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New Applications for Cryotherapy

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Abstract: Cryotherapy, or more commonly known as cold therapy, is the use of low temperatures in medical treatment. The most prominent use of cryotherapy is for cryosurgery where application of very low temperatures is used to ablate diseased tissue (e.g., most commonly in dermatology). Recent research, however, shows that low temperature may modulate collagen fibers beyond the already known effects of extreme cooling on joint pain relieve and inflammation. The goal of this brief review is to outline the known effects of extreme cooling on molecular, fiber and cell physiology and to leverage these properties in various potential medical applications. Specially, we will discuss potential cryotherapies for treatment of osteoarthritis and destruction of fat cells (i.e., cryolipolysis) for treatment of diabetes. Osteoarthritis (OA) is a degenerative disease, where joint pain and stiffness worsen over time. One of the most effective ways to relief joint pain is cooling the joint. Indeed, when evaluating different strategies to externally cool affected joints, it was found that reducing the internal joint temperature by ~ 10ºC has beneficial effects in terms of pain reduction and regression in local inflammation. Moreover, collagen, whose deterioration is a major part of OA pathophysiology, regains elasticity after several freeze-thaw cycle. Finally, cartilage cells response to cold by increasing collagen formation and reducing matrix enzyme production, and adipose tissue within the joint that promote OA by supporting inflammation is susceptible to cold temperatures. Obesity is also a devastating disease that contributes to OA. Reduction of the temperature within the joint results in reduced inflammation, renewed collagen synthesis and reduced pain. Similarly, induction of extreme low temperatures in adipose tissue results in adipocytes loss without damage to surrounding tissues. Hence, cryotherapy has applications to modulation of collagen and fat cells for various therapies.

Keywords: Cryotherapy; osteoarthritis; arthritis; pain management

1 Introduction

Cryotherapy, or more commonly known as cold therapy, is the use of low temperatures in surgical (cryosurgery) and medical therapy. Despite the current utility of cryotherapy, the field of cryobiology is relatively unexplored. Clearly, chemical kinetics are temperature sensitive and for small temperature variation can be reversible. Under extreme temperature lowering, however, the effects may be irreversible and, in some cases, can be leveraged for medical therapy. In this brief overview, we will focus on osteoarthritis and fat cell response to cryo-temperatures.

The response of synovial cells and cartilage to cooling seven days after trauma was studied in terms of cell viability, gene expression, type II collagen synthesis and cleavage, as well as the release of MMP-2, MMP-13, and interleukin 6 (IL-6) [1]. Two-hour hypothermic treatment (27°C) improved cell viability, attenuated the expression of catabolic MMP-13 and increased type II collagen synthesis. Moreover, cleavage of type II collagen was also inhibited. Seven-day long-term hypothermia further suppressed MMP release and type II collagen breakdown. Hypothermia significantly suppressed the gene expression of matrix-destructive enzymes and attenuated IL-6 expression. After blunt cartilage trauma, hypothermia for only 2 hours induced significant cell-protective and chondro-protective effects and promoted the anabolic activity of chondrocytes, while the expression of matrix-destructive enzyme was attenuated. These findings indicate that optimized cooling management after cartilage trauma may prevent matrix-degenerative processes associated with the pathogenesis of OA. In addition, increase in type II collagen synthesis due to the cryotherapy can lead to regenerative benefits.

Fat cells are sensitive to low temperatures as compared with other cell types. Cryolipolysis of subcutaneous fat using cooling plates placed on the skin reduce fat layer thickness by a mechanism involving apoptosis of adipose tissue [2,3]. Moreover, induction of subcutaneous fat cells death by cryolipolysis does not affect other tissue structure or lipids profile, making cold temperatures a plausible tool in resorption of adipose tissue. One of the mechanisms that explain their increased sensitivity is the fact that fat cells, due to their lipid content, freezes at 10°C. That temperature is much higher than the freezing temperature of water, hence while other cell types tolerate the decreased temperature, fat solidify and form needle-like crystals in the tissue [2,3]. In the clinic, studies have shown a significant reduction in subcutaneous fat mass with no significant side effects of the treatment especially in terms of blood lipid profile and liver functions [4-6]. No study has reported beneficial effects of subcutaneous fat reduction on biomarkers of diabetes, however, and other obesity-associated metabolic disorders. In one study, diabetic patients undergoing abdominoplasty for cosmesis were compared with patients undergoing bariatric surgery [7]. The results showed that reducing subcutaneous adipose tissue with abdominoplasty results only in a small improvement in glycemic control. Those patients who undergo bariatric surgery had beneficial effects in terms of glucose dysregulation. Thus, the use of cryolipolysis is mainly intended for cosmesis, emphasizing the urge to develop new tools to treat metabolic disorders in obesity.

