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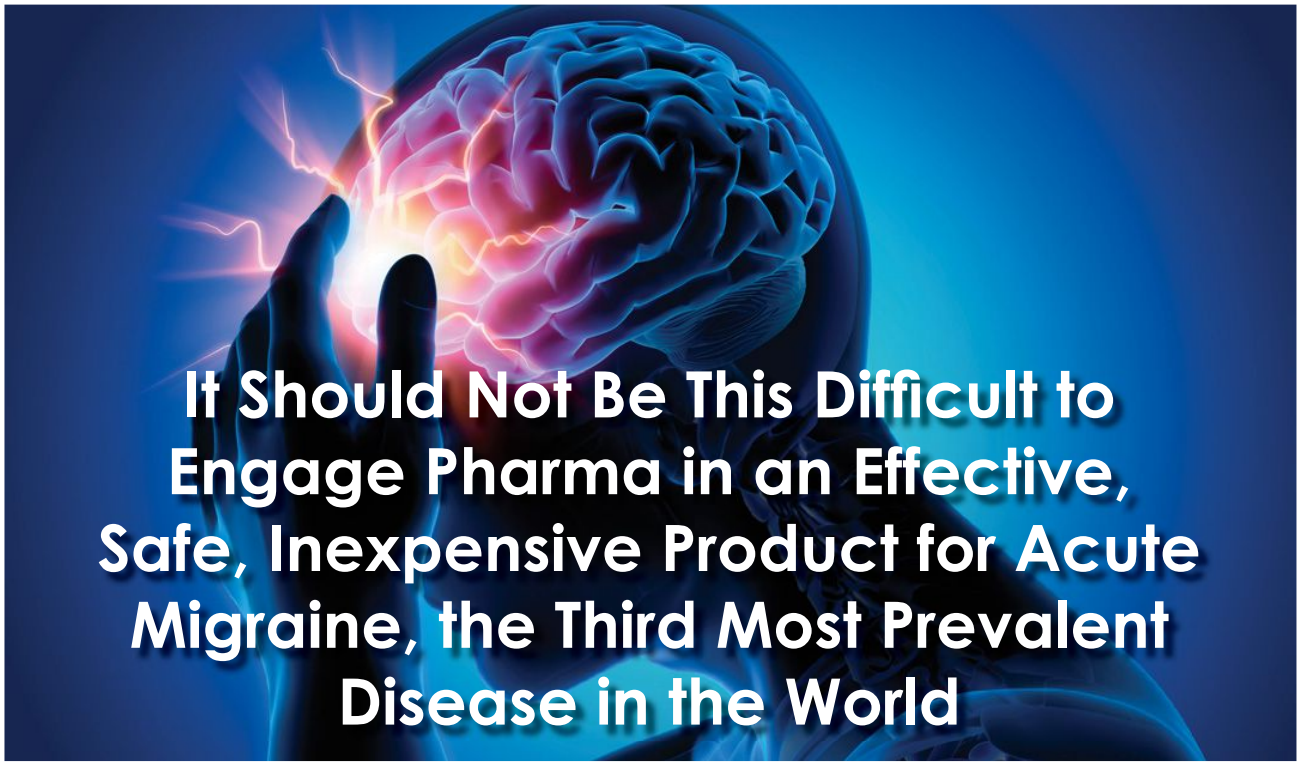


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It Should Not Be This Difficult to Engage Pharma in an Effective, Safe, Inexpensive Product for Acute Migraine, the Third Most Prevalent Disease in the World

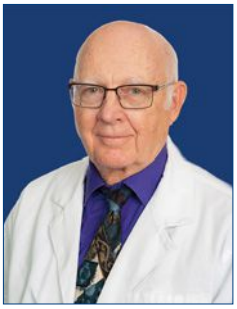
by John C. Hagan III, MD

A *JAMA Ophthalmology* study published in 2020 confirmed research first published in 2014 by *Missouri Medicine* on innovative acute migraine treatment.

Long time readers of *Missouri Medicine* hopefully recall that in 2014 Carl V. Migliazzo, MD, and I reported the largest series of case reports in the world's literature of acute migraines treated successfully with beta blocker eye drops (timolol maleate 0.5% solution).[1]

Our author-masked manuscript had been favorably peer-reviewed by two migraine headache experts. An accompanying editorial explained how this novel acute migraine therapy came about.[2] Three editorials also appeared in that July/August 2014 issue by neurologists,[3] headache specialists,[4] and a neuro-ophthalmologist.[5] They all enthusiastically endorsed the underlying pharmacological mechanism (rapid absorption) and urged further placebo-controlled studies with larger groups of migraineurs.

Dr. Migliazzo and I began contacting pharma: large, small, domestic, and foreign in an effort to find researchers to proceed with placebo-controlled studies. As ophthalmologists, we do not have the migraine volume to do these ourselves. Over the past seven years, we have contacted virtually every major and many minor pharmaceutical companies with a product line in migraine treatment and neurosciences. As of February 2022, the response from pharma has been almost uniform:



John C. Hagan, III, MD, FACS, FAAO, is a Kansas City, Missouri, ophthalmologist and *Missouri Medicine* Editor since 2000. He is a multi-year Diamond Contributor to MMPAC.

1. The mechanism of applying timolol eye drop solutions topical to the eye, sublingual, or nasally to achieve rapid therapeutic blood levels is likely effective but difficult to patent.
2. Why would (insert company name) want to develop a less costly product for acute migraine that competes with our existing more expensive product line?
3. As a company, we don't see enough profit in this product with or without intellectual property to fund it.

In 2018, researchers in ophthalmology and neurology at the University of Missouri-Kansas City School of Medicine reported[6] in *JAMA Neurology* the first placebo-controlled study using timolol eye drops instilled in normal eyes for acute migraine treatment. Sean Gratton, MD, and Matthew Cossack, MD, lead authors of this study, wrote in *Missouri Medicine* the same year another plea for larger studies and termed this a promising acute migraine treatment.[7] A first-person anecdotal long-term therapeutic success of timolol eye drops for acute migraine appeared in *Missouri Medicine* by Carolyn Csongradi, MS, a former chemistry and neurosciences faculty member at Santa Clara University.[8] Also in that issue, Dr. Migliazzo and I updated our clinical experience[9] using timolol eye drops for acute migraine which goes back over 20 years and includes scores of successfully treated, long-term patients, as well as over 60 anecdotal successes reported to us by other physicians or patients.

In 2020 a study, with dreadful flaws in my opinion and with which I had withdrawn as a collaborator, was published as a supplement to the *Kansas Journal of Medicine*.[10] This study purported to show that timolol eye drops were not helpful for acute migraine. I submitted a letter to the editor listing the numerous problems with the study and its erroneous conclusions. My critique was published[11] without the University of Kansas authors commenting or contesting any of my assertions and critiques.

Regarding route of administration of timolol eye drops, our patients have successfully used both topical installation onto normal eyes or sublingual. Given the convenience and ultra-fast absorption, a nasal spray would be the preferred method of delivery. Working with compounding pharmacists, I developed a compounded nasal spray of 0.25% timolol.[12] My request was for 0.5% timolol, but the compounding pharmacists did not agree to using the higher concentration. A small number of unreported patients tried the 0.25% nasal spray, found it more convenient to use but not as effective as the topical or sublingual 0.5% timolol. Timolol, at least 0.5% concentration, applied to the nasal mucosa would be the ideal way to test and develop for acute migraine use.

While 2020 was for the most part a bummer, it turned out to be a banner year for our research. *JAMA Ophthalmology*[13] published a large (N=50) randomized, masked, placebo-controlled, cross-over study of more than 600 acute migraine attacks that found timolol to be effective in meaningful pain reduction compared to placebo. Whimsically titled "Put a Drop of Timolol Into Each Eye and Call Me in the Morning," an enthusiastic invited commentary[14] by noted neuro-ophthalmologist Bradley J. Katz, MD, PhD, accompanied this study.

After this seminal 2020 *JAMA Ophthalmology* study was published, I contacted the India-based academic authors reviewing our research and proffered the best delivery mechanism would be the nasal route. Hopefully these researchers will be able to attract industry or academic funding for the larger studies necessary to bring an approved timolol beta blocker solution product to migraine sufferers for acute attacks.

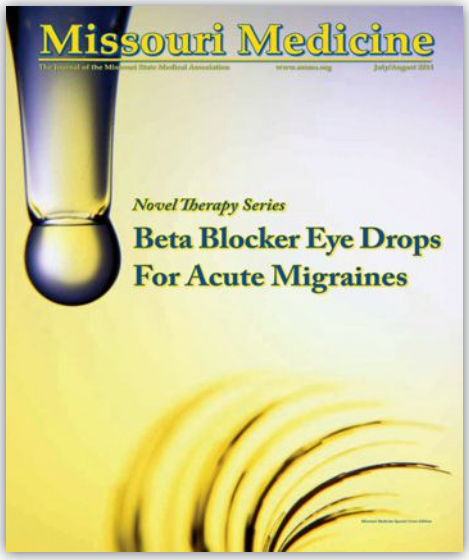
During the past six years, I have located two researchers that own intellectual property that might be utilized by pharma to develop a patent-protected, safe, effective, profitable but reasonably priced product that has the potential to be a new and welcome paradigm in the treatment of acute migraine. Migraine in its many manifestations is the leading cause of disability among neurological diseases. Companies or academic departments wishing to do research on a patented product can contact me for details.

Disclosure

When we had our "Eureka Moment" in 2013, I was certain that a Nobel Prize in Medicine and many millions of dollars in royalties would follow. That pipe dream has long ago dissipated. I have no financial interests in any drug or instrument product at this time. I do not accept monetary emoluments from pharma.

