REVIEW ARTICLE

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Hyperthermia for infectious diseases: Mechanisms and clinical potential

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ABSTRACT Hyperthermia, which involves the controlled application of heat, has been explored as a potential therapy for infectious diseases. This innovative approach applied upraised temperatures to boost immunological responses and directly disrupt pathogens viability. Hyperthermia can ameliorate the body's ability to fight infections by stimulating the immune system and growing, the circulation of immune cells. Furthermore, upraised temperatures could negatively influence pathogen's viability and virulence, making them less able to cause disease. When used as an adjunct therapy alongside traditional treatments, hyperthermia has the potential to upgrade patient's outcomes by working synergistically with other therapeutics modalities. However, several challenges must be considered to ensure the effectiveness and safety of this suggested treatment. If proven effective, hyperthermia could be a valuable inclusion to the present arsenal of treatments for infections agents, offering a novel approach to boosting immunological functions and directly targeting pathogens. This review provides a comprehensive overview of the importance of using fever therapy in combating infectious diseases, especially in light of the rapid development of antibiotic resistance among pathogens. The review presents important pathways for the use of heat as a therapeutic agent or as an adjuvant to conventional therapies. Each pathway described in this paper could open new avenues for future studies on combating bacterial infections using heat therapy.

KEYWORDS hyperthermia, infections, thermotherapy, therapeutic heat, infectious diseases

1. INTRODUCTION

Thermotherapy (or therapeutic hyperthermia) is a medicinal therapy that entails upraise body's temperature to levels over normal physiological levels that ranging between 40°C-45°C. This technique utilizes the body's response to heat for enhancing the efficacy of other traditional treatments, like chemotherapy, radiotherapy, as well directly combatting infection and tumors [1], [2]. By upraising tissues temperatures, hyperthermia boost raised blood flow and oxygen to the targeted region, which could boost the delivery and effectiveness of agents employs to chemotherapy and radiotherapy. Also, hyperthermia aids to disrupt tumor cell's structure, so being more susceptible to fight by medications [3], [4]. Moreover, hyperthermia had been proven to trigger the immune system, activating the producing of heat shock proteins that backing both recognition and destruction of tumor cells [2], [5].

Historically, therapeutic hyperthermia had been employed for treating infectious diseases prior to emergence of modern antibiotics. For instance, it was applied to treat syphilis and other bacterial infections by enhancing fevers to impede the growth of bacteria. In contemporary medicine, this technique is often utilized together with other therapies to upgrade clinical consequences in cancer patients, underscoring its possibility as a multi-faceted therapeutic tactic [6].

Generally, thermotherapy could provide a promising adjunctive treatment pattern, where it employs the physiological responses to heat to boost the performance of already existent medical therapy and to attack a range of pathological diseases [7], [8].

The use of thermotherapy for treatment of infectious diseases has acquired a mounting attention in the latest years. Hyperthermia has been revealed to exert a direct cytotoxic impact on pathogens as well as modifying the immunological response in ways that could amplify clearance of infection [9]. The fundamental mechanisms by which thermotherapy affects infectious disease are multi-faceted and including a complex interplay between thermal stress, immunity activation, and pathogens-specific sensitivity [10].

Hyperthermia can prompt the heat shock response of host cells, leading to upregulate the cyto-protective proteins along with signaling pathways that could boost cellular response to both thermal and oxidative stress [3]. Concurrently, hyperthermia can deactivate pivotal cellular pathways of pathogens, including proteins folding, membranes integrity, and nucleic acids replication, thus directly pathogen killing or making

it more sensitive to other therapy approach [11]. Additionally, hyperthermia could modulate immunological response in ways that can enhance infection's clearance. For instance, hyperthermia can catalyze natural killer cells activity, increase antigens presentation, and potentiate recruitment of cytotoxic leukocytes to infection's sites [3], [12].

Clinical implications of therapeutic modality by hyperthermia for infectious diseases are vast and unlimited, and have potential applications for various infections inclusive the viral infection, bacterial sepsis [12], as well as fungal pneumonia [11]. A recent review has further reconnoitered this potential, revealing that hyperthermia could boost immunological responses and directly impede pathogens viability [13].

