Is the Increase of Body Mass Index (BMI) A Risk Factor for Keloid?

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Abstract

Background: Although a number of hypotheses have been proposed for keloid pathogenesis, no single unifying hypothesis adequately explains its formation. For that reason, currently available therapies are palliative and have led to inconsistent results. The adipose tissue has been recognised as a reservoir of pro-inflammatory cytokines, which are directly involved in cell differentiation and proliferation, influencing fibrogenesis and wound healing. And, as the keloid is considered as a pro-inflammatory scar, increased adipose tissue could be a risk factor. Therefore, the objective of the present study was to evaluate the body mass index (BMI) of patients with keloids.

Methods: Analytic, observational, cross-sectional, controlled study. Forty-three patients with keloid and 39 patients with normal scars were enrolled and had their BMI measured. All scars in both groups were at least one year old. Patients were selected from Plastic Surgery Outpatient Clinic.

Results: BMI was higher in the keloid group than in the control group (p = 0.034). There was a higher prevalence of skin colour "white" patients (p = 0.003).

Conclusion: Patients with keloid had higher BMI than those with normal scars. This result reinforces the hypothesis of the neuroimmunoendocrine nature of keloid in which the inflammatory pathway (with the production of pro-inflammatory mediators by the adipose tissue) plays a pivotal role, as in other skin diseases such as psoriasis.

Keywords: Keloid; Body Mass Index; Adipose Tissue; Adipokines; Inflammation

Introduction

Keloid is a proliferative scar dysfunction that occurs only to human [1,2]. It is formed by an excessive build up of collagen fibers in response to dermal injury of exogenous (skin trauma or surgery incision) or endogenous origin (acne or chicken pox) [3]. Because of its deforming tumor aspect, it affects most of keloid patients not only in physical appearance and functional capacity (itching and throbbing pain), but also in
psychological and social aspects, with negative impact on the quality of life [4]. The mechanisms involved in keloid formation are only partially understood [3,5]. Therefore, current therapeutic modalities are only palliative and their results have been inconsistent [5]. However, several risk factors, including body constitution, scarring complications and associated comorbidities are known to cause keloid.

The adipose tissue is considered as an endocrine organ as it secretes active adipokines which include leptin, adiponectin, resist in and cytokines, such as Vascular Endothelial Growth Factor (VEGF), Insulin-like Growth Factor-1 (IGF-1), Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α) and Transforming Growth Factor-beta1 (TGF-beta1) [6-9]. Therefore, it can contribute directly toward an increase in acute systemic inflammation, as well as maintain this inflammation in a chronic state, promoting the perpetuation and recurrence of keloid. Thus, could it be possible that an excessive amount of adipose tissue predispose to the development of keloid or represent a risk factor?

A positive correlation between serum TGF-β1 and the body mass index (BMI) was described [10]. Moreover, TGF-β1 induces the secretion of plasminogen activator inhibitor-1 (PAI-1), which also has a positive correlation with BMI [11]. Therefore, the present study aimed to associate keloid with the amount of adipose tissue using the BMI.

Methods

The present study included 43 patients with keloid by endogenous origin (Keloid Group-KG). The control group (CG) comprised 39 patients with normotrophic scars. There were patients from both genders, white and non-white skin color, age between 15 and 50 years and all scars had at least 1 year long. All patients were from Plastic Surgery Outpatient Clinic. There were not included patients who underwent bariatric surgery, were under any treatment to lose weight or who routinely practice sports activities; previous history of malignant neoplasia or any other chronic and systemic disease. Were excluded any patient who wanted to leave this study or did not complete any of the study steps.

After anamnesis, the BMI (Body Mass Index) of each patient was calculated using the formula: weight (kg) / [height (m)]². The level of rejection of the null hypothesis was p<0.05.

The present study was approved by the Research Ethics Committee (378/06). All patients read, understood, agreed and signed the Free and Clarified Consent Term.

Results

The BMI was higher in the KG compared to CG (p=0.034). There was homogeneity between the groups with regard to age and gender (Table 1).

|                     | Keloid Group (n=43) | Control Group (n=39) |
|---------------------|--------------------|----------------------|
| BMI Kg/m² (median)  | 24.85              | 23.52                |
| p                   | 0.034              |                      |
| Age (median)        | 27                 | 30                   |
| p                   | 0.039              |                      |
| Gender              |                    |                      |
| Female              | 20                 | 23                   |
| Male                | 23                 | 16                   |
| p                   | 0.26               |                      |
| Skin color          |                    |                      |
| White               | 22                 | 32                   |
| Non-White           | 21                 | 7                    |
| p                   | 0.003              |                      |

Table 1: Body Mass Index (BMI) and characteristics between KG and CG (A- Mann-Whitney Test; B - Chi-Square Test).