Second Disclosure and First Digression

Nothing in this long journey has given me any admiration for pharma, COVID vaccines withstanding. I almost get a migraine at the widespread price gouging of pharma, e.g., seeing generic steroid eye drops that not long ago sold for $4 now going for $80, or reading how a drug company hiked a $40 bottle of pig ACTH to over



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$40,000 (https://khn.org/news/mallinckrodt-orphan-drug-acthar-turned-cash-cow-as-drugmaker-raised-price-to-40000-per-vial-emails-show/), and to note the enormous amount of money that is showered by pharma over physician 'opinion makers' for shilling their products. Interested in knowing if your favorite 'opinion leader' is one of more than 700 physicians that have been paid more than one million dollars by pharma? Find out at: https://projects.propublica.org/docdollars/.

And some of the products pharma does choose to develop through FDA approval are risible. What are some of these mind-blowing products pharma chose to develop? How about an electrode to shock the lining of the nose to produce tearing for a dry eye? You would think the Geneva Conventions would outlaw such a device. Or bring to market a century old medication (pilocarpine) to possibly forestall presbyopia reading glasses or bifocals for a few years. Or develop that infamous pig ACTH into an eye medication for uveitis or keratitis for the same bargain price of $40,000 a vial. Gag! Or in a single year to distribute $40 million in salary bonuses to drug representatives to entice physicians to use pain opioids described by the company as 'non-addicting." I'm red-lining near apoplectic so here I shall stop. Thanks for staying with me this far.

Feel free to contact me for questions about beta blocker solutions for acute migraine. It shouldn't be this difficult! Email me at drjhagan3@gmail.com.

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MM

Who Do YOU Trust?

by Alexander R. Hover, MD

For COVID, evolving science and rapid decisions have been necessary during this pandemic, and that is disconcerting to everyone.

I write this message because some intelligent and thoughtful people have lost trust in the Food and Drug Administration (FDA) and the Centers for Disease Control (CDC). There are many reasons, not the least of which is the confusing general messaging from the CDC. Many of the public do not know which organizations or why physicians trust them for recommendations on treatment or vaccines for COVID. People who read confusing or waffling messaging understandably may not trust treatment or vaccine recommendations.

I have over 45 years of clinical practice dealing with recommendations from the FDA, the FDA advisory committee for the safety and effectiveness of biologics such as vaccines from the Vaccines and Related Biological Products Advisory Committee (VRBPAC), and the CDC Advisory Committee on Immunization Practices (ACIP). In addition, I have previously served as the Chair of an Institutional Review Board (IRB) reviewing and approving human medical research. I believe I understand the decision processes.



Alexander R. Hover, Jr., MD, FACP, AGAF, is President of the Missouri State Medical Association for 2021-2022. He is a Gastroenterologist from Ozark, Missouri.

The application and approval process requires that a drug company petition the FDA for a new drug application or biologic license for vaccine. The request for scientific testing is explicitly detailed in 300 to 400 pages of a research study starting with toxicological animal studies followed by phase 1 human dose range safety studies. Next are phase 2 and phase 3 studies with progressively larger groups and modifications evaluating the effectiveness and safety of the drug or vaccine. The research is monitored both by the drug manufacturer and audited by the FDA. More importantly, the data is monitored by an Independent Data Monitoring Board (IDMB). The IDMB is typically composed of research experts and statisticians who make reports that are available to the approving IRB and FDA. The IDMB reviews the data for safety signals, futility, and sufficiency of data to allow a rigorous conclusion. The IDMB is composed of highly qualified scientists who work independently of the drug company.

When studies are complete, the drug company presents the research to an FDA committee which has access to all the data including any required longer-term safety data. The FDA considers approval for effectiveness and safety. If the vaccine is approved either under an emergency use authorization (EUA) or full approval, it is then considered by the CDC's ACIP. The recommendations of the ACIP then inform the nation's physicians on the use of the vaccine. Both the FDA VRBPAC and the ACIP are composed of clinicians, researchers, pharmacotherapy experts, and vaccine and infectious disease



experts. I have reviewed the membership roster and their credentials because of allegations that there is improper influence of industry on FDA decision-making. In my opinion, the voting members are independent of the FDA and industry. Representatives from the pharmaceutical industry, consumer groups, and other interested parties may attend the meetings and offer testimony, but these persons do not vote. The meetings are public, the roster is public, and voting member's credentials with potential financial conflicts of interest are public. I suppose one or two committee members might be somehow improperly influenced, but I have never thought that the entire committee could be improperly influenced. I have always practiced following the ACIP recommendations.

For COVID, evolving science and rapid decisions have been necessary during this pandemic, and that is disconcerting to everyone. Messaging by the CDC regarding general health recommendations has been inconsistent, confusing, and at times seems even contradictory. I want to divorce the confusing general messaging from the CDC from the ACIP vaccine recommendations. My discomfort and that of some physicians has been the lack of broader dissemination of the data and studies prior to decisions and recommendations by the FDA committees and the ACIP during this pandemic. I have no doubt, however, that the data was considered carefully, and the vaccine recommendations are generally sound.

I have 45 years of clinical practice following the recommendations of the ACIP. My personal review of multiple scientific research studies by pharmaceutical manufacturers and my knowledge of the FDA and CDC review processes all give me confidence in the recommendations. I believe that in general, our regulatory structures and processes are scientifically sound, and reasonably free of undue bias or influence. Moreover, physicians trust their colleagues, experts in fields of research who assess data and guide us for treatments. The clinical researchers and university professors who evaluate COVID treatment research for the Infectious Diseases Society of America (IDSA) guidelines are not improperly influenced by the pharmaceutical companies. These guidelines provide current best recommendation practices in the use of vaccines, biologics and medications for COVID.

Like most physicians, my training in scientific principles and critical thinking in the application of research data gives me confidence that our independent specialty societies like the IDSA treatment guidelines are sound and reasonably free of bias. Likewise, the ACIP, FDA, and CDC decisions for vaccines are generally sound. I believe the public can trust that these decisions are made in their best interest. **MM**

Clinical Care Considerations for Bereaved Patients

by Madeline O. Jansen, MD, Elie Abdelnour, MD & Tahir Rahman, MD

> **"The reality is that you will grieve forever. You will not 'get over' the loss of a loved one; you will learn to live with it. You will heal and you will rebuild yourself around the loss you have suffered. You will be whole again but you will never be the same. Nor should you be the same nor would you want to."**
>
> ***–Elisabeth Kubler-Ross***

Introduction

Grief is associated with a variety of features and each person may experience it differently. As clinicians, recognizing the limits of normative grief reactions in our patients can be challenging due to the variable and sometimes unfamiliar presentation. However, bolstering our awareness of these limits can greatly improve our clinical care practices. Based on available literature and clinical experience, care of bereaved patients can be distilled into a few main tenants.

This includes psychoeducation about grief itself, prudent diagnostic evaluation of symptoms that are uncharacteristic of grief, monitoring of known comorbidities to grief, and referral to counselling and other supports when indicated.



Madeline O. Jansen, MD, MPH, (left), Elie Abdelnour, MD, and Tahir Rahman, MD, are in the Department of Psychaitry, Washington University School of Medicine, St. Louis, Missouri.

Background

Case 1

A 55-year-old female with no psychiatric history presents to her primary care provider three weeks after the death of her wife. Since the funeral, she has been having odd experiences at home. She divulges that she feels her late-wife's presence at times, and has seen her sitting in her usual spot in the living room. She does not feel particularly distressed by the experience itself, yet worries that she might be "going crazy." She denies associated fluctuations in attention, memory, and alertness, which is corroborated by her family.

Definitions

The Fifth Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines bereavement as the state of having lost, through death, someone with whom one had a close relationship.[1] It may also present in the context of gradual deterioration of a loved one suffering from a chronic degenerative disease such as dementia.[2] Grief often centers around feelings of deprivation and desolation, though can involve a variety of thoughts, feelings, behaviors, and physiologic reactions which are often influenced by a multitude of social, cultural, and individual factors.[2] Likewise, duration and intensity of the experience can vary greatly.[2] Nevertheless, it is

Table 1. DSM-5 Proposed Diagnostic Criteria for Persistent Complex Bereavement-Related Disorder

Criterion A	The individual has experienced the death of a loved one
Criterion B	Presence of at least one of the following symptoms, experienced on most days for at least twelve months after the death: • Persistent yearning/longing for the deceased • Intense sorrow and emotional pain in response to the death • Preoccupation with the deceased • Preoccupation with the circumstances of the death
Criterion C	Presence of at least of the following symptoms, experienced on most days for at least 12 months after the death: • Marked difficulty accepting the loss • Experiencing disbelief or emotional numbness • Difficulty with positive reminiscing about the deceased • Bitterness or anger related to the loss • Self-blame • Excessive avoidance of reminders of the loss • Desire to reunite with the deceased • Difficulty trusting other individuals • Feeling alone or detached from other individuals • Feeling that life is meaningless or empty without the deceased, or the belief the one cannot function without the deceased • Confusion about one's role in life, or a diminished sense of one's identity • Difficulty or reluctance to pursue interests since the loss or planning for the future
Criterion D	The disturbances cause clinically significant distress or impairment
Criterion E	The bereavement reaction is out of proportion to or inconsistent with cultural/religious norms

frequently described as one of the most painful experiences an individual faces during their lifetime.[3]

Common Grief Reactions

Research in this area describes a number of common grief reactions, including waves of deep sorrow, numbness, disconnectedness, anger, and even transient physical symptoms.[4] It is not unusual to dream of deceased loved ones, sense their presence, or have auditory and visual hallucinations of them.[5] In fact, World-War-II era scientific literature describes numerous accounts of widows of veterans who had auditory and visual hallucinations of "seeing" their husbands.[6,7] This occurred in various countries and was usually perceived as comforting. Sometimes, a sense of connection is maintained by keeping certain beloved objects like clothing, writings, or jewelry.[2] Other times, efforts are made to continue their living legacies by taking on their life's mission or making memorial donations.[2]

Case 2

A 61-year-old male with hypertension, hyperlipidemia, and obesity presents to the emergency department (ED) after being found by his daughter in bed confused and unable to speak. Since his father passed away last week, he has been drinking heavily "to numb the pain." Basic labs are unremarkable and he is discharged home. His family is told that this is just a reaction to grief. Two days later, he continues to be dysarthric and disoriented. The family brings him back to the ED and requests further workup. Imaging reveals sub-acute stroke and he is admitted to the hospital.

