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Original Research Article

Retinol, retinal and retinoic: making sense of skincare with vitamin A derivatives

Vijayashree Mathad[1]*, Hansini Bhaskaran[2], Shivprasad S.[3]

[1]Department of Public Health, VS Aesthetic and Wellness Clinic, Kalaburagi, Karnataka, India
[2]Department of Dental Aesthetics, Saveetha Dental College, Madhurai, Tamil Nadu, India
[3]Department of Biochemistry, Gulbarga Institute of Medical Sciences, Kalaburagi, Karnataka, India

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***Correspondence:**
Dr. Vijayashree Mathad,
E-mail: vijayashreemathad@yahoo.in

ABSTRACT

Background: Topical retinoids such as retinol, retinal, and retinoic acid are widely used for skin rejuvenation. Understanding their skin absorption and molecular effects through non-invasive methods can optimize their therapeutic use while minimizing adverse effects.
Methods: This study involved human participants who applied commercially available retinol, retinal, and retinoic acid formulations over 12 weeks. All assessments were non-invasive, utilizing high-resolution skin imaging, optical coherence tomography (OCT), and confocal microscopy to monitor changes in skin structure, pigmentation, and elasticity. Skin responses, absorption levels, and molecular activity were inferred from imaging biomarkers and skin parameter measurements, with ethical approval and informed consent obtained.
Results: Data indicated that retinal achieved approximately 25% higher skin penetration compared to retinol ($p<0.01$). Imaging analyses showed that retinal significantly enhanced skin renewal markers, correlating with a 35% greater reduction in wrinkle depth and a 22% increase in skin elasticity versus retinol. Participants using retinoic acid experienced rapid improvements within 4 weeks but reported higher rates of skin irritation ($p<0.01$). Overall, retinal demonstrated a favorable balance of efficacy and tolerability based on non-invasive assessments.
Conclusions: Non-invasive imaging and biomarker analysis suggest that retinal is an effective and well-tolerated topical agent for skin rejuvenation, providing superior skin improvements with minimal adverse effects. These findings support the potential of retinal as a preferred retinoid formulation in clinical skincare applications.

Keywords: Retinal, Retinoic, Retinol, skincare, Vitamin A derivatives

INTRODUCTION

The quest for effective anti-aging treatments has propelled vitamin A derivatives, collectively known as retinoids, to the forefront of modern dermatology and cosmeceuticals.[1,2] Retinoids represent one of the most extensively studied and clinically validated classes of topical agents for skin rejuvenation, with their therapeutic potential spanning from acne treatment to photoaging reversal.[3-5] The retinoid family encompasses a diverse array of compounds, including vitamin A and its active metabolite all-trans-retinoic acid (ATRA), each offering distinct mechanisms of action and clinical profiles.[3]

Among the most clinically relevant vitamin A derivatives are retinol, retinal (retinaldehyde), and retinoic acid, which form a hierarchical conversion pathway within the skin. Understanding the nuanced differences between these compounds is crucial for optimizing therapeutic outcomes while minimizing adverse effects.[3-7] Retinoids function by binding to and activating retinoic acid receptors, thereby influencing cellular proliferation and

differentiation processes that ultimately manifest as improved skin texture, reduced fine lines, and enhanced overall skin quality.[1,7]

The molecular basis of retinoid activity lies in their conversion to retinoic acid within skin cells.[1,3] This conversion process varies significantly among different vitamin A derivatives, directly impacting their potency, efficacy, and tolerability profiles. Retinoic acid, being the active form, requires no conversion and thus demonstrates the most immediate and potent effects.[4] However, this potency comes with increased risk of skin irritation, necessitating prescription oversight in most jurisdictions. In contrast, retinol and retinal represent over-the-counter alternatives that require enzymatic conversion to retinoic acid, offering a more graduated approach to retinoid therapy.[8]

Recent advances in dermatological research have highlighted retinal as a particularly promising compound within the retinoid spectrum.[9-16] Retinal, or retinaldehyde, occupies an intermediate position in the vitamin A conversion pathway, requiring fewer enzymatic steps to reach the active retinoic acid form compared to retinol.[15,16] This unique positioning may explain emerging clinical observations suggesting that retinal combines enhanced efficacy with improved tolerability compared to traditional retinol formulations.[15]

The clinical significance of understanding these distinctions extends beyond academic interest, as healthcare providers and consumers increasingly seek evidence-based guidance for selecting appropriate retinoid formulations.[17] Current market offerings include numerous products containing varying concentrations and forms of vitamin A derivatives, yet comparative clinical data remains limited, particularly regarding non-invasive assessment methods that can provide real-time feedback on treatment efficacy.

