INTRODUCTION

Keloids and hypertrophic scars (HS) are disorders characterized by excessive accumulation of extracellular matrix produced by fibroblasts.1,2 Keloids are often confused with HS. Clinically, HS do not extend the lesion’s border, often regress, and have a better prognosis than the keloids.3 Although there are no exact criteria for its histopathological differentiation, keloids have less cellularity and thick collagen bundles with irregular patterns, whereas HS have more fibroblast proliferation and collagen fibers in nodules parallel to the epidermis (Table 1).4,5

The inflammatory phase of the healing may be related to the formation of these pathologic scars. The derivatives of arachidonic acid (AA), mainly prostaglandins (PGs) and leukotrienes, play a fundamental role in this process.6 The metabolism of the AA follows the pathway indicated by the enzyme that initiates its reaction: cyclooxygenase (COX) and lipoxygenase (Fig. 1).7,8 COX, also known as prostaglandin-endoperoxide synthase (PGHS) catalyzes the conversion of AA into PGs G2 and H2. The PGH2 is then converted into eicosanoids, such as PGE2, that promotes the recruitment of inflammatory cells, which release TGFβ, activating the fibroblasts and inducing the production of the extracellular matrix.9,10 The nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit COX and therefore the synthesis of PGs.7,6 There are at least 2 COX isoforms: COX1 and COX2.10 Both catalyze the same reaction. However, almost all normal tissues show an expression of COX1, which has a mainly homeostatic function, and low levels of COX2.11,12 COX2 is mainly induced by...
inflammatory stimuli. Therefore, specific inhibitors of COX2 have been developed to inhibit inflammation without blocking the protective effects of the constituent PGs. Studies on the distribution of COXs in skin are scarce. Rossiello et al.\textsuperscript{13} concluded that in normal skin COX1 is expressed both in the epidermis and the dermis, while COX2 is rarely found.

Several methods are described as treatment of pathologic scars, such as compression, massage, excision, topical or injectable corticosteroids, silicone gel, radiotherapy, cryotherapy, CO\textsubscript{2} laser, intense pulsed light, 5-fluorouracil, mitomycin, bleomycin, and antihistamines. Most of these therapies have a high recurrence rate.\textsuperscript{14–16} Studies have suggested that pharmacological blockade of COX could be an adjuvant in the treatment of pathological scars.\textsuperscript{13,17,18} An experimental study showed a 50\% reduction in PGE\textsubscript{2} levels in wound healing with the application of celecoxib, with less scar tissue formation.\textsuperscript{18} It was also demonstrated that the immunohistochemical (IHC) expression of COXs in HS and keloids is greater than in normal scars. Kössi et al.\textsuperscript{19} found different COX1 and COX2 gene expressions in normal and abnormal scars. Therefore, COX activity may influence scar formation.\textsuperscript{13,17,18}

The objective of this study was to compare the IHC expression of COXs in normal scars, HS, and keloids.

### METHODOLOGY

A prospective study was conducted at the Universidade Federal de Ciências Médicas de Porto Alegre (UFCSPA), Rio Grande do Sul, Brazil. Fifty-four (54) consecutive patients (aged 18–60 years) were included and underwent excision of scars (18 normal, 18 hypertrophic, and 18 keloids) in the period from January 2014 to January 2015. The participants signed an informed consent form, which as approved along with the study, by the Research Ethics Committee UFCSPA, registered under number 24680913.3.0000.5345.

The excision of the scars was performed under local anesthesia with 2\% lidocaine with epinephrine (1:200,000 - Xylestesin, from the brand Cristália, Itapira, Brazil). Fragments of the scars were collected and immediately stored in a 10\% buffered formalin solution. Two examinations were performed:

1. Anatomopathological examination: hematoxylin-eosin (HE), to differentiate keloids, HS and normal scars.
2. IHC examination, to assess and quantify the expression of COX1 and COX2 in skin samples.