Exceptions to Grief Designation

In grieving patients, certain situations indicate a need for further diagnostic workup and clinical management. First, if criteria for major depressive disorder are met, it should be managed as such.[1,4] While grief can appear similar to depression and can function as a trigger for a depressive episode, the two are managed differently.[3,4] Second, any patient experiencing acute changes in attention,

consciousness, or memory should be evaluated for delirium. Grief, alone, does not cause delirium. As demonstrated by Case 2, knowledge of these principles is important to avoid misattribution of vague or subtle symptomology to grief.

Epidemiology

Prevalence

As currently conceptualized, estimating prevalence rates of normal grief reactions can be challenging given lack of well-validated standardized measurements. Another way of examining this issue involves measurement of "complicated grief.[1]" Described by DSM-5, this more standardized condition, constitutes grief that is unusually prolonged, intense, disabling, and associated with dysfunctional behaviors, emotions, and thoughts that impede healthy adaptation to loss (Table 1).[1] It can be measured using instruments such as the Inventory of Complicated Grief Scale[8] or by clinician interview using proposed DSM-5 diagnostic criteria.[1] Available literature suggests that 7% of adults experience complicated grief after loss of a loved one.[9,10] Individuals at highest risk are those over age 61, females, Black, Indigenous, and People of Color (BIPOC), and those with lower socioeconomic status.[6] Other risk factors include loss of a child, spouse, or young person,[8] or loss by unexpected or violent means.[11] While useful for epidemiologic purposes, the clinical reliability of this diagnosis remains in question. The DSM-5 considers it to be a condition in need of more research that is not yet appropriate to be used in routine clinical practice.[1]

Comorbidities and Suicide Risk

Grief is known to confer increased risk of a number of psychiatric disorders, including major depression, post-traumatic stress disorder, anxiety disorders, and substance use disorders.[3,12] Suicidal ideation is seen in up to 57% of older adults who lost their spouse.[13] Bereavement is also known to compromise physical health as well. The sudden intense emotional stress associated with grief, can for example, precipitate stress cardiomyopathy, also known as takotsubo cardiomyopathy or "broken heart syndrome." This poorly understood condition is believed to be related to transient left ventricular dysfunction, and presents very similarly to acute coronary syndrome, with chest pain, ST-segment elevation and T wave changes on ekg, and moderate troponin elevations.[14] Finally, although the mechanisms are not clear, death of a child appears to be associated with an overall increased mortality in grieving mothers.[15] It is critical that providers have an awareness of these vulnerabilities and consider screening for mental health symptoms in grieving patients.

> **"O happy dagger!**
> **This is thy sheath;**
> **there rust,**
> **and let me die."**
>
> ***– Juliet before she commits suicide, in Romeo and Juliet by William Shakespeare Act 5 (1597)[16]***

Understanding and Coping with Grief

This excerpt from William Shakespeare's beloved tragedy, "Romeo and Juliet," touches on some of the darkest complexities of grief and loss. In this tale of double suicide, Juliet fakes her death to avoid marrying Paris, the man chosen for her by her parents. Romeo, believing Juliet is dead, ends up killing Paris before taking his own life. Juliet then "happily" stabs herself with Romeo's dagger. This passage powerfully illustrates the deep suffering, confusion, irrationality, and vulnerability that characterizes bereavement. As clinicians and scientists, we may wonder how to best understand this process and support our bereaved patients.

Stages of Grief Framework

The quote in the introduction is from Elisabeth Kubler-Ross, a Swiss-American psychiatrist who pioneered important and highly influential theories in this realm based upon clinical work with those dying and their loved ones. In her cornerstone work, On Death and Dying (1969), she outlined the stages of grief.[17] It emphasized the highly individualized nature of grief while hypothesizing that there are five stages: denial, anger, bargaining, depression, and acceptance.[17] Not everyone goes through every

Table 2. Kübler-Ross 5 Stages of Grief [16]

NOTE: There is no specific order to the stages. Each stage may be experienced more than once or not at all.

Denial	Avoidance of painful thoughts, emotions, and behaviors related to the loss Disbelief, shock, numbness Looking for evidence that the loss did not happen *"This can't be happening to me."*
Anger	Recognition that things are different Hostility, anger, guilt *"Why me? What did I do to deserve this?"*
Bargaining	Struggling to find meaning Internal negotiation, hope that things can still be changed *"I'll do anything to go back to the way it was before."*
Depression	Beginning to face the reality of loss Emptiness, yearning, sorrow Desire to withdraw socially
Acceptance	Accepting reality of the death Learning to live with loss Reaching out to loved ones

stage, and there is no prescribed order.[16] Her work aimed to provide a conceptual structure to aid those experiencing grief and to facilitate development of healthy coping strategies.[17] Subsequent work on grief has echoed this framework over the past four decades.[18,19,20,21] This model continues to be a useful patient education tool that can validate and provide structure to the experiences of many (Table 2).

Constructive Dealing with Grief

There are no standardized treatment modalities, however some grief therapists provide overarching ways of working through grief. For instance, there are those who believe that problematic grief reactions arise from an inability to find meaning in the loss.[22] They recommend a meaning-oriented approach to grieving, which centers on narrative interventions like re-telling the story of the loss, journaling about unforeseen benefits, and enacting imaginary dialogues with the deceased.[22] This can be done by patients individually, or with the assistance of a licensed therapist. Interpersonal psychotherapy is another modality which has been shown to be effective in helping patients cope with major life transitions, including grief.[1,2] Regardless of grief severity, many patients may benefit from counselling with licensed professionals or a spiritual advisor. Discussing these common therapeutic principles can be important to facilitate this process.

Certain situations may call for additional supports and considerations. For instance, those bereaved by violent or traumatic causes tend to experience more intense and prolonged stages of denial, anger, and depression.[22] Parents affected by suicide of a child seem to experience higher levels of guilt and distress compared to death by accident or chronic illness.[23,24] College students affected by suicide of a loved one report greater loneliness, isolation behaviors, and survivors guilt than those affected by death by natural causes.[25,26] Finally, an astonishing 25% of high school students who lost a close friend to suicide met criteria for clinical depression in the following six months.[27] Adolescents, in particular, appear to be at elevated risk of imitating suicidal behaviors in response to suicides in their community or those of public figures publicized by the media.[28] These phenomena, known as suicide contagion and clusters, are believed to result in 100-200 deaths annually.[28] It follows that patients in these situations may be in need of additional resources and close monitoring by friends, family, and classmates. Research indicates that informal supports, such as support groups, tend to be favored methods in these situations.[2,26]

Conclusion

Despite the near universal experience of grief and personal loss, caring for bereaved patients can feel like unfamiliar territory for clinicians.

Table 3. Take Home Points

- Grief has a variety of manifestations that can vary by person.
- DSM-V proposes certain diagnostic criteria for complicated grief reactions which persistently diminish functional capacity. These criteria are not fully validated and are not recommended for clinical use at this time.
- Brief psychoeducation on grief can promote healthy adaptation to loss for patients. The 5-stage model may provide a useful framework.
- Grief is an inadequate explanation for alerted mental status and focal neurologic deficits. The presence of these symptoms in a grieving person indicates a need for further medical work up.
- Grief confers increased risk of all-cause mortality, substance use disorders, depression, suicidal ideation, PTSD, and several other psychiatric conditions.
- Risk-management practices involves screening for cardiovascular disease, depression, PTSD, suicidal ideation, problematic substance use and other relevant conditions to the patient
- When appropriate, bereaved patients who meet diagnostic criteria for depression are likely to benefit from available evidence-based treatments.
- Bereaved patients may benefit from counseling, psychotherapy, or support groups. Interpersonal psychotherapy has been extensively studied and shown to be beneficial for grieving individuals.

Our understanding of grief is constantly evolving, however there are key aspects to be cognizant of (Table 3). This is especially relevant today in the midst of a global pandemic, where the grieving process may be complicated by physical isolation from loved ones and travel restrictions.

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From Craft to Profession: The Development of Modern Anesthesiology

Part II

by Rima S. Abhyankar, MD & Katherine M. Jessop, MD

While the history of medicine has a pattern of groundbreaking discovery often at the expense of cultural prejudice, exploitation of persons without consent, and lack of formal scientific analysis, the history of anesthesia from the 1840s to present day marks a cultural shift away from these themes.

In *Missouri Medicine's* Part I of the History of Anesthesia,[1] it was noted that Dr. Crawford Long, a physician in Jefferson, Georgia, performed the first recorded ether anesthetic in 1842. He subsequently performed several other successful anesthetics prior to 1846, yet he did not announce his medical discovery until 1849. Separately, others were experimenting with ether and nitrous oxide as party enhancers, but not as anesthetics.



