

SYSTEMIC REVIEW ON THE TREATMENT OF ACNE SCARRING

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Disclosures

- Sponsorship or research funding
 - Unrestricted research grants Galderma and GSK for basic science research one relating to acne scarring
- Honorarium
 - Unrestricted educational talks at international meetings Galderma, MEDA and GSK
 - As member of a drug-monitoring committee Galderma and independent monitor for a clinical study L'Oreal
- Shareholder
 - None
- Involvement in the review
 - Clinical expertise and intellectual input to the review and responses to referee comments

What will be covered

- Background
 - Why this systematic review is important
- Methods used
- Interventions assessed
- Results from studies
- Key messages
 - Relevance to future research






Scarring Is Frequent: Even With Mild/Moderate Acne

- **87%** prevalence of acne scars in a population of 973 subjects with **primarily mild-moderate acne** (843/973 pts)
- **50%** of acne scars are clinically relevant
- Also confirmed that acne scarring on **chest and back** is quite common
 - **38%** and **51%** of pts in this group

Acne of any severity can lead to scarring

Country	Frequency of scars in active acne patients	Scar frequency according to acne severity on face		
		Almost clear/mild	Moderate	Severe/very severe
France	37%	22%	48%	79%
Brazil	44%	30%	55%	74%
USA	43%	28%	51%	77%

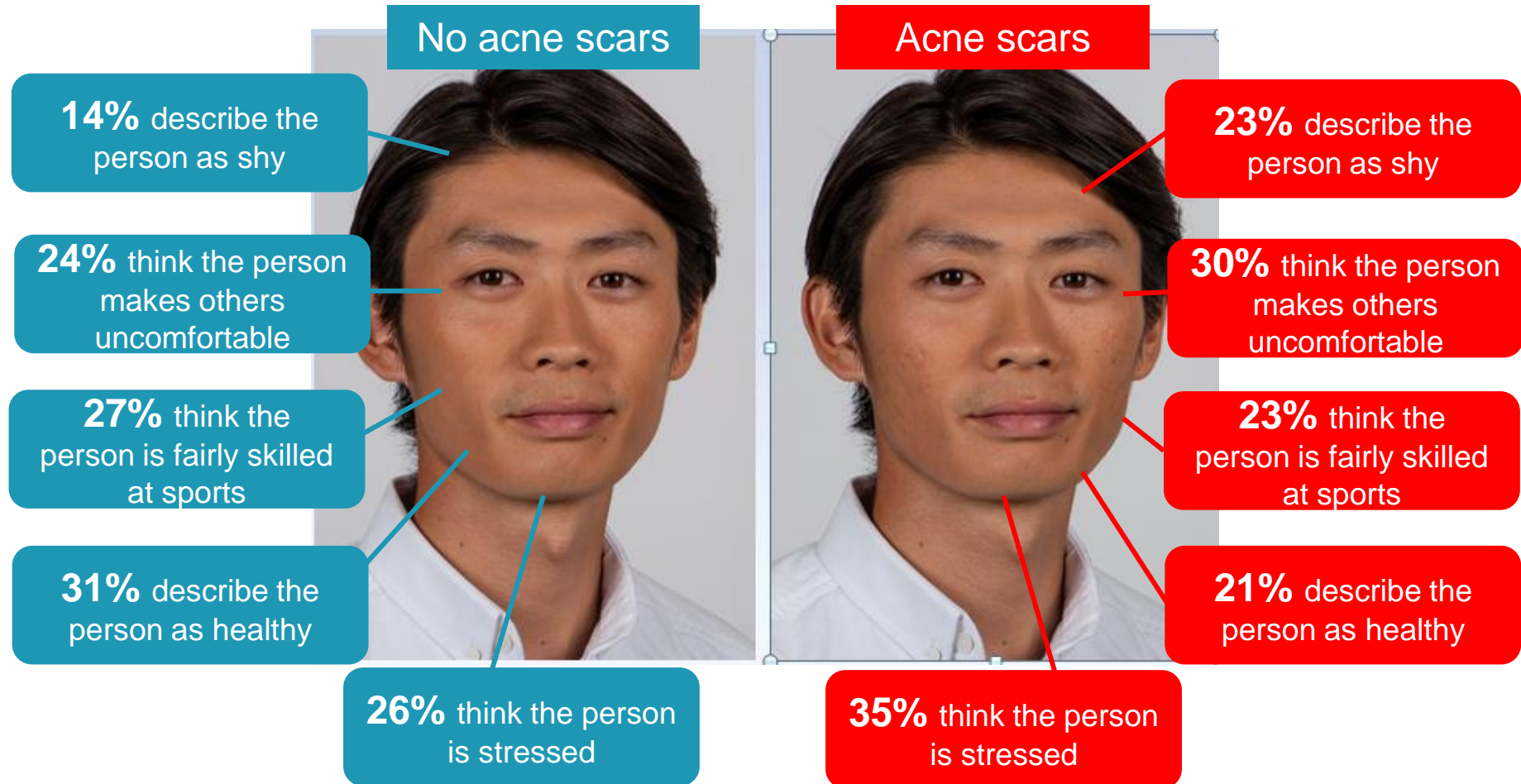
Risk factors	Probability of scarring (odds ratio)		
	 Brazil	 France	 USA
Acne severity Severe or very severe acne vs. other severities	3.4 [2.7–4.2]	6.8 [5.1–9.0]	6.5 [5.1–8.1]
Time elapsed between acne onset and first effective treatment 3 years or more vs. 0–<3 years	1.6 [1.4–1.8]	2.8 [2.4–3.3]	2.8 [2.4–3.2]
Relapse after treatment Yes vs. no	1.6 [1.4–1.9]	1.9 [1.6–2.2]	1.4 [1.2–1.5]

Qualitative survey involving dermatologists in France (n=106), Brazil (n=120) and the USA (n=120) who filled out a pen-and-paper census form for each active acne patient they saw in consultation over 1 week (France = 1,366; Brazil = 1,718; USA = 1,972)

Psychological Impact of Acne Scars Should Not Be Underestimated

- Acne scarring: “a risk factor for suicide”.
- Demonstrated significant psychosocial disability
 - Increased anxiety, depression, lowered self esteem
- Higher psychopathology than acne
 - Related to disease duration
 - Increased problems in females

Presence of acne scars has a negative impact on perceptions



Online survey in USA, UK, Japan, Germany, France and Brazil among respondents 18 years and over (n=4,618) who reacted to three randomly selected facial pictures of individuals with either clear skin or digitally superimposed acne scars, but no active acne lesions

ACNE PRIORITY SETTING EXERCISE

Launched in 2013.....



