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Monitoring the Level of Microalbuminuria, As A Prognostic Test in Severe Burns

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ABSTRACT

Purpose: To evaluate the effectiveness of microalbuminuria monitoring in management of severely burned patients.

Methods: Patients admitted to the burn unit of North West Armed Forces Hospitals, in the period between June 2010 and December 2011 with total body surface area burn between 20-50% were traced for microalbuminuria during the whole hospitalization period. The findings were correlated to different clinical variables usually encountered in these patients category.

Results: Microalbuminuria was found positive in most patients with inhalation injuries, systemic inflammatory response syndrome, burn sepsis and postoperatively.

Conclusion: Microalbuminuria is mainly remarkable in adults and it is an effective marker in burn patients who suffered local and systemic complications.

INTRODUCTION

Arturson **[1]** in 1961, demonstrated in animal models that there is a systemic capillary leak of proteins and fluids, occurring during the first 24 hours, when thermal injury exceeds 30% of total body surface area. Protein escape rate is known to increase 100-fold in thermally-injured skin and 5-fold in non injured tissues **[2]**. The mechanisms of capillary leak include histamine-induced endothelial cell contraction with formation of inter endothelial gaps, lipid peroxidation and loss of intercellular adhesions **[3,4]**.

In the renal glomeruli and tubular cells, the same effect occurs. This leads to leakage of significant amounts of albumin to the urine. Albuminuria is defined clinically as a urine albumin concentration more than 200mg/L. The term "Microalbuminuria" (MAU) refers to the excretion of pathologically significant amounts of normal molecular weight albumin in the range of 30-200mg/L **[5]**. A link between increased systemic vascular permeability to albumin and MAU was suggested by Parving **[6]** since 1974, who displayed a correlation between MAU and increased transcapillary escape rate of radiolabelled albumin in hypertensive and diabetic patients. Dramatic increased radiolabelled albumin escape rate had been demonstrated during surgery, sepsis and malignancy that were found to share a common time frame with MAU **[7]**.

Microalbuminuria following acute inflammatory insult, such as surgery, has been demonstrated in human models. This led to the hypothesis that MAU is a reflection of systemic vascular endothelial dysfunction **[8-10]**. Since that time MAU has been investigated as a significant marker of systemic inflammation and useful predictor of outcome in multiple trauma, major surgery, ischemia-reperfusion injury, pancreatitis, meningitis, anaphylaxis and critical illness **[8,11-16]**.

Several proinflammatory cytokines play a role in the pathogenesis of systemic inflammatory response syndrome (SIRS). They are also considered as markers of inflammation in the laboratory evaluation of burned patients. These include Tumor necrosis factor alpha (TNFα), interleukin 1 and interleukin 6 (IL1, IL6) **[17]**. IL6 is one of the most consistent markers of poor outcome in burned patients. It induces the production of C-reactive protein (CRP) by the liver. ,which is also considered as a marker of mortality in burned patients **[18]**.

Although proteinuria is a demonstrated phenomenon after burn injury, no prior studies were found to correlate MAU with ongoing capillary leak, fluid requirements, clinical evidence of ongoing shock, or development of SIRS or multiple organ failure. Relationships between MAU and clinical outcomes of burn patients have not been established in literature.

In this study we tried to correlate between MAU and clinical variables in post burn period in severe burns. Severe burn injury is defined by American

burn association as any second or third degree burn greater than 20% of the TBSA (or 10% in patients under 10 or over 50 years old) [19]. The study was carried out in an attempt to find a simple, cost-effective and at the same time reliable prognostic factor in burned patients.

PATIENTS AND METHODS

Consecutive patients admitted to the burn units of North West Armed Forces Hospitals, Tabuk, Saudi Arabia were recruited between June 2010 and December 2011. Any patient with total body surface area (TBSA) burn of 20-50% of both sexes and all age groups were enrolled in the study. Patients presented with delay more than 24 hours, and patients with history of any disease which may affect renal functions as diabetes, hypertension and systemic lubus erythematosis were excluded. Pregnant women were excluded because of the changes in hemodynamics accompanying pregnancy. The patients were classified according to their age into two groups; adult-age group: 15 years old and above, (Group 1) and pediatric-age group: under 15 years, (Group 2). Another grouping is planned to be done after collection of data. This will further sub-divide the patients into another two sub groups. Subgroup A will include patients who will develop SIRS during the post burn period. Subgroup B includes those who will not develop SIRS during the whole hospitalization period.

All patients were subjected to full history taking and proper examination with accurate estimation of the TBSA affected using the Lund and Browder chart. On admission to the burn unit, all patients were resuscitated with crystalloids followed by colloids according to the Parkland formula (4mL/kg/% TBSA/first 24hrs); colloids were given as human albumin, fresh frozen plasma during the next 24hrs. The infusion volume was adjusted to produce a mean hourly urine output of 30-50mL/h (0.5-1.0mL/h/kg in children).