This review aims to appraise the efficacy of hyperthermia in treatment of infectious diseases, with a focus on how hyperthermia impacts the immunological responses and the ability of a pathogen to survive and create an infection. In addition, the study exploring the potential importance of applied hyperthermia as an adjunctive therapy to standard treatments, and its affect the survival rates and enhance patient's clinical outcomes. The study also seeks to identify challenges related with the applied of hyperthermia, such as the thermal resistance of some pathogens, side effects, and difficulty of achieve precise temperatures control at infection site.

2. MECHANISMS OF THERAPEUTIC HYPERTHERMIA IN COMBATTING OF INFECTIOUS DISEASES

Given the ongoing challenges in combating infectious diseases, the trend towards alternative therapies has become imperative. One such therapy is therapeutic hyperthermia, which involves raising body temperature in a controlled manner to control infections. This trend is attributed to the increasing resistance of pathogens to conventional antibiotics, which calls for exploring new and effective approaches. The use of heat is emerging as a promising option to be used alone or as a complement to conventional therapies, to achieve beneficial effects including destruction of pathogens and enhancement of immune response. By raising body's temperature, hyperthermia could directly deactivate pathogens and enhance the immune response. Hyperthermia approach benefits from the natural heat shock response of host's body to ameliorate outcomes in patients infected with several microbial agents [14]. The mechanisms that mediate the impacts of hyperthermia on fighting infection include the following:

2.1. Direct microbial inactivation

2.1.1. Proteins denaturation

Upraised temperatures could denature proteins, which are crucial for the survival and replication of microbes; where proteins denaturation affect microbes viability by mean of enzymatic inactivation and disrupt structural integrity This leading to loss of biological action and inhibits microbial multiplication. In bacterial infections, thermotherapy could lead to disruption of bacterial activity and cell death. It is known that proteins are involved in numerous cellular functions, such as metabolism, structure, and replications; all these function are disrupting when protein denature, thus stop bacterial growth and gradually death of cells [15]. Also, bacterial biofilms are affected; where proteins denaturation within these structures could disrupt biofilm's structural integrity and metabolic process, so being more sensitive to antimicrobial medications [16]. With respect to viral infections, proteins play decisive roles in virus's structure and function. Denaturation of proteins could lead to morphological changes and mislaying of infectivity due to denature capsid's proteins, thus viruses being unstable [17]. In fungal infections, protein denaturation impacts overall cellular processes, including growth and metabolism. Fungal proteins are crucial to maintain cells structures and functions, so their denaturation leading to impair growth and viability [18].

2.2. Membranes disruption

Hyperthermia could lead to disrupt the cellular membranes of bacteria, viruses, as well as fungi, leading to cell lysis and death. Enomoto et al. [19] elucidates that thermal upraise escalates membrane permeability, and leading to cell lysis. Where if cells are exposing to hyperthermia, the lipid bilayer of their membranes being more fluid and permeable, thus ions, nutrients, and other molecules are leaking out from the cell, affecting the cellular homeostasis. Besides, the denaturation of proteins, which embedded within the membrane further affecting membrane's integrity and function. All these events leading to lysis the cells, where the membrane ruptures and all contents are releasing, leading to cell death.

2.3. Improvement of host immunological response

Hyperthermia has been revealed to boost the immune response against microbial infections by bacteria, viruses, and fungi. This technique leverages the natural heat shock responses of the body to upgrade outcomes of infected patients. High temperature can achieve these benefits through the following mechanisms:

2.3.1. Stimulation of immune cells

Hyperthermia can stimulate the key cells of immune system such as macrophage, dendritic cell, and T-lymphocytes, which play prime roles in microbial identifying and disposing. Enomoto et al. [19] explain that heat escalates membrane permeability, causing cell lysis and releasing of pathogen-associated molecular patterns, which further enhance immune response. Bergman et al. [20] explain how hyperthermia enhances innate immunity by boosting expressions of antimicrobial peptides and producing of reactive oxygen species (ROSs).

2.3.2. Improved pathogen clearance

Hyperthermia cans directly combating pathogens by denaturing crucial proteins and disruption of cellular membrane, which leading to loss of biological activity and block the replication and propagation of pathogens. Zhu et al. [21] revealed that thermal-killed Bacillus Calmette-Guérin joined with a squalene-based adjuvant notably boosts Tumor Necrosis

Factor-α (TNF-α) and Monocyte Chemoattractant Protein-one (MCP-1) releasing, indicating stimulation through Toll-Like Receptor 2/4 (TLR2/4) and Myeloid Differentiation Primary Response-88 dependent-pathways.

