The Role of Nerves and Sensibility in Keloids: Functional Sensory Testing and Clinical Correlation

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The primary objective will be to evaluate the sensation of the keloids as measured by Semmes-Weinstein monofilaments (SWM), Pressure Specified Sensory Device (PSSD) and/or Quantitative Sensory Testing (QST), compared between patients with and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Epidermal and dermal conditions
Study type	Observational non invasive

Summary

ID

NL-OMON52274

Source
ToetsingOnline

Brief title
Quantifying Sensibility in Keloids

Condition

- Epidermal and dermal conditions

Synonym
Keloid, keloid scar

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Stichting Annadal

Intervention

Keyword: Innervation, Keloid, Nerves, Sensibility

Outcome measures

Primary outcome

The primary outcome of the study is the sensibility of keloid (measured by SWM, PSSD and QST). Results will be compared between patients with versus patients without substantial clinical symptoms of pain and/or itch. All patients who are followed-up at the outpatient scar clinic fill in the Patient and Observer Scar Assessment Scale (POSAS) at each visit. The POSAS also evaluates pain and itch on a VAS of 1-10. Previous studies definied a score of 3 or more as substantial.

For the SWM monofilaments, the thinnest monofilament value that was identified by the participant will be used for analysis. Means and standard deviations will be calculated for the entire cohort, both for keloid skin and control skin, as for the clinical subgroups.

For the PSSD measurements, the mean of 3 measurements will be calculated and used for statistical analysis. Means and standard deviations will be calculated for the entire cohort, both for keloid skin and control skin, as for the clinical subgroups.

For the QST, we will perform measurements to determine cold detection threshold (CDT), cold pain threshold (CPT), warmth detection threshold (WDT) and heat pain threshold (HPT). For each threshold, we will also perform the measurements

3 times and calculate the mean to use for statistical analysis. Then means and standard deviations will be calculated for the entire cohort, both for keloid skin and control skin, as for the clinical subgroups.

Between-group differences will be tested using univariable linear regression analysis.

Secondary outcome

The secondary outcome that will be evaluated will be the sensibility (measured by SWM, PSSD and QST), compared between keloid skin and control skin. All patients will undergo sensory testing of the keloid and normal unaffected skin on the contralateral side. In case of keloid location in the midline, the healthy skin in the dermatoma inferior to the keloid will be used as control. The paired-sample t-test will be used to investigate whether there is a difference in sensibility between keloid and control skin within patients

For all sensory tests and comparison groups (substantial clinical symptoms versus no substantial clinical symptoms and keloid versus controle skin), adjusted between-group differences will be computed using multivariable linear regression analysis, in which potential confounding variables will be added as covariates in the model. The following study parameters that will be measured as possible confounders are

- Age of patient
- Gender

- Location of keloid (face, ears, chest, shoulders, abdomen, limbs)

- Age of keloid

- Skin type

- Previous treatment (type, timing and duration)

Additionally, abovementioned univariable and multivariable linear regression analyses will be repeated using itch and pain scores as continuous variables, instead of dichotomizing into substantial itch and pain.

Study description

Background summary

Almost every person develops scars during his or her life, as a result of dermal injury caused by either trauma, surgery or infection. When the skin is injured and skin integrity is disrupted, a physiological process, known as the wound healing cascade, is initiated. This finely orchestrated process involves several overlapping phases and starts with hemostasis. Dermal injury causes disruption of the vascular endothelium and exposure of the basal lamina, which results in platelet activation, initiating the coagulation cascade and the release of several growth factors and mediators. Immediately following hemostasis, inflammation takes place to clear debris and bacteria. This phase lasts 4 to 6 days. Subsequently, the proliferative phase starts, during which new tissue is formed and the epidermis is restored. Fibroblasts form a new matrix consisting of type III collagen, glycosaminoglycans and fibronectin. This matrix is later remodelled during the last phase of wound healing, the maturation phase which can last to over 1 year. A normal, matured scar then appears as a thin white line.

