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Radioisotope ^{32}P for Keloid Therapy: A Review

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Abstract

Keloids are skin disorders resulting from an abnormal wound healing response, often leading to excessive scar tissue growth. Keloids can be itchy, painful, and aesthetically disturbing. Keloid therapy varies, but until now, there is no standard method that is effective due to different patient responses. Racial, environmental, and genetic variables influence keloids. Various therapeutic techniques, such as surgery, cryotherapy, corticosteroid injections, laser light, and radiotherapy, have been used to treat keloids, but each has advantages and disadvantages. However, these treatments have limitations, such as high recurrence rates and patient discomfort. The application of radioisotope therapy, specifically using ^{32}P, has emerged as a promising alternative. Radioisotope ^{32}P emits β-particles, effectively inhibiting keloid cell growth by causing DNA damage and reducing collagen production. Studies show that ^{32}P therapy significantly reduces keloid size and recurrence rates while causing minimal patient discomfort. Although there are potential risks, such as damage to surrounding healthy tissue, ^{32}P therapy provides a practical and non-invasive option for keloid management. However, more research is required to fully understand this method's effectiveness, safety, and long-term impact on keloid therapy, optimize treatment protocols, and minimize side effects.

Keywords: keloid, keloid therapy, ^{32}P radioisotope, radiation, fibroblast cells

INTRODUCTION

Keloids are benign tumors or skin conditions caused by an aberrant connective tissue wound-healing response. However, in some people, the body's response to this healing process can be excessive, resulting in the growth of scar tissue larger than the original injury area. Keloids usually have a hard texture, are raised above the surface of the skin, and can be darker or lighter in color than the surrounding skin and tend to grow progressively over several months after the injury occurs (Blalock, 2020; Chike-Obi et al., 2009). Keloids can become itchy or painful, especially when growing and exposed to friction or pressure. Keloids located in areas of body movement, such as joints or muscles, can limit movement and cause discomfort (Bayat et al., 2004). Keloids are aesthetically very disturbing, besides feeling itchy and painful and making the surrounding tissue stiff. Reducing pain symptoms and itching in keloid scars after therapy or treatment can improve the sufferer's quality of life (Correa & Passos, 2019).

Keloid formation is commonly triggered by injuries to the skin, including surgical incisions, burns, piercing marks, tattoos, and other forms of trauma. This is largely due to an abnormal wound-healing process where excessive collagen is produced, causing the scar to expand beyond the original injury site (Xue & Jackson, 2015; Mathew-Steiner et al., 2021). Research suggests that the cause of keloid formation also involves genetic factors and an overactive inflammatory response, making some people more susceptible than others (Kim et al., 2023). Even minor skin injuries may lead to keloid scars in some individuals (Robles & Berg, 2007). Some keloids occur without cause, usually called spontaneous keloids. The causes of spontaneous keloids are not fully understood (Trufin et al., 2024). However, several variables, such as hereditary

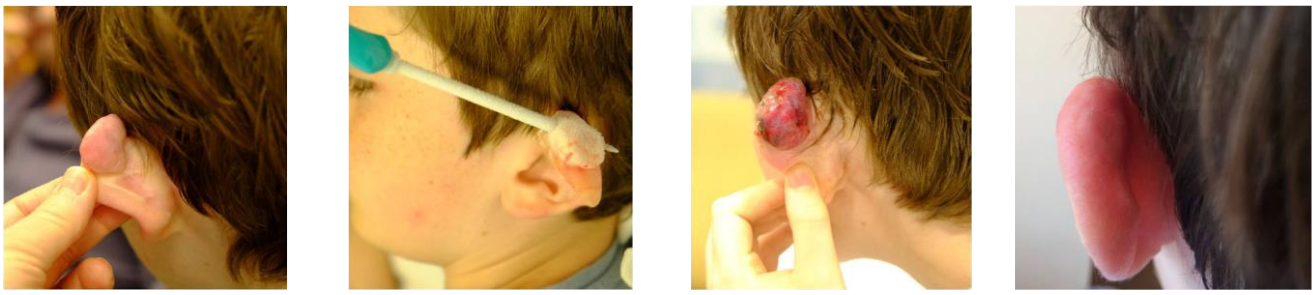
abnormalities, specific medical conditions, and environmental factors, are believed to contribute to the development of spontaneous keloids. Genetic disorders can cause spontaneous keloids (Huang et al., 2020). Spontaneous keloids have been linked to several hereditary syndromes, including X-linked syndrome with flamin A mutation (FLNA), Bethlem myopathy, Goeminne syndrome, Noonan syndrome, Rubinstein-Taybi syndrome, and Dubowitz syndrome (Jfri & Alajmi, 2018). Inheritance of keloids in the family also supports genetic factors that influence the occurrence of keloids (Glass, 2017).