Discussion

Traditionally, adipose tissue represents a passive storage depot of energy [12]. However, several adipokines and cytokines secreted by adipocytes have been identified, mainly pro-inflammatory molecules [8,9,13]. Because this knowledge, the adipose tissue is considered a very relevant endocrine organ [12], involving both systemic and local inflammation, focusing on skin, for its comprehensive body distribution.

The status of chronic inflammation present in overweight and obesity may predispose individuals to a wide variety of inflammatory illnesses or leverage other existing diseases [14]. Similar to keloid, psoriasis is an inflammatory hyper proliferative skin disease, in which obesity is a major risk factor and increased BMI is directly related to the severity of the disease [15]. Other studies have associated psoriasis with metabolic syndrome [14,15]. However, no associations were found between BMI and keloid.

In obesity, there is a proportional increase in the production and secretion of TGF-β1 and PAI-1 by visceral and subcutaneous adipose tissue [11]. Increased PAI-1 expression is associated with insulin resistance and...
excessive tissue fibrosis [6,16]. TGF-β1 stimulates the production and secretion of collagen via stimulation of skin fibroblasts, and in keloid, via stimulation and increased production of fibronectin [17].

The nutritional intake can be adjunct to the treatment, especially in the prevention of keloid. Louw (2000) [18] showed that essential fatty acid deficiency (EFAD) of the omega-6 series (linoleic acid (LA), g-linolenic acid (GLA) and dihomo-g-linolenic acid (DGLA)); and the omega-3 series (α-linolenic acid (ALA) and eicosapentaenoic acid (EPA)); but enhanced arachidonic acid (AA) levels were prevalent in keloid patients. Generally, keloid patients have an AA dietary intake higher than the recommended (7 - 11g/d), and lower recommended intake of ALA and EPA (1.1 - 1.5g/d) [19]. Enhanced AA associated with deficiency of its precursors (LA, GLA and DGLA) and inflammatory competitors (DGLA and EPA) are inevitably responsible for the overproduction of pro-inflammatory metabolites, such as prostaglandin E2 (PGE2).

PGE2 is involved in the expression of extracellular matrix metalloproteinases (MMP). The reduced levels of PGE2 in keloid tissue are responsible for the reduction of theses collagen cleavage enzymes, such as MMP-1 [20], and the subsequent accumulation of ECM. Therefore, there is an excessive deposit, and consequently, accumulation of collagen in the ECM. Prostaglandin D2 (PGD2), which is secreted by mast cells via several reactions from arachidonic acid, is an important pro-inflammatory factor in the role of allergic responses [21]. Keloid is histologic related to mast cell infiltrate and activation as well to atopic reactions. Accordingly, this evidence support increased mast cells and elevated levels of PGD2 within the fibrotic microenvironment in keloid [22]. Moreover, EPA can inhibit the production of pro-inflammatory cytokines, such as IL-1, IL-6 [23] and TNF-α [24]. Deficiency of fatty acid could exacerbate these pro-inflammatory factors [25] that are highly associated with keloid tissue inflammation [26, 27].

In the present study, BMI was higher in KG, although it was not classified as overweight (25 to 29.99 kg/m²). This finding corroborates with other authors and with the fact that hypertrophic scars are also related to increase BMI [28, 29]. However, the BMI 24.85 kg/m² in KG reported the median value. Possibly with a larger sample, the median would be above 25kg/m². Furthermore, it was not possible to say if the patient was overweight or obese at the time of keloid formation. On the other hand, BMI values were significantly increased in keloid patients, and this condition could create a self-sustaining inflammatory cycle that would perpetuate keloid, or even its postoperative recurrence. Our results suggest further studies to investigate the effects of increased adipose tissue in patients with pathological fibro proliferative scars. Moreover, modulatory diet and the amount of adipose tissue of these patients [27] are keys to prevention and treatment for keloid.

**Conclusion**

Patients with keloid had higher BMI than those with normal scars.

**Acknowledgement**

Tribute is paid to the great master Professor Bernardo Hochman. This is a posthumous tribute to him, he devoted much of his life to studying, understanding, teaching, and disseminating what the keloid really is. We will remember forever his words "If the eyes are the mirror of the soul, the skin is the mirror of the mind."

**Ethical Approval**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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