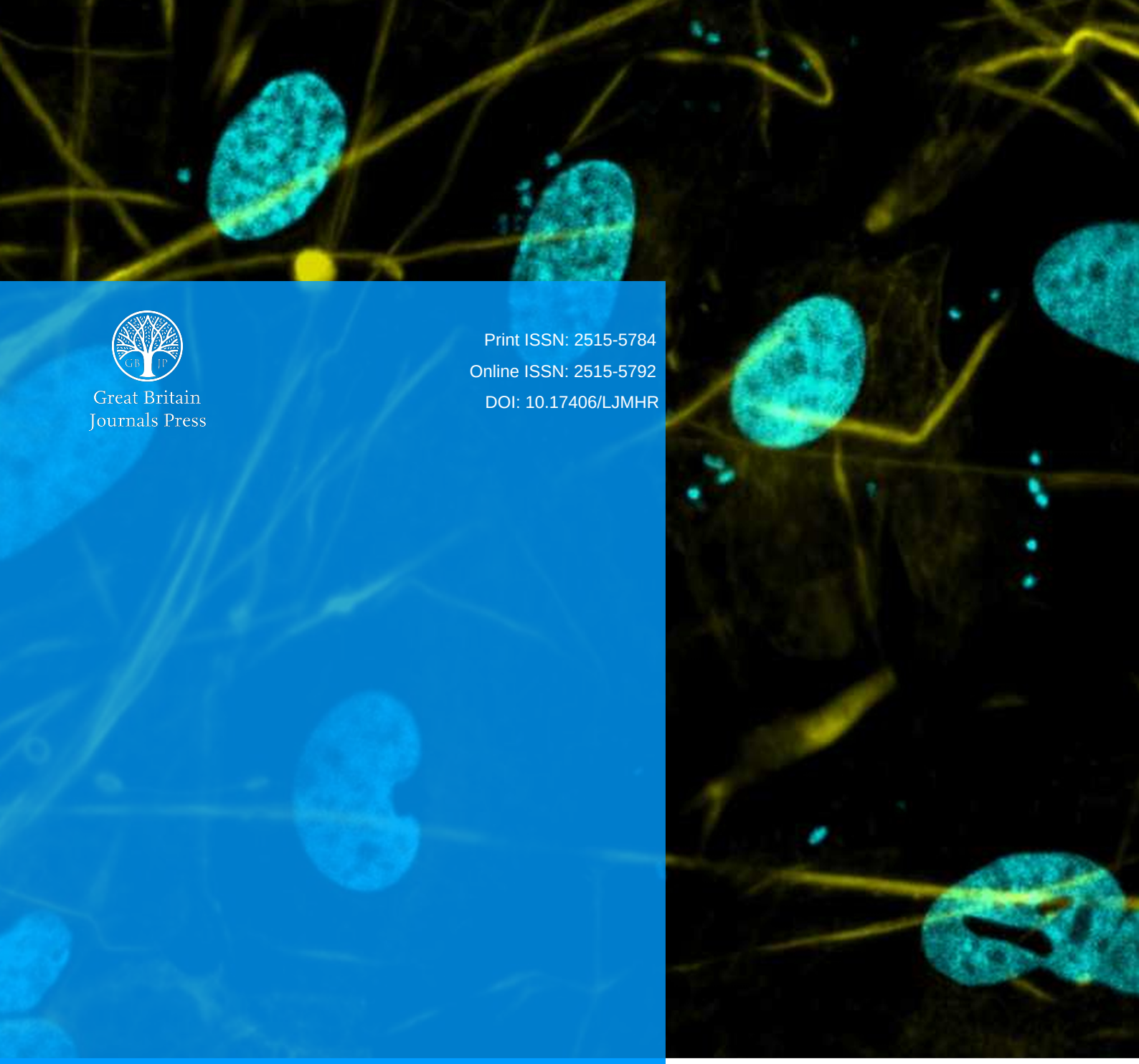

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Innovative Wound Dressings and Emerging Technologies for Wound Treatment: Trends and Perspectives – A Review

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ABSTRACT

Background/Objectives: Wound treatment has undergone significant advances with the development of dressings and therapies that provide not only simple protective coverage but also actively promote tissue regeneration. This work addresses the classification of dressings, ranging from primary and secondary types to cutting-edge technologies, including bioactive, innovative, 3D-printed, and nanotechnological dressings.

Methods: A structured narrative literature review was conducted by searching major health, nursing, and wound care databases major health, nursing, and wound care databases, complemented by specialized sources.

Results: The review indicates that auxiliary therapies, such as stem cells, growth factors, and cold plasma, are predominantly explored as adjunctive approaches alongside advanced wound dressings, with the literature reporting potential benefits in accelerating healing, especially in complex and chronic wound settings. It also highlights the primary challenges to implementing these approaches, including high production costs, a shortage of trained professionals, limited robust, long-term clinical studies, and regulatory hurdles. Additionally, the environmental impacts of dressing production and disposal were addressed, highlighting the role of biopolymers and nanotechnology as sustainable and ef icient

Index Terms: biomaterials • biopolymers • sustainable wound care • wound management • biomedical innovations • drug delivery systems • clinical challenges • healthcare technology

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REVIEW

Innovative Wound Dressings and Emerging Technologies for Wound Treatment: Trends and Perspectives – A Review

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Abstract

Background/Objectives: Wound treatment has undergone significant advances with the development of dressings and therapies that provide not only simple protective coverage but also actively promote tissue regeneration. This work addresses the classification of dressings, ranging from primary and secondary types to cutting-edge technologies, including bioactive, innovative, 3D-printed, and nanotechnological dressings.

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Conclusions: Despite current limitations, future prospects remain promising, with an emphasis on personalized medicine, intelligent monitoring systems, and bioengineering, underscoring the need for more in-depth research and clinical validation to consolidate these innovations in wound care practice.

Keywords: *biomaterials, biopolymers, sustainable wound care, wound management, biomedical innovations, drug delivery systems, clinical challenges, healthcare technology*

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1 Introduction

Skin wounds, whether acute or chronic, pose a significant global public health problem and are characterized by high morbidity rates, prolonged recovery times, and substantial costs to healthcare systems (Queen et al., 2004; Dhivya et al., 2015; Singh et al., 2017; Sen, 2019). Conditions such as diabetes, venous insufficiency, pressure injuries, and burns further aggravate the scenario, requiring effective, safe, and accessible therapeutic approaches (Bao et al., 2009; Lima et al., 2017; Sierra-Sánchez et al., 2021; Liu et al., 2024; Zhao et al., 2024). In this context, the appropriate choice of dressing is a central element in clinical management, as it not only protects the wound bed against external agents, but also directly influences the cellular processes involved in healing (Queen et al., 2004; Franco; Gonçalves, 2008; Anisuzzaman et al., 2022; Sinha et al., 2022; Herman et al., 2023).

In recent decades, scientific and technological advances have promoted a revolution in wound treatment, with the development of high-tech dressings capable of actively interacting with the wound microenvironment (Ovington, 2007; Jiang; Loo, 2021; Zhang et al., 2021; Tran et al., 2023; Alberts et al., 2025). Innovative, bioactive, 3D-printed dressings composed of nanomaterials or biopolymers have expanded therapeutic possibilities, whether through mechanisms such as the controlled release of drugs, electrical stimulation, incorporation of stem cells, growth factors, or other bioactive agents (He et al., 2023; Yayehrad et al., 2023; Zhang et al., 2023; Astaneh; Fereydouni, 2024; Khushnood, 2024; Alberts et al., 2025). However, despite the promising evidence reported, mainly through in vitro tests, these products still face significant barriers to their large-scale adoption, such as regulatory limitations, scarcity of quality clinical studies, high costs, and lack of professional training (Laurano et al., 2022; Luo et al., 2023; Ruan et al., 2023; Yang et al., 2023; Namgoong et al., 2023; Liu et al., 2024).

Given this scenario, a comprehensive analysis of the main categories of dressings, their classifications, characteristics, incorporated technologies, current limitations, and future perspectives becomes essential. Thus, the objective of this study was to discuss investigations into wound treatment using conventional and technological dressings.

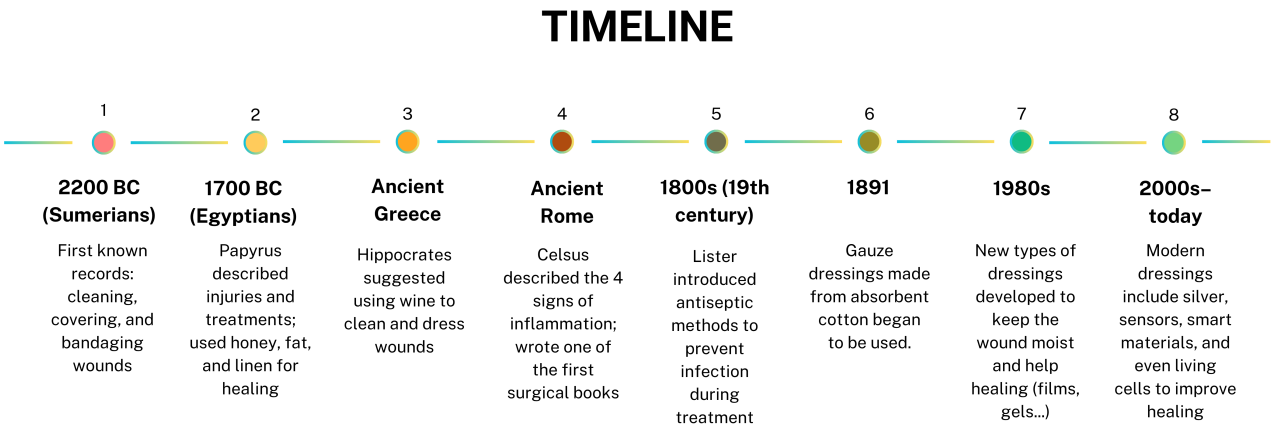

Figure 1. Timeline Highlights Showing the Evolution of Wound Treatment and Dressing Technologies

2 Methodology

This literature review was conducted using a structured narrative approach. Searches were conducted in databases focused on health, nursing, and wound care research. Access was achieved through university libraries, hospital libraries, or institutional portals. In addition to peer-reviewed scholarly articles, reports from relevant medical organizations and government agencies were consulted to address regulatory and clinical guidelines. The search focused on keywords such as "wound dressings," "bio-material," "nanotechnology," and "3D printing," combined with related terms to encompass the history, classification, and future prospects of wound treatment. The inclusion and exclusion criteria were applied to select the most relevant and up-to-date sources in the field.

3 History

Humanity comprises beings susceptible to various types of injury. Wound treatment is one of the oldest areas in medicine, with evidence of the application of dressings dating back to the earliest stages of human civilization (Majno, 1976). Several studies cite a Sumerian clay tablet dated to 2200 BC as one of the oldest manuscripts on wound treatment, describing a sequence of steps for wound care: washing, dressing, and bandaging (Shah, 2011; Teall, 2014; Ahmad et al., 2020). Ancient Egyptian history contains extensive medical knowledge. This includes the use of various methods and herbs for wound healing (De Paula, 1962; Pertile, 2020). The Edwin Smith Papyrus, also known as the Surgical Papyrus, dates back to approximately 1700 BC and contains a detailed description of 48 cases of injuries, including wounds to the head, throat, collarbone, arm, and chest, along with their corresponding treatments (Feldman & Goodrich, 1999). These same ancient people described using honey, fat, and linen to cover wounds, due to honey's antibacterial properties and linen's absorbent capacity (Leake, 1952; Ahmad et al., 2020; Gebarowski et al., 2020). These practices remain in use today and serve as a basis for studies on the efficacy of these materials in topical wound care. Flax fibers, for example, continue to be investigated for application in difficult-to-heal wounds (Gebarowski et al., 2020).

In Ancient Greece, Hippocrates suggested, in 460-370 BC, the use of wine in the treatment of wounds, both to clean them and to enrich the wool used as a dressing, by boiling, since wine help reduce infection and enhance healing (Majno, 1976; Dhivya et al., 2015). Following the path of ancient civilizations, the Romans also played a prominent role. Cornelius Celsus, a Roman who lived between 25 BC and 50 AD, wrote "De Medicina", the most significant medical document since the writings of Hippocrates, which was rediscovered by Pope Nicholas in 1443 and printed in 1478 AD, as the first medical and surgical book in history (Kockerling et al., 2013). Celsus is credited with documenting the four cardinal signs of inflammation: rubor (redness), tumor (swelling), calor (heat), and dolor (pain) (Tracy, 2006; Charles et al., 2011). These signs are still used today, reinforcing the importance of these writings.

In the 19th century, a significant advance in wound treatment occurred when Joseph Lister, a professor of surgery in London, introduced the concept of antisepsis in surgical procedures to prevent infections. Using carbolic acid (phenol), Lister sterilized wounds and surgical instruments to prevent sepsis. Additionally, the professor implemented changes to the environment surrounding patients, aiming to make it as sterile as possible (Bhattacharya, 2012). This practice revolutionized wound treatment and laid the foundations for modern surgery. In mid-1891, absorbent cotton-based gauze began to be used to cover wounds (Dhivya et al., 2015). The 20th century witnessed significant advances in the understanding and development of dressings. In the 1980s, the knowledge of the importance of a moist environment for healing led to the development of occlusive and semipermeable dressings, such as film dressings, hydrocolloids, and hydrogels (Queen et al., 2004; Dhivya et al., 2015). It is important to emphasize the importance of maintaining a moist environment for optimal wound healing, a finding reported to date (Lagoa et al., 2024).

Technological innovations mark the 21st century. Research into wound dressings focuses on developing advanced technologies. Examples of these are silver-impregnated dressings for antimicrobial action (Percival et al., 2011; Krishnan et al., 2020); innovative dressings that integrate temperature and pH sensors, in addition to a controlled drug release system, enabling continuous monitoring and personalized treatment of chronic wounds (Mostafalu et al., 2018); dressings with fluorescent nanosensors that glow under UV light when they detect infection, allowing monitoring without the need to remove the dressing (Truskewycz et al., 2021); the use of nanodiamonds embedded in silk fibroin membranes to create dressings that detect infections and promote wound healing (Khalid et al., 2020); in addition to techniques involving the use of tissue engineering technologies using, for example, cells and biomaterials (Hu et al., 2014; Dehkordi et al., 2019; Sindhi et al., 2025). These innovations aim to improve clinical outcomes and patients' quality of life. These topics will be discussed in more detail in a later session.

4 Classification of Wounds

A wound is defined as any discontinuity in the anatomical and functional integrity of the epithelial lining of the skin or mucous membranes, caused by physical, chemical, or thermal damage (Dhivya et al., 2015). Understanding and classifying these wounds has been crucial in the history of medicine, guiding therapeutic interventions and enhancing healing outcomes. Since ancient reports, such as in Egypt, Greece, and Rome, the need to differentiate clean wounds from infected wounds has been observed, as well as the time required for their recovery (Sipos et al., 2004; Tracy, 2006; Charles et al., 2011; Shah, 2011; Kockerling et al., 2013; Hartmann, 2016). With advances in microbiology, physiology, and modern clinical practices, it has become possible to classify wounds based on criteria such as healing time, depth, etiology, and presence of infection, contributing to more specific and practical therapeutic approaches (Lazarus et al., 1994; Cutting; White, 2004; Herman et al., 2023; Figure 2).

Regarding healing time, wounds are classified into two large groups: acute and chronic (Nagle et al., 2023). Acute wounds follow a well-defined healing process, occurring in an orderly and predictable manner, such as surgical wounds, superficial cuts, or lacerations (Justiniano, 2010). Chronic wounds are characterized by impaired tissue-healing capacity, which is generally due to etiologies such as diabetes, persistent pressure, venous reflux, sickle cell anemia, and arterial insufficiency, among others (Bao et al., 2009). Chronic wounds do not heal within the expected timeframe due to factors such as persistent infection, poor tissue perfusion, necrosis, chronic inflammation, microbial infection, and therefore, remain for weeks or months, requiring more complex clinical management (Justiniano, 2010). In this initial stage of wound characterization, it becomes apparent that the type of treatment and dressing applied during the healing process is crucial for a successful recovery, as each type of wound has its unique characteristics.

Given the importance of knowing which type of wound will be treated, more advanced studies are investigating technologies to help better classify these wounds, for example, through a multimodal classifier based on a deep neural network using images of wounds and their corresponding locations, presenting an accuracy that varied between 82.48 and 100% (Anisuzzaman et al., 2022). Regarding depth, some wounds, such as those caused by burns, are classified as superficial, involving only damage to the epidermis; superficial partial-thickness and deep partial-thickness, which affect the dermis; and full-thickness, reaching underlying tissues such as muscles and bones (Merten et al., 1997; Parvez et al., 2024; Rice et al., 2025). Assessing wound depth is crucial for determining injury severity and planning the most appropriate treatment. The classification of wounds by etiology refers to the cause of the wound. These causes can be diverse, including surgical, traumatic, pressure, vascular, and diabetic wounds (Leaper, 2006; Akagi et al., 2012; Boyko et al., 2018; Tobiano et al., 2022; Zaidi & Sharma, 2024).

Surgical wounds are those caused by incisions made during surgeries (Leaper, 2006; Akagi et al., 2012; Tobiano et al., 2022); traumatic wounds are caused by accidental injuries such as cuts or lacerations (Leaper, 2006); pressure wounds, also known as pressure ulcers or bedsores, are lesions on the skin resulting from prolonged pressure on the skin (Boyko et al., 2018; Zaidi; Sharma, 2024); vascular ulcers include venous and arterial ulcers, which are chronic wounds caused by prolonged venous insufficiency, due to poor circulation in the veins, which causes tissue wear (Raffetto, 2010; Robles-Tenorio; Ocampo-Candiani, 2022) and; Diabetic wounds, as the name suggests, are those that occur in patients with diabetes, and are characterized by persistent infection and inflammation, resulting in impaired skin healing (Chaffee et al., 2018).

Regarding the classification of infectious microorganisms, the National Academy of Sciences and the National Research Council of the United States developed the Surgical Wound Classification System (SWC), which was created to represent the bacterial load in a surgical field and was later refined by establishing four classes of wound status: class 1 clean wounds; class 2 clean-contaminated; class 3 contaminated; and class 4 dirty or infected (Herman et al., 2023). The presence of microorganisms in wounds is crucial in the healing process. The quantity and diversity of microorganisms present in any wound depend on the type of wound, its depth and location, and the patient's immune response (Bowler et al., 2001). The issue is that, if infected by pathogenic microorganisms, wounds have difficulty healing, patient suffering increases, treatment costs become higher, and the treatment process becomes more onerous and expensive, resulting in delayed healing (Bowler et al., 2001; Tom et al., 2019).

An aggravating factor in wound infections is the presence of biofilm-forming microbial species. This is because the biofilm forms a protective layer that protects microorganisms against the action of antimicrobial agents (Justiniano, 2010). The presence of these bacterial biofilms perpetuates the inflammatory state, as the bacteria protected by them are more resistant to antimicrobial treatments (Clinton; Carter, 2015; Jara et al., 2017; Gajula et al., 2020; Thaarup et al., 2022). Given the above, the importance of correctly classifying wounds for choosing the appropriate treatment method, as well as the ideal type of dressing and, consequently, the proper use of topical or oral medications for a successful healing process, becomes clear (Franco; Gonçalves, 2008; Anisuzzaman et al., 2022; Herman et al., 2023).

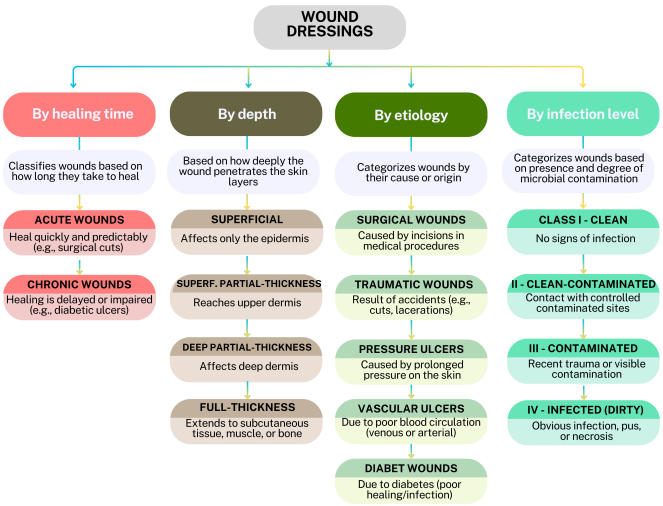

Figure 2. Schematic Representation of the Main Clinical Criteria used to Classify Wounds, Considering Healing Time, Depth, Etiology, and Infection Level

5 Wound Treatments

5.1 General Principles of Healing

Knowledge about wound healing is constantly evolving, as its basic mechanisms are continually being studied, leading to the development of new therapeutic models (Ho; Hantash, 2013). Wound healing is a complex and dynamic biological process essential for restoring tissue integrity after an injury (Singh et al., 2017). This process occurs in sequential, interdependent phases, each performing specific functions to ensure the effective repair of damaged tissue (Gonzalez et al., 2016; Figure 3). Physiologically, the healing process is divided into four main phases: homeostasis, inflammation, proliferation, and remodeling (Singh et al., 2017). Homeostasis occurs immediately after injury to stop bleeding. Platelets aggregate at the wound site, releasing clotting factors that promote fibrin clot formation, which is crucial for stopping blood loss and providing a temporary matrix for cells involved in the healing process. This phase is critical in preventing infection and preparing the wound bed for subsequent stages of the healing process (Daunton et al., 2012; Singh et al., 2017; Locatelli et al., 2021).

The inflammatory phase begins immediately after homeostasis has been established. The primary function of this stage is to prevent infection by infiltrating the site with neutrophils, aiming to destroy debris and pathogenic bacteria. This destruction process can occur in three ways: by phagocytosis; by the formation of chromatin and protease traps that capture and suppress bacteria; or by the release of toxic substances to them (Ho; Hantash, 2013; Singh et al., 2017). In general terms, the function of neutrophils in the inflammation phase is to promote the “cleaning” of wounds. Inflammation of a wound is a typical example of a biological process of stimulus-response. For example, when microorganisms infect wounds, the immune system reacts by trying to eliminate these invaders (Tracy, 2006). Still in the inflammation phase, known as late inflammation, vasodilation occurs, increasing blood flow and recruiting immune cells, such as macrophages, which improve healing conditions (Daunton et al., 2012).

The proliferative phase is accentuated around the fourth day after injury and is divided into four stages: reepithelialization, angiogenesis, granulation tissue formation, and collagen deposition (Campos et al., 2007). The proliferative phase is the primary phase of reepithelialization, during which the wound surface is covered, vascular function is restored, and granulation tissue forms (Landén et al., 2016). Reepithelialization consists of the proliferation of cells (keratinocytes) that migrate from the edges of the wound to cover it; angiogenesis is the process by which endothelial cells form new blood vessels, which are essential for the circulation of blood, oxygen, and nutrients in the affected area (Landén et al., 2016). Around the fourth day after the injury, granulation tissue begins to form, driven by fibroblast proliferation (Gonzalez et al., 2016). The collagen deposition of this phase refers to the initial production of a thinner and less resistant type of collagen, specifically type III collagen, which aims to achieve the skin’s initial firmness (Campos et al., 2007; Daunton et al., 2012).

Finally, the last phase of the healing process, remodeling, involves the gradual replacement of the initial collagen (type III) with thicker and stronger collagen types I and II, thereby increasing the wound’s tensile strength (Campos et al., 2007). Collagen plays a fundamental role in the healing process, and its deficiency or dysregulation hinders healing, complicating the process (Mathew-Steiner et al., 2021). As a result, adjuvant collagen-based therapies have been employed to regulate processes during healing and, consequently, promote more efficient healing (Mathew-Steiner et al., 2021; Gajbhiye & Wairkar, 2022).

Another critical point in the healing process is that, historically, it was believed that the wound healing process would be more efficient when the lesion remained dry and formed a crust, considering that this would prevent infections and accelerate tissue closure, as reported in an Egyptian medical text called the Edwin Smith Surgical Papyrus in 1615 BC (Dhivya et al., 2015). However, in recent decades, scientific evidence has shown that this concept is incorrect and that, in reality, maintaining a moist environment in the wound promotes faster, more efficient healing with less scar formation (Winter, 1962; Boateng et al., 2008; Junker et al., 2013; Dhivya et al., 2015; Frykberg and Banks, 2015; Nuutila and Eriksson, 2021). The study considered pioneering in this new approach of a moist environment rather than a dry one is that of Winter (1962), who demonstrated that wounds kept in a humid environment epithelialized faster than those kept in a dry environment. Later studies have shown that warm, moist environments in wounds facilitate quicker and more effective healing (Boateng et al., 2008; Nuutila and Eriksson, 2021).

In summary, wound healing is a highly coordinated process that depends on the interaction of several cell types and chemical mediators.

Figure 3. Simplified Flowchart Showing the Main Stages of Skin Wound Healing, from Injury to Complete Tissue Regeneration (Based on Singh et al. 2017, Campos et al. 2007, and others)

Understanding the general principles of this process is essential for the implementation of effective therapeutic strategies and for the promotion of adequate healing (Winter, 1962; Daunton et al., 2012; Ho; Hantash, 2013; Gonzalez et al., 2016; Singh et al., 2017; Locatelli et al., 2021; Mathew-Steiner et al., 2021; Nuutila and Eriksson, 2021).

5.2 Traditional and Modern Techniques

While conventional methods remain fundamental, modern approaches offer promising alternatives for complex and difficult-to-heal wounds (Panasci, 2014; Bigliardi et al., 2017; Thomas et al., 2021; Mayer et al., 2024). Traditional wound care techniques include adequate cleansing, debridement, and the use of basic and simple dressings, such as sterile gauze, to protect the wound, absorb exudates, and promote healing (Wilkins; Unverdorben, 2013; Wolcott; Fletcher, 2014; Dhivya et al., 2015). When the wound is covered with a dressing, it is continuously exposed to proteinases, chemoattractants, and growth factors, which are lost when the wound is exposed to the air (Dhivya et al., 2015). Therefore, the appropriate use of dressing aids supports the healing process. The treatment process still follows the same pattern; however, with increasingly advanced technologies, the aim is to achieve greater cure success and increased patient comfort.

Wound cleaning is a fundamental part of the traditional wound bed preparation process, removing dirt and bacteria that are lightly adhered to the wound, thereby preventing microbial infections (Panasci, 2014; Wolcott & Fletcher, 2014). However, this cleaning is not the decontamination of the wound, but rather the removal of the superficial layer of cellular residues or bacteria that may have accumulated on the wound bed (Panasci, 2014). Wound cleaning is still part of wound treatment, even in the most current techniques, and can commonly be done using various solutions, such as drinking water, sterile saline solution, iodine-based antiseptics, solutions containing surfactants, etc. (Silva et al., 2014; Panasci, 2014; Bigliardi et al., 2017; Mayer et al., 2024).

Debridement is considered a standard procedure in the treatment of wounds, especially chronic ones, and involves removing dead tissue and senescent bacteria from the wound bed to promote the formation of healthy granulation tissue and optimize wound healing (Wilkins; Unverdorben, 2013; Fumi et al., 2014). This procedure ranges from more conventional, "rustic" practices to more advanced ones. Thomas et al. (2021) report traditional forms of debridement, such as mechanical debridement, which involve more painful and advanced procedures. The conventional mechanical debridement method can cause significant pain for patients, as it involves, for example, the use of wet gauze on the wound bed. As the gauze dries and adheres to the wound's necrotic tissue, it is removed to remove this dead tissue (Atkin, 2014). Due to the discomfort generated by this procedure, more advanced techniques have been developed. Thomas et al. (2021) report that newer debridement methods, such as enzymatic debridement with collagenase, low-frequency ultrasound, hydrosurgery, and larval debridement, are efficient techniques for preparing the wound bed more quickly and causing less patient pain. However, the authors also demonstrate low consistency among these methods regarding patient safety. Table 1 summarizes traditional and modern wound care techniques.

In addition, surgical debridement techniques, as well as chemical, osmotic, and oxidative debridement methods, among others, are also being studied (Mayer et al., 2024). It is worth noting that the debridement procedure is essential for reducing bacterial load, including biofilm-forming bacteria, which are necessary for healing, especially in chronic wounds (Eriksson et al., 2022; Mayer et al., 2024). Reducing this load helps reverse a chronic wound environment into an acute condition, allowing the wound to undergo the normal healing process (Thomas et al., 2021). Therefore, research has been advancing to make this procedure as efficient and comfortable as possible. A recent study demonstrates professional consensus on efficient debridement techniques, such as selective sharp and surgical debridement, which

Table 1. Comparative Summary of Traditional and Modern Wound Care Techniques

Aspect	Traditional Techniques	Modern Techniques
Wound cleansing	Uses water, saline, or simple antiseptics to remove surface debris	Still applied, but with broader use of targeted and specialized solutions
Debridement	Mechanical method (e.g., dry gauze); simple but often painful	Includes enzymatic, larval, surgical, or ultrasound-assisted methods; more effective and less painful
Type of dressing	Basic sterile gauze, low-cost and protective	Advanced dressings (e.g., hydrogels, foams, bioactive); multifunctional and technology-based
Patient comfort	Lower comfort due to pain during dressing changes and poor conformity	Greater comfort, better anatomical fit, and fewer dressing changes needed
Infection control	Limited; mostly depends on cleansing	Actively reduces microbial load and biofilms, supporting healing
Healing speed	Slower, especially in chronic wounds	Promotes faster healing by improving the wound environment
Cost and accessibility	Low cost and widely available	Higher cost and limited availability, especially in resource-limited settings.
Treatment customization	A less personalized, general approach for most wounds	Greater treatment individualization based on wound type and patient condition
Limitations	Less effective in complex cases; higher discomfort	Requires trained professionals and may have specific contraindications

Based on Panasci (2014), Wilkins and Unverdorben (2013), Wolcott and Fletcher (2014), Dhivya et al. (2015), Thomas et al. (2021), and Mayer et al. (2024)

provide greater patient comfort. However, the authors also note that, in some instances, such as in patients with coagulation difficulties or those with injuries involving exposed bones, ligaments, or tendons, these procedures may be contraindicated (Mayer et al., 2024).

Regarding the use of dressings as part of treatments, there is a variety of these dressings ranging from the cheapest, most common and traditional ones such as gauze (Queen et al., 2004; Jones, 2006; Atkin, 2014; Parkale et al., 2023) to others that are more technological, enriched with enhancing substances, expensive and with more limited access, such as hydrogels, hydrofibers, bioactive, antimicrobial, tissue engineering dressings, foams and semipermeable films, etc. (Bülbül et al., 2022; Parkale et al., 2023; Zhao; Sun, 2024). This will be discussed in more detail in a later session. It is important to emphasize that the best procedure and dressing for wound treatment and healing should not be based on a single factor of the wound or on a specific function of the adopted method or dressing. The patient's wound, their reality, and their unique needs must also be considered (Queen et al., 2004).

5.3 Auxiliary Therapies in the Treatment of Wounds

In addition to what was mentioned above, wound treatment can also include modern, sophisticated auxiliary therapies to optimize the healing process (Table 2). These therapies include negative pressure therapy (Oliveira, 2010; Lima et al., 2017; Normandin et al., 2021; Wu et al., 2022), oxygen therapy (Smet et al., 2017; Nagarsheth et al., 2024), larval therapy or biodebridement (Bazalinski et al., 2023; Lam et al., 2025), low-level laser therapy (Hopkins et al., 2004; Misra et al., 2023), cold plasma therapy (Haertel et al., 2014; Martínez et al., 2024), growth factor therapies (Goldman, 2004; Park et al., 2017; Yamakawa; Hayashida, 2019) and stem cell therapies and tissue engineering (Riedl et al., 2021; Sierra-Sánchez et al., 2021; Downer et al., 2023; Soriano et al., 2023). These auxiliary therapies, also known as adjuvant therapies, aid in healing various types of wounds (Lima et al., 2017).

Negative pressure therapy (NPT) is a technique used since the 1990s that promotes healing by applying uniform negative pressure to the wound (Normandin et al., 2021; Wu et al., 2022). It is a non-invasive method that applies negative pressure to the wound to remove excess fluid in difficult-to-heal wounds (Astasio-Picado et al., 2022). The main indications for NPT are complex wounds, including pressure ulcers, diabetic wounds, open abdomen, traumatic wounds, skin grafts, burns, surgical wound dehiscence, and necrotizing wounds (Lima et al., 2017). This is because this technique, for example, promotes arterial vasodilation in the affected tissues, thereby boosting blood circulation in the area and improving oxygenation (Oliveira et al., 2010). In addition to these benefits, NPT reduces edema and exudate, reduces bacterial clearance, stimulates granulation tissue formation, and reduces inflammation (Lima et al., 2017; Wu et al., 2022). In general, NPT is considered a safe therapy; however, some reports demonstrate complications after its use. The work by Normandin et al. (2021) highlights some of these reports, including toxic shock syndrome, enteric fistula, and hemodynamic instability. However, these authors clarify that these complications were associated with poor patient selection or an inadequate technique for the case.

Oxygen therapy is another adjunctive technique in wound treatment. It presents promising results from both hyperbaric oxygen therapy (oxygen administered through the patient's inhalation) and topical application (Smet et al., 2017; Gupta et al., 2022; Nagarsheth et al., 2024). This is because oxygen is essential for wound healing, as this element is involved in several biological processes, such as protein synthesis, cell multiplication, angiogenesis, reduction of tissue degradation enzymes, reduction of inflammation, promotion of collagen synthesis and, consequently, in aiding the formation of granulation tissue and wound closure (Castilla et al., 2012; Gupta et al., 2022). However, it is essential to note that the relationship between oxygen therapy and wound healing remains complex and warrants further attention regarding its actual effect on the various phases of the healing process. Most studies are limited to surgical wounds, making it challenging to generalize the findings to other types of wounds or in vitro or animal tests (Yip, 2015).

Larval therapy is a procedure that uses disinfected fly larvae, particularly those of Lucilia sericata, to remove necrotic tissue from the wound bed (Nezakati et al., 2020; Gazi et al., 2021; Jafari et al., 2022; Bazalinski et al., 2023). The larvae of these flies are introduced into the wound, where they feed, removing dead tissue and helping to reduce bacterial infection (Nigam, 2021; Bazalinski et al., 2023). As mentioned in the previous topic, debridement is often essential in chronic wounds, and this treatment step can cause significant pain for the patient. Larval therapy, also known as biodebridement, presents an alternative to conventional debridement, aiming to remove dead tissue efficiently while minimizing patient pain (Lam et al., 2025). Studies have shown promising results for this debridement technique; however, there is still considerable resistance to its application due to the psychological

Table 2. Summary of Auxiliary Therapies Applied in Wound Management, Including Mechanisms of Action, Clinical Indications, and Practical Considerations

Therapy	Mechanism of Action	Clinical Indications	Practical Considerations
Negative Pressure	Pulls out fluids, improves blood flow, and promotes healing	Complex or draining wounds	Needs proper technique; may cause complications
Oxygen Therapy	Delivers oxygen to support cell repair and tissue growth	Surgical wounds, ischemic tissues	Effects vary; primarily used in specific cases
Larval Therapy	Larvae clean dead tissue and reduce bacteria	Chronic wounds with necrosis	May cause discomfort for some patients
Low-Level Laser	Stimulates cells, boosts collagen, and reduces inflammation	Slow-healing or chronic wounds	Requires equipment and trained staff
Cold Plasma	Destroys microbes and biofilm, helps tissue regeneration	Infected or chronic wounds	Still experimental in many settings
Growth Factors	Triggers healing signals to speed up recovery	Hard-to-heal wounds	Costly and still under study
Stem Cells & Bioengineering	Rebuilds tissue and modulates inflammation	Severe or non-healing injuries	Complex and expensive; not widely available

Based on Oliveira (2010), Panasci (2014), Lima et al. (2017), Bazalinski et al. (2023), Mayer et al. (2024), and others

discomfort it causes for patients and health professionals (Nigam, 2021; Bazalinski et al., 2023).

