

## REVIEW ARTICLE

# Update of pathophysiology and treatment options of seborrheic keratosis

Surajit Gorai<sup>1</sup> | Shahzaib Ahmad<sup>2</sup>  | Syeda Sadia Masood Raza<sup>3</sup> |  
Hadin Darain Khan<sup>4</sup> | Muhammad Asad Raza<sup>5</sup> | Farshid Etaee<sup>6</sup> |  
Clay J. Cockerell<sup>7</sup> | Zoe Apalla<sup>8</sup> | Mohamad Goldust<sup>9</sup> 

<sup>1</sup>Department of Dermatology, Apollo Multispecialty Hospital, Kolkata, West Bengal, India

<sup>2</sup>King Edward Medical University Lahore, Mayo Hospital Lahore, Lahore, Pakistan

<sup>3</sup>Karachi Medical and Dental College, Karachi, Pakistan

<sup>4</sup>Shalamar Medical and Dental College, Lahore, Pakistan

<sup>5</sup>Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, USA

<sup>6</sup>Yale School of Medicine, Yale-New Haven Health System, New Haven, Connecticut, USA

<sup>7</sup>Departments of Dermatology and Pathology, The University of Texas Southwestern Medical Center, Dallas, Texas, Cockerell Dermatopathology, Dallas, Texas, USA

<sup>8</sup>Second Dermatology Department, Aristotle University of Thessaloniki, Thessaloniki, Greece

<sup>9</sup>Department of Dermatology, University Medical Center of the Johannes Gutenberg University, Mainz, Germany

## Correspondence

Mohamad Goldust, Department of Dermatology, University Medical Center of the Johannes Gutenberg University, Mainz, Germany.  
Email: [mgoldust@uni-mainz.de](mailto:mgoldust@uni-mainz.de)

## Abstract

Seborrheic keratosis (SK) is a common, benign tumor that can occur on everybody site and can be conservatively managed. Cosmetic concerns, especially when a lesion involves the facial area, are the most common reason for excision. SK shows male gender preponderance and increasing age is an independent association with the condition. Even though more prevalent in the elderly, it has also been reported in younger age groups like adolescents and young adults. Precise pathogenesis is still obscure, but ultra-violet exposure represents a predisposing factor to SK by altering the biochemical concentration and expression of factors like Glutamine deaminases, endothelin, and stem cell factor. Moreover, the accumulation of amyloid-associated protein has also been postulated. Involvement of genitalia has been associated with human papillomavirus infection. Recently, Merkel cell polyomavirus nucleic acid was also detected in SK. Several oncogenic mutations involving FGFR-3 and FOXN1 have been identified. SKs are usually classified clinically and histologically. Dermatoscopy is a noninvasive alternative diagnostic technique widely used in differentiating SK from other benign and malignant tumors. In terms of treatment, topical agents, shave dissection, cryosurgery, electrodesiccation, laser application and curettage under local anesthesia are safe methods for eradication of SKs, mostly for cosmetic purposes. Though generally safe, the latter techniques may occasionally cause post-procedure depigmentation, scarring, and recurrence. Nanosecond-pulsed electric field technology is a promising new technique with fewer side-effects.

## KEYWORDS

excision, histology, lesion, seborrheic keratosis, sun exposure

## 1 | INTRODUCTION

Seborrheic keratosis (SK) is a frequently encountered skin condition, and it is one of the commonest benign epidermal tumors.<sup>1</sup> Despite its benign nature, removal can be considered for cosmetic or

diagnostic reasons, especially in the scenario of irritated or melanoacanthoma-type SK.<sup>2</sup> Face and upper trunk are sites of predilection, even though these lesions can occur at any body-site.<sup>3</sup> This review of SK is an attempt to collate all data and place it in one place.

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## 2 | EPIDEMIOLOGY

Common seborrheic keratosis (CSK) is one of the types of SK that is more prevalent in the Caucasian race, whereas dermatosis papulosa nigra (DPN), another subtype, is more common in Fitzpatrick skin phototype 3 and above.<sup>4</sup> SK are characterized by male preponderance.<sup>5</sup> Though the exact age-wise prevalence data vary in the different continents there is a common opinion that as the age increases prevalence and size of the lesion also increase. The age-wise correlation was proven by a European study with prevalence among 24- to 49-year-olds was 38%; 50- to 59-year-olds was 69%; 60- to 69-year-olds was 86%, and 70- to 79-year-olds was 90%.<sup>6</sup> The younger population is also affected by SK with Yeatman and colleagues reporting 12% prevalence in the age groups between 15 and 40.<sup>7</sup> A positive family history is often seen in patients with a higher number of lesions.<sup>8</sup> The pattern of inheritance is reported to be autosomal dominant, with incomplete penetrance.<sup>9</sup>

