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Systematic Review

Role of Calcium in Epidermal milieu and cutaneous disorders– A systemic review

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ABSTRACT

The defence against the external environment depends on the development of the epidermal barrier and the preservation of barrier homeostasis. Numerous skin processes, such as keratinocyte development, skin barrier creation, and permeability barrier homeostasis, are regulated by calcium ions (Ca2+) and the gradient in their concentration in the epidermis. Furthermore, a number of inflammatory skin conditions, such as psoriasis and atopic dermatitis, can be caused or exacerbated by a malfunctioning skin barrier and poor keratinocyte differentiation. To comprehend various skin conditions and develop a successful treatment plan, it is crucial to comprehend the mechanisms governing keratinocyte differentiation and skin barrier homeostasis, especially the processes which are dependent on the calcium concentrations.

Objective - This systematic review aims to evaluate the importance of calcium in the formation, regulation, and protection of the cutaneous milieu, from the external as well as internal confounding factors.

Methodology - PRISMA criteria was adhered to in this systematic review. Taking into consideration the very start, to the present, a thorough search of PubMed/MEDLINE, Embase, and Scopus was carried out. Randomised controlled trials, cohort, case-control, and cross-sectional studies, as well as review articles, were among the study designs that qualified. Editorials, commentary, conference abstracts, research without extractable data, non-English articles, and studies with unclear outcome measures were not included.

Results - Extracellular calcium stimulates regular keratinocyte differentiation, which is essential for the development of an intact epidermal barrier. Many skin conditions, including psoriasis, atopic dermatitis, basal and squamous skin cancer, and genetic skin conditions including Olmsted syndrome and Darier's disease, are caused by disruptions in the establishment of the epidermal barrier and aberrant keratinocyte differentiation. In this review, we provide an overview of the current understanding of the molecular pathways driving keratinocyte differentiation caused by calcium. We address the calcium gradient in the epidermis, which results in cornified skin and the creation of lipid envelopes, and give a summary of the genomic and non-genomic processes of calcium to induce differentiation. Lastly, we'll talk about skin conditions associated with poor differentiation.

Conclusions - In summary, keratinocyte differentiation, barrier creation, wound healing, and skin barrier homeostasis are all significantly influenced by the epidermal calcium gradient, endoplasmic reticulum calcium homeostasis, and calcium influx via transient receptor potential (TRP) channels. Additionally, keratinocytes can function as a biosensor that mediates, processes, or transmits the sensory signal in response to different physical or chemical stimuli since they

express a variety of calcium channels. Determining the regulatory mechanisms and activities of calcium and associated channels in skin barrier homeostasis is crucial from a therapeutic standpoint**.**

Keywords*: Calcium, Stratum Corneum, Endoplasmic Reticulum, keratinocyte, epidermal Barrier.*

INTRODUCTION

In keratinocytes, calcium ions (Ca2+) act as a universal signal to modify several facets of cellular processes. Epidermal homeostasis is significantly influenced by the distribution and dynamics of Ca2+ in the skin [Menon GK et al., 1985]. There is a distinctive calcium gradient between the lower and upper layers of the mammalian epidermis, with low levels in the spinous and basal layers and gradually rising levels as one moves towards the stratum granulosum before falling once more in the stratum corneum (SC) [Menon GK et al., 1991]. The differentiation of keratinocytes and the development of the epidermal permeability barrier depend heavily on the calcium gradient across the epidermis, which also enables the dynamic changes of calcium ions to produce calcium signalling. According to recent data, the control of epidermal structures and functions depends on both the release of Ca2+ from intracellular reserves and the influx of Ca2+ from external sources [Elias P et al., 2002; Lee SH et al., 1992]. The genesis and generation process of the epidermal calcium gradient, as well as its functions in keratinocyte development and epidermal barrier homeostasis, were the main topics of this study. We also talk about the endoplasmic reticulum's (ER) Ca2+ homeostasis and keratinocytes' ER stress response, as well as how these factors affect keratinocyte development.

