeated periodically during the later stages of burn wound healing in order to assess the relationship between hypertrophic scar formation and serum immunoglobulin levels.

Material and methods

The study included 20 burn patients who were hospitalized in our clinic. Burn surface area of the patients were about 15-30 % (mean 15 ± 1.58) and the depth of the injury was varied between second degree deep burns and third degree burns. The initial fluid replacement was done according to the Parkland formula in the first 48 hours, in the following days a flexible approach which allows calculating the specific requirements of each patient was undertaken. Systemic antibiotic therapy was instituted in all patients immediately after admission. Daily wound care was performed with topical silver sulfadiazine 1% initially and in time other antibacterial agents were used as well. In all of the patients wound care was performed using closed technique and healing was achieved in 20-45 days. None of the patients required tracheostomy, fasciotomy and escharectomy. In 10 patients skin grafts was performed beginning from 20 days after the thermal trauma. Blood samples were obtained (i) within 48 hours after the burn injury, (ii) 10th post-burn day and (iii) 90th days, and levels of IgE, IgG, IgA and IgM were measured. Five milliliters of blood samples were obtained from patients through intravenous route. Measurements were done using Shiaparelli device (Italy) and Alfa Wasserman kits were utilized. Normal immunoglobulin levels were accepted as, 7-16 g/L for IgG, 0.7-4 g/L for IgA, 0.4-2.3 g/L for IgM, 0-100 IU/mL for IgE. Evaluation of hypertrophic scars was performed using Vancouver Scar Scale which scores color, scar elevation, itching, skin elasticity and functional impairment quantitatively (Table 1).

Table 1. Evaluation of hypertrophic scar.

Hypertrophic scar	Mild	Moderate	Severe
Color	Pink	Pink-red	Red
Scar elevation	< 0.1 mm	0.1-1 mm	> 1 mm
Itching	Minimal	Moderate	Severe
Skin elasticity	Minimally impaired	Moderately impaired	Severely impaired, rigid skin
Functional Impairment	Minimal	Moderate	Severe

The mean age of the patients was 24.45 ± 3.64 and the mean hospitalization period was 44.75 ± 2.65 days. The data was evaluated via SPSS (ver 11.0 SPSS Inc., Chicago, IL, USA) program, One-way repeated-measures ANOVA, Tukey's test, exact test were used

to evaluate the data. Whenever a significant statistical value was obtained by ANOVA, the data was re-evaluated by Tukey's test. Table 2 demonstrates the immunoglobulin levels by post burn time. Immunoglobulin levels were expressed as g/L.

Table 2. Immunoglobulin levels of IgG, A, M, E by post-burn time.

Time	IgE $\bar{X}\pm Se$	IgG $\bar{X}\pm Se$	IgA $\bar{X}\pm Se$	IgM $\bar{X}\pm Se$
First 48 hours	89.89±16.05	5.35±0.51	1.03±0.10	0.47±0.06
10. day	122.29±21.26	7.44±0.86	2.09±0.27	0.86±0.07
90. day	93.60±16.43	8.07±0.60	2.43±0.30	0.98±0.09
ANOVA	F=4.78 p<0.05	F=12.05 p<0.05 significant	F=19.22 p<0.05 significant	F=6.76 p<0.05

Results

Significant results were obtained when IgG levels were compared by ANOVA with respect to time period. IgG levels were also evaluated in a paired fashion and there were statistically significant difference between the IgG levels of the first 48 hours and 10th-90th days (p<0.05) (Table 3).

Table 3. Cases, IgG levels and hypertrophic scar evaluation.

Cases	Burn type	Burn surface area *+**	IgG g/L First 48 hours	IgG g/L 10 th day	IgG g/L 90 th day	Hypertrophic scar evaluation
1	Flash burn	5+10	6.62	7.34	9.31	Mild
2	Flash burn	15+10	5.29	10.30	8.45	Moderate
3	Flash burn	5+20	5.74	13.20	12.50	Severe
4	Flash burn	20+5	4.44	8.74	6.75	Moderate
5	Flash burn	20	5.71	10.80	12.05	Severe
6	Flash burn	10+15	7.00	10.40	11.80	Moderate
7	Flash burn	15+5	12.80	16.20	13.80	Severe
8	Flash burn	15+15	6.19	5.85	7.86	Moderate
9	Flash burn	10+15	5.32	5.02	6.35	Severe
10	Flash burn	10+15	4.94	11.00	9.51	Severe
11	Flash burn	20+5	4.75	4.68	5.93	Severe
12	Flash burn	10+10	5.26	4.55	6.40	Moderate
13	Flash burn	10+10	2.29	-	7.79	Mild
14	Scald burn	10+10	7.64	5.01	8.15	Moderate
15	Scald burn	0+20	5.10	4.78	7.49	Moderate
16	Scald burn	15+10	2.52	3.90	4.60	Moderate
17	Scald burn	20	2.90	3.41	6.82	Severe
18	Scald burn	60	2.82	3.78	4.88	Severe
19	Scald burn	5+15	3.36	2.35	4.25	Mild
20	Scald burn	15+10	6.48	5.39	6.84	Mild

*: Signifies deep burn surface areas, **: Signifies superficial burn surface area

Significant results were obtained when IgA levels were compared by ANOVA with respect to time period. IgG levels were evaluated in a paired fashion and there were statistically significant difference between the IgG levels of the first 48 hours and 10th-90th days.