Antibiotics were not given routinely on admission. In cases of infection, antibiotics were given according to the sensitivity tests. The burn wound care was routinely done according to our unit protocol. Surgical treatment in-cluded immediate escherotomy in circumferential deep burns, early excision and grafting with auto grafts as indicated.

The clinical diagnosis of SIRS was based on at least two of the following parameters [20]. Body temperature of more than 38°C or less than 36ºC, heart rate of more than 90 beats per minute, respiratory rate of more than 20 breaths per minute or a $PaCO_2$ level of less than 32mmHg and/or abnormal white blood cell count (>12,000/mL or <4,000/mL or >10% bands).

Full laboratory investigations were collected to document the patient's baseline status. These include complete blood picture, electrolytes, liver and kidney function tests, serum albumin and C-reactive protein (CRP). Urine specimens were collected to scrutinize MAU. All laboratory investigations were repeated, every other day; with the addition of swab wound culture and blood culture as necessary to trace any local or invasive wound infections. Special attention was paid to both CRP and MAU with proper documentation.

Spot urine samples were collected soon after admission and on alternate days. Urine samples were either analyzed within two hours of collection or stored at –20ºC till analysis. The frozen samples were left to thaw till reaching the room temperature. If a sample became turbid after thawing, it was clarified by centrifugation prior to testing.

Urinary microalbumin was measured by the light-scattering technique (Dimension RxL Max, Dade Behring Inc., USA). In this immunochemical reaction, the protein in the urine form immune complexes with specific antibodies. These complexes scatter a beam of light passed through the sample. The intensity of the scattered light is proportional to the concentration of the relevant protein in the sample.

RESULTS

The study population consisted of 49 patients (27 males and 22 females), (37 adults, 12 children). The median age of enrolled patients was 28 years, and the median TBSA burn injury was 25%. Inhalation injury was present in 4 of the study patients (8.2%). Median time of hospitalization after burn injury was 33.2 days, and the patients who required surgical intervention were 39 patients (79.6%). All patients were discharged home after complete cure or with some minor complications as wound contracture, only two patients in the study groups were died (4.08%).

The baseline clinical and demographic characteristics of patients with and without MAU are shown in Table (1). Forty three patients among the total of forty nine patients (87.7%) had MAU. No significant difference could be detected between male and female patients. Patients with MAU were older compared with those without MAU; overall prevalence in adult patients was 72.3%. All patients (100%) with proved inhalation injury had documented MAU.

In depth analysis of the two study groups, although MAU did develop in both groups, its prevalence was higher in group 1; 94.6%. In group 2, MAU prevalence was 66.7%.

Microalbuminuria was traced started from admission time and continued in alternate days till patient's discharge. MAU was present in 95.1% of swab-documented infected wound patients and in 100% of all patients with proved (positive blood culture) invasive wound infection (Table 1). Both localized wound colonization and systemic invasive wound infections were much more common in group 1 (83.8% and 45.9% respectively), which is also the group with the most frequent positive MAU. The total number of patients subjected to burn wound infection was 41 patients (83.7%) whereas only 19 (38.8%) patients developed invasive systemic infection.

In correlation of MAU with the different types of surgical interventions, it was found that MAU was positive in 37 out of 39 patients who underwent surgeries (94.9%) (Table 1). This means that MAU, as a marker of systemic endothelial dysfunction, reflects the critical status of burn patients especially after surgical procedures.

Table (1): Characteristics of patients with and without MAU.

	MAU (+)	MAU (–)	Total
No. (%)	43 (87.8)	6 (12.2)	49
Sex (M:F)	23:20	4:2	27:22
Inhalation injury (%)	4 (100)	0 (0)	4
G1 (%); Adult ≥20%	35 (94.6)	2 (5.4)	37
G2 (%); Child ≥20%	8 (66.7)	4 (33.3)	12
GA (%); +ve SIRS	38 (92.7)	3 (7.3)	41
GB (%); -ve SIRS	5 (62.5)	3 (37.5)	8
Wound sepsis (%)	39 (95.1)	2 (4.9)	41
Invasive wound infection (%)	19 (100)	0 (0)	19
Surgical intervention (%)	37 (94.9)	2 (5.1)	39

Systemic Inflammatory Response Syndrome was monitored throughout the study period. The baseline clinical and demographic characteristics of patients with and without SIRS are shown in Table (2).

Systemic inflammatory response syndrome was significantly prevalent in group 1 (33 out of 37 patients) (89.2%) than group 2 (8 out of 12 patients) (66.7%). SIRS was accompanying patients who developed wound sepsis (85.4%) whereas in patients with invasive infection its presence increased to 94.7%. Also, it was more prevalent in patients with surgical interventions (89.7%). An 88.4% of patients with MAU are among the group who developed SIRS (Table 2). The course of MAU as noticed in patients of both groups is demonstrated in Table (3).

Table (2): Characteristics of patients with and without SIRS.