Geographic conditions and racial variations in skin pigmentation significantly influence the production of keloids. People of African descent, such as Africans, Afro-Americans, and members of various other African ethnic groups, are more likely to develop keloids, with a 5–10% tendency for dark-pigmented skin (Li et al., 2024). Individuals with Asian ancestry, including those from Southeast Asia (Indonesia, Thailand, Malaysia), South Asia (Indians and Pakistanis), East Asia (Chinese, Japanese, and Koreans), and South Asia (China, Japan, and Koreans), may also be 0.1–1% more likely to develop keloids. Some Hispanic ethnic groups, especially those with higher skin pigment, such as Mexicans, Central Americans, and South Americans, also have a higher risk of developing keloids by 0–0.1%. Keloids are less common in people with lighter skin (Huang et al., 2020). Keloids are more likely to form in individuals under 30, although they can develop at any age (Grabowski, Pacana, & Chen, 2020).

KELOID THERAPY METHODS

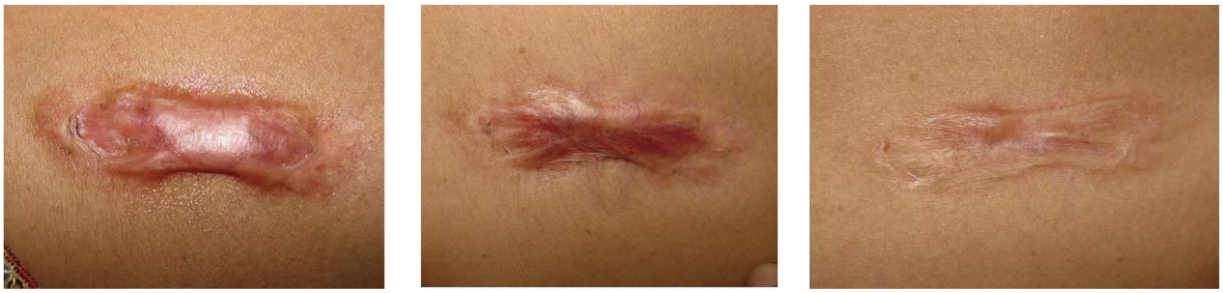
Keloid therapy aims to stop or slow further keloid growth and reduce or eliminate discomfort and an undesirable appearance by smoothing and flattening the keloid tissue to look more normal. There are many therapies or treatment methods for keloids, and the success rate of keloid therapy can vary from one individual to another. Until now, no therapy has been effective and can be used as a standard in treating keloids because responses vary in individuals (Trace et al., 2016). Keloid therapy through surgical removal of keloids with surgical techniques can remove keloids directly, but as a result of surgery, it can cause new keloids in the surgical scar. After surgery, the recurrence rate of keloids is fairly high, ranging from 45% to 100%. (Grabowski et al., 2020; Blalock, 2020). In overcoming this clinical failure, various additional therapies were carried out after the surgical removal of keloids. The recurrence rate decreased to 22% (Robles & Berg, 2007; Ogawa et al., 2019).

