Sciential

McMaster Undergraduate Science Journal

ISSUE 10 - APRIL 2023

CONTENTS

ORIGINAL RESEARCH

ACADEMIC REVIEW

RESEARCH PROPOSAL

INFOGRAPHIC

NEWS & VIEWS

DEAR READER,

Welcome to Issue 10 of the Sciential Journal! As we slowly start to see things going back to normal after a global pandemic, we're thrilled to publish a new issue with exciting research. Sciential gives students an opportunity to publish work that they are passionate and enthralled by. Our aim is to explore the interdisciplinarity of scientific fields through effective science communication. Over the years, especially during the pandemic, we have witnessed the importance of science communication and research. With this journal, we hope to shed light upon the accessibility and interdisciplinary nature of science.

This issue explores a range of scientific topics: the effects of knowledge on tuberculosis in Inuit communities, weighing the benefits and drawbacks of testosterone replacement therapy, understanding the relationship between β-blockers and mental health, the positive impacts of ComSciConCAN, blue wavelength light treatment for sleep in patients with post-traumatic stress disorder, the efficacy of scalp cooling in chemotherapy-induced alopecia, the social justice movements, and lastly, the effect of varying eccentric velocity on muscle hypertrophy.

We are extremely grateful to the members of the *Sciential team for their work and dedication to the journal. We would like to recognize the fantastic work done by our Senior Editors, Samini Hewa and Zani Zartashah, for overlooking the peer-review process. Additionally, we would like to acknowledge the incredible work ethic of our Editors, for their continuous determination to make sure our journal is of high standard. We also appreciate the remarkable work done by the creative board, led by our Creative Director Zachary de Guzman. Lastly, we would like to acknowledge the founders of Sciential, Aiman Shahid and Alisa Nykolayeva, along with our Senior Advisor Team Dr. Kimberley Dej, Dr. Veronica Rodriguez Moncalvo, Dr. Katie Moisse, and Science Librarian, Abeer Siddiqui.*

On behalf of the *Sciential team, we strive to provide the best quality of work and hope you enjoy Issue 10 of the Sciential journal!*

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ORIGINAL RESEARCH OPEN ACCESS

The Effect of Varying Eccentric Velocity on Muscle Hypertrophy

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Received 17 January 2023
Accepted 14 February 2023
Published 30 April 2023

ABSTRACT

Resistance training is essential to muscle hypertrophy as it fatigues fibres through time-under-tension (TUT). As myocyte energy depletes, metabolites accrete, leading to inflammation to increase cell size so it is adapted for future stimuli. TUT can be measured by varying eccentric velocities: i.e., the rate at which a muscle lengthens under load. A longer period of lengthening will lead to greater metabolite accretion and inflammation. However, it is unknown whether TUT has a threshold or if it can gradually increase and lead to more muscle growth. Through a literature review and an experiment, this project investigates the effect of varying eccentric velocity on muscle hypertrophy. Previous research in the field of muscle physiology and metabolism were explored, with an emphasis on eccentric training. The supplementary experiment measured shoulder growth in response to the medial deltoid exercise called lateral raises, where different eccentric velocities were assigned to groups. Individualistic daily calorie and protein intake were controlled to ensure that sufficient nutrients were available for recovery and performance. Post-experimental research suggested that high-velocity eccentric training was best for hypertrophy due to greater levels of force production. This was consistent with the experiment, which found that those with a fast-velocity eccentric, a lower TUT, experienced greater growth. They also exhibited greater strength gain due to a neuromuscular junction adaptation. These findings are significant for designing exercise regimens that are optimal for the prevention and rehabilitation of musculoskeletal injuries and disorders. The review's findings suggest that fast-velocity eccentric contractions are ideal for increasing muscle size and strength.

3.0 Keywords: Muscle hypertrophy, eccentric training, contraction velocity, medial deltoid

1. INTRODUCTION

Time-under-tension (TUT) is the duration a muscle actively contracts during resistance training. Time-under-tension as a contributor to muscle hypertrophy is rarely discussed in scholarly circles but is worth more consideration. This paper explores the effect of manipulating TUT for working muscles during resistance training, and if increased TUT equates to increased hypertrophic effects. First, a foundation of relevant muscle functionality will be established through a literature review of muscle hypertrophy. The concepts of metabolic stress and mechanical tension as mediators for muscle hypertrophy will be the central focus of the review. Next, the different types of muscle contractions will be outlined to determine which is most conducive to muscle hypertrophy. Altering muscular contraction velocity as a method of manipulating TUT will also be explored. Finally, a supplemental experiment measuring the effect of varying TUT on muscle hypertrophy will be outlined. This experiment measured shoulder growth over a 6-week period in response to different contraction velocities. The results of this experiment will be analysed and discussed. Specifically, we will explore what caused the experimental results and how the literature supports them. Conclusively, this paper will discuss the resistance training regimen most conducive to muscle hypertrophy, incorporating findings from the literature review and experiment.

2. LITERATURE REVIEW

2.1 Causes of Muscle Hypertrophy

2.1.1 Metabolic Stress

Metabolic stress following resistance training leads to numerous hypertrophic effects that impact the subcellular structure of myocytes, most notably the accretion of metabolites within the cells. Sufficient training intensity has been shown to elicit fast glycolysis for quick energy generation, in the form of ATP.[1] Lactic acid is released as a by-product of this process, which

dissociates in the blood plasma to form lactate. As resistance training progresses, plasma lactate saturates in the arteries and veins surrounding working muscles, increasing occlusal pressure and leading to an inhibition of blood flow, furthering metabolite accumulation.[2,3] Blood pools more in these areas due to a process known as reactive hyperaemia; a transient increase in blood flow following arterial and venous occlusion.[4] This mode of concentrating metabolites will lead to numerous hypertrophic effects, either by activating certain metabolic pathways within the myocytes or through extrinsic cellular interactions. The effectiveness of every metabolic stressor discussed in this section is dependent on the intensity and duration of resistance training. Essentially, as intensity and duration increase, metabolic stress will also increase.

Increased muscle fibre recruitment is one of the effects of metabolic stress following resistance training that can have hypertrophic effects. As resistance training progresses, more muscle fibres are incrementally recruited to sustain the contractions for the working muscle group holistically, eventually leading to full muscle group fatigue.[5] Before understanding muscle fatigue, it is important to note that total number of adenine nucleotide molecules within a myocyte remain constant.[6] Essentially, the ratio of ATP, ADP, and AMP must always be the same. For example, if one molecule of ATP is used by a muscle fibre for contraction, then two molecules of ADP will be converted to one molecule of ATP and AMP. The muscle now has another ATP molecule for energy, and the extra AMP will be degraded by AMP-deaminase to IMP and ammonia. Thus, the ratio is maintained. When muscles have an insufficient ATP supply, they will fail to generate sufficient force for the movement, leading to fatigue. Additionally, the continuous amount of ammonia molecules generated from maintaining the adequate ratio will be accumulated in blood plasma. These will be converted to urea nitrogen, which is harmful in high concentrations.[7] Muscles will inhibit further metabolism of ATP molecules to mitigate the downstream deleterious effects by urea nitrogen. The muscle fibres that are receiving blood from vessels with high concentration of this harmful substance will cease to function. But, if the resistance training is maintained, then other fibres not affected will be recruited. The generation and accumulation of the metabolites will cause muscle fibres not being employed for resistance training to become active, because the ones previously used are fatigued while the movement is maintained. Hence, metabolic stress is necessary to exhibit full activation of muscles.

Introducing the significant role of myokines must first be met with an overview of hypertrophic myocyte anatomy. Muscle cells are one of the few exceptions to the cell theory, as they are multinucleated. Additionally, the process for muscle growth would first involve increasing the myonuclei, and then increasing the size. This is because the extra genetic material in the new myonuclei is necessary for growth and development of the cell. The myonuclei are created through the differentiation of satellite cells: multipotent, muscle stem cells.[8] These satellite cells infiltrate and proliferate within myocytes to increase the myonuclear saturation, giving rise to greater size and strength capacity for the muscle.[9] Therefore, satellite cell accretion is a necessary precursor to muscle hypertrophy.

Resistance training also leads to the synthesis of myokines that contribute to hypertrophic adaptations over time. Myokines are cytokines synthesized and released within skeletal muscle cells during muscle contractions.[10] Some myokines that have been abundantly explored in the scientific literature are Interleukin-6 and Interleukin-15 (IL-6, IL-15). IL-6 is an essential regulator of satellite cell-mediated hypertrophic muscle growth.[11] IL-6 signaling has been associated with myogenesis through the regulation of the proliferative capacity of satellite cells. Satellite cells are activated and undergo asymmetric division to both maintain the satellite cell pool, and generate daughter committed myoblasts.[12] Myoblasts are mononucleated precursors that differentiate further to form multinucleated muscle fibres.[13] Hence, IL-6 mediating the infiltration and proliferation of satellite cells in myocytes leads to hypertrophic muscle effects. IL-15 is a different myokine that is used to increase protein accretion to induce muscle hypertrophy.[14] Specifically, proteins are accumulated in sarcomeric myosin-actin chains in myotubes, the microstructures of skeletal cells. Increasing these miniscule functional units enables a muscle to increase in volume and strength capacity. Thus, IL-15 is a significant myokine that allows for increases in muscle size. Both IL-6 and IL-15 are important myokines for inducing muscle hypertrophy.

Muscle fatigue because of resistance training can lead to heightened production of reactive oxygen species (ROS). ROS, both radical and non-radical oxidizing agents, in low concentrations can lead to muscle hypertrophy. The two most potent ROS regarding positive benefits are superoxide and hydrogen peroxide (Farooqui, 2008). ROS are primarily generated as the by-product of the mitochondrial electron transport chain (ETC). It has been shown that 0.2-2% of electrons in the ETC do not follow the normal transfer order and leak out to interact with free oxygen to yield radical or non-radical ROS.[15,16] These ROS are in the mitochondrial matrix, specifically the FMN site and the CoQ binding site. They are created during the transfer of electrons from NADH to CoQ. The accumulation of ROS can lead to acute hypoxia in the vessels surrounding working muscles, producing a superoxide burst in arterial endothelial cells.[17] Although chronically elevated levels of ROS have been implicated in negative effects on health, acute accumulation enhances cellular signaling pertaining to hypertrophy.[18–

[22] This is hormesis, a phenomenon in which a harmful substance gives beneficial effects at a low concentration.[23] At a relatively low concentration, ROS will stimulate extra Calcium (Ca^{2+}) release from the sarcoplasmic reticulum of myocytes.[24] Ca^{2+} binds to the C-component of the actin-filament in sarcomeres, exposing the binding site for the myosin head which generates a cross-bridge and stimulates muscle contraction.[25] Thus, increased Ca^{2+} release will enable the muscle to generate more force for contraction, which will lead to faster fatigue, and hypertrophic effects. ROS can also influence hypertrophy by mediating transcription of highly conserved stress proteins called heat shock proteins (HSPs).[26] These abundant proteins are synthesized in response to harmful agents such as environmental stresses, infection, gene transfer, or in this case, ROS. All functions of HSP can be attributed to molecular stress sensing and a subsequent protein folding synthesis response.[27] Exercise is the main stimuli associated with a robust increase in different HSPs in skeletal muscle tissue. Specifically, HSPs facilitate the cellular remodeling process during muscle growth.[28] Following resistance training, major oxidative damage to muscle proteins triggers HSP expression, to ensure that muscle growth is effective, efficient, and systematized. Clearly, the generation of ROS, a metabolic stressor, is an effective vehicle for inducing muscle hypertrophy following resistance training.

Cell swelling is a by-product of metabolic stress following resistance training that proves to exhibit hypertrophic effects. Cell swelling may physiologically regulate certain cell functions that enhance muscle growth.[29] During resistance training, veins surrounding the muscle tissue are compressed, restricting the removal of blood. However, arteries continue to supply blood and oxygen to the working muscles, thereby creating an increased concentration of intramuscular blood plasma. Higher intra-arterial pressure leads to plasma leakage from capillaries into the interstitial space, building a plasma extracellular pressure gradient.[30] This dense gradient, through passive diffusion, causes excess plasma to diffuse back into the muscle. The cascading signaling response is facilitated by integrin-associated volume osmo-sensors within the muscle fibres.[31] As the membrane of the myocytes undergo hydration-induced stretching, the aforementioned sensors activate anabolic protein-kinase transduction pathways. This hyperhydration has a direct effect on amino acid transport systems such as phosphatidylinositide 3-kinase modulating glutamine and methyl aminoisobutyric acid transport in muscle.[31] Improving the rapidity of amino acid transport, and subsequent protein accretion will enable hypertrophy. Fast-twitch fibres in particular are sensitive to osmotic changes, possibly related to a high concentration of water transport channels called aquaporin-4 (AQP4).[32] Given that fast-twitch fibres are the most susceptible to hypertrophy, it is possible that cellular hydration influences the hypertrophic response following resistance training, which includes protein accretion.[33] Thus, cell swelling proves to possess some hypertrophic effects.

2.1.2 Mechanical Tension

Mechanical tension on muscle contractions during resistance training plays an important role in the hypertrophic process. Mechanical tension applied to muscles has the ability to trigger a cascade of biochemical reactions from physical stimuli such as kinase activity, sarcomere stiffness, and rearrangement of myocyte architecture.[34] This section of the literature review will focus on the physical and biochemical cellular and subcellular manifestations of mechanical tension.

Mitogen-activated protein kinase (MAPK) is a regulator of gene expression that has been shown to contribute to the adaptive response in muscles that generates growth.[35] Specifically, MAPKs are involved in relaying extracellular stimulations to intracellular responses. This includes satellite cell proliferation and differentiation. One group of MAPKs, c-Jun amino-terminal kinases (JNKs) has been shown to be a mediator of hypertrophic responses in muscle cells.[36] Indeed, Aronson et al. (1998) found c-Jun mRNA levels elevated in Northern blot analysis of muscle samples taken from subjects who underwent an exercise regimen.[37] This is because the JNK pathway mediates cellular responses to environmental stressors, which includes rigorous activity.[36,38,39] More specifically, the metabolic stressors previously covered in this literature review can facilitate the JNK pathway, including high plasma pressure and myokine synthesis.[39] Relaying mechanical extracellular stimuli to intracellular signaling pathways proves to be the primary function of MAPKs, which recognizes them as mediators of muscle hypertrophy following resistance training.

Applied mechanical tension can be generated by the force of the weight as well as the stretch endured by the muscles being worked. The addition of the stretch in conjunction with the weighted force leads to an additive effect that pronounces muscle fatigue, leading to a hypertrophic response.[40–42] One enzyme that is often observed when studying the stretch of a muscle is p70S6k, a protein kinase that targets the substrate S6 ribosomal protein.[43,44] Phosphorylation of S6 results in protein synthesis at the ribosome. Hornberger and Chien (2006) checked the effect of mechanical stretch on the prevalence of p70S6k and witnessed a sizable increase.[42] This suggests that phosphorylation of S6 increased drastically following mechanical stretch, which would allow the ribosome to synthesize more usable proteins that could be accreted to the damaged muscle fibres. Hence, applied mechanical tension enables the muscles to fatigue and grow more.

Mechanical tension leads to localized muscle tissue damage that can accelerate growth and recovery. Lengthening muscle contractions in particular have been shown to produce ultrastructural damage such as microscopic tears in contractile proteins within the muscle cells.[45,46] This promotes muscle protein turnover, and increased protein accretion in the damaged area, leading to an increase in overall size within the sarcomeres. Resistance training initially causes myotrauma: damage to the underlying muscle tissue.[47] Indeed, Staron et al. (1990) found the cross-sectional area of specific muscles to be sizably lower.[47] However, cross-sectional areas of the same muscle in different participants, ones with adequate rest and nutrition, experienced sizable amounts of type-II muscle fibre increases. This suggests that the microscopic shearing on the muscle proteins was a result of the mechanical tension from the resistance training but was also a precursor to a larger muscle post-recovery. Another noticeable change was a substantial increase in mitochondrial density in the targeted muscle, which is to be expected given that a now larger cross-sectional area of the sarcomere would require more energy to sustain sufficient cross-bridge formations.

Mechanical tension applied through resistance training has been shown to alter ionic concentrations within the working muscles. The muscle damage that ensues resistance training most drastically affects the Ca^{2+} abundancy.[48] Mitochondrial Ca^{2+} increases have been observed, due to shear tears along the length of the sarcoplasmic reticulum, which harbors reservoirs of Ca^{2+} ions.[49] Additionally, T-tubules, which are located at the A-I junction in muscle fibres can be severely distorted or damaged, which would lead to rapid equilibration of the intracellular and extracellular spaces, causing an influx of Ca^{2+}.[50,51] The change in intracellular calcium concentration then leads to a cascade of chemical activations such as the previously mentioned MAPK, resulting in muscle hypertrophy.[52] Hence, the distortion of muscle architecture caused by mechanical tension can alter the growth of the muscle.