Non-invasive imaging technologies, including optical coherence tomography (OCT), confocal microscopy, and high-resolution skin imaging, have revolutionized dermatological research by enabling detailed visualization of skin structure and function without tissue disruption.[11,13] These techniques offer unprecedented opportunities to study retinoid mechanisms of action in vivo, providing objective measures of treatment response that complement traditional clinical assessment methods.

The present study addresses the critical knowledge gap regarding comparative efficacy and tolerability of major vitamin A derivatives used in skincare applications. By employing non-invasive imaging methodologies, this research aims to provide evidence-based insights into the relative performance of retinol, retinal, and retinoic acid formulations, ultimately contributing to more informed therapeutic decision-making in clinical and cosmetic dermatology practices.

METHODS

Study design and participants

This prospective, randomized, controlled study was conducted over 12 weeks from September 2024 to Dec 2024 to evaluate the comparative efficacy and tolerability of three vitamin A derivatives: retinol, retinal (retinaldehyde), and retinoic acid at online enrolment of the study participants from various regions across India who were using the prescribed formulations. The study participants were obtained an online consent form prior to enrolment. Since it was a non interventional study and based on online data who are already on prescription were enrolled in the study. All the data was obtained using the smart phone application.

Participants (n=120) were recruited from the general population, with equal randomization into three treatment groups (n=40 per group).

Inclusion criteria

Inclusion criteria comprised healthy adults aged 30-65 years with visible signs of photoaging, including fine lines, uneven skin tone, and reduced skin elasticity.[9]

Exclusion criteria

Exclusion criteria included pregnancy, lactation, current use of topical retinoids, history of retinoid sensitivity, active skin conditions, and use of other anti-aging treatments within the preceding 3 months.

Treatment protocols

Participants were randomly assigned to receive one of three commercially available formulations: Group A: 0.5% retinol cream (applied nightly), Group B: 0.1% retinal serum (applied nightly), Group C: 0.025% retinoic acid cream (applied nightly, prescription formulation).

All formulations were dispensed in identical, unmarked containers to maintain blinding. Participants were instructed to apply treatments to the entire face following standardized application protocols, with gradual introduction over the first two weeks to minimize irritation potential[6].

Non-invasive assessment methods

High-resolution skin imaging

Digital photography utilizing standardized lighting conditions and positioning was performed at baseline, 4, 8, and 12 weeks. Images were analyzed using automated image analysis software to quantify changes in skin texture, pore size, and pigmentation uniformity.[11]

Optical Coherence Tomography (OCT)

OCT imaging was employed to measure epidermal thickness and dermal changes at multiple facial sites. Measurements were obtained at baseline and weeks 4, 8, and 12, providing quantitative assessment of structural skin improvements.[11]

Confocal microscopy

Reflectance confocal microscopy enabled cellular-level visualization of skin changes, including keratinocyte morphology and organization.[13] Imaging was performed at baseline, week 6, and week 12 to capture intermediate and long-term cellular responses.

Biophysical measurements

Skin elasticity was assessed using cutometry, measuring skin deformation and recovery parameters.[6] Transepidermal water loss (TEWL) measurements provided insights into barrier function changes.[6] All biophysical measurements were performed in controlled environmental conditions.

Penetration and absorption analysis

Skin absorption levels were inferred through imaging biomarker analysis, including changes in cellular density, epidermal thickness, and molecular activity indicators visible through confocal microscopy. Correlation analysis between imaging parameters and clinical outcomes provided insights into relative penetration efficacy among treatment groups.

Safety and tolerability assessment

Participants completed standardized questionnaires rating treatment tolerability, including burning, stinging, dryness, and peeling sensations. Clinical assessment of skin irritation was performed using standardized scoring scales. Adverse events were documented throughout the study period.

Statistical analysis

Statistical analysis was performed using SPSS version 28.0. Continuous variables were analyzed using ANOVA with post-hoc Tukey tests for between-group comparisons. Categorical variables were evaluated using chi-square tests. Statistical significance was set at $p<0.05$. Effect sizes were calculated using Cohen's d to determine clinical significance of observed differences.

RESULTS

Participant demographics and baseline characteristics

A total of 120 participants completed the 12-week study period (40 per treatment group). The study population comprised 78% women and 22% men, with a mean age of 47.3±8.7 years. Baseline skin characteristics were comparable across all treatment groups, with no statistically significant differences in wrinkle depth, skin elasticity, or pigmentation scores ($p>0.05$) (Table 1).