## 3 | PATHOGENESIS

### 3.1 | Age

Based on epidemiology, the increasing age is an independent risk factor for the development of SK.<sup>3-5</sup>

### 3.2 | UV exposure

UV exposure has been proposed to be a risk factor, but exact causality remained questioned. A Korean study has found increased number of lesions on sun-exposed areas of the body. It also revealed that sunlight exposures of over 6 h/day during lifetime had a 2.28-fold increased risk for SK versus less than 3 h/day.<sup>10</sup> However, a study performed by Dutch researchers revealed that sunburns resulting from sunlight exposure or lifetime sun exposure resulted in an increased risk of SK.<sup>11</sup> Guanine deaminase (GDA) is upregulated in senescent UV-damaged skin. It, in turn, increases the synthesis of uric acid metabolites and reactive oxygen species (ROS) generation and DNA damage, GDA also upregulates the endothelin (EDN-1) and Stem cell factor (SCF). EDN-1 induces cytokine TNF- $\alpha$ .<sup>12</sup> EDN-1 is a factor strong melanogenic causing the production of melanin in the skin and it is a keratinocyte-derived mitogen.<sup>13</sup>

### 3.3 | Role of amyloid-associated protein (APP)

APP is found to be increased in UV-exposed and aged skin. The Presenilin 1 and 2 levels are reduced in senescent keratinocytes, resulting in the non-release of beta-amyloid from APP resulting in its accumulation, and this is implicated in SK formation in mice.<sup>14</sup>



**FIGURE 1** Clinical pictures of seborrheic keratosis

### 3.4 | Infectious etiology

HPV DNA was detected in SK by polymerase chain reaction and Fluorescent in situ studies (FISH). Though the prevalence of HPV DNA is much more common in genitalia as compared to non-genital ones.<sup>15</sup> HPV- DNA was detected only in the superficial portion of SK and deep biopsies revealed less percentage thus implicating surface contamination rather than the actual cause. Recently, Merkel cell polyomavirus nucleic acid was detected in SK, but the possibility of co-infection is more likely rather than the actual cause, as this virus replicates in rapidly dividing cells.<sup>16</sup>

### 3.5 | Oncogenic variation

Even though SK is a benign tumor, oncogenic mutations have been found in SK lesions. The most common somatic mutation was in Fibroblast Growth Factor Receptor 3 (FGFR3). However, this mutation is insufficient to cause cancer. Increased FGFR3 activity promotes FOXN1-mediated differentiation and results in a benign SK-like phenotype in previously malignant squamous cell carcinoma (SCC) cells, which may be explained by a positive FGFR3/FOXN1 feedback loop in SK.<sup>17</sup> FOXN1 knockdown, on the other hand, increases oncogenic RAS and causes SCC-like cancers.<sup>18</sup> Fibroblast growth factor deficiency causes epidermal abnormalities in inflammatory dermatoses, and the epidermal growth factor receptor (EGFR) has been linked to defective keratinocyte proliferation and differentiation in SK. Despite mutations in the PI3K-AKT and FGFR3-RAS-MAPK pathways, as well as mutations in the AKT1, HRAS, EGFR, and KRAS oncogenes, the AKT1, HRAS, EGFR, and KRAS oncogenes,<sup>19</sup> SK are genetically stable. SK does not show p53 mutation, which can explain this stability. This can be further substantiated by the fact that in an irritated variant of SK, p16 and p53 expression predisposes to malignant transformation.<sup>20</sup>