Cryotherapy, particularly intralesional cryotherapy, has successfully treated small keloids. Studies have indicated that cryotherapy using liquid nitrogen can reduce keloid volume by 51.4% to 67.4% after a year. This therapy uses extremely low temperatures to target and reduce keloid tissue, often reshaping collagen production in the affected area (Walsh et al., 2023). Success rates for this method vary depending on the keloid's condition, with reported effectiveness ranging from 32% to 74%. (Blalock, 2020; Abramovits et al., 2016; Stephanie & Susilowaty, 2017). However, a high recurrence rate of approximately 33% has been observed, indicating the need for careful follow-up and possible additional



Keloid on the ear Therapy with cryotherapy 1 week after therapy 11 weeks after therapy

Figure 1. Keloid therapy with cryotherapy (O'Boyle et al., 2017)



Keloid before therapy After therapy After 18 months of therapy

Figure 2. Keloid therapy using corticosteroid injection (Khalid et al., 2019)

treatments to maintain long-term results (Abramovits et al., 2016).

Several studies have shown that combining triamcinolone with 5-fluorouracil (5-FU) can enhance the effectiveness of therapy. For instance, compared to triamcinolone alone, this combination has been more successful in reducing the size of keloids and hypertrophic scars while also resulting in a slightly lower recurrence rate; this finding was supported by a meta-analysis (Bao et al., 2020; Jiang et al., 2020). However, this therapy often causes pain and discomfort for patients, especially when administered frequently (1–2 times per week). Therefore, it is important to innovate drug delivery methods to reduce pain without compromising the effectiveness of the treatment (Shah et al., 2016). Corticosteroid injections (triamcinolone or a mixture of triamcinolone and 5-fluorouracil) can reduce keloids by 50–80% by undergoing injections 1–2 times a week, but the recurrence rate is quite high, reaching 50-94% depending on the keloid's response to therapy. Therapy using injections makes the patient feel sick, in pain, and uncomfortable (Rachmantyo et al., 2018; Van Nguyen et al., 2023).

Keloids can also be treated with laser light, which is quite expensive and done repeatedly. Depending on the keloid to be treated, different types of laser equipment are employed, such as intense pulsed light (IPL), vascular-specific pulsed dye laser (PDL), and ablative fractional CO_2 laser. (AD Mamalis et al., 2014; A. Mamalis & Jagdeo, 2015; Magni et al., 2020). Laser-based therapy, an effective and viable option for treating hypertrophic burn scars, helps improve burn scars' abnormal texture, thickness, and stiffness (Scott Hultman et al., 2012).

Radiotherapy or radiation therapy can be used to treat keloids by shooting X-rays at the keloids. Due to the large distance between the radiation source and the scar, external radiation therapy necessitates a relatively high radiation dose. Furthermore, the nearby healthy skin is additionally subjected to needless radiation exposure. Since radiation-induced irreversible cell destruction (radionecrosis) is another common side effect of radiation therapy that involves firing X-rays at keloids, radiation therapy can leave normal skin looking blackish following treatment. Radiation therapy sufferers are reluctant to choose this kind of thing (Xu et al., 2017; Fenny Gozal, 2018). Low-dose rate (LDR) brachytherapy employs a low-dose radioactive source that is withdrawn after 20–72 hours, whereas keloid therapy uses high-dose-rate (HDR) brachytherapy with a high radioactive source delivered for a brief period of 5–10 minutes to the keloid (Van Leeuwen et al., 2015) and post-operative interventional radiotherapy (POIRT) as an effective strategy to control keloid recurrence (Franzetti et al., 2024).

Keloid Therapy Using Radioisotope ^{32}P

The radionuclides best suited for tumor therapy release energy close to their targets and emit ionizing radiation with brief tissue penetration, such as α (alpha) or β (beta) transmitters. Radionuclides for tumor therapy are most effective when they emit energy near the target and have limited tissue penetration. Alpha-emitters like Radium-223 and Actinium-225 are popular in targeted cancer therapies because they emit ionizing radiation over short distances, reducing damage to surrounding healthy tissue. Radium-223, for example, has been FDA-approved for treating bone metastases in prostate cancer due to its effectiveness in delivering alpha radiation precisely to the tumor. Similarly, beta-emitters like Yttrium-90 are used in therapies like radioimmunotherapy for lymphomas (A. Cahid Civelek, 2021; Pallares & Abergel, 2022; Ryan P. Coll et al., 2023). When exposed to external particles, particles with a weak penetrating power (α) stop at the epidermis and have no effect. However,

