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## Recent review on the role of MicroRNA-21 in Hypertrophic scar: A meta-analysis

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### Abstract

**Introduction:** A dermal form of fibroproliferative disease called hypertrophic scar (HTS) appears following serious burns, skin wounds, and surgical incisions. HTS is characterized as an apparent, raised scar that does not penetrate adjacent tissues. Small, non-coding RNA molecules fall under the category of microRNAs (miRNAs). They play a significant part in the control of protein expression, and both healthy and unhealthy cellular processes have been shown to involve them. The regulation of hypertrophic scarring is regulated by a number of miRNAs. Through its function in fibrogenesis, miRNA21 was discovered to be implicated in the control of HTs.

**Aim of the study:** In this meta-analysis, we discuss the importance of miRNA 21 in the pathogenesis, diagnosis, and management of hypertrophic scars as well as its significant contribution to the fibrosis process, with a focus on skin fibrosis, particularly the creation of HTS.

**Subject and methods:** Following the PRISMA flow diagram, this meta-analysis seeks to explore miRNA21's role in the development of hypertrophic scars by comparing the tissue levels of patients with hypertrophic scars to those of healthy people.

**Result:** The results of our meta-analysis suggest that miR-21 in tissue is considerably higher in the patient group compared with control ( $P < 0.0001$ ), and one study was eligible for inclusion after our search and screening.

**Conclusion:** In conclusion, the role of miR-21 in hypertrophic scarring and earlier research from years ago suggest that it may be a new marker and the foundation for a new treatment approach for HTS.

**Key words:** Hypertrophic scar; miR-21; Keloid; Scleroderma.

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## 1. Introduction

Hypertrophic scar (HTS), defined as a fibro-proliferative disorder that is brought on by poor wound healing, is characterized by abnormally high levels of extracellular matrix (ECM), a substance generated by fibroblasts [1]

MicroRNA (miR) is a short, non-coding RNA that plays a part in controlling the post-transcriptional expression of genes. Numerous crucial fibrogenic processes are involved in tissue repair; when these processes are imbalanced during the proliferation and transition of fibrogenic cells, excessive tissue remodeling and fibrosis result [2].

## 2. Subjects and methods

### 2.1. Subjects

This study was prepared as a systematic review and meta-analysis, and it complies with the Cochrane Handbook's requirements as well as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.

All samples were taken from tissues of hypertrophic scars, in addition to samples from normal skin tissue that were gathered to serve as a control. Patients were clinically assessed, and regular pathological work was used to confirm the examination.

### *Inclusion criteria*

Numerous studies have looked at fibrosis-related aberrant miRNA expression. A major function of trans-forming growth factor 1 (TGF-1) is to promote fibroblast proliferation in addition to the production of collagen and other extracellular matrix, which leads to the development of HS by causing an excessive buildup of ECM [3].

Numerous fibrotic disorders, such as hypertrophic scar, keloid, and scleroderma, exhibit biological progression due to the overexpression of miR-21, according to studies. MiR-21 is therefore anticipated to develop into a biomarker for the detection and management of fibrotic disorders [4].

Patients who have hypertrophic scars after a clinical dermatologist evaluation were included

### *Exclusion criteria*

Any patient receiving therapy for a hypertrophic scar, during pregnancy or breastfeeding, who had a skin, systemic, or other hypertrophic scarring condition, or was a psychiatrically unwell patient was excluded.

### 2.2. Information Sources

Up until 2022, we looked for relevant entries in a number of scholarly databases, including PubMed, Scopus, and Web of Science. We focused on three articles from among all relevant articles: Recent review

on the role of MicroRNA-21 in hypertrophic scars: A meta-analysis, MicroRNA-21 Affects Proliferation and Apoptosis by Regulating Expression of PTEN in Human Keloid Fibroblasts and MicroRNA-21 in Scleroderma Fibrosis and its Function in TGF- $\beta$ -Regulated Fibrosis-Related Gene Expression

### **2.3. Search and Study Selection**

Patients with hypertrophic scars were included in interventional and observational investigations. The included articles were reviewed in three stages. The first step was utilizing EndNote Software [5] to import the findings from electronic databases onto a Microsoft Excel sheet [6]. The second step involved two independent authors screening the article titles and abstracts that were loaded into the Excel sheet. The included citations from step 2 were subjected to full-text screening in the third stage. Finally, we manually examined the included publications' references to look for any potential missed studies.