The most potent effect of mechanical tension as physical stimuli relates to a change in muscle architecture that induces damage, fatigue, and biochemical changes that translate to muscle hypertrophy. Prado et al. (2005) assert that the contractile performance of skeletal fibres largely depends on the myosin heavy chain (MHC) isoform and the stiffness of the titin spring.[53] The MHC is the actin-based motor protein that generates mechanical force from ATP.[54] The titin-spring is a spring in sarcomeres that is activated by active mechanical tension. This provides the muscle with extra force during the stretch.[55] Using heavy resistance training during this stretch will disrupt the stiffness of the spring, and essentially degrade the elasticity of the I-band region which consists of the titin isoform. Now with regard to a different ultrastructure, the Z-band showcases a broadening and disruption effect during a mechanically active stretch, as demonstrated by Friden et al. (1981).[50] Indeed, the lattice pattern in the Z-bands became disorganized, suggesting that high tension leads to mechanical disruption of the interdigitating arrays of actinin-tropomyosin microfilaments.[56] As suggested by Sasuki et al. (1982), the Z-band's tropomyosin and actinin microfilaments have been shown to be susceptible to reconstitution by Ca^{2+}-activated factor (CAF).[56] This is a growth factor that is typically released by damaged muscle fibres after accumulation of Ca^{2+} due to sarcoplasmic reticulum disruption. Hence, the altercations in muscle architecture that result from resistance training are diverse and prove to be highly effective in triggering muscle damage, which will act as a precursor to muscle hypertrophy.

2.2 Types of Muscle Contractions

There are different types of muscle contractions employed by the human body during resistance training, each of which has unique characteristics. There are two kinds of dynamic contractions, eccentric and concentric.[57] Eccentric contractions occur when the muscle length is increased, usually for decelerating or controlling motions. This is also known as the "negative" of a resistance-based exercise. Differently, concentric contraction occurs when the muscle length is shortened. The third kind of muscle contraction, which is not dynamic, is isometric contraction.[57] Isometric, also known as a static hold, is when muscles contract without motion or length changes. This is typically done to actively stabilize a joint. Given this information, we will explore which type is most beneficial to centralize in a hypertrophy-focused training regimen.

2.3 Advantages of Increasing Time-Under-Tension During Muscle Contractions

This literature review has explored the hypertrophic effects of metabolic stress and mechanical tension, and the research has led to the belief that increasing the TUT for a muscle will exhibit hypertrophy. Regarding metabolic stress, a longer TUT for the working muscle will lead to more metabolite accumulation. Muscle contractions for longer periods of time will lead to restricted blood flow, allowing for more muscle fibre recruitment. Myokine activation will also increase, leading to a greater number of satellite cells infiltrating and proliferating, undergoing myogenesis. Lastly, reactive oxygen species (ROS) and cell swelling will

rise, leading to more damage and alterations to muscle architecture. With alternative regard to mechanical tension, MAPK and other myokines will be synthesized and released to a greater degree, resulting in more gene expression and stimulation of myogenesis. A longer duration will also lead to more muscular stretching that can disrupt microstructures such as the Z-band and titin-spring. Finally, activation of p70S6k will become more abundant, leading to a greater expression of S6 ribosomal protein, which will lead to elevated protein synthesis and accretion within the muscle tissue. When varying the TUT to test this hypothesis, it is best to focus on the eccentric movement of a muscle because a slower negative during resistance training is generally regarded as safer to maintain than a concentric or isometric movement, and has a greater plethora of data surrounding its safety.[51] Hence, it is predicted that increasing TUT in eccentric muscle contractions will lead to more hypertrophy.

3. EXPERIMENT

3.1 Methods

The experiment supplementing this literature varies the velocity of eccentric contractions during the medial deltoid exercise called dumbbell lateral raises to observe the change in shoulder width as a result of muscle hypertrophy. Four volunteering participants were split into two even groups. Each group was assigned a different eccentric velocity for the exercise being performed. Each participant in a group had another participant in the other group that had a similar starting shoulder width, in order for post-experimental comparative analysis to be consistent. For instance, participant E1-1 had a comparatively similar starting shoulder width to participant E4-1. Group E1 had an assigned velocity of 1-second, meaning that the lowering of the dumbbell after reaching shoulder height, or the peak, had to be completed over the course of one second. The eccentric velocity for this group was $90^{\circ}/s$, as the range of motion for the exercise is generally 90 degrees because the arm starts in a vertical position near the hip and rises to a horizontal position in line with the shoulder joint. Group E4 had to do the same motion, but lower the weight over the course of four seconds. This group had an eccentric velocity of $22.5^{\circ}/s$, precisely a quarter of the speed of the previous group. Having two different velocities that were magnitudes apart allowed for distinct comparisons after the experiment, to determine how pronounced the effect of increasing TUT would be. Participants were asked to start with a dumbbell weight that was comfortably performed for one complete set of twelve repetitions. This ensured that the exercise technique of the participants was consistently accurate, so as to avoid injury, and employ the correct muscle fibres. The experiment was conducted over the course of 6-weeks, with 3 sets of 12 repetitions every day for 6 days a week as the training regimen. This regimen provided the participants with a sufficiently rigorous routine to promote muscle fatigue, while giving them enough time for adequate recovery. The participants were offered the opportunity to increase the weight of the dumbbells during every session of training if the stimulus was not challenging enough. Shoulder width measurements were taken after the final weekly training session. Measuring tape was wrapped around the shoulder width of the participants, specifically over the peak of the medial deltoid muscle. Consistently measuring this point measured the maximum change in the muscle's size. The participants were provided with a diet set at maintenance level with elevated protein content. Essentially, the caloric intake was calculated to be at a daily maintenance, but the protein content was set to be 0.5 g/lb of body weight. This ensured that the participants had enough nutrients and protein to facilitate muscle growth. Additionally, the participants were suggested to sleep 8 hrs/night so as to promote adequate rest and recovery.

3.2 Analysis

The weekly shoulder width measurements of the participants can be found in Table 1. After the 6-week experimental period, it was found that the percent difference between starting and final shoulder width was nearly two-folds greater for the 1-second eccentric group than the 4-second eccentric group, as showcased in Table 2. Figure 3 and Figure 4 illustrate the results of Table 1 and Table 2, respectively. The participants with a faster negative exhibited significantly higher muscle growth than their slower negative partners who had similar starting shoulder width. This is contradictory to the hypothesis originally proposed which suggested that increased TUT via slower eccentric velocity would lead to more muscle growth. The fast-velocity eccentric group also developed more strength over the course of the 6-week period. Indeed, participants E1-1 and E12 increased the weight of the dumbbell by 10 lbs and 12.5 lbs, respectively. This is greater than the slow-velocity eccentric group, which added 5 lbs and 7.5 lbs for participants E4-1 and E4-2, respectively. After witnessing these results, a thorough literature review regarding fast-velocity eccentric contractions was done to determine why faster negatives were more conducive to muscle hypertrophy. Note, this project is primarily concerned with muscle hypertrophy, so a discussion of potential strength gains will not be included. However, strength gains as a result of this regimen are worth exploring in the future.

4. DISCUSSION

4.1 Advantages of Eccentric-Focused Resistance Training

Resistance training should center on the eccentric phase of an exercise as muscles are stronger during this period. Muscles exhibit greater strength and are more prone to fatigue during the eccentric loading phase, leading to a stronger hypertrophic effect during recovery.[58]

As demonstrated in an experiment by Colliander and Tesch (1990), the torsional force, or torque, generated by eccentric muscle contractions is statistically more significant in comparison to isometric or concentric contractions of the same exercise and weight.[59] Generating torque is crucial to inducing mechanical tension on muscle fibres, which has been shown to be essential in eliciting muscle breakdown and subsequent regeneration, as asserted previously in this literature review.[59,60] Indeed, Higbie et al. (1985) found that eccentric contractions of a resistance exercise generated greater voltage on electromyogram data, implying greater influx of Ca^{2+}, which would be required by more rigorous exercise utilizing more musculature.[61] Note, although the force generated by eccentric contractions is shown to be substantially more than isometric and concentric contractions, the oxygen consumption and heat generation is considerably less.[62,63] The experiments conducted by Hill (1960), and Elmer and LaStayo (2014) found that participants generated equal power during eccentric contractions as other modes of muscle contraction, but with a fraction of the oxygen consumption, and with a miniscule change in mean muscle temperature.[62,63] This suggests that eccentric contractions generate higher force with a lower cost; thus, it is logical to emphasize eccentric loading in training regimens if the goal is muscle hypertrophy with adequate recovery.

Another reason as to why force output during the eccentric phase is greater than other types of muscle contractions involve the characteristics of sarcomeres. The elasticity and stored energy of cross-bridges become pronounced during the eccentric loading phase of an exercise.[64,65] Indeed, Huxley (1957), and Huxley and Simmons (1971) found that muscle fibres maintain an unknown amount of residual energy after the concentric movement, which is then added upon by the force generated during the eccentric phase. This cumulative force effect leads to an energy output that is greater than concentric alone. The aforementioned authors assert that the increased force during stretch is induced by rapid detachment and reattachment of cross-bridges during the eccentric phase. Essentially, cross-bridges in sarcomeres quickly release and reattach numerous times over as the weight is lowered. This is different from concentric contractions, where the entire muscle length shortens, leading to all cross-bridges moving in one direction and holding at the final shortened length. During an eccentric contraction, the cross-bridges release to increase the length, but incrementally, and very quickly, reattach to shorten the length, which momentarily slows down the lengthening process and generates additional additive force during the movement. Additionally, the quicker the movement, the lesser the number of cross-bridges formed during the contraction, and the higher rate of cross-bridges detachment.[66] There is a shorter window of time for myosin and actin to rebind, so although there is a temporary cross-bridge created to shorten the sarcomere, the period is not sufficiently long enough, and the muscle will continue to lengthen but with more force placed upon it per unit time, leading to more fatigue and damage. Additionally, the flexible fragment of the myosin tail close to the globular head, or S2 complex, will not be fully extended during a fast-lengthening period, which results in compression of the S2 complex, decreasing the pulling force applied to actin.[3,67] This allows the velocity of the filament's movement to essentially approach zero for a minuscule amount of time, at which cross-bridges can rapidly form before being detached. Given that the cross-bridges will form quickly, and the myosin is fully stretched, breaking the cross-bridges will require more force. This greater force requirement must be generated by the muscle, leading to more fatigue.[68] Given how quick this process is, and how it occurs frequently during the lengthening process, it is clear why the force generated during the eccentric loading phase is high, and why it has a low associated energy cost.

The presence of titin is another explanation as to why muscles are stronger during the eccentric phase of contraction. As previously mentioned in this literature review, titin is a protein that increases stiffness in the sarcomeres and leads to stiffness during the active stretch.[69,70] Indeed, Bagni et al. (2002) found that sarcoplasmic stiffness increased after cross-bridge formations due to titin.[71] Powers et al. (2014) found that titin-based force during active stretching was an inherent property of skeletal muscle, explaining up to 85% of the extra force generated during the eccentric phase.[72] The titin binds to the thin actin filament at one end of the Z-band in the sarcomeres, and tightens that section of the band to increase structural rigidity. Note, in these experiments, titin-binding affinity was unhindered by Ca^{2+} saturation, which is consistent with previous theory mentioned in this literature review as Ca^{2+} is expected to accumulate during muscle contractions. In fact, one study by Joumaa et al. (2008) found that force enhancement was partly caused by a calcium-induced increase in titin stiffness, and this added to the extra cross-bridge stiffness effect previously mentioned.[73] It is unclear as to what this mechanism is, but the results were consistent with the existence of some causal pattern. An overview of the

scientific literature surrounding the protein titin suggests that it enhances force production within skeletal muscle tissue during the eccentric loading phase by increasing structural rigidity.

4.2 Advantages of Fast-Velocity Muscle Contractions

Lengthening muscles during the eccentric phase of an exercise should be done at a relatively fast velocity as it is the most beneficial for muscle hypertrophy. Contractile force production proves to be higher at faster velocities due to the greater amounts of torque generated.[74,75] Moreover, these higher forces are more pronounced during the eccentric phases of an exercise. Indeed, Farthing and Chilibeck (2003) found that peak torque generated between fast- and slow-velocity contractions, for both eccentric and concentric phases, was significantly higher for the fast-eccentric group.[76] The set velocities were $180^{\circ}/s$ and $30^{\circ}/s$.[76] Faster eccentric velocity is also suggested for exercises that target muscles with a higher density of type-2, intermediate- or fast-twitch muscle fibres. This is because the volume and size that type-2 muscle fibres possess is substantially more than that of type-1.[77] Additionally, these fibres are capable of lifting with tremendous force, and are recruited most during heavy weightlifting. Utilizing a fast-velocity eccentric for muscle contraction will require more concentrated force, a specialty of the type-2 muscle fibres. Hence, for muscle hypertrophy, using fast-velocity eccentric phases should be the primary goal of training.

5. CONCLUSION

This paper discussed the concept of time-under-tension, and whether it is a significant contributor to muscle hypertrophy. The preliminary literature review suggested that increased time-under-tension would induce more metabolic stress and mechanical tension, leading to more muscle fatigue, and subsequent hypertrophy. However, the supplemental experiment suggested that the opposite was true. Indeed, fast-velocity eccentric contractions were superior to the slow-velocity variations.

Further exploration of the literature supported this experimental finding. Specifically, the centrality of this superior mode of training is the concept of torsional force. Indeed, torque increases significantly during fast-velocity contractions. Coupled with eccentric-type contractions that are more conducive to higher loading on the working muscles, this method of training proves to be ideal for fatiguing the fibres, and generating hypertrophy. Although this topic requires more inquiry to definitively determine its validity, the promises of improving muscle mass through fast-velocity eccentric contractions appear to centralise on a method of resistance training that is superior to all others. Including fast-velocity eccentric exercises in one's regimen should increase muscle mass, and perhaps strength. This will prove fruitful for the prevention, and perhaps rehabilitation of musculoskeletal injuries and disorders.

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7. ACKNOWLEDGEMENTS

First and foremost, I sincerely thank my supervisor, Dr. Michelle MacDonald for all of her support throughout this project. She is an incredibly passionate and knowledgeable professor, and I would surely be lost without her insight. Next, I want to gratefully acknowledge the subjects who dedicated a great deal of time to participate in this study. How could I forget my parents; without them, I could not have made it this far in my academic career. Lastly, I would like to thank the Department of Interdisciplinary Sciences program for making this research possible.

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9. APPENDIX

Table 1. **Table 1: Weekly shoulder width measurements for each participant during the six-week experiment.**

Participant shoulder width (cm)		E1-1	E1-2	E4-1	E4-2
Week	1	47.9	43.2	47.3	44.7
	2	48.7	46	47.6	44.8
	3	49.2	47.7	47.9	45.7
	4	49.2	48.4	47.9	47
	5	50.3	48.5	48.5	47.2
	6	50.8	49	48.5	47.8

Table 2. **Table 2: Percentage difference between initial and final shoulder width for all four participants**

Participant	E1-1	E4-1	E1-2	E4-2
Difference between initial and final shoulder width (%)	5.88	2.51	12.6	6.7

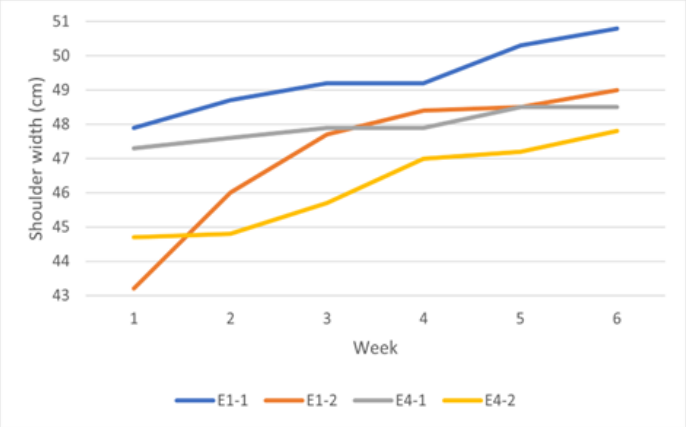

Figure 3. The changes in shoulder width (cm) in response to lateral raises (6x/week) over the course of 6 weeks. Participants of groups E1 and E4 were assigned 1-second and 4-second velocity eccentrics, respectively.

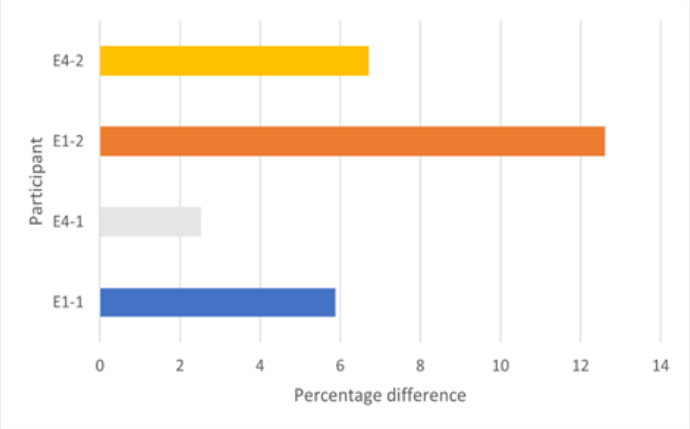

Figure 3. The percentage difference in shoulder growth between participants that had similar starting shoulder widths, but with different assigned velocity eccentrics.