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On September 25, 1846, a man named Edward Abbott presented to Massachusetts General Hospital for a medical evaluation. His chief complaint: a growth under his left jaw. By October 16, 1846, Dr. William Thomas Greene Morton, innovator, dentist, and anesthetist, had perfected his breathing apparatus, the Ether Dome, to demonstrate general anesthesia.[2] Abbot was reassured by Dr. Morton, and within four minutes, as Dr. Nathan Rice, a contemporary of Morton, describes in *Trials of a Public Benefactor*, Abbott soon "lay as quietly and soundly asleep as any child, in that curious state which is – 'Twist gloom and gleam, with Death and Life at Each Extreme.'"[3]

Unfortunately, a photographer was not present at the 1846 unveiling of etherization. What is left, however, is a steel engraving printed in Dr. Rice's summary of the day, which depicts the spectacle – Abbott, in the center, surrounded by eight colleagues as the procedure unfolds (Figure 1). The public display of the etherization of Edward Abbott at Massachusetts General Hospital opened the proverbial door to a whole world of new possibilities in surgical



Figure 1. Edward Gilbert Abbott and his ether demonstration.
Source: https://www.nejm.org/doi/pdf/10.1056/NEJM198410113111522

intervention. The demonstration set into motion the quest to advance general anesthesia practice.

However, the desire to understand, and thereby reduce, pain had long been part of medical discovery. In fact, Hippocrates was one of the first physicians to write about "anesthesia" and "analgesia" in his works. He observed that those who are "unconscious to everything" are "deaf to what is spoken, blind to what is happening and insensible to pain."[4] However, many centuries passed before this "unconsciousness" could be safely delivered and available for commercial, widespread use and was deemed a necessity for surgical intervention.[5] Historians argue that the reasons for the delay in understanding and widely accepting the need for anesthesia in surgical practice are most likely a result of the scientific community's disbelief in the ability to free oneself from pain. French surgeon Alfred Velpeau, in 1839, said, "The abolishment of pain in surgery is a chimera. It is absurd to go on seeking it...knife and pain are two words in surgery that must forever be associated in the consciousness of the patient."[5] The events that took place between the 1840s and present day, from advancements in medical technology to the development of the field of perioperative medicine, reflect the progression from the mysticism and disbelief in the existence of anesthetic to the firm understanding that reducing pain is not only possible but also entirely necessary. This shift is paralleled by advancements that have been centered in advancing patient safety, thereby cementing this value as a core tenet in the practice and field of anesthesiology.

Public Demonstrations of Anesthesia

Modern day anesthesia practice's earliest, and most recognizable roots, were set into motion in the American 1840s. While the thought of public demonstration of medical discovery, especially when said discovery involves potential harm to a patient, seems unethical in present-day medical practice, public demonstration was central to the discovery

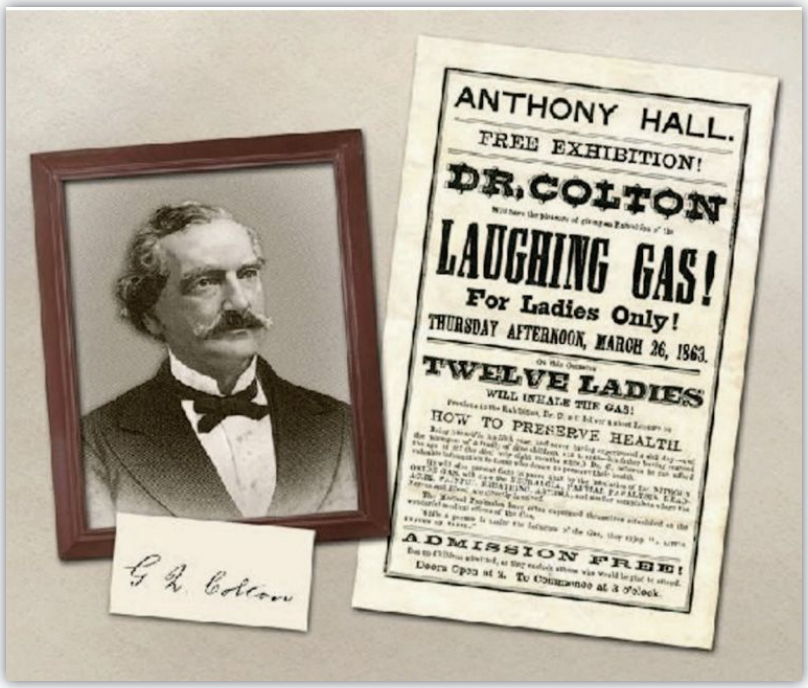


Figure 2. In Schenectady, New York, by mid-March of 1863, broadsides advertised a free "Exhibition of the LAUGHING GAS" scheduled for the afternoon of March 26, 1863. A traveling showman named "Doctor" Gardner Quincy Colton (1814–1898) promised to gas 12 women recreationaly with nitrous oxide, the same gas that he had provided as a dental anesthetic in 1844 for Horace Wells.
Source: https://www.woodlibrarymuseum.org/wp-content/uploads/reflections/011_Colton_N2O_Broadside_GS.pdf

of inhaled anesthetic. In 1844, Gardner Colton, a medical student at what is now Columbia University, displayed the intoxicating effect of nitrous oxide—for a fee. His advertisement in the Hartford Courant boasted that "Twelve Young Men have volunteered to inhale the Gas, to commence the entertainment." For twenty-five cents a ticket, attendees could partake in both watching others and inhaling, themselves, nearly "forty gallons of gas." They could observe their fellow participants' "laugh, sing, dance, speak, or fight...according to the leading trait of their character" (Figure 2).[6]

Horace Wells, a dentist and audience member at such a demonstration, noticed that while intoxicated, a participant who had inhaled nitrous oxide did not feel pain from an injury he sustained. Wells subsequently sought Colton's assistance in administering nitrous oxide to himself while one of his assistant's removed his tooth. He was eventually able to administer nitrous oxide to several of his patients, the success of which prompted him to approach John Warren, famed surgeon at Massachusetts General Hospital, to stage a public demonstration at Harvard Medical School. However, the event was unsuccessful, with attendees and his peers criticizing Wells' attempt as "humbug."[7] Dr. Morton, Wells' student and fellow dentist, posited that ether could be used as a substitute for nitrous oxide. He tested ether on pets, himself, and a handful of patients prior to approaching Dr. Warren for his own chance at a public demonstration of etherization of Mr. Edward Abbott. Public demonstration offered with it the prospect of public entertainment and its associated financial gain.

Morton's demonstration of etherization at Massachusetts General Hospital spurred the race to obtain patent rights for ether, and thereby commercialize its use. By contrast, Morton was soon embroiled in a battle with the U.S. government to deem his patent of ether, or "Letheon," as he named it, to be enforceable. Unfortunately for Dr. Morton, the use of ether spread across the U.S. and even abroad, with many European, Australian, and Latin American practitioners employing its use, and he did not amass a fortune from its increased use. However, the demand did encourage the discovery of safer methods to administer ether and develop alternative forms of inhaled anesthetic gas.[7]

Understanding Depth of Anesthesia

A professor of obstetrics in Scotland, Dr. James Simpson introduced the use of chloroform in 1847. Although hepatotoxic, more potent, and consequently more lethal than ether, its use was more manageable in his patients. After inhaling chloroform himself, Simpson claimed the substance was "far stronger and better than ether."[8]

Chloroform soon became the anesthetic of choice in the United Kingdom, mainland Europe, and much of South America. Chloroform was even famously used by Queen Victoria during the birth of her son, Prince Leopold, in 1853 (Figure 3).[8] This "celebrity event" significantly increased awareness, and subsequent demand, for labor analgesia.

Anesthetist and renowned epidemiologist, John Snow, most famously regarded for the discovery of the spread of cholera at the Broad Street pump wrote some of the first observations in delivering these inhaled anesthetics that became the foundations for much of modern-day anesthetic practice. He described five "degrees" of anesthesia. This spectrum began with the first "degree" as when a patient "retains correct consciousness...and a capacity to direct his voluntary movements." The fifth "degree" progressed to "respiratory movements [being] more or less paralysed and…difficult, feeble, or irregular."[10] This scale of sedation is reflected in the current American Society of Anesthesiology's "Continuum of Depth of Sedation," which classifies level of sedation from minimal anxiolysis to general anesthesia.[21] Through his observations, Snow observed differences in type of anesthesia and patient outcomes, further advancing strategies for patient safety. He compared death rates between ether and chloroform use, stating that deaths from chloroform were "accidents [that] would arise by it suddenly paralyzing the heart, if it were not sufficiently diluted with air." He thus embarked on the task of creating a delivery system for temperature-controlled, diluted ether, which is the most rudimentary version of the modern-day variable bypass vaporizer. His work also led to discoveries of minimum alveolar concentration and pharmacology of inhaled gases.[9] The retrospective analysis of outcomes from two different anesthetic agents further laid groundwork for large strides in patient safety in anesthesia; much of the following century's global anesthetic practice was based on Snow's foundational observations.

Advances in Airway Control

Along with a more clear understanding of the scope of anesthesia came the development of devices that could be used for airway control. Prior to the late 1800s, few oral airway devices existed, and their primary use was for treating neonatal distress and pediatric asphyxiation, a common complication of diphtheria at the time. These devices were not widely available, however, for most surgical procedures. In the late 1800s, the need for airway control came from the growing demand for oral surgery; surgeons desired a method to prevent blood and surgical debris from entering the airway.[11] Many versions of the modern-day endotracheal tube were developed during this time, primarily fashioned out of metal and rubber.