In this review, we discuss the established practices of the arthritis and obesity treatment and the potential future direction.

1.1 Osteoarthritis

Almost 23% of the US population (52.5 million adults) has some type of arthritis, with osteoarthritis (OA) being the most common [8]. Chronic inflammation in joints damages the articular cartilage and bone, ultimately resulting in disability. To date, Arthritis is the nation's most common cause of disability. Arthritis has a profound economic, personal, and societal impact in the United States. In 2013, the total national arthritis-attributable medical care costs and earnings losses among adults with arthritis were estimated to $303.5 billion or 1% of the 2013 US Gross Domestic Product (GDP) [9]. OA is a degenerative disease, where joint pain and stiffness worsen over time.

Abnormalities in the four components of the synovial joint (i.e., meniscus; majority of synovial joints, articular cartilage, subchondral bone, and synovial membrane) promote OA in the joint. Mechanical abrasion in the knee can lead to progressive degenerative changes in the meniscus with loss of both type I and, more severely, type II collagen [10]. Studies point to an inflammatory mechanism involving the release of cytokines, degradative enzymes and collagenases/matrix metalloproteinases (MMPs) by chondrocytes, osteoblasts, and synoviocytes as a key player triggering the process, mainly in response to injury caused by mechanical stimulation [10,11]. The released MMPs mediate collagen degradation, leading to the breakdown of the articular cartilage [12,13]. Under inflamed conditions, chondrocytes undergo hypertrophy, losing the ability to form new cartilage matrix. The subchondral bone undergoes abnormal remodeling and invades past the interface between the bone and calcified cartilage. Pain may originate from the remodeling of the subchondral bone due to its rich innervation [11]. Pain may also occur from the initial inflammation of the synovial membrane which becomes progressively fibrotic over time (synovitis) [11]. Moreover, peripheral neuronal sensitization can play a role in the pain of osteoarthritis. Adipokines secreted by adipose tissue and the infrapatellar fat pad in the knee, have been linked to the degradation of articular cartilage. This implicates the potential role of obesity, in the development of OA beyond weight bearing [14].

1.2 Obesity

The prevalence of diabetes, obesity and other co-morbidities of the metabolic syndrome is continuously rising and pose a major risk for morbidity and mortality from cardiovascular complications. According to a recent report from the Centers for Disease Control and Prevention (CDC), > 100 million US adults are living with diabetes or diagnosed as pre-diabetes [15,16]. Moreover, nearly three-quarters of American men and more than 60% of women are obese or overweight. Recent studies attributed a major role for excess abdominal fat in the progression of metabolic abnormalities associated with obesity [15-19]. Moreover, it was concluded that visceral adipose tissue, and not subcutaneous fat, is the key correlate of the metabolic abnormalities observed in overweight/obese patients [17-21]. In that regard, individuals matched for subcutaneous adiposity but with low versus high accumulation of visceral adipose tissue, have been shown to be markedly different in their levels of insulin resistance and glucose tolerance. For equal visceral adiposity, individuals with low or high levels of subcutaneous fat were not found to differ in insulin sensitivity. This finding provides evidence that despite the fact that numerous studies have shown that weight (i.e., body mass index, BMI), subcutaneous fat, and visceral fat are all well correlated with insulin resistance and with alterations in indices of plasma glucose-insulin homeostasis, it is the subgroup of overweight/obese patients with an excess of visceral fat that shows the most severe insulin resistant state [17-20].

There are several mechanisms by which visceral fat accumulation is related to and promotes metabolic dysfunction. Visceral fat itself is inherently diabetogenic, for example, it secretes hormones and adipokines that impair insulin sensitivity in tissues such as liver and muscle, which increase upon expansion of this depot. Furthermore, the accumulation of visceral fat is a surrogate indicator of abnormal lipid accumulation and lipotoxicity, which occur in parallel in liver and muscle, causing insulin resistance in these tissues. Another proposed mechanism is that excess lipid accumulation in visceral adipose tissue actually causes its acquisition of diabetogenic properties by recruiting inflammatory cells which release inflammatory cytokines and impair insulin sensitivity [22]. Although the deleterious effects of visceral fat are known, there is currently no pharmacological treatment to reduce its volume in obese patients, and current strategies to reduce its size include dietary and life style approaches as well as surgical approaches to reduce food intake in morbidly obese patients, with wide range of procedure related possible side effects.