### 3.6 | Types

#### 3.6.1 | Clinical types

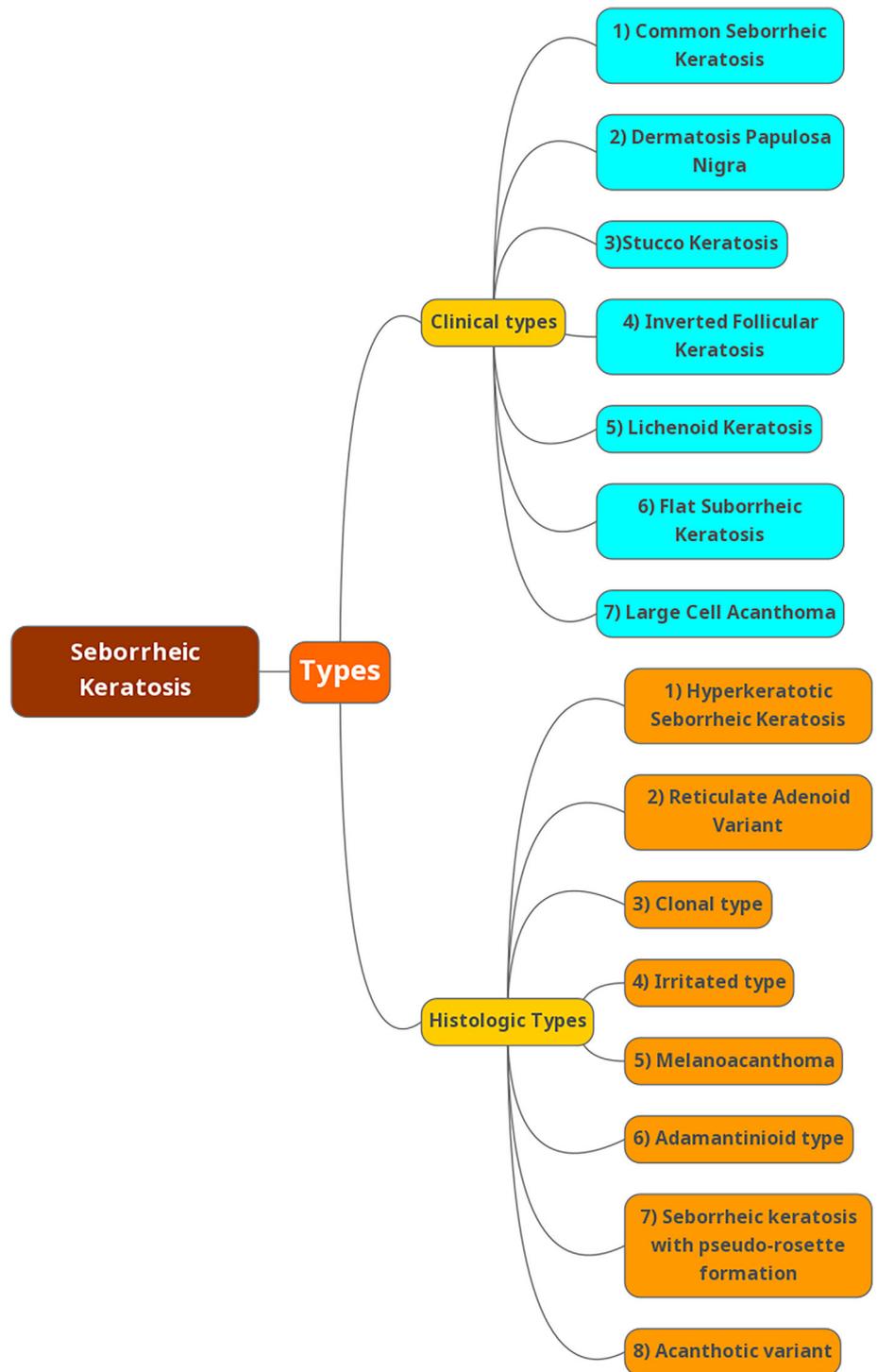
##### Common SK (CSK)

Clinically, it presents as a sharply demarcated, brown, “stuck on” papule with velvety or granular surface (Figures 1 and 2). CSKs occur on hair-bearing surface areas of the body. The lesions can have various colors like black, white, yellow, maroon, and blue-gray.<sup>21</sup> The