ARTICLE INFORMATION

Senior Editor
Samini Hewa

Reviewers and Section Editors
Aleena Khan, Eliana Abu-Manneh

Formatting and Illustrations
Zak de Guzman

ORIGINAL RESEARCH OPEN ACCESS

ComSciConCAN and the Positive Impacts on STEM Graduate Students' Confidence and Sense of Belonging

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Received 8 February 2023
Accepted 14 February 2023
Published 30 April 2023

SUMMARY

Science Communication (SciComm) has many implications for scientists and the larger community, including its role in public policy formation. Though a growing field, undergraduate and graduate level SciComm training programs currently exist worldwide, and the impacts of many have been previously explored. Two noted benefits of such programs include improvement in SciComm confidence and sense of belonging. ComSciConCAN, a Canadian version of the U.S. ComSciCon workshops, is a graduate-level SciComm conference, aiming to provide STEM students with an opportunity to improve their SciComm skills. We are not aware of any previous studies that analyzed the impacts of this conference, which encouraged us to initiate this study. We asked ComSciConCAN-2021 participants to complete surveys before and after the workshop. According to survey responses, the conference significantly enhanced the participants' confidence in communicating with other scientists and lay audiences. Additionally, the participants' perceptions of the conference revealed benefits for their sense of belonging and commitment to the scientific community.

ABSTRACT

Although Science Communication (SciComm) is a growing field, there currently exist many undergraduate-and graduate-level SciComm training programs worldwide. Two noted benefits of such programs are improvement in SciComm confidence and sense of belonging. ComSciConCAN is a graduate level SciComm conference; no studies have previously looked into the impacts of this conference, which encouraged us to initiate this study.

Purpose: To explore the impacts of ComSciConCAN on the participants' confidence in communicating with other scientists and the general public as well as their sense of belonging in current STEM programs and SciComm activities.

Methods: ComSciConCAN-2021 participants were asked to complete surveys before and after the workshop. Data analysis was done using Microsoft Excel, and unpaired t-test statistical analyses were conducted using Graphpad.

Results: With regards to confidence, significant differences ($p < 0.05$) were observed in the mean levels reported for all three cases pre-versus-post conference. Regarding sense of belonging, 65% and 83% of the participants reported at least "somewhat agreeing" that the workshops will help improve this in their current STEM program and SciComm activities, respectively.

Conclusion: The conference had a positive impact on the participants' SciComm confidence and senses of belonging.

Keywords: Male, mental health, progressive media, conservative media, written news media, stigma

INTRODUCTION

1.1 What is Science Communication (SciComm) and Why is it Important?

Science Communication (SciComm) is the practice of disseminating scientific knowledge to different audiences using appropriate strategies and media. Past research has revealed substantial deficits in the public's understanding of science and ineffective SciComm has been well identified as one of the main factors contributing to this issue.[1]

1.2 Implications of SciComm within the Community

The dangers of ineffective SciComm have been best highlighted throughout the COVID-19 pandemic. Concurrent with the pandemic, the world has experienced the rise of "infodemics" surrounding the virus, which refer to the presence of an overwhelming amount of information, including false or misleading information.[2] This has left various communities dealing with differing degrees of mistrust in science.[2] One instance includes the narrative portraying COVID-19 vaccines as a means of implanting microchips in human bodies for the purpose of those in authority, such as Bill Gates, to obtain surveillance over the global population.[3] A similar false belief has also been circulating regarding the messenger ribonucleic acid (mRNA) vaccine technology, which was used to develop the Pfizer/BioNTech and Moderna COVID-19 vaccines.[4] Some have stated that this technology is brand-new, unconventional, and thus, cannot be trusted.[4] Although it is true that this is a new technology used for vaccine development, research in the field has been advancing for almost two decades.[5] In addition, safety and efficacy trials for these vaccines have shown high efficacy rates of 94-95% after the delivery of two doses.[6]

Such false views and conspiracy theories can weaken the public's trust in science. In a study done in the United States (U.S.), researchers found that belief in false narratives related to COVID-19 correlated with significantly lower trust in science.[7] This result is followed by a range of real-life consequences with a negative impact on health behaviors, such as increased vaccine hesitancy, thus not only undermining the work of scientists but also harming the health of the community.[8]

During this time, it has been more important than ever for scientists to be able to both get their messages across to various audiences effectively and distinguish themselves from non-credible sources of information. This is where SciComm training programs step in, providing scientists with an opportunity to build on their skills in communicating science with non-expert audiences.[9]

The implications of SciComm and SciComm training programs have a history far beyond the current pandemic. The most evident instance involves the topic of climate change and its origins. Though it has been scientifically determined that the increased pace of global climate change over the past few decades is unequivocally attributed to human activity, the public awareness around this topic does not live up to its expectations.[10] A U.S. study in 2016 revealed that less than half of adults surveyed had views in line with those of scientists, while 31% reported believing in natural causes to be the driving force for climate change, and 20% indicated not believing in climate change at all.[11] Further, research has shown non-scientific grounds for beliefs about climate change. Specifically, a study by the Pew Research Centre uncovered a political basis: while 61% of Democrats considered climate change a major threat in 2009 and 88% in 2020, only 25% of Republicans did so in 2009 and 31% in 2020.[12]

The aforementioned research demonstrates that the path of science translation from scientists to the general public is already one of nonlinear nature with various confounds such as political and economic agenda potentially blurring the scientists' messages. The problem is only compounded in the presence of ineffective SciComm by scientists themselves. Time and time again, it has been suggested that inappropriate SciComm may indeed be the root cause of this knowledge gap between the experts and the larger community.[13,14,15] Considering that non-expert understanding of science is required for the public to support policy changes and governmental action, the broader implication of SciComm can be recognized. This once again highlights the importance of experts' ability to effectively communicate their findings with lay audiences and to differentiate themselves from biased sources of information.

1.3 Implications of SciComm within the Community

With more studies shedding light on the impacts of SciComm in the broader community, knowledge translation to non-expert audiences is now considered a duty of the scientist.[16] Indeed, the term *civic scientist* was coined in the late 1990's to emphasize the importance of communicating science as a civic duty for science experts.[16] Previously, this was primarily the responsibility of teachers, trained science writers and journalists, and outreach coordinators.[17] However, after recognizing that scientists themselves are the most reliable source of scientific information, they are now expected to contribute to the public understanding of science.[18,19]

This expectation from scientists has been followed by research funding institutions mandating or encouraging researchers to possess SciComm skills and communicate their research with the larger community. As early as 1995, five of the United Kingdom Scientific Research Councils, involved in physical and life sciences as well as engineering, suggested that all researchers receiving grants from public funds should be responsible for explaining to the general public what the grant is enabling, or has enabled them to do, what the implications of their work are, and how it fits into the big picture.[20] For instance, the Biotechnology and

Biological Sciences Research Council (BBSRC) established a requirement for all funded researchers to allocate a portion of their time to activities aiming to promote public understanding of science.[20]

A study reviewing the policies and guidelines of science research funding bodies in Europe, North and South America, Asia and Oceania , and Africa has also discovered that many funding institutions now require or encourage scientists to share their findings with non-scientific audiences through dialogue.[21] As an example, the United States National Institutes of Health (NIH) has established a policy which requires public access to researchers' findings, through the *PubMed Central* website, within 12 months of publication in an academic journal.[21] Similarly, the United States National Science Foundation (NSF) requires scientists applying for research grants to outline their project's "broader impacts", which may include elements like enhancing public scientific literacy and engaging the public with science and technology.[22]

In Canada, although not a funding requirement like the previous examples in the U.K. and the U.S., the Canadian Institutes of Health Research (CIHR) and the National Science and Engineering Research Council (NSERC) provide funding to research projects which may involve community engagement.[21] However, for such agencies that do not already have a SciComm criterion, there is a growing call to include this as a requirement for funding opportunities.[21]

As such, SciComm skills are now considered not only an asset but also a requirement for scientists. Sir Mark Walport, the U.K. government's Chief Scientific Advisor of 2013 to 2017, emphasized this in an interview: "Science isn't finished until it's communicated. The communication to wider audiences is part of the job of being a scientist, and so how you communicate is absolutely vital".[23]

1.4 What is SciComm Training and Why is it Important?

Knowing the implications of SciComm and the importance of effective SciComm practices, how can we ensure that scientists have the skillset to successfully disseminate their knowledge to various audiences? As mentioned earlier, this is where SciComm training programs step in, aiming to provide scientists with an opportunity to acquire and practice such skills.[9] Considering the crucial role that these trainings can bear in shaping a scientist's practices, it is reasonable to state that the earlier training takes place, the more beneficial it is.[24] This would maximize scientists' exposure to SciComm and their likelihood of fulfilling their role as *civic scientists*. Indeed, research into existing SciComm training programs on the undergraduate and graduate levels has revealed the many benefits of these programs, two of which include enhancing scientists' confidence and sense of belonging.

Confidence refers to scientists' belief in their ability to effectively communicate science with different audiences. In a U. K. study, researchers explored the impacts of an undergraduate SciComm module on science students, and concluded that those who completed the module were more confident during PhD interviews.[25] Similarly, Brownell & colleagues (2013) looked into the impacts of a Stanford University upper-level undergraduate Biology course with SciComm-focused assessments for 3 consecutive years. Based on survey results, students had a confidence boost in both communicating science with other scientists and with lay audiences after taking the course.[26] Participant surveys from other training programs in North America, specifically the ones offered by UNAVCO, the EarthScopeNationalOffice and the Incorporated Research Institutions for Seismology (IRIS), have also shown positive impacts on scientists' confidence in communicating with lay audiences.[27] In addition, highlighting the important role of confidence for science communicators, the IPCC released a SciComm handbook for their authors back in 2018. While acknowledging that *how* a messenger communicates a message is at least just as important as the message itself, this was released in hopes of enhancing the scientists' confidence in public engagement.[10] A summary of the guidelines is shown in Fig. 1.

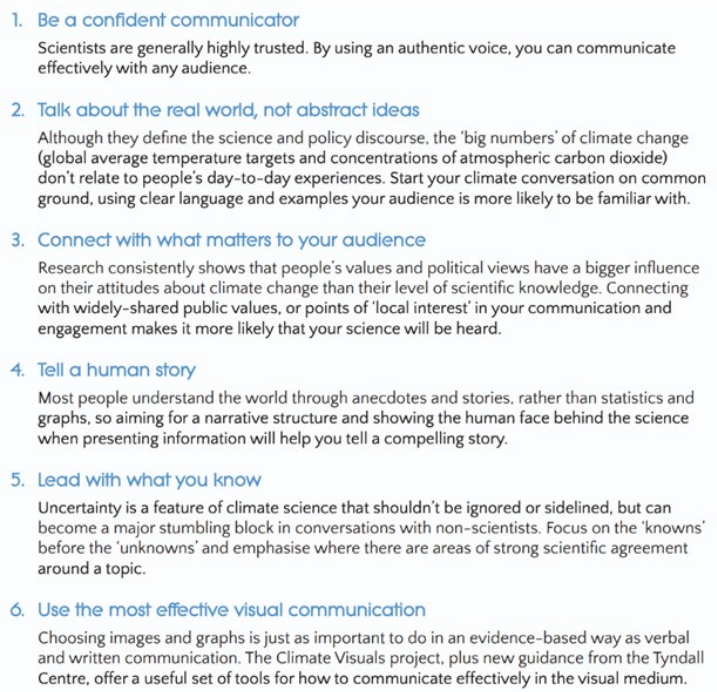

Figure 1. **IPCC's principles for authors to use in public engagement, as seen in their 2018 communications handbook**

Research into the aforementioned North American SciComm training programs has also revealed an enhanced sense of belonging at scientific meetings for the participants.[27] The researchers noted that this plays a critical role when it comes to student retention within the science field.[27] A sense of belonging to the institution and the academic community has been associated with greater student retention in previous studies as well. [28,29] For undergraduate students, this involves not only persistence in one's current program, but also pursuing research in the field through a Master's or a PhD degree.

1.5 ComSciConCAN and the Present Study

The Communicating Science Conference (ComSciCon) is an annual SciComm workshop series founded in the U.S. in 2013. This conference, run by graduate students, aims to empower North American STEM graduate students to share their research with not only other experts in the field, but further, with a broad range of audiences. To accomplish this goal, participants are provided with an opportunity to develop and finetune their SciComm skills through a variety of activities. These include learning about effective SciComm through panel discussions with invited SciComm experts (science writers, filmmakers, etc.), networking with the guests and other participants, and putting their newly gained knowledge to practice for written and oral SciComm through hands-on training sessions.[30] A study into the impacts of U.S. regional ComSciCon workshops in 2015-2017 found significant improvements in attendees' confidence levels for communicating science with different audiences.[31]

ComSciConCAN is an adaptation of the ComSciCon workshops within Canada and, as such, is designed to help STEM graduate students improve their skills in communicating their research with a variety of audiences. In 2021, this conference took place virtually on August 13th-15th, and comprised of the following components:

a) Panel discussions with both SciComm experts from diverse academic backgrounds and those involved in science policy,

b) Workshops on data visualization and visual storytelling,

c) "Create-a-thon", through which attendees developed a SciComm piece (in the format of their choosing), and received constructive feedback from a peer review group prior to the conference, and from a SciComm expert throughout the conference, and

d) An E-poster session, which aimed to highlight the attendees' SciComm contributions through abstract submissions and was an optional component.

Although the study by O'Keeffe and Bain (2018), as well as many other studies, have explored the outcomes of various SciComm training programs in different parts of the world, there is a gap in knowledge regarding the impacts of the ComSciConCAN workshop series. This paper will analyze this topic with a specific focus on attendees' confidence in publishing in popular science magazines and communicating science with different audiences, as well as their sense of belonging to the scientific community. Based on previous research findings regarding similar SciComm training programs, it is hypothesized that participation in this conference will indeed have a positive impact on both the confidence and sense of belonging of the participants.

METHODS

2.1 Data Collection: Surveys

To assess the effectiveness of ComSciConCAN-2021, all attendees were asked to complete online pre- and post- workshop surveys at least a few weeks apart in all instances. Similar surveys have been used previously for the purpose of assessing the effectiveness of the ComSciCon workshops in the U.S.[31] The pre-workshop survey contained 41 questions, and included ones that asked the attendees to rate their confidence level with regards to each of the following on a scale of 1 (not at all confident) to 9 (very confident): comfortability with submitting an article to a popular science medium (e.g. Scientific American, Wired, etc.), their ability to communicate science with other scientists, and their ability to communicate science with the general public. The survey after the conference asked the participants the same questions about confidence levels. Additionally, the post-workshop survey aimed to explore the impact of the conference on sense of belonging by asking the participants to indicate their level of agreement (strongly agree, somewhat agree, neutral, somewhat disagree, and strongly disagree) with statements indicating that these workshops will positively impact their sense of belonging to both their current STEM program and SciComm activities.

As the Canadian participant pool consisted of both English and French-speaking individuals, all workshops and surveys were run in both languages. Survey results were then translated to English for data analysis.

2.2 Data Analysis and Statistical Tests

Upon data collection, pre- and post- workshop survey responses were organized in an Excel spreadsheet. The use of identical questions regarding confidence in both surveys allowed for effective statistical analysis. The software Graphpad was used to conduct unpaired t-

test analysis, which allowed for the comparison of mean levels of confidence reported pre- and post- conference and to determine whether any meaningful difference existed between the two measures. Bar graphs and box and whisker plots were used to present the results. While no statistical analysis could be done for the data gathered regarding the sense of belonging, the frequency of each level of agreement was counted and pie charts were used to present these data. All results, including the figures mentioned, are shown in the following results section.

RESULTS

Here, we present findings from the online surveys regarding both confidence levels and sense of belonging, as reported by ComSciConCAN-2021 participants.