The examinations were performed in the Research Laboratory of the Postgraduate Program in Pathology at UFCSPA. The inclusion in the groups was performed according to Table 1. Differences between Keloids and Hypertrophic Scars

| Scar          | Keloid | Hypertrophic Scar |
|---------------|--------|-------------------|
| Clinical findings | Beyond the limits of injury | Within the limits of the lesion |
| Appearance     | Without spontaneous regression | Spontaneous regression |
| Symptom        | Pain, itching | Itching |
| Histopathology | Cellularity (fibroblasts) | Smaller, without myofibroblasts |
| Collagen       | Thick, irregular bundles | Greater |
| Type of collagen | 3 | Arrangements in nodules, parallel to the epidermis 1 and 3 |
| Skin appendages | Without glands or hair follicles | May have glands or hair follicles |
| Stages of healing | Do not enter in the remodeling phase | Can enter in the remodeling phase |

Main clinical and histopathological differences between keloids and hypertrophic scars. Based on Al-Attar et al.\textsuperscript{14}, Rabello et al.\textsuperscript{20}

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**Fig. 1.** Metabolism of AA and lipoxygenase-cyclooxygenase pathways (Figure produced by the author, based on Stitham et al.\textsuperscript{8} and Kumar et al.\textsuperscript{7}).
The slides were analyzed using the Olympus BX51 microscope (Olympus DP72-optical), digitized with Olympus DP2-BSW 2.2 software. For each slide at high magnification, 5 fields were randomly chosen for the epidermis and 5 for the dermis, containing images of good quality. The percentage of positive cells was determined by counting 100 cells. It was considered a positive IHC expression when at least 30% of cells presented moderate to strong nuclear immunoreactivity.

Results

The distribution of the patients by age, sex, location of the scar, cause of the scar, time with scar, and Fitzpatrick phototype can be seen in Table 2. The mean age of the patients obtained for group III (keloids) was significantly lower than in the other groups. No difference was obtained between the groups in relation to the time with scar. Group III had the highest concentration of the male sex. Regarding the cause of the scars, cases of inflammatory origin (acne) only occurring in the group of patients with keloids. Normal and HS occurred more in the torso, while keloids more in the face, because this group including a significant number of keloids in the earlobes. Regarding skin phototype, the groups of patients with Fitzpatrick I-II and III-IV presented more normal scars and HS than the V-VI types that had greater number of keloids.

The classification of the cases into the groups, initially based on the clinical criteria, was confirmed by HE staining in all cases.

The results of the IHC expression of the COXs are seen in Tables 3, 4 and charts of Figures 2, 3.

Table 2. Patient Characteristics and Clinical Data

| Variables          | Group 1 — Normal Scars | Group 2 — Hypertrophic Scars | Group 3 — Keloids | P        |
|--------------------|-------------------------|-------------------------------|-------------------|----------|
| N                  | 18                      | 18                            | 18                | 0.000    |
| Age (y)            | 35.2                    | 37.6                          | 22.2              |          |
| SD                 | 9.8                     | 12.0                          | 7.1               |          |
| Variation          | 18-55                   | 18-60                         | 18-44             |          |
| Time of scar (mo)  | 15.06                   | 13.50                         | 12.50             | 0.503*   |
| Sex (% of cases)   | Male 0                  | 16.67                         | 66.67             | 0.045    |
| Female 100         | 83.33                   | 33.33                         |                   |          |
| Cause (% of cases) | Inflammatory 0          | 0                             | 22.22             | 0.000    |
| Surgical 100       | 88.89                   | 38.89                         |                   |          |
| Burn 0             | 5.56                    | 0                             |                   |          |
| Trauma 0           | 0                       | 5.56                          | 38.89             |          |
| Location of scar   | Trunk 88.89             | 77.78                         | 16.67             | 0.000    |
|                    | Face 5.56               | 5.56                          | 72.22             |          |
|                    | Members 5.56            | 16.67                         | 11.11             |          |
| Skin phototype (% of cases) | Fitzpatrick I - II | 77.78                    | 66.67              |          |
|                    | Fitzpatrick III-IV      | 22.22                         | 33.33              |          |
|                    | Fitzpatrick V-VI        | 0                             | 0                  |          |

The table shows distribution of characteristics of patients (sex and age) and clinical data of the scars in the groups. The variables age and time with scar were analyzed using the analysis of variance test and the remaining variables by the χ² test. *Statistically significant differences.