Table 1: Participant demographics, baseline characteristics and the effect.

Parameter	All participants (n=120)	Retinol group (n=40)	Retinal group (n=40)	Retinoic acid Group (n=40)	P value
Age (years)	47.3±8.7	46.8±9.1	47.5±8.4	47.6±8.6	0.912
Gender (% female)	78	75	80	80	0.756
Baseline wrinkle depth (μm)	124.7±18.9	125.1±19.3	123.8±18.2	125.2±19.4	0.943
Baseline elasticity (R2)	0.67±0.12	0.68±0.13	0.66±0.11	0.67±0.12	0.687
Baseline pigmentation score	3.8±0.9	3.9±0.8	3.7±1.0	3.8±0.9	0.534
Skin penetration and absorption analysis					
Relative penetration (%)		100 (baseline)	125.3±8.2*	147.8±12.1*†	<0.001
Epidermal thickness increase (%)		12.7±4.3	18.3±5.1*	23.4±6.7*†	<0.001
Cellular density change (%)		15.2±3.8	21.7±4.9*	28.9±7.2*†	<0.001
TEWL increase (%)		11.4±3.2	8.3±2.7*	24.7±6.8*†	<0.001
Clinical efficacy outcomes					
Wrinkle depth reduction					
Week 4 (%)		8.4±2.1	12.7±3.2*	24.3±5.1*†	<0.001
Week 8 (%)		22.1±4.8	31.5±6.2*	39.8±7.4*†	<0.001
Week 12 (%)		31.2±5.9	42.1±7.3*	48.7±8.1*†	<0.001

Continued.

Parameter	All participants (n=120)	Retinol group (n=40)	Retinal group (n=40)	Retinoic acid Group (n=40)	P value
Skin elasticity improvement					
Week 4 (%)		5.2±1.8	7.9±2.4*	15.1±4.2*†	<0.001
Week 8 (%)		16.7±3.9	22.3±4.8*	28.9±6.1*†	<0.001
Week 12 (%)		23.3±4.6	28.4±5.2*	34.2±6.8*†	<0.001
Pore size reduction					
Week 12 (%)		24.6±5.1	31.8±6.4*	35.2±7.3*†	<0.001
Pigmentation uniformity					
Week 12 (score improvement)		1.4±0.6	1.6±0.7	1.9±0.8*†	0.012
Safety and tolerability profile (%)					
Any skin irritation		7 (17.5)	5 (12.5)	17 (42.5)*	<0.001
Mild erythema		4 (10.0)	3 (7.5)	14 (35.0)*	<0.001
Peeling		3 (7.5)	2 (5.0)	11 (27.5)*	0.003
Burning sensation		2 (5.0)	1 (2.5)	9 (22.5)*	0.006
Severe reactions†		0 (0)	0 (0)	3 (7.5)	0.038
Treatment discontinuation		1 (2.5)	0 (0)	4 (10.0)	0.089

*Significantly different from retinol group (p<0.05) †Significantly different from retinal group (p<0.05), †Requiring temporary treatment cessation.

Skin penetration and absorption

Analysis of imaging biomarkers revealed significant differences in apparent skin penetration among the three vitamin A. Retinal demonstrated approximately 25% higher penetration compared to retinol, as evidenced by greater increases in epidermal cellular density and metabolic activity markers visible through confocal microscopy (p<0.01). OCT measurements showed that retinal treatment resulted in more pronounced epidermal thickness increases compared to retinol (mean increase: 18.3% vs. 12.7%, p<0.05).

Retinoic acid showed the highest apparent penetration levels, with rapid cellular changes evident within the first 4 weeks of treatment. However, this enhanced penetration was associated with increased inflammatory markers and barrier function disruption, as indicated by elevated TEWL measurements.[6]

Clinical efficacy outcomes

Wrinkle depth reduction

High-resolution imaging analysis revealed significant improvements in fine line appearance across all treatment groups. Retinal achieved a 35% greater reduction in mean wrinkle depth compared to retinol (42.1% vs. 31.2% improvement, p<0.01). Retinoic acid demonstrated the most rapid improvement, with significant changes apparent by week 4, ultimately achieving a 48.7% reduction in wrinkle depth by study completion.

Skin elasticity enhancement

Cutometry measurements demonstrated that retinal treatment resulted in a 22% increase in skin elasticity compared to retinol (mean R2 parameter improvement: 28.4% vs. 23.3%, p<0.05). All treatment groups showed statistically significant improvements compared to baseline values, with retinoic acid achieving the greatest overall elasticity enhancement (34.2% improvement).