3.1 ComSciConCAN and its Impacts on Confidence

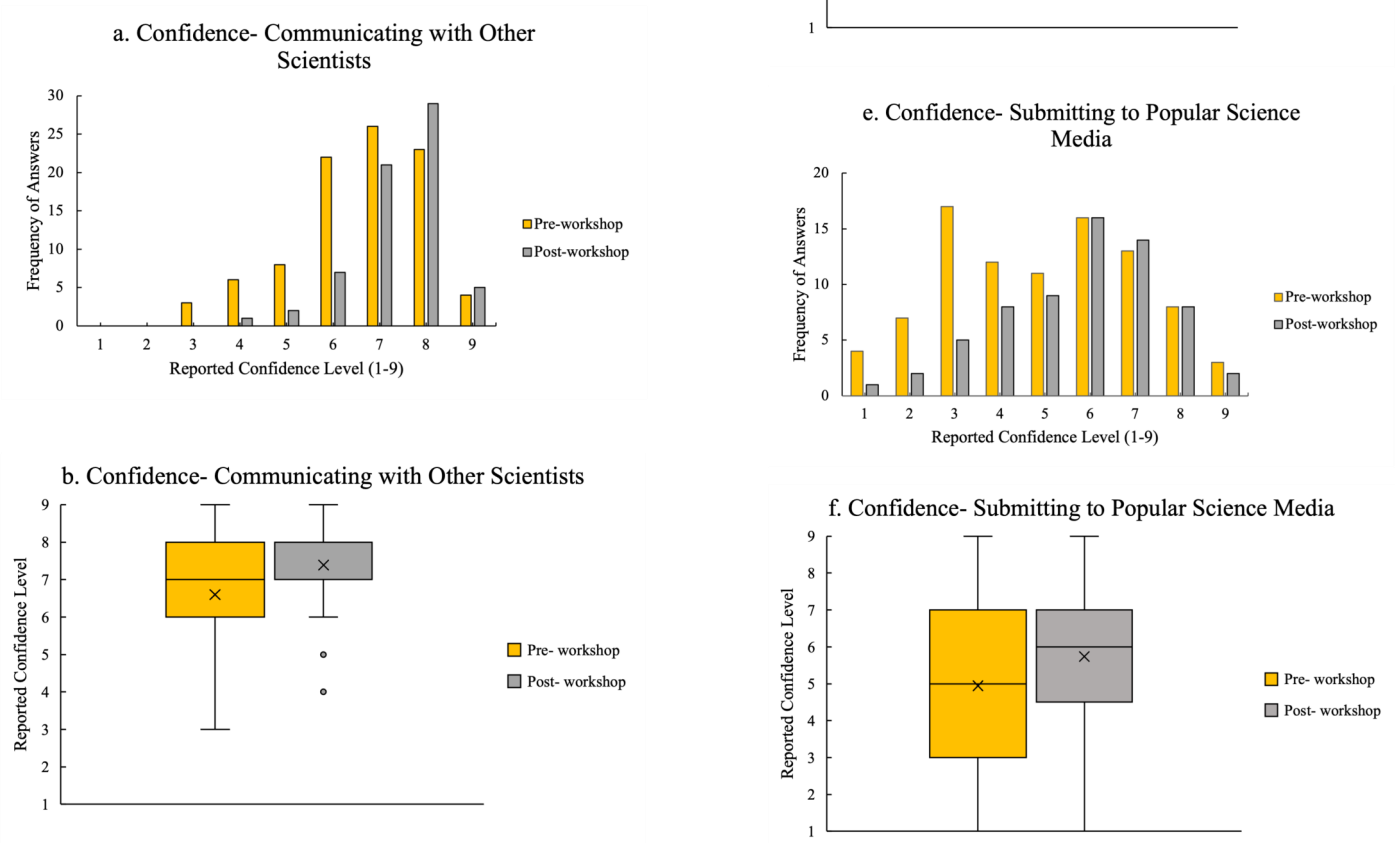

Figure 2. The change in attendees' self-reported confidence levels (from 1 to 9, where 1 = "not at all confident" and 9 = "very confident") regarding communication with various audiences pre- and post- workshop. Panels a and b display the results for communicating with other scientists, panels c and d display results for communicating with the general public, and panels e and f are for submission to popular science media. The bar graphs in panels a, c, and e depict the general trends observed in the attendees' confidence levels, while panels b, d, and f depict this information using box and whisker plots, highlighting the difference in means (presented by an "x" in each box). The p- values associated with the differences in means seen in panels b, d, and f are all smaller than 0.05. These values are 0.0002, 0.0001, and 0.0142 respectively.

As seen in all bar graphs in Fig. 2, there was a general shift to the right after the conference, indicating higher self- reported confidence levels by attendees post- versus pre- workshops. This difference can also be seen in all box and whisker plots in Fig. 2. These graphs show this shift through a reduction in size of each box (where 50% of data points lie) post- workshops, the shift in mean confidence values reported as well as a shortened whisker length in panels b and d. Any data point with a confidence level smaller than 6 is shown to be an outlier in these two panels, b and d. The box and whisker plots also compare the mean levels of confidence before and after workshops, and present an increase in this value in each case (from 6.598 to 7.385, 6.462 to 7.277, and 4.945 to 5.738, pre- versus post- workshops for communication with scientists, communication with the general public, and submission to popular scientific journals, respectively). Statistical analysis showed these differences to be significant, and the p-values are included in the figure caption for Fig. 2.

3.2 ComSciConCAN and its Impacts on Sense of Belonging

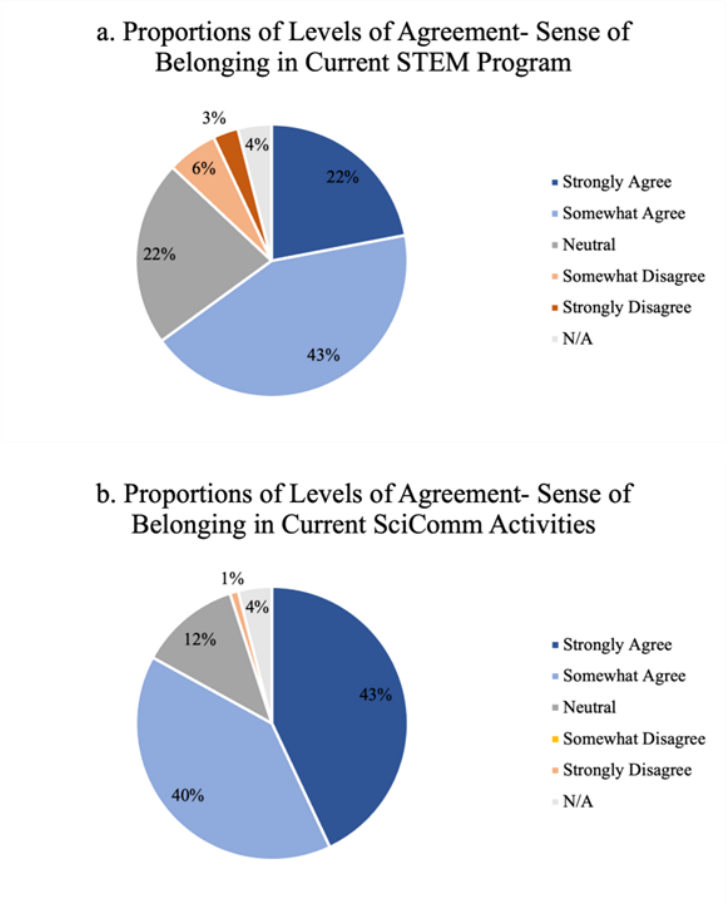

Figure 3. Levels of agreement with each statement regarding sense of belonging. The pie chart in panel a presents the results for the statement "ComSciCon Canada will increase my sense of belonging in my current STEM program," and that in panel b presents this information for the statement "ComSciCon Canada will increase my sense of belonging in my current sci comm activities."

As seen in Fig. 3 panel a, 65% of participants at least "somewhat agreed" that the workshops will be helpful in improving their sense of belonging in their current STEM program, with 22% of them strongly agreeing. Similarly, and as seen in Fig. 3 panel b, 83% of participants at least "somewhat agreed" that attending ComSciConCAN will have a positive role in improving their sense of belonging in their current SciComm activities, with 43% of them strongly agreeing.

DISCUSSION

4.1 ComSciConCAN and its Impacts on Sense of Belonging

The purpose of this study was to determine whether participating in the ComSciConCAN workshops had a positive impact on both the confidence and sense of belonging of graduate STEM students. Our hypothesis was that this impact would in fact be observed, which was tested through online pre- and post- workshop surveys.

As shown in Fig. 2, there was an increase in attendees' self- reported confidence levels after the workshops. Further analysis showed this difference between pre- and post- workshop confidence levels to be statistically significant (with p-values smaller than 0.05 in each case). This supports the first part of our hypothesis, which predicted a positive impact on confidence in communicating science with different audiences. As the surveys were sent at least a few weeks apart in every instance, it is unlikely that the participants remembered their original confidence levels reported. This eliminates a source of error that could potentially impact the results by reducing subjectivity in answering the post- workshop survey questions. These findings regarding a boost in confidence are consistent with the findings of previous studies on other SciComm training programs.[25-27,31] Particularly, O'Keeffe & Bain (2018) investigated the impacts of U.S. regional ComSciCon workshops on identical measures- confidence in communicating with other scientists and the general public, and in submitting to popular scientific outlets- and found similar statistically meaningful results.

Similarly, the attendees' perception of whether the workshops will improve their sense of belonging provides support for the latter part of our hypothesis. This is since a great proportion of the attendees (65% for sense of belonging in current STEM program and 83% for sense of belonging in current SciComm activities) at least somewhat agreed with the respective state-

ments. These findings are similar to those from previous post-training surveys for other SciComm training programs, which have found an enhanced sense of belonging at scientific meetings and to STEM fields as a result of attending these workshops.[27]

4.2 Limitations

There are some limitations to this study due to self-reporting. These include barriers associated with honesty (the participants may have been inclined to report more socially desirable answers), introspective ability (participants may have not been able to objectively assess themselves), interpretation of questions (different individuals may have interpreted the wording of the survey questions differently), and rating scales (the participants may have been inclined to give an extreme or middle answer to all questions). In addition, although 94 individuals completed the pre- workshop surveys, only 68 entries were received for the post- workshop surveys. This translates into an approximately 28% attrition rate, leaving open the possibility that the results/ positive impacts of the conference may have been an inflation of true results.

4.3 Next Steps

In the future, research studies can explore the outlined benefits of SciComm training programs, specifically ComSciCon in North America, to see whether the results of our study can be replicated. Our findings highlight some of the notable impacts of the ComSciCon workshop series, and provide support for other SciComm training program coordinators to adopt the framework used by ComSciCon to design new SciComm training programs. This also highlights the importance of funding opportunities to support these programs and provide the ground for SciComm experts to expand training and run these programs for a larger body of STEM students.

CONCLUSION

This study was designed to investigate the impacts of the ComSciConCAN workshops on STEM graduate students' confidence in communicating with both expert and lay audiences and their sense of belonging to the scientific community. We predicted, based on the findings of previous studies on various SciComm training programs, that a positive impact would result. In line with this hypothesis and through analyzing the participants' observations pre- versus post- workshops, we discovered meaningful improvement in the scientists' SciComm confidence in all three categories: communicating with other scientists, communicating with the general public, and submitting to popular science media. Also, upon attending the conference, a greater proportion of the participants more strongly believed that the workshops will enhance their sense of belonging in STEM activities.

ACKNOWLEDGEMENTS

This work did not receive any funding, and there were no conflicts of interest involved in the writing process. I would like to thank my supervisor, Dr. Katie Moisse, for her constant guidance and support throughout the process of completing this study and my undergraduate degree. I have learned so much along the way and feel incredibly grateful to have had such an inspirational supervisor and mentor. I would also like to thank Adina Silver for her valuable feedback and resources, and for making herself available to assist me at all times throughout the process.

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ACADEMIC REVIEW OPEN ACCESS

Weighing the Benefits and Drawbacks of Testosterone Replacement Therapy

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Received 31 January 2023
Accepted 14 February 2023
Published 30 April 2023

SUMMARY

Male hypogonadism—the deficiency of testosterone in the body—is a condition that has sparked increased interest in the discussion surrounding men's health. Many studies have previously explored the use of testosterone replacement therapy to improve the quality of life for patients with this condition. However, further research is required to weigh the long-term benefits and drawbacks of this therapy to determine its safety and efficacy for future patients. This review will highlight the advantages and disadvantages of testosterone replacement therapy in men suffering from hypogonadism. Improvements highlighted in this study include increased libido, muscle mass, and self-esteem. These improvements weigh against potential side effects such as organ cancers and systemic tissue damage. This review will also explore which patients are most suitable for the treatment and how the research surrounding this topic can be improved moving forward. By analyzing a range of short- and long-term studies with empirical data, observational and surveyable evidence, this review will provide insight into the basics of testosterone replacement therapy, the potential benefits and risks associated with its use.

ABSTRACT

Over the last few decades, the discussion surrounding men's health issues has sparked an increased interest in the treatment of male hypogonadism—the deficiency of testosterone in the body—through testosterone replacement therapy to improve patients' quality of life. A worthwhile consideration for further research a is to explore the long-term benefits and drawbacks that may testosterone replacement therapy prescription to patients moving forward. It is worth weighing treatment effects, as well as examining which patients are most suitable for the therapy and why, from a health cost-benefit analysis. Many of the benefits that this review will be related to the symptoms of hypogonadism—most notably decreased libido, muscle mass, and emotional well-being. This review will also consider the potential side effects of treatment through short- and long-term studies which include observational, surveyable, and empirical data. Some drawbacks include increased risk of various organ cancers and systemic tissue damage. Holistically, this review will provide insight on the basics of testosterone replacement therapy, who benefits from it the most, who is at risk, and how its understanding can be improved moving forward.

Keywords: Testosterone replacement therapy, hypogonadism, muscle hypertrophy, sexual function

INTRODUCTION

The perception of testosterone replacement therapy (TRT) for aging men is particularly controversial. TRT is a legalized treatment option that alleviates testosterone deficiency symptoms, such as decreased libido, erectile dysfunction, depressed mood, anemia, and loss of muscle and bone mass, by increasing serum testosterone levels to healthy physiological ranges.[1] Late-onset hypogonadism (LOH) has increased nearly 7% in men within the last 40 years according to a retrospective cohort study conducted in China.[2] Most doctors recommend that the first line of treatment should remove the root cause of LOH, such as treating obesity, type 2 diabetes (T2DM) or any metabolic syndrome (MetS).[2] However, many patients simply require the assistance of exogenous testosterone supplementation to reach recommended hormone levels. As TRT prescription rates increase, the treatment option's efficacy and safety are paramount. This systematic review's objective is to analyze the intended benefits as well as adverse effects of TRT for males with subnor-

mal free testosterone levels. This review will evaluate the current literature around TRT to determine its relevance and reliability.

1. METHODS OF TESTOSTERONE ADMINISTRATION

Testosterone can be administered in a multitude of ways into the body to increase serum testosterone levels. Oral testosterone supplements are sold in most recreational health outlets. However, they are considered to be ineffective due to a combination of poor intestinal absorption capacity and rapid hepatic metabolism, rendering them useless biochemicals once in the bloodstream.[3] Buccal testosterone is an uncommon way to improve serum concentrations, involving mucoadhesive tablets applied to the gums of the mouth to provide continuous release directly into the systemic circulation, bypassing the liver and yielding relatively high bioavailability.[4] Nasal testosterone is another uncommon form of deliverance, consisting of a thixotropic gel applied to the nasal cavity, continuously delivering testosterone directly into the circulatory vessels.[5] Next, the subdermal method employs testosterone pellets of a crystalline preparation which are designed and implanted for consistent and prolonged-release.[6] Lastly, intramuscular testosterone injections are commonly used to treat hypogonadal males and female-to-male transgender patients.[7]

2. TYPES OF TESTOSTERONES

Testosterone propionate, cypionate, and enanthate are different forms of testosterone. These forms differ in their esterification, which affects their pharmacokinetics. Essentially, the different compounds will vary in absorption, distribution, metabolism, and excretion by the body. Regarding esterification, propionate has the shortest ester chain, compared to cypionate's long chain and enanthate's even longer chain.[3] The shorter chain allows the compound to enter the bloodstream quicker. The time of action is also a significant factor to consider. Propionate has a shorter half-life than the others. Therefore, propionate is rapidly absorbed and eliminated from the body, which requires the user to take more frequent injections to maintain adequate serum concentrations.[4] The esterification and time of action also factor into the distribution of the compounds in the body. Propionate is rapidly distributed throughout the bloodstream due to its comparative size and pharmacokinetics and is excreted through metabolism at a faster pace as well.[5]

3. BENEFITS OF TRT

Restoring testosterone levels to the normal range using TRT can improve many facets of life for individuals suffering from hypogonadism. Notable and documented benefits of TRT include improved mood, energy, well-being, cognition, sexual function, muscle mass, strength, erythropoiesis, bone mineral density, and cardiovascular health.

3.1 Sexual Desire, Function, and Performance

Frequent erectile dysfunction is a common occurrence for men beyond their pubescent years.[7] This is likely due to the correlation that exists between free testosterone and erectile and orgasmic function.[8] As free testosterone decreases beyond puberty, we can expect sexual activity, functionality, and performance to decrease accordingly because of increasing dysfunction of androgen receptors.[9,10] Long-term follow-up of TRT in hypogonadal males and controls indicated, through self-assessment of the sexual characteristics, significant improvements in the testosterone-treated group only.[11] Indeed, Hajjar et al. (1997) showcased that TRT enhanced libido and frequency of sexual acts and sleep-related erections.[11]

Unfortunately, for some men, TRT alone is not enough to improve sexual performance, leading to a reassessment of the causes of erectile dysfunction. There is evidence by Shabsigh et al. (2004) that taking phosphodiesterase type-5 inhibitors—i.e., sildenafil or Viagra—could have a synergistic effect with TRT for men suffering from this condition.[12] These inhibitors work in the penis and lungs by blocking the breakdown of cyclic guanosine monophosphate (cGMP) which results in prolongation of the mediators of vasodilation, most notably including nitric oxide (NO).[13] Karazindiyanoglu and Cayan (2008) also suggests TRT can improve lower urinary tract symptomatology (LUTS) and overall bladder functionality by increasing capacity.[14] Mitigating these symptoms has shown to improve cases of erectile dysfunction in patients.[15]

3.2 Bone Mineral Density

Osteopenia, osteoporosis, and fracture prevalence rates are significantly greater in hypogonadal men, regardless of age, as suggested by Meier et al. (2008).[16] Testosterone supplementation has been shown to improve bone mass by increasing osteoblastic activity, and through aromatization to oestrogen, reducing osteoclastic activity.[17] Osteoblasts are responsible for new bone formation, while osteoclasts are responsible for aged bone resorption.[18,19] Morley et al. (1993) found that osteocalcin levels, indicative of osteoblast activity, were elevated, whereas hydroxyproline excre-

tion, indicative of bone resorption, were decreased.[20] At normal physiological conditions, formation and resorption rates are stable. However, when the balance is disturbed, as in the case of hypogonadism, bone architecture and function will be abnormal. TRT can aid in the return normal homeostatic conditions.