Obesity can promote OA by mechanical stress on joints. Yet, obesity is also a risk factor for non-weight-bearing joints through secretion of inflammatory factors that favor arthritis [23]. The infrapatellar fat pad (IPFP) can be regarded as a special form of adipose tissue due to its location, which is in close contact with synovial layers and articulating cartilage. Fat cells are known to be sensitive to low temperatures, and induction of apoptosis in adipose tissue is achieved without any significant side effects [2]. It is plausible that reducing the fat mass of the IPEP by cryotherapy will reduce inflammation in the joint. Nerves are also sensitive to freezing injury [24]. Temporary desensitization of nerves occurs in the 0°C-5°C range. This minor injury is reversible when the nerve is warmed, function will quickly recover with no structural injury. For temperatures < -5°C, return of function may be delayed for several hours or days. Permanent desensitization is produced at about -15 to -20°C where function is lost. Temperatures > -20°C are considered ablative. Cryoneurolysis of sensory peripheral nerves can provide pain relief for a variety of chronic pain conditions. A recent study evaluated the efficacy and safety/tolerability of cryoneurolysis for reduction of pain and symptoms associated with knee OA, showed a significant decrease in knee pain and improved symptoms up to 150 days and appeared safe and well tolerated [25].

2 Therapy Methods

2.1 Current Practice

2.1.1 Osteoarthritis

Clinical studies show that one of the most effective methods of relieving arthritis-related pain is low temperatures. In these studies, the cooling treatment was applied to the exterior of the joint (on the skin surface adjacent to the joint being treated). When evaluating the temperature within the knee joint cavity after treatment with ice chips and nitrogen cold air, it was found to decrease to only 29.1°C [26]. Although moderate intra-articular temperature reduction was seen, it improved joint motion, function and strength, together with reduced swelling, disease activity and local and systemic inflammation [27,28]. Moreover, other studies attributed cryotherapy with analgesic, antiphlogistic, myorelaxing, vasoconstrictive, anti-inflammatory, enzyme-blocking, and anti-oxidative effects [29].

2.1.2 Obesity

Obesity and related metabolic disorders in the US have reached epidemic proportions and rates are continuously increasing around the world. The latest estimates are that approximately 34% of adults and 15-20% of children and adolescents in the US are obese without differences between segments of the population. With no good pharmacological options, morbid obese patients are left with surgical options aimed to reduce food intake. These options, generally called “bariatric surgery”, while show efficacy in terms of weight loss and improvement in metabolic parameters, are also associated with severe complications such as internal bleeding, perforation of the intestine, leakage and many others. Thus, there is a need for development of new treatment modalities with reduced risk to target obesity.

Although no non-surgical treatments to combatant morbid obesity are available, surgical procedures have been shown to produce substantial and durable weight loss. The sleeve gastrectomy involves excision of approximately 80% of the stomach. This is a laparoscopic procedure and is non-adjustable and non-reversible. Gastric imbrication is a non-resectional variant of the sleeve gastrectomy where the gastric wall is imbricated to create a narrow lumen. Laparoscopic adjustable gastric banding involves placing a Lap-Band laparoscopically over the cardia of the stomach. This procedure is the safest among all surgical options and usually is considered the first option in obese patients. Roux en Y Gastric Bypass is a laparoscopic procedure where both reduction in the size of the stomach together with a narrow stoma passing from the gastric pouch to a Roux-en-Y loop of jejunum diverting food from the duodenum and proximal jejunum is achieved. Single Anastomosis Gastric Bypass is an alternative procedure to the Roux en Y Gastric Bypass. It is comprised with a loop of small bowel rather than a Roux limb, a long and narrow lesser curve gastric pouch and a longer bypass of the duodenum and proximal jejunum [30].

Therefore, there is a need to develop an efficacious and safe minimally invasive device to reduce visceral fat mass in obese patients.

2.2 New Concept

One of the main unresolved issues of OA is the progressive degenerative changes in the meniscus with loss of both type I and type II collagen. A recent study that evaluated the effect of freeze-thaw cycles on the rheological and thermal properties of bovine skin collagen found that the elasticity of collagen increased as the number of cycles increased. In addition, the collagen fibers became thicker indicating that the aggregation of collagen molecules was enhanced [31].

The data presented supports the hypothesis that delivery of cold temperatures directly to the inflamed arthritic joint will relief pain associated with OA concomitantly with improvement of inflammation and collagen synthesis as schematically shown in Fig. 1.