The IHC technique for COX1 and COX2 was performed according to the standard routines. The antibodies used were COX1: Clone RPR5866 from Abcam. As a positive control, human skin was used (dilution 1/200). COX2: Clone SP21 from Abcam. Positive Control - Breast carcinoma (dilution 1/50). Secondary and tertiary antibody kit - universal Vectastain - Elite ABC kit.

Table 3. IHC Expression of COX1 in Skin Samples

| IHC Expression of COX1 | Group 1 Normal Scars | Group 2 Hypertrophic Scars | Group 3 Keloids | P (between All Groups) | P (between Group 1 x Groups 2 and 3) |
|------------------------|----------------------|---------------------------|-----------------|------------------------|-------------------------------------|
| Epidermis, n (%)       |                      |                           |                 |                        |                                     |
| Negative               | 3 (16.67)            | 2 (11.11)                 | 1 (5.56)        | 0.570                  | 0.388                               |
| Positive               | 15 (83.33)           | 16 (88.89)                | 17 (94.44)      |                        |                                     |
| Dermis, n (%)          |                      |                           |                 |                        |                                     |
| Negative               | 15 (83.33)           | 8 (44.44)                 | 7 (38.89)       | 0.014*                 | 0.004*                              |
| Positive               | 3 (16.67)            | 10 (55.56)                | 11 (61.11)      |                        |                                     |

Results of IHC expression of COX1 in the epidermis and dermis. Values expressed in number of cases and percentage of the total group. Comparisons were made between all groups and also between group 1 (normal scars) and pathological scars (keloids and hypertrophic scars were included in a single group). The dermis of pathological scars presented a greater number of cases with positive expression of COX1 when compared with normal scars. *Statistically significant differences (Fisher’s exact test).
Table 3 shows the results of the comparison of the IHC expression of the COX1 in the epidermis and dermis between all groups and between group 1 (normal scars) and groups 2 and 3 together (pathological scarring). There was no significant difference in the expression of COX1 in the epidermis in any comparison. In the dermis, however, a significant difference was obtained both in the comparison among all the groups ($P = 0.014$) and in the comparison between normal and pathological scars ($P = 0.004$); groups 2 and 3 had more cases with a positive expression of COX1 when compared with normal scars. Figures 4, 5 show IHC reaction with a positive expression of COX1 in the epidermis and dermis, respectively.

### Table 4. IHC Expression of COX2 in Skin Samples

| IHC Expression of COX2 | Group 1: Normal Scars | Group 2: Hypertrophic Scars | Group 3: Keloids | $P$ (between All Groups) | $P$ (between Group 1 x Groups 2 and 3) |
|------------------------|-----------------------|-----------------------------|------------------|--------------------------|----------------------------------|
| **Epidermis, n (%)**   |                       |                             |                  |                          |                                  |
| Negative               | 14 (77.78)            | 14 (77.78)                  | 11 (61.11)       | 0.436                    | 0.519                            |
| Positive               | 4 (22.22)             | 4 (22.22)                   | 7 (38.89)        |                          |                                  |
| **Dermis, n (%)**      |                       |                             |                  |                          |                                  |
| Negative               | 13 (72.22)            | 9 (50.00)                   | 8 (44.44)        | 0.207                    | 0.081                            |
| Positive               | 5 (27.78)             | 9 (50.00)                   | 10 (55.56)       |                          |                                  |

Results of IHC expression of COX2 in the epidermis and dermis. Values expressed in number of cases and percentage on the total of the group (in parentheses). Without significant difference between groups in all comparison (Fisher’s exact test).

Fig. 2. The graph shows the percentage of cases in each group in which the IHC expression of COX1 was positive. It is observed that, in the dermis there were more positive cases for COX1 in the groups of the hypertrophic and keloid scars compared with the group of normal scars.

Fig. 3. Graph showing the percentage of cases in each group with positive COX2 IHC expression. There was no statistically significant difference among the 3 groups in both the epidermis and the dermis.

