

CHRONIC STRESS IN THE HEALING PROCESSES OF ELDERLY SUBJECTS WITH CHRONIC SKIN LESIONS (DIABETIC FOOT)

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ABSTRACT

Introduction: Foot ulcers result from a combination of factors such as increased biomechanical stress, reduced skin perfusion, loss of protective sensations, and external trauma. A major complication of the diabetic foot is infection, which in most cases sets in on an ulcer that has been open for a long time and not specifically and adequately treated. The AA have evaluated changes in chronic stress with the efficacy of HAM on subjects with chronic diabetic foot skin lesions versus nondiabetic control subjects with peripheral arterial disease.

Materials and methods: Study design: 20 subjects (4 F - 16 M mean age 68.5±4.9) group "A" with chronic diabetic skin foot lesions (CDSFL) were admitted to our study, according to a randomization scheme, and evaluated versus 20 healthy subjects group "B" (9 F-11 M mean age 67.2±7.1 controls) with peripheral arterial disease.

Results: The two groups showed no statistically significant differences in sex and age variables. Sample analysis showed a higher MSP regulation score than the 75th percentile values significant among subjects "A" with CDSFL versus subjects in group "B" with AP for the variables of MSP scores and the percentage of patients with clinically significant stress ($p = 0.01$ and $p = 00:05$). Individual cluster analysis showed a statistically significant difference between the two groups for only clusters 1 and 2 ($p = 0.03$ and $p = 0.04$, respectively).

Discussion-conclusion: In this study we showed the existence of a close correlation between infectious markers and emotional and functional stress factors in both male and female populations. The data of this study show a close correlation between subjects with chronic skin lesions with CDSFL and the loss of control, irritability, sense of confusion, depression and anxiety that are frequently present in elderly subjects with disabling diseases. The diabetic foot is a multifactorial pathology that requires an integrated multidisciplinary therapeutic approach where the support of clinical psychology.

Keywords: Chronic stress, chronic skin lesions, type II diabetes, diabetic foot.

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Introduction

Ulcerative lesions of the diabetic foot represent the most common consequence of neuropathy and peripheral arterial disease. Foot ulcers result from a combination of factors such as increased biomechanical stress, reduced skin perfusion, loss of protective sensations, and external trauma. The international consensus document on the diabetic foot (2003), confirms and extends this definition to all those diabetic subjects who are at

risk of ulceration, and defines as diabetic foot the consequences of anatomic-functional alterations determined by peripheral occlusive arteriopathy and/or diabetic neuropathy⁽¹⁻²³⁾. An important complication of the diabetic foot is infection, which in most cases occurs on an ulcer that has been open for a long time and has not been specifically and adequately treated. However, obtaining precise data on the incidence and prevalence of infectious risk is rather difficult. Some AA. have evaluated the infectious risk of having an ulcer in the foot between

15 and 25% of subjects with type II diabetes. Our previous studies have evaluated the therapeutic role of human amniotic membrane (HAM) in chronic skin lesions⁽²⁴⁻³⁰⁾. The antibacterial activity of HAM is mainly due to the presence of lactoferrin and IL-1RA both of which have "in vitro" and "in vivo" a remarkable antimicrobial and anti-inflammatory power. It was also highlighted the close correlation between chronic negative stress condition with the deep biological levels that are at the base of many chronic diseases such as diabetes type II.⁽²¹⁾

Although the exact nature of this relationship is still not completely clear, several hypotheses have been proposed, the most important of which is that of Hans Selye according to which the biological reactions that accompany the general adaptation syndrome (GAS) are the effect of short and long-term physical changes. A state of agitation causes in a subject the release of stress hormones such as cortisol, adrenaline and noradrenaline that determine a burst of energy to be able to face new negative situations. However, too high levels of these hormones or repeated exposure to them can begin to negatively affect important functions of our body. A physiological reaction to a state of chronic stress is also the activation of the orthosympathetic nervous system. In fact, stress involves a state of "pressure" that can evolve in two phases: a temporary and a chronic one. This last state of stress persists beyond the real external needs determining a chronic imbalance in the functioning of the same organism. Chronic stress, before evolving to determine systemic diseases, begins with a phase of increasing psychophysical pathology: headaches, pain, fatigue, panic attacks, insomnia, sense of alarm, difficulty in concentration and decision-making, repetitive thoughts, irritability. In particular, a number of AAs have sought to investigate the importance of psychosocial factors in the healing process of chronic skin lesions (CSL)⁽³²⁻³⁷⁾. On the basis of this knowledge, we proposed to evaluate the variation of chronic stress with the effectiveness of HAM on subjects with chronic diabetic foot skin lesions in comparison with non-diabetic control subjects and with peripheral arterial disease.