Low-level laser therapy (LLLT), also known as photobiomodulation, is a therapeutic approach that uses low-power light, typically in the 600–1000 nm range, to promote wound healing by stimulating tissue growth (Chung et al., 2012). Its mechanism of action involves the absorption of light by opsins, generating cellular chromophores, mainly cytochrome c oxidase in mitochondria, which results in increased ATP production, mild reaction with reactive oxygen species (ROS), and increased nitric oxide (Hamblin, 2017). In addition, LLLT promotes wound healing by stimulating fibroblast proliferation, increasing collagen synthesis, enhancing vascularization in affected areas, facilitating contraction of surrounding tissues, and reducing inflammation (Hopkins et al., 2004; Yang et al., 2022; Misra et al., 2023). A study found that after LLLT, the average healing time for complex skin wounds was 48 days (Otsuka et al., 2022).

Cold plasma therapy, also known as non-thermal atmospheric plasma, is a technique that uses a partially ionized gas at room temperature to treat living tissue (Haertel et al., 2014). Among its benefits, it reduces bacterial load and destabilizes biofilms, thereby promoting wound sterilization (Spiegel et al., 2025). Additionally, it functions as an antiseptic, stimulates the proliferation and migration of skin cells, activates integrin receptors, and promotes angiogenesis (Haertel et al., 2014). In addition to treating exposed wounds, cold plasma treatment exhibits selective cytotoxicity in cancer cells, for example, by inducing the production of reactive oxygen and nitrogen species, which results in oxidative stress within these cells (Martínez et al., 2024).

Factor therapy is an approach that utilizes signaling molecules to stimulate cellular processes essential for wound healing (Goldman, 2004; Yamakawa & Hayashida, 2019). For example, they function as potential supplements to standard treatments for chronic wound healing (Mullin et al., 2024). Growth factors act as triggers that initiate biochemical reactions throughout the phases of healing (Vaidyanathan, 2021). Depending on their structure, they can be administered in various ways, such as particle systems, scaffolds, hydrogels, and different strategies (Park et al., 2017). Some of these growth factors are PDGF (platelet-derived growth factors), VEGF (vascular endothelial growth factor), EGF (epidermal growth factor) and FGF (fibroblast growth factor), which act on cells such as platelets, macrophages, keratinocytes and fibroblasts, resulting in the activation of macrophages to release growth factors, in the promotion of fibroblast proliferation and the production of extracellular matrix, in the promotion of re-epithelialization, in the proliferation of keratinocytes and vascular endothelial cells, among others (Park et al., 2017).

Stem cell therapy and tissue engineering are innovative approaches to restructuring skin integrity in difficult-to-heal wounds. Stem cells, specifically mesenchymal stem cells (MSCs), derived from tissues such as bone marrow and adipose tissue, are notable for their role in wound healing due to their ability to differentiate into various cell types and secrete bioactive factors that promote tissue regeneration (Marti et al., 2011; Maxson et al., 2012). The excretion of bioactives contributes to immune modulation, tissue remodeling, and cellular homeostasis during the regeneration of affected tissues (Han et al., 2022). The combination of differentiation capacity and the secretion of bioactive factors enables MSCs to be utilized in therapies for regenerating soft tissues, including skin, muscles, and blood vessels (Riedl et al., 2021; Rehman et al., 2023).

Tissue engineering involves combining biomaterials, cells, and growth factors to create mechanisms and structures that can replace or regenerate tissues damaged by various conditions, ranging from skin to internal organs (Olson et al., 2011; Borges et al., 2023). It plays a vital role in regenerative medicine, as it is used in various ways, including the development of biocompatible scaffolds that support cell adhesion, proliferation, and differentiation, thereby facilitating the formation of new functional tissue (Krishani et al., 2023). Biomaterials used in tissue engineering can be natural, synthetic, or a combination of both types (Downer et al., 2023). Examples of this therapy include skin substitutes used to treat burns or chronic wounds, such as autologous cultured epithelial substitutes, which consist of keratinocytes and fibroblasts; autologous skin substitutes, composed of biomaterials; and allogeneic cultured dermal substitutes, composed of biomaterials and fibroblasts (Sierra-Sánchez et al., 2021). It is essential to note that these auxiliary therapies can be applied independently as clinical procedures or in conjunction with wound dressings (Garcia et al., 2016; Park et al., 2017; Catanzano et al., 2021).

6 Classification and Types of Dressings

Choosing the ideal dressing for wound treatment is an ongoing challenge in clinical practice, as this choice represents only one component of a comprehensive therapeutic plan and is associated with various models, benefits, and contraindications (Queen et al., 2004). In addition, there is significant heterogeneity in access, choice, and use of these dressings across regions of the world, driven by factors such as resource availability, local guidelines, cultural practices, and socioeconomic factors (Queen et al., 2004; Koka et al., 2016; Bishop, 2023). It is known that an ideal

dressing should perform several functions, mainly to treat wounds efficiently and economically and to be easily removed with minimal inconvenience to the patient (Bülbül et al., 2022). Furthermore, it is expected to promote moisture balance and oxygen exchange, stimulate growth factors, prevent infections, facilitate debridement, promote granulation tissue formation, and promote re-epithelialization (Shi et al., 2020). However, as the healing process is not static, it requires different conditions at each healing phase. Consequently, a single dressing cannot perform all these functions (Gonzalez et al., 2016; Shi et al., 2020; Tottoli et al., 2020).

Furthermore, the diversity of products available on the market and patients' social conditions make choosing a dressing a complex task (Shi et al., 2020; Sinha et al., 2022). Selecting the wrong dressing can lead to several negative consequences, including prolonged healing time, increased risk of infection, and higher treatment costs (Lima et al., 2017; Nussbaum et al., 2018; Atkin et al., 2019; Santos, 2022; Lagoa et al., 2024). In general, choosing the ideal dressing involves four basic principles: dehydrated wounds require dressings that provide hydration; wounds with high exudate production will require an absorbent dressing; infected wounds will need antibiotic dressings; necrotic wounds or those with visible dirt will require debridement (Morin; Tomaselli, 2007; Sood et al. 2014). Therefore, understanding the phases of the healing process, its classification, and the types of dressings available on the market is crucial for effectively treating various wound types.

6.1 General Functions of Dressings

Dressings play a fundamental role in the wound-healing process, acting as physical barriers that protect the wound bed from external agents, such as microorganisms, chemical contaminants, and mechanical trauma (Boateng et al., 2008; Dhivya et al., 2015; Ferraz, 2025). This protection is essential for preventing infections and promoting an environment conducive to tissue regeneration. Furthermore, dressings help maintain local temperature and absorb exudates, contributing to wound homeostasis and facilitating the healing process (Boateng et al., 2008; Dhivya et al., 2015; Ghomi et al., 2019; Tan et al., 2019; Gou et al., 2024; Alberts et al., 2025).

Maintaining a moist wound environment is one of the most essential functions of modern dressings. Studies have shown that adequate moisture accelerates epithelialization and reduces crusting, promoting more efficient healing and greater patient comfort (Winter, 1962; Boateng et al., 2008; Dhivya et al., 2015; Nuutila; Eriksson, 2021). Dressings that maintain this moist environment, such as hydrocolloids and hydrogels, are particularly effective (Tan et al., 2019; Guillen et al., 2022).

In addition to protecting and maintaining moisture, dressings also perform functions such as debridement of necrotic tissues, odor control, and controlled release of therapeutic agents (Dhivya et al., 2015; Jiang; Loo, 2021; Bhoyar et al., 2023; Koumaki et al., 2023; Alberts et al., 2025). For example, dressings impregnated with antimicrobial substances, such as silver, help reduce bacterial load in the wound, preventing infections and promoting faster healing (Jiang; Lo0, 2021; Alberts et al., 2025). Therefore, knowing the types of dressings available and their optimal application becomes essential for successful wound treatment.

6.2 Types of Dressings

In general, dressings are classified into several categories based on their class, behavior, clinical performance, physical form, and origin (Boateng et al., 2008; Ghomi et al., 2019; Tan et al., 2019; Table 3). Based on the class, they are divided into primary, secondary, and island dressings (Boateng et al., 2008; Vowden; Vowden, 2017; Shi et al., 2020). Primary dressings are in direct contact with the wound bed (Fahimirada; Ajalloueian, 2019). Therefore, their functions include promoting a suitable environment for healing, controlling moisture, absorbing exudate, releasing bioactive agents, and acting as a barrier against microorganisms (Boateng et al., 2008). Examples of primary dressings include foams, hydrofibers, micronized collagen, hydrogels, hydrocolloids, alginates, nanosilver, and films (Boateng et al., 2008; Frykberg; Banks, 2015; Vowden; Vowden, 2017).

On the other hand, secondary dressings, such as gauze, cotton, natural and synthetic bandages, adhesive tapes, hydrogel films, and sheet dressings, have as their primary function to provide support, fixation, additional absorption, and protection to the primary dressing (Boateng et al., 2008; Fahimirada; Ajalloueian, 2019; Moradifar et al., 2025). In other words, the primary dressing is designed to be in direct contact with the wound. In contrast, a bandage (secondary dressing), for example, holds the primary dressing in place (Dhivya et al., 2015). It is essential to note that, in some instances, the same product can serve as both a primary and secondary dressing, depending on the clinical situation (Jones, 2014; Shi et al., 2020). Island dressings are those that "unite" primary and secondary dressings in the same dressing, as they have a central absorbent region (island) that is surrounded by an adhesive portion; that is, this type provides treatment of the wound and its fixation (Rippon et al., 2007; Boateng et al., 2008).

Dressings are categorized as passive, interactive, or bioactive based on their behavior. Passive dressings protect the wound without incorporating non-occlusive substances that promote healing, such as gauze and tulle, which are often used to cover wounds (Tan et al., 2019). In contrast, interactive or bioactive dressings, usually occlusive or semi-occlusive, provide or stimulate the release of substances that aid and improve wound healing (Guillen et al., 2022). Based on their clinical performance, dressings can be classified into five categories: absorbent, occlusive, semi-occlusive, adhesive, and antimicrobial (Ghomi et al., 2019). Absorbent dressings are designed to manage excess exudate, maintain a moisture balance in the wound bed, and are essential for healing, as they remove excess fluid, prevent maceration of the peripheral skin, and reduce the risk of infection (Jones, 2014; Gardner, 2016). Examples of these dressings include foam, alginate, and hydrofiber (Frykberg; Banks, 2015). However, they have limitations in dry or low-exudate wounds, as they can adhere to the wound bed and require a secondary dressing for maintenance (Brito et al., 2024).

Occlusive dressings are made of materials that are impermeable to liquids and gases, forming a physical barrier that prevents moisture loss from the wound surface (desiccation) and the entry of microorganisms, providing an ideal microenvironment to promote healing (Helfman et al., 1994; Dhivya et al., 2015; Tan et al., 2019; Guillen et al., 2022). Maintaining occlusion promotes a moist environment that favors epithelialization, as demonstrated by Winter (1962) and in subsequent literature (Boateng et al., 2008; Junker et al., 2013; Dhivya et al., 2015; Frykberg & Banks, 2015; Nuutila & Eriksson, 2021). Occlusive dressings facilitate faster re-epithelialization, promote angiogenesis, aid in collagen synthesis, and decrease the pH of the wound surface, thereby reducing the risk of infection (Dhivya et al., 2015). Examples of these dressings include films, hydrofibers, foams, charcoal, alginates, hydrogels, and hydrocolloids (Tan et al., 2019; Guillen et al., 2022). In the Brazilian health service, hydrocolloids are the most widely used occlusive dressings (Guillen et al., 2022). It is worth noting that these dressings may be contraindicated in highly exudative wounds and may cause skin maceration if used for prolonged periods (Tan et al., 2019; Brito et al., 2024). However, non-occlusive dressings, such as gauze, dry out and adhere to the wound, causing damage during removal and potentially leading to bleeding and pain for the patient (Queen et al., 2004).

Table 3. Classification of Wound Dressings by Criteria, Type, Key Characteristics, and Examples

Classification Criteria	Types	Key Characteristics	Examples
By class	Primary	Contact with the wound bed	Foams, hydrogels, and hydrocolloids
	Secondary	Fixation, support	Gauze, bandages, adhesive tapes
	Island	Primary + secondary	Self-adhesive with central pad
By behavior	Passive	Basic protection	Gauze, tulle
	Interactive/Bioactive	Healing stimulation, substance release	Nanofibers, hydrogels
By clinical performance	Absorbent	Controls exudate, prevents maceration	Foams, alginates
	Occlusive	Maintains a moist environment	Hydrocolloids, films
	Semi-occlusive	Gas exchange, autolytic debridement	Polyurethane films
	Adhesive	Easy fixation, protective barrier	Island dressings
	Antimicrobial	Infection control	Silver, iodine, and honey dressings
Physical form and origin	Animal	Protein-based, biocompatible, promotes healing	Collagen
	Plant	Natural, antimicrobial, good moisture retention	Cellulose
	Synthetic	Durable, customizable, controlled drug release	Polyurethane

Based on Boateng et al. (2008), Ghomi et al. (2019), Tan et al. (2019), Vowden & Vowden (2017), and others.

In turn, as the name suggests, semi-occlusive dressings, such as polyurethane films, allow a limited degree of oxygen and water vapor exchange between the wound and the environment while remaining impermeable to liquids and bacterial contamination (Colenci et al., 2018; Hodge et al., 2022). In this way, they continue to play a role in moisture retention, providing a moist environment for healing and favoring autolytic debridement and epithelialization of wounds (Bhoyar et al., 2023). These dressings have been increasingly studied and have demonstrated satisfactory results in wound treatment and healing (Madden et al., 1989; Esmaeil et al., 2025). Adhesion dressings, also known as adhesive dressings or island dressings, feature an absorbent central pad and adhesive edges that promote wound stability and protection (Rippon et al., 2007; Matsumura et al., 2014). Although they are easy to apply, as they eliminate the need to cut and prepare surgical tapes to keep the dressing in place, their adverse effects are related to the injuries that they can cause, at the time of their removal, to the epithelium and surrounding healthy skin, generating pain and even increasing the wound area (Waring et al., 2008; Matsumura et al., 2014).

Antimicrobial dressings incorporate active agents that act to reduce the local microbial load, being indicated for infected wounds or those at high risk of infection, and can be presented in the form of films, foams, or hydrogels, among others (Hewish, 2012; Gou et al., 2024; Alberts et al., 2025; Peng et al., 2025). They are varied and composed of different raw materials, including silver, iodine, biguanide, antibiotics, natural products such as medical-grade honey and plant compounds, nanoparticles, chitosan, antimicrobial peptides, and metals, among others (Yousefian et al., 2023; Peng et al., 2025). The importance of this dressing class in treating wounds, especially chronic ones, is well established, and several studies support its use. However, only 1% of antimicrobials are used clinically because most testing is in vitro or, when in vivo, is limited to animal models, and, consequently, there are concerns about their side effects (Gou et al. 2024) among the advances in antimicrobial dressings based on nanotechnology, such as nanoparticles (Alberts et al., 2025).

These are promising avenues for developing innovative dressings that enhance their antimicrobial effect and, consequently, efficient healing (Jiang and Loo, 2021). The use of antimicrobial dressings is essential in the treatment of wounds because infections represent one of the most significant problems in the normal course of the healing process, resulting in increased wound complexity, mortality, length of hospital stay, and treatment costs (Lima et al., 2017; Peng et al., 2025). Regarding other classifications of dressings, based on physical form and origin, they are broadly categorized as gels, ointments, films, foams, and those of animal, vegetable, and synthetic origin (Ghomi et al., 2019). Therefore, based on what has been revealed so far, the correct selection of dressings, taking their classification into account, is crucial for therapeutic success, directly influencing the progression of healing, the prevention of complications, and the reduction of treatment costs.

6.3 High-Technology Dressings

High-tech dressings represent a significant evolution in wound care, incorporating scientific and technological advances to optimize healing. These dressings extend beyond their traditional coverage function, offering bioactive properties, real-time monitoring, and controlled drug release, thereby adapting to the specific needs of each injury (Ovington, 2007; Zhang et al., 2021; Tran et al., 2023; Alberts et al., 2025). High-tech dressings are advanced therapeutic devices designed to actively interact with the wound bed, promoting tissue regeneration and preventing complications (Zhang et al., 2021; Tran et al., 2023; Zhang et al., 2025). Among its main types are nanotechnology-based dressings, smart dressings, bioactive dressings, and 3D-printed dressings, among others (Figure 4; Jiang; Loo, 2021; Zhang et al., 2021; Chopra et al., 2023; Nie et al., 2023; Alberts et al., 2025).

Among the various advantages that these dressings present, concerning conventional dressings, are the promotion of cell regeneration more efficiently (Colenci et al., 2018; Zhang et al., 2021; Hodge et al., 2022; Zhang et al., 2024; Moradifar et al., 2025); the reduction in the risk of infections provided by dressings with antimicrobial functions (Jiang; Loo, 2021; Gou et al., 2024; Alberts et al., 2025); and; greater patient comfort, due to the reduced need for changes and the greater anatomical adaptation of semipermeable films, for example (Ovington, 2007; Sood et al., 2014; Weller et al., 2020; Lagoa et al., 2024). One of the main disadvantages is the high cost. Advanced dressing technologies are generally expensive, limiting access in some contexts (Laurano et al., 2022; Alberts et al., 2025).

Figure 4. Main types of high-tech wound dressings with key features, applications, and challenges

6.4 Nanotechnology and Dressings

The definition of nanomaterials is not simple or uniform; however, they are usually defined as structures with at least one dimension in the nanoscale, ranging from 1 to 100 nanometers (Yokel; MacPhail, 2011; Baig et al., 2021). These materials possess specific physical and chemical properties that depend on their size and shape (Baig et al., 2021). For example, some nanoparticle shapes may be more efficient as antimicrobial agents than others. This is observed in the study by Cheon et al. (2019), which demonstrates differences in the antimicrobial activity of silver nanoparticles based on their shape. The results of this study show that spherical nanoparticles exhibit greater action against Escherichia coli strains, followed by disk-shaped and triangular-shaped nanoparticles (Cheon et al., 2019). These authors demonstrated that this difference is due to variations in the release rate of silver ions, resulting from differences in nanoparticle surface area, specifically morphology.

Based on Zhang et al. (2021), Jiang and Loo (2021), Deng et al. (2025), Albert et al. (2025), He et al. (2023), and others

The research conducted by Barroso et al. (2023) demonstrated that triangular nanoparticles were more effective against strains such as *E* coli. These researchers reported that this greater efficiency may be linked precisely to the triangular shape of the nanoparticles and their sharp edges, which can facilitate interaction with microbial cell membranes. One point worth highlighting when comparing these two studies is that, in the work by Cheon et al. (2019), the spherical nanoparticles were 100 nm in size, and the triangular ones were 200 nm ; that is, the triangular ones are outside what is typically considered a nanomaterial. The triangular nanoparticles of Barroso et al. (2023) were 20 nm in size. Therefore, although some studies indicate that nanoparticles of a particular shape exhibit greater antimicrobial efficacy, others yield different results under specific conditions. Hence, factors such as particle size, ion release rate, target microorganism type, and synthesis method can significantly influence the results (Cheon et al., 2019; Sayed et al., 2022; Barroso et al., 2023). Therefore, investigations into the specific properties of each nanomaterial remain a vast field with significant gaps.

Nanomaterials can be produced in two ways: top-down and bottom-up. In the top-down approach, larger materials are broken down to form nanomaterials using techniques such as mechanical milling and electroexplosion. In contrast, the bottom-up approach produces nanomaterials by constructing nanostructures from smaller individual particles, atoms, or molecules. It can be done using techniques such as chemical vapor deposition (Baig et al., 2021). Various types of nanomaterials are used in technologies collectively referred to as nanotechnologies. Nanotechnology is the science involved in the design, synthesis, characterization, and application of materials whose functional organization, at least in one dimension, is on a nanometric scale (Saini et al., 2010).

Among the properties achieved with nanotechnology, the high surface-to-volume ratio, greater reactivity, ability to penetrate biological tissues and altered optical and mechanical behavior stand out, which makes nanomaterials attractive for diverse applications such as administration, pharmaceuticals, renewable energies, biomedicine, especially in the treatment of wounds, etc. (Sun et al., 2008; Zhang et al., 2023; Khushnood, 2024). Among the technological advances in which nanotechnologies are being increasingly investigated is their application in wound treatment (Leppiniemi et al., 2017; Adamu et al., 2021; He et al., 2023; Astaneh & Fereydouni, 2024; Deng et al., 2025). In this context, they can act as antimicrobial agents (Cheon et al., 2019; Sayed et al., 2022; Barroso et al., 2023; Deng et al., 2025); promoters of cell regeneration or controlled drug release systems (Cheon et al., 2019; Truskewycz et al., 2021; He et al., 2023; Ruan et al., 2023; Deng et al., 2025), and biomolecules directly in the wound bed (Luo et al., 2023).

The application of metallic nanoparticles, such as silver, gold, titanium, cerium, and zinc, for example, has shown efficacy in inhibiting multidrug-resistant microorganisms, while nanofibers and nanostructured hydrogels have been used to provide structural support for tissue

regeneration and modulate the inflammatory response (Lu et al., 2022; Liu et al., 2024; Zhang et al., 2024). Investigations into nanofibers are underway, and these materials are emerging technologies with unique characteristics and properties that can be used to develop effective dressings (Zhang et al., 2024). In the study by Partovi et al. (2024), spun nanofibrous dressings demonstrated antimicrobial action against various microbial strains. Additionally, the incorporation of citrate into the nanofibers enhanced the dressing's porosity, hydrophilicity, and degradability, properties favorable for wound healing. Electrospun nanofibers from gelatin and chitosan-polyvinyl alcohol have also been investigated, yielding satisfactory results with good physical properties and efficient antimicrobial activity against certain microorganisms (Campa-Siqueiros et al., 2020).

Regarding the application of nanoparticles in wound treatment, a summary of the articles discussed in this session is shown in Table 4. In the study by Barroso et al. (2023), silver nanoparticles incorporated into bacterial cellulose biopolymers and other components demonstrated satisfactory inhibitory action against *E* . coli and Staphylococcus aureus strains. In this research, the authors attributed this action to several factors, including the triangular shape of the nanoparticles and their sharp edges, which may have facilitated their penetration into the bacterial cell. Nanosilver was also investigated through green synthesis from Ficus benghalensis leaf extract for incorporation into postoperative dressings (Lu et al. 2022). The results demonstrated higher antimicrobial activity and accelerated cell regeneration compared to the isolated plant extract. A study using nanosilver associated with carbon fiber and synthetic drugs achieved bacterial growth inhibition results of 97% for E. coli and 80% for S. aureus (Luo et al., 2022).

Zinc and selenium nanoparticles have demonstrated promising results both in vitro and in vivo for treating pediatric wounds (Ruan et al., 2023). This study showed that nanoparticles formulated in a bioactive chitosan scaffold accelerated wound closure and enhanced collagen deposition when administered in vivo to treat rat wound models. Additionally, it improved re-epithelialization and granulation tissue formation, reduced inflammation and microbial infections in the wound area. Similar results were achieved by Luo et al. (2023), using cerium oxide nanoparticles. The results revealed significant antimicrobial action against S. aureus and E. coli, as well as improved re-epithelialization, cell proliferation, and the formation of new blood vessels. In in vivo tests, the dressing accelerated healing, resulting in 98.5% wound closure after 14 days, whereas the control group showed only 71% closure. Furthermore, the healing hydrogel exhibited rapid gelation, high fluid-absorption capacity, and good mechanical stability.

6.5 Smart Dressings

Smart dressings, also known as intelligent dressings, are designed to incorporate sensors and technologies to monitor the physiological parameters of the wound bed in real time (Jiang; Loo, 2021; Deng et al., 2025; Moradifar et al., 2025). These devices are designed to detect critical factors, such as pH, reactive oxygen species, specific enzymes, glucose levels, light, heat, and temperature, allowing for more precise and personalized interventions (Alberts et al., 2025; Deng et al., 2025; Zhang et al., 2025). In addition, many innovative dressings are responsive, releasing therapeutic agents, such as antibiotics, in a controlled manner in response to specific wound conditions (Jiang; Loo, 2021). One example is pH-responsive dressings. The normal pH of the skin ranges from 5 to 6; however, in wounds colonized by microorganisms, the pH can range from 7 to 10. Thus, smart dressings that respond to pH stimuli will release their antimicrobials when the pH level increases, thereby controlling microbial proliferation in a personalized manner (Alberts et al., 2025). These dressings can respond to one or more stimuli (Jiang; Loo, 2021). They have been increasingly researched and have shown promising results. In vitro and in vivo studies have demonstrated that a smart hydrogel, combining materials such as gelatin and chitosan methacrylate, nanoparticles, and a pH indicator, can be analyzed using machine learning and is an efficient, regenerative, biocompatible, bioactive, antibacterial, and anti-inflammatory product (Deng et al., 2025). In China, a chitosan-based dressing incorporates smart sensors to monitor wound temperature and humidity in real time, enabling rapid responses from medical staff (Yang et al., 2023). These are some results from applying various technologies to the development of new dressings.

6.6 Bioactive Dressings

Bioactive dressings are designed to interact actively with the wound bed, releasing bioactive compounds that modulate inflammation, stimulate cell proliferation, promote angiogenesis, and accelerate tissue regeneration (He et al., 2023). These dressings are developed from natural or synthetic matrices, often incorporated with biological agents, such as natural extracts, nanoparticles, growth factors, or even cells, thus optimizing the healing microenvironment (Maxson et al., 2012; He et al., 2023). In this context, researchers have extensively studied natural compounds, such as chitosan, collagen, and cellulose, in the development of bioactive dressings. Nanotechnology has also played a pivotal role in this field, enabling the controlled release of bio-active agents and enhancing their therapeutic efficacy (Dhivya et al., 2015). Another study reports that a hydrogel based on polyhydroxyethyl methacrylate (PHEM) and chitosan (CS), incorporated with cerium oxide nanoparticles (CeONPs), showed antimicrobial properties, biocompatibility, and accelerated healing in chronic wounds (Luo et al., 2023). Other examples are bioactive dressings based on medicinal plant extracts. Studies reveal that electrospun nanofibrous dressings coupled with plant extracts represent an essential alternative for treating wounds, owing to their efficiency, the high availability of plant material, costeffectiveness, and environmental compatibility (Adamu et al., 2021). These reports demonstrate how bioactive dressings integrate materials engineering and biotechnology to provide highly effective therapeutic solutions. Thus, these dressings represent a promising and innovative approach, particularly for treating difficult-to-heal wounds.

6.7 3D-Printed Dressings

3D-printed dressings represent one of the most significant advances in bioengineering applied to wound treatment. This technology enables the manufacture of personalized dressings tailored to the exact dimensions of the lesion and the patient's anatomical shape (Leppiniemi et al., 2017; Yayehrad et al., 2023; Astaneh & Fereydouni, 2024). These dressings are generally manufactured from biopolymers such as methacrylated gelatin, chitosan, hyaluronic acid, and nanocellulose, often combined with therapeutic agents, such as antimicrobials, growth factors, nanoparticles, or living cells (Leppiniemi et al., 2017; Boateng et al., 2023; Yayehrad et al., 2023; Astaneh; Fereydouni, 2024; Rossi et al., 2024). Studies on this technology have been conducted with increasing frequency in recent years. A bioactivated nanocellulose-alginate hydrogel showed excellent structural stability after 3D printing, maintaining its shape and mechanical properties (Leppiniemi et al. 2017). Additionally, the material exhibited tunable mechanical properties and good moisture retention, which are essential characteristics for applications in wound dressings and tissue engineering.

Another study reports that a methacrylated gelatin hydrogel incorporating lignin-derived carbon dots was evaluated for its antimicrobial properties in the development of a 3D-printed dressing. The results demonstrated that the dressing has effective antimicrobial activity

Table 4. Main Articles on Biomaterials and Dressings Combined with Nanotechnology for Wound Treatment

Authorship	Country	Type of Study	Objective
(Luo et al., 2023)	China	Biomaterial development and in vitro and in vivo evaluation	To develop and characterize a hydrogel based on polyhydroxyethyl methacrylate (PHEM) and chitosan (CS), incorporated with cerium oxide nanoparticles (CeONPs); to evaluate the antimicrobial properties, biocompatibility, and healing effect of this dressing in chronic wounds
Zhao and Sun (2024)	China	Biomaterial development and in vitro evaluation	Demonstrate how combining nanotechnology (AgNPs) with natural biopolymers (chitosan) can offer a more efficient and safe treatment for patients with chronic wounds, especially in nursing care contexts for diabetic patients
Liu et al. (2024)	China	Biomaterial development and in vitro evaluation	To develop and characterize a bioactive hydrogel based on chitosan (CS) and hyaluronic acid (HA), incorporated with gold nanoparticles (AuNPs) and fibroblast growth factors (FGFs); to evaluate the effectiveness of the hydrogel in healing diabetic wounds, emphasizing antimicrobial properties and stimulation of tissue regeneration
Yang et al. (2023)	China	Biomaterial development and in vitro and in vivo evaluation	To develop chitosan-based wound dressings with titanium nanoparticles (TiO2) for hospital and pediatric use; to evaluate the ability of these dressings to monitor wound temperature, humidity, and pH, in addition to their antimicrobial efficacy, reduce the risk of hospital infections, and improve patient comfort
Ruan et al. (2023)	China	Biomaterial development and in vitro and in vivo evaluation	To develop and evaluate chitosan-based antibacterial dressings incorporated with zinc oxide (ZnO) and selenium nanoparticles (SeNPs) for the treatment of post-surgical wounds in children; to evaluate antimicrobial properties, healing, and biocompatibility through in vitro and in vivo tests
Luo et al. (2022)	China	Clinical evaluation of dressings with silver nanoparticles	To evaluate the efficacy of dressings with nanostructured silver ions in the treatment of infected surgical wounds; to compare the antimicrobial action of silver nanoparticle dressings (Ag-PVP NPs) with conventional antibiotics; to investigate the impact of the use of these dressings in reducing the risk of infection and healing time
Lu et al. (2022)	China	Synthesis and characterization of nanoparticles, antimicrobial and healing evaluation in vitro	To develop an antimicrobial dressing based on sustainably synthesized silver nanoparticles (AgNPs) for application in surgical wounds after rectal surgery; to evaluate the antimicrobial properties, bioactivity, and healing capacity of AgNPs in comparison to the plant extract used in the synthesis

against Staphylococcus aureus and Escherichia coli and does not present cytotoxicity in human fibroblasts. The material also maintained a hydrated environment in the wound area, a crucial factor for optimal healing (Rossi et al., 2024). Growth factors are also associated with 3D printing technology and have shown promising results for application in these dressings, with a relatively long release profile (Boateng et al., 2023). Other studies report the integration of silver nanoparticles with 3D printing technology to develop dressings, demonstrating promising results (Astaneh and Fereydouni, 2024). However, these authors also note challenges in nanoparticle applications within 3D structures, including the uniform dispersion of these nanomaterials and the potential cytotoxicity at high concentrations. 3D-printed dressings, therefore, offer an innovative and personalized solution in treating wounds. Their ability to combine biomaterials, bioactive agents, and adaptable design makes this technology promising for regenerative medicine.

6.8 Sustainability and Development of New Dressings

Sustainable development in wound dressings has become an urgent issue, given the environmental impacts associated with their production, use, and disposal. Among the concerning data on waste generated in the healthcare system, materials used to treat wounds are a significant portion of this waste, originating from dental and veterinary clinics, offices, medical departments, and other sources (Janik-Karpinska et al., 2023). In addition, many dressings have traditionally included synthetic polymers derived from petroleum, such as polyurethane, in part of their composition (Sood et al. 2014; Nguyen et al., 2023; Zhang et al., 2024). These materials have low biodegradability and generate persistent waste in the environment. The inadequate disposal of these materials, coupled with their greater permanence in the environment, not only contributes to the generation of solid waste but also carries biological and chemical contaminants, thereby increasing health and environmental risks (Borowy, 2020).

Given this scenario, there is growing interest in sustainable alternatives for manufacturing dressings. The use of natural biopolymers, such as chitosan, bacterial cellulose, collagen, hyaluronic acid, and fibrin, has been highlighted due to their biodegradability, biocompatibility, and often intrinsic antimicrobial properties (Leppiniemi et al., 2017; Boateng et al., 2023; Nguyen et al., 2023; Yang et al., 2023; Yayehrad et al., 2023; Astaneh; Fereydouni, 2024; Rossi et al., 2024). These characteristics can help reduce environmental damage and contamination caused by the accumulation of waste resulting from wound treatment. Another sustainable strategy is to use industrial waste to formulate biomaterials. Lignin, for example, has been increasingly investigated for application in wound dressings due to its adhesive, antibacterial, and antifungal properties, and has shown promising results even in more advanced technologies such as 3D printing dressings (Domínguez-Robles et al., 2023; Rossi et al., 2024; Wan et al., 2024).

Research shows that approximately 10 million tons of lignin are generated as a byproduct of paper and ethanol production (Bajwa et al., 2019). Using this bioproduct in the development of dressings could be a sustainable alternative. Another example of a byproduct is cellulose, which can be extracted from lignocellulosic waste from paper production

(Souza et al., 2017), and the wood vinegar generated during the wood carbonization process for charcoal production (Gama et al., 2023). In addition to these examples, several other promising bioproducts can be found as byproducts from various production processes. Incorporating them into the production of biodegradable and efficient dressings qualifies as an alternative to make wound treatment more sustainable.

7 Limitations and Future Prospects

Despite significant advances in wound dressing science and adjunctive therapies, wound care continues to face substantial challenges. Essential limitations include the lack of in vivo testing, human clinical trials, long-term evaluations, skilled labor, costs, and potential regulatory challenges (Laurano et al., 2022; Luo et al., 2023; Ruan et al., 2023; Yang et al., 2023; Namgoong et al., 2023; Liu et al., 2024). A study conducted in South Korea demonstrated that skilled labor in handling dressings improves care performance, patient and healthcare professional satisfaction, and yields more satisfactory wound care outcomes (Namgoong et al., 2023). These findings demonstrate that, even in large centers, the introduction of advanced dressings requires trained professionals and specific protocols, and that the absence of these results in inadequate application increases the risk of complications and inferior clinical outcomes. The lack of in vivo testing and clinical trials in humans is also a limitation to the implementation of new technologies for the practical treatment of wounds, as it generates a lack of robust evidence of the efficacy and safety of the products being developed (Ruan et al., 2023; Yang et al., 2023; Liu et al., 2024). In other words, dressings that work well in vitro may fail in vivo due to the complexity of the human biological environment, including enzymes, microbiota, the immune system, and blood flow, which can compromise their effectiveness. Another limitation reported in the research is the lack of long-term evaluations (Luo et al., 2022; Ruan et al., 2023; Luo et al., 2023; Yang et al., 2023).