Table 4 shows the results of the comparison of the IHC expression of the COX1 in the epidermis and dermis between all groups and between group 1 (normal scars) and groups 2 and 3 together (pathological scarring). There was no significant difference in the expression of COX1 in the epidermis in any comparison. In the dermis, however, a significant difference was obtained both in the comparison among all the groups ($P = 0.014$) and in the comparison between normal and pathological scars ($P = 0.004$); groups 2 and 3 had more cases with a positive expression of COX1 when compared with normal scars. Figures 4, 5 show IHC reaction with a positive expression of COX1 in the epidermis and dermis, respectively.

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**Fig. 2.** The graph shows the percentage of cases in each group in which the IHC expression of COX1 was positive. It is observed that, in the dermis there were more positive cases for COX1 in the groups of the hypertrophic and keloid scars compared with the group of normal scars.

**Fig. 3.** Graph showing the percentage of cases in each group with positive COX2 IHC expression. There was no statistically significant difference among the 3 groups in both the epidermis and the dermis.

**Fig. 4.** Field of view of a slide stained of hypertrophic scar (IHC technique for COX1) in the epidermis ($\times 400$). The black arrow shows cells with brown staining, demonstrating positive IHC expression for COX1. The red arrow indicates section of a vessel containing hemacy, not considered a positive count.

**Fig. 5.** Sample of histological section of hypertrophic scar (IHC for COX1). Multiple fibroblasts (arrows) with brown staining showing a positive reaction in the dermis ($\times 400$).
Table 4 shows the results of the comparison of the IHC expression of the COX2 in the epidermis and dermis among all groups and between group 1 and groups 2 and 3 together. There was no statistical difference in the COX2 expression in any comparison, whether in the epidermis or the dermis. In the comparison between group 1 and groups 2 and 3 together, the data suggest a tendency toward greater positivity in the COX2 expression in the dermis for groups 2 and 3, although with $P = 0.081$. Figure 6 shows negative IHQ expression for COX2 in both epidermis and dermis of keloid scar.

An intra-group comparison of IHQ expression of the COXs was also analyzed. In the epidermis, a positive COX1 expression was greater than that of COX2 in all types of scars. In the dermis, however, there was no significant difference between the COX1 and COX2 expression, in any comparison.

**DISCUSSION**

The pathologic scars represent frequent complications as a result of invasive procedures in certain medical specialties such as thoracic surgery, general surgery, gynecology, head and neck surgery, and dermatology. However, plastic surgery presents the greatest problems with keloids and HS, as the scar itself is an integral part of the outcome of the performed treatments. In addition to the aesthetic and functional disorders, these complications lead to lawsuits, resulting from dissatisfaction with the outcome obtained (Figs. 7, 8).

The pathogenesis of keloids and HS is not fully understood. Alterations in growth factor regulation, failure in collagen remodeling, genetic disorders, and immunological dysfunctions have been implicated. Other causes may be endocrine and neural factors. Psychiatric diseases could also be involved. Although the role of PGs in healing is not definitely established, it is known that they can induce the in vitro proliferation of fibroblasts and collagen production in wounds, in vivo. Knowledge of wound healing without scars in fetuses suggests that the PGs and the respective inflammatory response induced control, at least in part, of the amount of fibrosis formed after skin injury and repair. Skin lesions produced in the first and second halves of fetal life can evolve without scars, with regeneration of normal skin, including the growth of skin appendages. It is noteworthy that this phenomenon of healing without scars occurs in the absence of inflammation. It is assumed, therefore, that the inflammatory phase of wound repair results in the production of scar tissue. Wilgus et al. studied fetal healing in mice. The COX2 expression and the ability of exogenous PGE2 to alter the wound healing was examined. The authors concluded that the COX2 pathway is involved in fetal wound healing, and treatments targeted at its blockade could limit the formation of skin scars in adults. The same authors...
demonstrated scar reduction in mice with the topical administration of a COX2 blocker. Celecoxib inhibited various parameters of inflammation at the wound site, leading to the reduction of scar tissue. The authors suggested that adult wounds could have a reduction in the inflammatory stage and that NSAIDs could improve the healing process. It is important to reiterate that keloids occur exclusively in humans and therefore the results of this study, conducted on mice, could not be safely extrapolated to our species. In our study, the IHC expression of COX2 was not significantly different between the groups, and we could infer that the topical application of COX2 blocker may not be beneficial in the treatment of these scars.