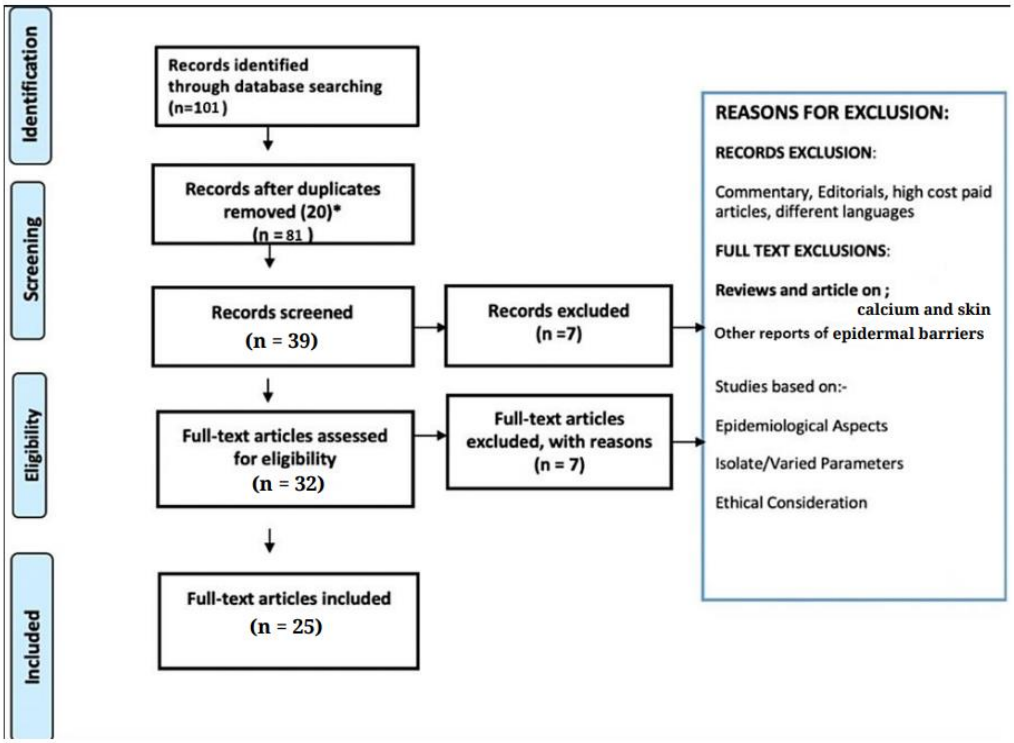
One micromineral that is vital to the organism is calcium. Most of the calcium in the human body is found in bones and teeth. The blood, muscles, and other tissues, including the skin, all contain calcium [Lee SH et al., 1994]. The body can use the calcium stored in the bones as a reserve when needed. Because calcium is eliminated from the body through perspiration, skin, and feces, its concentration tends to decline with age. Research indicates that the amount of calcium that each nation consumes through its food varies. Human diets typically include between 175 and 1233 mg of calcium per day. Many countries in Asia have an average calcium intake of less than 500 mg/day [Menon GK et al., 1992]. The stratum corneum (SC), which is made up of corneocytes, the byproducts of keratinocyte development, is where the skin barrier function is discussed in the epidermis. A variety of keratinocyte biological functions can be modulated by calcium ions, which act as universal signals. The permeability barrier of the epidermis and keratinocyte development are both significantly influenced by the calcium gradient along the epidermis, which enables dynamic changes in calcium ions to produce calcium signals [Menon GK et al., 1992]. According to recent research, the structure and function of the epidermis are regulated by the release of calcium ions from intracellular reserves and the inflow of external calcium ions [Lee SH et al., 1992; Yuspa SH et al., 1989].

METHODOLOGY

PubMed, Cochrane Information Services, and Scopus platforms were searched for English-language publications from November 2000 to March 2026. This literature search has employed medical subject heading (MeSH) phrases such as "calcium," "skin," "cutaneous pathologies," "calcium gradient," and "skin barrier function." Reports of calcium channels, Dariers disease, and several subtypes of calcinosis cutis were also taken into account. Scope reviews, editorials, letters to the editor, narrative reviews, and abstracts were not included. There were 101 articles found in total, 25 of which were used for this review. The authors double-checked each of the articles they chose.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) approach was applied in this review of the literature. A variety of original scientific research publications, case reports, reviews, and some observational studies were included. For this review, only the most current papers were taken into account. Figure 1 displays a flowchart illustrating the approach and study selection.

Figure 1.