The difference was not significant between 10th and 90th days (p>0,05) (Table 4). Significant results were obtained when IgM levels were compared by ANOVA with respect to time period. IgM levels were evaluated in a paired fashion and there were statistically significant difference between the IgM levels of the first 48 hours, 10th-90th days. The difference was not significant between 10th and 90th days (p>0.05) (Table 5).

Table 4. Cases, IgA levels and hypertrophic scar evaluation.

Cases	Burn type	Burn surface area *+**	IgA g/L First 48 hours	IgA g/L 10 th day	IgA g/L 90 th day	Hypertrophic scar evaluation
1	Flash burn	5+10	1.50	2.14	1.89	Mild
2	Flash burn	15+10	1.33	2.05	4.50	Moderate
3	Flash burn	5+20	1.33	4.01	2.39	Severe
4	Flash burn	20+5	1.13	2.69	1.45	Moderate
5	Flash burn	20	1.55	3.16	3.40	Severe
6	Flash burn	10+15	1.78	3.99	4.70	Moderate
7	Flash burn	15+5	1.08	2.20	1.29	Severe
8	Flash burn	15+15	0.93	1.54	1.66	Moderate
9	Flash burn	10+15	1.27	2.96	4.70	Severe
10	Flash burn	10+15	1.59	3.46	2.79	Severe
11	Flash burn	20+5	0.93	2.94	4.85	Severe
12	Flash burn	10+10	1.40	1.62	2.00	Moderate
13	Flash burn	10+10	0.83	-	1.44	Mild
14	Scald burn	10+10	0.71	0.69	2.80	Moderate
15	Scald burn	0+20	0.29	0.44	0.82	Moderate
16	Scald burn	15+10	0.17	0.33	0.56	Moderate
17	Scald burn	20	0.56	0.79	1.75	Severe
18	Scald burn	60	0.74	0.96	1.36	Severe
19	Scald burn	5+15	0.34	0.76	1.43	Mild
20	Scald burn	15+10	1.11	2.42	2.85	Mild

*: Signifies deep burn surface areas, **: Signifies superficial burn surface area

Table 5. Cases, IgM levels and hypertrophic scar evaluation.

Cases	Burn type	Burn surface area *+**	IgA g/L First 48 hours	IgA g/L 10 th day	IgA g/L 90 th day	Hypertrophic scar evaluation
1	Flash burn	5+10	0.864	1.150	0.952	Mild
2	Flash burn	15+10	0.963	1.184	0.806	Moderate
3	Flash burn	5+20	0.743	0.764	1.250	Severe
4	Flash burn	20+5	0.551	0.965	0.672	Moderate
5	Flash burn	20	0.350	0.626	0.588	Severe
6	Flash burn	10+15	0.874	0.953	0.825	Moderate
7	Flash burn	15+5	0.596	0.837	0.715	Severe
8	Flash burn	15+15	1.300	1.570	1.710	Moderate
9	Flash burn	10+15	0.644	0.845	0.630	Severe
10	Flash burn	10+15	0.548	0.741	0.726	Severe
11	Flash burn	20+5	0.585	1.210	2.250	Severe
12	Flash burn	10+10	0.484	1.658	0.784	Moderate
13	Flash burn	10+10	0.963	-	1.370	Mild
14	Scald burn	10+10	1.100	0.783	1.500	Moderate
15	Scald burn	0+20	0.375	0.722	0.822	Moderate
16	Scald burn	15+10	0.380	0.688	0.830	Moderate
17	Scald burn	20	0.597	0.313	0.860	Severe
18	Scald burn	60	0.521	0.467	0.790	Severe
19	Scald burn	5+15	0.283	0.335	0.657	Mild
20	Scald burn	15+10	0.802	0.630	0.960	Mild

*: Signifies deep burn surface areas, **: Signifies superficial burn surface area

Significant results were obtained when IgE levels were compared by ANOVA with respect to time period. When the IgE levels were compared in a paired fashion, a significant difference was found between the measurements of 48 hours and 10th days ($p < 0.05$). No difference was found between the measurements of 48 hours and 90th days. There was also significant difference between the 10th and 90th day measurements (Table 6).

Table 6. Cases, IgE levels and hypertrophic scar evaluation.