2.3.3. Enhancement of cytokine production

Production of cytokines also enhanced by thermotherapy, this is could achieved by stimulation cellular stress response and immune cells. When cells exposed to higher temperatures, they recognize it as a stressor, so trigger pathways of stress response, inclusive the heat shock responses; leading to produce the heat shock proteins (HSP), which work as molecular chaperones conserving cells from thermal-induced damage. HSP interact with immune cells and work as danger-associated molecular pattern, warning the immune system that damages or stresses have taken place and enhancing cytokine production [22]. What's more, hyperthermia could directly affect immune cells by augmented expression of TLRs, which TLRs recognize DAMP, including HSP, and stimulate signaling pathways such as NF-κB that boost the producing of pro-inflammatory cytokines including IL-6, IL-1β, and TNF-α [23].

2.4. Improvement innate immunity

Hyperthermia based technique can enhance innate immunity by boosting expressions of antimicrobial peptides, ROSs production, and stimulation of autophagy. Bergman et al. [20] exhibit how innate effectors comprise a potent defense weapon against infections. Hyperthermia boosts the innate immune response via various mechanisms. When the temperature is raised, production of HSP and helper molecules is stimulated, which stimulates antigens presentation to dendritic cells. These cells have an influential role in activating killer T cells that target infected. Additionally, fever, which is a natural response of the host when there is an invading microbe, can as well ameliorate the effectiveness of macrophages in killing invading bacteria and blocking their proliferation [20], [24].

2.5. Enhancement heat shock proteins

Heat shock proteins are a family of proteins that cells produce in response to stressful conditions, including high temperatures. These proteins act as molecular chaperones, helping to properly shape other proteins and preventing aggregation of degraded proteins [25]. Under normal physiological conditions, HSP help maintain cellular homeostasis by assuring that proteins are properly folding and function effectively. However, during high-temperature treatment, HSP are significantly increased in expression to counteract the damaging effects of heat on cellular proteins [26]. In the context of remodeling of degraded proteins, HSP remodel proteins that are degraded by heat, protecting cells from damage caused by heat stress. This process helps maintain the integrity of cellular proteins and prevents aggregation of damaged proteins [27]. Regarding the degradation of damaged proteins, HSP direct degraded proteins to the Ubiquitin-Proteasome Pathway, which helps in the clearance of harmful proteins and maintaining cellular homeostasis. The supporting cell survival achieved by preventing the initiation of cell death, HSPs help cells survive under extreme thermal conditions, which enhances the body's ability to resist heat-related diseases [26].

2.6. Supportive antibiotics therapy

a) Increasing Permeability: Hyperthermia could enlarge the permeability of germ cells, allowing antibiotics to easy entering and act more potently. Iba et al. [28] explain how hyperthermia boosts the permeability of microbial membrane, facilitating drugs entrance.

b) Minimize Resistance: The integration between hyperthermia and antibiotics can minimize the resistance of microbes to treatment. Gazel et al. [29] revealed that hyperthermia joint with antibiotics being more functional against resistant microbes.

3. APPLICATIONS OF THERMOTHERAPY IN MEDICAL FIELD

In addition to the importance of elevated hyperthermia in combating microbial diseases, hyperthermia has other medical applications of clinical importance, which can be summarized as follows:

3.1. Hyperthermia and cancer treatment

Hyperthermia is employed in combination with cancer therapy to boost their efficacy. It has been used to different kinds of cancer, such as breast, cervical, esophageal, liver, lung, and melanoma. Clinical experiments have revealed that heat therapy could shrink tumors and upgrade patients outcomes when used together with radiotherapy and chemotherapy [30], [31], [31].

There are various types of thermotherapy applied in cancer treatment, be conditional on the area being treated; Local Hyperthermia that picks out a small region, like a tumor, employing techniques like radiofrequencies ablation, microwaves, or ultrasounds. Regional Hyperthermia that picks out larger areas, such as limbs or organs, utilizing external heat source or perfusion (heat blood and reintroduce it into the body). Whole-Body Hyperthermia that could treat the entire body, such as treat metastatic cancer that spread throughout the body [32].