3.3 Muscle Mass and Strength, and Fat Mass

Unfortunately, for ageing men, body composition has shown to change in negative ways. Indeed, muscle tissue tends to decrease, and redistributed fat mass increases.[21] Decreases in overall muscle mass and strength can limit functionality and increase injury risk, and deter overall quality of life, especially for those who lead active lifestyles, habitually or professionally. Differently, increased fat mass can lead to morbidity through increased cardiovascular and immune system stress. However, the declining testosterone levels are a contributing factor to these negative changes, but not entirely culpable. Furthermore, Mauras et al. (1998) suggested that human growth hormone (HGH) decreases with age because of somatopause.[22] HGH binds to hepatic receptors and stimulates the expression and release of IGF-1.[23] IGF-1 then stimulates testosterone production by testicular interstitial cells to enhance steroidogenesis.[24] This results in increased muscle protein synthesis and growth.

Given this information about the testosterone production cascade, one would reasonably consider supplementing growth hormone to treat the testosterone deficiency directly, however, this is inadvisable. HGH is not an effective treatment for low testosterone. While it impacts overall body composition, the safety and validity of this treatment option is not sufficiently grounded. As suggested by Birzniece et al. (2011), HGH vs TRT had no statistically significant difference in serum free testosterone concentration.[25] However, growth hormone is a more broadly utilized drug compared to testosterone, which can lead to many unintended physiological effects if the goal is simply to treat hypogonadic symptoms. Hence, supplementing with TRT is the safest and most efficient means to improve muscle mass and strength.

Testosterone can also decrease fat mass by inhibiting the expression of lipogenic genes in fat cells resulting in global lipid oxidation.[26,27] While the underlying mechanisms aren't entirely understood, some researchers suggest that certain genes within the fat cells are inhibited by testosterone and reactivated through its aromatization into oestrogen.[28] Miller et al. (2016) supported this hypothesis, suggesting that oestrogen levels can modulate hepatic lipogenesis.[29] This is a common issue in men who take anabolic steroids, most famously represented through gynecomastia—fat accumulation in breast tissue from increased testosterone aromatization into oestrogen.[30] Hence, aromatase inhibitors are recommended to be taken in conjunction with TRT to mitigate this unnecessary fat accumulation, while still reaping the benefits outlined thus far.[31]

3.4 Mood, Energy, and Quality of Life

Several studies have correlated low serum testosterone levels with lower quality of life.[32] The attributes measured included low libido, dysphoria, fatigue, and irritability—all of which correspond to major depressive disorders.[33] Schmidt et al. (2004) found that the depressive symptoms of hypogonadal patients were significantly reduced, if not entirely reversed, by TRT.[34] However, it is important to be critical of this evidence as contrary results have also been published. Specifically, a study by Tricker et al. (1996) found that TRT administration had no significant effect on depressed hypogonadal men, relative to their nondepressed test subjects.[35] This begs the question of whether TRT should be prescribed to men who suffer from depressive symptoms, which are likely the result of serum testosterone deficiencies.

For this, we will have to compare the effects of depression treatment and TRT. Ehrenreich et al. (1999) suggested that testosterone may serve as an effective antidepressant, given that their study explored a large sample of men with depressive symptoms and found that testosterone gel significantly improved depressive symptoms in groups that did not receive placebos nor selective serotonin reuptake inhibitors (SSRIs). It is important to note that a possible limitation of this data is that there was no follow-up study several weeks beyond the trial treatment period, limiting its long-term applicability. Indeed, further trials should be conducted to thoroughly explore this topic as the evidence proposed thus far has been conflicting to say the least. Nonetheless, if mental health is an issue for someone suffering from hypogonadism, TRT is worth considering because as the benefits previously outlined, it clearly suggests that it can improve physical health and has limited negative side effects on mental health.

3.5 Cognition

Gillett et al. (2003) have demonstrated through clinical research that androgen deficiency may enhance the expression of peptides involved in Alzheimer's disease, including beta-amyloid.[36,37] Indeed, decreases in serum testosterone may be responsible for visual and verbal memory declines as men with equivalent ratios of sex-hormone binding globulin with serum testosterone have higher incidences of dementias.[38]

Spatial abilities and mathematical reasoning are components of verbal and visual memory that may be impacted. Gouchie and Kimura (1991) found that a

strong relationship exists between men's testosterone levels and their memory and cognitive capacity, even after it was adjusted for age and education as confounding variables.[39] Lu et al. (2006) found patients suffering from Alzheimer's disease experienced significant improvements in cognition and mood following TRT.[40] However, there is some contradictory evidence in this discussion as Maki et al. (2007) found that TRT accelerated working memory declination and brain impedance.[41] Finally, Tan and Culberson (2003) found that there was no significant difference in cognitive capacity and function following TRT in androgen-deficient men, suggesting that this area is prudent for further investigation before one considers TRT if they are at risk for dementia-related diseases.[42]

With TRT being a relatively novel therapy, only becoming popularised in the early 1990s and 2000s, the rise in concern over potential adverse effects is significant. Due to the lack of factual data surrounding the relationship between TRT and adverse health effects, this review will delve deep into the literature to find any causational or correlational evidence of the treatment's medical safety.

4. DRAWBACKS OF TRT

4.1 Liver Dysfunction

The causal relationship between TRT and hyperandrogenism with liver function is certainly understudied. Numerous concerns associated with TRT has found in the liver including hepatic tumours, cholestasis, hepatotoxicity, peliosis, hepatitis, hepatocellular adenoma, and total failure. These deleterious effects do not seem to be associated with transdermal or intramuscular injection; therefore, it is recommended that oral forms of TRT are not administered.[43]

However, a general lack of testosterone or LOH has been known to predict even worse outcomes, such as Hepatitis B and total liver failure.[44] Moreover, Westaby et al. (1977) found that a low testosterone serum (<142.39 ng/dL) is independently associated with severe outcomes of HBV-related acute-onset liver failure.

4.2 Prostate Dysfunction and Cancer

With the use of TRT becoming more common, the correlation between its use and incidents of prostate dysfunction and cancer is becoming more prominent. Fowler and Whitemore (1982) reported that exogenous testosterone given to metastasized prostate cancer patients resulted in increased advancement of malignant cells.[45] One longitudinal study found a signification between the relationship between men diagnosed with prostate cancer and endogenous testosterone supplementation.[46] However, a 3-year meta-analysis composed of 18 prospective studies with 3,500 men investigated the correlation between prostate cancer and TRT and found no association between serum androgen levels and the risk of prostate cancer.[47]

Concerning premalignancy and prostatic intraepithelial neoplasia (PIN) are risk factors for developing prostate cancer.[47] However, there is a lack of long-term data on the use of TRT in men with PIN.

Nevertheless, there have been reports of metastatic prostate cancer in older men on testosterone therapy. Due to this potential, risk practitioners and doctors are reluctant to administer testosterone to those who may be at risk of PIN.[47] Therefore, men being administered with TRT should have frequent monitoring within the first 3-6 months.

4.3 Elevated Red Blood Cell Count

Strong evidence suggests that increased testosterone levels, regardless of way-of-entry, stimulates erythropoiesis: production of red blood cells.[48] This can progress to polycythaemia: abnormal levels of red blood cells in the blood. While polycythaemia doesn't have a statistically significant correlation with TRT, it is an accepted side effect of. Considering this information, TRT is often a suggested remedy for men who suffer from anemia—low red blood cell count—due to its erythropoietic properties.

Increasing haematocrit—red blood cell count—past the regular male concentration of 4.0-5.9 x 10*12/L can have adverse side effects, ranging from increased blood pressure from thickening of blood to blurry vision and headaches. Polycythaemia may have an increased incidence of vascular events, including but limited to, stroke, myocardial infarction, or deep vein thrombosis. Therefore, it is highly suggested that while on TRT, individuals should not only monitor their complete blood count (CBC) but have their baseline CBC measured prior to the start of their treatment plan.

4.4 Compromised Immune System

For unknown reasons, men have always been more susceptible to bacterial, fungal, and parasitic infections than women.[49] In a retrospective explorative analysis conducted by Lanser et al. (2021), testosterone levels measured through PCR confirmed SARS-CoV-2 infection.[50] Interestingly, they recorded that lower testosterone levels were linked with a more advanced immune activation. This was further supported by the aforementioned comment on women's better immune systems, while they possess lower levels of testosterone than men.[50]

A Stanford lead study looked to prove a relationship between higher levels of serum testosterone with a

lowered immune response. They were unable to find any indication that testosterone actively suppresses the immune system in any direct way. However, the researchers noticed a peculiar interaction where testosterone was able to dampen the immune response, but additional research was suggested before drawing any conclusions between TRT and a reduced immune response.[49]

The sperm production hypothesis offered an alternative hypothesis that the immunosuppressive effect of testosterone protects haploid spermatozoa. Hillgarth et al (1997) suggested testosterone suppresses antibody protection within the blood-testis barrier.[51] However, this theory fails to explain the change in the numbers of circulating leukocytes associated with elevated testosterone.

However, the question remains about why testosterone, a hormone designed to increase libido, bone density, and lean muscle mass, dampens the immunity of the organism. These are questions to consider with one's clinician if they are considering TRT, especially individuals who suffer from autoimmune or chronic illnesses. Nevertheless, the inherent properties of TRT to objectively increase serum testosterone raises concern for those considering administering it.

4.5 Damaged Cardiovascular System

The relationship between TRT and cardiovascular outcomes is conflictive to say the least. Hypogonadism is an increasingly diagnosed disorder in age, overlapping with increasing risk of cardiovascular events.[52] Patients with established cardiovascular disorders considering TRT should heavily weigh the benefits, drawbacks, and possible side effects, as TRT can have variable responses on different individuals. TRT has been depicted as having cardio-protective, vasodilatory, and anti-inflammatory properties, but in some instances, it can be vasoconstrictive, pro-atherosclerotic.[52]

To shed some light on this conundrum, Michos et al. (2022) completed a meta-analysis on 35 placebo-controlled trials of TRT that included 5,601 men with low baseline testosterone concentrations.[53] During the short follow-up, there was no increase in cardiovascular events between the TRT group and the placebo group (odds ratio 1.07). The authors did witness an increase in cholesterol, but this change was statistically insignificant.

Relating to red blood cell count, those who undergo any form of testosterone therapy will undergo stimulation of erythropoietin. This will evidently increase red blood cell count, which in some circumstances can have a sharply increased risk of high blood pressure (hypertension).[54] According to Dalmasso et al. (2017), men who used synthetic derivatives of testosterone have a higher risk of ventricular remodelling and sudden cardiac death, but there was no direct correlation to TRT.[54] Hence, further investigation is required to elucidate the relationship between TRT and cardiovascular outcomes.

5. WEIGHING THE BENEFITS AND DRAWBACKS OF TRT

To adequately weigh the benefits and drawbacks of TRT, future patients are recommended to explore contraindications with their healthcare provider to ensure that the treatment is a safe and viable option. This will include looking at all the possible risks associated with TRT and properly evaluate if the safety risk is minimized during the treatment period. This will vary significantly between individuals as some men need a few weeks to 'jumpstart' their endogenous production through TRT, while others become entirely dependent on exogenous dosages to sustain their serum testosterone levels for life.

Infections at the site of intramuscular injection are not uncommon for patients undergoing TRT as properly cleaning the site can be challenging. This is because the patients are likely not given sufficient training and literature on how to minimize infection risk, during injection, by their physician. Additionally, most injection sites are at the glutes, which are hard to reach and see for most individuals. These instances of infections are easily treated with antibiotics, and a proper consultation with an attending physician can improve the future treatment, but the risk should be noted regardless.[55]

Prostatic carcinoma is a strong opponent for anyone considering TRT. This applies to any males who are genetically at risk for or have previously been diagnosed with prostate cancer. It has been suggested by Huggins and Hodges (1941) that prostate cancer is androgen-dependent, so taking exogenous testosterone to raise serum concentrations may put oneself at risk for the disease.[56] There is no clear evidence of a causational relationship. A collaborative analysis by Roddam et al. (2008) demonstrated that the men with the highest risk of prostate cancer had the lowest serum testosterone levels.[57] Conversely, Mohr et al. (2001) found no correlation between the two variables.[58] Regardless, it is likely not wise to administer TRT as it may exacerbate the likelihood to acquire prostate cancer, especially if there is concern from family history or previous cancer incidents.

Erythrocytosis is another consideration for physicians and patients deliberating TRT. As previously mentioned, TRT can significantly elevate hematocrit.[59] Consulting a physician on one's hematocrit before discussing TRT options is crucial because a higher red

blood cell count than a normal can be extremely problematic throughout and after treatment. Erythrocytosis can cause symptoms of hyperviscosity, such as headaches, fatigue, blurred vision, and paresthesias.[59] Additionally, elevated erythrocytosis can lead to secondary effects. For instance, congenitally, the body will have a high oxygen affinity Hb and altered intracellular oxygen sensing, coupled with EPO receptor upregulation.[60] This will lead to hypoxic states. Systemically, lung disease, shunt, and hypoventilation are expected; locally, renal artery stenosis and ESRD are exected.[60]

Congestive heart failure (CHF) is a growing health problem around the world, especially among aging men. Despite modern medicine, advancement concerning the detection, diagnosis, and treatment of CHF is bleak. However, TRT has been discussed significantly in the scientific literature as being a viable supplement to regular practice in correctly treating and managing CHF. While the physiopathological mechanism and effectiveness of TRT concerning the cardiovascular system is unclear, some evidence has emerged that TRT could improve muscle strength, exercise tolerance, functional pulmonary capacity, insulin sensitivity, and adjust the neuroendocrine factors in patients with CHF.[61] A collection of studies revealed that TRT could significantly improve the exercise capacity of patients, measuring factors such as 6MWD (6 -min walk distance) and SWD (shuttle walk distance), as suggested by Malkin et al. (2006).[62] Mirdamadi et al. (2014) replicated this same study and found similar results.[63] A similar study conducted by Caminit et al. (2009) found that TRT groups improved their exercise capacity, but the study explored more details beyond just that.[64] They found that there was a tendency toward blood pressure decrease, possibly suggesting that this treatment option be considered more favourably for patients with CHF. In CHF, most patients suffer a gradual decline in muscle mass, strength, and endurance, which is reflected in the maladaptive imbalance and relative deficiency of anabolic hormones, mainly testosterone. A testosterone deficit leads to the metabolic shift favouring catabolism, a major underlying mechanism for tissue wasting seen in CHF. Whether that testosterone deficiency is a precursor to the development of CHF, a consequence of the condition, or a combination of both is unclear at this time.[61] However, testosterone supplementation in patients with CHF is associated with an improvement in exercise capacity and muscle strength which will be beneficial in improving quality of life, clinical events, and safety.

CONCLUSION

As men age into their 30s, 40s, and 50s, peak testosterone steadily declines, with the most rapid decline occurring around the mid-50s.[1] However, the advancements of TRT have provided a remedy to this issue for middle-aged men. TRT is proven effective in reducing the effects of testosterone deficiency discussed above.[3] While research outlining the benefits of TRT are plentiful, those highlighting its connection to various pathologies and morbidities are certainly lacking.

Certain pathologies relating to the immune system and cardiovascular systems have some underlying concerns, but not enough definitive data is available to make any clear-cut recommendations. However, the underlying concern should be sufficient in encouraging caution and extreme monitoring when administering TRT.

Male hypogonadism and its treatment are a rapidly evolving area. The benefits and risks of testosterone therapy must be discussed with the patient. An assessment of risk factors previously outlined in this literature review should be explored thoroughly before deciding if TRT is a viable option for the patient. There are benefits to TRT, such as improvements in muscle mass and strength, fat mass, sexual function, and general well-being. However, it is illogical to ignore the plethora of negative impacts that can arise in certain individuals if they were to engage with exogenous testosterone supplementation. Patients and physicians should be cognizant of their knowledge gaps as well; the academic literature surrounding many of the risk factors is unexplored or in their novel stages of discovery. Studies conducted to date have been too small to address long-term potential adverse effects and there are risks in extrapolating benefits from epidemiological studies. Larger clinical trials coupled with meta-analyses of the extensive short-term data and limited long-term data will benefit many physicians and patients in exploring the long-term benefits and risks of TRT. Patients will have to carefully weigh their options with their medical advisor, so they are tending to their underlying conditions safely and effectively. If treatment is considered, there should be constant monitoring of symptoms and signs of improvement. If not observed, then treatment should be discontinued, and the patient will be investigated for other possible diagnoses.