This scenario raises uncertainty about the durability of therapeutic effects, as without long-term follow-up studies, it is challenging to determine whether the benefits observed in the early stages of healing are sustained over time. The high costs of developing and producing more technologically advanced dressings also pose a significant limitation to their implementation in wound treatment (Luo et al., 2022; Laurano et al., 2022; Ruan et al., 2023). These costs are reflected in higher hospital and patient prices, making it difficult for them to be incorporated on a large scale into public health systems. Additionally, regulatory processes make it highly challenging for advanced dressings to enter the market quickly (Laurano et al., 2022). Therefore, these limitations compromise the widespread implementation of new dressings in the health system. These challenges delay patients' access to more effective therapies and impede scientific and technological innovation in wound healing. Overcoming them ensures more advanced, safe, and sustainable treatments.

Prospects for wound treatment point to the development of multifunctional smart dressings capable of continuously monitoring the wound microenvironment and releasing therapeutic agents in a controlled manner, responsive to specific stimuli such as pH, temperature or the presence of infections (Alberts et al., 2025; Jiang; Loo, 2021; Deng et al., 2025; Moradifar et al., 2025; Zhang et al., 2025). The integration of technologies such as nanotechnology and 3D printing allows the creation of personalized devices that are adaptable to the individual characteristics of each patient, optimizing therapeutic results (Leppiniemi et al., 2017; Adamu et al., 2021; He et al., 2023; Yayehrad et al., 2023; Astaneh; Fereydouni, 2024; Deng et al., 2025). Furthermore, advances in bioengineering, for example, have driven the use of stem cells, growth factors, and bioactive scaffolds for tissue regeneration, which could revolutionize the treatment of chronic and complex wounds (Yamakawa; Hayashida, 2019; Riedl et al., 2021; Sierra-Sánchez et al., 2021; Han et al., 2022; Downer et al., 2023; Soriano et al., 2023; Ferreira et al., 2024). However, for these innovations to become accessible clinical practices, it is essential to overcome regulatory challenges, reduce production costs, expand clinical studies with long-term follow-up, and train professionals to handle them.

8 Conclusion

Wound treatment represents one of the most significant challenges in modern medicine, especially given the increasing complexity of skin lesions. Choosing the appropriate dressing based on the characteristics of the wound (such as exudate, depth, and infection status) is crucial for therapeutic success. This work has highlighted the wide range of dressings, from traditional and conventional approaches (gauze, tulles, adhesive tapes) to high-technology systems (bioactive, smart, nanotechnological, and 3D-printed dressings).

Although conventional dressings remain useful in clinical practice, advanced dressings offer innovative solutions that extend beyond simple protection, such as real-time monitoring of clinical parameters and the controlled release of therapeutic agents. Furthermore, adjunctive therapies, including stem cells, growth factors, and non-thermal plasma, provide a multitherapeutic approach that significantly improves the healing of chronic and complex wounds. Despite promising prospects, challenges such as high costs, limited clinical validation, and environmental impacts still need to be addressed. Sustainable development in dressing production, including the use of natural biopolymers and industrial byproducts, is an emerging field that promises to reconcile clinical efficacy with environmental responsibility.

In conclusion, the evolution of wound dressings and adjunctive therapies reflects a continuous search for more efficient, personalized, and sustainable solutions. Collaboration between different fields of knowledge, such as materials engineering, biology, nursing, and medical care, is essential to consolidate these innovations and ensure their effective implementation in global wound care practice.

USE OF ARTIFICIAL INTELLIGENCE

AI or AI-assisted tools were not used in drafting or final writing of this manuscript.

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REFERENCES

[1] Adamu, B. F.; Gao, J.; Jhatial, A. K.; Kumelachew, D. M. A review of medicinal plant-based bioactive electrospun nano- fibrous wound dressings. Materials & Design, v.209, 2021. Doi: https://doi.org/10.1016/ j.matdes.2021.109942.

[2] Ahmad, W.; Aquil, Z.; Alam, S.S. Historical background of wound care. Hamdan Med. J., 13:189-95, 2020. DOI: 10.4103/HMJ.HMJ _37_20.

[3] Akagi I, Furukawa K, Miyashita M, Kiyama T, Matsuda A, Nomura T, Makino H, Hagiwara N, Takahashi K, Uchida E. Surgical wound

management made easier and more cost- effective. Oncol Lett, 4(1):97-100, 2012. Doi: 10.3892/ol.2012.687.

[4] Alberts, A.; Tudorache, D.-I.; Niculescu, A.-G.; Grumezescu, A.M. Advancements in Wound Dressing materials: highlighting recent progress in hydrogels, foams, and antimicrobial dressings. Gels, v.11, n.123, 2025. Doi: https://doi.org/10.3390/gels11 020123.

[5] Anisuzzaman, D. M., Patel, Y., Rostami, B., Nezgoda, J., Gopalakrishnan, S., Yu, Z. Multi-modal wound classification using wound image and location by deep neural network. Sci Rep 12, 20057 (2022). https://doi.org/10.1038/s41598-022-21813-0

[6] Astaneh, M.E.; Fereydouni, N. Silver nanoparticles in 3d printing: a new frontier in wound healing. ACS Omega, v. 9, n. 40, p. 4110741129, 2024. Doi: https://doi.org/ 10.1021/acsomega.4c04961.

[7] Astasio-Picado, Å.; Montero, M.D.M.; López-Sánchez, M.; Jurado-Palomo, J.; Cobos-Moreno, P.; Gómez-Martin, B. The Effivness-negati ressueherapy approach. J. Pers. Med., 12, 1813, 2022. Doi: https://doi.org/10.3390/ipm12 111813.

[8] Atkin, L. Understanding methods of wound debridement. British Journal of Nursing, v.23, n.12, 2014.

[9] Atkin, L.; Buko, Z.; Montero, E.C.; Cutting, K.; Moffatt, C.; Probst, A.; Romanelli, M.; Schultz, G.S.; Tettelbach, W. Implementing TIMERS: the race against hard-to-heal wounds. Journal of Wound Care, v.28, n.3, 2019. Doi: https://doi.org/10.12968/jowc.2019.28.Sup3a.S1.

[10] Baig, N.; Kammakakam, I.; Falath, W. Nanomaterials: a review of synthesis methods, properties, recent progress, and challenges. Mater. Adv., 2, 1821, 2021. Doi: 10.1039/d0ma00807a.

[11] Bajwa, D.S.; Pourhashem, G.; Ullah, A.H.; Bajwa, S.G. A concise review of current lignin production, applications, products and their environmental impact. Industrial Crops and Products, v.139, 2019. Doi: https:/doi.org/ 10.1016/j.indcrop.2019.111526.

[12] Bao, P.; Kodra, A.; Tomic-Canic, M.; Golinko, M.S.; Ehrlich, H.P.; Brem, H. The Role of Vascular Endothelial Growth Factor in Wound Healing. Journal of Surgical Research, v.153, p.347-358, 2009. https://doi.org/10. 1016/j.jss.2008.04.023.

[13] Bazalinski, D., Przybek-Mita, J., Pytlak, K., Kardy, D., Bazalinski, A., Kucharzewski, M., Wich, P. Larval wound therapy: possibilities and potential limitations-a literature review. Journal of clinical medicine, 12(21), 6862, 2023. Doi: https://doi.org/10.3390/jcm12216862.

[14] Bhattacharya, S. Wound healing through the ages. Indian J Plast Surg., 45(2):177-179, 2012. doi: 10.4103/0970-0358.101255.

[15] Bhoyar, S. D.; Malhotra, K.; Madke, B. Dressing materials: A comprehensive review. J Cutan Aesthet Surg, 16:81-9, 2023. Doi: 10.4103/JCAS.JCAS_163_22.

[16] Bigliardi, P. L.; Alsagoff, S. A. L.; El-Kafrawi, H. Y.; Pyon, J. K.; Wa, C. T. C.; Villa, M. A. Povidone iodine in wound healing: A review of current concepts and practices. International Journal of Surgery, v.44, p.260- 268, 2017. Doi: https://doi.org/10.1016/j.ijsu.2017.06.073.

[17] Bishop, A. Factors influencing dressing choice in wound care: a discussion. British Journal of Nursing, 32(Sup20): S12-S20, 2023. Doi: 10.12968/bjon.2023.32.Sup20.S12.

[18] Boateng, J. S.; Matthews, K.H.; Stevens, H.N.E.; Eccleston, J.M. Wound healing dressings and drug delivery systems: a review. Journal of Pharmaceutical Sciences, v.97, n.8, p. 2892-2923, 2008. Doi: https://doi.org/ 10.1002/jps.21210.

[19] Boateng, J.S.; Hafezi, F.; Tabriz, A.G.; Douroumis, D. 3D printed composite dressings loaded with human epidermal growth factor for potential chronic wound healing applications. Journal of Drug Delivery Science and Technology, v.86, 2023. Doi: https://doi.org/10.1016/j.jddst.2023.104684.

[20] Barroso, L.G.R.; Garcia, E.L.; Mojicevic, M.; Huerta, M.; Pogue, R.; Devine, D.M.; Brennan-Fournet, M. Triangular silver nanoparticles synthesis: investigating potential application in materials and biosensing. Appl. Sci. 13, 8100, 2023. Doi: https://doi.org/10.3390/app13148100.

[21] Borges, I.L.; Silva, W.R.; Silva, M.C.Q.; Barros, P.S.; Souza, F.S.; Nascimento, L.S. Biotecnologia: aplicações da engenharia tecidual na regeneraço de órgãos e tecidos humanos - reviso bibliográfica. Research, Society and Development, V. 12, n. 13, 2023. Doi: http://dx.doi.org/10.33448/rsd-v12i13. 44279.

[22] Borowy, I. Medical waste: the dark side of healthcare. História, Ciências, Saúde Manguinhos, v.27, p.231-251, 2020. Doi: https://doi.org/10.1590/S0104-5970202000030001 2.

[23] Boyko TV, Longaker MT, Yang GP. Review of the Current Management of Pressure Ulcers. Adv Wound Care (New Rochelle), 1;7(2): 57-67, 2018. Doi: 10.1089/wound. 2016.0697.

[24] Bowler, P. G., Duerden, B. I., Armstrong, D. G. Wound microbiology and associated approaches to wound management. Clin Microbiol Rev., 14(2):244-69, 2001. Doi: 10.1128/CMR.

[25] BRITTO, E. J.; NEZWEK, T. A.; ROBINS, M. Wound Dressings. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2024. Disponível em: https://www.ncbi.nlm.nih.gov/books/NBK470199/. Acesso em: 26 de maio de 2025.

[26] Bülbül, E. O.; Okur, M. E.; Okur, N. U. Siafaka, P.I. Traditional and advanced wound dressings: physical characterization and desirable properties for wound healing. In: Sah, M. K.; Kasoju, N.; Mano, J. F. Natural polymers in wound healing and repair. London: Elsevier, p.19-50, 2022. Doi: https:// doi.org/10.1016/B978-0-323-90514-5.00020-1.

[27] Campa-Siqueiros, P.; Madera-Santana, T. J.; Ayala-Zavala, J. F.; López-Cervantes, J.; Castillo-Ortega, M. M.; Herrera-Franco, P. J. Nanofibers of gelatin and polivinyl- alcoholchitosan for wound dressing application: fabrication and characterization. Polímeros, 30(1), e2020006, 2020. Doi: https://doi.org/ 10.1590/0104-1428.07919.

[28] Campos, A. C. L.; Borges-Branco, A.; Groth, A. K. Cicatrização de feridas. ABCD Arquivos Brasileiros de Cirurgia Digestiva, 20(1):51-8, 2007.

[29] Catanzano, O., Quaglia, F., Boateng, J. S. Wound dressings as growth factor delivery platforms for chronic wound healing. Expert Opinion on Drug Delivery, 18(6), 737759, 2021. Doi: https://doi.org/10.1080/174252 47.2021.1867096.

[30] Castilla, D. M., Liu, Z. J., Velazquez, O. C. Oxygen: Implications for Wound Healing. Advances in wound care, 1(6), 225230, 2012. Doi: https://doi.org/10.1089/wound.2011.03 19.

[31] Chaffeea, S.; Dasa, A.; Santra, S.; Roy, S. Diabetic wound inflammation. In: Bagchi, D.; Nair, S. Nutritional and therapeutic interventions for diabetes and metabolic syndrome. London: Academic Press, 2018. p.269-278. Doi: https://doi.org/10.1016/B978-0-12-812019-4.00022-2.

[32] Charles, N.S.; Peter, A.W.; Derek, W.G. Fundamentals of Inflammation. Yale J Biol Med, 84(1):6465, 2011.

[33] Cheon, J. Y.; Kim, S. J.; Rhee, Y. H.; Kwon, O. H.; Park, W. H. Shape-dependent antimicrobial activities of silver nanoparticles. Int J Nanomedicine, 14:2773-2780, 2019. Doi: https://doi.org/10.2147/IJN.S196472.

[34] Chopra, H., Priyanka, Choudhary, O. P., Emran, T. B. Three-dimensional printed wound dressings: recent progresses. International journal of surgery (London, England), 109(3), 549550, 2023. Doi: https://doi.org/10.1097/JS9.0000000000000129.

[35] Chung, H., Dai, T., Sharma, S. K., Huang, Y. Y., Carroll, J. D., Hamblin, M. R. The nuts and bolts of low-level laser (light) therapy. Annals of biomedical engineering, 40(2), 516533, 2012. Doi: https://doi.org/10.1007/s10439- 011-0454-7.

[36] Clinton, A.; Carter, T. Chronic wound biofilms: pathogenesis and potential therapies. Laboratory Medicine, v.46, p.277 284, 2015. Doi: https://doi.org/10.1309/ LMBNSWKUI4JPN7SO.

[37] Colenci, R.; Patricia, L.; Abbade, F. Fundamental aspects of the local approach to cutaneous ulcers. An Bras Dermatol., 93(6):859-70, 2018. Doi: http://dx.doi.org/ 10.1590/abd1806-4841.20187812.

[38] Cutting, K. F.; White, R. Defined and refined: criteria for identifying wound infection revisited. Br J Community Nurs., 9(3): S6-15, 2004. doi: 10.12968/bjcn.2004.9.Sup1.12495.

[39] Daunton, C.; Kothari, S.; Smith, L.; Steele, D. A history of materials and practices for wound management. Wound Practice and Research, v.20, n.4, 2012.

[40] Dehkordi, A. N.; Babaheydari, F. M.; Chehelgerdi, M.; Dehkordi, S. R. Skin tissue engineering: wound healing based on stem-cell-based therapeutic strategies. Stem Cell Research & Therapy, 10, 111, 2019. Doi: https://doi.org/10.1186/s13287-019-1212-2.

[41] Deng, D.; Liang, L.; Su, K.; Gu, H.; Wang, X.; Wang, Y.; Shang, X.; Huang, W.; Chen, H.; Wu, X.; Wong, W.L.; Li, D.; Zhang, K.; Wu, P.; Wu, K. Smart hydrogel dressing for machine learning-enabled visual monitoring and promote diabetic wound healing. Nano Today, v.60, 2025. Doi: https://doi.org/10.1016/ j.nantod.2024.102559.

[42] De Paula, E.S. As origens da medicina: a medicina no Antigo Egito. Revista de História, v.25, n.51, p.13, 1962. Doi: 10.11606/issn.2316-9141.rh.1962.121683.

[43] Dhivya, S.; Padma, V. V.; Santhini, E. Wound dressings - a review. BioMedicine, v.5, n.4, p.24-28, 2015. Doi: 10.7603/s40681-015-0022-9.

[44] Domínguez-Robles, J.; Cuartas-Gómez, E.; Dynes, S.; Utomo, E.; Anjani, Q. K.; Detamornrat, U.; Donnelly, R. F.; Moreno-Castellanos, N.; Larrañeta, E. Poly (caprolac- tone)/lignin-based 3D-printed dressings loaded with a novel combination of bioactive agents for wound-healing applications. Sustainable Materials and Technologies, v.35, 2023. Doi: https:// doi.org/10.1016/j.susmat.2023.e00581.

[45] Downer, M.; Berry, C.E.; Parker, J.B.; Kameni, L.; Griffin, M. Current Biomaterials for Wound Healing. Bioengineering, v.10, n.1378, 2023. Doi: https://doi.org/10.3390/ bioengineering10121378.

[46] Eriksson, E.; Liu, P. Y.; Schultz, G. S.; Martins-Green, M. M.; Tanaka, R.; Weir, D.; Gould, L. J.; Armstrong, D. G.; Gibbons, G. W.; Wolcott, R.Olutoye, O.O.Kirsner, R.S. Gurtner, G. C. Chronic wounds: treatment consensus. Wound Rep. Reg., 30:156171, 2022. Doi: 10.1111/wrr.12994.

[47] Esmaeil, A.; Al-Naseem, A.O.; Lari, A.; Prada, C. Semi-occlusive dressings for the management of fingertip amputations: A systematic review. Journal of Hand and Microsurgery, v.17, n.3, 2025. Doi: https://doi.org/10.1016/j.jham.2025.100241.

[48] Fahimirad, S.; Ajalloueian, F. Naturally- derived electrospun wound dressings for target delivery of bio-active agents, International Journal of Pharmaceutics, v.566, p.307-328, 2019. Doi: https://doi.org/ 10.1016/j.ijpharm.2019.05.053.
. material science andclinical practice. Appl. Sci., 15, 1725, 2025. Doi: https:// doi.org/ 10.3390/app15041725.

[49] Ferreira, L. M. d. M. C.; Cruz, N. F. d.; Lynch, D. G.; Costa, P.F.d.; Salgado, C. G.; Silva- Júnior, J.O.C.; Rossi, A.; Ribeiro-Costa, R.M. Hydrogel containing propolis: physical characterization and evaluation of biological activities for potential use in the treatment of skin lesions. Pharmaceuticals, 17, 1400, 2024. Doi: https://doi.org/10.3390/ph17101400.

[50] Fumi, N.; Marinovi, M.; Brajan, D. Algorithm of nursing procedure in debridement protocol. Acta Med Croatica, v.68 Suppl 1:103-8, 2014.

[51] Franco, D.; Gonçalves, L.F. Feridas cutneas: a escolha do curativo adequado. Rev. Col. Bras. Cir. v.35, n.3, 2008. Doi: 10.1590/ S0100-69912008000300013.

[52] Frykberg, R. G., Banks, J. Challenges in the treatment of chronic wounds. Advances in Wound Care, 4(9), 560582, 2015. Doi: https://doi.org/10.1089/wound.2015.0635

[53] Gajbhiye, S.; Wairkar, S. Collagen-fabricated delivery systems for wound healing: A new roadmap. Biomaterials Advances, v.142, 2022. Doi: https//doi.org/10.1016/j.bioadv. 2022.213152.

[54] Gajula, B.; Munnamgi, S.; Basu, S. How bacterial biofilms affect chronic wound healing: a narrative review. International Journal of Surgery: Global Health, 3(2): p. e16, 2020. Doi: 10.1097/GH9.0000000000 000016.

[55] Gama, G. S. P.; Pimenta, A. S.; Feijó, F. M. C.; Santos, C. S.; Fernandes, B. C. C.; Oliveira, M. F.; Souza, E. C.; Monteiro, T. V. C.; Fasciotti, M.; Azevedo, T. K. B.; et al. Antimicrobial activity and chemical profile of wood vinegar from eucalyptus (Eucalyptus urophylla × Eucalyptus grandis—Clone I144) and bamboo (Bambusa vulgaris). World J. Microbiol. Biotechnol., 39, 186, 2023. Doi: https://doi.org/10.1007/s11274-023-03628-x

[56] Garcia, C. C. S.; Garcia, C. L. C.; Henriques, P. J. A.; Ely, R. M.; Garcia, C. P. M. Adipose tissue-derived stem cell autologous grafts: a new approach to application in the treatment of burn victims and reconstructive plastic surgery. Rev. Bras. Cir. Plást., 31(3):417-423, 2016. Doi: 10.5935/2177-1235.2016RBCP00 68.

[57] Gardner, S. Wound dressings: absorbent dressings. Dermatological Nursing, 15(4): 10-19, 2016.

[58] Gazi, U., Taylan-Ozkan, A., Mumcuoglu, K. Y. The effect of Lucilia sericata larval excretion/ secretion (ES) products on cellular responses in wound healing. Medical and veterinary entomology, 35(3), 257266, 2021. Doi: https://doi.org/10.1111/mve.12497.

[59] Gebarowski, T., Wiatrak, B., Janeczek, M., Zuk, M., Pistor, P., Gasiorowski, K., were our ancestors right in using flax dressings? research on the properties of flax fibre and its usefulness in wound healing. Oxidative medicine and cellular longevity, 2020, 1682317, 2020. Doi: https://doi.org/10.1155/ 2020/1682317.

[60] Ghomi, E.R.; Khalili, S.; Khorasani, S.N.; Neisiany, R.E.; Ramakrishna, S. Wound dressings: Current advances and future directions. J. Appl. Polym. Sci. p.1-12, 2019. Doi: 10.1002/APP.47738.

[61] Goldman, R. Growth factors and chronic wound healing: past, present, and future. Advances in skin & wound care, 17(1), 2435, 2004. Doi: https://doi.org/10.1097/00129 334-200401000-00012

[62] Gonzales, A.C.O.; Costa, T.F.; Andrade, Z.A.; Medrado, A.R.A.P. Wound healing - A literature review. An. Bras. Dermatol. v.91, n.5, 2016. Doi: https://doi.org/10.1590/abd1 806-4841.20164741.

[63] Gou, Y.; Hu, L.; Liao, X.; He, J.; Liu, F. Advance so fantimicrobial dressings loaded with antimicrobial agents in infected wounds. Front. Bioeng. Biotechnol., 12:1431949, 2024. Doi: 10.3389/fbioe.2024.1431949.

[64] Guillen, M. R. S.; Guedes, A. C. M.; Borges, E. L.; Amorim, G. L.; Vieira, P. C.; Barcelos, L. S. The use of occlusive dressings: influence on excisional wound healing in animal model. Acta Bras Cir, v.37, n.12, 2022. Doi: https://doi.org/10.1590/acb371206.

[65] Gupta, S., Mujawdiya, P., Maheshwari, G., Sagar, S. Dynamic role of oxygen in wound healing: a microbial, immunological, and biochemical perspective. Archives of Razi Institute, 77(2), 513-523, 2022. doi: 10.22092/ari.2022.357230.2003.

[66] Haertel, B., von Woedtke, T., Weltmann, K. D., Lindequist, U. Non-thermal atmospheric- pressure plasma: possible application in wound healing. Biomolecules & therapeutics, 22(6), 477-490, 2014. Doi: https://doi.org/10.4062/biomolther.2014.105.

[67] Hamblin M. R. Mechanisms and applications of the anti-inflammatory effects of photobiomodulation. AIMS biophysics, 4(3), 337361, 2017. Doi: https://doi.org/10.3934/ biophy.2017.3.337.

[68] Han, Y., Yang, J., Fang, J., Zhou, Y., Candi, E., Wang, J., Hua, D., Shao, C., Shi, Y. The secretion profile of mesenchymal stem cells and potential applications in treating human diseases. Sig Transduct Target Ther, 7, 92, 2022. Doi: https://doi.org/10.1038/s41392-022-00932-0.

[69] Hartmann, A. Back to the roots dermatology in ancient Egyptian medicine. JDDG: Journal der Deutschen Dermatologischen Gesells chaft, 14: 389-396, 2016. Doi: https://doi. org/10.1111/ddg.12947. He TXiY.Go ZShiYTan Q Y.; Xie, H. Modulation of macrophage function by bioactive wound dressings with an emphasis on extracellular matrix-based scaffolds and nanofibrous composites. Pharmaceutics, 15, 794,

[70] Doi: https://doi.org/10.3390/pharmaceutics15030794.

[71] Helfman, T.; Ovington, L.; Falanga, V. Occlusive dressings and wound healing. Clinics in Dermatology, v.12, v.1, p.121-127, 1994. Doi: https://doi.org/10.1016/0738- 081X(94)90262-3.

[72] Herman, T.F.; Popowicz, P.; Bordoni, B. Wound Classification. StatPearls [Internet], 2023.

[73] Hewish, J. Understanding the role of antimicrobial dressings. Wounds Essentials, v.1, 2012.

[74] Ho, J. K.; Hantash, B. M. 'The principles of wound healing. Expert Review of Dermatology, 8(6), p. 639658, 2013. Doi: 10.1586/17469872.2013.857161.

[75] Hodge, J. G., Zamierowski, D. S., Robinson, J. L., Mellott, A. J. Evaluating polymeric biomaterials to improve next-generation wound dressing design. Biomaterials research, 26(1), 50, 2022. Doi: https:// doi.org/10.1186/s40824-022-00291-5

[76] Hopkins, J. T., McLoda, T. A., Seegmiller, J. G., David Baxter, G. Low-Level Laser Therapy Facilitates Superficial Wound Healing in Humans: A Triple-Blind, Sham-Controlled Study. Journal of Athletic Training, 39(3), 223229, 2004.

[77] Hu, M. S.; Maan, Z. N.; Wu, J. C.; Rennert, R. C.; Hong, W. X.; Lai, T. S.; Cheung, A. T. M.; Walmsley, G. G.; Chung, M. T.; Mcardle, A.; Longaker, M. T.; Lorenz, H. P. Tissue engineering and regenerative repair in wound healing. Ann Biomed Eng. 42(7): 14941507, 2014. Doi:10.1007/s10439-014-1010-z.

[78] Jafari, A., Hosseini, S. V., Hemmat, H. J., Khazraei, H. Lucillia Sericata larval therapy in the treatment of diabetic chronic wounds. Journal of diabetes and metabolic disorders, 21(1), 305312, 2022. Doi: https://doi.org/ 10.1007/s40200-022-00973-w.

[79] Janik-Karpinska, E.; Brancaleoni, R.; Niemcewicz, M.; Wojtas, W.; Foco, M.; Podogrocki, M.; Bijak, M. Healthcare waste: serious problem for global health. Healthcare, 11, 242, 2023. Doi: https://doi.org/10.3390/ healthcare11020242.
JaraC. P; Silva, J. L.G. ZancheaF.C.Rojo, T.; Lima, M. H. M. Biofilme e feridas crônicas: reflexões para o cuidado de enfermagem. Revista Enfermagem Atual, v.81, 2017.

[80] Jiang, L., Loo, S. C. J. Intelligent Nanoparticle-based dressings for bacterial wound infections. ACS Applied Bio Materials, 4(5), 38493862, 2021. Doi: https://doi. org/10.1021/acsabm.0c01168.

[81] Jones, V. J. The use of gauze: will it ever change? Int Wound J., 3(2):79-86, 2006. Doi: 10.1111/j.1742-4801.2006.00215.x.

[82] Jones M. L. An introduction to absorbent dressings. British journal of community nursing, Suppl Wound Care, p.28-S30, 2014. https://doi.org/10.12968/bjcn.2014.19.Sup12.S28.

[83] Junker, J. P., Kamel, R. A., Caterson, E. J., Eriksson, E. Clinical impact upon wound healing and inflammation in moist, wet, and dry environments. Advances in wound care, 2(7), 348356, 2013. Doi: https://doi.org/ 10.1089/wound.2012.0412.

[84] Justiniano, A. Feridas crónicas: fisiopatología y tratamento. Cadernos de Saúde, v. 3 n. Especial (2010), 2010. Doi: https://doi.org/10.34632/cadernosdesaude.2010.3015.

[85] Khalid, A.; Bai, D.; Abraham, A. N.; Jadhav, A.; Linklater, D.; Matusica, A.; Nguyen, D.; Murdoch, B. J.; Zakhartchouk, N.; et al. Electrospun nanodiamond-silk fibroin membranes: a multifunctional platformfor biosensingand wound-healing applications. ACS Appl. Mater. Interfaces, 2020. Doi: https://dx.doi.org/10.1021/acsami.0c15612.

[86] Khushnood, M. Nanomaterials: surface area to volume ratio. Journal of Materials Science and Nanomaterials, v.8, n.5, 2024. Doi: 10.4172/jmsn.1000159.

[87] Kockerling, F.; Köckerling, D.; Lomas, C. Cornelius Celsus: ancient encyclopedist, surgeon-scientist, or master of surgery?. Langenbecks Arch Surg., 24;398(4):609616, 2013. doi: 10.1007/s00423-013-1050-0.

[88] Koka, E., Yeboah-Manu, D., Okyere, D., Adongo, P. B., & Ahorlu, C. K. Cultural Understanding of Wounds, Buruli Ulcers and Their Management at the Obom Sub-district of the Ga South Municipality of the Greater Accra Region of Ghana. PLoS neglected tropical diseases, 10(7), e0004825, 2016. Doi: https://doi.org/10.1371/journal.pntd.0004825.

[89] Koumaki, D.; Kostakis, G.; Boumpoucheropoulos, S.; Ioannou, P.; Katoulis, A.C. A narrative review of management of wounds in palliative care setting. Ann Palliat Med, 12(5):1089-1105, 2023. Doi: https://dx.doi.org/10.21037/apm-23-138.

[90] Krishnan, P. D.; Banas, D.; Durai, R. D.; Kabanov, D. Hosnedlova, B.; Kepinska, M.; Fernandez, C.; Ruttkay-Nedecky, B.; Nguyen, H.V.; Farid, A.; Sochor, J.; Narayanan, V.H.B.; Kizek, R. Silver nanomaterials for wound dressing applications. Pharmaceutics, 12(9), 821, 2010. Doi: https://doi.org/10.3390/pharmaceutics12090821.

[91] Krishani, M.; Shin, W. Y.; Suhaimi, H.; Sambudi, N. S. Development of scaffolds from bio-based natural materials for tissue regeneration applications: A review. Gels, 9, 100, 2023. Doi: https://doi.org/10.3390/gels 9020100.

[92] Lagoa, T.; Queiroga, M.C.; Martins, L. An overview of wound dressing materials. Pharmaceuticals (Basel), 23;17(9):1110, 2024. doi: 10.3390/ph17091110.

[93] Lam, T.; Beraja, G.E.; Lev-Tov, H. Efficacy of larval therapy for wounds: a systematic review and meta-analysis. J. Clin. Med., 14, 315, 2025. Doi: https://doi.org/10.3390/jcm140 20315.

[94] Landén NX, Li D, Sthle M. Transition from inflammation to proliferation: acritical stepduring wound healing. Cell Mol Life Sci. 73(20):3861-85, 2016. Doi: 10.1007/s00018- 016-2268-0.

[95] Laurano, R.; Boffito, M.; Ciardelli, G.; Chiono, V. Wound dressing products: A translational investigation from the bench to the Market. Engineered Regeneration, v.3, n.2, p. 182-200, 2022. Doi: https://doi.org/10.1016/ j.engreg.2022.04.002.

[96] Lazarus, G. S.; Cooper, D. M.; Knighton, D. R.; Percoraro, R.E.; Rodeheaver, G.; Robson, M. C. Definitions and guidelines for assessment of wounds and evaluation of healing. Wound Repair Regen, 2(3):165-70, 1994. doi: 10.1046/j.1524-475X.1994.20305.x.

[97] Leake, C.D. The Old Egyptian Medical Papyri. University Of Kansas Press, Lawrence, Kansas, 1952.

[98] Leaper, D. J. Traumatic and surgical wounds. BMJ., 4; 332(7540): 532-5, 2006. Doi: 10.1136/bmj.332.7540.532.

[99] Leppiniemi, J.; Lahtinen, P.; Paajanen, A.; Mahlberg, R.; Metsa-Kortelainen, S.; Pinomaa, T.; Pajari, H.; Vikholm-Lundin, I.; Pursula, P.; Hytonen, V.P. 3D-Printable bioactivated nanocellulose-alginate hydrogels. ACS Appl. Mater. Interfaces, 9, 2195921970, 2017. Doi: 10.1021/acsami. 7b02756.

[100] Lima, R. V. K.; Coltro, P. S.; Farina Júnior, J. A. Negative pressure therapy for the treatment of complex wounds. Rev. Col. Bras. Cir., 44(1): 081-093, 2017. Doi: 10.1590/ 0100-69912017001001.

[101] Liu, X.; Peng, S.; Pei, Y.; Huo, Y.; Zong, Y.; Ren, J.; Zhao, J. Facile fabrication of chitosan/hyaluronic acid hydrogel-based wound closure material Co-loaded with gold nanoparticles and fibroblast growth factor to improve anti-microbial and healing efficiency in diabetic wound healing and nursing care. Regenerative Therapy, v.26, p. 1018-1029, 2024. Doi: https://doi.org/10.1016/j.reth.2024.10.003.

[102] Locatelli, L. Colciago, A. Castiglioni, S. Maier, J.A. Platelets in wound healing: what happens in space?. Front. Bioeng. Biotechnol. 9: 716184. 2021. Doi: 10.3389/fbioe.2021. 716184.

[103] Lima, R. V. K. S.; Coltro, P. S.; Farina Júnior, J. A. Negative pressure therapy for the treatment of complex wounds. Rev. Col. Bras. Cir., 44 (1), 2017. Doi: https://doi.org/10. 1590/0100-69912017001001.

[104] Luo, H., Li, N., Li, D., Xu, L. Teaching research on using nano silver ion dressing in clinical nursing of surgically infected wounds. Cellular and molecular biology (Noisy-le- Grand, France), 68(3), 270281, 2022. https://doi.org/10.14715/cmb/2022.68.3.30.

[105] Luo, J.; Liu,W.; Xie, Q.;He, J.; Jiang L. Synthesis and characterisation of a novel poly(2 hydroxyethyl methacrylate)-chitosan hydrogels loaded cerium oxide nanocomposites dressing on cutaneous wound healing on nursing care of chronic wound. IET Nanobiotechnol., 17(4):312325, 2023. Doi: https://doi.org/10.1049/nbt2.12 118.
10.Lu, H.; Liu, S.; Zhang, Y.Development of novel green synthesized silver nanoparticles with superior antibacterial and wound healing properties in nursing care after rectal surgery. Journal of Inorganic and Organometallic Polymers and Materials, n.3, p.773-780, 2022. Doi: 10.1007/s10904-022-02223-1.

[106] Madden, M. R., Nolan, E., Finkelstein, J. L., Yurt, R. W., Smeland, J., Goodwin, C. W., Hefton, J., Staiano-Coico, L. Comparison of an occlusive and a semi-occlusive dressing and the effect of the wound exudate upon keratinocyte proliferation. The Journal of Trauma, 29(7), 924931, 1989. Doi: https://doi.org/10.1097/00005373-198907000-000 04.

[107] Majno, G. The healing hand: man and wound in the ancient world. Med Hist., 20(4):461., 1976.

[108] Marti, L. C.; Ribeiro, A. A. F.; Hamerschlak, N. Immunomodulatory effect of mesenchymal stem cells O efeito imunomodulatório de células-tronco mesenquimais. Einstein, 9(2 Pt 1):224-8, 2011.

[109] Mathew-Steiner, S.S.; Roy, S.; Sem, C.K. Collagen in wound healing. Bioengineering (Basel). 11; 8(5): 63, 2021. Doi: 10.3390/bioengineering8050063.

[110] Martínez, D. D; Méndez, V. A.; Islas, R. J.; Sánchez-Carranza, J.N. Studies of applications of cold plasma systems in cancer treatment: mechanisms of oxidant stress and pathway signaling. Stresses, 4, 896915, 2024. Doi: https://doi.org/10.3390/stresses 4040060.