The Top Ten

YOU JOINED THE FIGHT AGAINST ACNE!!

NHS
**National Institute for
Health Research**

Here are the top ten questions you voted for...

Clinical Research Network
Yorkshire and Humber

1. What management strategy should be adopted for the treatment of acne in order to optimise short and long-term outcomes?
2. What is the correct way to use antibiotics in acne to achieve the best outcomes with least risk?
3. **What is the best treatment for acne scars?**
4. What is the best way of preventing acne?
5. What is the correct way to use oral isotretinoin (Roaccutane) in acne in order to achieve the best outcomes with least risk of potentially serious adverse effects?
6. Which lifestyle factors affect acne susceptibility or acne severity the most and could diet be one of them?
7. What is the best way of managing acne in mature women who may/may not have underlying hormonal abnormalities?
8. What is the best topical product for treating acne?
9. Which physical therapies including lasers and other light based treatments are safe and effective in treating acne?
10. How long do acne treatments take to work and which ones are fastest acting?



Delivering research to make patients, and the NHS, better

Questions and concerns about managing acne scars

- Do physical interventions work?
- Is preventative treatment of acne the best policy?
- Concerns about payments made for treatments in the private sector
 - Laser treatments £1,700 - £3,500
 - Dermabrasion £1,000 - £5,000
 - Chemical peels £60 - £100
 - Microneedling £200- £350



Previous reviews

- Cochrane systematic review of lasers in 2000
 - No RCTs where lasers compared to placebo or alternative lasers
 - 27 studies of poor quality case series with small numbers
 - Lack of studies prevented any conclusions to be drawn about effectiveness of lasers
 - Recommended well designed randomised controlled comparisons of laser therapies

Background


- <http://www.nets.nihr.ac.uk/identifying-research>
- NIHR HTA (Health Technology Assessment Programme) panel prioritised the review for funding
- Commissioned the Cochrane Group
- Objectives
 - **To assess the effects of interventions for treating acne scars**
 - **Recognising the need to better inform caregivers and consumers**

What's next?


The top ten questions will be added to the James Lind Alliance web site. In addition, every single suggestion, whether in the top ten or not, will be recorded within the publicly available database, UK DUETs (<http://www.library.nhs.uk/duets/>), for future reference. Nothing will be lost and acne researchers here in the UK and overseas will use DUETs to identify the topics their work should address.

We would like to thank everyone who has voted for the top ten, without your input, this list would not have been possible!

More information available at:
www.acnepsp.org/index.php
www.lindalliance.org



In collaboration with:



Methods

- **Randomised controlled trials**
 - Split face or parallel arms
 - Any active intervention or combination vs active intervention, placebo or no treatment
- **Participants**
 - All ages, gender and ethnic groups diagnosed by dermatologist or clinician appropriately skilled to confirm the diagnosis of acne scars
 - All grades of scar severity
 - Excluded studies predominantly or only looking at keloid scarring
- **Active interventions included**
 - Chemical peels, dermabrasion, microdermabrasion, laser therapy, radiofrequency, punch techniques, dermal grafting, tissue-augmenting agents, needling, subcision, intralesional steroid injections, silicone gel, cryotherapy, retinoids, imiquimod, 5-fluoruracil, interferon, bleomycin, surgery or combined therapy.

Methods

- **Primary outcomes**

- Participant reported scar improvement
 - Measured by a scar improvement, grading or severity scale over
 - 24 weeks (short term)
 - > 24 weeks considered long term
- Adverse effects enough to cause withdrawal from the study
 - Serious if life threatening or impact on ability to function
 - Severe defined by the intensity

Methods

- **Secondary outcomes**

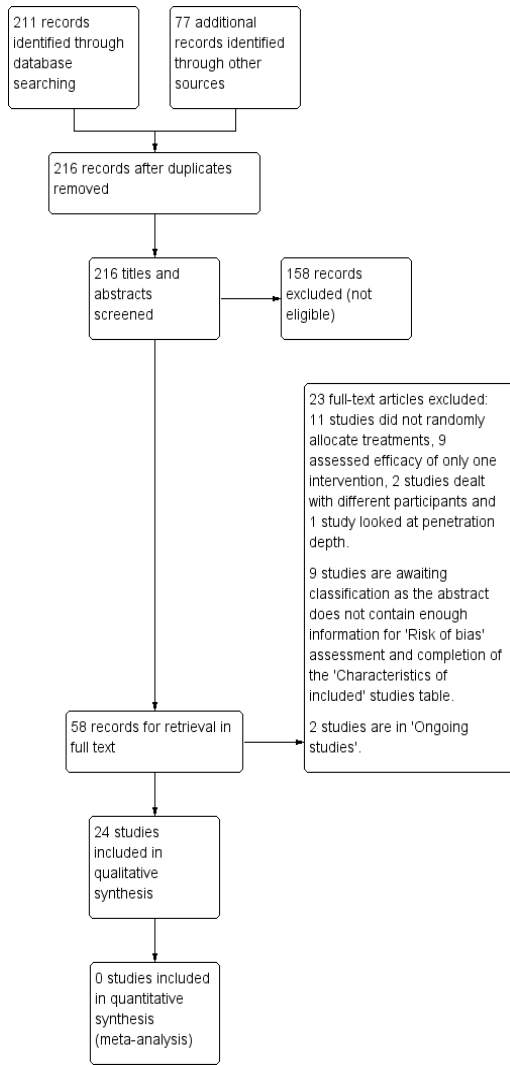
- Investigator assessed scar improvement
 - measured by a scar improvement, grading or severity scale
- Participant satisfaction
 - measured by a satisfaction questionnaire
- Quality of life impact
 - measured by global of disease specific means
- Participant reported short term adverse effects
 - up to 4 weeks, e.g. pain, erythema, oedema, infection
- Investigator reported short term adverse effects
 - up to 4 weeks
- Duration in days of the post-procedure downtime
 - the number of days participant unable / unwilling to go out into the public