ACKNOWLEDGEMENTS

First and foremost, we sincerely thank the Department of Health Sciences and the Department of Integrated Sciences for providing us with all the resources necessary to conduct this academic literature review. Without their knowledge, expertise, and scientific literature on biochemistry and physiology, we would not have been able to complete our project. Finally, how could we forget our parents; without them, we could not

have made it this far in our academic careers. However, no financial aid was provided in the production of this review by any parties. The authors report no conflicts of interest

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Effects of knowledge about tuberculosis on its prevalence in Inuit communities in Nunavut, Northern Canada: A mixed Methods study

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Received 23 January 2023
Accepted 14 February 2023
Published 30 April 2023

SUMMARY

Tuberculosis (TB) is an infectious disease that affects marginalized communities disproportionately. While TB incidences are rooted in factors that are characteristic of developing countries, some communities in developed countries, such as Canada, face a high prevalence of TB. Indigenous people, being a community alienated within healthcare, are the target population for this research proposal. Due to the historical Indigenous cultural ignorance that persists today, this research aims to employ a participatory approach to promote inclusivity and conduct research in a culturally sensitive manner. Findings from this research will provide insight into Inuit people's lived experiences and concerns, aiding in understanding the correlation between access to resources such as disease knowledge and its impact on TB prevalence. On a broader scale, this research will promote advocacy for communities excluded in healthcare and raise awareness regarding the poor living conditions often ignored in developed countries.

ABSTRACT

Rising tuberculosis cases are a global health issue that the United Nations Member States have committed to eradicating by 2030. In developed countries such as Canada, TB affects Indigenous populations disproportionately. Inuit people have 300 times greater risk of TB infections compared to non-Indigenous people. Due to Canada's colonial history, Indigenous people remain underrepresented in healthcare. Therefore, this research proposal aims to understand the link between the lack of access to resources, such as knowledge about tuberculosis and the rising TB cases, among Inuit people in Northern Canada. It is hypothesized that due to marginalization and cultural ignorance, preventative measures are not accessible to Inuit people and can influence the high transmission of the disease. Based on the results of the inclusive design of this research, future studies can aim to help voice the concerns of Indigenous people and advocate for their right to access equitable healthcare.

Keywords: Tuberculosis, TB, Infection, Indigenous health, Inuit People

INTRODUCTION

In 2018, all United Nations Member States declared a commitment to eradicate tuberculosis (TB) by 2030.[1] Yet, World Health Organization reports that TB still accounts for the highest mortality rates of all infectious diseases globally.[1] Research has shown that the prevalence of TB is mainly rooted in factors such as poverty, overcrowding, and the conditions of developing countries.[2] Research by Abdollahi et al.[3] highlighted the disproportionate impacts of TB on the Inuit population. As Inuit people experience 300 times greater rates of active TB infections, there is a need to understand factors which exacerbate infections in a developed country such as Canada.[3] Abdollahi et al.[3] also showcased the importance of the time-to-identification of TB in controlling its prevalence which is significantly longer for Inuit people. Current research does not focus on gaps in knowledge about the disease among the Indigenous.

An article by Hick[4] sheds light on Canada's colonial history, which has neglected the Indigenous peoples in

all aspects, including healthcare. The cultural ignorance of Indigenous people is deeply rooted in the lack of appreciation of their existence, resulting in the lack of support available for them.[4] The horrifying historical events represent a series of attempts to eradicate the Indigenous culture, which is why to this day, they remain excluded, marginalized, and alienated.[4] The following research proposal, therefore, hopes to investigate the impact of a possible lack of access to knowledge about TB on the Inuit Indigenous community.

This proposal's rationale is further influenced by the key findings presented in research by Patterson and colleagues.[5] The Inuit communities in Canada lack infrastructure, with few roads that limit access to healthcare and impede the ability of staff to visit.[5] Moreover, communication is attenuated as the staff, upon arrival, cannot understand the cultural and other barriers, such as the language of the Inuit people.[5] This tyranny of distance, combined with the barriers mentioned earlier, yields ineffective communication with the Inuit people. Research by Hick[4] shows that the dichotomy created between Indigenous and non-Indigenous communities ignores aspects of the Indigenous culture that do not fit in the boundaries of "what is acceptable." In fact, most hospitals and hospital staff do not offer services in native Indigenous languages, which further impedes the transfer of knowledge to them regarding infectious diseases such as TB.[4] Knowledge about diseases shapes patients' illness experiences and affects their outcomes.[6] There remains an abundance of scientific research regarding cures for TB since the 20th century.[4] Therefore, it deems essential to understand factors such as access to knowledge about TB among Inuit people and its correlation with the rising infections.

Research by Orr[7] shows the benefits of tuberculosis control programs in connecting with individuals from diverse backgrounds. Projects such as "stop tuberculosis" involve intimate education protocols that help raise awareness, including door-to-door visits.[7] These initiatives have shown success in engaging diverse communities at the street level, empowering those in need, and ensuring the delivery of culturally sensitive care.[7] Looking at the example of the United States, TB control efforts by communicating with the public intimately have prevented more than 300,000 people from developing TB disease.[8] These efforts have reduced the prevalence of TB to 2.4 cases per 100,000 persons.[9] Conversely, the disparity in TB cases can be seen by the striking 170.1 cases per 100,000 people among Inuit people compared to 0.6 cases per 100,000 non-Indigenous Canadians.[10] Based on the success of other countries, it would be advantageous to establish strong partnerships with the Inuit to understand their conditions and remove barriers to care.

1.1 PHILOSOPHICAL ORIENTATION

Adopting the pragmatism orientation will allow innovative and dynamic research to be conducted. This orientation perfectly aligns with the research question due to its belief that objective and subjective realities can co-exist.[11] The knowledge regarding TB that previous research has constructed needs to be further developed by analyzing the challenges faced by marginalized communities and their personal experiences. It is also vital to understand the cultural differences and barriers, including language, that bolster the lack of awareness. Therefore, a pragmatism philosophy deems appropriate as it accounts for the lived experiences of individuals to co-create knowledge.[11] The person-in-environment perspective is the main feature of pragmatism, which suggests that it is not possible to completely understand a person's situation without considering the impacts of their environment.[11] When working with the Inuit, it is vital to examine their environment with regard to knowledge transfer regarding TB following the historical disconnection with the Canadian government.

Figure 1: ETR's Health Equity Framework

Note. Education, Training and Research (ETR) is a non-profit organization committed to improving health outcomes and advancing health equity. From Peterson A, Charles V, Yeung D, Coyle K. The Health Equity Framework: A science-and justice -based model for public health researchers and practitioners. Health Promotion Practice. 2021 Nov;22(6):741-6.

1.2 CONCEPTUAL FRAMEWORK

The conceptual framework represented above shapes the study purpose and research question, as well as explains factors anticipated to influence the disproportionate rates of TB infections among Inuit people. The "Systems of Power" of the ETR framework guide the research question as a disconnect exists between the Canadian government and the Inuit people.[12] Therefore, access to resources, the proposed variable of interest, is to be analyzed. In alignment with the pragmatism philosophical orientation, this proposal acknowledges the subjective experiences of Inuit people relevant to the reasons for high TB incidence among them. Thus, this proposal conceives access to knowledge about TB as an opportunity embedded in social relations through which its meaning would emerge. Here, the "Individual factors" outlined by the ETR framework guide the outcome of interest: how access to knowledge can reduce infection rate while explaining current barriers to knowledge based on their living conditions.[12]

2.1 STUDY SETTING

The number of reported cases per year in Nunavut has increased drastically, from 138 cases in the 2001-2004 period to 464 cases in 2017-2020.[13] Inuit people constitute more than four-fifths of the total population of Nunavut.[14] With regards to the age structure of the Inuit in Nunavut, more than one-third of the Inuit people are younger than age [15.14] The territory of Nunavut comprises 28 villages.[15] Of these, this study focuses on Iqaluit, the most densely populated region in Nunavut, with the highest number of people identifying as Inuit.[15] Not only this, but Iqaluit is the largest community in Nunavut, with a population of 7,250.[16]

Inuit people in Iqaluit are exposed to the impact of social determinants of health, such as contaminated water supply.[17] Research also indicates that 5.7% of Inuit people here have no English or French knowledge as of 2016.[18] There are, in total, six schools in Iqaluit, and only one post-secondary educational institution, the Nunavut Arctic College.[16] In Iqaluit, there are only four healthcare facilities catering to the needs of the entire population.[19] Furthermore, reports show the lack of broadband coverage in the area exacerbates the

disconnect between the government and the public.[20] Within the territory of Iqaluit, and by extension, Nunavut, there remains a shortage of healthcare staff.[21] The healthcare system relies heavily on short-term healthcare providers, as most individuals trained within Iqaluit prefer to practice in areas outside of Nunavut.[21] Statistics indicate that more than half of healthcare personnel are on a contract of fewer than 20 days.[21]

3.1 RESEARCH QUESTION

This paper aims to address the following research question: “Does the level of knowledge regarding the pathophysiology of tuberculosis (TB) affect the incidence of the disease among Inuit Indigenous communities in the Territory of Nunavut, Northern Canada?”

- **What:** Education regarding the pathophysiology of tuberculosis:

Understanding the pathophysiology of TB helps raise awareness regarding how the disease is transmitted, what it does to the body, and ways to improve health outcomes. Thus, disease education can be vital in early detection, prevention, and effective treatment measures.

- **Who:** Inuit Indigenous communities:

The Indigenous Peoples of Canada are divided into three groups: First Nations, Inuit, and Métis. These are distinct groups with diverse histories, languages, beliefs, and cultural values. The word “Inuit” translates to “the people” in their native language, Inuktitut.[22]

- **Where:** Territory of Nunavut, Northern Canada:

This region covers 2 million square kilometres (km^2), with 33,330 residents. Of these, 28,000 (84.0%) identify as Inuit.[16] Given the high incidence of TB in this region, it is essential to investigate factors that siphon attention and energy from prevention measures.

3.2 HYPOTHESIS

The lack of access to knowledge about the etiology of TB and preventative measures are correlated with the disproportion rate of infections among Inuit People.

4.1 STUDY DESIGN AND METHODS

A mixed-method explanatory sequential design would help determine how many individuals are knowledgeable about TB and the number of individuals unaware of TB. The knowledge to be assessed involves what TB is, how it is transmitted, how it affects the body and preventative measures that can reduce its spread. Based on the individuals' level of knowledge, they will be assigned to the "knowledgeable" and “non-knowledgeable" categories. Following this data collection, a histogram will be used to document the frequency of individuals belonging to the two knowledge categories mentioned above. As the variable of question (level of knowledge) is a categorical variable, a histogram allows for gathering numerical data while reducing errors by the identification of outliers.[23] Furthermore, the number of TB cases for the "level of knowledge" will be quantified. A line graph allows researchers to evaluate trends clearly, and by adding the line graph to the histogram chart, comparisons between the two variables "TB incidence" vs "Level of knowledge" can be made swiftly.[24] After using these methods and removing outliers, a regression analysis will be conducted to examine the relationship between our two variables of interest.[25] This analysis will allow us to understand if an association between the level of knowledge and the risk of TB infection exists.[25]

After analysis, the next step is to collect qualitative data to understand why knowledge regarding TB helps reduce the prevalence and current barriers within the Inuit people, which minimize access to knowledge. The qualitative data collection process is driven by quantitative data analysis. By first assessing the number of TB infections relative to knowledge about the disease, we can explore the reasons for the relationship between both variables.

This observational cross-sectional study also aims to pursue a community-based research (CBR) approach as per the chosen community of Inuit people. Given the colonial history, a culturally sensitive approach such as CBR allows a participatory study driven by the Inuit peoples' priorities concerning TB prevalence.[26] Therefore, through CBR, the Inuit people of Iqaluit are to be involved in the entire research process: from the proposal to analyzing the results to taking appropriate actions using outcomes.[26] By prioritizing the needs and interests of Inuit people, CBR empowers Indigenous communities to pursue a co-learning process regarding our variables of interest.[26]

Open-ended structured questionnaires and surveys will gather quantitative data on the number of TB cases and level of knowledge among the selected sample of Inuit people in Iqaluit. The questionnaires/surveys will start with an introduction explaining the study purpose, components, and outcomes to ensure transparency and provide them with context. The questionnaires/surveys will include the following questions:

1) What is your age?
2) What is your place of residence?
3) Do you identify as an Inuit person?
   Yes
   No

4) Are you knowledgeable about the causes, mode of transmission, impacts, and preventative measures of tuberculosis (TB)?
   - Yes
   - No
5) Are you currently infected with TB, or have you tested positive in the past?
   - Yes, I am currently infected
   - No, but I have been infected in the past
   - No, but I have been infected
   - Don't know
6) Do you consent to participate in this study?
   - Yes
   - No

To gather qualitative information, focus group discussions will be conducted with study participants. Here, trained researchers will put the Inuit participants at the center of the discussion and prioritize actively listening to their experiences, beliefs, and perceptions about whether knowledge helps reduce TB prevalence.[27] Interviews will also be prioritized to accommodate one-on-one qualitative data collection for individuals preferring this method. Door-to-door visits, as per the aforementioned CBR design, will allow for surveying individuals while building strong relationships and empowering Inuit people to ensure further transparency will occur.[27] Moreover, key informant interviews will be conducted both online and in person with partners such as healthcare providers, Iqaluit district officials, and residents that possess first-hand knowledge about the impact of knowledge about TB on its prevalence. These interviews and discussions also aim to identify bottlenecks and ways to improve the delivery of knowledge about TB to the Inuit population.[28]

Questionnaires and surveys can be distributed to a large number of people at once, which can save time and hence reduce costs.[29] The yes/no answer format allows a simple collection of data, which can be easily analyzed. However, the disadvantages of these quantitative data collection methods include Inuit people refusing to participate as the matter is a sensitive topic and requires culturally appropriate methods.[30] Also, the responses are superficial and in-depth data cannot be collected, which can lead to different interpretations of questions from the participants and can impact the accuracy of responses.[30]

For the qualitative methods chosen according to this study design, there are numerous positive and negative aspects. Focus group discussions with Inuit people allow researchers to look beyond facts and numbers and instead learn the meaning behind those facts shaped by participants' experiences.[31] However, weaknesses of this method include the high costs required to conduct these sessions and the limitation of some Inuit people not being able to voice their concerns freely.[31] To counter these weaknesses, interviews with key informants and participants will allow sharing of beliefs one-on-one while fostering trust.[32] The interviews provide more open-ended questions to explore the Inuit peoples' behaviours and experiences that shape access to knowledge and its impacts on TB infections.[32] However, this method lacks cost-effectiveness and can place emotional stress on the interviewees, which needs to be considered.[32]

In addition to the tools above, electronic tablets will be utilized to administer surveys/questionnaires to the sampled Inuit people. Online free-to-use translation software will be used to make the surveys accessible to Inuit people in English and their native language, Inuktitut. To ensure accurate translation, a translator fluent in Inuktitut will be assigned to review the surveys/questionnaires. The responses will be screened to see if the data fits the inclusion/exclusion criteria. To do this, survey/questionnaire responses will be entered into the Statistical Package for the Social Sciences (SPSS) software, which can screen quantitative data according to the research requirements outlined earlier.[33] This software can also conduct statistical analysis such as regression, histogram, and line graph formulation.[33]

The location of data collection is Iqaluit, Nunavut. Houses will be randomly selected via the Iqaluit demographic surveillance site, which is free for public use.[34] Houses will receive visits from a team of trained researchers, along with a translator fluent in Inuktitut, to ensure accurate relaying of information. Furthermore, Iqaluit City Council representatives will also be involved in making visits as they possess knowledge about the conditions of Inuit people in Iqaluit and can help foster research success by suggesting changes to research protocols. Taima TB is an organization dedicated to reducing the disproportionately high prevalence of TB in Iqaluit.[13] As our study design calls for a CBR approach, partnering with these organizations can help solidify the research purpose and collaborate with Inuit people effectively. As the Council hosts regular meetings with the residents of Iqaluit, the Inuit people might be more comfortable conversing with council members about the study purpose.[16] Survey data will be stored in encrypted password-protected files to avoid any breach of privacy and maintenance of confidentiality.[35] The names of participants will not be included in the questionnaires/surveys to maintain participant anonymity. The expected duration of this study is six months; one month for quantitative data collection, one month for data analysis, two months for qualitative data collection, one month for data analysis, two months for qualitative data collection, and two months for data analysis.