### **2.4. Data Collection**

We collect information with reference to: A) the participants' baseline demographics. B) The outcome endpoints included tissue miR-21; and C) The third category contained information for determining the possibility of bias. Microsoft Excel was used to complete this process [7].

### **2.5. Risk of bias Assessment**

Using the Cochrane risk of bias method for clinical trials, two authors

evaluated the risk of bias among the included papers [8]. Through seven domains, the instrument evaluates patient randomization, allocation concealment, and sufficient blinding [8]. Each domain is assigned a risk of bias rating of "low," "unclear," or "high."

### **2.6. Main outcome and measures**

All outcomes were formulated prior to data collection. Outcomes included elevated levels of miR-21 in individuals with hypertrophic scars, in addition to increased levels in patients with various fibrosis-related dermatological illnesses like keloid and scleroderma.

### **2.7. Analysis**

We used Review Manager software to apply a meta-analysis on this study, which contained both continuous and dichotomous outcomes. All the data were presented as mean standard deviation from many independent experiments [9], with mean difference (MD) and 95% confidence interval (CI) used for continuous data analysis and risk ratio (RR) and 95% CI used for dichotomous data analysis. Statistical significance is defined as a P-value of 0.05.

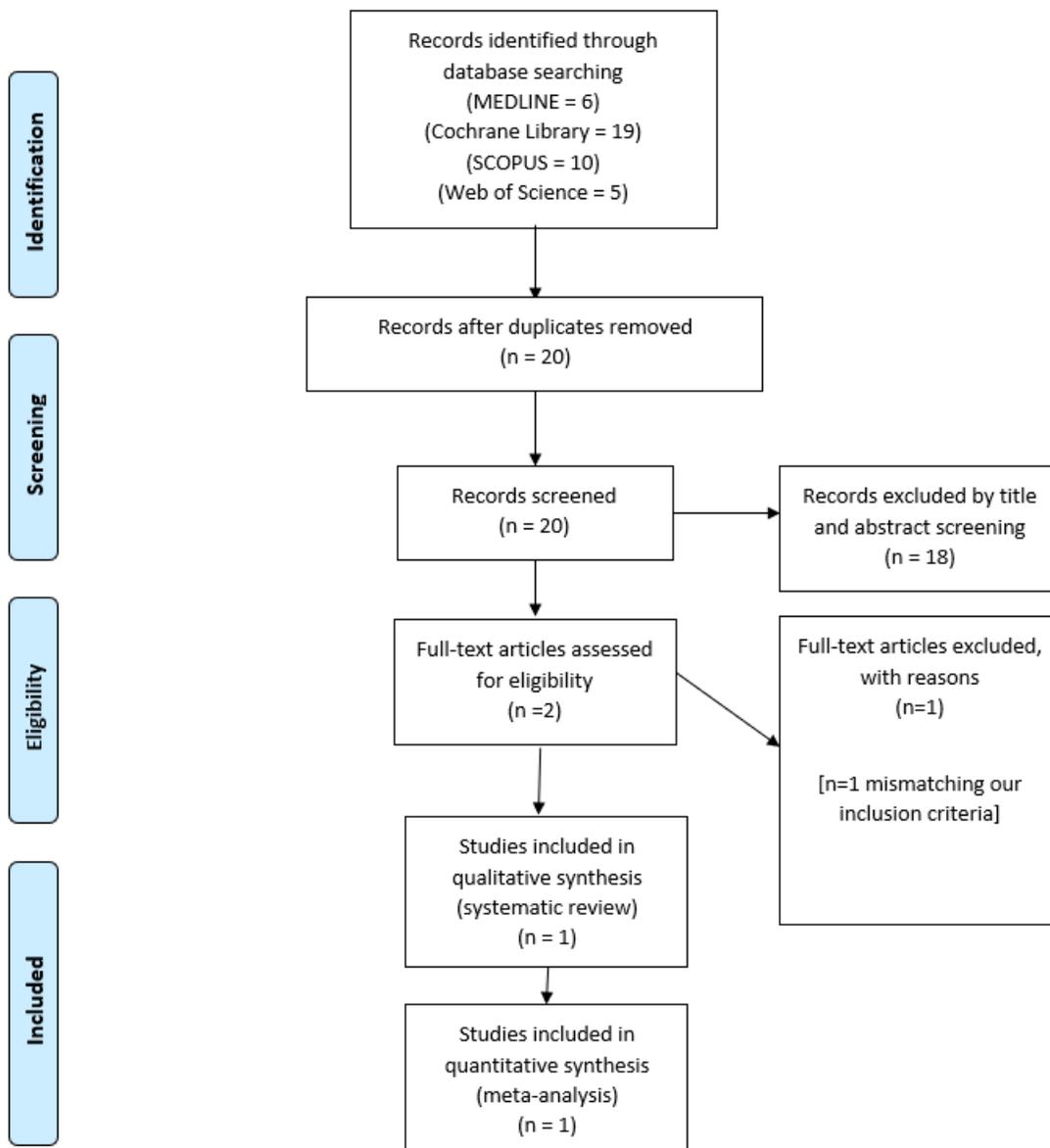
### **2.8. Statistical analysis**

The findings information was displayed as the mean and standard deviation. The right software was used to do a stoical analysis. A statistically significant set of data is one with a P-value less than 0.05.

### 3. Results

A systematic evaluation of three publications revealed that miR-21 was considerably elevated in patients with hypertrophic scars, suggesting that it may have a role in the pathophysiology of the condition **Figure 1**. Additionally, it was discovered to be much higher in keloid

tissues and patients with scleroderma, supporting our findings about the function of miR-21 in the pathogenesis of fibrogenesis (**Table 1**). Regarding miR-121 levels in tissue, there was a very statistically significant difference between the patient and control groups ( $P = 0.0001$ ) (**Table 2**).



**Figure 1:** PRISMA Flow diagram of literature search process.

**Table 1:** Age and gender distribution among groups.

Variables	Hypertrophic scar		Control (N=20)	<i>P-value</i>
	Patients (N=20)			
Age (years)	24.8 ±2.2		31.05 ±2.3	0.368
Gender	Female	18 (90%)	17 (85%)	0.1
	Male	2 (10%)	3 (15%)	

**Table 2:** miR-121 levels in patients and control.

Variables	Hypertrophic scar		Control (N=20)	<i>P-value</i>