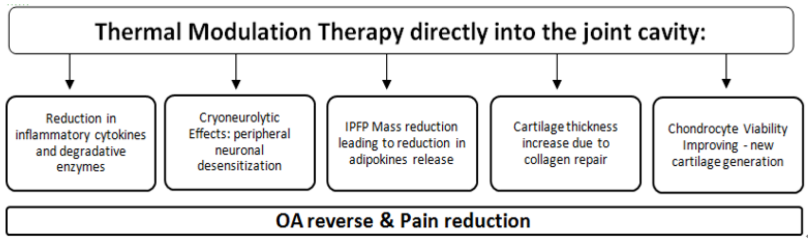

Figure 1: ***Hypothesis***: TMT device will benefit OA patients by relieving chronic pain (through decreasing inflammation and neuronal desensitization) while attenuating the progression of the disease by stimulating collagen repair and cartilage regeneration

We propose cryotherapy technology for the treatment of OA and cryolipolysis for treatment of diabetes. It has been shown that delivery of cold temperatures directly to the inflamed arthritic joint, will relief pain associated with OA concomitantly with improvement of inflammation and collagen synthesis. Accordingly, there is a need for minimally invasive Thermal Modulation Technology (TMT) technology that will internally deliver cold temperatures directly to affected joints. This device should have the capability to rapidly switch between cooling and warming cycles. This effect was shown to be beneficial for collagen elasticity and for stimulation of collagen synthesis [1,31] but has not been tested in OA before.

Fat cells comprising the adipose tissue are more sensitive to cold temperatures compared to other cell types. Therefore, induction of cold temperatures in visceral adipose tissue will result in adipocytes loss without damage to surrounding tissues. This principal is being applied for body contouring by externally cooling the subcutaneous adipose tissue leading to reduction in its size. Recent studies point to the visceral fat as a major contributor to metabolic abnormalities in obesity. Thus, reducing this fat deposit have become of major interest. Studies indicate a major role for excess visceral fat in the progression of metabolic abnormalities in obesity [17-21]. Unlike subcutaneous fat, the visceral fat is anatomically hard to access, and only a few studies report the outcomes of its manipulation. In Obese baboons, lipectomy to remove the visceral fat using liquidation (only 1% of total body mass in visceral fat was removed) resulted in substantial metabolic improvements, including reversal of insulin resistance and weight loss [32].

Bariatric surgery is still the preferred method to treat morbidly obese patients, with good results in terms of weight loss and improvement in metabolic parameters. Yet, these rather harsh procedures have many inherent risks making cryolipolysis a plausible new technique to treat obesity. The identification of the visceral fat as a major organ contributing to metabolic dysfunctions in obesity renders it as a prime target for cryo-treatment. With the evolution of cryo-technology, new treatment modalities to specifically target the visceral fat will be developed. These new techniques will effectively target the visceral adipose tissue without damaging surrounding tissues and with minimal side effects, while still are efficacious in terms of reducing weight and associated metabolic abnormalities

Cooling the tissue is a heat conduction process. It is described mathematically by the heat equation, which is derived from the first law of thermodynamics (i.e., conservation of energy). Given a region of interest and appropriate boundary conditions, it is possible to solve this equation numerically to predict the evolution of temperature distribution within the region of interest. The computational heat transfer methods based on the Finite Element Analysis (FEA) to solve the heat equation and study temperature distribution over the joint space during cooling and thawing with the device should be utilized. Actual geometry of a tissue space should be reconstructed for the analysis using medical imaging (e.g., MRI scans). The specific 3D geometry should be reconstructed based on 2D images using the open-source software ITK-SNAP [33]. This process involves multiple steps. First, the 2D images should be segmented. The segmented images should then be stacked, and the 3D structure should be generated using well established surface rendering and smoothing techniques. The different components of the reconstructed geometries (i.e., cartilage, bone, ligaments, etc.) should be identified. The reconstructed geometry should be imported in the FEA software Abaqus. Thermal properties, which are well established for the tissues of interest [34], should be assigned to each components of the geometry. The TMT device should be included in the model. Heat transfer between device and surrounding components through conduction should be simulated. The domain of influence of the device should be identified for each case. Simulations should be conducted with various combinations of cooling/thawing time and temperature. The evolution of the tissue space area at temperature 0ºC-10ºC should be tracked during each simulation. The best performing temperature/time combination should be identified as the ones achieving the most area to 0-10ºC within the least amount of time.

3 Conclusion

We propose a new method to treat OA and reduction of visceral fat through thermal modulation cryotherapy technology. The method must be safe and the device is portable, minimally-invasive and simple to use by medical technician in medical offices. Future studies are required to provide therapeutically related data using TMT technologies to treating humans in clinical trials.

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