Selection of studies and data extraction

- Searches extensive
 - Electronic searches of databases, trial registers, manufacturers websites for trial information, authors for information on missing data and on-going trials
- Two independent review authors
 - Identified studies from abstracts and literature for retrieval
 - Then reviewed full text for eligibility for inclusion
 - Assessed risk of bias
 - Extracted and analysed the data
 - If information not clear contacted authors
 - Third author included if consensus not reached on any point
 - Used **GRADE** = **G** Grading of **R** Recommendations, **A** Assessment, **D** evelopment and **E** valuation to assess quality of evidence and to inform strength of recommendations
 - Created summary of findings tables



Interventions for acne scars



24 RCTs

7 parallel RCTs

17 within-individual split face studies

Active intervention to placebo or no treatment

2 parallel RCTs

5 split face RCTs

Active interventions compared

17 RCTs

- 23 single centre
- 789 participants in total
- Sample sizes
 - 6 -147;
 - 15 studies had < 30 participants

Demographics

Studies conducted in:

USA = 7

China = 1

Denmark = 2

Egypt = 3

Iran = 2

South Korea = 6

Thailand = 2

Turkey = 1



Participants:

Adults aged 18 years or older with facial scarring

20 studies Males and females; 706 participants

3 studies females only; 76 participants

1 study males only; 8 participants

No studies examined scars on the back

Funding of the 24 trials:

5 supported by industry

4 by academic institutions

15 did not report source of funding

Interventions examined in RCTs

RESURFACING PROCEDURES

Chemical peeling

Laser resurfacing

- **Non fractional non- ablative**
- **Fractional**

- **Fractional radiofrequency**

LIFTING PROCEDURES

Subcision

Injectable fillers

OTHER

Needling

COMBINATION INTERVENTIONS

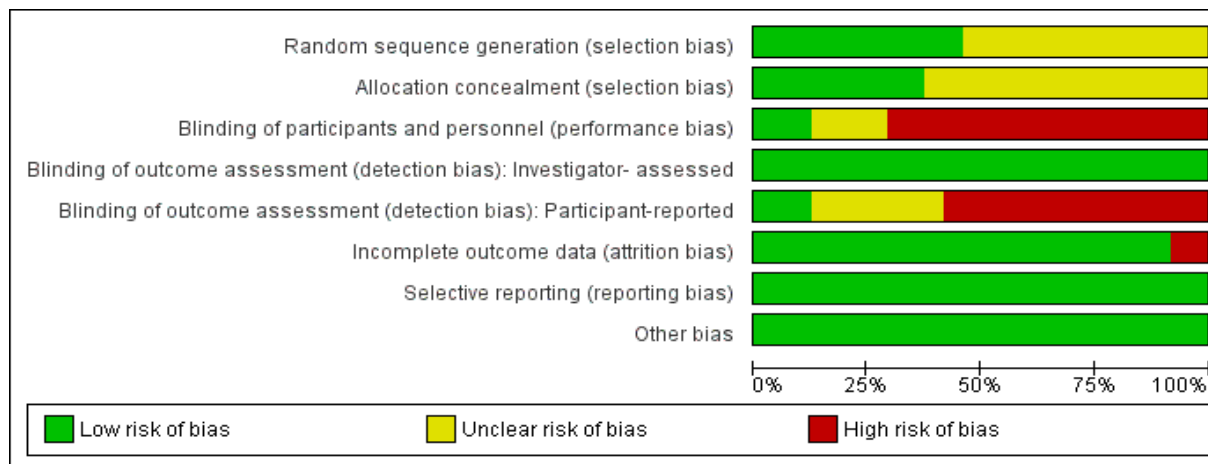
Fractional laser plus intradermal platelet-rich plasma (PRP)

Fractional laser plus punch elevation

Microdermabrasion plus photodynamic therapy with aminolevulinic acid (ALA-PDT)

Needling plus chemical peeling

Risk of bias table showing risk of bias against each item presented as percentages across all included studies



Risk varied from low to high

Blinding of participants and personnel (performance bias)

Blinding of outcome assessment (detection bias): participant-reported

Risk of bias summary across individual studies

Performance bias

Blinding of participants and personnel

Detection bias

Blinding of outcome assessment

Participant reported

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) Investigator-assessed	Blinding of outcome assessment (detection bias) Participant-reported	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Alam 2014	?	+	+	+	+	+	+	+
Asilian 2011	+	?	+	+	+	+	+	+
Bernstein 2001	?	?	+	+	+	+	+	+
Chae 2015	?	?	+	+	+	+	+	+
Cho 2010	?	?	+	+	+	+	+	+
Erbağci 2000	?	?	+	+	+	+	+	+
Faghihi 2015	+	+	+	+	+	+	+	+
Hedelund 2010	+	+	+	+	+	+	+	+
Hedelund 2012	+	+	+	+	+	+	+	+
Karnik 2014	?	?	+	+	+	+	+	+
Kim 2009	?	?	+	+	+	+	+	+
Lee 2009	?	?	+	+	+	+	+	+
Lee 2011	?	?	?	+	?	+	+	+
Leheta 2011	+	+	+	+	+	+	+	+
Leheta 2014a	+	+	+	+	+	+	+	+
Leheta 2014b	+	+	+	+	+	+	+	+
Linkner 2014	?	?	+	+	+	+	+	+
Manuskiatti 2013	+	?	?	+	?	+	+	+
Min 2009	?	?	+	+	+	+	+	+
Munavalli 2013	?	?	+	+	+	+	+	+
Rongsaard 2014	+	+	+	+	?	+	+	+
Sage 2011	+	+	+	+	+	+	+	+
Tanzi 2004	?	?	+	+	?	+	+	+
Zhang 2013	?	?	+	+	+	+	+	+