Dr. Frederic Hewitt, in 1902, delivered a chloroform-ether mixture to future King Edward VII, who was known to have a large beard. In anticipation of the challenges of safely delivering inhaled gas with an interfering beard, Hewitt developed the oral "air-way," fashioned out of rubber and metal (Figure 4).[12] He described its intended use: "If at the conclusion of the induction period...the breathing be laboured and noisy with sniffing or snorting sounds...the jaws should be separated and the whistle-shaped end of the 'air-way' passed backwards." He also noted that Trendelenburg positioning was more likely to cause airway obstruction. However, without full control of the airway, pulmonary complications with anesthesia remained common.[12]

From here, in 1928 Dr. Paluel Flagg, American anesthesiologist and fierce patient safety advocate, sought to better understand and prevent asphyxiation during surgical procedures. While commonly using variations of Hewitt's oral airway to prevent obstruction during surgery, Flagg developed a two-piece metal endotracheal tube that had a rigid stylet that could be removed following insertion; a rubber stopper could be added on top to create an airtight seal. Dr. Flagg's interest in developing better endotracheal tubes eventually led him to create the Society for the Prevention of Asphyxial Death, an organization that instructed physicians to understand and practice cardiopulmonary resuscitation.[13] The emphasis on patient outcomes and safety during the early 1900s allowed for widespread practice of anesthesia during the World Wars.

Demand for Anesthesia Soars

Between World War I and II, due to battlefield trauma, there was a sudden increase in surgical procedures, and with it, the need for anesthesia increased as well. This change coupled with the advertisement of anesthesia as the "hit show" at the 1939 World Fair increased public awareness of the field.[24] With World War I came the establishment of the first nurse anesthesia schools and subsequently the first academic department of anesthesia at the University of Wisconsin. The Long Island Society of Anesthetists, founded in 1905 and the precursor to the present-day American Society of Anesthesiology,



Figure 3. From left to right, are a chloroform drop flask, a drop bottle with a control valve manufactured by Pilling & Son, and one of unusual, alembic form. Introduced just one year after ether, chloroform was the second drug to be used as a modern surgical anesthetic.
Source: Wood Library-Museum of Anesthesiology, Schaumburg, Illinois.

became a rapidly growing organization during this time period.[25] By World War II, with the growing need for anesthesia in wartime surgery, many physicians were drafted to provide anesthesia.[14] With the sudden rise in the global death rate, as surgeon Erwin Schmidt wrote in the Annals of Surgery in 1937, "Anesthesia was gladly welcomed, but received little aid or stimulation...by the surgical profession." He continues, "This attitude placed anesthesia in the hands of young assistants who looked upon it as a necessary evil." Necessary evil or not, the largest growth in advancements in technology, pharmacology, and anesthetic practice standards took place in the World War era. With the growing possibilities of the anesthetic expertise that physicians could offer surgeons for their procedures, anesthesia soon became its own medical specialty.

Noting the growing opportunities for anesthesiology, war-time anesthesiologist Henry Ruth wrote, "After such an experience, it is to be seriously doubted whether many of [the surgeons] will be content on their return to civilian practice to retrogress to the inferior type of unsupervised technician anesthesia."[18] Between 1940 and 1950, the percent growth of the number of members in the American Society of Anesthesiologists was more than 230%.[18]

Advances in Patient Safety

With the development of better technology to deliver anesthetic gas, instruments to maintain airway patency, and new pharmacotherapies that could facilitate anesthesia, the focus of anesthetic practice soon centered on improving patient safety. This growth was reflected in the new instruments and medications that physician-anesthetists, as they were referred to at the time, could use.[18]

War-time anesthesiologist and one of the first anesthesiologists to study patient outcomes, Henry Beecher, cataloged the number of "anesthesias," or delivered anesthetics, in a multi-institution analysis as 7,650 in 1943 and 19,914 in 1944. In that one year interval, the overall anesthesia-related death rate fell from 1:1,000 to 1:5,000.[19] Simultaneously, discovery in pre-operative preparation, antibacterial technique, and new surgical technique made the realm of possibilities even wider.

In 1937, Professor Robert Macintosh, appointed as chair of anesthesia at Oxford, developed the curved laryngoscope blade. In 1948, Dr. Lucien Morris designed the copper kettle vaporizer, which could better regulate the temperature of liquid and thereby better control the speed and delivery of anesthetic vaporized gas.[16] Advances in pharmacology, too, meant that new intravenous induction agents, such as

sodium pentothal, were available. As Beecher writes, the use of sodium pentothal is "admirably suited to the needs of warfare."[19] Beecher conducted an analysis on the death rate associated with pentothal and reported a decrease in the death rate from 1:450 to 1:5,500 between 1943 and 1944.

Anesthesiology was progressing to become a safer, more predictable field. Additionally, curare, a muscle relaxant derived from plants native to Ecuador and Peru, where it was commonly used as an agent that could coat arrows and darts to facilitate hunting, was brought into anesthetic practice in 1942.[17] By 1944, lidocaine was introduced in Sweden as a local anesthetic. With these advancements and the advent of controlled ventilation, longer surgical procedures, and even one-lung ventilation were possible.

The early development of anesthesia focused on strategies to address pain; with rapid advancements in anesthesia during World War II, considerations about post-operative outcomes, infection control, and patient satisfaction expanded anesthesiology's scope to include what is now known as "perioperative medicine."

Specialization in anesthesia first started in the post-World War II era. Pediatric anesthesia became a subspecialty, along with obstetric anesthesia and the use of spinal anesthetic. Dr. Virginia Apgar, best known as the creator of the "Apgar Score" to assess the health of a newborn child, became a pioneer in obstetric anesthesia and neonatology during this time.[14]

Regional anesthesia was also established as a tool for orthopedic and peripherally localized surgical intervention, with 19.8-38.2% of anesthetics in 1944 being spinal anesthesia and 9-19.7% being local.[19]

In tandem with regional anesthesia, pain medicine also saw major strides in medications and interventions; Beecher's works analyzed effective use of morphine in analgesia of surgical patients, for instance. The concurrent development of new antibiotic medications, antiseptic technique, and pre-operative preparation meant that anesthesiologists had many elements of surgical care to manage beyond simply the delivery of a safe anesthetic.

The development of the first blood bank in the U.S. in 1935 helped advance patient safety during surgery. Patients could now be medically optimized prior to surgical intervention through a variety of measures, which significantly reduced the anesthesia-related death rate at the end of the 20th century.[14]

With the growing concern for patient safety and post-anesthesia outcomes, anesthesia soon emerged in the late 20th century as a field centered on facilitating monitored, medically optimized, and ethical care. Following his appointment to the first department chair of anesthesiology at Harvard, Beecher advocated for the importance of bringing ethics into anesthesia practice. He wrote that in order for the field of anesthesia to make advancements through research, human experimentation needed to be conducted safely and ethically. "First, there is the problem of consent, seemingly so simple and straightforward, but often far from simple; second, there is the problem of the ethical justification for experimentation on one subject which cannot in any way be construed as for his benefit but is for patients in general."[15] This discussion led to the formal process of informed consent prior to administering anesthesia.[14]

Creation of Safety Standards

Established standards for safety were also a key addition to the field. Beginning in the 1970s, the number of medical malpractice lawsuits started to increase, and anesthesia-related complications were more commonplace than they are today. For instance, it was not uncommon for an anesthesiologist to leave an intubated and sedated patient's bedside to procure medications or take a break. The adverse events that ensued were reflected in the rise in malpractice lawsuits; in the 1980s, anesthesiologists at all Harvard hospitals accounted for 3% of the physician staff but a staggering 12% of all medical malpractice cases.[20] ASA President Dr. Ellison Pierce grew increasingly concerned at this statistic and started the ASA Standards Committee.

What was revolutionary about these "standards" were that they were not recommendations or suggestions, but enforceable measures that, if not followed, could result in an anesthesiologist's culpability in these malpractice cases. The result is that anesthesiologists were forced to follow a set of standards that were validated through retrospective analysis, and anesthesia became one of the first fields to enforce universal safety standards.[20] The creation of the Anesthesia Patient Safety Foundation (APSF)in 1985 was the next large step in improving

patient outcomes. Following this growing concern that anesthesia care itself was the cause of patient mortality, a focus that was further emphasized by national media coverage of several adverse events from anesthesia, the APSF was created with the goal that "no patient shall be harmed by anesthesia."[26] This goal was reflected in improved patient outcomes with anesthesia; by the 1990s, the mortality rate fell to 1 in 200,000 anesthetics delivered.[27] In an effort to reduce medical malpractice, the ASA Closed Claims Project subsequently began, with the goal of creating a database of all closed malpractice claims for analysis. The result was that anesthesia-related complications could be quantified and categorized, which ultimately facilitated injury prevention standards that are now routine.[21]

The gradual reduction in adverse patient outcomes and severity of malpractice cases reflects what has ultimately always been at the heart of anesthetic practice: patient safety. While the history of medicine has a pattern of groundbreaking discovery often at the expense of cultural prejudice, exploitation of persons without consent, and lack of formal scientific analysis, the history of anesthesia from the 1840s to present day marks a cultural shift away from these themes. The progression of anesthesiology from a craft that could be capitalized for entertainment to a trade that many did not want to take on to, ultimately, a profession with a wide breadth of practice is relatively recent. The inspiring and creative physicians and scientists that paved the way for modern-day anesthesia understood that established practices can and must always be adapted for the best interest of the patient. To understand the history of anesthesia, it would serve the field well to remember that progress, whether in technology, pharmacology, or patient outcomes, is only possible by continuing to strive for improvement, a practice that has long been set as a precedent.