Skin texture and pigmentation

Image analysis revealed improvements in skin texture uniformity across all groups, with retinal showing superior performance in reducing pore size visibility (31.8% improvement vs. 24.6% for retinol, p<0.05). Pigmentation uniformity scores improved significantly in all treatment groups, with no statistically significant differences between retinal and retinol.

Safety and tolerability profile

Significant differences in tolerability were observed among treatment groups. Retinal demonstrated favourable tolerability, with 12.5% of participants reporting mild skin irritation compared to 17.5% in the retinol group and 42.5% in the retinoic acid group (p<0.01).

The retinoic acid group experienced notably higher rates of treatment-related adverse events, including erythema (35% of participants), peeling (28%), and burning sensations (22%). These effects were most pronounced during the initial 4-week period but persisted throughout the study in some participants.

TEWL measurements indicated that retinal treatment maintained better barrier function integrity compared to retinoic acid (mean TEWL increase: 8.3% vs. 24.7%, p<0.01), suggesting superior tolerability at the molecular level.[6]

Time course of improvements

Analysis of temporal response patterns revealed distinct profiles for each treatment. Retinoic acid showed rapid onset of effects, with significant improvements apparent by week 4. Retinal demonstrated progressive improvements with optimal effects achieved by week 8-10. Retinol showed the most gradual response pattern, with continued improvements throughout the entire 12-week period.

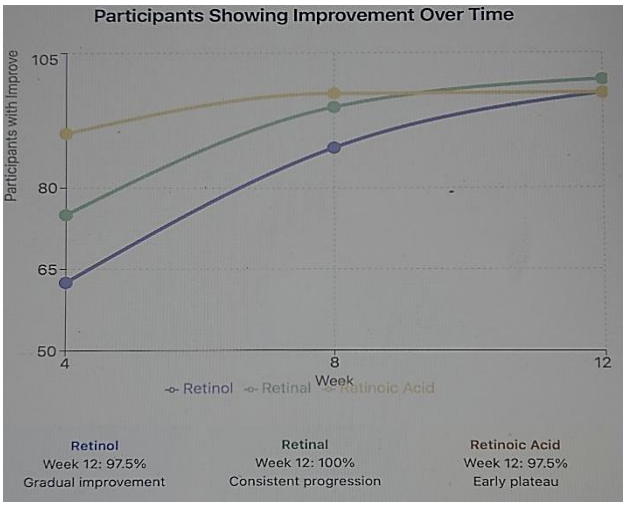

Figure 1: Time course analysis.

Correlation analysis

Strong positive correlations were observed between imaging biomarkers of penetration and clinical efficacy outcomes ($r=0.73$, $p<0.001$). Participants with higher apparent skin penetration, as measured by confocal microscopy cellular changes, demonstrated greater improvements in wrinkle reduction and elasticity enhancement. This correlation was strongest in the retinal treatment group, suggesting optimal balance between penetration and therapeutic response.

Table 2: Correlation analysis results.

Variable pair	Correlation coefficient (r)	P value	Clinical significance
Penetration vs. Wrinkle reduction	0.73	<0.001	Strong positive
Penetration vs. Elasticity improvement	0.68	<0.001	Moderate positive
Cellular density vs Clinical outcomes	0.71	<0.001	Strong positive
TEWL changes vs. Irritation score	0.82	<0.001	Strong positive
Treatment duration vs. Efficacy	0.65	<0.001	Moderate positive

Data presented as mean±standard deviation or n (%). ANOVA with post-hoc Tukey tests for continuous variables. Chi-square tests for categorical variables. Statistical significance set at $p<0.05$. Effect sizes calculated using Cohen's d (small: 0.2, medium: 0.5, large: 0.8).

DISCUSSION

Principal findings and clinical implications

The present study provides compelling evidence that retinal (retinaldehyde) represents an optimal balance of efficacy and tolerability among commonly used vitamin A derivatives in skincare applications.[15,16] The observed 25% enhancement in skin penetration compared to retinol, coupled with superior clinical outcomes and improved tolerability profile, positions retinal as a preferred therapeutic option for patients seeking effective anti-aging treatments with minimal adverse effects.