[111] Matsumura, H., Imai, R., Ahmatjan, N., Ida, Y., Gondo, M., Shibata, D., Wanatabe, K. Removal of adhesive wound dressing and its effects on the stratum corneum of the skin: comparison of eight different adhesive wound dressings. International wound journal, 11(1), 5054, 2014. Doi: https://doi.org/10.1111/ j.1742-481X.2012.01061.x.

[112] Maxson, S., Lopez, E. A., Yoo, D., Danilkovitch-Miagkova, A., Leroux, M. A. Concise review: role of mesenchymal stem cells in wound repair. Stem cells translational medicine, 1(2), 142149, 2012. Doi: https://doi.org/10.5966/sctm.2011-0018.

[113] Mayer, D. O.; Tettelbach, W. H.; Ciprandi, G.; Downie, F.; Hampton, J.; Hodgson, H.; Lázaro-Martínez, J. L.; Probst, S.; Schultz, G. S.; Serra, E.; Kirsner, R. S.; Parnham, A.; Frescos, N.; Stang, D.; Holloway, S.; Percival, S. L. Best practice for wound debridement. Journal of Wound Care, v. 33, n.Sup6b, 2024. Doi: https://doi.org/10.12968/jowc.2024.33.Sup6b.S1.

[114] Mertens, D. M., Jenkins, M. E., Warden, G. D. Outpatient burn management. Nurs Clin North Am., 32(2):343-64, 1997.

[115] Misra, P., Kalsi, R., Anand Arora, S., Singh, K. S., Athar, S., Saini, A. Effect of low-level laser therapy on early wound healing and levels of inflammatory mediators in gingival crevicular fluid following open flap debridement. Cureus, 15(2), e34755, 2023. Doi: https://doi.org/10.7759/cureus.34755.

[116] Moradifar, F.; Sepahdoost, N.; Tavakoli, P.; Mirzapoor, A. Multi-functional dressings for recovery and screenable treatment of wounds: A review. Heliyon, v.11, n.1, 2015. Doi: https://doi.org/10.1016/j.heliyon.2024.e41465.

[117] Morin, R. J.; Tomaselli, N. L. Interactive dressings and topical agents. Clin Plast Surg, 34:643, 2007. Doi: 10.1016/j.cps.2007.07.004.

[118] Mostafalu, P.; Tamayol, A.; Rahimi, R.; Ochoa, M.; Khalilpour, A.; Kiaee, G.; Yazdi, I. K.; Bagherifard, S.; Dokmeci, M. R.; Ziaie, B.; Sonkusale, S. R.; Khademhosseini, A. Smart Bandage for Monitoring and Treatment of Chronic Wounds. Small, p.1-9, 2018. Doi: 10.1002/smll.201703509.
Mullin,J.A.Rah E.KiickK.L. Sullivan, M. O. Growth factors and growth factor gene therapies or eating cronic wounds. Beng Transl Med., 9:e10642, 2024. Doi: https://doi.org/10.1002/btm2.1064.

[119] Nagarsheth, K.; Kankaria, A.; Marsella, J.; Dunlap, E.; Hawkins, S.; Ucuzian, A.; Lal, B.K. Systematic review of the effects of topical oxygen therapy on wound healing. JVS- Vascular Insights, v.2, n.100051, 2024. Doi: https://doi.org/10.1016/j.jvsvi.2023.100051.

[120] Nagle, S. M.; Stevens, K. A.; Wilbraham, S. C. Wound Assessment. StatPearls, 2023. Disponível em: https://www.ncbi.nlm.nih.gov/books/NBK482198/.

[121] Namgoong, S., Baik, S., Han, S. K., Son, J. W., Kim, J. Y. Developing and establishing a wound dressing team: experience and recommendations. Journal of Korean Medical Science, 38(21), e168, 2023. Doi: https://doi.org/10.3346/jkms.2023.38.e168.

[122] Nguyen, H. M.; Le, T. T. N.; Nguyen, A. T.; Le, H.N.T.; Pham, T.T. Biomedical materials for wound dressing: recent advances and applications. RSC Adv., v.13, p.55095528, 2023. Doi: 10.1039/d2ra07673j.

[123] Nigam, Y. The principles of maggot therapy and its role in contemporary wound care. Nursing Timaa Tonlinal 117. 0, 20 44 2021

[124] Nezakati, E.; Hasani, M. H.; Zolfaghari, P.; Rashidan, M.; Sohrabi, M.B. Effects of Lucilia sericata maggot therapy in chronic wound treatment: a randomized clinical trial. Chronic Wound Care Management and Research. 7:11-17, 2020. Doi: https://doi.org/10.2147/CWCMR.S248149.

[125] Nie, L, Wei, Q., Li, J., Deng, Y., He, X., Gao, X., Ma, X., Liu, S., Sun, Y., Jiang, G., Okoro, O. V., Shavandi, A., Jing, S. Fabrication and desired properties of conductive hydrogel dressings for wound healing. RSC advances, 13(13), 85028522, 2023. Doi: https://doi.org/10.1039/d2ra07195a.

[126] Normandin, S., Safran, T., Winocour, S., Chu, C. K., Vorstenbosch, J., Murphy, A. M., Davison, P. G. Negative pressure wound therapy: mechanism of action and clinical applications. Seminars in plastic surgery, 35(3), 164170, 2021. Doi: https://doi.org/10.1055/s-0041-1731792.
Nu.kn with commonly available dressings. Advances in wound care, 10(12), 685698, 2021. Doi: https://doi.org/10.1089/wound.2020.1232,

[127] Nussbaum, S. R.; Carter, M. J.; Fife, C. E.; DaVanzo, J.; Haught, R.; Nusgart, M.; Cartwright, D. An economic evaluation of the impact, cost, and medicare policy implications of chronic nonhealing wounds. Value Inhealth, v.21, p.2732, 2018. Doi: http://dx.doi.org/10.1016/j.jval.2017.07.007

[128] Oliveira, M. S. L.; Komutsu, C. A.; Ching, A. W.; Faiwichou, L. Tratamento de feridas complexas com uso de pressão negativa local método a vácuo. Rev. Bras. Cir. Plást. 25(supl): 1-102, 2010.

[129] Olson, J. L., Atala, A., Yoo, J. J. Tissue engineering: current strategies and future directions. Chonnam Medical Journal, 47(1), 113, 2011. https://doi.org/10.4068/cmj.20 11.47.1.1.

[130] Otsuka, A. C. V. G.; Moreira, C. L. V.; Pasquarelli, E. W.; Pavani, K. C. P.; Anjos, P. P. dos; Hashimoto, S. Y.; Lima, M. C. de A. e; Duprat Neto, J. P. Low-level laser therapy in the management of skin wound healing. Rev. Bras. Cir. Plást., 37(4):451-456, 2022. Doi: 10.5935/2177-1235.2022RBCP.640-en.

[131] Ovington, L.G. Advances in wound dressings. Clinics in Dermatology, v.25, n.1, p. 33-38, 2007. Doi: https://doi.org/10.1016/j.clindermatol.2006.09.003.

[132] Panasci, K. Burns, and wounds. In: Paz, J. C.; West, M.P. Acute care handbook for physical therapists. London: W.B. Saunders, p.283 -311, 2014. Doi: https://doi.org/10.1016/B9 78-1-4557-2896-1.00012-3.

[133] Park, J. W., Hwang, S. R., Yoon, I. S. Advanced growth factor delivery systems in wound management and skin regeneration. Molecules (Basel, Switzerland), 22(8), 1259, 2017. Doi: https://doi.org/10.3390/molecu les22081259.
gv easy-to-use, cost-effective wound dressing material by coating commercial cotton bandages with nanomaterials. International Journal of Materials Research, v.114, n.4-5, p. 243-250, 2023. Doi: https://doi.org/10.1515/ ijmr-2022-0081.

[134] Partovi, A., Khedrinia, M., Arjmand, S., Siadat, S.O.R. Electrospun nanofibrous wound dressings with enhanced efficiency through carbon quantum dots and citrate incorporation. Sci Rep, 14, 19256, 2024. Doi: https://doi.org/10.1038/s41598-024-70295-

[135] Parvez MA, Yashiro K, Nagahama Y, Tsunoi Y, Saitoh D, Sato S, Nishidate I. In vivo visualization of burn depth in skin tissue of rats using hemoglobin parameters estimated by diffuse reflectance spectral imaging. J Biomed Opt., 29(2):026003, 2024. doi: 10.1117/1.JBO.29.2.026003.

[136] Peng, H.; Dong, D.; Feng, S.; Guo, Y.; Yu, J.; Gan, C.; Hu, X.; Qin, Z.; Liu, Y.; Gao, Y. Metal-based antimicrobial agents in wound Dressings: Infection management and the challenge of antibiotic resistance. Chemical Engineering Journal, v.507, 2025. Doi: https://doi.org/10.1016/j.cej.2025.160726.

[137] Percival, L.S.; Slone, W.; Linton, S.; Okel, T.; Corum, L.; Thomas, J.G. The antimicrobial efficacy of a silver alginate dressing against a broad spectrum of clinically relevant wound isolates. Int Wound J., 7;8(3):237243, 2011. doi: 10.1111/j.1742-481X.2011.00774.x.

[138] Pertile, R.A. A História das técnicas médicas a partir das ilustraçes em papiros do Egito Antigo. Khronos, Revista de História da Ciência, n.10, 2020.

[139] Queen, D.; Orsted, H.; Sanada, H.; Sussman, G. A dressing history. International Wound Journal, v.1, p.1-84, 2004. Doi: https://doi.org/10.11/j.1742-4801.2004.0009.x.

[140] Raffetto, J.D. The definition of the venous ulcer. Journal of Vascular Surgery, v.52, p. 46S-49S, 2010.

[141] Rehman, A., Nigam, A., Laino, L., Russo, D., Todisco, C., Esposito, G., Svolacchia, F. Giuzio, F., Desiderio, V., Ferraro, G. Mesenchymal stem cells in soft tissue regenerative medicine: a comprehensive review. Medicina (Kaunas, Lithuania), 59(8), 1449, 2023. Doi: https://doi.org/10.3390/ medicina59081449.

[142] Rice Júnior, P. L.; Orgill, P. Assessment and classification of burn injury. 2025. Disponível em: https://www.uptodate.com/contents/as sessment-and-classification-of-burn-injury/print.

[143] Riedl, J.; Popp, C.; Eide, C.; Ebens, C.; Tolar, J. Mesenchymal stromal cells in wound healing applications: role of the secretome, targeted delivery and impact on recessive dystrophic epidermolysis bullosa treatment. Cytotherapy, 23(11):961-973, 2021. doi: 10.1016/j.jcyt.2021.06.004.
.Rippon, M. White, R. Davies, P. Skin adheives and their role in wound dressings. Wounds UK, v.3, n.4, 2007.

[144] Robles-Tenorio, A.; Ocampo-Candiani, J. Venous Leg Ulcer. Stat Pearls [Internet], 2022. Disponível em: https://www.ncbi.nlm.nih.gov/books/NBK567802/.

[145] Rossi, P. F.; Santos, F. V.; Alves, A. L. M. M.; Semensato, L. H.; Oliveira, L. F. R.; Santos, D. M.; Bianchi, T. P.; Inada, N. M.; Campana- Filho, S. P.; Oréfice, R. L.; Correa, D. S. 3D-Printed methacrylated gelatinlignin carbon dot hydrogel combined with PLA nanofibers for wound dressings. ACS Applied Nano Materials, v. 7, n. 20, p.2351923531, 2024. Doi: 10.1021/acsanm.4c03615.

[146] Ruan, Q., Yuan, L., Gao, S., Ji, X., Shao, W., Ma, J., Jiang, D. Development of *Z*nO/ selenium nanoparticles embedded chitosan- based anti-bacterial wounddressing or potenial heling ability and nursing care after paediatric fracture surgery. International wound journal, 20(6), 18191831, 2023. Doi: https://doi.org/10.1111/iwj.13947.

[147] Saini, R., Saini, S., Sharma, S. Nanotechnology: the future medicine. Journal of cutaneous and aesthetic surgery, 3(1), 3233, 2010. Doi: https://doi.org/10.4103/ 0974-2077.63301

[148] Santos, C. S. A. Wound care and management: a review. Journal of Medical and Health Studies, 3(3):01-06, 2022. Doi: 10.32996/jmhs.2022.3.3.7.

[149] Sayed, F. A., Eissa, N. G., Shen, Y., Hunstad, D. A., Wooley, K. L., Elsabahy, M. Morphologic design of nanostructures for enhanced antimicrobial activity. Journal of nanobiotechnology, 20(1), 536, 2022. Doi: https://doi.org/10.1186/s12951-022-01733-x.

[150] Sen, C. K. Human wounds and its burden: an updated compendium of estimates. Advances In Wound Care, v.8, n.2, 2019. Doi: 10.1089/wound.2019.0946.

[151] Shah, J. B. The history of wound care. J Am Col Certif Wound Spec, 3(3):65-6, 2011. doi: 10.1016/j.jcws.2012.04.002.

[152] Sierra-Snchez, Á.; Kim, K. H.; Blasco- Morente, G.; Arias-Santiago, S. Cellular human tissue-engineered skin substitutes investigated for deep and complex to heal injuries. npj Regen Med, v.6, n.35, 2021. Doi: https://doi.org/10.1038/s41536-021-00144-0

[153] Silva, P. N.; Almeida, O. A. E.; Rocha, I. C. Terapia tópica no tratamento de feridas crônicas. Enfermería Global, n.° 33, 2014.
..e S.; Rahaman, J.; Mukherjee, D. The role of biomaterials-based scaffolds in advancing skin tissue constructs. Journal of Tissue Viability, 34(2), 100858, 2025. Doi: https://doi.org/10.1016/j.jtv.2025.100858.

[154] Sinha, S. N.; Free, B.; Ladlow, O. The art and science of selecting appropriate dressings for acute open wounds in general practice. AJGP, v. 51, n.11, 2022. Doi: 10.31128/AJGP-06- 22-6462.

[155] Singh, S.; Young, A.; McNaught, C.E. The physiology of wound healing. Surgery (Oxford), v.35, n.9, p.473-477, 2017. Doi: https://doi.org/10.1016/j.mpsur.2017.06.004

[156] Sipos, P.; Gyory, H.; Hagymasi, K.; Ondrejka, P.; Blazovics, A. Special wound healing methods used in Ancient Egypt and the mythological background. World J. Surg., 28, 211-216, 2004 Doi: 10.1007/s00268-003- 7073-x.

[157] Shi, C., Wang C, Liu H, Li Q, Li R, Zhang Y, Liu Y, Shao Y, and Wang J. Selection of Appropriate Wound Dressing for Various Wounds. Front. Bioeng. Biotechnol. 8:182, 2020. Doi: 10.3389/fbioe.2020.00182.

[158] Smet, G. H. J., Kroese, L. F., Menon, A. G., Jeekel, J., van Pelt, A. W. J., Kleinrensink, G. J., Lange, J. F. Oxygen therapies and their effects on wound healing. Wound repair and regeneration, 25(4), 591608, 2017. Doi: https://doi.org/10.1111/wrr.12561.

[159] Sood, A., Granick, M. S., & Tomaselli, N. L. Wound dressings and comparative effectiveness data. Advances in wound care, 3(8), 511529, 2014. https://doi.org/10.1089/ wound.2012.0401.

[160] Souza, A.G.; Kanoa, F.S.; Bonventa, J.J.; Rosa, D.S. Cellulose nanostructures obtained from waste paper industry: a comparison of acid and mechanical isolation methods. Materials Research, 20 (Suppl. 2): 209-214, 2017. Doi: http://dx.doi.org/10.1590/1980-5373-MR-2016-0863.

[161] Spiegel, C.; Coraça-Huber, D.C.; Nogler, M.; Arora, R.; Putzer, D. Cold plasma activity against biofilm formation of prosthetic joint infection pathogens. Pathogens, 14 (10), 2025. Doi: https://doi.org/10.3390/pathogens1401 0010.

[162] Soriano, J. L.; Ríos, M.; López, E.; Garrido, M.T.; Clares, B.; Gálvez, P. Tissue engineering in wound healing. In: Santana, M.H.; Souto, E.B.; Shegokar, R. Nanotechnology and Regenerative Medicine. Cambridge: Academic Press, p.411-453, 2023. Doi: https://doi.org/10.1016/B978-0-323-90471-1.00017-7.

[163] Sun, X.; Liu, Z.; Welsher, K.; Robinson, J.T.; Goodwin, A.; Zaric, S.; Dai, H. Nano-graphene oxide for cellular imaging and drug delivery. Materials Science, 2008. Doi: https://doi.org/10.48550/arXiv.0808.3396.

[164] Tan, S. T.; Winarto, N.; Dosan, R.; Bennya, P. The Beneits of occlusive dressings in wound healing. The Open Dermatology Journal, v.13, p.27-33, 2019. Doi: 10.2174/18743722019130 10027.

[165] Teall, E.K. Medicine and doctoring in ancient Mesopotamia. Grand Valley Journal of History, v.3, 2014.
Thaarup, I.C.; Ivers A.K.S. Lichteber, M.; Bjarnsholt, T.; Jakobsen, T.H. Biofilm survival taaiaa in alrania dM: 10 775, 2022. Doi: https:// doi.org/10.3390/microorganisms 10040775.

[166] Thomas DC, Tsu CL, Nain RA, Arsat N, Fun SS, Sahid Nik Lah NA. The role of debridement in wound bed preparation in chronic wounds: A narrative review. Ann Med Surg (Lond). 4;71:102876, 2021. Doi: 10.1016/j.amsu.2021.102876.

[167] Tobiano, G.; Walker, R. M.; Chaboyer, W.; Carlini, J.; Webber, L.; Latimer, S.; Kang, E.; Eskes, A. M.; O'Connor, T.; Perger, D.; Gillespie, B. M. Patient experiences of, and preferences for, surgical wound care education. IWJ Wiley, 2022. Doi: 10.1111/iwj.14030.

[168] Tom, I., Ibrahim, M., Umoru, A., Umar, J., Bukar, M., Haruna, A., and Aliyu, A. Infection of wounds by potential bacterial pathogens and their resistogram. Open Access Library Journal, 6, 1-13, 2019. Doi: 10.4236/oalib.110 5528.

[169] Tottoli, E. M., Dorati, R., Genta, I., Chiesa, E., Pisani, S., & Conti, B. Skin wound healing process and new emerging technologies for skin wound care and regeneration. Pharmaceutics, 12(8), 735, 2020. Doi: https://doi.org/10.3390/pharmaceutics12080735.

[170] Tracy, R.P. The five cardinal signs of inflammation: calor, dolor, rubor, tumor ...and penuria (apologies to Aulus Cornelius Celsus, De medicina, c. A.D. 25). J Gerontol A Biol Sci Med Sci., 61(10):1051-2, 2006. doi: 10.1093/gerona/61.10.1051.

[171] Tran, H. Q., Shahriar, S. M. S., Yan, Z., Xie, J. Recent Advances in Functional Wound Dressings. Advances in wound care, 12(7), 399427, 2023. Doi: https://doi.org/10.10 89/ wound.2022.0059.

[172] Truskewycz, A.; Truong, V.; Ball, A.S.; Houshyar, S.; Nassar, N.; Yin, H.; Murdoch, B.J. Fluorescent magnesium hydroxide nanosheet bandages with tailored properties for biocompatible antimicrobial wound dressings and pH monitoring. ACS Appl. Mater. Interfaces, 13,2790427919, 2021. Doi: https://doi.org/10.1021/acsami.1c0590 8.

[173] Vaidyanathan L. Growth Factors in Wound Healing A Review. Biomed Pharmacol J, 4(3), 2021. Doi: https://dx.doi.org/10.13005/bpj/2249.

[174] Vowden, K.; Vowden, P.; Wound dressings: principles and practice. Surgery, v.35, n.9, p.489-494, 2017. Doi: http://dx.doi.org/10.1016/ i.mpsur.2017.06.005.

[175] Wang, Y.; Tang, S.; Jiang, L.; Yuan, Z.; Zhang, Y. A review of lignin application in hydrogel dressing. International Journal of Biological Macromolecules, v.281, Part 3, 2024. Doi: https://doi.org/10.1016/jijbiomac.2024.135786.

[176] Waring, M.; Rippon, M.; Bielfeldt, S.; Brandt, M. Cell attachment to adhesive dressings: qualitative and quantitative analysis. Wounds UK, v.4, n.3,

[177] Weller, C. D.; Team, V.; Sussman, G. First-line interactive wound dressing update: a comprehensive review of the evidence. Front. Pharmacol., 11:155, 2020. Doi:
10.3389/fphar.2020.00155.

[178] Wilkins, R. G.; Unverdorben, M. Wound cleaning and wound healing: a concise review. Adv Skin Wound Care. 26(4):160-3, 2013. Doi:
10.1097/01.ASW.0000428861.26671.41.

[179] Winter, G. D. Formation of the scab and the rate of epithelialization of superficial wounds in the skin of the young domestic pig. Nature, 193(4812),
293-294, 1962. Doi: https:// doi.org/10.1038/193293a0.

[180] Wolcott, R.; Fletcher, J. The role of wound cleansing in the management of wounds. Wounds Middle East Journal, v.1(1): 3338, 2014.

[181] Wu, L.; Wen, B.; Xu, Z.; Lin, K. Research progress on negative pressure wound therapy with instillation in the treatment of orthopaedic wounds. Int Wound J. 19(6): 1449-1455, 2022. doi: 10.1111/iwj.13741.

[182] Yamakawa, S., Hayashida, K. Advances in surgical applications of growth factors for wound healing. Burn Trauma 7, 10, 2019. Doi: https://doi.org/10.1186/s41038-019-0148-1.

[183] Yang, T.S.; Nguyen, L.T.H.; Hsiao, Y.C.; Pan, L.C.; Chang, C.J. Biophotonic effects of low-level laser therapy at different wavelengths for potential wound healing. Photonics 9, 591, 2022. Doi: https://doi.org/ 10.3390/photonics9080591.

[184] Yang, M., Wang, H., Li, K., Chen, Z., Seamirumi, D. T. A new soft tissue constructed with chitosan for wound dressings, incorporating nanoparticles for medical and nursing therapeutic efficacy. Regenerative therapy, 24, 103111, 2023. Doi: https://doi.org/10.1016/j.reth.2023.06.005.

[185] Yayehrad, A. T.; Siraj, E. A.; Matsabisa, M.; Birhanu, G. 3D printed drug-loaded nanomaterials for wound healing applications. Regenerative Therapy, v.24, p.361-376, 2023. Dois: https://doi.org/10.1016/j.reth.2023.08.007.

[186] Yip W. L. Influence of oxygen on wound healing. International wound journal, 12(6), 620624, 2015. Doi: https://doi.org/10.1111/iwj.12324.

[187] Yokel, R. A.; MacPhail, R. C. Engineered nanomaterials: exposures, hazards, and risk prevention-Journal of Occupational Medicine and Toxicology, 6:7, 2011.

[188] Yousefian, F.; Hesari, R.; Jensen, T.; Obagi, S.; Rgeai, A.; Damiani, G.; Bunick, C.G.; Grada, A. Antimicrobial wound dressings: a concise review for clinicians. Antibiotics, v.12, n.1434, 2023. Doi: https://doi.org/10.33 90/antibiotics12091434.

[189] Zaidi, S. R. H.; Sharma, S. Pressure Ulcer. National Library of Medicine, 2024. Disponível em: https://www.ncbi.nlm.nih.gov/books/NBK553107/.

[190] Zhang, Y. H.; Li, T.; Zhao, C. Y.; Li, J. Q.; Huang, R.; Zhang, Q. R.; Li, Y. Q.; Li, X. Y. An integrated smart sensor dressing for real-time wound microenvironment monitoring and promoting angiogenesis and wound healing. Front. Cell Dev. Biol., 9:701525, 2021. Doi: 10.3389/fcell.2021.701525.

[191] Zhang, Z.; Yang, S.; Su, H.; Qian, K. Porous noble metal-based nanomaterials in biomedical applications. Adv. Nano Biomed Res., 4, 2300078, 2024. Doi: 10.1002/anbr. 202300078.

[192] Zhang, X.; Wang, Y.; Gao, Z.; Mao, X.; Cheng, J.; Huang, L.; Tang, J. Advances in wound dressing based on electrospinning nanofibers. J Appl Polym Sci., 141:e54746, 2024. Doi: https://doi.org/10.1002/app. 54746.

[193] Zhang, W.; Hu, J.; Wu, H.; Lin, X.; Cai, L. Stimuli-responsive hydrogel dressing for wound healing. APL Mater., v.13, n.010601, 2025. Doi: 10.1063/5.0245545.

[194] Zhao, Y.; Sun, Q. Silver nanoparticles incorporated chitosan hydrogel as a potential dressing material for diabetic wound healing in nursing care. Ind. J. Pharm. Edu. Res., 58(1):139-144, 2024. Doi: 10.5530/ijper.58. 1.14.

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Pharmacotherapy of Heart Failure in Infants with Congenital Heart Disease

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ABSTRACT

Every second patient who dies from congenital heart disease is an infant with heart failure. However, infants were de facto excluded from the US Carvedilol trial and PANORAMA HF trial (Sacubitril/Valsartan), probably due to their high mortality risk. Despite the negative results of the US Enalapril trial in infants with univentricular hearts, ACE inhibitors are further recommended in the guidelines. Propranolol is the only drug that has been successful in two prospective randomized trials but was not recommended in the guidelines. This review discusses the dif erences between myocardial heart failure and congestive circulatory failure in infants with congenital heart disease that do not benefit from vasodilators but from beta-blockers that significantly improve clinical symptoms, neurohormonal activation and heart rate variability. The case of a non-invasive monitoring of heart rate variability, blood pressure and oxygen saturation of an infant with Down syndrome and complete atrioventricular septal defect visualize cardiac decompensation after enalapril and the benefits of beta-blocker treatment.

Index Terms: congenital heart disease • heart failure • pharmacotherapy • heart rate variability • beta blocker • ace inhibitor

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REVIEW

Pharmacotherapy of Heart Failure in Infants with Congenital Heart Disease

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Abstract

Every second patient who dies from congenital heart disease is an infant with heart failure. However, infants were de facto excluded from the US Carvedilol trial and PANORAMA HF trial (Sacubitril/Valsartan), probably due to their high mortality risk. Despite the negative results of the US Enalapril trial in infants with univentricular hearts, ACE inhibitors are further recommended in the guidelines. Propranolol is the only drug that has been successful in two prospective randomized trials but was not recommended in the guidelines. This review discusses the dif erences between myocardial heart failure and congestive circulatory failure in infants with congenital heart disease that do not benefit from vasodilators but from beta-blockers that significantly improve clinical symptoms, neurohormonal activation and heart rate variability. The case of a non-invasive monitoring of heart rate variability, blood pressure and oxygen saturation of an infant with Down syndrome and complete atrioventricular septal defect visualize cardiac decompensation after enalapril and the benefits of beta-blocker treatment.

Keywords: *congenital heart disease, heart failure, pharmacotherapy, heart rate variability, beta blocker, ace inhibitor*

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1 THE HISTORY OF HEART FAILURE IN INFANTS WITH CONGENITAL HEART DISEASE

Heart failure in infants with congenital heart disease — the most common birth defect — is closely related to prognosis. Every second patient who died from congenital heart disease is an infant[1]. Retrospective data from Germany[2, 3] show the improvement in the prognosis of patients with congenital heart disease due to successful heart surgery. However, heart failure in infancy remains the most frequent cause of death (Table 1), as currently confirmed by Swedish register data[4]. Despite approximately 4000 additional percutaneous interventions yearly in Germany, the mortality from congenital heart defects has actually been rising again since 2010[5]. The hypothesis of a link of this rising mortality and an irrational heart failure therapy in infants with congenital heart defects will be explained.

Table 1. Retrospective Single Center Data of Children with Congenital Heart Disease from Germany[2, 3]

	1931–1963 (N=275)	1963–1966 (N=163)	2005 (N=1755)
Mortality	44% (121)	31% (108)	6.3% (111)
Death from Heart Failure	82% (99)	66% (71)	74% (82)
Death in Infancy	92% (111)	88% (143)	67% (74)

2 THE PATHOPHYSIOLOGY OF HEART FAILURE IN INFANTS WITH CONGENITAL HEART DISEASE

Pharmacotherapy of heart failure depends on evolving pathophysiological models, which are predominantly developed on left ventricular dysfunction in adults. The neurohormonal hypothesis of Milton Packer[6] led to an improvement in the prognosis of adults with reduced ejection fraction (HFrEF), as shown in a lot of prospective, randomized trials.

More than 65 years ago, Katz, Feinberg and Shaffer[7] were the first who make a distinction of heart failure either as “myocardial failure” (today HFrEF) or “congestive circulatory failure” as inadequate output associated with volumetric overloading of the systemic or the pulmonary circuits — the predominant cause of heart failure in infants with congenital heart defects.

Unfortunately, the current guidelines for pediatric heart failure[8] as well as the few prospective randomized trials in children with congenital heart disease[9, 10] do not make a clear distinction between “myocardial failure” and “congestive circulatory failure”. Moreover, these trials de facto exclude infants with heart failure due to congenital heart defects. This exclusion of the most vulnerable group of infants with congenital heart disease probably depends on the high mortality in the enalapril trial of infants with univentricular hearts[11].

The most critical point is the use of vasodilators — designed for adult myocardial failure — in infants with “congestive circulatory failure”. In a review of 350 cases of infants with heart failure due to congenital heart disease, Elton Goldblatt wrote in 1962[12]: “…there is peripheral vasodilatation which normally results in increased cardiac output and venous return. The failing heart cannot adapt to these extra demands; thus, the clinical condition is made worse.” Genetic data now

clearly confirm the advantage of blood pressure increasing alleles on outcome in children with congenital heart disease[13]. It must be feared that the misuse of vasodilators as well as ACE inhibitors[14] in infants with heart failure due to congenital heart disease is one of the reasons for the persistently high mortality rate.

Before introducing beta-blocker treatment in infants with severe heart failure due to congenital heart disease in 1996, we carried out extensive measurements of invasive hemodynamics, ventricular function, neurohormonal activation and early life stress. Early life stress was measured by norepinephrine plasma levels and heart rate variability as shown in Figure 1[15]. Arterial hypotension is the most significant hemodynamic cause of tachypnea and neurohormonal activation in these infants. In addition, 24-hours mean heart rate (and heart rate variability) is the most important predictor of tachypnea in infants with heart failure. Recent data now confirm that heart rate variability is an important predictor of prognosis in children with congenital heart disease[16].

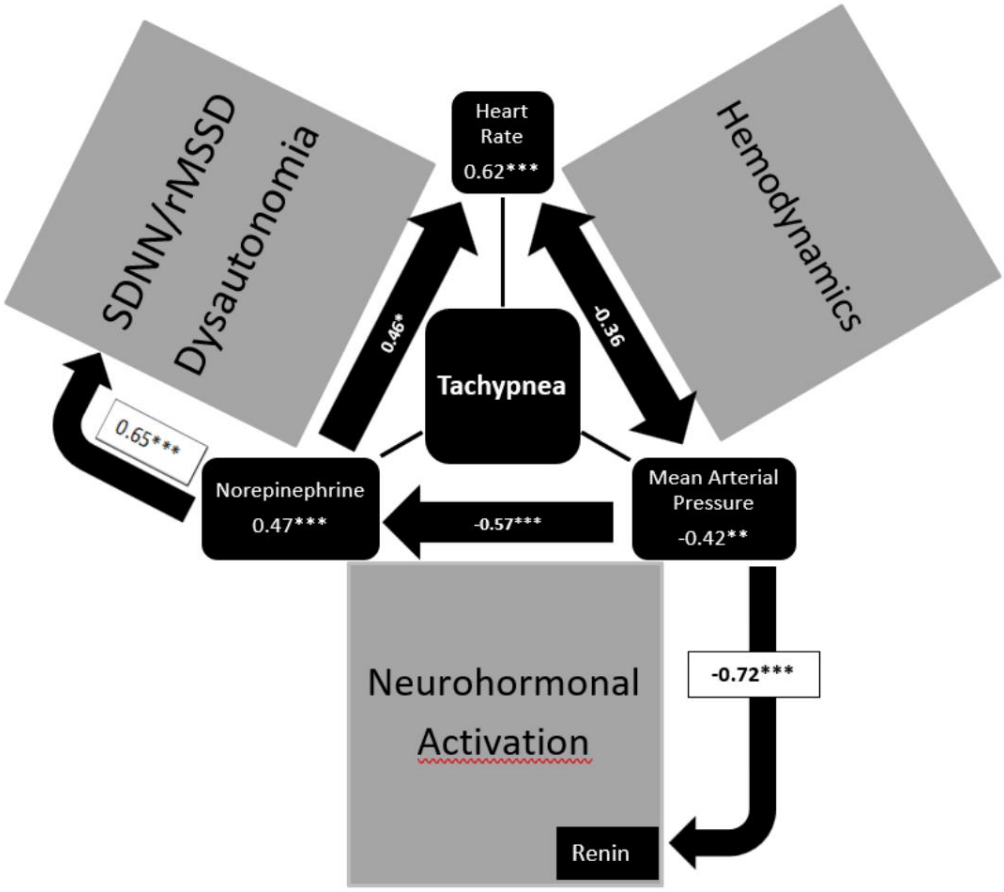

Figure 1. The Impact of Dysautonomia, Hemodynamics and Neurohormonal Activation on Clinical Heart Failure Indicated by the Parameter Tachypnea.

Tachypnea is significantly related to heart rate ($r = 0.62^{***}$), norepinephrine plasma levels ($r = 0.47^{***}$) and mean arterial pressure ($r = -0.42^{**}$). The mean arterial pressure has a highly significant impact on plasma renin activity ($r = -0.72^{***}$) and norepinephrine levels ($r = -0.57^{***}$). Dysautonomia measured as 24-hour heart rate variability (SDNN/rMSSD) is related to plasma norepinephrine levels ($r = 0.65^{***}$).

3 PHARMACOTHERAPY OF HEART FAILURE IN INFANTS WITH CONGENITAL HEART DISEASE

The following therapy of heart failure in infants with congenital heart disease was introduced in the 1950s[12]: Digoxin, Sedation, and Diuretics. Today, enalapril seems to be the only "new" innovation as recommended in the current guideline from 2025 (Table 2). However, a prospective randomized trial showed significantly poorer head growth in infants with heart failure treated with enalapril compared to placebo[11] but no improvement of clinical symptoms, weight gain, and prognosis.

The beta-blocker propranolol is the only pharmacotherapy that improves clinical symptoms in two prospective randomized trials[17, 18] in infants with heart failure due to congenital heart disease but was not mentioned in the current guideline[8]. The CHF-Pro-Infant trial clearly shows a significant clinical improvement measured by the Ross Score, lower plasma renin activities and a significant improvement of heart rate variability (Figure 2)[17]. However, Beta-blockers are traditionally considered contraindicated in pediatric cardiology based on the cardiocirculatory, hemodynamic heart failure model. Unfortunately, this view has not clearly changed even after the convincing prospective beta-blocker trials in adults with heart failure.