	Patients (N=20)			
<b>miR-121 (Tissue)</b>	16.76±0.839		1.2±0.01	0.0001*

#### 4. Discussion

Hypertrophic scar (HTS) is defined as a dermal type of fibroproliferative disorder that occurs following deep burns, skin trauma, and surgical incisions [10].

More than 30% of all human genes are regulated by microRNAs (miRNAs), a class of tiny, 18–28 nucleotide-long, noncoding RNA molecules that bind to their target genes in a base-pairing fashion and either cause mRNA degradation or prevent mRNA from being translated [11].

The prevalence of abnormal hypertrophic scarring is 1.5 to 4.5 percent of the general population. 40 to 70 percent of people experience hypertrophic scarring following surgery, and more than 67 to 90 percent do so after suffering a burn injury [12].

Anti-miR-21 was observed to diminish the expression of fibrosis-related markers in fibroblasts, while over-expression of miR-21 enhanced fibroproliferative expression in fibroblasts, leading to the discovery that miR-21 can be used as a marker for HTS fibroblasts. Additionally, miR-21 increased TGF-1-induced fibroproliferative expression, and the miR-21 inhibitor inhibited HTS tissue growth in vivo (in an experimental model using naked mice) [13].

It was discovered that the TGF-1/miR21/Smad7 pathway may be a suitable therapeutic base for the treatment of HTS and that miR-21 is thought to be a crucial regulator for HTS development [13].

Following stimulation with TGF-1, the expression of miR-21 was upregulated, while the mRNA level of SMAD7 decreased in fibroblasts. Experiments showed that miR-21 expression is associated with a problem and that the TGF-/miR-21/Smad7 pathways may contribute to the pathogenesis of HS [14].

MicroRNA-21 was found to have the highest fold change (6.87-fold) among the 23 up-regulated miRNAs in keloid [15].

### Conclusion

MiR-21 may be involved in the pathogenesis of scleroderma, keloid, and other fibrotic illnesses, as well as hypertrophic scarring, according to this

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MiR-21 regulates scleroderma fibrosis via Smad7, and this suggests a unique strategy for treating SSc fibrosis that uses small compounds that target miRNAs [16].

The meta-analysis of this study revealed a significant increase in the tissue level of miR-21 in hypertrophic scar patients, keloid patients, and scleroderma patients as compared to controls.

systematic review and meta-analysis. We recommend further studies for its role in the treatment of hypertrophic scars.

patients and healthy controls who agreed to participate in the study signed consent forms.

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