Summary of results

Types of scars included

- 21/ 24 trials included “atrophic scars”
- 2/24 did not specify the atrophic scars mentioned acne scars
- 1/24 included atrophic and hypertrophic scars
- 0/24 trials included mention of scars on the back

Summary of results

Primary outcome measures

- Participant-reported scar improvement
 - 14/24 trials included this primary efficacy outcome measure
- Participants with serious or severe adverse effects enough to withdraw from the study
 - 20/24 trials included this primary outcome

Secondary outcome measures

- Participant satisfaction
 - 8/24 studies considered this outcome
- Quality of life
 - **No** trials considered QoL as a measure
- Participant and Investigator reported short-term adverse effects
 - 23/24 studies

Outcomes reported under 14 pair-wise comparisons

- Non-fractional non-ablative laser vs placebo or no treatment
- Fractional laser vs non-fractional non-ablative laser
- Fractional laser vs placebo or no treatment
- Fractional laser vs radiofrequency
- Fractional laser vs combined fractional laser plus any active intervention
- Fractional laser vs chemical peeling
- Fractional laser vs combined chemical peel plus needling
- Chemical peeling vs placebo or no treatment
- Chemical peeling vs combined chemical peeling plus active intervention
- Chemical peeling vs needling
- Needling vs placebo or no treatment
- Injectable filler vs placebo or no treatment
- Injectable filler vs subcision
- Combined microdermabrasion plus ALA-PDT vs combined microdermabrasion plus placebo-PDT

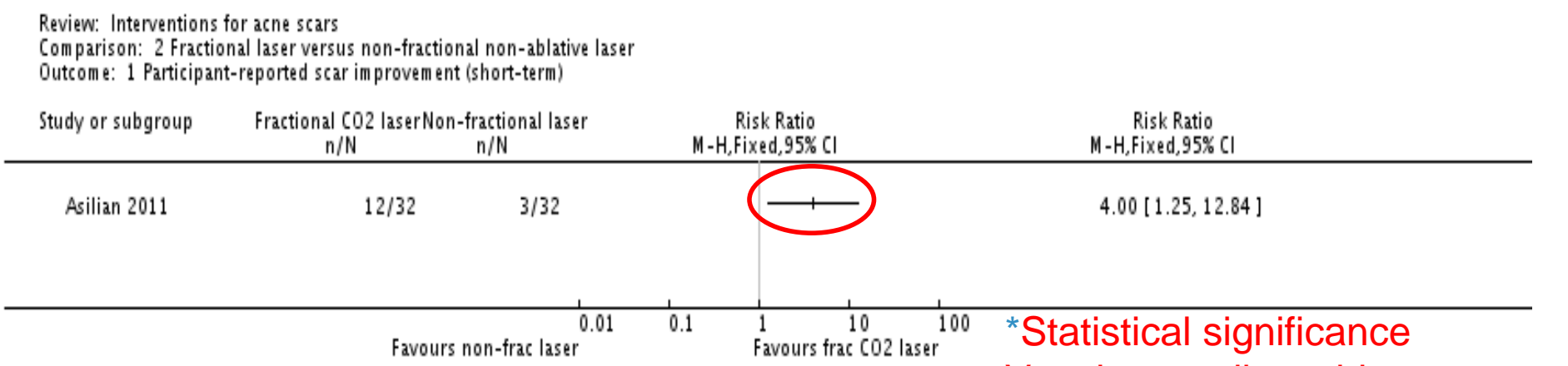
Fractional laser vs non-fractional non ablative laser

Participant and investigator short term > 50% improvement

32 participants per arm showed that fractional CO2 laser given for 4 sessions at monthly intervals improves acne scars significantly more than non fractional non-ablative Q switched 1064 nm Nd:YAG laser at week 24*

Investigator assessed adverse effects demonstrated PIH lasting 2-3 weeks in

6/32 treated with the fractional CO2 laser
10/32 with the non-fractional non-ablative laser



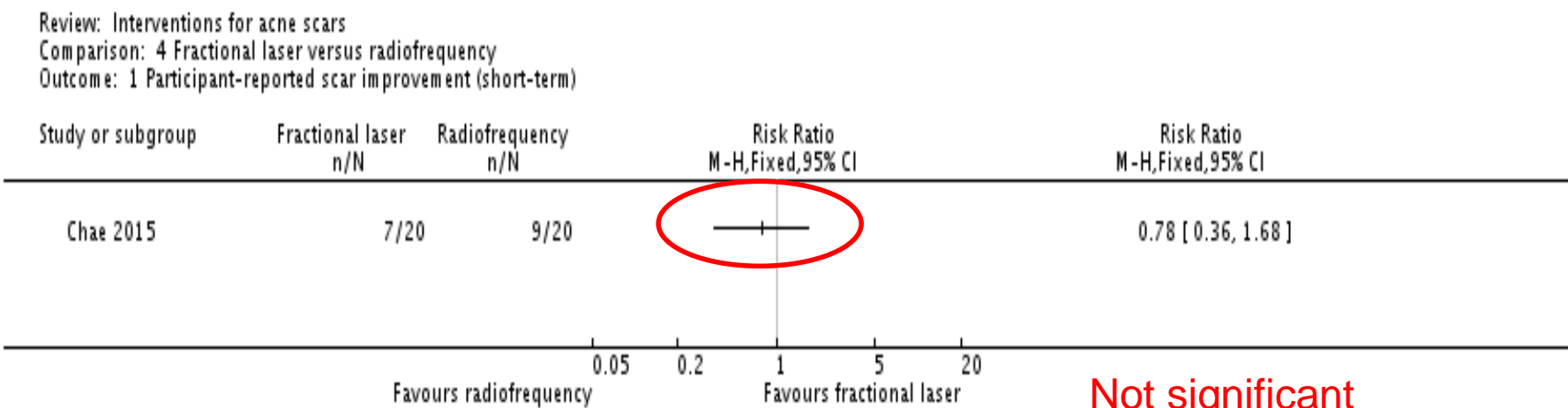
*Statistical significance
Very low quality evidence
Unclear risk of detection bias