With respect to these data (Figure 2), pediatric cardiologists are standing at a therapeutic crossroad either to follow the guideline recommendations with Diuretics, ACE inhibitors and vasodilators, that clearly further escalate neurohormonal activation and early life stress or to use beta-blockers, that are not recommended in the guidelines. The current guideline recommendations[8] further prefer pharmacotherapies, which are based upon the cardio-circulatory/hemodynamic heart failure model (Table 2). In infants with circulatory failure, hypotension due to enalapril leads to a counter-regulatory increase of plasma renin activity by 450% as shown in the prospective European LENA

project[19]. These data clearly show that an effective inhibition of the renin-angiotensin-aldosterone system is not achieved with enalapril in infants with congenital heart disease. We exclude ACE inhibitors in our trials, after showing this aldosterone escape phenomenon in a retrospective analysis in 2000[20].

Table 2. The Impact of Pharmacotherapy on Clinical Heart Failure (Ross Score), Neurohormonal Activation and Heart Rate Variability in Infants with Severe Heart Failure Due to Congenital Heart Disease

		Escalation	De-escalation	
Parameter	**Pharmacotherapy**	**Diuretics**	**ACE Inhibitor**	**Beta-blocker**
Prospective Trials	Ross Score	−20%*	±0%	−60%**
	Norepinephrine	+91%		−21%
	Plasma Renin Activity	+406%**	+450%*	−52%***
	Aldosterone	+58%	−59%*	
	NT-BNP		±0%	
Heart Rate Variability	Heart rate		0%	−15%**
	SDNN			+47%**
	rMSSD			+79%**

Table 3. Pharmacotherapy of Heart Failure in Infants with Congenital Heart Disease

Model	Therapy	Trial	Year	Guideline 2025[8]	Note on Infant Use
Cardio-renal	Diuretics	350 infants	1962	Class I	Retrospective[12]
	SGLT2 Inhibitors	No infants		May be considered	
Cardio-circulatory/ hemodynamic	Digoxin	816 infants	2016	May be considered	Retrospective interstage mortality[21, 22]
	Levosimendan	120 infants	2026	Bridge to transplant	Retrospective[23]
	Milrinone	≈ 400 infants	2015	Palliative setting	Meta-analysis Cochrane[24]
Neurohormonal	Enalapril	115 infants	2010	May be considered	Poorer head growth[11]
	Sacubitril/ Valsartan	6 infants	2025	Class IIa	Panorama HF Trial[10]
	Carvedilol	1 infant	2007	Worsen, caution	US-Carvedilol Trial
	β-selective BB	51 infants	2021		Bisoprolol HLHS Giessen[25]
	Propranolol	50 infants	2001/2013	Not mentioned	CHF-Pro-Infant[17], VSD-PHF[18]
Heart rate	Ivabradine	No infants		Is reasonable	Anti-arrhythmic use

CHD: congenital heart disease. Green (implied): benefit in a clinical trial or guideline recommendation. Yellow (implied): no benefit in a clinical trial. Red (implied): disadvantage in a clinical trial or guideline warning.

4 ECONOMIC AND ETHICAL CONTEXT OF THE DEVELOPMENT OF BETA BLOCKER THERAPY IN INFANTS WITH HEART FAILURE DUE TO CONGENITAL HEART DISEASE

After safety and efficacy of propranolol in infants with severe heart failure due to congenital heart disease has been shown in a prospective randomized trial[17], beta-blocker therapy in infants heart failure was only investigated at the university Giessen[26] and the All-India Institute of Medical Sciences[18] in the last 25 years. This lack of interest is surprising when one considers that death from heart failure is the second most common cause of infant mortality and the most frequent cause of death in patients with congenital heart disease (> 200 infant deaths/year in Germany). One reason for this lack of interest is that the objective mortality rates of congenital heart defects are very badly communicated up to 2010. The publications of the Pediatric Heart Network's single Ventricle Reconstruction Trial and Swedish registry data revealed the persistently high mortality, especially in univentricular hearts. At a mean age of 11 years 41% of the original 549 infants of the Pediatric Heart Network's single Ventricle Reconstruction Trial are dead or transplanted in 2025[27]. The current German data published in 2024[5] confirm this high mortality.

Research into pediatric heart failure at the University Göttingen was stopped after the decision-makers are convinced that the mortality in infants with congenital heart disease will be improved by the new percutaneous cardiac interventions. Moreover, interventional cardiology promised profits in a rapidly growing market (3796 procedures in 2023). The pharmaceutical industry was not interested in Propranolol therapy for infant heart failure, as no profits were expected.

In this economic and ethical context, beta-blocker therapy of infants with severe heart failure due to congenital heart defects was further developed at a small children's hospital with low case numbers at the Caritas Hospital in Bad Mergentheim, Germany. In summary, we treated 43 infants with severe heart failure due to congenital heart disease (Ross Score > 7) from 1996–2020. As shown in Table 3, more than 50% of these very ill infants had chromosome anomalies and all infants suffer from pulmonary hypertension. The 4 infants with univentricular hearts and Down syndrome died. All other infants survive heart surgery without

heart failure in later life with perfect neurodevelopment and physical performance.

Table 4. Our Whole Group of Patients Treated with Propranolol for Severe Heart Failure Due to Congenital Heart Disease (Ross Score > 7) in Infancy

Patients (N=43)	AVSD (N=21)	Biv. Repair (N=7)	Univ. Heart (N=12)	Spont. Closure (N=3)	Down Syndrome (N=15)
Göttingen (N=16) 1996–2004	8	1	7	0	5
Bad Mergentheim (N=27) 2005–2020	13	6	5	3	10
Chromosome Anomaly (N=22)	15 (71%)	3 (43%)	4	0	15
Pulmonary Hypertension	100%	100%	100%	100%	100%
Mortality (N=4)	0	0	4 (33%)	0	4 (27%)

5 IMPROVING PHARMACOTHERAPY OF HEART FAILURE IN INFANTS WITH CONGENITAL HEART DISEASE BY NONINVASIVE MONITORING OF HEMODYNAMICS AND HEART RATE VARIABILITY

The question remains, how to treat infants with severe heart failure due to congenital heart disease with a high mortality risk. The guidelines recommend enalapril, who failed to improve clinical symptoms and prognosis in a prospective randomized trial and not take into account propranolol, who improves clinical symptoms, heart rate variability and neurohormonal activation in 2 prospective randomized trials?

In the last 30 years, we only treated the most vulnerable infants with a Ross Score ≥ 7 and pulmonary hypertension in a compassionate use setting (Table 3). To ensure the safety of the babies, we monitored them up to 2020 by Holter ECG or HRV-online monitoring on our intensive care unit. Today, we use a non-invasive real-life monitoring of hemodynamics, oxygen saturation and heart rate variability in an outpatient setting as recently published[28]. For therapy control we are aiming the following targets: heart rate (110–130 bpm) and vagus activity measured as High Frequency Power (≥ 20 ms^2) or rMSSD (≥ 10 ms). The available high frequency power data of 24 hours heart rate variability analysis in infants with heart failure are illustrated in Figure 2. We include 6 infants treated from the university hospitals, who prefer the beta blocker metoprolol. The targets were reached in all surviving infants treated with propranolol ± digoxin. Despite a clinical improvement, the targets are not reached with metoprolol therapy (heart rate 125 ± 20 bpm, rMSSD 8 ± 4 ms and high frequency power 11 ± 14 ms^2).

Recently, we had the opportunity to monitor cardiac decompensation of an infant with Down syndrome and complete atrioventricular septal defect during treatment with enalapril, spironolactone and hydrochlorothiazide (Figure 3). The most impressive result is the complete loss of vagus activity measured as high frequency power with a mean heart rate of 150 bpm. The rescue therapy with the inodilator milrinone leads to severe arterial hypotension — measured invasively and noninvasively — that have to be treated with the vasoconstrictor norepinephrine. After introduction of the beta-blocker metoprolol, the vagus activity recovered on a low level with mean heart rate of 140 bpm (Figure 4) and the baby is gaining weight for the first time in his life.

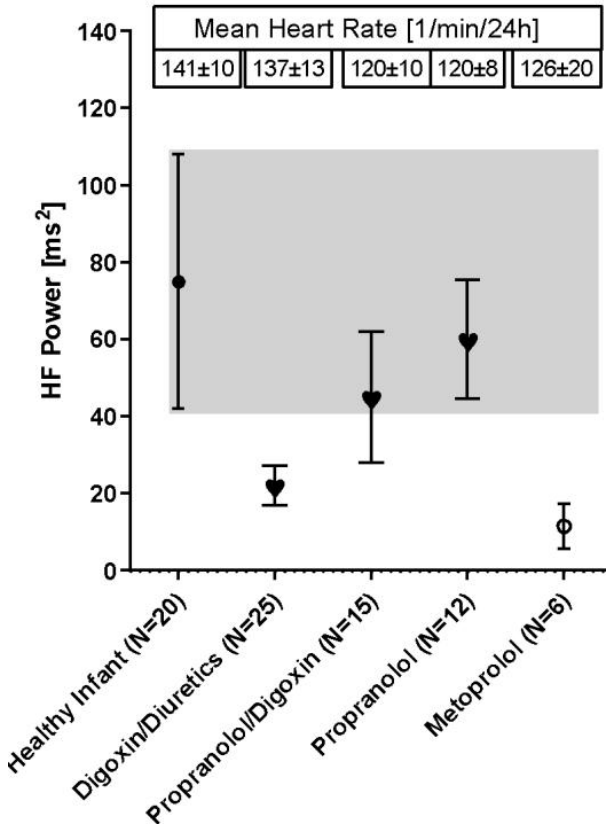

Figure 2. 24-Hour Mean Vagus Activities, Measured with Fast Fourier Analysis (HF-Power) and Mean Heart Rates in Infants with Severe Heart Failure Due to Congenital Heart Defects

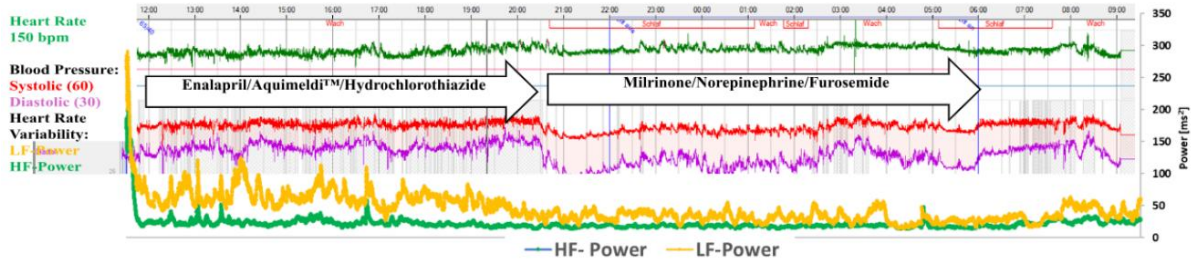

Figure 3. Noninvasive Monitoring of Hemodynamics and Heart Rate Variability after Cardiac Decompensation in an Infant with Atrioventricular Septal Defect Treated with Enalapril

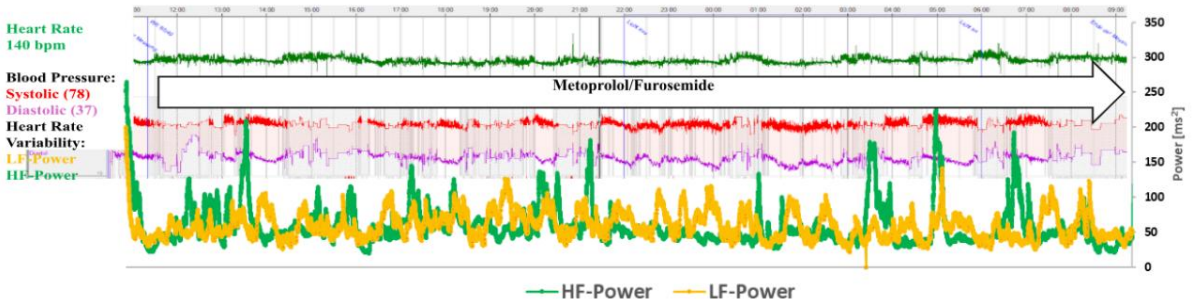

Figure 4. Noninvasive Monitoring of Hemodynamics and Heart Rate Variability after Cardiac Recompensation in an Infant with Atrioventricular Septal Defect Treated with Metoprolol

6 AUTONOMIC IMPRINTING BY EARLY LIFE STRESS: THE DETRIMENTAL CONSEQUENCE OF HEART FAILURE IN INFANTS WITH CONGENITAL HEART DEFECTS ON LONG-TERM PROGNOSIS

Early life stress in infants, measured by norepinephrine plasma levels and heart rate variability, has longtime consequences on growth[29] and neurodevelopment[30]. Congenital heart disease and genetic syndromes showed the largest reductions of heart rate variability in long-term follow up. We introduce the term “autonomic imprinting” to explain the long-term effects of early life stress on the autonomic nervous system[31]. We analyzed somatic growth and heart rate variability up to the 13th year of life of 17 children who are treated with propranolol for heart failure in infancy in Bad Mergentheim. The data show normal vagus activities measured as rMSSD in these children (Table 5) in contrast to older patients after surgery of congenital heart defects who are treated with standard heart failure therapy. We further found a better catch-up growth of length and head circumference (Figure 5) compared to a German cohort of children with congenital heart defects[29]. Neonatal head circumference is one of the top 10 candidate variables for longtime neurodevelopmental outcome[27]. Head circumference growth is significantly worse in enalapril treated infants compared to placebo[11] but nearly normal after propranolol treatment of infants with heart failure due to congenital heart defects (Figure 5).

Table 5. Long-term Data of Vagus Activities Measured by Heart Rate Variability (rMSSD) in Patients after Surgery of Congenital Heart Disease, Treated with Beta-Blocker or Standard Therapy in Infancy[32]

Group	N	Age [Years]	RMSSD [ms/24h]	RMSSD [ms/day]	RMSSD [ms/night]	RMSSD ratio [%]
Grown Up with CHD[32]	43	34.3 ± 12.0	47.0	39.0	53.1	146.3
Standard Therapy	124	33.7 ± 10.5	39.3**	35.9	43.5***	117.4***
Children						
Controls	59	9.8 ± 2.0	53.0 ± 17	39.2 ± 14.8	69.5 ± 24.3	186 ± 60
Propranolol Therapy	17	9.6 ± 3.6	51.2 ± 35.6	34.9 ± 13	54.0 ± 19.6*	160 ± 65

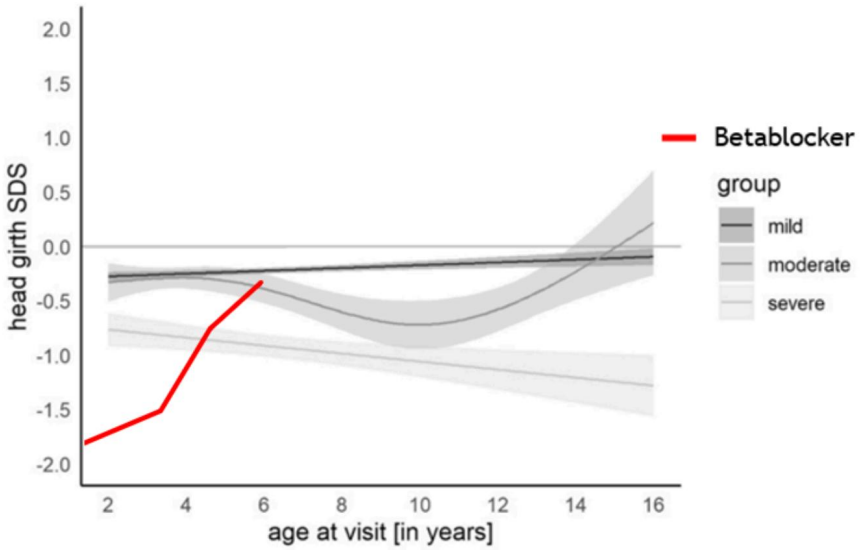

Figure 5. Standard Deviation of the Head Circumferences (SDS) of 14 Patients with Severe Heart Failure Treated with Propranolol in Infancy Compared to the German Average of Children with Congenital Heart Disease Treated with Standard Therapy as Recently Published[29]

7 CONCLUSION

Despite a very high mortality of infants with severe heart failure due to congenital heart defects, pediatric cardiologists are further standing at a therapeutic crossroad either to follow the guideline recommendations with Diuretics, ACE inhibitors and vasodilators which clearly escalate neurohormonal activation and early life stress or to de-escalate early life stress with beta-blockers, that are not recommended in the guidelines. Propranolol showed a significant benefit of clinical symptoms, neurohormonal activation and heart rate variability in two prospective randomized trials. Enalapril is further recommended in the guidelines also a large, prospective trial showed a significantly poorer head growth in infants with heart failure compared to placebo[11] but no improvement of clinical symptoms, weight gain, and prognosis. Since the first reports in 1998, there are only a few long-term data available from patients with early life stress from heart failure in infancy, who are treated with beta-blockers. Our data gives cause for hope, that beta-blockers in infants with heart failure improve catch up growth and heart rate variability in long-term follow up that is clearly related to neurodevelopment and long-term cardiovascular risk.

REFERENCES

[1] Levin A, Li J, Krasuski R, et al. Abstract 4369203: Mortality Rates and Causes of Death in Patients with Congenital Heart Disease (CHD) Across the Lifespan: Population-Based Findings from the CDC- Funded STAR1 Study. *Circulation* 2025; 152 (Suppl_3):A4369203A03. doi: 10.1161/circ.152.suppl_3.4369203

[2] Apitz J, Beuren AJ. [Congenital Heart Defects During The 1st Year of Life. A Survey of 630 Infants with Heart Disease]. *Arch Kreislaufforsch* 1963;42:264–76.

[3] Sommers C, Nagel BH, Neudorf U, et al. [Congestive heart failure in childhood. An epidemiologic study]. *Herz* 2005;30(7): 652–62.

[4] Bergh N, Skoglund K, Fedchenko M, et al. Risk of Heart Failure in Congenital Heart Disease: A Nationwide Register-Based Cohort Study. *Circulation* 2023;147(12):982–84. doi: 10.1161/circulationaha.122.061546 [published Online First: 20221219]

[5] Abdul-Khaliq H, Gomes D, Meyer S, et al. Trends of mortality rate in patients with congenital heart defects in Germany-analysis of nationwide data of the Federal Statistical Office of Germany. *Clinical Research in Cardiology* 2024 doi: 10.1007/s00392-023-02370-6 [published Online First: 20240304]

[6] Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. *Journal of the American College of Cardiology* 1992; 20(1):248–54. doi: 10.1016/0735-1097(92)90167-1

[7] Katz LN, Feinberg H, Shaffer AB. Hemodynamic aspects of congestive heart failure. *Circulation* 1960;21:95–111. doi: 10.1161/01.cir.21.1.95

[8] Irving C, Azeka E, Adorisio R, et al. The International Society for Heart and Lung Transplantation Guidelines for the Management of Pediatric Heart Failure (Update From 2014). *J Heart Lung Transplant* 2025; 44(10): e21–e71. doi: 10.1016/j.healun.2025.06.003 [published Online First: 20250821]

[9] Shaddy RE, Boucek MM, Hsu DT, et al. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. *JAMA* 2007;298(10):1171–79.

[10] Shaddy R, Burch M, Kantor PF, et al. Sacubitril/Valsartan in Pediatric Heart Failure (PANORAMA-HF): A Randomized, Multicenter, Double-Blind Trial. *Circulation* 2024; 150(22):1756–66. doi: 10.1161/circulationaha.123.066605 [published Online First: 20240925]

[11] Hsu DT, Zak V, Mahony L, et al. Enalapril in infants with single ventricle: results of a multicenter randomized trial. *Circulation* 2010;122(4):333–40.

[12] Goldblatt E. The treatment of cardiac failure in infancy. A review of 350 cases. *Lancet* 1962; 2(7249):21–25. doi: 10.1016/s0140-6736(62)92312-7

[13] Breeyear JH, Keaton JM, Torstenson ES, et al. Diastolic Blood Pressure Alleles Improve Congenital Heart Defect Repair Outcomes. *Circ Res* 2022;130(7):1030–37. doi: 10.1161/circresaha.121.319842 [published Online First: 20220224]

[14] Wilson TG, Iyengar AJ, d'Udekem Y. The Use and Misuse of ACE Inhibitors in Patients with Single Ventricle Physiology. *Heart Lung Circ* 2016; 25(3): 229–36. doi: 10.1016/j.hlc.2015.10.005 [published Online First: 20151027]

[15] Buchhorn R, Hammersen A, Bartmus D, et al. The pathogenesis of heart failure in infants with congenital heart disease. *Cardiol Young* 2001;11(5):498–504.

[16] Vaida M, Feins E, Khei J, et al. Abstract 4147589: Heart Rate Variability as a Predictor of Postoperative Outcomes in Congenital Heart Surgery. *Circulation* 2024; 150 (Suppl_1): 4147589. doi: 10.1161/circ.150.Suppl1.4147589

[17] Buchhorn R, Hulpke-Wette M, Hilgers R, et al. Propranolol treatment of congestive heart failure in infants with congenital heart disease: The CHF-PRO-INFANT Trial. *Int J Cardiol* 2001;79(2-3):167–73.

[18] Ramakrishnan S, Ghati N, Ahuja RS, et al. Efficacy and safety of propranolol in infants with heart failure due to moderate-to-large ventricular septal defect (VSD-PHF study) - A prospective randomized trial. *Annals of Pediatric Cardiology* 2021;14(3):331–40. doi: 10.4103/apc.APC_94_21 [published Online First: 2021/10/21]

[19] Steichert M, Cawello W, Bajcetic M, et al. Influence of Age, Heart Failure and ACE Inhibitor Treatment on Plasma Renin Activity in Children: Insights from a Systematic Review and the European LENA Project. *Frontiers in Bioscience (Landmark edition)* 2023;28(12):335. doi: 10.31083/j.fbl2812335

[20] Buchhorn R, Ross RD, Hulpke-Wette M, et al. Effectiveness of low dose captopril versus propranolol therapy in infants with severe congestive failure due to left-to-right shunts. *Int J Cardiol* 2000;76(2-3):227–33.

[21] Brown DW, Mangeot C, Anderson JB, et al. Digoxin use is Associated with Reduced Interstage Mortality in Patients with No History of Arrhythmia After Stage I Palliation for Single Ventricle Heart Disease. *Journal of the American Heart Association* 2016; 5(1) doi: 10.1161/jaha.115.002376 [published Online First: 20160111]

[22] Oster ME, Kelleman M, McCracken C, et al. Association of Digoxin With Interstage Mortality: Results From the Pediatric Heart Network Single Ventricle Reconstruction Trial Public use Dataset. *Journal of the American Heart Association* 2016;5(1) doi: 10.1161/jaha.115.002566 [published Online First: 20160113]

[23] Flórez-Rodríguez C, Rubio-Duarte AF, Basto-Duarte MC, et al. Perioperative use of levosimendan in complex congenital heart disease management. *European Journal of Pediatrics* 2026;185(2):100. doi: 10.1007/s00431-025-06719-z [published Online First: 20260123]

[24] Burkhardt BE, Hummel J, Rücker G, et al. Inotropes for the prevention of low cardiac output syndrome and mortality for paediatric patients undergoing surgery for congenital heart disease: a network meta-analysis. *The Cochrane Database of Systematic Reviews* 2024;11(11):Cd013707. doi: 10.1002/14651858.CD013707.pub2 [published Online First: 20241126]

[25] Mienert T, Esmaeili A, Steinbrenner B, et al. Cardiovascular Drug Therapy during Interstage After Hybrid Approach: A Single-Center Experience in 51 Newborns with Hypoplastic Left Heart. *Paediatric Drugs* 2021; 23(2):195–202. doi: 10.1007/s40272-021-00438-2 [published Online First: 20210313]

[26] Recla S, Schmidt D, Logeswaran T, et al. Pediatric heart failure therapy: why β_1-receptor blocker, tissue ACE-I and mineralocorticoid-receptor-blocker? *Translational Pediatrics* 2019; 8(2):127–32. doi: 10.21037/tp.2019.04.08 [published Online First: 2019/06/05]

[27] Miller TA, Sharma B, Gongwer R, et al. Neurodevelopmental Outcomes in Early Adolescence: The Pediatric Heart Network's Single Ventricle Reconstruction Trial. *Circulation* 2025;152(17):124–61. doi: 10.1161/circulationaha.125.074523 [published Online First: 20250717]

[28] Buchhorn R, Hofmann E. Real-Life Measurement of Vasoregulation in Patients with Cyanotic Congenital Heart Disease: A Feasibility Study. *Hearts* 2025;6(4):33.

[29] Kiess A, Bimboese P, Gausche R, et al. Severity of Congenital Heart Defects Affects Long-Term Somatic Development. *Pediatric Cardiology* 2026; 47(2):642–51. doi: 10.1007/s00246-025-03815-7 [published Online First: 20250305]

[30] Toyofuku A, Ehrler M, Naef N, et al. Heart rate variability and cognitive functions in adolescents with complex congenital heart disease. *Pediatr Res* 2024 doi: 10.1038/s41390-024-03432-9 [published Online First: 20240730]

[31] Buchhorn R, Meint S, Willaschek C. The Impact of Early Life Stress on Growth and Cardiovascular Risk: A Possible Example for Autonomic Imprinting? *PloS One* 2016; 11 (11): e0166447. doi: 10.1371/journal.pone.0166447

[32] Schöneburg C, Uphoff I, Oberhoffer-Fritz R, et al. Heart Rate Variability in Congenital Heart Disease and Controls Using Wearable Technology and a Health Application Programming Interface — A Cross-sectional Study. *CJC Pediatric and Congenital Heart Disease* 2025 doi: 10.1016/j.cjcpc.2025.07.004

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Cross-Scale Analogies between Astrophysics and Human Biology: Conceptual and Technological Parallels in the Study of Complex Systems

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ABSTRACT

Over the last few decades, our uderstanding of both the universe and the microscopic world has progressed remarkably. The rise of modern science, bolstered by the evolution of observational instruments, such as the Hubble and James Webb telescopes for cosmic exploration, and next-generation microscopes for the study of living organisms, has led to significant discoveries. Since the invention of the telescope, astronomers have progressively unveiled the structure and dynamics of the universe, establishing the foundations of astrophysics. In parallel, advances in microscopy have enabled the exploration of the infinitely small, revealing the fundamental mechanisms of the human body and laying the groundwork for physiology and molecular biology. Nanotechnology has further refined telescopes and revolutionized medical care, particularly in targeted therapy and regenerative medicine. At...

Full abstract continues on the metadata continuation sheet.

Index Terms: astrophysics • human physiology • biological systems • cosmic structures • microscopy • telescopes • nanotechnology • complex systems • interdisciplinary science • scientific analogies

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RESEARCH ARTICLE

Cross-Scale Analogies between Astrophysics and Human Biology: Conceptual and Technological Parallels in the Study of Complex Systems

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Keywords: *astrophysics, human physiology, biological systems, cosmic structures, microscopy, telescopes, nanotechnology, complex systems, interdisciplinary science, scientific analogies*

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1 INTRODUCTION

The microscopic universe within the human body and the vastness of the cosmos seem, at first glance, to belong to two radically different realities. Exploring the human body leads us to structures such as cells, organelles, macromolecules, and protein complexes, whose sizes range from the micrometer to the nanometer scale, and even smaller, down to about 10^{-12} m for certain atomic structures.

In contrast, astrophysics deals with objects whose sizes extend from several light-years ($\sim 10^{16}$ m) to megaparsecs ($\sim 10^{22}$ m), involving positively exponential orders of magnitude. These two domains therefore appear to operate in entirely separate metric regimes: one in the ultramicroscopic, the other in the ultramassive.

Although the invention of the microscope is often associated with a simple adaptation of Galilean optics [1], the history of science emphasizes instead a parallel development in lens-polishing techniques and refractive principles, which allowed for the simultaneous exploration

of both extremes of the metric scale. While these two instruments were initially intended for distinct phenomenological domains, their technical evolution has revealed an unforeseen structural reality: the existence of morphological convergences transcending the opposition between the infinitely large and the infinitely small.

Beyond mere visual resemblance, these similarities, such as neural networks and cosmic filaments, or arborescent and spiral patterns, are now integrated into the theoretical frameworks of fractal geometry and network theory. These disciplines suggest that the organization of matter, whether biological or cosmological, responds to principles of self-organization and universal topological constraints. Thanks to advancements in computational imaging and multi-messenger astrophysics, these "inverted mirrors" are no longer perceived as optical coincidences, but as manifestations of a fundamental scale invariance.

The present article proposes to examine exhaustively two of the most complex natural systems identified to date: the universe and the human body, based on literature data and the analysis of visual patterns. The central objective of this study is to identify and characterize potential analogies, whether numerical, historical, morphological, structural, or technological. This comparative approach, still marginal in conventional scientific literature, raises fundamental questions regarding the universality of the laws governing complex structures.

2 THE MACRO AND THE MICRO: NUMERICAL INSIGHTS INTO THE COSMOS AND THE HUMAN BODY

At the subvisible scale of the human body, biological structures are organized across a wide range of sizes, from tens of micrometers down to nanometers and beyond. A typical human cell measures between 10 and 30 micrometers (10^{-6} m), while intracellular organelles such as the nucleus, mitochondria, or lysosomes range from 0.1 to 5 micrometers [2]. At a smaller level, protein complexes (such as ribosomes) and macromolecules extend within the 10 to 30 nanometer range, with the DNA double helix measuring about 2 nm in diameter. Beyond that, lipid membranes have an average thickness of 4 to 5 nm, and interatomic distances approach 0.1 nm [3]. Although the human body appears compact and limited in size, it conceals an organization of staggering complexity, revealed through the scale of the numbers that characterize its biological structures.

At the microscopic level, the human nervous system is also a marvel of complexity, comprising about 86 billion neurons (8.6×10^{10}) [4]. These nerve cells are interconnected by a colossal number of synapses, estimated at 100 trillion (10^{14}), forming an unparalleled communication network underlying thought, emotions, and vital functions.

The vascular network within the human body contains an immense number of capillaries, about 10 billion (10^{10}), ensuring blood exchange with all body tissues [5].

The lungs contain approximately 480 million alveoli (4.8×10^8), true gas-exchange units responsible for oxygenating the blood and eliminating carbon dioxide, with an exchange surface estimated between 70 and 100 m^2 [6].

The visual system relies on an impressive structure comprising more than 250 million photoreceptors ($\approx 2.5 \times 10^8$) for extremely fine visual perception; each eye contains about 6 million cones (6×10^6), specialized for color vision, and nearly 120 million rods (1.2×10^8), dedicated to night and peripheral vision [7].

The kidneys, true biological filters, contain about 1 million nephrons per kidney (10^6), or 2 million in total (2×10^6), filtering roughly 180 liters of blood daily [8].

The skin, the largest external organ, covers about 1.7 to 2 m^2 and houses nearly 5 million hair follicles (5×10^6), including 100,000 (10^5) on the scalp, as well as 2 to 4 million sweat glands ($2–4 \times 10^6$), playing a key role in thermoregulation [9].

In humans, DNA is organized into a genome containing approximately 3 billion base pairs (3×10^9), distributed across 23 pairs of chromosomes and encoding the genetic information required for cellular processes [10–12]. This information governs gene expression and orchestrates protein production, fundamental to cellular structure and function.

On the other hand, the observable universe is of dizzying vastness, populated by an incredible variety of celestial objects. It is estimated to contain about 2 trillion galaxies (2×10^{12}), each harboring on average between 100 billion (10^{11}) and 400 billion (4×10^{11}) stars, leading to an astronomical total of around 10^{24} stars, more than the total number of grains of sand on Earth [13, 14].

Orbiting these stars are planets: more than 6,000 exoplanets have been confirmed to date [15], but estimates suggest there could be up to about 100 billion planets in the Milky Way alone [16]. Meanwhile, the universe contains many compact objects such as stellar black holes, whose number in our galaxy may exceed 100 million [17], as well as neutron stars, observed in large numbers though their true galactic population is estimated at several million. On even larger scales, galaxies group into clusters and superclusters; our own supercluster, Laniakea, contains about 100,000 galaxies [18]. Finally, the universe is structured on the largest scales by cosmic filaments, true gravitational bridges stretching across billions of light-years.

Despite its relatively small size, the human body rivals the most complex systems in the universe in sophistication and structural density.

The fact that a single organ, the human brain, contains almost as many connections as there are stars in a galaxy reveal a fractal structure of complexity linking humanity and the universe.

3 TELESCOPE AND MICROSCOPE: A TECHNOLOGICAL SYNERGY BETWEEN THE COSMOS AND LIVING SYSTEMS

Historically, the invention of the microscope was inspired by the telescope. In the early 17th century, Galileo Galilei, after improving the astronomical telescope, adapted the same optical principle, a converging lens combined with a diverging lens, to observe the microscopic world, thus inaugurating a new era in the visualization of living systems [19, 20]. Telescopes and microscopes therefore share a common physical foundation: the capture of light, its focusing by lenses or mirrors, and the magnification of the image to reveal structures invisible to the naked eye [21, 22].

Over the centuries, these two instruments have evolved in parallel, exploiting the same technological advances. The James Webb Space Telescope (JWST) observes the universe in the infrared to detect distant galaxies and stellar nurseries hidden by cosmic dust [23]. Similarly, infrared fluorescence microscopes make it possible to image biological tissues in depth and are widely used in oncology, nephrology, and neurobiology [24].

Moreover, immunofluorescence, which relies on antibodies coupled to fluorescent markers, enables the targeting and visualization of specific cellular structures at the nanometer scale [25], just as the JWST uses filters and coronagraphs to isolate a star's light and observe exoplanets [26].

Likewise, confocal laser scanning microscopes use tunable laser sources to generate fine optical sections, while modern telescopes employ lasers for real-time correction of atmospheric turbulence through adaptive optics [27], a technology now transferred to ophthalmology, particularly for high-precision retinal surgery [28].