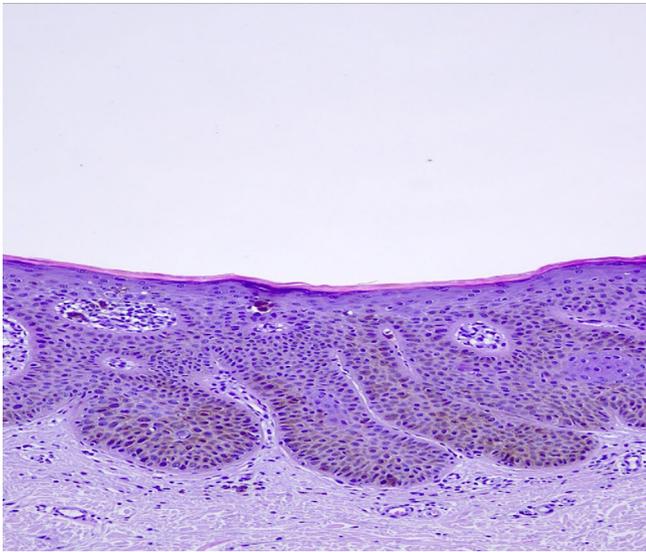
frequency of CSK is slightly higher in males. Initially, the CSK may start as a flat lesion but as it grows the surface becomes verrucous. Histopathology of these lesions shows predominant orthokeratosis hyperkeratosis with papillomatosis. Horn pearls are minimal or absent with pseudo horn pearls as a common finding.<sup>22</sup>

##### Dermatitis papulosa nigra (DPN)

It occurs predominantly in dark individuals and clinically appears as a papule, which is round, or filiform, hyper-pigmented, and smooth-



**FIGURE 2** Types of seborrheic keratosis



**FIGURE 3** Flat/macular seborrheic keratosis

surfaced with an approximate size of 1 to 5 mm. These lesions are more common in females and occur predominantly over the face and upper trunk. Family history is positive in many cases.<sup>23</sup>

#### *Stucco keratosis*

These lesions involve the lower leg (around the ankle) and are more often seen in elderly males. They are clinically characterized by a white to yellow, warty surface.<sup>24</sup> The name Stucco Keratosis is derived from its typical “stuck on” appearance. They have the characteristic of being easily removable. Stucco keratosis slightly bleeds when scraped.

#### *Inverted follicular keratosis (IFK)*

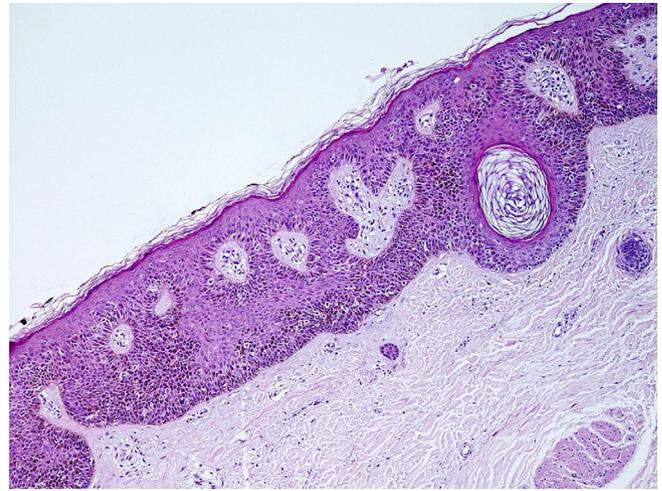
In older or middle-aged people, inwardly developing irritated SK can manifest as asymptomatic white-tan to pink isolated lesions on the face, generally on the cheek and upper lip.<sup>25</sup> An IFK appearing on the conjunctiva has also been described. Cowden's syndrome has several IFKs, which can be used as a cutaneous marker.<sup>26</sup> Due to their apparent similarities, IFK and squamous cell carcinoma may be confused. A diagnostic biopsy with histologic examination is recommended in the latter scenario.

#### *Lichenoid keratosis (LK)*

Clinically, LK appears as a slightly elevated, red-brown plaque on the upper chest, face, or forearms, more often in white-skinned elderly women in their fourth and seventh decades of life. Non-scaly lesions often mimic BCC, making LK difficult to detect.<sup>27</sup>

#### *Flat seborrheic keratosis*

These lesions present as tan-brown macules over chronically sun-exposed areas of the body (Figure 3). Flat seborrheic keratoses are similar to solar lentigines in appearance. They grow in size with age and are asymptomatic.<sup>24</sup>



**FIGURE 4** Melanoacanthoma seborrheic keratosis

#### *Large cell acanthoma (LCA)*

On sun-damaged skin, LCA appears as a solitary, scaly, tan, reddish or orange colored papule or plaque. It is frequently described as a “stuck on” lesion on the neck and face including the eyelids, although it can also affect the extremities and trunk.<sup>28</sup> Skin-colored or hypopigmented variants are not infrequent.<sup>29</sup>

### 3.6.2 | Histological subtypes

The following eight histological subtypes of SK have been described in the literature.