Fractional laser vs radiofrequency

Patient reported scar improvement of > 50% at 8 weeks

A parallel study 20 patients per arm randomly divided received 3 sessions at monthly intervals of 1550 nm Er.Glass non-ablative fractional laser or comparator fractional radiofrequency

Both treatments improved scars



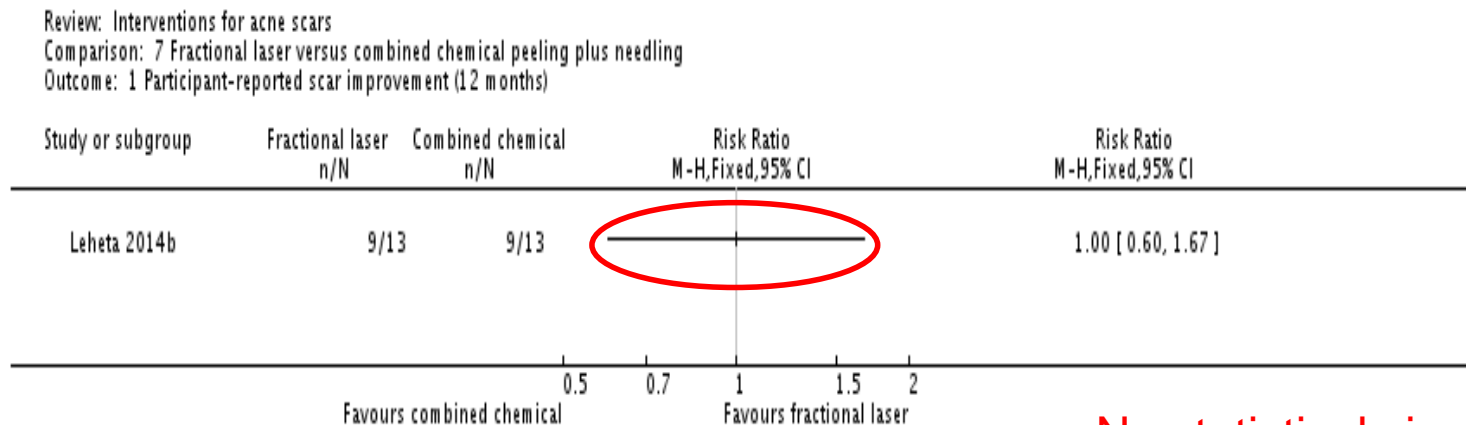
Not significant
Very low quality evidence
High risk of detection bias

Fractional laser vs combined chemical peel plus needling

Patient reported scar improvement of > 50% at 12 months

A parallel group study 13 patients per arm demonstrated both fractional non ablative laser 1540nm Er:Glass laser vs chemical peeling TCA 20% combined with skin needling given monthly for 6 sessions improved scars

All participants in both groups reported pain, transient oedema and erythema for < 4 weeks



No statistical significance
Very low quality evidence
High risk of detection bias

Chemical peeling vs placebo

A study comparing chemical peeling (varying strengths of glycolic acid peels or 15% glycolic acid cream given bi-weekly) to placebo showed chemical peeling given for 24 weeks significantly better than placebo*

48 patients completed the study

No severe adverse events that resulted in withdrawal from the study,
7 withdrew as intolerant of the higher concentration of the peeling agent

Treatment	Good response > 60%	Partial 30-60%	Minor <30%
Chemical peel	6/34	22/34*	6/34*
Placebo	0	4/14*	6/14*

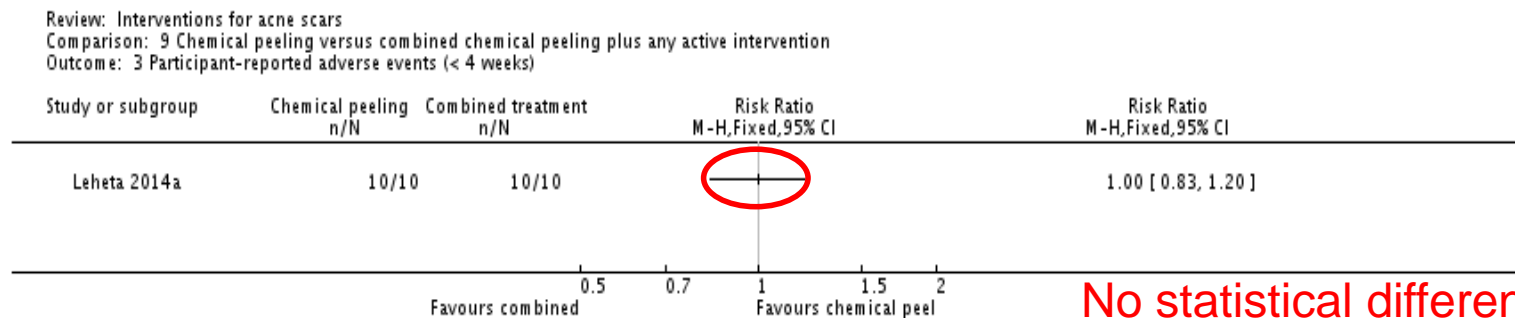
*Significantly better response with chemical peeling $p < 0.05$