4 ONE VIEW, TWO SCALES, TWO DOMAINS

Scientific imagery, whether derived from observations of deep space or from cross-sections of biological tissue, is often perceived as an objective representation of a reality invisible to the naked eye. Yet when certain images from astrophysics, nebulae, galaxies, cosmic filaments, are placed side by side with histological images (neural networks, cellular structures, connective tissues), a sometimes striking visual resemblance emerges. These morphological, structural, and aesthetic similarities invite deeper reflection. Some of these resemblances are illustrated in the following figures:

Stars can form magnificent patterns as they age; the Butterfly Nebula is a remarkable example. Although its gaseous wingspan extends over more than 3 light-years ($\approx 10^{15}$ m) and its estimated surface temperature exceeds 200,000 °C, this planetary nebula shines intensely in visible and ultraviolet light, yet remains hidden from direct observation by a dense torus of dust [29]. The morphological appearance of this nebula is reminiscent of a cell undergoing division, whereas the size of chromatin ranges between 11 and 30 nm ($\approx 10^{-9}$ m) [30]. (Figure 1)

The Helix Nebula is often compared to a giant eye floating in space. Its circular structure, luminous center reminiscent of a pupil, and shades of blue and green strikingly evoke a human iris. This resemblance is so strong that it is sometimes nicknamed the "cosmic eye." Yet the difference in scale is staggering. A human eye measures about 2.5 centimeters in diameter, whereas the Helix Nebula extends across approximately 2 to 3 light-years ($\approx 10^{16}$ meters). What appears to be a simple bright "pupil" is in reality a dying star, and what resembles a colored iris corresponds to clouds of ionized gas expelled into space. (Figure 4)

Astronomers have been fascinated by recent images from the James Webb Space Telescope, which bear a striking resemblance to a transparent cosmic skull, revealing the "brain" it appears to contain. The nebula, officially named PMR 1, was formed by an aging star expelling its outer layers. The differences between what the James Webb Telescope's infrared instruments reveal and conceal within the PMR 1 nebula ("Exposed Skull") are evident in this comparative image. More background stars and galaxies shine in the field of view of Webb's Near-Infrared Camera (NIRCam), while cosmic dust appears more intensely in the light captured by the Mid-Infrared Instrument (MIRI). The central dark band that contributes to the nebula's distinctive brain-like appearance is more visible in NIRCam images, but its apparent role in the ejection of material at the top and bottom of the nebula is more clearly seen in MIRI images. Observing the cosmos at different wavelengths of light provides a deeper understanding of how the universe functions. (Figure 5)

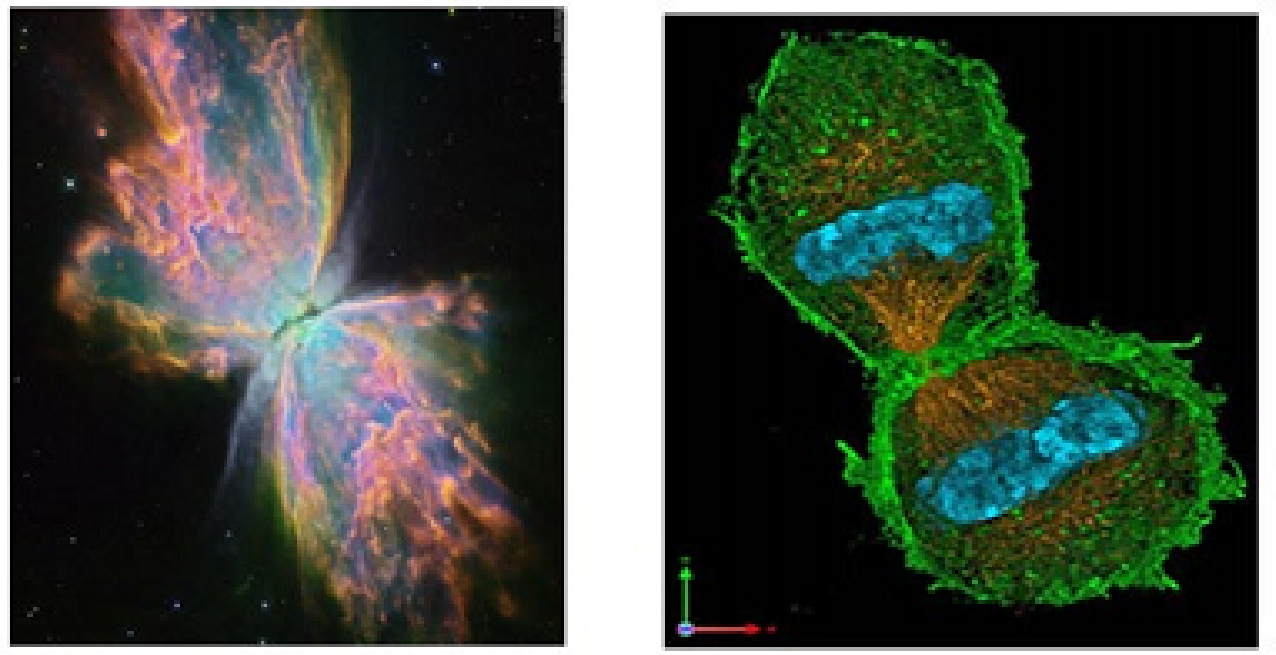

Figure 1. Morphological similarity between the Butterfly Nebula as seen by Hubble and a cell undergoing division. *Left:* The Butterfly Nebula as seen by Hubble Space Telescope. Highlighted light emitted by oxygen (blue), hydrogen (green), and nitrogen (red). Image credit: NASA, ESA, Hubble; Processing: William Ostling [29]. *Right:* A cell undergoing division (in telophase). New nuclear membrane forms, microtubules disappear (red), nucleolus reforms, and chromatin is present (blue) [30].

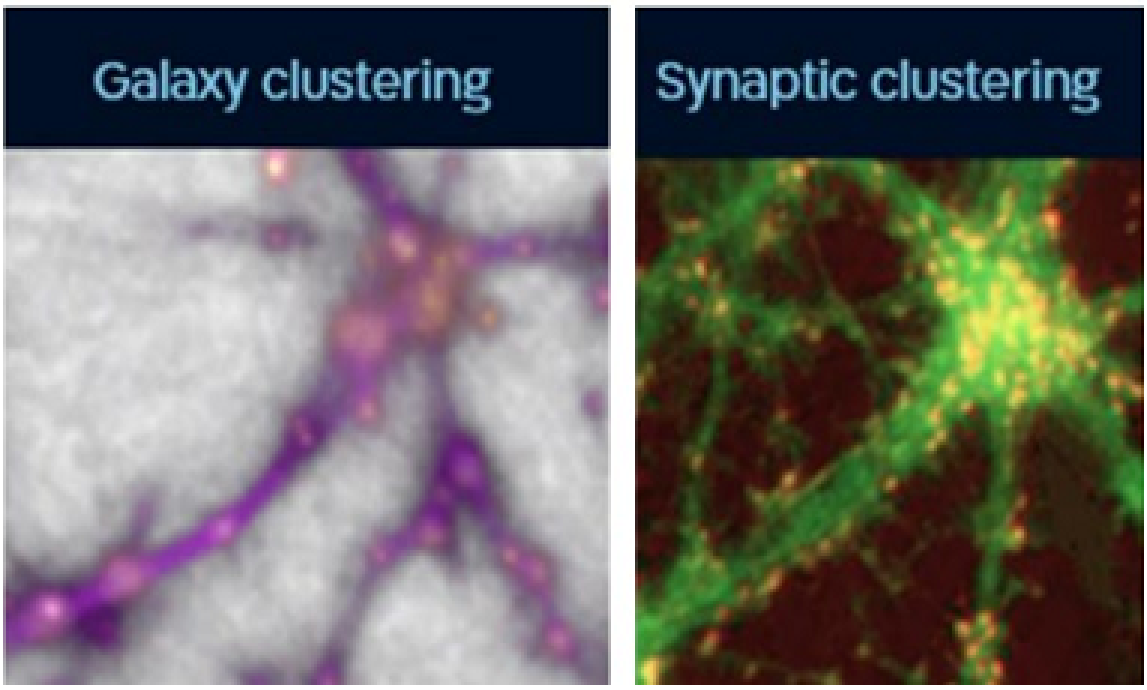

Figure 2. Morphological similarities between a simulated cosmic web and a neuronal culture. *Left:* A simulated cosmic web (violet) with filaments connecting dense nodes of galaxy clusters (pink-brown points). *Image credit: NASA, ESA, and University of California, Santa Cruz (J. Burchett and O. Elek) [31]. Right:* A neuronal network in culture showing a dendritic hub (green) enriched with synaptic puncta (yellow) [31].

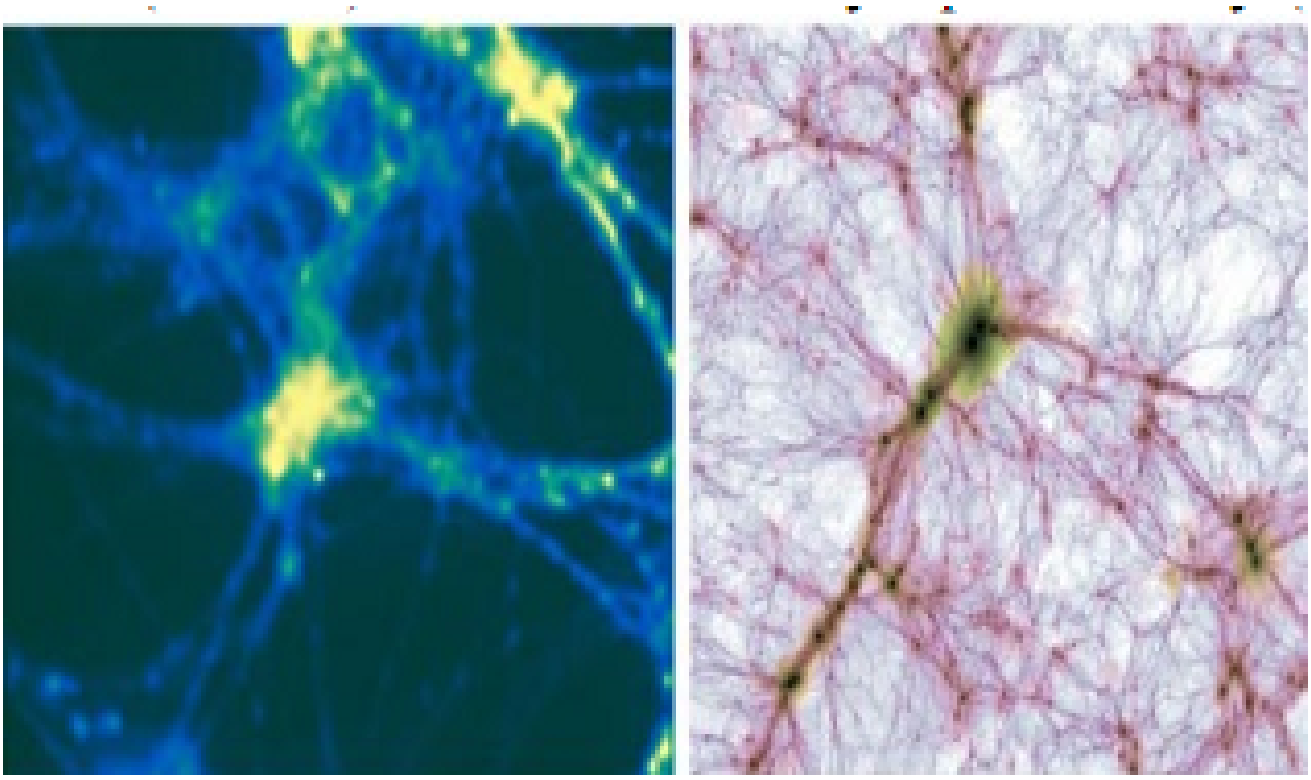

Figure 3. Enrichment at convergence sites in both networks. *Left:* Convergence sites of neuronal processes (in blue) show increased synaptic activity (in yellow). Width = 60 mm. *Right:* Cropped image of a thin slice through the large-scale cosmic structure from the IllustrisTNG TNG300 simulation. *Credit: IllustrisTNG Collaboration (IllustrisTNG, TNG300).*

Figure 4. The Helix Nebula, the "Cosmic Eye," as seen by the James Webb Telescope. The Helix Nebula (2–3 light-years wide) strikingly evokes a human iris. What appears to be a pupil is a dying star, and the colored iris corresponds to ionized gas. *Image credit: ESO, VISTA, NASA, ESA, CSA, STScI, J. Emerson (ESO) [34].*

Figure 5. The PMR 1 Nebula, the "Cosmic Skull," as seen by the James Webb Telescope. Image credit: NASA, ESA, CSA, STScI; Processing: Joseph DePasquale [35].

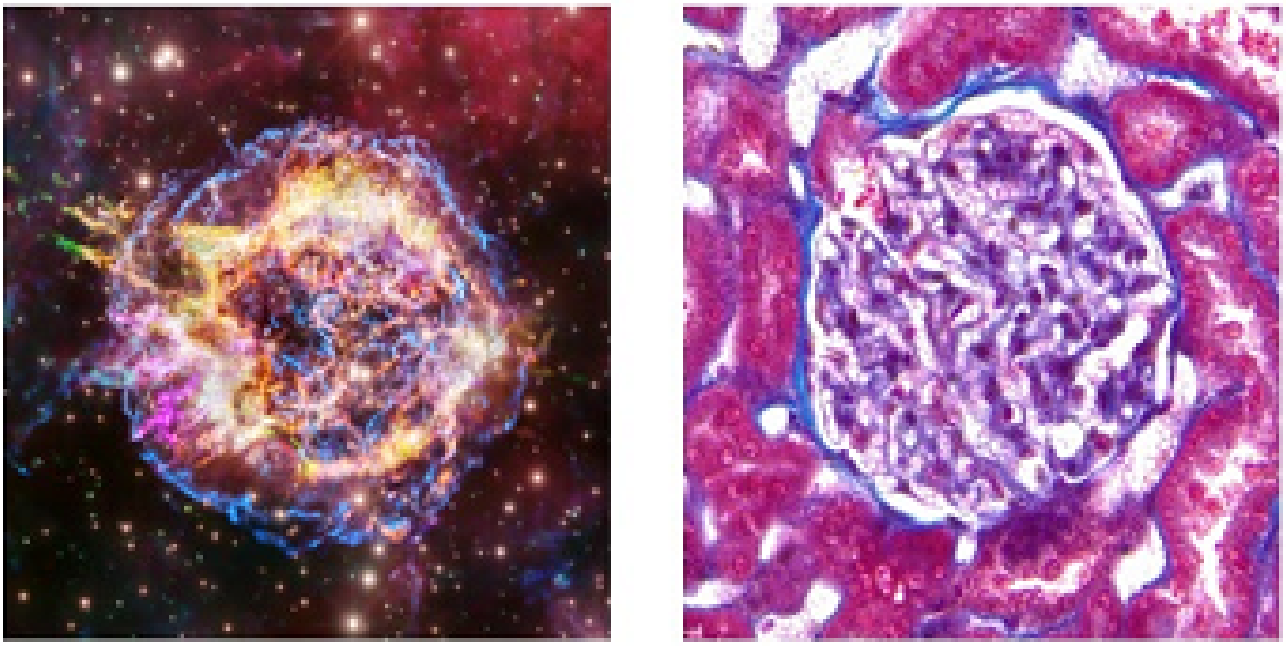

Figure 6. Morphological similarity between the supernova "Cassiopeia A" and a renal glomerulus in histological section. *Left:* Image of Cassiopeia A, a supernova remnant located about 11,000 light-years away. *Image credit: Deep Sky Collective (DSC) and NASA Chandra team [32]. Right:* A histological section of the renal cortex with a Malpighian corpuscle (glomerulus) at its center. Responsible for urine production in the vertebrate kidney [33].

5 COMMON SYSTEMIC AND DYNAMIC PRINCIPLES

The human cardiovascular system ensures the continuous distribution of blood, oxygen, and nutrients through a branched network of vessels, comparable to the flows of matter and energy observed in galaxies, nebulae, or the interstellar medium [36, 37]. Similarly, the electrical signals circulating within the nervous system can be paralleled with the propagation of electromagnetic waves in space, which transmit information across vast distances [38, 39].

Moreover, gas exchange in the lungs (O_2/CO_2) recalls the cosmic cycles of transformation of interstellar gas, contributing to the birth and death of stars [40, 41]. A certain balance governs both the human body and the cosmos: in the organism, this takes the form of homeostasis, ensuring the stability of vital functions [42], while in the universe, it manifests through gravitational and thermodynamic equilibria that structure stellar and galactic systems [43].

6 ASTRONOMY, OPHTHALMOLOGY, AND ONCOLOGY: TECHNOLOGICAL TRANSFER BEYOND SIZE SCALES

In ophthalmology, adaptive optics, originally developed to correct atmospheric turbulence in ground-based telescopes [44], is now used in retinal surgery. It improves the precision of surgical instruments in real time by compensating for micro-eye movements and individual optical irregularities, enabling ultra-detailed visualization of the retina and its capillaries [45, 46].

Similarly, in oncology, the analysis of suspicious pigmented lesions and breast nodules indicative of potential cancer benefits from advanced imaging techniques inspired by astronomical image processing. Models originally designed to identify complex galactic structures are adapted to discriminate asymmetric, irregular, or evolving patterns in skin and breast tissue, sometimes achieving detection rates higher than those of clinicians [47–49].

7 NANOMEDICINE AND NANOASTRONOMY

Nanotechnology involves manipulating matter at the nanometer scale. In medicine, it has enabled major advances in the diagnosis, treatment, and prevention of diseases [50, 51]. In astronomy, it plays a crucial role in the design of instruments, satellites, and space missions [52].

Nanomedicines target cells directly, including neoplastic cells, reducing the side effects of anticancer treatments. These nanomolecules are also used in vaccination, as in COVID-19 vaccines, where lipid nanoparticles protect RNA and facilitate its entry into cells [51]. Nanomaterials serve both regenerative medicine, for the repair of tissues and organs, and astronomy, where they improve telescope precision and the performance of telescope mirrors [52].

8 ARTIFICIAL INTELLIGENCE: MAPPING THE HUMAN BRAIN AND DECIPHERING THE SECRETS OF THE MILKY WAY

Magnetic resonance imaging (MRI) allows for non-invasive visualization of the internal composition of the human body [53], while radio astronomy uses radio waves to probe the most distant and obscured regions of the universe [54]. In both fields, the analysis of massive, noisy datasets increasingly relies on artificial intelligence, which is used in astronomy to classify galaxies or detect exoplanets [55], and in medical imaging to enhance resolution and automate diagnoses [56].

9 CONTEMPLATING THE UNIVERSE: SILENT PSYCHOTHERAPY NURTURING WONDER AND SOOTHING THE MIND

Contemplating the starry sky or vast cosmic structures is not merely an aesthetic experience; it produces measurable effects on psychological and emotional well-being. Research in cognitive psychology and neuroscience has shown that this visual and mental engagement with the immensity of the cosmos induces a sense of awe, associated with reduced stress and anxiety, increased curiosity, and the development of a beneficial sense of humility [57–59].

1. **Cosmic awe: a powerful psychological trigger** — The concept of awe, a complex emotion often translated as wonder or amazement, was defined by psychologists Dacher Keltner and Jonathan Haidt as an emotion triggered by the perception of something vast, beyond one's usual frame of reference [60]. Contemplating celestial phenomena such as the Milky Way, nebulae, or the rising Moon can evoke this type of emotional response, fostering fascination, curiosity, and introspection [61].

2. **Proven anti-stress and anti-anxiety effects** — Multiple studies have shown that experiences of awe induced by observing the night sky or cosmic scenes can reduce stress levels and improve markers of mental well-being. Experimental work has highlighted decreased anxiety and improved mood in participants exposed to images or videos of space, compared to control groups [62–64]. Observing the sky, especially in natural environments or away from artificial light, activates the parasympathetic nervous system, promoting physiological relaxation responses [65]. This experience induces a mental state similar to meditation, comparable to effects seen in mindfulness practices, with reduced cognitive and emotional activation [66, 67].

3. *Humility and re-centering:* **a salutary perspective** — Contemplating the unparalleled dimensions of the universe, galaxies millions of light-years away, filamentary cosmic structures, reminds us of our tiny place in an almost infinite space-time. This awareness generates what researchers call "existential humility," which, far from causing despair, is often linked to reduced narcissism, increased solidarity, and a sense of connection to the world [68]. Cosmic experiences can reorient priorities, dissolve excessive ego, and highlight the beauty of a universe of which we are only an infinitesimal part.

4. **Hypnotic and sensory experience** — The night sky also exerts a hypnotic sensory power. The slow movement of the stars, the steady rhythm of the universe, and the gentle alternation between light and darkness create a visual scene conducive to deep relaxation. Prolonged exposure to these images—whether through telescopes, astronomical simulation applications, or simple naked-eye observation—can produce an altered state of consciousness, akin to daydreaming or meditation.

10 CONCLUSION

This study demonstrates that the convergence between the universe and the human body transcends simple aesthetic analogy, anchoring itself in a reality of systemic complexity and scale invariance. The analysis of visual patterns, supported by the theoretical frameworks of fractal geometry and network theory, reveals that neural structures and the cosmic web share universal topological properties of self-organization, analogously optimizing the flow of information and energy.

This porosity between the infinitely large and the infinitely small is concretely manifested through major technological transfers, such as the application of astronomical adaptive optics to retinal microsurgery or the use of galactic detection algorithms in breast oncology. While the contemplation of these "inverted mirrors" evokes a sense of wonder with genuine psychotherapeutic benefits, it primarily calls for a scientific paradigm shift. Future research should prioritize systematic quantitative morphometric analysis and the application of astrophysical multi-spectral imaging to high-resolution biomedical visualization. Understanding living systems thus amounts to deciphering the fundamental laws presiding over the architecture of the universe, unifying reason, technology, and the profound unity of nature.

REFERENCES

[1] Van Helden A. The Invention of the Telescope. Transactions of the American Philosophical Society. 1977;67(4):1–67.

[2] Alberts B, Johnson A, Lewis J, Morgan D, Raff M, Roberts K, Walter P. Molecular Biology of the Cell. 6? éd. New York: Garland Science; 2014.

[3] Goodsell DS. The Machinery of Life. 2nd ed. New York: Springer; 2009. Chap. 1, p. 10–15.

[4] von Bartheld CS, Bahney J, Herculano-Houzel S. The search for true numbers of neurons and glial cells in the human brain: A review of 150 years of cell counting. J Comp Neurol. 2016; 524(18):3865–3895. https://doi.org/10.1002/cne.24040

[5] Correlation between the Capillary Blood Flow Characteristics and Endothelium Function in Healthy Volunteers and Patients Suffering from Coronary Heart Disease and Atrial Fibrillation: A Pilot Study. Life (Basel) [Internet]. Disponible sur: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10608205/

[6] Weibel ER. What makes a good lung? Morphology and function of the respiratory apparatus. In: Johnson MH, Petersen SA, Biscoe MB, editors. Comparative Physiology of the Vertebrate Respiratory System. Cambridge: Cambridge University Press; 2009. p. 99–111.

[7] Curcio CA, Sloan KR, Packer O, Hendrickson AE, Kalina RE. Distribution of cones in human and monkey retina: Individual variability and radial asymmetry. Science. 1987;236(4801): 579–582.

[8] Brenner BM, Rector FC. Brenner & Rector's The Kidney. 10th ed. Philadelphia: Elsevier; 2016.

[9] Tortora GJ, Derrickson BH. Principles of Anatomy and Physiology. 15th ed. Hoboken, NJ: Wiley; 2017.

[10] International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. Nature. 2001;409(6822): 860–921. doi:10.1038/35057062.

[11] Willard HF. The Human Genome. In: Genomic and Personalized Medicine. 2nd ed. Academic Press; 2013. p. 1–20.

[12] Collins FS, et al. Finishing the euchromatic sequence of the human genome. Nature. 1999;431(7011):931–945. doi:10.1038/nature03001.

[13] Conselice CJ, Wilkinson A, Duncan K, Mortlock A. The evolution of galaxy number density at $z < 8$ and its implications. The Astrophysical Journal. 2016;830(2):83. doi: 10.3847/0004-637X/830/2/83.

[14] European Space Agency. How many stars are there in the Universe? ESA Science & Exploration. Estimations basées sur des données astronomiques de galaxies.

[15] NASA Exoplanet Science Institute. The NASA Exoplanet Archive Hits 6,000 Planets. IPAC/Caltech; 2025. https://www.ipac.caltech.edu/news/the-nasa-exoplanet-archive-hits-6-000-planets

[16] NASA Hubble Mission Team. The Milky Way Contains at Least 100 Billion Planets According to Survey. NASA News Release; 2012. https://science.nasa.gov/missions/hubble/the-milky-way-contains-at-least-100-billion-planets-according-to-survey/

[17] The Milky Way Galaxy Houses 100 Million Black Holes. SNexplores.org; 2017. Disponible sur: https://www.snexplores.org/article/milky-way-galaxy-houses-100-million-black-holes

[18] Laniakea Supercluster. Phys.org; 2014. https://phys.org/news/2014-09-laniakea-newly-galactic-supercluster-home.html

[19] Van Helden A. The Invention of the Telescope. Trans Am Philos Soc. 1977;67(4):1–67.

[20] Ford BJ. The Optical Microscope: The History of Its Invention and Development. In: Single Lens: The Story of the Simple Microscope. HarperCollins; 1992.

[21] Hecht E. Optics. 5th ed. Pearson Education; 2017.

[22] Born M, Wolf E. Principles of Optics. 7th ed. Cambridge University Press; 1999.

[23] Gardner JP, Mather JC, et al. The James Webb Space Telescope. Space Science Reviews. 2006;123(4):485–606.

[24] Weissleder R. A clearer vision for in vivo imaging. Nature Biotechnology. 2001;19 (4): 316–317.

[25] Lichtman JW, Conchello JA. Fluorescence microscopy. Nature Methods. 2005; 2(12): 910–919.

[26] Beichman CA, Krist JE, et al. Imaging young giant planets from ground and space. Publications of the Astronomical Society of the Pacific. 2010;122(894):162–200.

[27] Roddier F. Adaptive Optics in Astronomy. Cambridge: Cambridge University Press; 1999.

[28] Roorda A, Duncan JL. Adaptive optics ophthalmoscopy. Annual Review of Vision Science. 2015;1:19–50.

[29] Nemiroff RJ, Bonnell JT. APOD: 2022 November 21 – The Butterfly Nebula from Hubble [Internet]. NASA Astronomy Picture of the Day; 21 Nov 2022 [cité le 22 févr 2026]. Disponible sur: https://apod.nasa.gov/apod/ap221121.html

[30] Biology Dr. La division cellulaire. ASU Ask A Biologist; 31 mai 2017 [cité le 22 févr 2026]. Disponible sur: https://askabiologist.asu.edu/divisions-cellulaire

[31] Kurz W, Baranes D. AI-assisted geometric analysis of cultured neuronal networks: Parallels with the cosmic web. In: Proceedings of the 2nd European AI for Fundamental Physics Conference (EUCaIF Con2025), Cagliari, Italy; 2025 Jun 20.

[32] NASA/JPL Caltech/O. Krause. Cassiopeia A: Death Becomes Her [Internet]. Spitzer Space Telescope – Spitzer Science Center; 9 Jun 2005 [cité le 22 févr 2026]. Disponible sur: https://www.spitzer.caltech.edu/image/ssc2005-14c-cassiopeia-a-death-becomes-her

[33] Heusser S. Semaine 16 2017 [Internet]. Codex virtualis; 17 avril 2017 [cité le 22 février 2026]. Disponible sur: https://codexvirtualis.fr/codex/semaine-16-2017

[34] NASA. Helix Nebula Context (VISTA and Webb). NASA Science; 2026. Disponible sur: https://science.nasa.gov/asset/webb/helix-nebula-context-vista-and-webb

[35] NASA. Exposed Cranium Nebula (NIRCam and MIRI Images). NASA Science; 2026. Disponible sur: https://science.nasa.gov/asset/webb/exposed-cranium-nebula-nircam-and-miri-media/

[36] Guyton AC, Hall JE. Textbook of Medical Physiology. 13th ed. Philadelphia: Elsevier Saunders; 2016.

[37] Klessen RS, Glover SCO. Physical processes in the interstellar medium. Annual Review of Astronomy and Astrophysics. 2016; 54:97–13 8.

[38] Kandel ER, Koester JD, Mack SH, Siegelbaum SA. Principles of Neural Science. 6th ed. New York: McGraw-Hill; 2021.

[39] Jackson JD. Classical Electrodynamics. 3rd ed. New York: Wiley; 1998.

[40] West JB. Respiratory Physiology: The Essentials. 10th ed. Philadelphia: Wolters Kluwer; 2016.

[41] McKee CF, Ostriker EC. Theory of star formation. Annual Review of Astronomy and Astrophysics. 2007;45:565–687.

[42] Guyton AC, Hall JE. Textbook of Medical Physiology. 13th ed. Philadelphia: Elsevier Saunders; 2016.

[43] Binney J, Tremaine S. Galactic Dynamics. 2nd ed. Princeton: Princeton University Press; 2008.

[44] Roddier F. Adaptive Optics in Astronomy. Cambridge: Cambridge University Press; 1999.

[45] Roorda A, Duncan JL. Adaptive optics ophthalmoscopy. Annual Review of Vision Science. 2015;1:19–50.

[46] Li KY, Zhang Y, Caruso C, et al. Adaptive optics in ophthalmology: Applications in imaging and surgery. Progress in Retinal and Eye Research. 2020;78:100844.

[47] Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, Thrun S. Dermatologist-level classification of skin cancer with deep neural networks. Nature. 2017;542(7639):115–118.

[48] McKinney SM, Sieniek M, Godbole V, et al. International evaluation of an AI system for breast cancer screening. Nature. 2020; 577: 89–94.

[49] Ball N, Brunner R, Beyer F, et al. Astroinformatics meets medicine: Cross-disciplinary imaging analysis techniques. Journal of Medical Imaging. 2018;5(3):031210.

[50] Farokhzad OC, Langer R. Impact of nanotechnology on drug delivery. ACS Nano. 2009; 3(1):16–20.

[51] Zhang C, Maruggi G, Shan H, Li J. Advances in mRNA vaccines for infectious diseases. Frontiers in Immunology.

[52] Bhushan B. Nanotechnology: The science and technology of nano-materials. Springer Handbook of Nanotechnology. 4th ed. Springer; 2017. p. 3–50.

[53] Brown RW, Cheng YCN, Haacke EM, Thompson MR, Venkatesan R. Magnetic Resonance Imaging: Physical Principles and Sequence Design. 2nd ed. Hoboken, NJ: Wiley; 2014.

[54] Burke BF, Graham-Smith F. An Introduction to Radio Astronomy. 3rd ed. Cambridge: Cambridge University Press; 2014.

[55] Baron D. Machine learning in astronomy: a practical overview. Astrophysics e-prints. 2019; arXiv:1904.07248.

[56] Litjens G, Kooi T, Bejnordi BE, Setio AAA, Ciompi F, Ghafoorian M, et al. A survey on deep learning in medical image analysis. Medical Image Analysis. 2017;42:60–88.

[57] Keltner D, Haidt J. Approaching awe, a moral, spiritual, and aesthetic emotion. Cognition and Emotion. 2003;17(2):297–314.

[58] Stellar JE, Gordon AM, Anderson CL, Piff PK, McNeil GD, Keltner D. Awe and humility. Journal of Personality and Social Psychology. 2015;108(6):883–899.

[59] van Elk M, Karinen A, Specker E, Stamkou E, Baas M. "Standing in awe": The effects of awe on body perception and the relation with absorption. Frontiers in Psychology. 2019;10:180.

[60] Keltner D, Haidt J. Approaching awe, a moral, spiritual, and aesthetic emotion. Cognition and Emotion. 2003;17(2):297–314.

[61] Shiota MN, Keltner D, Mossman A. The nature of awe: Elicitors, appraisals, and effects on self-concept. Cognition and Emotion. 2007; 21(5):944–963.

[62] Stellar JE, Gordon AM, Anderson CL, Piff PK, McNeil GD, Keltner D. Awe and humility. Journal of Personality and Social Psychology. 2015;108(6):883–899.

[63] Piff PK, Dietze P, Feinberg M, Stancato DM, Keltner D. Awe, the small self, and prosocial behavior. Journal of Personality and Social Psychology. 2015;108(6):883–899.

[64] Chirico A, Ferrise F, Cordella L, Gaggioli A. Designing awe in virtual reality: An experimental study. Frontiers in Psychology. 2018; 8:2351.

[65] Ulrich RS, Simons RF, Losito BD, Fiorito E, Miles MA, Zelson M. Stress recovery during exposure to natural and urban environments. Journal of Environmental Psychology. 1991; 11(3): 201–230.

[66] Tang YY, Hölzel BK, Posner MI. The neuroscience of mindfulness meditation. Nature Reviews Neuroscience. 2015; 16(4): 213–225.

[67] Kaplan S. The restorative benefits of nature: Toward an integrative framework. Journal of Environmental Psychology. 1995; 15(3): 169– 182.

[68] Piff PK, Dietze P, et al. Awe, the small self, and prosocial behavior. Journal of Personality and Social Psychology. 2015;108(6):883–899.

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Is Primary Hypothyroidism Truly Primary? A Systems-based Reframing of Thyroid Dysfunction

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ABSTRACT

Primary hypothyroidism is traditionally defined as intrinsic failure of the thyroid gland, most commonly attributed to autoimmune destruction or idiopathic atrophy. While this framework has guided diagnosis and treatment for decades, it may oversimplify the complex neuroendocrine, immune, and metabolic interactions that precede overt thyroid dysfunction. Emerging evidence suggests that immune dysregulation, chronic inflammation, hypothalamic–pituitary–adrenal (HPA) axis activation, nutrient insufficiency, mitochondrial dysfunction, and altered thyroid hormone signaling frequently predate biochemical thyroid failure. In this context, thyroid hypofunction may represent a downstream adaptive response rather than a primary isolated glandular disorder. This narrative review reexamines the concept of "primary" hypothyroidism through an integrative systems-based lens, highlighting mechanisms of functional hypothyroidism, impaired peripheral hormone conversion, thyroid hormone resistance, and immune- mediated loss of tolerance. Clinical implications include recognition of patients who remain symptomatic despite normalization of thyroid-stimulating hormone levels and the limitations of levothyroxine monotherapy in select populations. Reframing hypothyroidism as a secondary manifestation of upstream physiologic stressors may improve diagnostic precision and support more personalized therapeutic strategies.

Index Terms: primary hypothyroidism • functional hypothyroidism • thyroid hormone signaling • deiodinases • non-thyroidal illness syndrome • autoimmune thyroiditis • levothyroxine therapy • precision endocrinology

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REVIEW

Is Primary Hypothyroidism Truly Primary? A Systems-based Reframing of Thyroid Dysfunction

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Abstract

Primary hypothyroidism is traditionally defined as intrinsic failure of the thyroid gland, most commonly attributed to autoimmune destruction or idiopathic atrophy. While this framework has guided diagnosis and treatment for decades, it may oversimplify the complex neuroendocrine, immune, and metabolic interactions that precede overt thyroid dysfunction. Emerging evidence suggests that immune dysregulation, chronic inflammation, hypothalamic–pituitary–adrenal (HPA) axis activation, nutrient insufficiency, mitochondrial dysfunction, and altered thyroid hormone signaling frequently predate biochemical thyroid failure. In this context, thyroid hypofunction may represent a downstream adaptive response rather than a primary isolated glandular disorder. This narrative review reexamines the concept of "primary" hypothyroidism through an integrative systems-based lens, highlighting mechanisms of functional hypothyroidism, impaired peripheral hormone conversion, thyroid hormone resistance, and immune- mediated loss of tolerance. Clinical implications include recognition of patients who remain symptomatic despite normalization of thyroid-stimulating hormone levels and the limitations of levothyroxine monotherapy in select populations. Reframing hypothyroidism as a secondary manifestation of upstream physiologic stressors may improve diagnostic precision and support more personalized therapeutic strategies.

Keywords: *primary hypothyroidism, functional hypothyroidism, thyroid hormone signaling, deiodinases, non-thyroidal illness syndrome, autoimmune thyroiditis, levothyroxine therapy, precision endocrinology*

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1 Introduction

1.1 Conventional Classification of Hypothyroidism and its Limitations

Hypothyroidism is conventionally classified according to the anatomic level of dysfunction within the hypothalamic—pituitary—thyroid (HPT) axis. Primary hypothyroidism refers to impaired thyroid hormone production due to intrinsic thyroid gland pathology, most commonly autoimmune thyroiditis, iodine imbalance, or idiopathic thyroid atrophy. In contrast, secondary hypothyroidism arises from pituitary dysfunction with inadequate thyroid-stimulating hormone (TSH) secretion, while tertiary hypothyroidism reflects hypothalamic impairment resulting in deficient thyrotropin-releasing hormone (TRH) signaling. This anatomic framework has served as the foundation for diagnostic algorithms and therapeutic decision-making in thyroid disease for decades.