#### *Hyperkeratotic SK*

Orthohyperkeratosis and papillomatosis are more common in this type. There is mild or no acanthosis and horn pearls are usually lacking. There are several studies describing areas that look like “pseudo-horn cysts” in cross-section.<sup>22</sup>

#### *Reticulate/adenoid variant*

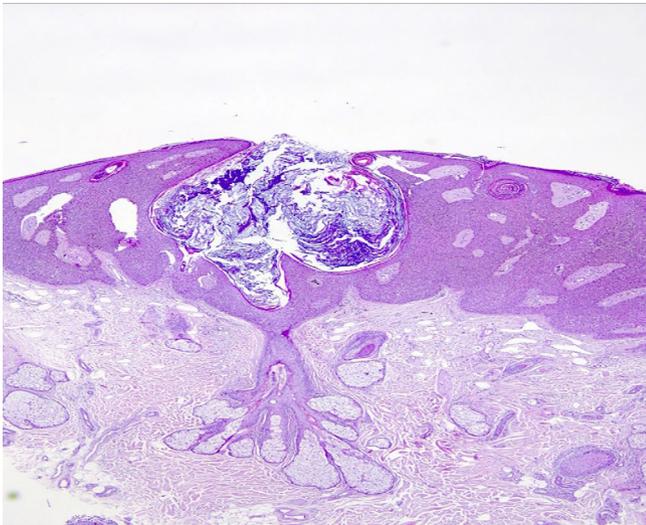
Reticulate/Adenoid SKs have thin, double-row reticular acanthosis with mild-to-moderate hyperkeratosis and papillomatosis. Hyperpigmented variants are common. Horn pearls are rare. Sun-exposed sites are more likely to have this subtype.<sup>30</sup>

#### *Clonal type*

Orthohyperkeratosis is accompanied by significant acanthosis and papillomatosis in this form. Tumor cells are shaped like spindles. Islands of basaloid cell nests can be detected in a defined tumor.<sup>30</sup>

#### *Irritated type*

The proliferation of spindle-shaped eosinophilic tumor cells is seen in this kind of tumor, occasionally in whorl-like forms. There may be dyskeratotic cells present. Differentiation of SCC and irritated SK is challenging. Dermoscopy is a useful tool toward this discrimination.



**FIGURE 5** Melanoacanthoma seborrheic keratosis

However, if any diagnostic doubts are present, excision and histologic examination with immunohistochemistry is highly recommended.<sup>30,31</sup> A recent study indicated that combining the U3 small nucleolar ribonucleoprotein protein IMP3 with the B-cell lymphoma 2 regulatory protein (Bcl-2) was protective.<sup>32</sup>

#### *Melanoacanthoma*

This is a hyperpigmented acanthotic form of SK, with basaloid cell growth and minimal or no hyperkeratosis (Figure 4). These lesions are heavily pigmented, with numerous melanocytes mixed up. Melanophages can be also presented in the dermis.<sup>30</sup>

#### *Adamantinoid type*

The lesion was an acanthoma constituted of tiny basaloid keratinocytes separated from the neighboring normal epidermis in histology. Throughout the acanthotic epithelium, there were several pseudo-horn cysts. The most visible feature of the intraepidermal nests was the intercellular blue granular material within the neoplastic cells, which gave them a paler appearance. As a result of these intercellular mucinous deposits, neoplastic cells with elongated nuclei and stellated cytoplasm extended as thin, linking bridges over vacant regions.<sup>33</sup>

#### *SK with pseudo-rosette formation*

The lesion was also an acanthotic SK with thicker epidermis and orthokeratotic hyperkeratosis, according to histopathology. Some places have pseudo-horn cysts as well. The most noticeable observation was the unusual configuration of basaloid keratinocytes inside the acanthotic epithelium, where they were radially oriented around central tiny empty spaces, resulting in the creation of numerous regions.<sup>30,33,34</sup>

#### *Acanthotic variant*

It is characterized by acanthosis accompanied by hyperkeratosis and moderate papillomatosis, especially in basaloid cells, a large number of

horn pseudocysts, roughly a third of which are pigmented, and lymphocytic lichenoid or restricted infiltration are all features.<sup>30,34</sup> (Figure 5).