long-term exposure to radioactively emitting β particles will affect the skin's basal cells and hair root cells, which are sensitive to X-rays, neutron radiation, and γ (gamma) radiation, which can penetrate the skin's layers and radiate to the body's tissues and organs. The interaction of radiation, internal and external to the body or organs, can have biological effects on cells. The kind and energy of radiation, the dose used, the exposure level, cell radiosensitivity, and the exposure region are all affect how radiation affects biology. (Mohan & Chopra, 2022).

Radioisotope ^{32}P was chosen for keloid therapy because it highly β^- emitting ionizing radiation effectively inhibiting new cell tissue growth. Research has shown that radioisotope ^{32}P is effective in keloid therapy due to its strong β-emitting ionizing radiation, which helps inhibit new cell growth and target the TGF-β/Smad signaling pathway involved in cell proliferation. The therapy induces apoptosis (programmed cell death) in keloid cells and prevents further growth by inhibiting collagen synthesis. Both injection and topical application of ^{32}P have been found to significantly reduce keloid size and collagen deposition, making it a promising treatment method. Studies also suggest that the treatment has a notable impact on reducing the recurrence of keloids, offering a novel approach to managing this challenging condition (Xie et al., 2023).

Beta particles emitted by ^{32}P have an average penetration range of about 2 mm in tissue and a maximum range of 8 mm (University of Michigan, 2018). This makes ^{32}P suitable for targeted therapies, such as keloid treatment, as it can effectively inhibit cell growth within this range. The radiation from ^{32}P damages cells by inducing DNA double-strand breaks, which prevents the proliferation of cells responsible for excessive tissue growth in keloids. This therapy induces apoptosis (programmed cell death) in keloid cells and inhibits further growth by blocking collagen synthesis.Both injecting and applying ^{32}P topical have demonstrated significant keloid size and collagen deposition reductions, highlighting its potential as a therapeutic method. Research indicates that the radioisotope ^{32}P is effective in keloid therapy due to its strong β-radiation, which inhibits new cell growth and targets the TGF-β/Smad signaling pathway involved in cell proliferation, contributing to the overall reduction of keloid mass. Studies also suggest that this therapy significantly reduces keloid recurrence (Cheng et al., 2015).

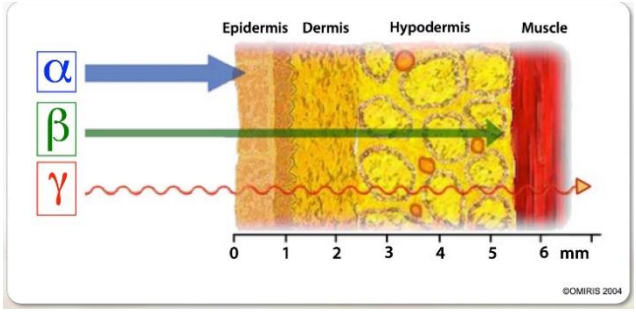


Figure 3. Radiation exposure to body tissues and organs (Benitez-Nelson et al., 2018)

The interaction of beta-particle radiation from the ^{32}P radioisotope with bodily cells leads to direct DNA damage, including single-strand breaks (SSBs) and double-strand breaks (DSBs), which are critical forms of damage that can lead to cell death. (Penninckx et al., 2021; Cheng et al., 2011; Cheng et al., 2015; Vítor et al,. 2020). The interaction of β-particle radiation from the radioisotope ^{32}P with water molecules (H_2O) in cells can cause indirect cellular damage. This occurs when ionizing radiation, such as β particles, breaks the bonds in water molecules, generating free radicals like hydroxyl radicals (•OH) (Caër, 2011). These radicals, in turn, lead to oxidative stress and DNA damage within the cells, contributing to cellular death or dysfunction. Indirect radiation damage is especially significant since cells contain a high percentage of water, leading to the formation of reactive oxygen species (ROS) a prevalent mechanism of radiation-induced damage (Zhang et al., 2024). As a result of this interaction, water molecules (H_2O) break down into hydroxyl radicals (OH•) and hydrogen ions (H^+). The hydroxyl radical (OH•) is among the most reactive free radicals found in biological systems. Due to their high reactivity, hydroxyl radicals can harm numerous biological components such as DNA, proteins, lipids, and carbohydrates, potentially causing substantial cellular damage. DNA damage is one of radical reactions' most severe hydroxyl consequences (Mokari et al., 2018). Hydroxyl radicals can oxidize DNA bases, cause DNA double-strand breaks, and sever DNA links, disrupting the cell's genetic integrity (Jia et al., 2021).