PRISMA FLOW CHART

Review –

Role of calcium in skin barrier homeostasis

The epidermis, namely the stratum corneum (SC), the outermost cornified layer, is responsible for the skin barrier function. The final product of keratinocyte terminal differentiation, corneocytes, and SC intercellular lipid—the lamellar bilayers made of ceramides, cholesterol, and free fatty acids—make up SC [Behne MJ et al., 2011]. By supplying the SC with pro-barrier lipids, enzymes essential for lipid processing, proteases, and antimicrobial peptides, the specialized skin organelles known as lamellar bodies (LBs) play a key role in the development of the SC lipid, protein, and antimicrobial barrier. Previous research showed that fluctuations in the extracellular calcium concentration of the upper epidermis, which are brought on by permeability barrier disturbance, control the pace of LBs secretion, lipid synthesis, and permeability barrier homeostasis [Celli A et al., 2010]. Acute barrier breakdown caused by topical solvent application or tape-stripping causes the usual epidermal calcium gradient to disappear and causes an instantaneous depletion of both extracellular calcium ions in the epidermis, particularly in the higher granular layers [Celli A et al., 2011]. Parallel to barrier healing, the top epidermis's calcium levels gradually recovered over the course of 6–24 hours [Celli A et al., 2012]. Barrier regeneration is hampered when extracellular calcium loss in the top epidermis is prevented by occlusion with a vapor-impermeable membrane or by submerging barrier-damaged skin in solutions containing high calcium. The abrupt drop in calcium concentration in the stratum granulosum after barrier disruption is a crucial regulatory signal that starts the instantaneous release of the contents of pre-stored LBs into the SC interstices, speeds up the synthesis of new LBs, and causes epidermal lipid synthesis, all of which contribute to barrier repair [Kirschner N et al., 2013].

Research has demonstrated that variations in the extracellular calcium ion concentration of the upper epidermis, which are brought on by compromised barrier permeability, control levels of lipid production and barrier permeability homeostasis [Celli A et al., 2011]. Calcium ions are essential for the development of the epidermal barrier. The sheath of the corneum, a protein coat produced by keratinocytes, is essential to the integrity of the epidermal barrier. High calcium concentrations cause keratinocytes to differentiate into corneocytes, which create the corneum sheath [Menon GK et al., 1992; Celli A et al., 2012]. A number of processes in the development of the corneum sheath depend on calcium ions. Calcium is necessary for the action of several enzymes involved in the differentiation process and activates certain genes for the corneum sheath.

Keratinocyte differentiation

One important regulator of keratinocyte differentiation and proliferation is the calcium ion [Kurasawa M et al., 2011]. The vertical variations from the basal layer to the SC is what defines the skin. There are proliferating cells in the basal layer. Along with stage-specific changes in the expression of several differentiation markers, keratinocytes advance upward through the various epidermal layers as differentiation progresses, ultimately becoming terminally differentiated corneocytes in the SC's cornified layer [Kurasawa M et al., 2011]. From the commitment to differentiation in the basal and spinous layer to the final differentiation in the stratum granulosum, calcium is essential for every step of keratinocyte

differentiation. The transcription of all genes encoding proteins relevant to keratinocyte development is controlled by calcium [Forslind B et al., 1987].

Epidermal calcium gradient

The variation in calcium ion concentration in each stratum of the epidermis is known as the epidermal calcium gradient. A significant part of the epidermal calcium gradient, extracellular calcium serves as a signal for barrier restoration when the barrier is disrupted [Feingold KR et al., 2012]. The stratum basalis is where the epidermal barrier begins to develop. Since calcium is necessary for both keratinocyte differentiation and corneocyte production, the stratum Basale has a comparatively low concentration of calcium ions [Mao-Qiang M et al., 1997]. Calcium concentrations rise in the stratum spinosum, peak in the stratum granulosum, and then sharply decline in the SC, where keratinocytes finish differentiating into corneocytes [Celli A et al., 2010]. The purpose of the epidermal calcium gradient is to compensate for the variations in keratinocyte calcium needs. High calcium for differentiation and low calcium for proliferation [Mauro T et al., 1989]. Skin barrier development, barrier permeability homeostasis, and keratinocyte differentiation are all influenced by calcium ions and the gradients in their concentration in the epidermis. According to recent research, a significant part of the epidermal calcium gradient is the intracellular calcium ion storage in the endoplasmic reticulum (ER) [Behne MJ et al., 2011, Grubauer G et al., 1989]. The calcium gradient, which is the foundation of skin function, is created by the relative concentrations of calcium ions in the extracellular and intracellular compartments. According to recent research, a calcium ion gradient may be created simply by the passive diffusion of calcium ions [Elias PM et al., 2002]. These results imply that the epidermal calcium gradient is influenced by ER calcium reserves. Numerous skin processes are regulated by calcium gradients and calcium signalling. Through a signalling system that governs cell migration, it has been shown that an uneven distribution of calcium concentrations modulates polarity and cell movement [Choi EH et al., 2003]. Some illnesses are characterized by poor differentiation due to the lack of a calcium ion gradient. For healthy development and differentiation, the calcium gradient is essential.