Within this paradigm, serum TSH has emerged as the central biomarker guiding diagnosis, treatment initiation, and dose titration. Contemporary clinical guidelines emphasize normalization of TSH as the primary therapeutic goal in the management of overt and subclinical hypothyroidism, with levothyroxine (LT4) monotherapy recommended as first-line treatment for the vast majority of patients.[1, 2] This TSH-centric approach reflects the sensitivity of the anterior pituitary to circulating thyroid hormone levels and the practicality of TSH measurement in population-based care.

However, reliance on mainly anatomic classification and biochemical targets alone may oversimplify the complex, multi-level regulation of thyroid hormone action. The HPT axis does not function in isolation, and thyroid hormone signaling depends not only on glandular hormone production but also on hypothalamic and pituitary regulation, peripheral conversion of thyroxine (T4) to triiodothyronine (T3), cellular transport, receptor responsiveness, and mitochondrial utilization. As a result, normalization of serum TSH may not fully capture disruptions occurring downstream of the thyroid gland or reflect thyroid hormone action at the tissue level. These limitations have become increasingly apparent in clinical practice and have prompted reconsideration of whether the traditional classification adequately reflects the heterogeneity of hypothyroid phenotypes encountered in real-world settings.

1.2 The Clinical Paradox: Biochemical Euthyroidism Does Not Always Equate To Symptomatic Euthyroidism

Despite adherence to guideline-directed therapy and achievement of biochemical euthyroidism, a substantial subset of patients treated with LT4 continues to report persistent symptoms consistent with hypothyroidism. These include fatigue, cognitive impairment, weight gain, mood disturbances, cold intolerance, and reduced quality of life. Early investigations into patient-reported outcomes demonstrated that individuals receiving LT4 therapy often exhibit impaired psychological well-being and persistent symptom burden compared with euthyroid controls, even when serum TSH levels fall within the reference range.[3]

Subsequent studies and large patient surveys have reinforced these findings, revealing widespread dissatisfaction among treated hypothyroid patients and highlighting a disconnect between biochemical markers and perceived health status. In a large survey-based analysis, Peterson and colleagues reported that many patients receiving LT4 therapy continued to experience hypothyroid symptoms and expressed dissatisfaction with treatment despite laboratory values considered "normal" by conventional standards.[4] These observations challenge the assumption that normalization of serum TSH reliably reflects restoration of thyroid hormone action across peripheral tissues.

Importantly, this clinical paradox has fueled renewed interest in individualized thyroid hormone replacement strategies, including combination therapy and selective use of T3 in appropriately selected patients. Personalized thyroid hormone replacement therapy plays a significant role in addressing persistent symptoms, considering factors such as impaired T4-to-T3 conversion, tissue-specific hypothyroidism, and individual variability in thyroid hormone signaling.[5] While these therapeutic considerations address how thyroid hormone replacement may be optimized, they also raise a more fundamental question: whether the underlying classification of hypothyroidism itself sufficiently captures the upstream pathophysiology driving thyroid hypofunction in many patients.

2 Thesis and Aims

Taken together, accumulating clinical and mechanistic evidence suggests that what is commonly labeled as primary hypothyroidism may, in many cases, represent a downstream manifestation of broader systemic dysregulation rather than isolated thyroid gland failure. Immune activation, chronic inflammation, neuroendocrine stress signaling, metabolic dysfunction, micronutrient insufficiency, and mitochondrial impairment can each influence thyroid hormone production, conversion, and tissue responsiveness, often preceding overt biochemical thyroid failure.

The central thesis of this review is that primary hypothyroidism is frequently secondary to upstream immune, inflammatory, neuroendocrine, metabolic, nutrient, and mitochondrial drivers, with the thyroid gland functioning as an end-organ responder within a complex adaptive system. The aims of this paper are to: (1) examine the mechanistic pathways through which upstream physiologic stressors contribute to thyroid hypofunction; (2) describe clinical phenotypes consistent with functional or downstream hypothyroidism; and (3) discuss the diagnostic and therapeutic implications of reframing hypothyroidism through a systemsbased, personalized lens.

3 Why "Primary" May Be Misnamed: A Systems View

3.1 Hypothyroidism as an end-organ phenotype

Traditional models of hypothyroidism conceptualize the disorder primarily as a failure of thyroid hormone production at the level of the gland. While reduced hormone synthesis is a defining feature of overt hypothyroidism, this gland-centric view does not fully account for the multiple regulatory steps required for thyroid hormone action at the tissue level. Thyroid hormone physiology encompasses a coordinated sequence of processes, including thyroidal secretion of T4 and T3, peripheral conversion of T4 to T3, transport of hormone into target cells, binding to nuclear thyroid hormone receptors, and downstream effects on mitochondrial function and cellular energetics.

This broader framework supports a phenotypebased model of hypothyroidism, in which reduced thyroid hormone action reflects dysfunction across one or more levels of hormone production, activation, signaling, or utilization. In such cases, diminished metabolic activity may arise despite structurally intact thyroid tissue and serum thyroid function tests within reference ranges. Accordingly, hypothyroidism can be understood not solely as a glandular disorder, but as an end-organ phenotype emerging from impaired hormone bioavailability or responsiveness at the tissue level.

Central to this concept is the role of iodothyronine deiodinases, which regulate the intracellular activation and inactivation of thyroid hormone. Type 1 and type 2 deiodinases (D1 and D2) catalyze the conversion of T4 to biologically active T3, whereas type 3 deiodinase (D3) inactivates T4 and T3 to reverse T3 (rT3) and diiodothyronine, respectively. These enzymes are differentially expressed across tissues and are dynamically regulated by physiologic stress, inflammation, and illness.[6] As a result, circulating thyroid hormone concentrations may not accurately reflect intracellular T3 availability in metabolically active tissues.

Beyond conversion, effective thyroid hormone action requires intact cellular transport mechanisms and functional receptor signaling. Thyroid hormone enters cells via specific transporters, and once inside the nucleus, T3 binds thyroid hormone receptors to regulate transcription of genes involved in oxidative metabolism, thermogenesis, lipid handling, and mitochondrial biogenesis.[8] Disruption at any point along this signaling cascade-whether due to altered conversion, impaired transport, receptor resistance, or downstream mitochondrial dysfunction-can produce a clinical phenotype consistent with hypothyroidism in the absence of overt thyroid gland failure.

Importantly, thyroid hormone is a key regulator of mitochondrial function and energy production. Mitochondria serve as critical amplifiers of thyroid hormone signaling, translating hormonal cues into ATP generation and metabolic output. Chronic inflammation, oxidative stress, and nutrient insufficiency can blunt mitochondrial responsiveness to thyroid hormone, further contributing to tissue-level hypothyroidism. Within this framework, reduced thyroid hormone action may represent an adaptive metabolic response to systemic stress rather than an isolated defect of the thyroid gland itself.

4 The HPT axis does not function in isolation

The hypothalamic—pituitary—thyroid axis operates within a tightly integrated neuroendocrine and immune network and is profoundly influenced by stress physiology and inflammatory signaling. Crosstalk between the HPT axis, the hypothalamic-pituitary-adrenal (HPA) axis, and the immune system plays a central role in modulating thyroid hormone regulation under both physiologic and pathologic conditions.

Activation of the stress response leads to increased glucocorticoid secretion, which can suppress hypothalamic TRH expression, alter pituitary TSH secretion, and modify peripheral thyroid hormone metabolism. Glucocorticoids and pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α have been shown to influence deiodinase activity, favoring reduced T4-to-T3 conversion and increased production of rT3.[9] These changes are thought to represent an adaptive mechanism aimed at conserving energy during periods of acute or chronic stress.

Seminal work by Chrousos and others established the concept of stress-related neuroendocrine adaptation, emphasizing that endocrine axes do not function independently but rather respond collectively to perceived physiologic threat.[10] Within this context, suppression of thyroid hormone signaling may serve to reduce basal metabolic rate and energy expenditure during times of illness, inflammation, or psychosocial stress. When these stressors become chronic, however, such adaptive responses may persist maladaptively, contributing to sustained thyroid hormone dysregulation.

This phenomenon is well illustrated by the non-thyroidal illness syndrome, in which alterations in central thyroid regulation and peripheral hormone metabolism occur without intrinsic thyroid disease. Inflammatory and critical illness states induce coordinated changes in hypothalamic signaling, TSH secretion, and deiodinase expression, resulting in low T3 levels and impaired thyroid hormone action despite an intact thyroid gland have been described.[11] These findings underscore the sensitivity of the HPT axis to systemic signals and challenge the notion that thyroid hypofunction necessarily originates at the level of the thyroid gland.

Taken together, these observations support a systems-based understanding of hypothyroidism, in which immune activation, stress physiology, and metabolic signaling converge to influence thyroid hormone regulation across multiple levels. In this model, the thyroid gland functions as one component of a broader adaptive network and reduced thyroid hormone action may reflect downstream integration of upstream stress signals rather than primary glandular failure. This conceptual framework is illustrated in Figure 1.

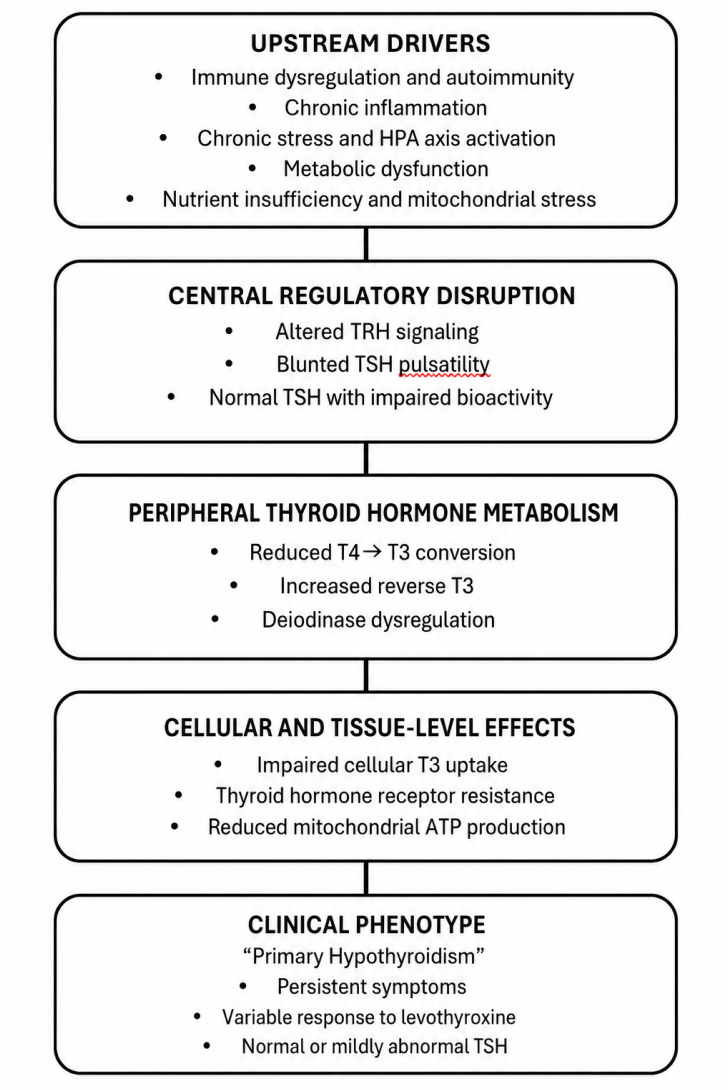

Figure 1. Reframing primary hypothyroidism as a downstream adaptive phenotype.

This schematic illustrates a systems-based model in which reduced thyroid hormone action frequently reflects downstream effects of upstream immune dysregulation, chronic inflammation, stress physiology, metabolic dysfunction, nutrient insufficiency, and mitochondrial stress. These factors influence central hypothalamic-pituitary regulation, peripheral thyroid hormone metabolism, cellular transport, receptor responsiveness, and mitochondrial energy production, culminating in a clinical phenotype consistent with hypothyroidism despite structurally intact thyroid tissue and, in some cases, normal serum TSH levels.

Table 1. Upstream Drivers of Thyroid Hypofunction and Proposed Mechanisms

Upstream Driver	Key Mechanisms	Clinical Clues	Implications
Immune dysregulation	Loss of tolerance, Th1/Th17 skew, autoreactive T cells, cytokine-mediated thyroid injury	Positive TPO/Tg antibodies, comorbid autoimmunity, fluctuating thyroid function	Thyroid is immune target rather than primary origin
Chronic inflammation	IL-6, TNF-α, NF-κB signaling; altered deiodinase activity; impaired receptor signaling	Chronic inflammatory disease, elevated CRP, fatigue disproportionate to labs	Reduced tissue T3 despite normal serum TSH
Stress/HPA axis activation	Cortisol-mediated suppression of TRH/TSH; ↓ T4→T3 conversion; ↑ rT3	High stress burden, sleep disturbance, normal TSH with symptoms	Adaptive energy conservation masquerading as hypothyroidism
Metabolic dysfunction	Insulin resistance, leptin resistance, hepatic conversion impairment	Obesity, metabolic syndrome, NAFLD	Impaired thyroid hormone activation and responsiveness
Nutrient insufficiency	Iron, selenium, zinc, iodine, vitamin D deficiencies	Low ferritin, restricted diets, malabsorption	Compromised hormone synthesis, conversion, and signaling
Environmental/iatrogenic factors	Iodine extremes, endocrine disruptors, immune-modulating drugs	Medication history, occupational exposures	Secondary thyroid hypofunction without intrinsic gland disease

This table summarizes major upstream physiologic contributors that may influence thyroid hormone production, peripheral metabolism, transport, receptor signaling, and tissue-level responsiveness. These factors frequently coexist and interact, shaping clinical phenotypes consistent with hypothyroidism even in the absence of overt thyroid gland failure.

5 Upstream Drivers that Precede Thyroid Hypofunction

Accumulating evidence suggests that thyroid hypofunction frequently arises in the context of broader systemic disturbances that precede overt glandular failure. Immune dysregulation, chronic inflammation, stress physiology, metabolic dysfunction, and environmental or iatrogenic exposures each exert significant influence on thyroid hormone regulation across multiple levels of the HPT axis. Rather than acting as isolated triggers, these factors often coexist and interact, shaping a physiologic milieu in which reduced thyroid hormone action may emerge as a downstream adaptive response. Hypofunction

5.1 Immune Dysregulation and Loss of Tolerance

Autoimmune thyroid disease, particularly Hashimoto's thyroiditis, represents the most common cause of hypothyroidism in iodine-sufficient regions. Traditionally conceptualized as a primary disorder of the thyroid gland, Hashimoto's thyroiditis is increasingly recognized as the consequence of systemic immune dysregulation in genetically susceptible individuals. In this framework, thyroid tissue destruction reflects the target of immune attack rather than the initiating site of pathology.

Foundational work by Weetman and others established that autoimmune thyroid disease arises from complex interactions between genetic predisposition, environmental triggers, and immune regulatory failure. Susceptibility genes influencing antigen presentation, T-cell activation, and immune tolerance contribute to aberrant recognition of thyroid antigens, including thyroid peroxidase (TPO) and thyroglobulin (Tg).[12] Loss of central and peripheral tolerance allows autoreactive T cells to escape regulation, promoting sustained immune activation within the thyroid microenvironment.

More recent insights highlight the role of T-helper cell polarization, with skewing toward Th1 and Th17 responses driving pro-inflammatory cytokine production and cytotoxic injury. In parallel, impaired regulatory T-cell function and checkpoint failure limit immune restraint. Molecular mimicry, bystander activation, and epitope spreading further amplify autoimmune responses, linking thyroid autoimmunity to infections, gut dysbiosis, and systemic inflammatory states.[13] Collectively, these mechanisms support the view that thyroid destruction in Hashimoto's disease is a downstream manifestation of immune imbalance rather than an isolated organ-specific defect.

Chronic Inflammation and Cytokine Signaling

Chronic low-grade inflammation exerts profound effects on thyroid hormone metabolism and action, independent of overt autoimmune thyroid disease. Pro-inflammatory cytokines—including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)—have been shown to alter multiple components of thyroid hormone physiology, including deiodinase activity, hormone transport, and receptor signaling.

Experimental and clinical studies demonstrate that inflammatory signaling shifts deiodinase expression toward reduced activation of T4 to T3 and increased inactivation via type 3 deiodinase, resulting in lower tissue T3 availability and elevated rT3 levels. These changes are mediated in part through nuclear factor κB (NF-κB) signaling pathways, which integrate immune activation with metabolic regulation. Inflammatory cytokines may also impair thyroid hormone transport into cells and interfere with receptor-mediated transcriptional responses, further attenuating thyroid hormone action at the tissue level.

The clinical relevance of these mechanisms is well illustrated in both chronic inflammatory conditions and acute illness. Fliers and colleagues have described coordinated alterations in central thyroid regulation and peripheral hormone metabolism in inflammatory states, emphasizing that reduced thyroid hormone action can occur despite an intact thyroid gland.[10] These findings reinforce the concept that inflammation-driven thyroid hypofunction represents an adaptive metabolic response to systemic stress, which may become maladaptive when inflammation is sustained.

6 Stress Physiology and HPA Axis Activation

Activation of the HPA axis represents a central adaptive response to physiologic and psychosocial stress. Cortisol and related glucocorticoids exert regulatory effects on the HPT axis at multiple levels, influencing hypothalamic TRH expression, pituitary TSH secretion, and peripheral thyroid hormone conversion.

Chronic stress leads to coordinated suppression or modulation of anabolic endocrine pathways, including thyroid hormone signaling, in favor of short-term survival.[9] Elevated or dysregulated cortisol levels suppress TRH transcription, blunt TSH pulsatility, and shift deiodinase activity toward reduced T3 production. These changes lower basal metabolic rate and energy expenditure, serving an adaptive role during periods of threat or resource scarcity.

When stress exposure becomes chronic—as occurs with persistent psychosocial stress, sleep disruption, or inflammatory illness—these

adaptive responses may persist, giving rise to a phenotype consistent with functional hypothyroidism. Importantly, this state may be characterized by normal or minimally altered serum TSH levels, masking underlying tissue-level hypothyroidism. Observations from non-thyroidal illness and chronic stress states further support the view that stress-mediated suppression of thyroid hormone action reflects integration of central and peripheral signals rather than primary thyroid gland failure.[10]

6.1 Metabolic Dysfunction and Adipose-Thyroid Signaling

Metabolic health plays a critical role in thyroid hormone regulation, with bidirectional interactions between thyroid function, insulin sensitivity, and adipose-derived signaling molecules. Insulin resistance, obesity, and metabolic syndrome are associated with alterations in thyroid hormone metabolism and central regulation, even in the absence of overt thyroid disease.

Adipokines such as leptin influence hypothalamic TRH expression and link energy availability to thyroid hormone regulation. In states of leptin resistance, this signaling pathway may be disrupted, contributing to altered central thyroid regulation. Additionally, insulin resistance and hepatic steatosis can impair peripheral conversion of T4 to T3, given the liver's central role in thyroid hormone metabolism.

Thyroid hormone itself is a key regulator of lipid handling, mitochondrial oxidation, and hepatic energy balance, creating a feedback loop between metabolic dysfunction and reduced thyroid hormone action. Reviews of thyroid hormone signaling emphasize that metabolic and inflammatory states can modify tissue responsiveness to thyroid hormone, reinforcing the concept that hypothyroid phenotypes may emerge secondary to metabolic stress rather than primary glandular pathology.[12]

7 Environmental and Iatrogenic Contributors

Environmental exposures and medical therapies represent additional upstream factors capable of precipitating thyroid hypofunction. Both iodine deficiency and iodine excess have been linked to thyroid dysfunction, particularly in genetically susceptible individuals. Cigarette smoking, endocrine-disrupting chemicals, and environmental toxicants may influence thyroid autoimmunity and hormone metabolism through immune modulation and direct effects on thyroid tissue.

A growing body of literature implicates environmental factors in the rising incidence of autoimmune thyroid disease. Antonelli and colleagues have reviewed evidence linking environmental pollutants, occupational exposures, and lifestyle factors to thyroid autoimmunity and dysfunction.[14] These exposures may act synergistically with genetic and immune susceptibility to lower the threshold for thyroid hypofunction.

Iatrogenic factors are also well recognized contributors to thyroid dysfunction. Medications such as amiodarone and lithium directly affect thyroid hormone synthesis and release, while immune-modulating therapies—including interferon-α, tyrosine kinase inhibitors, and immune checkpoint inhibitors—can precipitate thyroiditis and hypothyroidism through immune activation.[15] Recognition of these contributors underscores the importance of viewing thyroid hypofunction within a broader systemic and environmental context rather than as an isolated endocrine disorder.

Collectively, these upstream factors do not act in isolation but frequently converge to influence thyroid hormone production, activation, and tissue responsiveness. For clarity, the principal upstream drivers and their proposed mechanistic contributions to downstream thyroid hypofunction are summarized in Table 1.

8 Mechanistic Pathways: How Upstream Drivers Become A "Primary Hypothyroid" Phenotype

Upstream immune, inflammatory, neuroendocrine, metabolic, and environmental stressors converge on shared regulatory pathways that govern thyroid hormone signaling across the HPT axis and peripheral tissues. Disruption at one or more of these mechanistic checkpoints-central regulation, peripheral metabolism, cellular transport, receptor responsiveness, and mitochondrial utilization-can culminate in a clinical phenotype consistent with hypothyroidism, even in the absence of intrinsic thyroid gland failure. Understanding these pathways provides a biologic bridge between upstream drivers and the downstream hypothyroid phenotype commonly labeled as primary."

9 Central Regulation: Hypothalamic and Pituitary Changes

Central regulation of thyroid function begins at the hypothalamus, where TRH integrates signals related to energy availability, stress, inflammation, and circadian rhythm. TRH secretion is not static; it is dynamically modulated by glucocorticoids, cytokines, leptin, and neural inputs. Chronic stress and inflammatory states suppress TRH transcription and alter hypothalamic sensitivity to peripheral thyroid hormone feedback, leading to subtle but clinically meaningful changes in downstream signaling.

At the pituitary level, TSH secretion exhibits circadian and ultradian pulsatility, which is essential for normal thyroid hormone production and peripheral signaling. Inflammatory cytokines and glucocorticoids blunt TSH pulsatility and may alter post-translational glycosylation of the TSH molecule, potentially reducing its biologic activity despite preserved immunoreactivity on standard assays. As a result, measured serum TSH concentrations may not accurately reflect effective thyrotropic signaling at the thyroid gland.

These mechanisms are well described in the context of non-thyroidal illness syndrome, where central suppression of the HPT axis occurs without intrinsic thyroid disease. Fliers and colleagues demonstrated that acute and chronic illness induce coordinated changes in hypothalamic TRH expression, pituitary TSH secretion, and peripheral thyroid hormone metabolism, emphasizing that central regulation is highly sensitive to systemic signals.[10] Importantly, similar patterns of altered central signaling may occur in chronic stress, inflammation, and metabolic disease, contributing to a phenotype of reduced thyroid hormone action that does not conform neatly to traditional classifications of secondary or tertiary hypothyroidism.

10 Peripheral Thyroid Hormone Metabolism

Peripheral metabolism of thyroid hormone represents a critical determinant of tissue-level thyroid hormone availability. While the thyroid gland secretes predominantly T4, intracellular conversion to biologically active T3 is required for genomic and non-genomic thyroid hormone action. This conversion is governed by iodothyronine deiodinases, whose expression and activity vary by tissue and physiologic context.[9]

Type 1 and type 2 deiodinases (D1 and D2) catalyze the conversion of T4 to T3, whereas type 3 deiodinase (D3) inactivates thyroid hormone, producing rT3 and diiodothyronine. Under conditions of inflammation, illness, or stress, deiodinase expression shifts toward reduced D1 and D2 activity with increased D3 expression, resulting in diminished intracellular T3 availability despite normal or near-normal circulating T4 and TSH levels.[7]

Bianco and colleagues have emphasized that deiodinase regulation is a primary mechanism by which tissues locally control thyroid hormone action, independent of serum hormone concentrations.[6]

Consequently, serum TSH normalization does not guarantee restoration of tissue euthyroidism. This dissociation between circulating markers and intracellular hormone action provides a mechanistic explanation for persistent hypothyroid symptoms in patients with "biochemical euthyroidism" and reinforces the concept of functional or tissue-level hypothyroidism as a downstream phenomenon.

11 Transport of Thyroid Hormone into Tissues

Effective thyroid hormone signaling requires transport of hormone across the plasma membrane into target cells. This process is mediated by specific thyroid hormone transporters, including monocarboxylate transporter 8 (MCT8), monocarboxylate transporter 10 (MCT10), and members of the organic anion transporting polypeptide (OATP) family. Transporter expression is tissue-specific and subject to regulation by developmental, metabolic, and inflammatory signals.

Disruption of thyroid hormone transport provides an additional mechanism by which tissue hypothyroidism may occur despite normal circulating hormone levels. Genetic defects in MCT8, for example, result in severe tissue-specific hypothyroidism with paradoxical serum thyroid hormone patterns, underscoring the importance of transport as a determinant of thyroid hormone action.[14] While such mutations are rare, inflammation and illness may downregulate transporter expression or function, limiting intracellular hormone availability in acquired settings.

These observations further challenge the assumption that serum thyroid hormone concentrations uniformly reflect tissue exposure. Impaired transport represents another point at which upstream stressors can decouple circulating thyroid hormone levels from end-organ effects, contributing to a hypothyroid phenotype without primary glandular failure.

Receptor Sensitivity and "Tissue Hypothyroidism"

Once inside the cell, thyroid hormone action depends on binding to nuclear thyroid hormone receptors and interaction with transcriptional co-regulators that modulate gene expression. Variability in receptor isoform expression, cofactor availability, and intracellular signaling pathways can influence tissue responsiveness to thyroid hormone, creating a spectrum of thyroid hormone sensitivity across individuals and clinical contexts.

The concept of thyroid hormone resistance is well established in rare genetic syndromes involving mutations in thyroid hormone receptor genes, most notably resistance to thyroid hormone.[16] However, emerging evidence supports the existence of acquired or functional forms of reduced thyroid hormone responsiveness, driven by inflammation, oxidative stress, and metabolic dysfunction. In these states, receptor signaling may be attenuated despite adequate intracellular hormone levels, producing tissue-specific hypothyroidism.[17] Brent highlighted that thyroid hormone action is not solely determined by hormone concentration but by integrated signaling across receptors, cofactors, and downstream metabolic pathways.[7] This framework allows for the possibility that patients may experience hypothyroid symptoms due to impaired receptor or post-receptor signaling, even when standard laboratory values fall within reference ranges.

12 Mitochondria as the end-Organ Amplifier

Mitochondria serve as the final common pathway through which thyroid hormone exerts its metabolic effects. Thyroid hormone regulates mitochondrial biogenesis, oxidative phosphorylation, ATP production, and thermogenesis, positioning mitochondria as key amplifiers of thyroid hormone signaling.[8] Reduced mitochondrial responsiveness therefore has profound implications for energy metabolism and symptom expression.

Chronic inflammation, oxidative stress, and nutrient insufficiency impair mitochondrial function and reduce the capacity of cells to respond to thyroid hormone signals. In such settings, even normal intracellular T3 levels may fail to translate into expected metabolic effects, resulting in fatigue, cold intolerance, and reduced metabolic flexibility. Reviews of thyroid hormone-mitochondrial interactions emphasize that mitochondrial health is essential for effective thyroid hormone action and that mitochondrial dysfunction can masquerade clinically as hypothyroidism.[6]

This concept aligns with a systems-based model in which thyroid hormone signaling, mitochondrial resilience, and inflammatory burden are tightly interwoven. From this perspective, hypothyroid phenotypes may reflect impaired energy transduction at the mitochondrial level rather than deficient hormone production alone. Integrating mitochondrial function into the assessment of thyroid dysfunction provides a mechanistic foundation for understanding persistent symptoms and supports a more comprehensive, personalized approach to hypothyroidism management.

13 Nutrient Insufficiency as A Modifier and Driver of Thyroid Hypofunction

Adequate thyroid hormone production, activation, and signaling depend on a network of micronutrients that serve as enzymatic cofactors, structural components, and signaling modulators. Nutrient insufficiency rarely acts as an isolated cause of hypothyroidism; rather, it frequently coexists with immune activation, inflammation, metabolic dysfunction, and gastrointestinal dysregulation.Within a systems-based framework, micronutrient deficiencies may lower physiologic resilience and amplify upstream stressors, contributing to impaired thyroid hormone action and the emergence of a hypothyroid phenotype.

Importantly, nutrient-related thyroid dysfunction may occur in the absence of overt deficiency syndromes. Subclinical insufficiency-often reflected by laboratory values within reference ranges but below optimal thresholds-can meaningfully impair thyroid physiology, particularly in populations with increased demands, chronic inflammation, or impaired absorption.

14 Iron Status and Thyroid Hormone Synthesis

Iron plays a central role in thyroid hormone synthesis, serving as an essential cofactor for TPO, the heme-containing enzyme responsible for iodination of thyroglobulin and coupling reactions within the thyroid gland. Inadequate iron availability can impair thyroid hormone production even in the presence of sufficient iodine intake.

Clinical studies have demonstrated associations between low ferritin levels and reduced thyroid hormone concentrations, as well as increased symptom burden in hypothyroid patients. Iron insufficiency is particularly prevalent among women of reproductive age, individuals with heavy menstrual bleeding, chronic inflammatory states, or gastrointestinal malabsorption, and may coexist with autoimmune thyroid disease.[18] Importantly, iron deficiency may blunt the response to thyroid hormone replacement, contributing to persistent symptoms despite biochemical treatment targets.

Zimmermann and colleagues have highlighted the interaction between iron status and thyroid function, noting that iron deficiency can exacerbate hypothyroidism and impair response to iodine repletion.[18] These findings support the assessment of iron status as a

foundational component of thyroid evaluation, particularly in patients with unexplained symptoms or suboptimal treatment response.

Selenium and Redox Regulation of Thyroid Hormone Metabolism

Selenium is a critical micronutrient in thyroid physiology, serving as an essential component of iodothyronine deiodinases and antioxidant enzymes such as glutathione peroxidases and thioredoxin reductases. Through these roles, selenium supports both thyroid hormone activation and protection of thyroid tissue from oxidative stress.

Multiple randomized trials and meta-analyses have demonstrated that selenium supplementation can reduce TPO antibody titers in patients with autoimmune thyroiditis, although effects on clinical outcomes and thyroid hormone levels are variable.[19, 20] This variability underscores the importance of contextualizing selenium status within a broader systems framework, rather than viewing supplementation as a stand-alone intervention.

Selenium insufficiency may impair peripheral conversion of T4 to T3 and increase susceptibility to oxidative injury within the thyroid gland, particularly in inflammatory states.[19] However, excessive selenium intake carries potential risks, emphasizing the need for individualized assessment rather than indiscriminate supplementation.

15 Zinc and Thyroid Hormone Signaling

Zinc contributes to thyroid hormone physiology through multiple mechanisms, including involvement in TRH synthesis, TSH secretion, and thyroid hormone receptor structure and function. Zinc fingers are integral to nuclear receptor DNA binding, and zinc deficiency may impair transcriptional responses to thyroid hormone at the cellular level.

Observational studies have linked zinc insufficiency to hypothyroid-like symptoms and altered thyroid hormone levels, particularly in populations with malnutrition, chronic illness, or restrictive diets.[1] While interventional data are limited, mechanistic evidence supports zinc as a modulator of thyroid hormone signaling rather than a primary driver of thyroid disease. Within a systems-based model, zinc insufficiency may amplify existing impairments in receptor responsiveness and mitochondrial function.

16 Iodine Balance: Deficiency and Excess

Iodine is an essential substrate for thyroid hormone synthesis, and both iodine deficiency and iodine excess can precipitate thyroid dysfunction. While iodine deficiency remains a global public health concern, excess iodine exposure-through dietary supplements, medications, or contrast agents-has become increasingly relevant in iodine-sufficient regions.[22]

Excess iodine may trigger or exacerbate autoimmune thyroid disease in genetically susceptible individuals, leading to hypothyroidism via immune-mediated mechanisms. Conversely, inadequate iodine intake limits hormone synthesis and can compound the effects of other upstream stressors.[22] The U-shaped relationship between iodine intake and thyroid function highlights the importance of balanced exposure rather than simplistic supplementation strategies.

17 Vitamin D and Immune—Thyroid Interactions

Vitamin D plays an immunomodulatory role that is increasingly recognized in autoimmune diseases, including autoimmune thyroiditis.[23] Vitamin D receptors are expressed on immune cells, and deficiency has been associated with increased prevalence of thyroid autoantibodies and autoimmune thyroid disease in observational studies.

Although causality remains an area of active investigation, vitamin D insufficiency may contribute to immune dysregulation and loss of tolerance, indirectly influencing thyroid function.[23] Correction of deficiency may therefore support immune balance rather than directly altering thyroid hormone levels. As with other micronutrients, vitamin D status should be interpreted within the broader context of immune, inflammatory, and metabolic health.

Integrated Nutrient Insufficiency and Thyroid Resilience

Micronutrient insufficiencies rarely occur in isolation. Iron, selenium, zinc, iodine, and vitamin D status are often interrelated and influenced by dietary patterns, gastrointestinal health, inflammation, and metabolic demand. Inflammatory states may reduce nutrient absorption and increase turnover, while mitochondrial dysfunction increases reliance on micronutrient-dependent enzymatic pathways.

Within a systems-based framework, nutrient insufficiency can be understood as a modifier of thyroid resilience rather than a singular cause of hypothyroidism. Suboptimal nutrient availability may lower the threshold at which immune activation, stress physiology, or metabolic dysfunction translates into clinically apparent thyroid hypofunction. Addressing nutrient status therefore represents an important component of personalized thyroid care, particularly in patients with persistent symptoms or incomplete response to conventional therapy.

18 Clinical Phenotypes that Signal Downstream Hypothyroidism

A systems-based understanding of hypothyroidism has important clinical implications, particularly for identifying patients in whom reduced thyroid hormone action reflects downstream dysregulation rather than isolated thyroid gland failure. Several recurring clinical phenotypes emerge in practice that challenge traditional classification and underscore the limitations of a purely TSH-centric model. Recognition of these phenotypes can guide more nuanced diagnostic evaluation and personalized management strategies.

19 The "Normal TSH, Symptomatic Patient"

One of the most commonly encountered-and clinically challenging-phenotypes is the patient who reports persistent hypothyroid symptoms despite serum TSH levels within the reference range. These individuals may experience fatigue, cognitive slowing, weight gain, cold intolerance, mood disturbances, or reduced exercise tolerance, often leading to frustration for both patient and clinician.

Mechanistically, this phenotype can reflect impaired peripheral thyroid hormone activation, increased reverse T3 production, altered cellular transport, receptor resistance, or reduced mitochondrial responsiveness, as described in prior sections. Inflammatory signaling, chronic stress, and metabolic dysfunction can each contribute to reduced tissue-level T3 availability without substantially altering serum TSH concentrations. As a result, reliance on TSH alone may obscure clinically meaningful thyroid hormone insufficiency at the cellular level.

Observations from non-thyroidal illness and chronic inflammatory states provide a physiologic parallel, demonstrating that reduced thyroid hormone action may occur as an adaptive response to systemic stress despite preserved central regulation.[10] Recognition of this phenotype supports a broader diagnostic lens that considers symptom burden, contextual drivers, and complementary laboratory markers rather than biochemical thresholds alone.