Hyperthermia could achieve this ability via several mechanisms that include: Sensitizing cancer cells, enhancing blood flow, inducing HSP, and direct cytotoxic impacts [32].

3.2. Thermotherapy ablation of tumors

It is a slight invasive procedure that employs heat to break down cancer cells. In particularly, the technique is practical to treat tumors that being surgically hard to reach. The procedure involving insert a probe into the tumor, and then heat it to a high temperature, this is usually applied radiofrequencies, microwaves, or a laser energy [33].

The principal mechanism of thermotherapy ablation involving direct applied of heat to the tumor tissues, resulting the cellular destruction as well as coagulative necrosis. The heat leads to protein's denaturation and disrupting cellular membrane and as consequence the irreversible cell death. Furthermore, thermotherapy ablation can boost the immunological response, amplifying the body's capacity to pick out and break down residual cancer cells [34]. Thermal ablation is applied to treat many types of cancers such as liver, kidney, lungs and even bone tumors. This technique is particularly suitable for small tumors or those in critical areas where conventional surgery is risky. Recent advances in imaging techniques, such as magnetic resonance imaging-guided ultrasound, have improved the accuracy and effectiveness of thermal ablation. Ou et al. [33] reported that thermal ablation used for papillary thyroid carcinoma and remembered that is being a promising conventional treatment, especially for individuals who have difficulty with surgery. Another investigation conducted by Bulatović et al. [35] estimated a robotic approach to configure thermal ablation volume, revealing ameliorated repeatability and accuracy versus to standard technique.

3.3. Hyperthermia alleviate chronic pain

Heat therapy has shown potential in the management of chronic pain; hyperthermia could escalate blood flow, diminish muscle tension, and enhance healing, which can help relieve pain [36]. The consensus on the applied of hyperthermia for chronic pain handling is still evolving. While this technique had been explored as a novel therapy toward chronic pain, but the scientific evidences boost its impacts is not yet potent, yet, there is an increasing attention in its prospective benefits.

A Delphi-based consensus investigation by Lubrano et al. [37] among European experts on thermotherapy in musculoskeletal pain shed a light on the mechanism of action, uses, effectiveness and safety. Regarding its mechanism of action in relief pain, heat could improve muscles flexibility, augments blood flow as well metabolism, and stimulates heat-sensitive nerve endings, which could block pain signal. Hyperthermia therapy is used to non-specific low back pain, long-term nociceptive pain, as well as mechanical pain, while it isn't recommended to acute inflammatory joint pains. In the context of effectiveness, superficial thermotherapy has a short-term impact on alleviate pain and can minimize the demand for analgesics. As well, it could contribute to manage long-term pain when combined into multimodal approaches. In general, hyperthermia is safe and well-tolerated, with a virtue safety profile when applied appropriately.

3.4. Hyperthermia for metabolic diseases

Metabolic diseases represent a significant health burden due to their increased prevalence, chronic nature, related-complications and highly mortality rates associated with them. These diseases inclusive of wide ranges of conditions that influence the body's ability for processing and utilizing nutrients and energy such as Diabetes mellitus, obesity, hyperlipidemia, and metabolic syndrome [38], [39].

Hyperthermia has garnered considerable attention in the field of metabolic diseases management. Despite the fact that the exact mechanisms underlying the relation between thermotherapy and metabolic diseases are complex and future research are required to shed a light on the potential therapeutic advantages of leveraging this physiological condition. One principle aspect of impacts of hyperthermia on metabolic disorders is its ability to adjust cellular signaling pathways. Hyperthermia has been revealed to impact critical intracellular processes, like DNA repair pathways and systemic immunological responses, which are usually dysregulated in these disorders [40], [41]. Others suggesting mechanisms of hyperthermia's action are including Beige fat activation, enhancement of insulin sensitivity, and increased energy expenditure. Regarding to Beige fat activation this type of fat possess ability to burn sugar and lipids, and producing heat via thermogenesis, where this pathway can help in reduction of obesity and enhancing metabolic health. In the context of enhancement of insulin, hyperthermia has been revealed to boost insulin sensitivity, which is a key determinant in type 2 diabetes management. Also, hyperthermia found to escalate overall energy expenditure, helping in losing weight as well metabolic regulation [22], [42], [43]. Xu et al. [42] revealed that the applied of local hyperthermia to convert white fat into beige one, which can aid in managing of obesity and metabolic diseases. Also, applied of whole body Hyperthermia like using of sauna, could have several metabolic benefits, such as improving glucose metabolism and lessen body fat [28].