This disruption in calcium gradient affects the cutaneous homeostasis which further leads to several pathologies some of which are mentioned in table 1 below.

Table 1.

Cutaneous Pathology	Trigger	Implicated pathogenesis
Psoriasis	**Calcium**	It appears to be a secondary metabolic phenomenon that psoriasis and hypocalcaemia are related, particularly in pregnant women with pustular psoriasis. The widespread cutaneous irritation brought on by albumin and albumin-bound calcium extravasating into the interstitial space is the secondary cause of hypocalcaemia. Since hypocalcaemia can harm cell adhesion molecules, it has been proposed that calcium homeostasis may play a role in the onset or aggravation of psoriasis [MONTGOMERY PR et al., 1964]. Although the exact mechanism underlying the relationship between calcium and keratinocyte differentiation is unknown, these aspects of pathophysiology may help to explain why the patient's psoriasis flared up in response to hypocalcaemia and why the psoriasis significantly improved after serum calcium levels returned to normal.
Calcinosis Cutis	**Calcium**	The levels of calcium and phosphorus in the serum are normal. Phosphate-binding proteins are released by dying cells as a result of tissue damage in these cases [Jiménez-Gallo D et al., 2015]. When phosphate is bound by the phosphate-binding protein, calcification occurs. Vascular hypoxia and persistent inflammation are further effects of this tissue injury. Crystal formation and cell necrosis are further exacerbated by the release of high quantities of calcium and phosphate from the mitochondria.
Dariers Disease (DD)	**Calcium**	An example of an abnormality of Ca2+ signalling disruptions is caused by mutations in the isoform 2 of the sarco- (endo) plasmic reticulum Ca2+ ATPase (SERCA2) [Ambur A et al., 2022]. Keratinocytes in DD patients have a smaller pool of endoplasmic reticulum (ER) Ca2+ due to loss of function mutations in SERCA2. Crucially, the activation of a class of plasma membrane Ca2+ channels known as store operated Ca2+ channels (SOCs) depend on the state of ER Ca2+ [Savignac M et al., 2010].

The human epidermis serves as a highly effective barrier against environmental disturbances that are chemical, physical, or microbiological. Only because the epidermis is constantly renewing itself is this feasible. An apparently limitless supply of keratinocytes, which develop and then enroute to the surface where they are shed off as scales, is provided by stem cells at the basal lamina, which forms the dermo epidermal junction. The keratinocyte turnover rate is drastically slowing down, which causes the epidermis to age despite its constant replacement. Thinning of the epidermis, elastosis, melanocyte loss

linked to increased skin paleness and lucency, and a diminished barrier function are all characteristics of ageing. Since keratinocyte development is entirely dependent on calcium, calcium is also crucial for the ageing of the epidermis.

It was recently demonstrated that as skin ages, the epidermal calcium gradient that promotes keratinocyte proliferation in the stratum Basale and allows differentiation in the stratum granulosum is eliminated. In addition to being unique to skin ageing, this loss of the epidermal calcium gradient is also present in skin conditions such psoriasis, atopic dermatitis, Darier disease, and Hailey-Hailey disease, which may be very useful in gaining a deeper understanding of skin ageing.

CONCLUSION

Keratinocyte differentiation, barrier creation, wound healing, and skin barrier homeostasis are all significantly impacted by the epidermal calcium gradient, ER calcium homeostasis, and calcium influx. Furthermore, keratinocytes can function as a biosensor that mediates, processes, or transmits the sensory signal in response to a variety of chemical or physical stimuli since they express a large number of calcium channels. Determining the regulatory mechanisms and roles of calcium and associated channels in skin barrier homeostasis is crucial from a therapeutic standpoint.

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