4.2 STUDY POPULATION AND SAMPLING STRATEGY

Our population of interest is Inuit people living in the community of Iqaluit within the territory of Nunavut, Northern Canada. The age group that this research aims to target is 18-40 years. According to Health Canada[36], individuals aged 18 can provide consent in Northern Canada and participate in research studies. Furthermore, research has shown that the cognitive abilities of individuals start to decline around age 40.[37] Although the decline does not maximize until approximately age 60, this study focuses on the 18-40-year age bracket as relevant to retaining knowledge about infectious diseases and consenting to research participation to avoid potential confounding variables. Furthermore, the private dwellings, identified as 3093 in total, will be sampled from the Iqaluit demographic surveillance site.[38]

For research sampling, both probability and non-probability methods will be utilized to select a sample from the population of interest. The quantitative data collection methods outlined earlier will use multi-stage sampling, whereas qualitative methods will require purposive maximum variation sampling. The first step for multi-stage sampling would involve dividing the Inuit people in Iqaluit into clusters. These clusters will be developed based on the 3093 private dwellings accessible by roads.[38] In stage two, systematic sampling of these dwellings would occur where at least one person between the age of 18-40 resides. Therefore, the final sample left would include Inuit people who consented to participate in this study, which is challenging to predict. For the purposive sampling, we intend to select information-rich cases that would provide insight into how knowledge about TB can influence its prevalence. Inuit people with diverse experiences would be sampled here to allow researchers to look at the interaction between our variables of interest through multiple angles to develop a robust understanding of the phenomenon.[39]

As per probability sampling, the multi-stage sampling method reduces bias as individuals within our target population of interest are selected randomly.[40] The purposive sampling method outlined earlier provides benefits such as gathering large amounts of information while pursuing the CBR approach to working cohesively with the Inuit people. However, this method opens points of selection bias as Inuit people with experiences of maximum variation are more likely to be selected over others.

Since the estimated time for the study is a few months, it is critical to make adjustments to ensure participant retention. Firstly, this study aims to reduce the burden on Inuit people and facilitate participants through reimbursement. Inuit people will be provided with remote access options if they are unable to attend in-person interviews or focus group discussions.[41] Also, transportation costs would be reimbursed to participants that commute to ensure continued participation.[41] The study progress will be communicated through newsletters and update phone calls, facilitating participants' engagement.[41] Lastly, the personal reflections of Inuit participants will be collected in a meaningful manner to empower them and remind them of the larger cause they are tied to.[41]

4.3 INCLUSION CRITERIA

Inclusion criteria for individuals participating in this study are: (i) identifying as an Inuit person living in Iqaluit, (ii) dwelling accessible via road, (iii) belonging to the 18-40 years age bracket, and (iv) providing informed consent. The eligible dwellings will be screened, asked for informed consent, and enrolled in the research study. Therefore, with the help of the Iqaluit City Council and Inuit representatives mentioned earlier, research assistants (RAs) will visit and screen dwellings. Here, the study will be introduced, and the participants' inclusion criteria will be verified. Once informed consent is received, the individual will be recruited to the study and presented with the questionnaire/survey.

5.1 OPERATIONAL AND ETHICAL CONSIDERATIONS

As this study aims to work with Indigenous communities, ensuring compliance with ethical standards is critical. This study will utilize the CCGHR principles as a guideline to adopt ethical and equitable forms of global health research.[42] Therefore, as part of the "Inclusion" portion of the CCGHR framework, we will ask the important question: "How do our research practices proactively promote the involvement of historically marginalized people?".[42] By virtue of their social, cultural, and economic identities, this study understands that all these factors intersect to produce health and well-being.[42]

Furthermore, due to the history of traumatization of Indigenous communities, this study acknowledges supporting Inuit people and the potential re-traumatization of study participants. Instead of solely focusing on the symptoms of inequities related to TB infections, this study will shift its gaze toward structural and social determinants of health, as mentioned in "Responsiveness to causes of inequities" in the CCGHR framework.[42] Participants and non-participants will be provided support resources such as the Kamatsiaqtut Nunavut Helpline, dedicated to supporting the mental health needs of people in Iqaluit.[43]

Moving forward, it is vital to consider the expectations of Inuit people while conducting this study. The "Authentic partnering" aspect outlined in the CCGHR is beneficial in engaging Inuit people by employing a series of dialogue workshops aiming to understand their needs and wants.[42] Inuit people in Iqaluit have lived experiences of the level of access to knowledge about TB and the reasons for the gaps in knowledge. Thus, by authentically partnering, we can foster a strong partnership to help develop a holistic outlook toward the problems and formulate innovative solutions.[42]

The "Shared benefits" aspect of the CCGHR framework will also be adopted to ensure equitable distribution of benefits for Inuit participants.[42] Compensation will be used to encourage research participation only and will not be promoted before enrollment into the study to avoid swaying/influencing the consent process. Previous research has shown that financial incentives and compensation methods might unduly influence people to enroll in a study if the payment is high enough that they fail to adequately consider the risks of the research.[44] All individuals will be compensated, regardless of their continuation in the study, following consultation with Inuit community leaders to determine acceptable compensation methods. While the questionnaires/surveys provide a background of the study before the questions section, a separate consent form will be provided to all Inuit people approached by the research team. Sufficient time will be provided to Inuit people to minimize the possibility of coercion or undue influence. A verbal explanation will also be provided to the approach Inuit people to mitigate areas of confusion while addressing their questions and concerns. To further enhance the informed consent process, graphics and visual aids will be utilized to promote understanding of key concepts among study participants.[45]

Upon ensuring these essential elements, the study protocol will be submitted to the Research Ethics Board (REB), which Health Canada shares with the Public Health Agency of Canada.[46] This committee reviews all research involving human participants. Upon approval from the ethics board, permission will be obtained from the Regional Inuit Association (RIA) in Nunavut to access and use Inuit Owned Lands in Iqaluit for the purpose of this research.[47] Simultaneously, a review by the Nunavut Planning Commission (NPC) will be pursued to assess potential impacts and determine if this project conforms to the regional land use plan.[47] After obtaining approval, an application for a Scientific Research License will be sent to the Nunavut Research Institute, as per the policies regarding conducting research in Nunavut, Canada.[47]

Additionally, it is vital to recognize the potential of power imbalances between marginalized Indigenous communities and privileged researchers. The last principle of the CCGHR framework, "Humility," is key to ensuring positive power dynamics.[42] By stepping away from positions of authority over others and pursuing a position of solidarity, curiosity, and openness, we aim to adopt an attitude of learning rather than knowing.[42] By actively listening to the members of the Inuit community, we can ensure positive participant-researcher partnerships. It is also deemed essential to educate the team about the Inuit ways of living, cultural practices, and beliefs prior to visiting the area. Doing so will allow us to understand how to operate in their community in a culturally competent manner.

CONCLUSION

Given the disproportionate TB infection rates among Inuit people, it is vital to understand the reasons behind this high incidence. This research proposal helps guide one of the potential factors influencing TB rates among Inuit people: Knowledge about TB. By employing a community-based research design, we hope to work towards developing a deeper understanding of the Inuit communities in their contexts.

ACKNOWLEDGEMENTS

I would like to express my gratitude to Mercy Lilian Gichuki for their assistance with the review of the research question; any errors are my own and should not tarnish their reputation. This research proposal project did not receive any funding, and there are no conflicts of interest.

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ARTICLE INFORMATION

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Formatting and Illustrations
Zak de Guzman

Social justice movements

Fighting for a better tomorrow

Fight for justice

Help save lives

Role of social justice movements in Global Health

Social justice is the idea that everyone deserves equal rights and access to good health. Therefore, social justice movements are the unified efforts of society to make our world a better place to live in. Such campaigns are global, and many have successfully ensured high-quality health and wellness for everyone.

Some popular movements and their impacts:

Black Lives Matter

- Global effort to end racial inequality.[1]
- Helped raise $10.6 billion for the security and good health of Black people.[1]
- 67% adult Americans now support the cause.[1]

Climate change activism

- Global call for climate change.
- Protests across 150 countries with 7.6 million participants.[2]
- 80% Americans are willing to make supportive efforts.[3]

Global citizens movement

- Global call to tackle health issues worldwide.
- Since 2011, $7.2 billion has been collected.[4]
- NGOs and multiple organizations are working together.[5]

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Received: 23 January 2023
Accepted: 14 February 2023
Published: 30 April 2023

Senior Editor
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Blue Wavelength Light Treatment for Improving Sleep in Patients with Post-Traumatic Stress Disorder

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Received 27 January 2023
Accepted 14 February 2023
Published 30 April 2023

SUMMARY

Post-traumatic stress disorder (PTSD) is a mental health condition triggered by a traumatic event and is known to cause various symptoms, such as disturbed sleep. Research has proven that sleep improves brain function and other capacities, including judgment, decision-making, and physiological maintenance. Recently, blue-light therapy has been explored, and clinical experiments have illustrated their ability to alter sleeping patterns in PTSD patients. Daily morning exposure to blue light for 30 minutes helps to reduce daytime sleepiness and fatigue, causing PTSD patients to sleep earlier in the night. Being a non-pharmacological intervention, blue-light therapy's safety prospects have attracted the attention of researchers to aid in improving the health outcomes for PTSD patients.

ABSTRACT

Traumatic life events comprise the etiology of post-traumatic stress disorder (PTSD). PTSD patients are known to face adverse impacts on their mental and physical health. Symptoms of concern relating to PTSD include heightened anxiety levels, intrusive memories, nightmares, and problems with sleeping. Disrupted sleep leads to exhausted brain function that impedes the daily activities of individuals and impacts their perceived quality of life. Therefore, researchers have sought to examine interventions that help to improve sleep and circadian rhythms. Recently, blue-light therapy has been the target of clinical research to understand its role in alleviating PTSD symptoms. Results from clinical trials indicated that patients receiving blue light showed significant reductions in daytime sleepiness and fatigue. Furthermore, these individuals displayed faster reaction times and greater phase advances in circadian rhythms, leading to earlier sleep onset at night. As we work towards focusing our attention on addressing mental health issues, investigating the benefits of non-pharmacological interventions such as blue-light therapy can help improve the health outcomes of PTSD patients.

Keywords: Blue light, Circadian rhythm, Light therapy, Post-traumatic stress disorder, PTSD

1.0 INTRODUCTION

Post-traumatic stress disorder (PTSD) is a psychiatric condition that is correlated with significant levels of impairment, poor quality of life, and adverse impacts on physical health.[2] Individuals differ in the level of exposure to stressful life events, and due to their varying capacities of resilience, they showcase vulnerability to adversity differently.[8] Thus, individuals have vastly different health outcomes following objectively similar traumatic life events.[8] In recent years, there has been increasing attention directed at the psychological impact of trauma and ways to reduce its effects on human health.[8]

Although there remains an abundance of pharmacologic treatments for PTSD symptoms, there are few non-pharmacologic treatment methods.[8] Recently, exposure to blue-wavelength light has been discovered to improve sleep and circadian rhythms, both of which are disrupted in PTSD patients.[5] Proper sleep and circadian rhythms have potent effects on cognitive functioning in humans, including their critical impact on the retention of extinction memories.[5,8] Therefore, it is vital to target sleep deprivation symptoms of PTSD as a way to alleviate distress and improve health outcomes. This news article will analyze the efficacy of blue-light therapy in improving sleep among PTSD patients.

2.0 POST-TRAUMATIC STRESS DISORDER

Upon exposure to chronic stress, the neuroendocrine system is prime to prepare the body for survival.[8] The brain regions that are functionally adapted to respond to this signal include the anterior cingulate cortex (ACC), insula, and amygdala.[8] However, chronic stress can result in these regions becoming hyper-responsive to any situation perceived as a threat.[8] Exaggerated activation of the amygdala enhances the encoding of emotional memories.[8] These salient memories can lead to subsequent changes in behaviour and reach a point where it manifests itself as PTSD.[8] The development of PTSD in an individual leads to a conditioned fear response following a traumatic event.[8]

2.1 Symptoms

PTSD can present itself via the following symptoms: hyperarousal, intrusive memories, and persistent nightmares that can persist long-term and have pronounced implications on patients' daily activities.[8] Problems with sleeping are the most common complaint among individuals with PTSD, leading to the symptom of memory recall issues.[8]

2.1 Sleep Deprivation Incidence and Impacts

The self-reported rates of sleep deprivation are as high as 90% among PTSD patients; it is the driving factor in the persistence and severity of symptoms presented by the disorder.[8] In fact, clinical research shows that the severity of sleep disturbance is associated with PTSD severity.[8] Restorative sleep is found to be the most effective non-pharmacological mechanism for controlling the symptoms of the disorder.[8]

3.0 BLUE LIGHT THERAPY

Recently, researchers have identified it to be an effective method that can help alleviate the disturbances faced by PTSD patients.[5] Exposure of PTSD patients to blue light is found to result in a greater phase advance in circadian rhythms, sleep pattern improvements, and enhanced daytime alertness.[5] Consequently, morning blue-light exposure can produce improvement in neurocognitive performance and PTSD symptom reduction.[5] Blue light, specifically in a narrow spectral band from wavelength 460 to 480 nanometres, is illuminated from a light box provided to patients undergoing blue-light therapy.[7]

Within blue-light therapy, the light box device is to be placed at arm's length and at a slight angle from the gaze of the patient, such that it is sufficient to cover their eyes and face with the light.[6] This therapy is to be conducted for 30 minutes in the morning within two hours of waking up for maximum efficacy.[3] The light box is portable and can be utilized at the convenience of the patient within the comfort of their home.[3] Daily home-based blue light therapy that is self-administered can significantly improve depressive symptoms and is known to reduce sleep disruptions among people that have experienced trauma.[3] Furthermore, due to the non-pharmacological nature of this intervention, patients avoid the adverse side effects associated with pharmacological interventions.[3]

3.1 Mode of Action

Blue light exposure selectively stimulates intrinsically photosensitive ganglion cells located in the retina of the eye that synapses with the suprachiasmatic nucleus, which is known to be the brain's master circadian rhythm clock.[7] Upon stimulation, retinal ganglion cells signal to supper melatonin secretion in the brain, which leads to greater wakefulness.[7] According to the timing of the administration of blue light, there is a phase shift in circadian rhythms.[7] In a therapeutic setting, blue light can be utilized in a way that induces wakefulness in PTSD patients and circadian shifts to result in earlier onset of sleep.[7] Exposure to blue light in the morning reduces fatigue during the day along with sleepiness, to shift patient sleeping patterns so that they sleep earlier in the night.[7]

Neuroimaging evidence in a clinical trial shows that blue-light therapy is correlated with improved functional and structural connectivity between the thalamus and the parietal cortex of the brain.[6] Improved interconnectedness between these regions helps improve cognition, memory, and processing speeds.[4] Furthermore, blue light alters white matter diffusion characteristics in tracts passing through the thalamus, which contributes to improved white matter integrity in PTSD patients.[6,7] Research has shown that disruptions of sleep due to disorders can result in reduced white matter integrity in patients.[1] Sleep architecture is related to white matter microstructure in healthy individuals with healthy sleeping patterns.[1] Therefore, positive structural changes within white matter following blue-light therapy can help improve sleep quality significantly.

3.2 Success

Randomized-controlled clinical trials have shown the success of blue-light therapy in improving sleep among PTSD patients. Exposure to blue light produced significant phase advances in sleep onset com-

pared to control groups that received no treatment.[5] Throughout the clinical trial, participants with PTSD assigned to the blue-light therapy (BLT) group showed significant phase advances, generally falling asleep 57.5 minutes earlier compared to the control group.[5] Results showcased these earlier sleep onsets in 80% of the participants in the BLT group.[5] Compared to the control group, 87.5% of the participants in the BLT group showed significant reductions in daytime sleepiness post-treatment.[5] Furthermore, 93.8% of participants who underwent BLT showed improvements in executive functioning by completing puzzles 1280 milliseconds faster compared to the control group.[5]

Another study aimed to investigate the benefits of morning blue-light therapy at home with portable light box devices. Patients experiencing symptoms of trauma, such as daytime sleepiness, sleep disturbance, and insomnia symptoms, were recruited.[3] The results indicated significant differences between the blue-light and control groups.[3] Researchers found significantly greater decreases in sleep disturbance, insomnia symptoms, and reaction time in individuals who were exposed to daily morning blue-light therapy.[3] Additionally, participants in the blue-light therapy group reported more significant improvements in productive activity compared to the non-treatment group.[3]

4.0 CONCLUSION

Morning blue-light therapy exposure proves to be an effective tool in alleviating the symptoms associated with PTSD, such as sleep disturbances. Understanding the role of blue light in neurological changes that reduce the severity of PTSD symptoms is essential as it can help provide patients with a convenient and safe non-pharmacological approach to improving their health outcomes.

ACKNOWLEDGMENTS

No acknowledgments.