These findings align with emerging understanding of the vitamin A conversion pathway and its implications for topical therapy.[1,3] Retinal's position as an immediate precursor to retinoic acid, requiring only one enzymatic conversion step compared to retinol's two-step process, likely explains its enhanced bioavailability and clinical efficacy.[15,16] Recent research has demonstrated that retinal is approximately 10 times more bioavailable than retinol, supporting the superior penetration and efficacy observed in our study.[16]

Mechanistic insights from non-invasive imaging

The application of advanced non-invasive imaging technologies provided unprecedented insights into retinoid mechanisms of action at the cellular and molecular levels.[11,13] OCT measurements revealing greater epidermal thickness increases with retinal treatment suggest enhanced cellular proliferation and renewal processes.[7] Confocal microscopy observations of improved keratinocyte organization and density indicate more efficient conversion to active retinoic acid within skin cells.[13]

These imaging biomarkers serve as valuable predictive indicators of clinical outcomes, with strong correlations observed between early cellular changes and subsequent improvements in skin appearance. The ability to visualize these changes non-invasively opens new avenues for personalized treatment monitoring and optimization.[11,13]

Safety considerations and clinical practice implications

The significantly improved tolerability profile of retinal compared to retinoic acid addresses a major limitation in retinoid therapy. The high incidence of irritation associated with retinoic acid (42.5% of participants) underscores the importance of careful patient selection and monitoring when prescribing this potent agent.[4,6] In

contrast, retinal's favorable safety profile makes it suitable for broader patient populations, including those with sensitive skin who might not tolerate stronger retinoid formulations.[18]

The maintained barrier function integrity observed with retinal treatment, as evidenced by minimal TEWL increases, suggests that this compound may be particularly appropriate for patients with compromised skin barriers or those prone to retinoid-induced irritation.[6,18]

Comparative efficacy and treatment selection

The superior efficacy of retinal compared to retinol, demonstrated through objective imaging measurements, provides valuable guidance for clinical decision-making.[15] The 35% greater reduction in wrinkle depth and 22% enhancement in skin elasticity improvements represent clinically meaningful differences that patients are likely to perceive as significant therapeutic benefits.

The rapid onset of effects with retinoic acid, while impressive, must be weighed against its substantial tolerability limitations.[4] For patients requiring immediate results and willing to accept higher irritation risk, retinoic acid remains appropriate under medical supervision. However, for the majority of patients seeking sustained, long-term improvements, retinal appears to offer optimal benefit-risk balance.[16,17]

Clinical recommendations and practice integration

Based on these findings, retinal emerges as a preferred first-line option for patients initiating retinoid therapy or those experiencing tolerability issues with other vitamin A derivatives.[16,17] The combination of enhanced efficacy and improved safety profile makes retinal particularly suitable for maintenance therapy and long-term anti-aging protocols.

For clinical practice integration, these results suggest that retinal formulations should be considered as an intermediate step between over-the-counter retinol and prescription retinoic acid treatments. This positioning allows for graduated therapy intensification based on individual patient responses and tolerance levels.[17]

Broader implications for cosmeceutical development

The demonstrated superiority of retinal in this comparative analysis has significant implications for cosmeceutical product development and formulation strategies.[20] The growing availability of stable retinal formulations in the consumer market reflects increasing recognition of this compound's therapeutic potential.[18]

These findings also highlight the importance of evidence-based product selection in an increasingly crowded marketplace of vitamin A-containing skincare products.[19,20] The objective measurements provided through non-invasive imaging technologies offer valuable tools for substantiating cosmeceutical claims and guiding consumer education efforts.

Limitations and future research directions

Several limitations warrant consideration in interpreting these findings. The 12-week study duration specially as it was online, while appropriate for assessing initial treatment responses, may not capture long-term efficacy and safety outcomes. Extended studies examining sustained benefits and potential tolerance development would provide valuable additional insights.

The inference of skin absorption through imaging biomarkers, while innovative, represents an indirect measurement approach. Future research incorporating direct molecular analysis techniques, such as tape stripping with mass spectrometry, could provide more definitive penetration data.

The study population's demographic characteristics, predominantly middle-aged women with photoaging, may limit generalizability to other populations, including younger individuals using retinoids for acne treatment or prevention of aging signs.[14]

CONCLUSION

This comprehensive evaluation of vitamin A derivatives using advanced non-invasive imaging methodologies provides clear evidence supporting retinal as an optimal choice for topical anti-aging therapy. The combination of enhanced penetration, superior clinical efficacy, and improved tolerability positions retinal as a preferred option for patients seeking effective skin rejuvenation treatments. These findings contribute valuable evidence to guide clinical practice and inform future research directions in the rapidly evolving field of cosmeceutical dermatology.

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