Materials and methods

Study design

20 subjects (4 F - 16 M mean age 68.5±4.9) group "A" with chronic diabetic skin foot lesions (CDSFL) were admitted to our study, according to

a randomization scheme, and evaluated versus 20 healthy subjects group "B" (9 F-11 M mean age 67.2±7.1 controls) with peripheral arterial disease (PAD). These two groups were studied and compared on a behavioral basis to analyze the possible presence of functional stress. The baseline characteristics of the two study groups "A" and "B" are described in Table 1.

| Characteristics | Group "A" N°20 | Mean ±Standard Deviation | Range |
|---------------------------------|-------------------|-----------------------------|---------|
| Sex (F/M) | 4/16 | | |
| Age (years) | | 68±4.8 | |
| BMI (kg/m ²) | | 26.8±3.5 | |
| Heart Rate (b.p.m.) | | 85±10 | |
| Systolic blood pressure (mmHg) | | 136±16 | |
| Diastolic blood pressure (mmHg) | | 87±20 | |
| Smokers (yes/no) | 8/12 | | |
| Plasma glucose (mg/dl) | | 204±16 | |
| HbA1c % (range) | | | 7.5-9.5 |
| Cholesterol (mg/dl) | | 240±16 | |
| HDL cholesterol (mg/dl) | | 39±12 | |
| LDL cholesterol (mg/dl) | | 178±10 | |
| Triglycerides (mg/dl) | | 291±14 | |

| Characteristics | Group "B" N° 20 | Mean ±Standard Deviation | Range |
|---------------------------------|--------------------|-----------------------------|---------|
| Sex (F/M) | 9/11 | | |
| Age (years) | | 67.2±7.1 | |
| BMI (kg/m ²) | | 26.10±3.1 | |
| Heart Rate (b.p.m.) | | 82±12 | |
| Systolic blood pressure (mmHg) | | 135±15 | |
| Diastolic blood pressure (mmHg) | | 87±12 | |
| Smokers (yes/no) | 3/13 | | |
| Plasma glucose (mg/dl) | | 100±10 | |
| HbA1c % (range) | | | 6.5-7.5 |
| Cholesterol (mg/dl) | | 221±10 | |
| HDL cholesterol (mg/dl) | | 38±10 | |
| LDL cholesterol (mg/dl) | | 146±12 | |
| Triglycerides (mg/dl) | | 265±12 | |

Table 1: The basal characteristics of the two study groups "A" subjects with chronic diabetic foot injury and "B" controls.

Treatment

Diabetic patients with chronic diabetic foot skin lesions (CDSFL) included in our study were treated according to the outcome of bacteriological examinations and related "in vitro" sensitivity test (MIC) in targeted therapy with particular reference to amino glycosides⁽¹⁹⁾. Subsequently, human amniotic membrane (HAM) grafting was performed according to the specific surgical techniques from previous experience described⁽²¹⁻³⁴⁾.

Measure of perceived Stress" (MPS) test

The test proposed to assess the self-perceived aspects of stress, "feeling stressed" was derived from an instrument widely established in the international field, the Mesuredu Stress Psychologique (MSP) developed by researchers at the Ecole de Psychologie of Laval University in Quebec^(19,21).

It is a questionnaire consisting of 49 items based on the different aspects related to the perception that the individual has of his state (cognitive-affective, physiological, behavioral), in very recent time: the purpose is in fact to describe the current state of stress. The stress indices contained in this measure come from the normal population (in the sense of not ill), and thus reflect the variability observable in this population. The criteria for constructing the original scale, the characteristics of reliability and construct validity, predictiveness and concurrentness, have been described in the volume cited above^(34, 37) in which the clinical and research applications of the test both in Canada and in other countries including Italy are also described in detail, as well as the procedures followed for the translation, Italian adaptation and standardization and calibration of the test.

MPS test evaluation grid (measure of perceived stress)

Calculation of the overall score

The scores indicated by the subject for each item will be added. For the four items and inverted scoring: 22, 24, 43, 49 the evaluation is done by assigning:

- 4 points if the subject has indicated 1
- 3 points if the subject has indicated 2
- 2 points if the subject has indicated 3
- 1 point if the subject has indicated 4

In the case where the score is missing for some items, make a correction to the score obtained using the formula: (sum of items completed*49)/Number of Items complete.