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Disclosure

None reported.

Scan code to read Part I of the History of Anesthesiology.

MM

5 Things to Know About Delta-8 Tetrahydrocannabinol: Delta-8 THC

by the Food and Drug Administration

It is important for consumers to be aware that delta-8 THC products have not been evaluated or approved by the FDA for safe use in any context.

Delta-8 tetrahydrocannabinol, also known as delta-8 THC, is a psychoactive substance found in the Cannabis sativa plant, of which marijuana and hemp are two varieties. Delta-8 THC is one of over 100 cannabinoids produced naturally by the cannabis plant but is not found in significant amounts in the cannabis plant. As a result, concentrated amounts of delta-8 THC are typically manufactured from hemp-derived cannabidiol (CBD).

It is important for consumers to be aware that delta-8 THC products have not been evaluated or approved by the FDA for safe use in any context. They may be marketed in ways that put the public health at risk and should especially be kept out of reach of children and pets. Here are five things you should know about delta-8 THC to keep you and those you care for safe from products that may pose serious health risks.

1 Delta-8 THC products have not been evaluated or approved by the FDA for safe use and may be marketed in ways that put the public health at risk.

The FDA is aware of the growing concerns surrounding delta-8 THC products currently being sold online and in stores. These products have not been evaluated or approved by the FDA for safe use in any context. Some concerns include variability in product formulations and product labeling, other cannabinoid and terpene content, and variable delta-8 THC concentrations. Additionally, some of these products may be labeled simply as "hemp products," which may mislead consumers who associate "hemp" with "non-psychoactive."

Furthermore, the FDA is concerned by the proliferation of products that contain delta-8 THC and are marketed for therapeutic or medical uses, although they have not been approved by the FDA. Selling unapproved products with unsubstantiated therapeutic claims is not only a violation of federal law, but also can put consumers at risk, as these products have not been proven to be safe or effective. This deceptive marketing of unproven treatments raises significant public health concerns because patients and other consumers may use them instead of approved therapies to treat serious and even fatal diseases.

2 The FDA has received adverse event reports involving delta-8 THC-containing products.

From December 2020 through July 2021, the FDA received adverse event reports from both consumers and law enforcement describing 22 patients who consumed delta-8 THC products; of these, 14 presented to a hospital or emergency room for treatment following the ingestion. Of the 22 patients, 19 experienced adverse events after ingesting delta-8 THC-containing food products (e.g., brownies, gummies). Adverse events included vomiting, hallucinations, trouble standing, and loss of consciousness.

National poison control centers received 661 exposure cases of delta-8 THC products between January 2018 and July 31, 2021, 660 of which occurred between January 1, 2021, and July 31, 2021. Of the 661 exposure cases:

- 41% involved unintentional exposure to delta-8 THC and 77% of these unintentional exposures . affected pediatric patients less than 18 years of age.

- 39% involved pediatric patients less than 18 years of age.

- 18% required hospitalizations, including children who required intensive care unit (ICU) admission following exposure to these products.

3 Delta-8 THC has psychoactive and intoxicating effects.

Delta-8 THC has psychoactive and intoxicating effects, similar to delta-9 THC (i.e., the component responsible for the "high" people may experience from using cannabis). The FDA is aware of media reports of delta-8 THC products getting consumers "high."

The FDA is also concerned that delta-8 THC products likely expose consumers to much higher levels of the substance than are naturally occurring in hemp cannabis raw extracts. Thus, historical use of cannabis cannot be relied upon in establishing a level of safety for these products in humans.

4 Delta-8 THC products often involve use of potentially harmful chemicals to create the concentrations of delta-8 THC claimed in the marketplace.

The natural amount of delta-8 THC in hemp is very low, and additional chemicals are needed to convert other cannabinoids in hemp, like CBD, into delta-8 THC (i.e., synthetic conversion). Concerns with this process include:

- Some manufacturers may use potentially unsafe household chemicals to make delta-8 THC through this chemical synthesis process. Additional chemicals may be used to change the color of the final product. The final delta-8 THC product may have potentially harmful by-products (contaminants) due to the chemicals used in the process, and there is uncertainty with respect to other potential contaminants that may be present or produced depending on the composition of the starting raw material. If consumed or inhaled, these chemicals, including some used to make (synthesize) delta-8 THC and the by-products created during synthesis, can be harmful.
- Manufacturing of delta-8 THC products may occur in uncontrolled or unsanitary settings, which may lead to the presence of unsafe contaminants or other potentially harmful substances.

5 Delta-8 THC products should be kept out of the reach of children and pets.

Manufacturers are packaging and labeling these products in ways that may appeal to children (gummies, chocolates, cookies, candies, etc.). These products may be purchased online, as well as at a variety of retailers, including convenience stores and gas stations, where there may not be age limits on who can purchase these products. As discussed above, there have been numerous poison control center alerts involving pediatric patients who were exposed to delta-8 THC-containing products. Additionally, animal poison control centers have indicated a sharp overall increase in accidental exposure of pets to these products. Keep these products out of reach of children and pets.

Why is the FDA Notifying the Public About Delta-8 THC?

A combination of factors has led the FDA to provide consumers with this information. These factors include:

- An uptick in adverse event reports to the FDA and the nation's poison control centers.

- Marketing, including online marketing of products, that is appealing to children.

- Concerns regarding contamination due to methods of manufacturing that may in some cases be used to produce marketed delta-8 THC products.

The FDA is actively working with federal and state partners to further address the concerns related to these products and monitoring the market for product complaints, adverse events, and other emerging cannabis-derived products of potential concern. The FDA will warn consumers about public health and safety issues and take action, when necessary, when FDA-regulated products violate the law.

Source: https://www.fda.gov/consumers/consumer-updates/5-things-know-about-delta-8-tetrahydrocannabinol-delta-8-thc?utm_medium=email&utm_source=govdelivery



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Sajidul Ansari, MD – Gastroenterology – St. Louis
Debbie Bennett, MD – Diagnostic Radiology – St. Louis
Michael Boin, MD – Orthopedic Surgery – Kansas City
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In Memoriam

William Marshall, MD – Family Practice – Fayette, MO – 9/25/2021
John Kelly, MD – Internal Medicine – St. Louis, MO – 9/28/2021
George Richardson, MD – Family Practice – Sarasota, FL – 11/1/2021

MSMA Members in the News

Did you make the news? Submit your success story and photo to lfleenor@msma.org.



Missouri Medicine Managing Editor 20 Year Anniversary

This issue of *Missouri Medicine* marks the 20th year that Lizabeth Fleenor has served as the journal's Managing Editor. Liz has worked at MSMA since 1993 as the Director of Communications. In addition to working on *Missouri Medicine*, Liz serves as the liaison to the MSMA Alliance. She also manages the MSMA website and produces other association print and electronic publications. Liz earned her Bachelor of Journalism and Masters in Mass Communication degrees from the University of Missouri-Columbia.

Congratulations Liz on 20 years with *Missouri Medicine!*

New *Missouri Medicine* Editorial Board Member



Sanjay K. Havaldar, MD, is the new Editorial Board member for Gastroenterology beginning in 2022. Dr. Havaldar is a Gastroenterologist for CoxHealth in Springfield and an Assistant Professor of Clinical Medicine at the University of Missouri-Columbia. He replaces **David H. Cort, MD**, who has been on the Editorial Board for almost two decades. *Missouri Medicine* thanks Dr. Cort for his service.

New Contributing Editor Board Member



Amy A. Cabbabe, MD, MMSc, FASA, is the new *Missouri Medicine* Contributing Editor beginning in 2022. Dr. Cabbabe is an Anesthesiologist and an acute Pain Medicine physician who practices at South County Anesthesia Associates which is affiliated with Mercy Hospital South in St. Louis. She replaces **Jeffrey G. Copeland, MD,** who has been a Contributing Editor for eight years, is an MSMA Past President, and a Cosmetic Plastic Surgeon in St. Charles. *Missouri Medicine* thanks Dr. Copeland for his service.

MSMA Members in the News

From the ranks of our retired MSMA members, **Barbara Buchanan-McCanse, MD,** was honored with the KC Shepherd's Center 2021 "70 Over 70" award that recognizes older adults for their significant contributions and achievements in their endeavors. In addition to her professional activities, **Dr. Buchanan-McCanse** volunteers at St. Luke's Hospice House and the Loose Park Rose Garden. In photo shown, **Dr. Buchanan-McCanse** is receiving her 50-year Physician pin from then President **Jeffrey Copeland, MD** in 2015.



St. Louis Metropolitan Medical Society announces recently installed officers: below, **Erin Gardner, MD,** (left), was recently installed as President, and two MSMA member physicians began three-year terms on the SLMMS Council: **Kathleen Nemer, MD**, (middle), and **Evan Schwarz, MD,** (right).







Retired MSMA member **Terry Hall, MD**, has been recognized as Rural Health Champion by the Missouri Department of Health and Senior Services and the Office of Rural Health and Primary Care. Dr. Hall has displayed his dedication to the Harrison County community by providing primary care services, emergency services, and even house calls.





George Hruza, MD, MBA, has been named the AADA Advocate of the Year for his advocacy work with the FDA on do-it-yourself fillers and neuromodulators that has led to the FDA taking legal action against the purveyors; his effort in a USP compounding monograph for buffered local anesthetics; and chairing the SkinPAC Board of Advisors raising more than $930,000 in 2021.

The Kansas City Medical Society has named officers for 2022. Among them are MSMA members **Scott Kujath, MD,**



(left), President and **Carole Freiberger-O'Keefe, MD,**



(right), President-Elect.

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- Opinions - Praise, criticism, and comments about particular articles, events, or issues.