Chemical peeling vs chemical peeling and needling

Participant reported scar improvement at 32 weeks

A study showed that 1 session of deep chemical peeling (using non-hydro-alcoholic solution of phenol oil in 60% concentration formula) vs chemical peeling with TCA 20% combined with skin needling for 4 sessions at 6 weekly intervals, improved acne scars in 10 participants in each treatment arm

All participants in both groups reported transient erythema lasted
4 weeks in the chemical peeling group
2-4 days in the chemical peeling plus needling group



No statistical difference
Very low quality evidence
High risk of detection bias

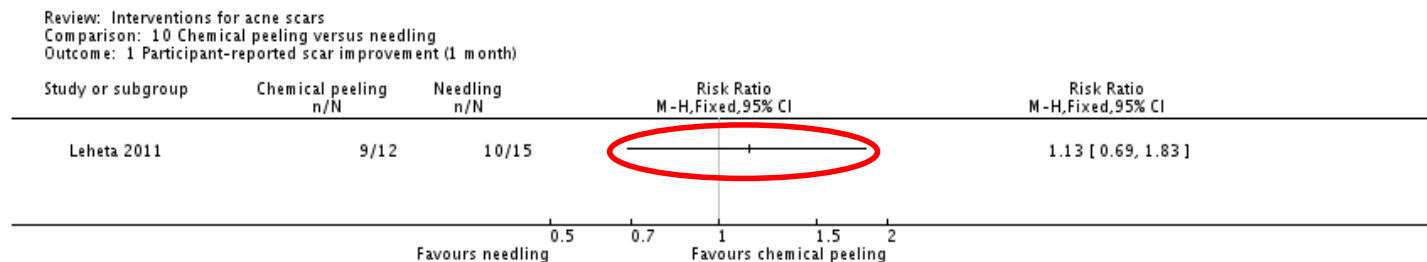
Chemical peeling vs needling

Participant reported short term assessment at week 4

A study in 27 participants showed that both chemical peeling (full strength TCA 100% CROSS n=12) and skin needling (dermaroller n=15) given for 4 sessions at monthly intervals improved acne scars by at least 50%

Participant satisfaction was positive for both treatments

Short term adverse effects showed no differences between interventions



No statistical difference
Very low quality evidence
High risk of detection bias

Chemical peeling with TCA



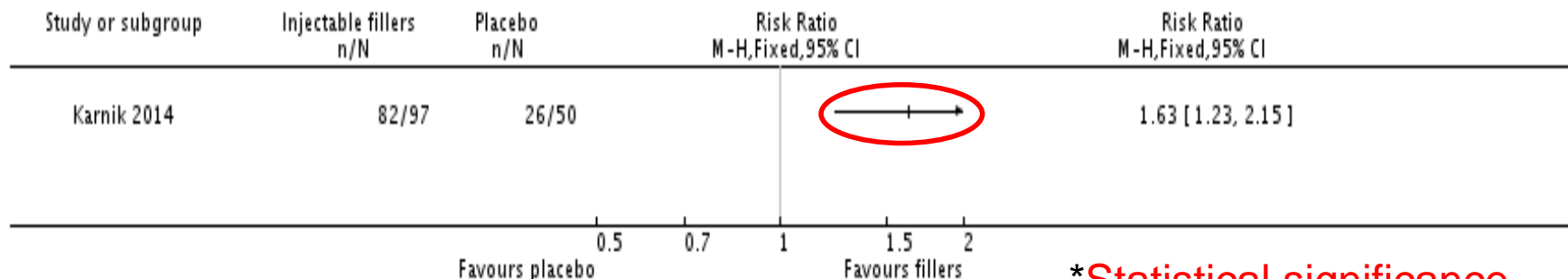
Injectable filler vs placebo

Parallel study of 147 participants showed injectable filler (polymethylmethacrylate suspended in bovine collagen) vs saline injections given for 1 session improves atrophic acne scars by 24 weeks.

Global Aesthetic Improvement Scale reported a significant difference in favour of Injectable fillers with 77% of participants confirming improvement vs 42% of placebo group*

No difference between the adverse effects was noted between groups
Participant satisfaction significantly higher with injectable filler.

Review: Interventions for acne scars
Comparison: 12 Injectable fillers versus placebo or no treatment
Outcome: 3 Participant satisfaction



*Statistical significance
Moderate quality evidence
Low risk of detection bias

Challenges in interpretation

- Scar subtypes and classification
- Genesis of scars
 - Immune mechanisms
 - Natural history
- Standardised tools



Acne Scars



- Subtypes of scars depends on increase or loss of collagen
 - Atrophic, hypertrophic and keloid
- Severity of scarring not necessarily related to severity of acne

Several risk factors are linked with scar development

Acne severity

- Any severity
- More frequent in severe/very severe acne



Timing of treatment

- Delay to first effective treatment

Genetic predisposition

- Ethnicity, family history

Site of lesion

- Face vs. back and chest

Inflammation and abnormal remodelling

- Inflammation extent/duration
- Prolonged angiogenesis
- Different immune response
- Overactive collagenases and/or MMP/TIMP ratios



MMP – matrix metalloproteinase; TIMP – tissue inhibitors of metalloproteinases

1. Holland DB, *et al. Br J Dermatol* 2004;150:72–81; 2. Kang S, *et al. Am J Pathol* 2005;166:1691–1699; 3. Dréno B, *et al. Presented at: 23rd EADV Congress, Amsterdam, The Netherlands, 8–12 October 2014; P024*; 4. Tan J, *et al. J Cutan Med Surg* 2010;14:156–160.