Cases	Burn type	Burn surface area *+**	IgE IU/mL First 48 hours	IgE IU/mL 10 th day	IgE IU/mL 90 th day	Hypertrophic scar evaluation
1	Flash burn	5+10	3.00	1.0	25.5	Mild
2	Flash burn	15+10	201.00	260.3	127.5	Moderate
3	Flash burn	5+20	127.00	139.6	91.3	Severe
4	Flash burn	20+5	106.00	219.9	154.0	Moderate
5	Flash burn	20	111.00	109.4	37.1	Severe
6	Flash burn	10+15	84.00	61.1	41.6	Moderate
7	Flash burn	15+5	1004.10	1085.7	1300.0	Severe
8	Flash burn	15+15	241	363.4	311.6	Moderate
9	Flash burn	10+15	187.60	199.0	125.1	Severe
10	Flash burn	10+15	6.80	14.9	81.6	Severe
11	Flash burn	20+5	8.10	97.0	12.3	Severe
12	Flash burn	10+10	136.00	164.7	148.5	Moderate
13	Flash burn	10+10	44.20	-	22.6	Mild
14	Scald burn	10+10	5.00	1.0	10.6	Moderate
15	Scald burn	0+20	107.50	128.0	110.8	Moderate
16	Scald burn	15+10	95.40	118.2	135.8	Moderate
17	Scald burn	20	63.78	118.5	126.4	Severe
18	Scald burn	60	83.50	61.4	72.5	Severe
19	Scald burn	5+15	110.30	125.7	105.5	Mild
20	Scald burn	15+10	11.20	18.9	38.1	Mild

The degree of hypertrophic scars were mild in 4 of the patients (20%), moderate in 8 of the patients (40%) and severe in 8 of them (40%). Ten patients healed with spontaneous epithelization (50%) and in ten of them skin grafting was performed (50%). In summary, levels of IgG, IgM and IgA were either unchanged or slightly decreased in the early period after burn injury and the levels returned to normal at 90th day. However, the levels of IgE displayed a considerable variability. For assessing the relation between the course of IgE levels and the hypertrophic scar formation exact test was performed. For the adjustment of the groups IgE levels were classified as normal and above normal. There was no significant difference between the degree of hypertrophic scarring and the levels of IgE at 48 hours, on days 10 and 90 (Tables 7, 8, 9).

Table 7. IgE levels at 48 hours and the corresponding scar evaluation.

	Mild	Moderate	Severe
Normal	2	3	4
Above normal	1	4	6
p > 0.05			

Table 8. IgE levels on day 10 and the corresponding scar evaluation.

	Mild	Moderate	Severe
Normal	2	2	2
Above normal	1	5	5
p > 0.05			

Table 9. IgE levels on day 90 and the corresponding scar evaluation.

	Mild	Moderate	Severe
Normal	2	2	2
Above normal	1	5	5
p > 0.05			

Discussion

Although the exact mechanism is still unclear, hypertrophic scar and keloid formation is expected to be seen after deep burns [9, 10]. In third degree burns which were allowed to heal by secondary intention and second degree burns in which the spontaneous epithelization time exceeded three weeks, the risk of hypertrophic scarring and contracture increases [9]. The most important methodological problem in designing clinical studies to investigate this phenomenon is to standardize patients and the burn wound itself. There were abundant studies which investigated the serum immunoglobulin levels in burn patients, however, the ones which suggested a relation with hypertrophic scar mechanism were rare [3-6]. Our data relating the levels immunoglobulin G, M and A revealed a decrease in the early postburn period and this is parallel to the literature [11]. There were two studies in the literature suggesting the relation of high IgE levels with hypertrophic scar formation [7, 8]. In the study of Polacek et al. [7], it was shown that the levels of IgE levels increased after burn injury. The degree of this increase was not consistent and in some cases twentyfold rises have been detected. In another study Smith et al. [8] dealt with anticollagen IgG antibodies and suggested the role of them in the formation of hypertrophic scars. Their data showed that IgE levels were also high in those cases. Molina et al. [12] suggested immunoglobulin treatment for alleviating fibrosis, similar to the use of immunoglobulins in other diseases going with fibrosis such as cirrhosis and cystic fibrosis. Our data about serum IgE levels displayed some peculiarities. In eight of the patients the levels stayed within the normal levels in the course of the study (patient numbers 1, 6, 10, 11, 13, 14, 18, 20). In eight of them the levels were above normal in all samples (patient numbers 2, 4, 7, 8, 9, 12, 15, 19). In two of the patients while the levels at 48 hours were above normal, by the 90th day they returned to normal (patient numbers 3, 5). In two of the patients while the levels at 48 hour were within the normal range, they increased and stayed high on day 90 (patient numbers 16, 17). Severe hypertrophy was detected in eight patients (Patient numbers 3, 5, 7, 9, 10, 11, 17, 18). Obviously, these result are quite variable to suggest a consistent response of IgE levels to the burn injury unlike the previous studies [7, 8]. Moreover, the occurrence of severe hypertrophic scarring seemed totally irrelevant to the IgE levels in the course of the study. The Exact test also verified this suggestion. This study was unable to establish a significant relation between the immunoglobulin levels and the formation of hypertrophic scars. However; the patient no 7, merits special attention. His serum IgE levels stayed very high (tenfold of normal) during our study and severe hypertrophic scar developed. There no story of allergy or atopy in this patient and further studies did not reveal a reason for this high IgE levels.

The relative short duration of the follow up is the main shortcoming of this study. However, it should also be noted that overt hypertrophic scarring was already fully developed in many of the patients.

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