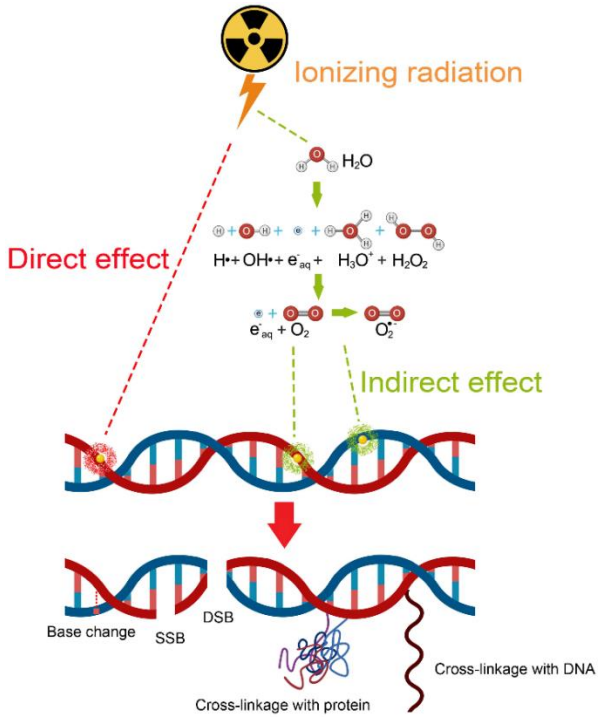


Figure 4. Cell and DNA damage due to direct and indirect ionizing radiation (Gong et al., 2021)

Emission of β^- particles from radioisotope ^{32}P causes fibroblast cell death in keloid cells and inhibits cell proliferation, causing keloids to stop growing and shrink, reducing the size of large, thick, and difficult-to-operate keloids and potentially minimizing the effects of recurrence after therapy. Keloid cells are known to continuously divide and produce excessive amounts of collagen, leading to abnormal scar tissue growth. Ionizing radiation, such as that from radioisotopes ^{32}P, interferes with the cell division process, particularly affecting fibroblasts—the cells responsible for collagen production. By causing DNA damage, ionizing radiation disrupts fibroblast proliferation and reduces collagen production, which is a hallmark of keloid development (Xie et al., 2023). The damage to DNA induced by ionizing radiation triggers cellular responses, including apoptosis (programmed cell death) and the inhibition of cell cycle progression. These processes help control fibroblast overproduction and limit the buildup of excess collagen, reducing the size and thickness of keloids. The suppression of collagen production via pathways such as TGF-β/Smad signaling, which is essential for keloid formation, further enhances the therapeutic effects of radiation in treating keloids (Xu et al., 2017).

The dose used for keloid therapy is 40 μCi/cm^2, equivalent to 139.57 mGy (Indrawati, 2014). The ^{32}P radioisotope is used in keloid therapy by applying media (topical) containing ^{32}P radioisotope for three days. According to the findings, most keloids had more than 50% flattening in a week and 70% flatness in the fourth week. (H. Vivante et al., 1994; Indrayati et al., 2016). Using ionizing radiation, including radioisotope ^{32}P, has proven effective in treating keloids by reducing fibroblast activity and collagen production. However, there are potential risks associated with this treatment, particularly the possibility of damaging normal tissue surrounding the keloid. Studies highlight that exposure to ionizing radiation can lead to complications such as erythema, infection, and other acute tissue damage, especially in sensitive areas.Thus, while ^{32}P offers a promising treatment for keloids with good aesthetic results, medical professionals must carefully monitor such therapy to minimize risks to healthy tissues. Therapy using ^{32}P radioisotope is easier and more comfortable for patients because it does not cause pain, is more effective, and can reduce the recurrence rate.