	SIRS (+)	SIRS (–)	Total
No. (%)	41 (83.7)	8 (16.3)	49
Sex (M:F)	21:20	6:2	27:22
Inhalation injury (%)	3 (75)	1 (25)	4
G1 (%); Adult ≥20%	33 (89.2)	4 (10.8)	37
G2 (%); Child ≥20%	8 (66.7)	4 (33.3)	12
Wound sepsis (%)	35 (85.4)	6 (14.6)	41
Invasive wound infection (%)	18 (94.7)	1 (5.3)	19
Surgical intervention (%)	35 (89.7)	4 (10.3)	39
MAU (%)	38 (88.4)	5 (11.6)	43

Table (3): Behaviors of MAU in the study groups.

	No.	Mean	SD	Min.	Max.
Appearance day:					
G1	37	4.6216	4.5847	0	21
G2	12	10.1818	15.27624	0	46
Total	49	4.1264	6.96804	0	46
Appearance value:					
G1	37	103.4892	147.71591	0	678.1
G2	12	52.2091	58.98285	0	193
Total	49	62.5379	110.60937	0	678.1
Peak day:					
G1	37	12.1351	5.6429	0	23
G2	12	15.5455	19.64873	0	53
Total	49	8.4828	10.07514	0	53
Peak value:					
G1	37	356.9757	218.59324	0	831
G2	12	77.9273	108.59259	0	372.1
Total	49	187.4954	222.15629	0	831
Disappearance day:					
G1	37	27.2432	13.8492	0	53
G2	12	18	21.87693	0	60
Total	49	15.7931	17.18107	0	60

DISCUSSION

This prospective study was carried out in an attempt to find a simple, cost-effective and at the same time reliable prognostic factor in burned patients, which could be used in developing countries with limited resources.

Different authors studied previously microalbuminuria. They found it is a consistent finding in inflammatory states, including ischemia-reperfusion injury, pancreatitis, systemic inflammatory response syndrome, sepsis, and metabolic syndromes. Transient MAU has also been associated with surgical stress **[21]**. In addition, MAU provides an early indicator of ARDS, sepsis, and mortality in critical illness **[16]**.

In our study we got some results which confirm a definite significance of MAU in burn patients. This role is not universal for all patients. MAU seems to be more valuable in certain patients'

group which is adults with severe burn (≥20% TBSA). It was found to be positive in 94.6% in this category. These findings explain why most of the published articles concerning MAU resolute on adult patients. Very few studies on children was established as with Schultz and colleagues **[20]** where they found that blood pressure will rise in children with type I diabetes mellitus only after appearance of MAU.

In the present study, MAU was prevalent in most patients with inhalation injury. So we suggest that it is of no benefit to monitor MAU in these patients' categories. This is completely compatible with others **[23]** where they documented that Inhalation injury was present in 30% of their studied patients, and all patients with inhalation injury had MAU at the time of admission.

Systemic inflammatory response syndrome is much more common in adult patients. It is of interest also to notice that this was parallel to the result of MAU in the same groups. So, MAU could be effectively used as an indicator for the SIRS in burned patients. This finding was found compatible with Greenhalgh and colleagues **[24]**.

Microalbuminuria was present in 77.2% of swab-documented infected wound patients and in 100% of all patients with proved (positive blood culture) invasive wound infection. This may be attributed to the inflammatory state accompanying infection. No other studies had been found to correlate MAU with burn wound infection before. MAU had been investigated extensively with other specific infections as urinary tract infection, AIDS and viral hepatitis but not with burn wound infection.

In our study, MAU was positive in 80% of subjects who underwent surgeries. There are also a lot of studies that correlated MAU with surgical stress. Mercatello **[25]** and Vlachou **[26]** had monitored MAU as a marker of systemic endothelial dysfunction during burn excision. They concluded that systemic endothelial dysfunction of acute thermal injury assessed by MAU recurs with surgery, is minimal at 2-7 days post-burn and affected by % TBSA burn excised and postoperative complications.

Local wound complications and generalized systemic complications showed high prevalence of MAU (86.7% and 88.6% respectively). This is very evident in most of studies concerned with the systemic upset in burned patients but no studies were found to correlate MAU with the possibility of development of local wound complications.

Some limitations to our study are that data were not collected regarding either actual or suspected alcohol or drug intoxication. Based on prior study, substance intoxication may result in more pronounced MAU **[5]**. Antibiotics were not recorded as well; some groups have nephrotoxic effect. In addition that we did not record the body mass index (BMI) of patients; which may have an effect on MAU **[27]**.

This study was designed as a preliminary investigation, and represents the first study we are aware of that evaluates the clinical relevance of microalbuminuria after burn injury during the whole hospitalization period. Although microalbuminuria correlates with injury severity in trauma and in a mixed patient population **[23]** our results suggest that it does not correlate with the traditional believe for burn injury severity of age and TBSA burn injury.

To conclude, microalbuminuria was found going parallel to the occurrence of SIRS and was positive in severe burns, inhalation injury, invasive wound infection, and after surgical intervention; this is mainly in adults. So, monitoring of microalbuminuria could be used effectively as a marker for SIRS, invasive wound infection, and to monitor systemic disorders following surgery in burns.

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