Autoimmune Thyroiditis With Early or Disproportionate Symptom Burden

Another important phenotype includes patients with autoimmune thyroiditis who exhibit significant symptoms despite minimal biochemical abnormality or preserved thyroid hormone levels. These individuals may have elevated TPO or Tg antibodies with normal or mildly altered

TSH and free hormone concentrations, yet report fatigue, cognitive symptoms, musculoskeletal pain, or mood changes.

In this context, immune activation and cytokine signaling may impair thyroid hormone conversion, transport, or receptor function prior to substantial thyroid tissue destruction. Thyroid autoimmunity frequently coexists with other autoimmune or inflammatory conditions, amplifying systemic immune burden and increasing vulnerability to functional hypothyroidism. Rather than representing "early primary hypothyroidism," this phenotype may reflect downstream effects of immune dysregulation on thyroid hormone signaling across multiple levels.

Clinically, this group often demonstrates fluctuating thyroid function over time and variable response to standard replacement strategies. Recognition of immune-mediated downstream effects highlights the importance of addressing inflammatory drivers and monitoring disease evolution, rather than focusing exclusively on glandular failure.

Persistent Symptoms Despite Levothyroxine Therapy

A subset of patients treated with levothyroxine continues to report incomplete symptom resolution despite achievement of guideline-recommended biochemical targets. This phenotype has been consistently described in observational studies and patient-reported outcome surveys and represents a key driver of dissatisfaction with hypothyroidism care.[4]

Multiple mechanisms may contribute to this presentation, including impaired T4-to-T3 conversion, altered tissue transport, receptor-level resistance, gastrointestinal malabsorption, drug-nutrient interactions, and mitochondrial dysfunction. In some cases, levothyroxine monotherapy may normalize serum TSH while failing to restore physiologic T3 availability at the tissue level.

This phenotype underscores the heterogeneity of hypothyroidism and challenges the assumption that biochemical normalization equates to physiologic restoration. It also provides a clinical rationale for individualized assessment and, in selected cases, consideration of alternative or adjunctive therapeutic strategies within an evidence-informed framework.[5]

20 Perimenopausal and Menopausal Women with Stress-Dominant Physiology

Women in the perimenopausal and menopausal transition represent a population in whom downstream hypothyroid phenotypes are particularly prevalent. Fluctuating sex hormones, altered cortisol dynamics, sleep disruption, and increased inflammatory burden can all influence thyroid hormone regulation and tissue responsiveness.

In this population, symptoms commonly attributed to thyroid dysfunction-such as fatigue, weight gain, cognitive complaints, and mood changes-may occur in the setting of normal TSH and free hormone levels.[5] Stress-mediated suppression of thyroid hormone action, changes in deiodinase activity, and mitochondrial vulnerability may contribute to a functional hypothyroid phenotype that is not readily captured by standard testing.

Recognition of this phenotype emphasizes the importance of contextualizing thyroid function within broader neuroendocrine and metabolic changes, rather than reflexively escalating thyroid hormone doses or dismissing symptoms as nonspecific.

21 Chronic Illness and Multisystem Dysregulation

Patients with chronic inflammatory, autoimmune, metabolic, or infectious conditions frequently exhibit alterations in thyroid hormone metabolism consistent with downstream hypothyroidism.[10] In these settings, reduced thyroid hormone action may reflect an adaptive response aimed at conserving energy and limiting oxidative stress.

This phenotype often overlaps with features of non-thyroidal illness syndrome, including low or low-normal T3 levels, elevated rT3, and blunted TSH responses. Importantly, these changes may persist beyond acute illness and contribute to chronic symptom burden. Differentiating adaptive responses from maladaptive persistence requires careful clinical judgment and longitudinal assessment.

22 Clinical Implications of Phenotype Recognition

Identification of downstream hypothyroid phenotypes has important implications for diagnosis and management. Rather than signaling failure of thyroid hormone replacement or patient nonadherence, persistent symptoms may reflect incomplete characterization of the underlying physiologic context. Incorporating symptom patterns, immune and inflammatory markers, metabolic status, nutrient sufficiency, and stress physiology can improve diagnostic precision and guide more individualized care.

Reframing these presentations as downstream manifestations of systemic dysregulation supports a shift away from rigid classification toward a more flexible, mechanism-informed approach. Such a framework aligns more closely with clinical experience and provides a foundation for personalized therapeutic strategies discussed in subsequent sections.

23 Diagnostic Implications: toward a Systems-based Evaluation of Hypothyroidism

Reframing hypothyroidism as a downstream manifestation of multisystem dysregulation has important diagnostic implications. While serum TSH remains a valuable and sensitive marker of central thyroid regulation, exclusive reliance on TSH-centered algorithms may fail to identify tissue-level thyroid hormone insufficiency or upstream drivers that influence thyroid hormone action.[4, 7] A systems-based diagnostic approach does not replace guideline-directed testing but rather expands upon it to improve diagnostic precision in patients with persistent symptoms or atypical clinical presentations.[11] Integrating these elements into clinical practice requires a structured yet flexible approach. A systems-based diagnostic pathway for patients with persistent hypothyroid symptoms is illustrated in Figure 2.

Figure 2: Systems-based Diagnostic Pathway

- **Patient with hypothyroid symptoms** (fatigue, weight gain, cognitive dysfunction, cold intolerance, mood changes)
- **Initial evaluation:**
  - TSH, free T3, free T4
  - Medication adherence and interactions
  - Exclude pregnancy/acute illness
- **TSH normal or mildly abnormal with persistent symptoms**
  - → consider downstream hypothyroidism phenotype
- **Expanded Systems Assessment:**
  - Reverse T3
  - Thyroid peroxidase and thyroglobulin antibodies
  - Ferritin, vitamin D, B12, zinc

  - Hs-CRP, inflammatory markers
  - Metabolic markers (A1c, insulin)
  - Stress and sleep patterns
- **Identify dominant drivers:**
  - Immune/inflammatory
  - Stress/HPA Axis
  - Metabolic dysfunction
  - Nutrient insufficiency
  - Medication/environmental factors
- **Personalized intervention:**
  - Address upstream drivers
  - Optimize LT4 therapy
  - Consider LT4 + LT3 in select patients
  - Shared decision-making
- **Reassess Longitudinally:**
  - Symptoms
  - Labs in context
  - Iterative adjustment

This algorithm outlines a systems-based approach to patients with persistent hypothyroid symptoms. After appropriate initial biochemical evaluation, clinicians are encouraged to consider downstream phenotypes when symptoms persist despite normal or mildly abnormal TSH levels. Expanded assessment of immune, inflammatory, metabolic, stress-related, nutrient, and environmental contributors supports individualized therapeutic strategies and longitudinal reassessment. (LT4 = levothyroxine, LT3 = liothyronine)

24 Limitations of a TSH-centric diagnostic paradigm

Measurement of serum TSH has long served as the cornerstone of hypothyroidism diagnosis and management.' Its sensitivity to small changes in circulating thyroid hormone concentrations makes it a practical and widely accessible screening tool. However, TSH reflects pituitary sensing of thyroid hormone availability and does not directly assess peripheral thyroid hormone activation, transport, receptor responsiveness, or mitochondrial utilization.[7]

In patients with chronic stress, inflammation, metabolic dysfunction, or immune activation, TSH may remain within reference ranges despite impaired tissue-level thyroid hormone action." Altered TSH pulsatility, changes in TSH bioactivity, and central adaptive responses can further decouple serum TSH values from end-organ effects."1 As a result, exclusive reliance on TSH may obscure clinically meaningful hypothyroid phenotypes and contribute to under-recognition of patients with functional or downstream thyroid dysfunction.[4]

Expanded Thyroid Hormone Assessment

In patients with persistent symptoms or discordant clinical and biochemical findings, assessment beyond TSH may provide additional insight.[4] Measurement of FT4 and free FT3 allows evaluation of peripheral hormone availability and conversion. A low or low-normal FT3 in the context of normal TSH and FT4 may suggest impaired T4-to-T3 conversion or increased inactivation through reverse T3 pathways.[7, 11]

While the clinical utility of rT3 measurement remains debated, selective use may be informative in specific contexts, such as chronic illness, significant stress burden, or unexplained symptoms despite adequate LT4 therapy.[1] Importantly, interpretation of rT3 should be contextual and hypothesis-driven rather than routine, recognizing its role as a marker of altered peripheral metabolism rather than a standalone diagnostic criterion.[7]

25 Immune and Inflammatory Markers

Given the strong association between immune dysregulation and downstream hypothyroidism, evaluation of thyroid autoantibodies-including TPO and Tg antibodies-provides important prognostic and mechanistic information.[12] The presence of autoantibodies may signal active immune processes influencing thyroid hormone signaling even before overt thyroid failure develops.[13]

Assessment of systemic inflammatory markers, such as high-sensitivity C-reactive protein (hs-CRP), may further contextualize thyroid dysfunction within a broader inflammatory milieu. Elevated inflammatory burden can impair deiodinase activity, receptor responsiveness, and mitochondrial function, contributing to tissuelevel hypothyroidism independent of serum thyroid hormone concentrations.[7, 11]

26 Nutrient and Metabolic Evaluation

Evaluation of micronutrient status is an essential component of a systems-based thyroid assessment. Iron status, particularly ferritin, should be assessed given its role in thyroid hormone synthesis and its frequent insufficiency in populations at risk for hypothyroidism.[7]

Additional assessment of micronutrients, including vitamin D, iodine, zinc, and selenium, may be appropriate in selected patients, particularly those with autoimmune disease, gastrointestinal disorders, or dietary restrictions.[13]

Metabolic evaluation, including markers of insulin resistance, glycemic control, and lipid metabolism, provides further insight into thyroidmetabolic interactions. Metabolic dysfunction can impair peripheral thyroid hormone activation and tissue responsiveness, reinforcing the importance of integrating metabolic health into thyroid evaluation.[7, 11]

27 Neuroendocrine and Stress-Related Context

Assessment of stress physiology and circadian health represents an often-overlooked component of thyroid evaluation. Chronic psychosocial stress, sleep disruption, and circadian misalignment can suppress central thyroid regulation and alter peripheral hormone metabolism." While routine measurement of cortisol is not universally indicated, careful clinical assessment of stress burden, sleep quality, and lifestyle factors is essential for interpreting thyroid function tests within an appropriate physiologic context.

Incorporating neuroendocrine context into diagnostic reasoning allows clinicians to distinguish between primary glandular failure and adaptive suppression of thyroid hormone action driven by chronic stress or illness."

28 Structural and Imaging Considerations

Thyroid ultrasound provides valuable structural information that can complement biochemical and clinical assessment. In patients with autoimmune thyroiditis, ultrasound may reveal characteristic hypoechogenicity and heterogeneity even before significant biochemical abnormalities arise.[13] Structural assessment can aid in distinguishing

Table 2. Evaluation framework for patients with persistent symptoms despite biochemical euthyroidism

Clinical Scenario	Potential Mechanism	Suggested Evaluation	Clinical Considerations
Persistent symptoms with normal TSH	Impaired T4→T3 conversion; increased rT3; altered tissue responsiveness	FT4, FT3 ± rT3 (contextual use)	Consider peripheral conversion variability; interpret in clinical context
Autoimmune thyroiditis with minimal biochemical abnormality	Immune activation affecting signaling before gland failure	TPOAb, TgAb; inflammatory markers (hs-CRP)	Monitor longitudinally; address inflammatory burden
Fatigue disproportionate to labs	Mitochondrial dysfunction; stress physiology	Ferritin, B12, vitamin D; metabolic markers; stress/sleep assessment	Consider upstream contributors rather than dose escalation alone
Suboptimal response to LT4	Malabsorption; deiodinase variability; receptor-level resistance	Review adherence; GI history; medication interactions; FT3	Evaluate for individualized dosing strategies
Metabolic syndrome phenotype	Insulin resistance impairing conversion and tissue signaling	A1c, fasting insulin, lipid panel, waist circumference	Address metabolic health alongside hormone replacement
High stress / sleep disruption	HPA axis suppression of thyroid signaling	Clinical stress assessment; sleep quality review	Lifestyle modification; avoid reflexive overtreatment
Iatrogenic or environmental exposure	Drug-induced or immune-mediated thyroid dysfunction	Medication review (amiodarone, lithium, TKIs, immune therapies)	Consider temporality and adjust therapy accordingly

This table outlines common clinical scenarios in which thyroid-related symptoms persist despite serum TSH within reference range. It integrates potential mechanistic contributors with suggested evaluation strategies to support a systems-based, individualized diagnostic approach.

inflammatory or autoimmune processes from nodular disease and provide additional context for disease progression.

Importantly, structural abnormalities do not always correlate with functional impairment, reinforcing the need to integrate imaging findings with biochemical and clinical data rather than interpreting them in isolation.[1]

29 Toward a Personalized Diagnostic Framework

A systems-based diagnostic approach to hypothyroidism emphasizes pattern recognition rather than single-marker thresholds.[4, 24] By integrating biochemical data, symptom burden, immune and inflammatory status, nutrient sufficiency, metabolic health, and neuroendocrine context, clinicians can more accurately characterize hypothyroid phenotypes and identify upstream drivers amenable to intervention.[7, 11]

Such an approach supports earlier identification of patients at risk for progression to overt hypothyroidism and provides a rational framework for individualized management strategies. Importantly, this model complements rather than replaces existing guidelines, offering a pragmatic pathway toward more precise and patient-centered thyroid care. Common clinical presentations and suggested evaluation strategies are summarized in Table 2.

30 Therapeutic Implications: Treating Upstream Drivers and Personalizing Thyroid Hormone Replacement

Reconceptualizing hypothyroidism as a downstream manifestation of multisystem dysregulation has important therapeutic implications. While levothyroxine monotherapy remains an effective and appropriate treatment for many patients, a systems-based framework highlights why a subset of individuals experiences incomplete symptom resolution despite biochemical euthyroidism. In such cases, treatment strategies focused exclusively on normalizing serum TSH may fail to address the upstream drivers and mechanistic pathways contributing to impaired thyroid hormone action.

A personalized therapeutic approach recognizes heterogeneity in hypothyroid phenotypes and emphasizes alignment of treatment strategies with underlying pathophysiology, symptom burden, and patient context.

Levothyroxine Monotherapy: Strengths and Limitations

Levothyroxine monotherapy is the standard of care for hypothyroidism and is supported by robust evidence demonstrating safety, efficacy, and long-term tolerability. For the majority of patients, LT4 adequately restores biochemical euthyroidism and improves symptoms. Current guidelines appropriately recommend LT4 as first-line therapy, with dose titration guided primarily by serum TSH.[1]

However, LT4 therapy assumes intact peripheral conversion of T4 to T3 and preserved tissue responsiveness to thyroid hormone. As outlined in prior sections, chronic inflammation, stress physiology, metabolic dysfunction, nutrient insufficiency, and mitochondrial impairment may disrupt these processes. In such contexts, LT4 may normalize serum TSH without restoring physiologic T3 availability or cellular thyroid hormone action, resulting in persistent symptoms.

Recognition of these limitations does not undermine guideline-based care but rather clarifies why a “one-size-fits-all” approach may be insufficient for certain patients.

Addressing Upstream Drivers as a Therapeutic Foundation

A systems-based approach to hypothyroidism prioritizes identification and mitigation of upstream drivers that impair thyroid hormone signaling. Interventions targeting immune dysregulation, inflammation, stress burden, metabolic health, and nutrient sufficiency may enhance thyroid hormone responsiveness and improve symptom burden, either independently or in conjunction with hormone replacement.

For patients with autoimmune thyroid disease, addressing inflammatory load and immune triggers-such as sleep disruption, psychosocial stress, and metabolic dysfunction-may help stabilize disease progression and reduce symptom severity. Correction of nutrient insufficiencies, particularly iron and selenium, can support thyroid hormone synthesis and metabolism when deficiencies are present. Importantly, these interventions should be individualized and evidence-informed, avoiding overgeneralization or excessive supplementation.

Addressing upstream factors does not replace thyroid hormone therapy when indicated, but may reduce the degree of hormone replacement required and improve overall treatment response. Personalizing Thyroid Hormone Replacement

In patients who remain symptomatic despite optimized LT4 therapy and correction of modifiable upstream contributors, consideration of personalized thyroid hormone replacement strategies may be appropriate. This includes careful evaluation of free T3 levels, symptom patterns, comorbid conditions, and patient preferences.

Combination therapy with LT4 and liothyronine (LT3) or the use of T3-containing formulations has been explored in randomized trials with mixed results. While population-level data do not uniformly demonstrate superiority over LT4 monotherapy, subgroup analyses and patientreported outcomes suggest that selected individuals may derive benefit.[24, 25] Variability in deiodinase activity, transport, receptor sensitivity, and mitochondrial responsiveness likely contributes to heterogeneous treatment responses.

A recent narrative review emphasized the importance of individualized thyroid hormone replacement and aligning therapy with patientspecific physiology rather than relying solely on biochemical targets.[5] Within a systems-based framework, T3-containing strategies may be viewed not as first-line therapy, but as a rational option for carefully selected patients with persistent symptoms and evidence of impaired peripheral thyroid hormone action.

30.1 Clinical Safeguards and Shared Decision-Making

Personalized thyroid hormone therapy requires thoughtful clinical judgment and shared decisionmaking. Potential benefits must be balanced against risks, including overtreatment, cardiovascular effects, and bone health concerns. Careful dosing, gradual titration, and close monitoring of symptoms and laboratory values are essential.

Equally important is setting appropriate expectations. Not all symptoms attributed to hypothyroidism are thyroid-mediated, and improvement may depend on addressing coexisting conditions such as sleep disorders, depression, metabolic syndrome, or chronic inflammatory disease. Transparent communication regarding therapeutic goals reinforces trust and supports patient-centered care.

Integrating Therapy within a Systems-Based Care Model

A systems-based therapeutic model reframes hypothyroidism management as an iterative process rather than a static prescription. Treatment response should be assessed longitudinally, with attention to symptom trajectories, physiologic context, and evolving clinical needs. This approach supports flexibility in therapy while maintaining adherence to evidence-based principles.

By integrating upstream interventions with personalized hormone replacement strategies, clinicians can move beyond rigid classification toward a more nuanced, mechanism-informed approach. Such a model acknowledges the complexity of thyroid hormone physiology and aligns treatment with the lived experience of patients whose symptoms persist despite conventional care.

31 Future Directions and Research Priorities

Reframing hypothyroidism as a downstream manifestation of multisystem dysregulation highlights important gaps in current knowledge and underscores the need for research approaches that move beyond gland-centric and TSH-centric paradigms.[4, 24] Future investigations should aim to better characterize tissue-level thyroid hormone action, identify clinically meaningful subphenotypes, and evaluate personalized diagnostic and therapeutic strategies within a systems-based framework.

Defining functional and downstream hypothyroid phenotypes

One of the most pressing research priorities is the development of standardized criteria to define functional or downstream hypothyroidism. Current classifications rely primarily on serum biomarkers that reflect central regulation rather than tissue-level hormone action.[4] Prospective studies are needed to delineate phenotypes characterized by impaired peripheral conversion, altered transport, receptor resistance, or mitochondrial dysfunction, particularly bin patients with persistent symptoms despite biochemical euthyroidism.[6, 7, 11]

Such efforts may involve integration of biochemical markers (e.g., FT3, rT3), immune and inflammatory profiles, metabolic indicators, and symptom-based assessments. Establishing reproducible phenotype definitions would enable more precise patient stratification in both clinical practice and research settings.

Biomarkers of Tissue-Level Thyroid Hormone action

The development of biomarkers that more accurately reflect tissue-level thyroid hormone activity represents a critical unmet need. While serum TSH and circulating hormone levels provide valuable information about central regulation, they offer limited insight into intracellular hormone availability and end-organ responsiveness.[4, 7]

Emerging approaches may include gene expression signatures of thyroid hormoneresponsive pathways, metabolomic profiles associated with thyroid hormone action, or imaging-based assessments of tissue metabolism.[6, 7] Validation of such biomarkers could improve diagnostic precision, facilitate earlier identification of downstream hypothyroidism, and support more targeted therapeutic interventions.

Longitudinal studies of upstream driver modification

Another key research priority is the evaluation of interventions targeting upstream drivers of thyroid hypofunction. Longitudinal studies examining the impact of reducing inflammatory burden, improving metabolic health, correcting nutrient insufficiencies, or mitigating chronic stress on thyroid hormone signaling are needed to clarify causal relationships.[7, 11]

Importantly, these studies should assess both biochemical outcomes and patient-reported symptom measures, recognizing that clinical improvement may precede or occur independently of changes in traditional thyroid function tests.[4] Such data would help define the role of upstream interventions as adjuncts to, or modifiers of, thyroid hormone replacement therapy.

Personalized Thyroid Hormone Replacement trials

While randomized trials comparing levothyroxine monotherapy with combination or T3-containing therapies have yielded mixed results at the population level,[24] future studies should focus on phenotype-specific responses rather than uniform treatment effects. Stratifying participants based on conversion efficiency, inflammatory status, metabolic health, or genetic factors influencing thyroid hormone signaling may clarify which subgroups derive benefit from personalized replacement strategies.[6, 7]

Adaptive trial designs and real-world evidence approaches may be particularly well suited to capturing interindividual variability and informing clinical decision-making in heterogeneous patient populations.

Integrating Systems Biology into Thyroid Research

Advances in systems biology, including multiomics platforms and computational modeling, offer powerful tools for understanding the complex interactions that govern thyroid hormone physiology.[6, 7] Integrating genomic, transcriptomic, metabolomic, and microbiome data with clinical phenotypes may reveal novel regulatory pathways and therapeutic targets.

Such approaches align with a broader shift toward precision endocrinology and have the potential to redefine hypothyroidism as a dynamic, contextdependent condition rather than a static glandular disorder.[24]

Implications for Clinical Guidelines and Education

As evidence supporting systems-based models of hypothyroidism accumulates, future guideline development may benefit from incorporating broader diagnostic and therapeutic considerations for patients with persistent symptoms or atypical presentations.[4, 26] Educational initiatives aimed at clinicians should emphasize the distinction between biochemical normalization and physiologic restoration, fostering more nuanced interpretation of thyroid function tests.[4]

Ultimately, integrating systems-based insights into clinical practice has the potential to improve patient satisfaction, optimize therapeutic

outcomes, and reduce the burden of unresolved symptoms in hypothyroidism care.

32 Conclusion

Hypothyroidism has traditionally been conceptualized as a disorder defined by the anatomic site of dysfunction within the hypothalamic—pituitarythyroid axis, with primary hypothyroidism attributed to intrinsic thyroid gland failure. While this framework has guided effective diagnosis and treatment for many patients, it does not fully account for the heterogeneity of clinical presentations or the persistent symptom burden observed in a substantial subset of individuals despite biochemical euthyroidism.

Accumulating evidence supports a broader, systems-based understanding of hypothyroidism in which reduced thyroid hormone action frequently reflects downstream effects of immune dysregulation, chronic inflammation, neuroendocrine stress signaling, metabolic dysfunction, nutrient insufficiency, and impaired mitochondrial responsiveness. Within this context, the thyroid gland functions as an end-organ responder rather than the sole origin of disease, and normalization of serum TSH may not reliably indicate restoration of tissue-level thyroid hormone activity.

Reframing hypothyroidism as a downstream adaptive phenotype does not negate the importance of thyroid hormone replacement or established clinical guidelines. Rather, it provides a physiologic rationale for why standard approaches may be insufficient for some patients and highlights the need for diagnostic and therapeutic strategies that extend beyond gland-centric and TSH-centric paradigms. Integrating symptom patterns, peripheral hormone dynamics, immune and inflammatory context, metabolic health, and mitochondrial function offers a more precise and patientcentered approach to care.

Recognizing hypothyroidism as a manifestation of multisystem dysregulation encourages earlier identification of upstream drivers, supports individualized treatment strategies, and aligns clinical practice with the lived experience of patients whose symptoms persist despite conventional therapy. As the field moves toward precision endocrinology, adopting a systems-based framework may improve diagnostic accuracy, therapeutic outcomes, and quality of life for individuals affected by hypothyroidism.

Key Takeaways

- **Primary hypothyroidism is often downstream.** In many patients, reduced thyroid hormone action reflects immune, inflammatory, neuroendocrine, metabolic, nutrient, and mitochondrial dysregulation rather than isolated thyroid gland failure.
- **TSH normalization does not guarantee tissue euthyroidism.** Serum TSH reflects central regulation and may not capture impairments in peripheral conversion, cellular transport, receptor responsiveness, or mitochondrial utilization of thyroid hormone.
- **Hypothyroidism is best understood as a phenotype, not a single disease.** Clinical presentations vary widely, with distinct downstream phenotypes explaining persistent symptoms despite "normal" laboratory values.
- **Upstream drivers matter.** Immune activation, chronic inflammation, stress physiology, metabolic dysfunction, and nutrient insufficiency can precede and perpetuate thyroid hypofunction.
- **A systems-based diagnostic approach improves precision.** Integrating symptoms, peripheral thyroid markers, immune and inflammatory context, metabolic health, and nutrient status allows more accurate characterization of hypothyroid phenotypes.
- **Levothyroxine monotherapy is effective for many—but not all—patients.** Persistent symptoms should prompt reassessment of underlying mechanisms rather than reflexive dose escalation or dismissal.
- **Personalized therapy requires shared decision-making.** Addressing upstream contributors and, when appropriate, individualizing thyroid hormone replacement may improve outcomes for selected patients.
- **Reframing hypothyroidism aligns care with patient experience.** Viewing hypothyroidism as a downstream adaptive response supports more patient-centered, mechanism-informed management strategies.

REFERENCES

[1] Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association task force on thyroid hormone replacement. Thyroid. 2014 Dec;24 (12):1670-751. doi: 10.1089/thy.2014.0028. PMID: 25266247; PMCID: PMC4267409.

[2] Pearce SH, Brabant G, Duntas LH, et al. 2013 ETA Guideline: Management of Subclinical Hypothyroidism. Eur Thyroid J. 2013 Dec; 2(4):215-28. doi: 10.1159/000356507. Epub 2013 Nov 27. PMID: 24783053; PMCID: PMC3923601.

[3] Saravanan P, Chau WF, Roberts N, et al. Psychological well-being in patients on "adequate" doses of L-thyroxine: results of a large, controlled community-based questionnaire study. Clin Endocrinol (Oxf). 2002;57(5):577-585. DOI: 10.1046/j.1365-2265.2002.01654.X

[4] Peterson SJ, McAninch EA, Bianco AC. Is a normal TSH synonymous with "euthyroidism" in levothyroxine monotherapy? J Clin Endocrinol Metab. 2018;103(9):3333-3345. Doi: 10.1210/jc.2016-2660

[5] Mazza AD. Personalized approaches to hypothyroidism: the role of triiodothyronine (T3) in thyroid hormone replacement. Cureus. 2025; 17(8):e90685. DOI: 10.7759/cureus.90685

[6] Bianco AC, Salvatore D, Gereben B, et al. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev. 2002; 23(1): 3889. DOI: 10.1210/edrv.23.1.0455

[7] Brent GA. Mechanisms of thyroid hormone action. N Engl J Med. 2012;367(1):29-41. DOI: 10.1172/JCI60047

[8] Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. Physiol Rev. 2014 Apr;94(2):355-82. doi: 10.1152/physrev.00030.2013. PMID: 24692351; PMCID: PMC4044302.

[9] Boelen A, Kwakkel J, Fliers E. Beyond low plasma T3: local thyroid hormone metabolism during inflammation and infection. Endocr Rev. 2011;32(5):670-693. DOI: 10.1210/er.2011-0007

[10] Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol. 2009 Jul;5(7):374-81. doi: 10.1038/nrendo.2009.106. Epub 2009 Jun 2. PMID: 19488073.

[11] Fliers E, Bianco AC, Langouche L, et al. Thyroid function in critically ill patients. Endocr Rev. 2015;36(2):159191. DOI: 10.1016/S2213-8587(15)00225-9

[12] Weetman AP. Autoimmune thyroid disease: propagation and progression. Eur J Endocrinol. 2003 Jan;148(1):1-9. doi: 10.1530/eje.0.1480001. PMID: 12534350.

[13] Caturegli P, De Remigis A, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. Nat Rev Endocrinol. 2014;10(6): 357365. DOI: 10.1016/j.autrev.2014.01.007

[14] Antonelli A, Ferrari SM, Corrado A, et al. Autoimmune thyroid disorders. Autoimmun Rev. 2015 Feb;14(2):174-80. doi: 10.1016/j.autrev.2014.10.016. Epub 2014 Oct 25. PMID: 25461470.

[15] De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet. 2016 Aug 27;388 (10047):906-918. doi: 10.1016/S0140-6736 (16)00278-6. Epub 2016 Mar 30. PMID: 27038492; PMCID: PMC5014602.

[16] Visser WE, Friesema ECH, Visser TJ. Minireview: thyroid hormone transporters: the knowns and the unknowns. Endocr Rev. 2011;32(5):793-831. Doi: 10.1210/me.2010-0095

[17] Refetoff S, Dumitrescu AM. Syndromes of reduced sensitivity to thyroid hormone: genetic defects in hormone receptors, cell transporters and deiodination. Nat Rev Endocrinol. 2007;3(5): 112. Doi: 10.1016/j.beem.2007.03.005

[18] Zimmermann MB. The influence of iron status on iodine utilization and thyroid function. Annu Rev Nutr. 2006;26:367-389. DOi: 10.1146/annurev.nutr.26.061505.111236

[19] Gartner R, Gasnier BC, Dietrich JW, et al. Selenium supplementation in patients with autoimmune thyroiditis decreases thyroid peroxidase antibodies concentrations. J Clin Endocrinol Metab. 2002;87(4):16871691. Doi: 10.1210/jcem.87.4.8421

[20] Winther KH, Wichman J, Bonnema SJ, et al. Insufficient documentation for clinical efficacy of selenium supplementation in autoimmune thyroiditis: a systematic review and meta-analysis. Thyroid. 2017;27(4):494502. Doi: 10.1007/s12020-016-1098-z

[21] Mahmoodianfard S, Vafa M, Golgiri F, et al. Effects of zinc and selenium supplementation on thyroid function in overweight and obese hypothyroid female patients: a randomized double-blind controlled trial. J Am Coll Nutr. 2015;34(5):391-9. doi: 10.1080/07315724.2014.926161. Epub 2015 Mar 11. PMID: 25758370.

[22] Kvicala J, Zamrazil V. Effect of iodine and selenium upon thyroid function. Cent Eur Public Health. 2003 Jun;11(2):107-13. PMID: 12884559.

[23] Bendotti G, Mele C, Costantini L, et al. The role of vitamin D in autoimmune thyroid diseases: From immunomodulation to clinical implications. Nutrients. 2026 Jan 9;18(2):217. doi: 10.3390/nu18020217. PMID: 41599829; PMCID: PMC12845051.

[24] Wiersinga Wm. Therapy of Endocrine Disease: T4 + T3 combination therapy: is there a true effect? Eur J Endocrinol. 2017 Dec;177(6):R287-R296. doi: 10.1530/EJE-17-0645. Epub 2017 Aug 30. PMID: 28855267

[25] Hoang TD, Olsen CH, Mai VQ, Clyde PW, Shakir MK. Desiccated thyroid extract compared with levothyroxine in the treatment of hypothyroidism: a randomized, double-blind, crossover study. J Clin Endocrinol Metab. 2013 May; 98(5): 1982-90. doi: 10.1210/jc.2012-4107. Epub 2013 Mar 28. PMID: 23539727.

[26] Wiersinga WM. Paradigm shifts in thyroid hormone replacement therapies for hypothyroidism. Nat Rev Endocrinol. 2014; 10(3):164174. DOI: 10.1038/nrendo.2013.258

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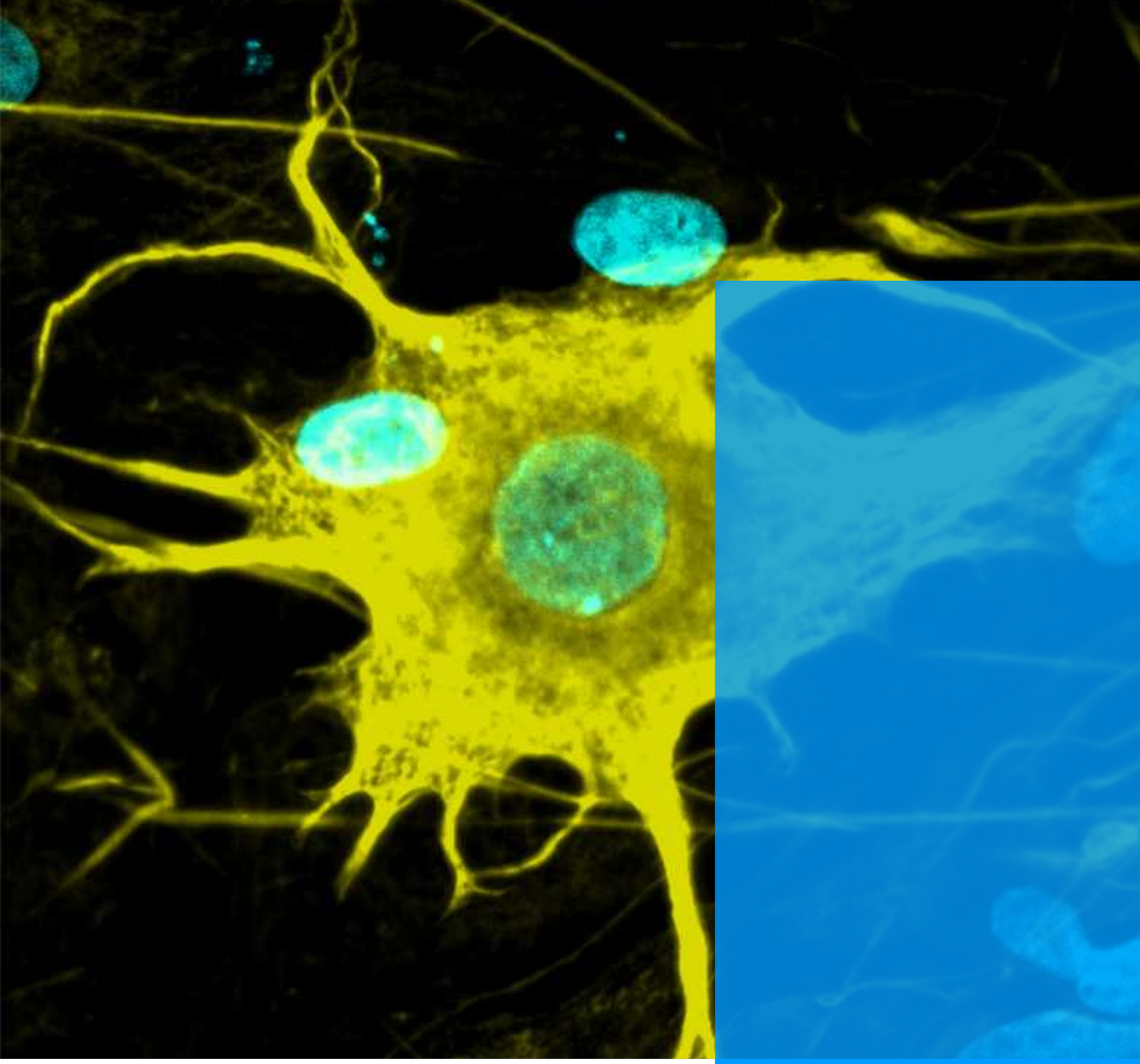

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