Clusters Assessment:

- Clusters I - Loss of control, irritability.

Sum the scores of items: 11, 22, 32, 35, 36, 46 and divide the sum by 6.

- Clusters II - Psychophysiological Sensations.

Add the scores of the items 16, 25, 34, 40 and divide the sum by 4.

- Clusters III - Sense of Strain and Confusion.

Add the scores of items 33, 37, 41, 42 and divide the sum by 4.

- Clusters IV - Depressive Anxiety.

Add the scores of the items 6,13,15,29 and divide the sum by 4.

- Clusters V- Pain and Physical Problems.

Add the scores of items 12, 14, 28 and divide the sum by 3.

- Clusters VI- Hyperactivity, accelerated behaviors.

Sum the scores of the items: 26,44,45 and divide the sum by 3.

Statistical analysis

Data were analyzed using STATA 11.0 software. Data were entered into the data base twice and were checked for completeness and consistency before analysis. Quantitative variables were described using mean and standard deviation. Given the normal distribution of the data (Shapiro's test for normal data was used) appropriate parametric tests were used. The difference between means and the difference between proportions was assessed by T test and Chi-square respectively.

A multivariate analysis was also performed and the following was calculated for each variable included in the study: Odds Ratio (OR), 95% Confidence Interval (CI), p value (two-tailed test, p=0.05). Variables associated with out as in the multivariate analysis with a p=0.2 were included consecutively in the final model.

Results

The clinical and psychological demographic characteristics of the subjects enrolled in the study and divided into two groups "A" and "B" are highlighted in Table 1. The sample was subdivided: 20 subjects with chronic diabetic foot skin lesions (CDSFL) ("A") for at least one year and signs and symptoms of skin infections in the diabetic foot group "A" and 20 subjects with peripheral arterial disease (PA) group "B" controls for at least one year. The two groups showed no statistically significant differences with

regard to sex and age variables Table 2. Analysis of the sample showed a higher MSP regulation score than the 75th percentile values (Table 3).

Through a more detailed analysis by individual subgroups we noted a statistically significant difference between subjects "A" with CDSFL versus subjects in group "B" with AP for MSP score variables and with the percentage of patients with clinically significant stress ($p=0.01$ and $p=0.05$ respectively) (Table 3). Individual cluster analysis showed a statistically significant difference between the two groups for only clusters 1 and 2 ($p=0.03$ and $p=0.04$, respectively) (Table 3 and Figure 1).

Multivariate analysis that extracted as the main the presence or absence of clinically significant stress, found that, controlling for age and sex and the presence of chronic diabetic foot ulcers represent two risk factors for the development of stress. Consequently, all subjects in group "A" with chronic diabetic foot ulcers were treated with local and systemic tobramycin antibiotic therapy.

After the treatment with antibiotic and with the relative negative microbiological finding from the culture examination, we proceeded to the grafting of the human amniotic membrane specifically following the method of the authors Grasso et al.^(19, 37).

Figure 2 shows a chronic cutaneous lesion of diabetic foot before the beginning of the antibiotic therapy. Figure 3 shows chronic diabetic foot skin lesions being treated (2 weeks) with targeted antibiotic therapy.

| | Total | "A" (CDFSL) | "B" (controls) | p |
|------------------------|------------|-------------|----------------|------|
| Number (%) | 40 | 20(75) | 20 (45) | |
| M/F (%) | 19/21 (65) | 18 (60) | 12 (60) | 1 |
| Età (mean ±DS) | 67.8±5.7 | 68.4±4.8 | 67.2±7.1 | 0.8 |
| MSP score (mean±DS) | 103± 23.5 | 107.5±24.6 | 93.2±26.6 | 0.06 |
| N° pat. con stress (%) | 32 (72,4) | 24 (73,3) | 20(40) | 0.05 |
| cluster 1 (mean±DS) | 2,4±0,6 | 2,6±0,7 | 1,9±0,4 | 0,3 |
| cluster 2 (mean±DS) | 2,6±0,4 | 2,5±0,6 | 1,4±0,2 | 0,03 |
| cluster 3 (mean±DS) | 2,5±0,6 | 2,9±1,8 | 1,8±0,6 | 0,04 |
| cluster 4 (mean±DS) | 2,2±0,6 | 2,5±0,9 | 1,9±0,7 | 0,06 |
| cluster 5 (mean±DS) | 2,3±0,5 | 2,6±1,0 | 1,9±0,6 | 0,05 |
| cluster 6 (mean±DS) | 2,6±0,7 | 3,1±0,8 | 2,2±0,5 | 0,01 |