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Correspondence

COVID-19 Pills – A Long Awaited Ally for Out-Patient Therapeutics

While vaccines are the best defense to reduce severity of illness and thereby hospitalizations, the oral agents against coronavirus disease 2019 (COVID-19) that recently received emergency use authorization (EUA) from the Unites States Food and Drug Administration (U.S. FDA), block the replication of severe acute respiratory syndrome coronavirus – 2 (SARS CoV-2) when administered early in clinical course i.e., <5 days of symptom onset. These agents include nirmatrelvir-ritonavir (Paxlovid, Pfizer) and molnupiravir (Lagevrio, Merck), that received EUA on December 22 and December 23, 2021.[1-3]

Nirmatrelvir is a SARS-CoV-2 main protease (Mpro) inhibitor that inhibits the early phase of viral replication. It is reportedly (Pfizer internal data – published online in ref 5) active against all clinically significant SARS CoV-2 variants including the Omicron.[4-6] The approved formulation is in combination with ritonavir, an HIV protease inhibitor which has no effect on SARS CoV-2, but increases plasma nirmatrelvir levels above the maximum effective concentration 90%, by inhibiting hepatic enzyme CYP3A.[5] The EUA is based on an interim analysis of the evaluation of protease inhibition for COVID-19 –high-risk (EPIC-HR) phase II/III randomized double-blind and placebo controlled clinical trial (N=1219 at interim analysis) demonstrating an 89% [Paxlovid arm 5/697 (0.8%) vs placebo arm 44/682 (6.4%), p< 0.0001] and 85% [Paxlovid 6/607 (1%) vs placebo 41/612 (6.7%), p< 0.0001] relative risk reduction for hospitalization or death at 4 weeks in unvaccinated, symptomatic (at least one symptom of mild COVID-19), test positive (antigen or PCR) and non-hospitalized adult patients with a risk factor for severe disease, when administered ≤ 3 days and ≤ 5 days of symptom onset, respectively. There was a 10-fold reduction in viral load by day 5, claimed to be the strongest viral load reduction to-date for an oral pill. Reported adverse effects include dysgeusia, diarrhea, hypertension, and myalgia. The EUA is approved for adults (≥18 years of age) and the recommended dose is nirmatrelvir 300 mg (two 150 mg tablets) + ritonavir 100 mg (1 tablet), both co-packaged together. This same dose is EUA approved for pediatric age >12 years provided their weight is >40 kg, assuming to result in efficacious serum levels akin to adults. While dose reduction to nirmatrelvir 150 mg (1 tablet) + ritonavir 100 mg (1 tablet) is recommended for moderate renal impairment (eGFR ≥ 30 to <60 mL/min), use is not recommended for severe renal (eGFR <30 mL/min) or severe liver failure (Child-Pugh Class C). The recommended duration of treatment is only 5 days, but within this period serious drug-drug interactions related to CYP3A inhibition by ritonavir is possible in patients already taking other drugs that are metabolized by or inhibit CYP3A. Similarly, drugs that induce CYP3A may void Paxlovid's efficacy.[1] Pfizer's EPIC-HR trial is continuing to target recruitment of 3000, along with on-going enrollment for clinical trials in patients with standard risk (EPIC-SR, for unvaccinated with no risk factors or vaccinated with risk factors, available at https://clinicaltrials.gov/ct2/show/NCT05011513) and for post-exposure prophylaxis (EPIC-PEP for household contacts of COVID-19 patients, available at https://clinicaltrials.gov/ct2/show/NCT05047601).

Molnupiravir is a nucleoside analog that induces lethal mutations via RNA dependent RNA polymerase during viral replication and is also active against all SARS CoV-2 variants of clinical significance.[6-8] The EUA was based on the efficacy and safety report of the MOVe-OUT randomized double-blind and placebo controlled phase III clinical trial in unvaccinated adult outpatients with test confirmed and symptomatic mild to moderate COVID-19. [3,9] In this trial, molnupiravir arm had 31% lower hospitalization or death by day 29 than the placebo group [48/709 (6.8%) vs 68/699 (9.7%)], whereas a risk of death alone was lower by 89% (95% CI, 14 - 99) in the molnupiravir arm (0.1% vs 1.3%). The recommended dose is 800 mg (4 capsules of 200 mg each) twice daily for 5 days. No dose adjustments are necessary for renal or liver dysfunction or failure. Use is not recommended in pregnancy because of animal data showing fetal harm. Similarly, the EUA has excluded lactating mothers and pediatric age <18 years because of possible bone

or cartilage affection. Adverse effects include diarrhea, nausea, and dizziness. There were no concerns for drug interactions or potential other contra-indications in non-pregnant adults. [10] As it causes mutations, scientists and the U.S.FDA have disputing concerns regarding its potential to create a variant of concern in the future with its use. The Centers for Disease Control and Prevention (CDC) has recommended to use molnupiravir, only if other options are unavailable because of reduced efficacy.[11]

With Omicron surging across the U.S., the widely used monoclonal antibodies (bamlanivumab-etesevimab and casirvimab-imdevimab) have become less efficacious in preventing hospitalizations. These two drugs, offer the advantage of convenient oral administration at home and have mechanisms of action that are independent of spike protein variability (i.e., pan-genotypic anti-viral activity) offering hope for those vaccinated individuals with breakthrough mild-moderate COVID-19 and have high-risk factors for severe disease, the immunocompromised hosts who have not mounted or not sustained an immune response to the vaccine and most importantly, to those yet to be (or choose not to be) vaccinated individuals with symptomatic mild-moderate COVID-19 with high-risk factors for severe COVID-19. In this last category, it is still important to recommend vaccination by educating that full vaccination offers the best preventive measure than treatment. Testing to confirm COVID-19 is equally important to be done soon after symptom onset, in order to benefit from early institution of treatment within 5 days of symptom onset, as recommended by the EUA. The national institutes of health (NIH) treatment guidelines for COVID-19 (https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/) and the infectious diseases society of America's (IDSA) COVID-19 treatment guidelines (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/) are constantly updated as clinical trials are published, to guide health care providers. Production, distribution and supply chain issues are expected to improve in the following months according to the CDC, offering a hopeful glimpse into a better and healthier 2022. [11] Just like any other new drug embarking on wide-spread use, only time will reveal their true and long-term impact on this resurgent pandemic.

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Marijuana Killed My Son! Doctors, Let Me Tell You Something About the Dangers of Cannabis

I appreciated the opportunity to speak directly with physicians about my experience with my son Johnny's marijuana addiction, development of psychosis, and ultimate suicide in my article, "Marijuana Killed My Son! Doctors, Let Me Tell You Something About the Dangers of Cannabis." (*November/December 2021 Missouri Medicine*) If anyone has connections with any other journals that might be interested in my firsthand experience, please contact me.

Missouri will be going from the frying pan into the fire if legal high-THC recreational marijuana is passed into law via constitutional amendment in the fall 2022 elections. In my home state of Colorado, which legalized recreational marijuana in 2012, the revenues from the sale of legal cannabis accounts for less than 0.8% of the state budget, which are dwarfed by the increased costs of easy-access cannabis causing increase of automobile accidents, addiction treatment, educational problems, and increased domestic and street violence. *Not to mention suicide is the #1 cause of death in our youth ages 15-19 and over 51% of suicides have THC in their toxicology reports.* Legalization has also not stopped the illegal sale of cannabis by dealers and cartels. Most notably, Johnny's Ambassadors Scientific Advisory Board member, Karen Randall, MD, an ER physician in Pueblo, says she treats teens in the ER every day with episodes of acute psychosis, cyclical vomiting, and poisoning. If marijuana passes in Missouri, you'll suddenly see much of the same with youth in your ERs.

As a member of the coalition that helped pass Colorado House Bill 1317 Regulating Marijuana Concentrates (and the proud owner of the pen Governor Polis used to sign the bill into law), we have had to go to extreme lengths to protect our 18-to-20 year-olds from the harms of the extremely potent marijuana concentrates available in our medical and recreational dispensaries (often 90%+ THC).

The resources of Big Marijuana Industry are almost unlimited, so to defeat the bill, you'll need to start now to build a coalition like we had in Colorado. You'll need the unprecedented cooperation of legislators, coalitions, parents, medical professionals, schools, hospitals and healthcare facilities, business, and law enforcement. Get a leader and a bunch of angry parents like me. Contact legislators to find a sponsor and write the bill. Secure backers and hire a lobbyist or a dozen. Show up in force and testify (we had over nine hours of testimony from those harmed by marijuana). Attend the bill signing with the governor.

Please become one of Johnny's Ambassadors and help us educate on the dangers of youth marijuana use and prevent further youth addiction, psychosis, and suicide: https://JohnnysAmbassadors.org/join.

Laura Stack, Founder & CEO, Johnny's Ambassadors
Author, The Dangerous Truth About Today's Marijuana: Johnny Stack's Life and Death Story
Laura@JohnnysAmbassadors.org

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ONE PICTURE = 1,000 WORDS



Letters to the Editor

Submissions reflect readers' opinions and may be edited for length. Use in subject line: "Letter to Editor."