## 4 | DIAGNOSIS

The majority of SK can be easily diagnosed on a clinical basis. In the event of a dilemma, a punch, or shave biopsy of the skin can be performed. Dermoscopy has recently gained popularity as a noninvasive diagnostic procedure.<sup>1-5,35</sup>

### 4.1 | Dermoscopic features

The features suggestive of SK on dermoscopy are Comedo-like opening (CL), fissures and ridges (FR), fingerprint-like pattern (FP), moth-eaten borders (ME), sharp demarcation (SD), milia-like cyst (ML), fat fingers and hairpin vessels with white halos. It is not mandatory that all findings can be seen in a single lesion. The dermoscopic findings of SK were described by Rajesh et al. in 250 cases, in which they discovered that CL apertures, FR, and SD were the most prevalent findings on dermoscopy in CSK, whilst ME boundaries, ML cysts, and NL structures were less common. CL openings, FR, and SD were the only findings seen on DPN. The pedunculated SK had only FR and CL.<sup>36</sup> In all cases, stucco keratoses showed SD and NL structures, a ME border in one, and ML cysts in two cases.<sup>30</sup>

### 4.2 | Treatment

SK is removed primarily due to cosmetic reasons. Various modalities like cryotherapy, shave dissection, and electrodesiccation and curettage can be utilized to get rid of lesions.<sup>37</sup>

The most frequent treatment, especially for flat or thin lesions, is cryotherapy. If the clinical diagnosis is certain, then cryotherapy should be employed.

After anesthesia with a 1% lidocaine solution, a no. 15 scalpel blade can be used to execute curettage or shave excision with specimen submission for pathology.<sup>37</sup> Treatment of seborrheic keratoses with cryotherapy or curettage with a no. 15 scalpel achieved equivalent aesthetic improvement as judged by patients in a short study of 25 patients.<sup>37</sup> However, since cryotherapy requires less postoperative wound care than curettage, most patients preferred it over curettage.

Anesthesia with 1% lidocaine is typically required for electrodesiccation alone or in combination with curettage.<sup>38</sup> But these modalities are associated with significant side effects like post-procedure depigmentation, scarring, and recurrence to mention a few.<sup>38,39</sup> For the treatment of SK, several lasers have been utilized, including the pulsed carbon dioxide (CO<sub>2</sub>) laser, the erbium yttrium aluminum garnet (YAG) laser, the 755 nm alexandrite laser, and the 532 nm diode laser.<sup>38</sup> Recently, 40% H<sub>2</sub>O<sub>2</sub> has been approved by FDA for treatment.<sup>40</sup> The nitric-zinc solution showed a good clinical response with