Radioisotope ^{32}P

Radioisotope ^{32}P is a beta-emitting radioisotope (β^-) with a half-life of 14.26 days and energies of 1.71 MeV (Emax) and 0.6949 MeV (Eav) (Butler & Gissel, 1947).

$$^{32}_{15}P \rightarrow {}^{32}_{16}S + e^- + \bar{\nu}_e \qquad (1)$$

The radioisotope ^{32}P can be made from nuclear reactions such as $^{31}P(n,\gamma)^{32}P$ and $^{32}S(n,p)^{32}P$ with nuclear reactions as follows:

$$^{31}_{15}P + {}^{1}_{0}n \rightarrow {}^{32}_{15}P + \gamma, \; {}^{32}_{15}P \rightarrow {}^{32}_{16}S \qquad (2)$$

$$^{32}_{16}S + {}^{1}_{0}n \rightarrow {}^{32}_{15}P + {}^{1}_{1}p, \; {}^{32}_{15}P \rightarrow {}^{32}_{16}S \qquad (3)$$

The radioisotope ^{32}P decays in the nuclear reactions (2) and (3), emitting particles β^- with an energy of 1.71MeV and producing the stable isotope ^{32}S.

Reaction $^{31}P(n,\gamma)^{32}P$ takes place in a thermal neutron flux with a cross-section of 0.17 barn, and the abundance of the ^{31}P isotope reaches 100%. This reaction allows the rapid production of the ^{32}P radioisotope in large quantities through irradiation of the element Phosphorus or its compounds. The main weakness of this production process is the low-type activity because not all ^{31}P elements are converted into ^{32}P radioisotope. Nevertheless, low specific

activity ^{32}P has applications for some things, such as the characteristics of phosphorus-organic compounds (Vimalnath et al., 2014).

A fast neutron flux with a cross-section of 0.065 barns with a ^{32}S abundance of 95.05% is used in the $^{32}S(n,p)^{32}P$ reaction (Rahman et al., 2024). The choice of natural sulfur as the target material was due to the different chemical elements between the irradiated and resulting elements, resulting in a carrier-free ^{32}P radioisotope. This reaction makes the radioisotope ^{32}P simple to separate from sulfur (Vimalnath et al., 2014).

The radioisotope ^{32}P was separated from irradiated sulfur using a dry distillation technique (Anom, 2021; Mustam et al., 2023; Fitri et al., 2023). Sulfur is distilled at 440 ℃ using nitrogen gas to prevent it from burning at the flash point (150 °C) and to separate Sulfur from the resulting ^{32}P radioisotope. Using an ion exchange column with AG50 WX8 resin, the remaining distillation product containing the ^{32}P radioisotope was purified chromatographically. The eluate used is an HCl solution, and the resulting filtrate is the ^{32}P radioisotope (Pratama et al., 2020).

CONCLUSION

Therapeutic methods for keloids vary, but only some treatments are universally effective due to individual differences in response. However, keloids often recur after treatment. An innovative and promising method is the use of the radioisotope ^{32}P. The ^{32}P radioisotope is produced in a nuclear reactor with the $^{32}S(n,p)^{32}P$ nuclear reaction from irradiated Sulfur. This radioisotope emitts beta particles that induce fibroblast cell death, halting keloid growth and significantly reducing keloid size. It effectively inhibits collagen synthesis, a key component in keloid formation. Studies show that ^{32}P therapy is effective in flattening keloids and reducing excessive scar tissue, offering a potential solution to manage this challenging condition. Although ^{32}P therapy shows good results in reducing keloid size and recurrence, it must be administered carefully to minimize damage to surrounding healthy tissue. Overall, radioisotope ^{32}P provides a more comfortable and effective alternative for keloid treatment, potentially reducing pain and recurrence risk.

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