According to the direct translation of preclinical outcomes, the scientific evidences suggesting that hyperthermia could be a hopeful complementary approach in the handling of metabolic diseases.

4. ETHICAL ASPECTS OF HYPERTHERMIA THERAPY

The ethical aspects of thermotherapy have a number of considerations, which inclusive the participants consent, potential risk and advantages, and unbiased access to treatment; some of these key points are explained below [1]:

4.1. Informed Consent

All participants should be fully informed regarding the potential risk as well the benefits of thermotherapy. They should know the procedure, potential side effects, and alternative therapy options prior to presenting consent.

4.2. Risks/Benefits Analysis

Thermotherapy providing significant advantages, it enhances the potency of other treatments as chemotherapy. Nevertheless, it also has some risks, as burns, dehydration, along with systemic inflammations. A comprehensive risks-benefits analysis is crucial to assure that the potential advantages surpass the risks.

4.3. Equitable Access

assurance that thermotherapy is attainable to all patients, regardless of their socioeconomic, is a principle ethical consideration. This encompasses address differences in healthcare obtaining and providing enough resources for treatments.

4.4. Clinical experiments and Research

Ethical behavior in clinical experiments and research is important. This includes assurance that experiments are conducted with translucence, integrity, and respecting for patients' rights. Researchers should as well consider the ethical implication for utilizing hyperthermia in experimental setting.

4.5. Patients Autonomy

Respect the patient's autonomy is essential. Patients must have rights for making informed awards about their treatment, such as the choice to agree or decline thermotherapy.

4.6. Professional Responsibilities

Healthcare workers must being responsibility to remain informed with the recent developments in thermotherapy and to offer a best possible management to their patients. This performed by ongoing education and obligation to ethical guideline.

5. CHALLENGES OF APPLIED HYPERTHERMIA THERAPY IN TREATMENT OF INFECTIOUS DISEASES

Despite the great importance of hyperthermia therapy in the management of infectious diseases, and while it has shown promising results in boosting immune response and destroying pathogen's ability to survive; but, a number of challenges should be considered in account to achieve hopeful and safe outcomes. Our review illustrates some key challenges related with applied hyperthermia in treatment of infectious diseases [44], [45]:

1) *Heat Toleration of Pathogens:* Some pathogens can withstand elevated temperatures, reducing the effectiveness of hyperthermia as a treatment.
2) *Side Effects:* Applied heat therapy thought entire body can give rise to systemic side impacts like dehydration, electrolyte dysregulation, as well cardiovascular stresses.
3) *Target Delivery:* Attaining and maintaining the required temperature at infection site without influencing surrounding healthy tissue may be challenging.
4) *Immunological Responses:* While hyperthermia could stimulate immune system, but undue heat may as well leading to immune repression or systemic inflammatory response.
5) *Technical Limitation:* The apparatus and techniques required to accurate control temperatures and monitoring may be multiplex and expensive.

6. CONCLUSIONS

The clinical implication of applied hyperthermia in treatment of infectious diseases is considerable and multifaceted. This type of therapy could magnify the immunological responses, making the body more active in combating microbes. By upraising body's temperature, hyperthermia negatively influences the viability and virulence of pathogens, directly hindering their ability to create disease. Furthermore, when applied as an adjunct therapy alongside traditional therapy, hyperthermia could improve patient's outcomes by functioning synergistically action with other therapeutics modalities.

Despite these promising outcomes, further investigations are required to set up standardized protocols and emphasize the effectiveness and safety of thermotherapy as a potential treatment for infections. If proven effective through more inclusive clinical trials, thermotherapy could be a valuable inclusion to the current arsenal of treatment for infection agents, providing a novel approach to boosting immune functions and directly target pathogens. This approach would present a significant advancement in the management of infectious diseases, potentially upgrading survival rate and clinical outcomes for infected patients [13].

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