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ARTICLE INFORMATION

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The Relationship between β-blockers and Mental Health

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Received 10 February 2023
Accepted 14 February 2023
Published 30 April 2023

ABSTRACT

Beta-blockers (β-blockers) are pharmacotherapeutics used to treat patients with cardiovascular symptoms since their discovery in the 1960s. They target B1 and B2 receptors which are involved in the stress response, leading to reduced activation of the "flight-or-fight mechanism." β-blockers have also been beneficial in treating anxiety disorders and other mental health complications. Currently, the only approved drugs for anxiety and other mental health conditions are benzodiazepines and selective serotonin reuptake inhibitors. Historically, there has been strong resistance to the use of β-blockers in mental health treatment because of the prevalence of depressive symptoms during treatment. Recently, multiple studies have not seen a strong correlation between β-blockers and depression in patients. Although there are still other adverse effects related to the usage of β-blockers, investigating the relationship between depressive symptoms and β-blockers may suggest a potential therapeutic option in mental health treatments. This review explores the history of β-blockers, their mechanism of action, developments in their use as a mental health treatment, and currently approved pharmacotherapeutics for mental health.

Keywords: Beta-blockers, anxiety, depression, mental health, cardiovascular

1.0 INTRODUCTION

Beta-blockers (β-blockers) are a class of pharmacotherapeutics used to manage cardiovascular symptoms such as angina, hypertension, and arrhythmia.[1] propranolol, a nonselective beta-blocker for epinephrine, and norepinephrine for angina pectoris treatment for more than fifty years.[2] These medications work by blocking the action of specific hormones, such as adrenaline in the central nervous system to prevent the stress-inducing "fight-or-flight" reaction. The activation of the "fight-or-flight" stress response leads to increased blood pressure, heart palpitations, and anxiety, making β-blockers very advantageous for those with cardiovascular symptoms.[3] β-Blockers also often help with mental health disorders such as anxiety and post-traumatic stress disorder (PTSD). For a while, there was resistance to using these agents in treatment because the scientific community believed that β-blockers usage leads to side effects such as tiredness and fatigue, as well as cases of severe depression.[4] However, more recent developments have shown that depressive behaviour may not be as strongly related to β-blockers usage as previously believed.[5] This would drastically change β-blockers usage in mental health management and treatment.

2.0 β-BLOCKERS MECHANISM OF ACTION

β-blockers, also known as beta-adrenergic antagonists, are a class of medications most prescribed to lower blood pressure.[1] Their mechanism of action is facilitated by their ability to block the endogenous effects of epinephrine (adrenaline). Since the 1970s, β-blockers have been used to alleviate symptoms of social anxiety disorder, generalized anxiety disorder, and PTSD because of their mechanism of action.[6] Propranolol and atenolol are two of the most popular β-blockers. Propranolol is lipophilic, meaning it can cross the blood-brain barrier to potentially affect both somatic and central nervous system target tissues.[6] These molecules are adrenoreceptor antagonists, which compete with catecholamines, hence stopping their effects on the autonomic nervous system.[7] Catecholamines molecules are neurotransmitters and hormones essential for the homeostasis of the autonomic nervous system.[8] Dopamine, norepinephrine, and epinephrine are examples of catecholamines, but β-blockers target norepinephrine and epinephrine. By targeting the B1 and B2 receptors, the β-blockers attach to receptors specific to norepinephrine and epinephrine, preventing

them from binding, thus mitigating their impact. For example, under a 'trigger' situation for anxiety, epinephrine, cortisol, and norepinephrine are released, causing various effects associated with the 'flight-or-fight' response. Some effects include tachycardia, palpitations, hypertension, hyperventilation, nausea, vomiting, and sweating.[6] By targeting norepinephrine and epinephrine, β-blockers reduce the overall symptomatic response, reducing the severity of the attack. Despite this, β-blockers have not been approved by the U.S. Food and Drug Administration (FDA) and are prescribed out of scope for anxiety disorders.[6]

3.0 DEVELOPMENTS AROUND β-BLOCKERS

One of the earliest indications that β-blocker usage may cause depressive symptoms came from a study conducted in 1967 by Waal. The study observed that 50% of patients prescribed more than 120 mg/day of propranolol for hypertension reported signs of depression.[9] β-blockers inhibit serotonin receptors in the central nervous system, which are responsible for feelings of happiness and pleasure. After that initial report, numerous studies have refuted and supported the argument, making this a frequently discussed topic. One of these reports stated how the research team found no significant difference in depressive symptom assessment between non-β-blocker users and β-blocker users.[10] Those findings would suggest that β-blockers might not be able to affect serotonin inhibitors as strongly as previously believed. A multitude of contrasting opinions can potentially explain the resistance that many overlooking bodies, such as the FDA, feel about using β-blockers in a role for mental health treatment.

While many previous studies state this causal relationship, recent papers also conclude similar findings. In a 2022 study by Lengton et al.,[11] the association between depression and β-blockers was investigated in chronic dialysis patients with and without diabetes. The investigation of 684 chronic dialysis patients revealed a possible association between lipophilic β-blockers and an increased risk of depressive symptoms in dialysis patients, specifically those with diabetes.[11] Similar to other studies, the correlation was observed with no specific biological factors examined to justify the findings.

On the contrary, in March 2021, a report investigating the link between β-blockers and depression was shared in the American Heart Association Journal and presented some significant findings. In the systemic review, the team looked at psychiatric adverse events (PAEs) in over 50,000 individuals exposed to β-blockers, specifically during treatment.[5] During the study, symptoms observed during β-blocker therapy were like those observed in previous findings where depression and β-blockers were not linked. Their findings provided substantial evidence against a relationship between β-blocker use and increased PAEs in depression. Sleep-related disorders such as insomnia and unusual dreams, however, there are possible exceptions.[5] The report shares how PAEs are common during β-blocker treatment, but there is no direct association between β-blocker use and most PAEs. The study focused on patients prescribed β-blockers for hypertension and patients with cardiovascular ailments that tend to develop mental health disorders. Hence, there is no association between β-blockers and depression, which is why concerns about an increased risk of PAEs are unjustifiable and should not affect β-blocker use.[5]

Other recent work builds on this idea that there is no causal relationship between depression and β-blockers. For example, in a study by Bornand et al.,[12] the researchers used a case-control study to see if β-blockers led to an increased risk of new-onset depression. After investigating data from 118,705 patients, researchers observed limited elevated risk of depression among short-term propranolol users compared to patients with neuropsychiatric disorders.[12] Instead, this relationship is due to a protopathic bias. Protopathic bias occurs when treatment is initiated as a response to a symptom being observed because of the disease which is under surveillance.

4.0 MENTAL HEALTH TREATMENTS

Currently, the only approved medications for anxiety, PTSD, and other mental health disorders are benzodiazepines (BZDs), sedatives, and antidepressants such as selective serotonin reuptake inhibitors (SSRIs). BZDs side effects include drowsiness, lethargy, and fatigue.[13] At higher concentrations, BZD causes motor impairment, vertigo, and mood swings. Along with those side effects, BZDs are metabolized in the liver, meaning that certain drugs can increase or decrease the elimination half-life of BZDs.[13] Overall, it shows that it may not be ideal to treat patients with BZDs as several factors can drastically impact treatment. As for SSRIs, some common side effects are sexual dysfunction, weight changes, dizziness, headaches, and gastrointestinal distress.[14] SSRIs also have the potential to prolong the QT interval, a measurement that represents the duration of ventricular depolarization to complete repolarization, which can lead to fatal arrhythmia and torsade de pointes.[14] Although SSRIs are beneficial, there are significant adverse effects associated with them. The effectiveness overweighs the side effects to an extent, which is why SSRIs are still commonly used.

5.0 CONCLUSION

That is not to say that β-blockers do not have adverse effects; adverse effects range from insomnia, fatigue to cardiac problems.[1] However, there have been limited studies regarding β-blockers and mental health treatments due to the perceived notion that these molecules lead to depression and would offset any progression made during treatment for mental health disorders. The recent developments in the field are a promising sign towards further usage of β-blockers in the treatment of mental health disorders. With increasing confidence that β-blockers treatment and depression are not directly correlated, there is a strong possibility that significant research will be conducted to solidify β -blockers as a treatment modality for anxiety disorders and PTSD. Additional evidence might even lead to FDA approval for anxiety disorders, meaning that the way healthcare providers approach mental health disorders may change along with developments in the field of β-blockers.

ACKNOWLEDGEMENTS

There is no funding associated with this work.

The authors declare no competing interests.

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NEWS AND VIEWS OPEN ACCESS

Efficacy of Scalp Cooling in the Prevention of Chemotherapy Induced Alopecia Among Breast Cancer Patients

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Received 25 January 2023
Accepted 14 February 2023
Published 30 April 2023

SUMMARY

Patients undergoing chemotherapy treatment for cancer are known to develop alopecia. Alopecia is the loss of hair from different parts of the body depending on the type of alopecia. Chemotherapy-induced alopecia (CIA) results in the loss of hair from the entire scalp as a side-effect of the majority of the anti-cancer drugs provided under the chemotherapy treatment. These drugs disrupt the growth cycle of hair follicles, leading to alopecia. To prevent CIA, scalp cooling has been discovered as an effective procedure that preserves hair follicles. These initial findings sparked interest due to this method's safety and tolerance among patients. Results from clinical trials add to the evidence for scalp cooling's efficacy in hair preservation as well as hair regrowth following chemotherapy. As alopecia is known to influence body image perception negatively, investigating scalp cooling can aid in reducing stigmatization surrounding CIA and improve patient health outcomes.

ABSTRACT

Alopecia refers to hair loss, which is a common side-effect of chemotherapy regimens for cancer. Anthracyclines and Taxanes are the common anticancer drugs prescribed within chemotherapy that result in significant alopecia. Scalp cooling is identified to be an effective method that prevents chemotherapy-induced alopecia (CIA) in patients. This method has been present since 1974; however, novel technologies have enhanced the efficacy via modern scalp-cooling devices. By maintaining a low scalp temperature, vasoconstriction aids in the reduced absorption of anticancer drugs into the bloodstream, which reduces intrafollicular metabolism. Randomized controlled trials conducted recently found statistically significant results, evidencing the hair preservation and hair regrowth abilities yielded via scalp cooling. These results attracted the attention of researchers due to the treatment success and the patient safety aspect of the process. Extensive scientific research reveals that alopecia affects the perceptions of patients regarding their body image and lowers their self-esteem significantly. Furthermore, the quality of life of alopecia patients is reduced due to public stigmatization. The effectiveness of scalp cooling in preventing CIA is of high significance as it can help improve patient outcomes of patients undergoing chemotherapy and their mental well-being.

Keywords: Scalp cooling, Alopecia, Hair loss, Chemotherapy, Quality of life

1.0 INTRODUCTION

Clinical literature defines alopecia as "hair loss" irrespective of its cause of onset. Alopecia can affect any body part and is not exclusive to the scalp.[1] There are many different types of alopecia, categorized by scientists based on their etiology.[1] One of the major causes of alopecia in oncological patients that is underestimated by physicians is Chemotherapy-Induced Alopecia (CIA).[9] Following chemotherapy, a variety of treatment measures are pursued to combat the resulting hair loss, such as the commonly used micro-needling procedure.[5] Recently, the use of scalp cooling has been rigorously investigated as a potential therapeutic option for the prevention of CIA in patients undergoing chemotherapy.[2] The efficacy of scalp cooling in a

meaningful number of patients represents a promising step toward the prevention of alopecia in breast cancer patients undergoing treatment.[10] This paper will analyze the onset of CIA and the mode of action of scalp cooling in preventing the occurrence of hair loss.

2.0 CHEMOTHERAPY-INDUCED ALOPECIA

Alopecia is a non-life-threatening but disruptive side effect of the majority of the adjuvant chemotherapy regimens for breast cancer.[7] The severity of alopecia is determined by the nature of drugs used in chemotherapy treatment.[7] In particular, chemotherapeutic agents such as Anthracyclines and Taxanes are known to commonly result in significant alopecia.[7] These anti-cancer drugs are known to target the matrix keratinocytes present in the hair during the anagen phase, the state when hair cells are most proliferative.[9] Given their high sensitivity to anti-cancer drugs, rapid apoptosis occurs, leading to alopecia.[9] Research studies indicate that over 70% of the patients experiencing alopecia are undergoing chemotherapy involving one of the two drugs that were mentioned.[7] However, there are several risk factors known to exacerbate the chances of developing alopecia in cancer patients.[9] These are treatment-related aspects such as drug dose, administration regime, and exposure to risk rays.[9] Furthermore, patient-related risk factors include age, nutrition, and hormonal status.[9]

2.1 Impact on Patient's Lives

Alopecia after chemotherapy treatments is known to affect the quality of life of patients and the most notable public stigma of this treatment.[7] Research indicates that the CIA negatively influences the body image, sexuality, and self-esteem of patients.[9,10] Statistics show that approximately 8% of patients decide to opt out of receiving chemotherapy due to the risk of hair loss.[9]

3.0 SCALP COOLING

Utilizing scalp cooling devices was documented in the 1970s as a method to potentially reduce CIA.[10] Its efficacy data were unknown; therefore, recently, randomized control trials have provided insight into statistically significant data providing evidence for its efficacy.[10] There are different types of devices that utilize the scalp cooling procedure for the prevention of CIA.[7] The newer self-contained technologies use a machine to cool and circulate fluid in channels within a cap.[7] These channels contain glycol-based fluid and allow the scalp temperature to be maintained throughout the duration of the treatment.[7]

According to scientific research, the cap placed on the patient's head during scalp cooling is silicone based.[7] Once placed, the desired temperature for treatment is between 3 °C and 5 °C.[7] The cap comprises two sensors, one located at the front and one at the back of the cap.[7] These sensors are used to monitor the temperature to ensure it is within the desired limits.[7] An additional sensor is present to ensure the temperature does not drop below the freezing point.[7] Novel scalp cooling devices include the DigniCap® Scalp Cooling System, a popular device capable of providing continuous scalp cooling during chemotherapy infusion.[7] Despite its benefits, systemic recurrences of diminishing hair follicles continues to remain an unanswered question.[2]

3.1 Mechanism of Action

Scalp cooling directly causes scalp vasoconstriction, which results in a reduction of blood flow to the area.[2,3] As blood perfusion is reduced, the cellular drug uptake is diminished.[2] Hence, the anti-cancer chemotherapy drugs that are known to cause alopecia cannot be delivered to the scalp, which reduces intrafollicular metabolism.[7] The low temperature of the cap placed on the patients' heads leads to a reduction in the scalp temperature and consequent altering of exposure and metabolism of cytotoxic agents within their hair follicles.[4] For the cap to reduce the scalp's temperature significantly to cause vasoconstriction, a pre-cooling time of around 30 minutes is required.[4] It is articulated that a time of greater than 30 minutes does not result in further cooling of the scalp via the device.[4] Scalp cooling as a treatment method for preventing CIA deems safe and well-tolerated.[6]

3.2 Results

Preliminary analysis of data using a randomized controlled trial (RCT) by a group of researchers showcases the successful results of scalp cooling in breast cancer patients. After following the chemotherapy regime, patients were randomly assigned to two groups.[2] One group underwent scalp cooling (SC), whereas the other group was a control and did not receive scalp cooling treatment. 56.3% of the patients in the SC group had successful hair preservation.[2] Conversely, all patients in the control group faced hair loss due to alopecia.[2] The results were statistically significant, with a vast difference in the hair re-growth rate.[2] The SC group demonstrated hair re-growth in 89% of the patients.[2]

Another clinical trial study alludes to the success of SC by completely preventing hair loss in 43% of the total evaluated patients.[7] 32% remaining discontinued the SC treatment, while the remaining experienced failure in the complete prevention of hair loss.[7] Furthermore, an RCT conducted in breast cancer patients undergo-

ing chemotherapy showcases the efficacy of SC in reducing CIA. Researchers observed successful hair preservation in 50.5% of patients that received SC treatment compared to 0% in the control group that did not receive the treatment.[8] A 95% confidence interval was obtained, which ensures that the results are statistically significant.[8]

4.0 CONCLUSION

Although scientists discovered scalp cooling in the 1970s, innovative technologies have bolstered its ability to prevent CIA in breast cancer patients undergoing chemotherapy. Since the SC treatment is documented to be safe and tolerated, it represents an effective method for improving patient outcomes by preventing alopecia development following chemotherapy. Due to the adverse effects of alopecia on body image, further research should focus on evolving the SC treatment process to maximize the chances of success.

ACKNOWLEDGEMENTS

No acknowledgements.

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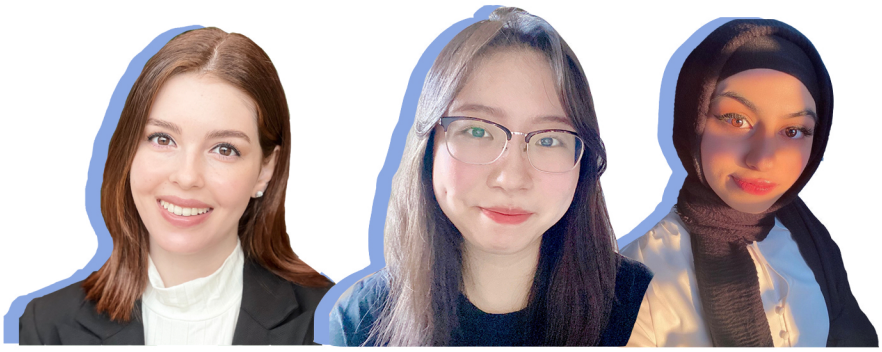

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ISSN 2562-1483