Table 2: Cluster characteristics of subjects "A" with chronic diabetic foot skin lesions (CDFSL) and subjects "B" with peripheral arterial disease (controls) compared.

| Val. Cluster | "A" (CDFSL) | "B" (controls) | S.V.N.75° percentile |
|--------------|-------------|----------------|----------------------|
| cluster 1 | 2,6 | 1,9 | 2,4 |
| cluster 2 | 2,5 | 1,4 | 2 |
| cluster 3 | 2,9 | 1,8 | 2 |
| cluster 4 | 2,5 | 1,9 | 2,21 |
| cluster 5 | 2,6 | 1,9 | 2 |
| cluster 6 | 3,1 | 2,2 | 3 |

Table 3: Evaluation of individual clusters between cluster "A" (CDFSL) compared with cluster "B" (controls) and with normative values.

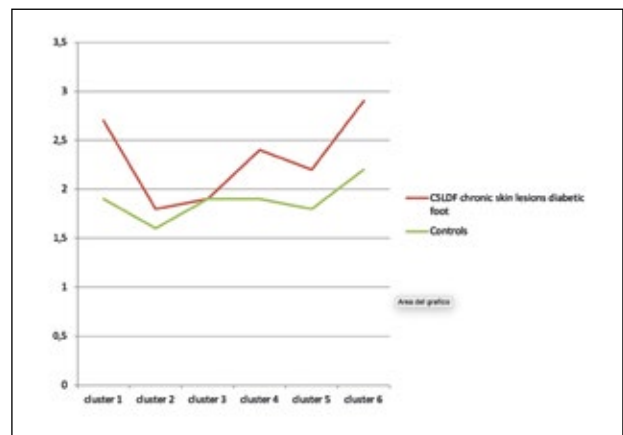


Figure 1: Evaluation of MPS in subjects with chronic diabetic foot skin lesions group "A" (CDFSL) compared to subjects with peripheral arterial disease group "B" controls (PAD).



Figure 2: Shows a chronic diabetic foot skin lesion (CDFSL) prior to initiation of antibiotic therapy.

Discussion and conclusions

The diabetic foot is a multifactorial pathology that requires an integrated multidisciplinary therapeutic approach where the support of clinical

psychology plays a central role. In addition to measures of local character, dedicated to the localization of the organ of the pathology, it is necessary to manage both the general conditions that have determined the pathology at the level of the foot, and the systemic physiological and psychological conditions of the patient, burdened by an important co-morbidity. Undoubtedly, this integrated multidisciplinary approach requires a team of highly qualified personnel to treat this important and complex pathology. Despite the obvious complexity of the pathology, once an appropriate therapeutic program is implemented, the results will be comforting, managing to prevent serious consequences such as amputation⁽³⁸⁻⁴²⁾.



Figure 3: Shows chronic diabetic foot skin lesions (CDFSL) being treated (2 weeks) with human amniotic membrane.

The treatment of the diabetic foot does not end with the management of the acute phase, but must take charge of both the induction phase, pre-ulcerative, with interventions aimed at preventing the evolution of the disease, and the chronic phase, with appropriate orthotic-rehabilitative interventions and a follow-up program. In the acute ulcerative phase, revascularization, surgical therapy and treatment of systemic psychological conditions are the cornerstones of therapy to achieve good results. In this study we have highlighted the existence of a close correlation between infectious markers and emotional and functional stress factors in both male and female populations. In fact, there is a close correlation between chronic pathologies such as diabetic foot lesions (CDFSL) and behavioral alterations assessable with functional stress tests. The data of this study show a close correlation between subjects with chronic skin lesions with CDFSL and the loss of control, irritability, sense of confusion,

depression and anxiety that are frequently present in elderly subjects with disabling diseases⁽³⁴⁻³⁷⁾.

This approach allows us to understand how anxiety disorders, committed with chronic stress, cannot be differentiated and understood by looking at them from a single angle. In the light of these our first results, some general considerations can be drawn, subjects with chronic skin lesions such as CDFSL with the related biological problems of scarring significantly trigger the process of chronic functional stress than subjects with peripheral arterial disease. These first data need further study and confirmation to evaluate the pathological nature of these neuro-psychological alterations and their close relationship with the skin microbiota. The related psychological aspects have been treated by Dr. Chisari Eleonora Margherita

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