**TABLE 1** Treatment Modalities for seborrheic keratosis

Treatment modalities	Description
<i>Surgical</i>	
Cryotherapy	Cryotherapy is the most frequent and most accessible treatment for seborrheic keratosis. This procedure requires little post-operation care for the treated area, however, it can result in erythema, discomfort, and bulla formation. With the healing of these areas following therapy, there have been occasional reports of post-procedure hypopigmentation or hyperpigmentation. <sup>44</sup>
Curettage/shave excisions.	This form of treatment is typically used for skin diseases that predominantly affect the epidermis and do not involve the dermis. <sup>45</sup> With curettage, specialists noticed increased redness at 6 weeks and a predisposition for hypopigmented scar formation at over 12 months. <sup>4</sup>
Electrodessication	This procedure is another method for the elimination of epidermal lesions that are just on the surface but have not penetrated the dermis. Curettage and desiccation (C&D) produces effective results with a typically low incidence of complications. Infection, scarring, and hyperpigmentation are possible side effects of C&D. <sup>45</sup>
<i>Topical</i>	
Hydrogen peroxide (H <sub>2</sub> O <sub>2</sub> ) 40% (RCT)	On face lesions, this therapy was most effective. Truncal SKs (46%) and SKs on the extremities were next (38%). Additionally, facial SKs responded far more immediately than lesions on other body areas, likely as a result of their frequent thinness. Scarring and other delayed adverse responses including pigmentary changes were the least obvious for the facial SKs. <sup>46</sup> In comparison to cryosurgery, HP40 appears to be less toxic to melanocytes, indicating a favorable safety profile with regard to post-procedure related pigmentary variations. <sup>47</sup>
Tacalcitol 2 µg/g, Calcipotriol 50 µg/g, Maxacalcitol 25 µg Ointments (RCT)	With topical vitamin D3 therapy, 30% of all lesions showed excellent improvement. The maxacalcitol group showed the most improvement, with 15% of patients demonstrating an exceptional improvement, compared to 12% in the calcipotriol group and 8% in the tacalcitol group. The typical application process took 7.3 months. There were no adverse reactions as redness, swelling, or scarring. <sup>48</sup>
Ammonium Lactate 12% Lotion(NON-RCT)	Significantly decreased lesion height in the treatment group. There was no discernible change in the breadth of the lesions between the study and control groups. There was no significant variance between the study group and the control group's lesions' surface features or color. <sup>49</sup>
Tazarotene 0.1% Cream, Calcipotriene 0.05% Ointment, Imiquimod 5% Cream.(NON-RCT)	The study's findings demonstrated that once-daily administration had no positive impact on clinical outcomes. In comparison to 0% in the moisturizer group, tazarotene twice daily produced a full clinical and histologic clearance in 47% of patients. Cryosurgery completely resolved the lesions in every patient who received treatment. In lesions treated with imiquimod twice daily, adverse events included redness, burning, and ulceration, while transitory irritation was seen in lesions treated with tazarotene. After a month, complete re-epithelialization resulted from the swelling, blister formation, crusting, and erosion brought on by cryosurgery. No assessment was made of lesion recurrence. <sup>50</sup>
Artemether (Eleven patients were enrolled in an open-label, non-randomized, single centre study.)	The effectiveness of therapy on lesions was evaluated using IGA (Investigator Global Assessment) scoring. At week 12, 18.1% of lesions had IGA scores of good response and full clearance. An improvement in the subjective evaluation was accompanied with a shortening of the lesion. In the course of the trial, there were no significant adverse events (SAEs). Six patients reported mild temporary itching, five patients' skin burning, and two patients slight erythema. <sup>51</sup>
Trichloroacetic acid 65% peel (cohort study)	According to the results of the clinician's evaluation, 57% had a great response to treatment, and 58% of patients said they were completely satisfied. Results remained consistent for over 13 months. Patients with seborrheic keratosis showed the best progress in comparison to those with other pigmented lesions. <sup>52</sup>
Urea 50% Ointment (cohort study)	It was concluded in the study that there has been minimal decrease in thickness without any adverse effects. The average treatment time was not provided. Recurrence wasn't assessed. <sup>53</sup>
Nitric-Zinc 30–50% Solution (cohort study)	74% of lesions indicated complete clinical and microscopic clearance after an average of three treatments. After a six-month follow-up, no relapses were noted. Mild persistent hypopigmentation and brief temporary post-treatment erythema were observed as adverse effects. <sup>54</sup>

TABLE 1 (Continued)

Treatment modalities	Description
Fluorouracil 5% Cream (case study)	The lesion had fully disappeared after 21 days of therapy, with the majority of the hairs unharmed. At 6 months after treatment, clearance was noted. After 7 years, there was no recurrence. Erythema, edema, and erosion were side effects that occurred during therapy but went away within a few weeks. <sup>55</sup>
10. Potassium dobesilate 5% cream (case study)	For 6 months, the patient took the drug every day. The clinical disappearance of lesions was used to determine clearance. The patient's lesions were completely gone by the time the treatment was over. After a year, the outcomes remained stable. No skin atrophy, changes in pigmentation, skin thinning, or application-site reactions were noticed. <sup>56</sup>
11. Diclofenac gel (case report)	After 1 month of applying diclofenac gel twice a day, the lesion was completely gone. Diclofenac is an anti-inflammatory agent. <sup>57</sup>
<i>Laser options</i>	
1. Er:YAG (erbium-doped yttrium aluminum garnet) laser. (RCT)	Complete healing was observed in all of the lesions (100%) treated with Er:YAG lasers, whereas the cryotherapy group had a healing rate of 68%. Hyperpigmentation was significantly less in the Er:YAG laser-treated group than in the cryotherapy group. <sup>58</sup>
2. CO <sub>2</sub> laser	It does not require surface anesthetic, but it is an effective alternative choice with a somewhat increased risk of scarring and pigmentary alterations. At the 8-month follow-up, there had been no recurrence. <sup>59</sup>
3. Intense-pulsed light	IPL was effective in treating superficial and minor seborrheic keratoses. After an average of two treatments, seborrheic keratoses typically disappeared with a slight inflammatory reaction and a full recovery within 30 days. Keratosis typically vanishes entirely, leaving no erythema behind. <sup>60</sup>
4. Pulsed-dye laser (case report)	The patient experienced little erythema, edema, and pain during the procedure, each of which subsided within 24 to 48 h. Since there were numerous lesions present, positive results were obtained. Negative effects were not noticed, like scars or hypo- or hyperpigmentation. <sup>61</sup>
5. Nd:YAG (neodymium-doped yttrium aluminum garnet) laser. (case report)	Patients reported only minor discomfort and did not require sedation. The average treatment time per patient was only 5–10 min. The potential dangers do include pigmentary changes and possibly scarring, although this method provided great cosmetic outcomes without any side effects. <sup>62</sup>
6. 755-nm alexandrite picosecond laser	Flat lesions, which account for 61% of total clearance. 3.60 was the average score for increased, popular disorders (65% of clearance). Mild erythema and discomfort during the first 2 to 3 days after treatment were the most frequently reported side effects. For the treatment of pigmented endogenous cutaneous lesions of various types, the picosecond laser with an alexandrite wavelength of 755 nm can be thought of as an efficient, quick, and secure choice. It could be used for lesions that are flat or just slightly raised.
7. Nanosecond-pulsed electric field technology (also known as Nano-Pulse Stimulation or NPS)(RCT)	Lesions typically had a thin crust, or a thicker crust if they were larger. When at least partial clearance was seen, the treated lesion was deemed to have improved. When all three clearance levels—clear, mostly clear, and partially clear—were combined, 87% of the lesions had improved at 1 month and 93% had done so at 106 days following therapy. 78% of participants said they were happy or mainly satisfied with the result. Low risk of long-term hyperpigmentation and scarring, safe and efficient treatment for SKs. <sup>43</sup>