Acne scars have previously been classified by scar shape



Icepick scars

- Narrow (<2 mm)
- Extend to deep dermis/subcutaneous tissue
- Sharply margined
- Opening often wider than apex



Rolling scars

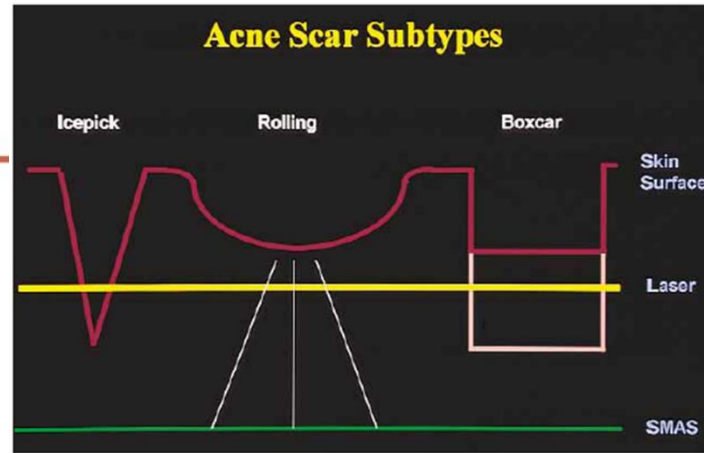
- Usually >4–5 mm
- Shallow
- Occur from dermal tethering
- Give an undulated appearance to skin



Boxcar scars

- Usually 1.5–4 mm
- Shallow or deep
- Round to oval shape
- Sharp vertical edges
- Do not taper

Inconsistencies in classifying acne scars



JEADV

LETTER TO THE EDITOR

Classification of acne scars is difficult even for acne experts

Editor

There is relatively little information available concerning validated acne scar description.¹⁻⁶ In the regular meetings of the Global Alliance to Improve Outcomes in Acne, an international group of dermatologists with an interest in acne research and management,^{7,8,9} we have also noticed that there are often variations in how dermatologists describe and/or classify acne scars. We therefore organized a short survey to identify how much agreement is there on acne scar classification within our membership of dermatologists with a specific interest in acne.

terminology is currently in use, we specifically avoided supplying any terminology or scar definitions within the survey. A total of 23 (43%) completed surveys were received.

Results: general questions

Fourteen (61%) of the respondents indicated that they were not satisfied with existing acne scar classifications, yet 17 (74%) felt that scar classification affects treatment choice. Seventeen (74%) of the respondents indicated that they classify scars using the system published by Jacob (Fig. 1)⁵; four individuals classify simply based on 'atrophic' or 'hypertrophic,' one individual classified scars by severity (mild, moderate, severe), and the last individual said general shape/size. One person also reported using the Jacob system in the general practice setting, but the more detailed system pub-

Immunity and acne scarring

Acne scarring is determined by an inability to mount an effective immune response

Non Scarrers:

Immune response - more rapid, more potent, greater innate component

Scarrers:

Immune response – slower, extended and more highly sensitised to antigens

Potential targets involved in scar formation

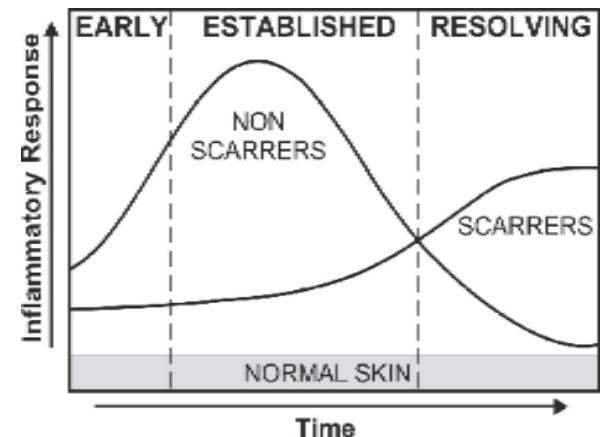
Strong increase in level of IL-2 +++ in normal skin and acne lesions in patients prone to scarring

Supports persistent chronic activation and proliferation of CD4+ T lymphocytes

Moderate increase in level of IL-10 ++ in normal skin and acne lesions in patients prone to scarring

IL-10 inhibits function of antigen-presenting cells

Inhibits IFN- γ production by T-cells and macrophages



Activation of innate immunity



Suggests different profiles of skin innate immunity
in the normal skin of acne patients who
develop and do not develop scars