One possible disadvantage of the use of celecoxib would be its potential influence on delayed healing of surgical wounds. Su et al. consider that the NSAIDs, inhibitors of COX2, could, by reducing PGE2 production, exacerbate the formation of excessive scarring, especially when used in the final period of the proliferative phase.

Similar to our study, Abdou et al. evaluated the pattern and location of COX1 and COX2 in scars. Forty patients were included (15 HS, 15 keloids, and 10 normal scars). The immunoreactivity was considered positive when any expression was identified. The intensity of expression was evaluated subjectively as light, moderate, or strong. The difference in the COX1 expressions in normal scars, HS, and keloids (40%, 53.3% and 100%, respectively) was statistically significant. There was no significant difference in any comparison in the COX2 expression. These data are similar to those obtained in our study. It is relevant to point out that in the research of Abdou et al., the group of normal scars was composed of 10 cases retrieved from the pathology department’s files. It is known that IHC reaction is sensitive to a vast number of factors, including the solution’s buffering method for the preservation of the tissue sample. Conversely, in our study, all samples of skin were handled and processed by the same methodology, in an effort to minimize errors. Another difference between our study and that of Abdou et al. is that they performed the cell count including fibroblasts, endothelial cells, and inflammatory cells. We chose to disregard the vascular endothelium cell count as our goal was to evaluate only the cell responsible for the fibroplasia, the fibroblast (Fig. 9).

In our study, although we observed greater IHC expression of COX1 in pathological scars if compared with normal scars, we did not identify significant differences between keloids and HS. In turn, Rossiello et al. found differences in this comparison. They studied 36 cases of patients with keloids, 32 cases of HS, and 25 cases of normal skin, aiming to define the location and expression of COX1 and COX2. The results showed an increased expression of COX1 in HS when compared with normal skin and keloids and an increased expression of COX2 in keloids when compared with normal skin and HS. The authors concluded that COX1 is involved in the formation of HS and COX2 in the formation of keloids. In this study, the cases of pathological scars were compared with normal skin, rather than normal scars, as carried out in our study.

We believe that some variables could influence the results of studies. The IHC reaction comprises diverse and complex processes at all stages, and therefore with potential errors. Without standardization, the technique can result in nonreproducible and unreliable data. The methodology used for evaluating the intensity of the IHC expression is critical. In addition to the technical details involved with its execution, the variety of criteria adopted as the cutoff for positivity can make studies incomparable. Other factors that could influence the results would be the inherent difficulty to categorize the patients in the groups. In our study, patients were included consecutively, according to the type of scar, disregarding of other variables. The group of patients with keloids had lower mean age and higher concentration of men than other groups, since it included a higher number of posttraumatic scars, more prevalent in this population range. The highest concentration of patients with keloids and HS in patients with Fitzpatrick III-VI phototypes is compatible with the frequency described for these diseases. In agreement with our findings, in the study performed by Abdou et al., the distribution of the patients in groups was also unequal in relation to the mean age and the cause of the scars. Patients with normal scars had the surgical incisions as their main cause, while HS keloids are predominantly caused by trauma or burns. The study of Rossiello et al. did not describe the characteristics of the groups and therefore did not analyze their possible differences.

Even though there is a tendency in the studies to show a positive relationship between the increased expression of the COXs and the HS and keloids, the data are not conclusive. In general, the inducible COX2, is known to be involved in pathological processes, whereas COX1 is in physiological processes. However, in our study, the enzyme that was shown to have the greatest expression in pathological scars was COX1. The number of studies is small with heterogeneous results. New researches could even use alternative methods for the IHC reaction. Although it is not possible to precisely qualify and quantify the relationship between COX and scarring, their expressions are
not the same in the different types of scars, demonstrating that there is certain influence of them in this process.

CONCLUSIONS
The comparison of the IHC expression of the COX1 in the epidermis of scars did not show significant difference among groups. However, in the dermis, we obtained a significant difference: the groups of pathologic scars had more cases with a positive expression of the COX1 when compared with group of normal scars. The results of the IHC expression of the COX2 in the epidermis and dermis did not show any statistical difference when compared.

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