no recurrence in clinical trials.<sup>41</sup> However, none of the therapies listed above have been thoroughly tested in randomized trials.<sup>38–41</sup> The size and thickness of the lesion, the patient's skin type, and clinical expertise all influence the treatment options.<sup>37–41</sup>

Other topical agents used are 5% imiquimod,<sup>28</sup> topical dobesilate,<sup>42</sup> and 3% diclofenac gel,<sup>42</sup> but the response rate is varying. The ablative lasers like Er: Yag has shown good response with minimal side effect profile, but the cost is the limiting factor. The CO<sub>2</sub> laser is also effective but associated with significant side effects such as

scarring and post-inflammatory hyperpigmentation.<sup>38</sup> Other lasers tried are PDL, 1064 nm Q switched Nd: YAG. Nanosecond pulsed electric field technology (also referred to as Nano-Pulse Stimulation or NPS) is a non-thermal, drug-free, energy-based treatment for SK. Hruza et al. investigated the safety and efficacy of a single NPS treatment for clearing SK. The assessing physician rated 82% of treated seborrheic keratoses as clear or mostly clear. The treatment resulted in 78% of the subjects being satisfied or mostly satisfied. There were no reported side effects.<sup>43</sup> (Table 1).

## 5 | CONCLUSION

Seborrheic keratosis is a benign tumor that can be managed conservatively, and one of the most common reasons for the excision of lesions is for cosmetic reasons. It is more common in the elderly, but it has also been reported in younger age groups such as adolescents and young adults. Ultraviolet exposure and increasing age are associated with the condition. Dermoscopy is a noninvasive alternative diagnostic technique that has recently gained popularity. Topical agents, shave dissection, cryosurgery, electrodesiccation, laser application, and curettage under local anesthesia are all safe cosmetic procedures, but some of them can result in post-procedure depigmentation. Nanosecond-pulsed electric field technology is a promising new method that has fewer side effects.

### AUTHOR CONTRIBUTIONS

*Writing and revising the manuscript:* Surajit Gorai. *Review and revising the manuscript:* Shahzaib Ahmad. *Review and revising the manuscript:* Syeda Sadia Masood Raza. *Review and revising the manuscript:* Hadin Darain Khan. *Review and revising the manuscript:* Muhammad Asad Raza. *Review and revising the manuscript:* Farshid Etaee. *Review and revising the manuscript:* Clay J. Cockerell. *Review and revising the manuscript:* Zoe Apalla. *Conception, writing, review and revising the manuscript:* Mohamad Goldust.

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### CONFLICT OF INTEREST

The authors have no conflict of interest to report.

### DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

### ORCID

Shahzaib Ahmad  <https://orcid.org/0000-0001-9060-6636>

Mohamad Goldust  <https://orcid.org/0000-0002-8646-1179>

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