Patients not prone to scar: IL-10, IL-2 low & MMPs/TIMPs high

Patients prone to scar: IL-10, IL-2 high & MMPs/TIMPs low

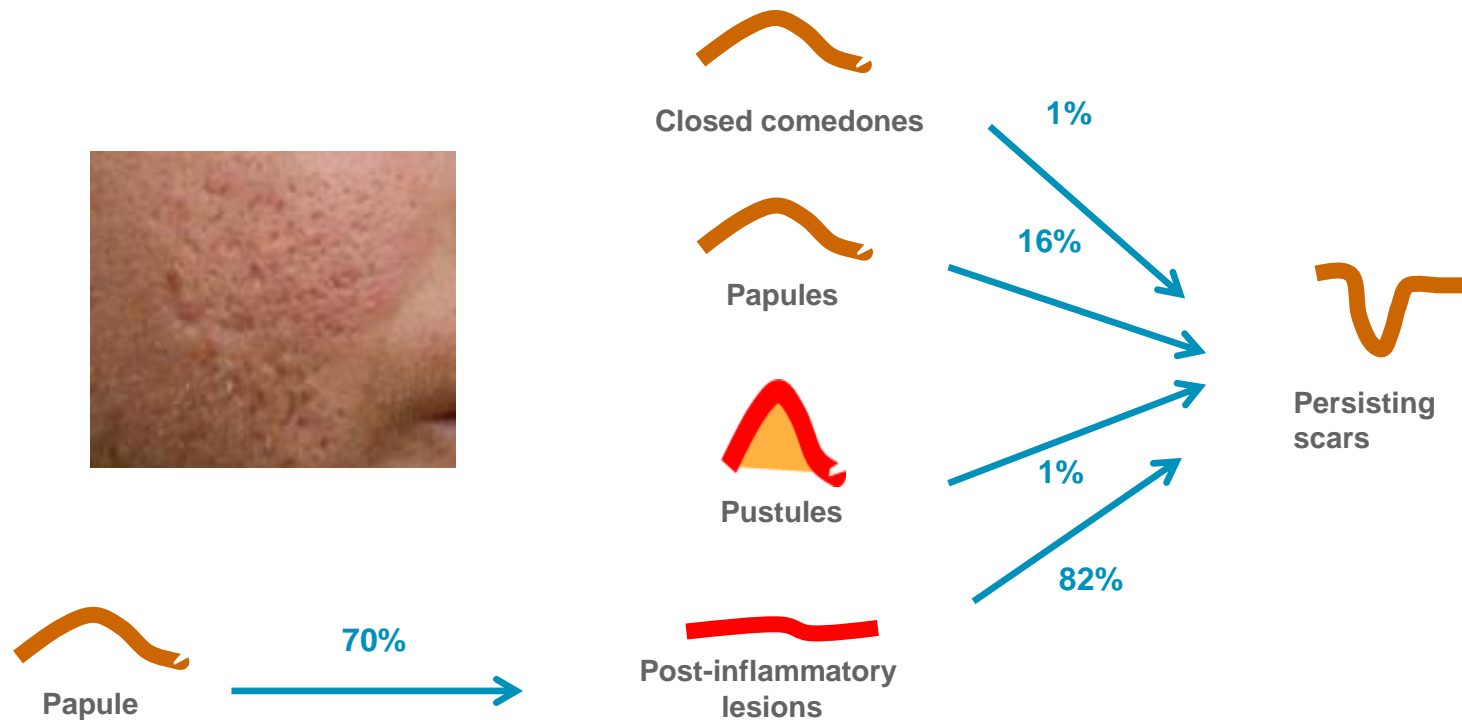
Relevant to trial design.....

Genesis of atrophic acne scars

- Global assessments and lesion counting (including scars ≥ 2 mm)
- Digital photography tracking of lesions determined by expert on live assessment
 - Visia CR[®] system (Canfield)



Genesis of atrophic acne scars



- 99% of scars were derived from papules/pustules and post-inflammatory lesions
- Only 1% of scars were derived from comedones
- **52%** of scars that appear during the first 6 months still present at 2 years

Natural History Atrophic Acne Scars

- **Atrophic acne scars continually form**
 - ...some resolve
 - 36% resolved within 6-months
 - 64% did not
- **Duration of transient acne scars:**
 - mean 41 days; median 28 days
- **Derivation: 98% from papules and post-inflammatory lesions**



IMPLICATIONS

Importance of early treatment of primary acne lesions in scar prevention

Relevant to trial design – need long term follow up

Associated acne - macules



Standardised tools

Acne Scar System	Severity Scheme	Regional Relevance
Leeds 1994	Numeric (Maximum 30 for each region)	Face, chest and back
Echelle d'Evaluation Clinique des Cicatrices d'Acne 2007	Numeric (maximum 540)	Face
Qualitative Global Acne Scarring Grading System 2006	Four descriptive grades	Face, chest and back
Quantitative Global Acne Scarring Grading System 2006	Numeric (maximum 84)	Face
Patient and Observer Scar Assessment Scale (POSAS) 2004	Numeric (maximum 50 observer/maximum 60 patient)	Face
Global Aesthetic improvement Scale (GAIS) 2013	Five descriptive grades	Face
Facial acne scar evaluation tool (FASET) to assess atrophic scars 2015	Global, Dispersion, Numeric	Face

Conclusions on quality of evidence

- Lack of good quality evidence of different interventions due to
 - poor methodology
 - underpowered studies
 - lack of standardised assessments of improvement
 - confounding factors such as acne and scar duration & skin phototype
- Lack of studies that establish efficacy of treatments compared to placebo or sham
- Comparator studies of active treatments suggest no difference
 - In the absence of studies that establish efficacy compared to placebo or sham interventions, this finding of no evidence of difference between two active treatments could mean that neither work

Conclusions on clinical benefits

- No studies included the back
- Nothing to confirm short term benefit will translate to long term effects
- Moderate quality evidence for dermal fillers
- No high quality evidence to advocate any treatment for first-line use in the management of acne scars

Key results

- Based on participant reported scar improvement
 - Fractional ablative laser was more effective in producing scar improvement than non-fractional non-ablative laser.
 - Fractional radiofrequency was similar to fractional non ablative laser
 - Chemical peeling was more effective than placebo
 - Chemical peeling showed similar improvement to skin needling
 - Chemical peeling combined with skin needling showed similar improvement to fractional non ablative laser and deep chemical peeling
 - Injectable fillers provided better scar improvement vs placebo
- Based on short term adverse effects participant reported and investigator assessed
 - No significant difference between treatments and all acceptable

Future studies

- Consider
 - Placebo/sham trials
 - to establish whether any of the active treatments produce meaningful patient benefits
 - Adopting patient-reported outcomes as a primary measure,
 - Utilisation of standardised / validated core outcome measures
 - Evaluation several months after the treatment has been done
 - Given the genesis of scars split face designs
 - Reporting serious adverse events
 - was a research gap found in this review

Acknowledgements

www.cochranelibrary.com

Cochrane Database of Systematic Reviews
2016,

Issue 4. Art.No.:CD011946.

DOI:10.1002/14651858.CD011946.pub2.

Rania Abdel Hay, University of Cairo, Egypt

Khalid Shalaby, University of Cairo, Egypt

Zaher Hesham, University of Cairo, Egypt

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Thank you!



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