Complex interactions between different cell types occur, as does the release of several growth factors and mediators to finely orchestrate the wound healing process. Any disturbance of this complex process can lead to problems such as chronic wounds or excess formation of scar tissue, ranging from hypertrophic to keloid scars.
Hypertrophic scars are raised, red, firm and thick scars that develop rather

early in the maturation phase (usually several weeks after injury) and tend to regress spontaneously after a prolonged maturation phase.
Keloid scars are less common and develop sometimes months to even years after injury and are characterized by raised exophytic growth beyond the borders of the original wound. As opposed to hypertrophic scars, keloids do not regress spontaneously and are often refractory to many treatments. These pathologic scars give rise to a range of aesthetical, psychological and physical symptoms, impairing both psychological and physical quality of life. A recent study by Bijlard et al investigated the impact of keloid disease of health-related quality of life (HRQL) and found that keloid disease was associated with a considerable impairment of emotional and mental HRQL. Of keloid patients with substantial pain and itch scores (> 3 on a 10 point scale), 70% had severe emotional HRQL impairment compared with 16% in keloid patients who had low pain and itch scores, showing that pain and pruritus are the main indicators of emotional HRQL impairment. Pruritus has been reported to occur in 86% of keloids and the prevalence of keloid-related pain has been reported to be 46%.

To date, the questions of why keloid patients experience pain and which are the underlying mechanisms remain unanswered. Saffari et al explored whether the keloid-related pain was rather nociceptive or neuropathic, but their study showed a wide variation of possible pain mechanisms involved and a wide variation between the pain experiences in individual patients.

Previously, a possible role for nerve fibres was hypothesized in keloid pathogenesis. Using quantitative sensory testing (QST), thermosensory thresholds to warmth and cold were assessed in the keloids and a loss of sensory perception was found, showing abnormalities in small fibre function, which suggests the presence of small fibre neuropathy. However, both of the studies that performed QST were explorative and included a very small number of patients, which limits the generalisability of the conclusions.

Based on the current knowledge, we hypothesize that clinical symptoms of pain and pruritus in keloids are correlated with nerve fibre function and thus with functional sensory testing. A better understanding on the role of nerves and the pathogenesis of keloids can lead to new insights for future therapeutic options.

Study objective

The primary objective will be to evaluate the sensation of the keloids as measured by Semmes-Weinstein monofilaments (SWM), Pressure Specified Sensory Device (PSSD) and/or Quantitative Sensory Testing (QST), compared between patients with and patients without substantial clinical symptoms of pain and pruritus.

Secondarily, each patient will serve as their own control to compare functional sensibility between keloids and control skin. Furthermore, we will investigate

the association between patient characteristics and sensibility.

Study design

This prospective observational study will be conducted at the department of Plastic, Reconstructive and Hand Surgery of the Maastricht UMC+. Maastricht UMC+ has a specialized multidisciplinary outpatient clinic for complex scar management, where patients from all over the region are followed up on a regular basis. The specialized *scar* clinic focuses mainly on hypertrophic and keloid scar care. The multidisciplinary team consists of a physiotherapist specialized in scar treatment, an orthotist, a resident in plastic surgery and/or a plastic surgeon.
Patients who wish to participate with this study, will undergo functional sensory testing of their keloids and contralateral unaffected control skin. Other than functional sensory testing no interventions that aren*t part of standard care will be performed.

Study burden and risks

This study doesn*t create specific additional risks, nor does it provide additional benefits to participants. The participants will undergo sensory testing in order to investigate the role of nerves in keloids and whether there is a correlation between clinical symptoms and functional sensibility. The main burden associated with participation is the time investment for sensory testing, which is estimated at 20 minutes.

Contacts

Public
Medisch Universitair Ziekenhuis Maastricht

P Debeyelaan 25
Maastricht 6229 HX
NL
Scientific
Medisch Universitair Ziekenhuis Maastricht

P Debeyelaan 25
Maastricht 6229 HX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- 18 years or older
- Diagnosed with keloid disease (A keloid is defined as a well-demarcated area of fibrous tissue overgrowth which extends over the margins of the original injury)
- Keloid size must be 1.5cm in length or more

Exclusion criteria

- Known (neurological) conditions that affect the sensation such as diabetes mellitus and neuropathy regardless of cause
- Patients with eczema or psoriasis within a 5 cm margin of their keloids
- Keloids smaller than 1.5cm
- Bilateral keloids on the same location, causing lack of control area

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-05-2022
Enrollment:	79
Type:	Actual

Ethics review

Approved WMO

Date:	17-03-2022
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL78955.068.21

Study results

Date completed:	31-12-2023
Actual enrolment:	9

Summary results

Trial ended prematurely