Email
- drjhagan3@gmail.com
- lfleenor@msma.org



164th Missouri State Medical Association Annual Convention

April 1-3, 2022 | Renaissance St. Louis Airport Hotel **www.msma.org/convention**

Pre-Convention Meetings

Friday, April 1

3:00-4:00 pm	MSMA Insurance Agency Board Meeting
4:00-6:00 pm	Registration
4:30-6:00 pm	MSMA Executive Committee Meeting
5:00-6:00 pm	Women Physicians Section Reception
6:00 pm	MSMA Council Reception & Dinner

Convention Meetings

Saturday, April 2

6:00 am-5:00 pm	MSMA Registration
6:00-6:30 am	Women Physicians Section Business Meeting
6:30-7:30 am	Moneta Product Theater Breakfast
7:30-8:30 am	MSMA House of Delegates – 1st Session
8:30-11:00 am	MSMA Reference Committees A and B (consecutive)
11:00 am-Noon	Caucus Meetings • St. Louis Metropolitan Medical Society • Kansas Medical Society
11:00 am-Noon	MSMA General Session
Noon-1:00 pm	Product Theater Lunch
1:00-2:00 pm	MSMA General Session
2:00-3:00 pm	MSMA General Session
2:00-3:00 pm	Missouri State Medical Foundation Board Meeting
2:00-3:00 pm	Medical Student Section Business Meeting
3:00-4:00 pm	MSMA General Session
3:00-4:00 pm	Missouri Medical Political Action Committee Meeting
3:00-4:00 pm	Resident and Fellow Section Business Meeting
3:00-4:00 pm	Missouri Physicians Health Program Board Meeting
4:00-6:00 pm	Medical School Receptions
5:30-6:30 pm	Reception for 50-Year Pin Recipients, MSMA & MSMA Alliance Past Presidents & MMPAC Diamond Club
6:30-7:30 pm	MSMA Presidential Inauguration
7:30 pm	MSMA Presidential Reception

Sunday, April 7

6:30-7:00 am	Women Physicians Section Business Meeting
7:00-8:00 am	District Breakfasts & Caucuses
8:15 am	MSMA House of Delegates – 2nd Session
Following	MSMA Council Meeting

REGISTRATION
FREE Registration for MSMA members at www.msma.org/convention

HOTEL RESERVATIONS
Make Hotel Reservations by March 9 www.msma.org/convention or call the Renaissance St. Louis Airport Hotel at 1-800-468-3571 and mention code MEDMEDA. Group rates available until March 9, 2022. Rates start at $103 per night plus charges and taxes.

RESOLUTION SUBMISSION
Resolution Policy Research
www.msma.org/policies

RESOLUTION SUBMISSION DEADLINE
Wednesday, February 16 - 5:00 pm
Email resolution to Cheri Martin
cmartin@msma.org

ONLINE RESOLUTION COMMENTS
Comment online beginning February 23.

SERVE ON A REFERENCE COMMITTEE
MSMA staff will provide the background and instructions.
Email Jeff Howell at jhowell@msma.org

Program subject to change.
For more information, contact MSMA's Benita Stennis, at 573-636-5151 or bstennis@msma.org.

In These Changing Times, What is the Role of Local County Medical Societies?

A Perspective from Boone County

by Albert L. Hsu, MD

What is the role of a local or county medical society? Across the country, many state medical societies have been experiencing membership crises, as burned-out residents and young physicians focus on their specialty societies to establish their credentials and board certifications; on a local level, many county medical societies have also been closing shop due to declining membership.

Meanwhile, many of us are alarmed by proposed state legislation to repeal state school immunizations requirements this spring. Earlier this month, the board members of the Boone County Medical Society (BCMS) had a vibrant discussion about the role that organized medicine can play on a local level.

Overall, our BCMS has educational, social, and advocacy missions. Educationally, we use some of our dues (and endowments) to fund a few medical student scholarships. Pre-pandemic, we also held a popular "financial bootcamp series" for young physicians and graduating residents, to discuss loan repayment, home-buying, contracts, taxes, and other aspects of "business-in-medicine" that many of us never learned in medical school or residency training. With the University of Missouri in our backyard, we also participate in some medical student events, including an annual roundtable with residency program directors, as well as the "MUlation" student-physician event where physicians of every specialty share perspectives with medical students considering their fields.

Socially, we host an annual gala, hold summer family fishing trips, and invite speakers to present at our quarterly membership meetings. From an advocacy standpoint, BCMS membership is a gateway to representation at the state (Missouri State Medical Association or MSMA) and national (American Medical Association) levels. We also view organized medicine as a "force-multiplier." For example, one of our Mizzou medical students introduced a 2019 MSMA resolution on "addressing healthcare needs of children of incarcerated parents." This year, our state legislature will address a bill to enact a Prison Nursery program in the state's women's prison, shown in other states to reduce recidivism and be beneficial for mother-baby bonding.

What does this mean for us locally? In 1997, Boone County ranked #15 among the top U.S. counties with the highest number of physicians per 100K population (at 657).[1] Our three major hospitals include University Hospital (including the soon-to-be moved Women's and Children's Hospital), the Truman VA Hospital, and Boone Hospital; all three serve a 25-county largely-rural catchment area. Over the past few decades, BCMS has been a collegial venue for local physicians to meet, socialize, and collaborate on educational activities. And then came COVID-19.



Albert L. Hsu, MD, (left), is an Ob/Gyn and a reproductive endocrinology and infertility subspecialist at the University of Missouri-Columbia and President of the Boone County Medical Society, Columbia, Missouri.

COVID-19

In March 2020, we started a weekly Zoom webinar with public health and infectious disease experts, to update our local community physicians on the state of COVID-19 in mid-Missouri. Our featured topics included: "Controversies over Wearing Masks," "Potential Risks of Re-opening," "A Comparison of the 1918 Flu and COVID-19 in Four Missouri Counties," "COVID-19 in Children and Collateral impacts of the Pandemic on Pediatric Care," "The Impact of COVID-19 on Underserved Communities," "COVID-19 in Private Practice," "COVID-19 among Veterans and at our VA Hospital," and "Legislative Updates on COVID-19 in our State Capitol."[2] With over 3,000 participants in our 76 webinars to date, we intend to continue these webinars as long as a need is identified. The Missouri Public Health Association recognized our efforts with their 2021 "Group Merit Award."[3]

One interesting pair of speakers has been Marc Johnson, MD, (Department of Molecular Microbiology and Immunology at the University of Missouri) and Jeff Wenzel (Chief of the Bureau of Environmental Epidemiology, with Missouri Department of Health and Senior Services), who have now given us six presentations on "Wastewater Surveillance for COVID-19 and its Variants." In May 2021, when most of the country was breathing a sigh of relief and de-masking (in accordance with CDC recommendations, for those fully vaccinated), Marc and Jeff warned us about the soon-to-be-named "Delta" variant, which had just shown up in southwest Missouri sewersheds. In December 2021 and again in January 2022, Marc and Jeff gave us further updates on how the Omicron variant has spread throughout Missouri.

Our BCMS also participated in some local advocacy. In summer of 2020 (pre-vaccine), during a local debate over whether to mandate masks county-wide, our BCMS board met to discuss the issue. While many favored a mask mandate at the time, several private practice physicians made a compelling argument, that it would hurt their business to needlessly-antagonize some of their patients with an overly-strong statement, so we issued a public statement emphasizing the science supporting masks, without making a strong statement about mandates either way. Indeed, COVID-19 has also helped us all develop a "finer appreciation of the anxiety, uncertainty, feelings of helplessness, and fears of the unknown that regularly complicate decision-making for our patients."[4] We could all probably stand to be a little less dogmatic, as we start appreciating and learn to communicate the nuances[4,5] and gray areas in medicine.

In my specialty of Reproductive Endocrinology and infertility, the average physician only stays in their first position for about three years, and one of the hallmarks of being a young physician is constant transition. COVID-19 has exacerbated this "churn" of physicians, as we all complete our training, establish new practices, and then confront consolidation and the many other forces (family, financial, pandemics) that cause physicians to move. Constant changes of locale also discourage physicians from involvement in their state and local societies.

In this era of contentious public discourse, where everything seems overly politicized, organized medicine is an opportunity for all of us to collaborate on shared interests and advocacy. No matter what your political beliefs, we are all interested in advocating for our patients and our profession, which is part of what makes national physician meetings so much fun. Many of us are active in our respective specialty societies, but there is also an important social, educational, and advocacy role for local collaborations in our local and state medical societies. Communicating our work and our successes is also important, and there will likely be an ever-increasing role for social media outreach to boost our membership. As health systems continue to consolidate, and as we start learning to live with COVID-19 long-term, our hope is that physicians new to Missouri will see value in joining our state and local medical societies.

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2021 Contributors to Missouri Physicians Health Program

The Missouri Physicians Health Program is proud to recognize the following organizations and individuals that contributed to our annual fund drive. We are truly grateful for their generosity which helps provide crucial support as we strive to provide high quality physician care services and meet the demand for our services statewide. Many of our participants are physicians-in-training who are unable to pay for services rendered. Your contribution helps us to defray those costs. We encourage you to generously contribute to our 2022 campaign.
Thank you for your compassionate support.

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Missouri Physicians Health Program Updates

2021 came with many challenges for the MPHP as we continued to navigate through the global pandemic. Without our dedicated staff and generous donors we would not have been able to provide services to physicians in need.

"The ongoing pandemic has underscored the importance of our services, as many physicians in our state have suffered from depression, anxiety, substance abuse and burn-out and have reached out to us for help," stated William L. Woods, MD, chair of the MPHP Board of Directors. Missouri physicians, residents and medical students are in need our services now more than ever. Even before the pandemic, physician mental health was suboptimal.

Over the years, we have assisted countless physicians in the state of Missouri with their health issues and, in the grand majority of cases, have helped them to continue their practice of medicine safely and effectively. Although we are still operating under very challenging times, we remain focused on our mission. MPHP is dedicated to enhancing patient care and safety through facilitating the return to healthy personal and professional lives for those physicians' struggling with mental/behavioral health issues, substance abuse, stress and burnout

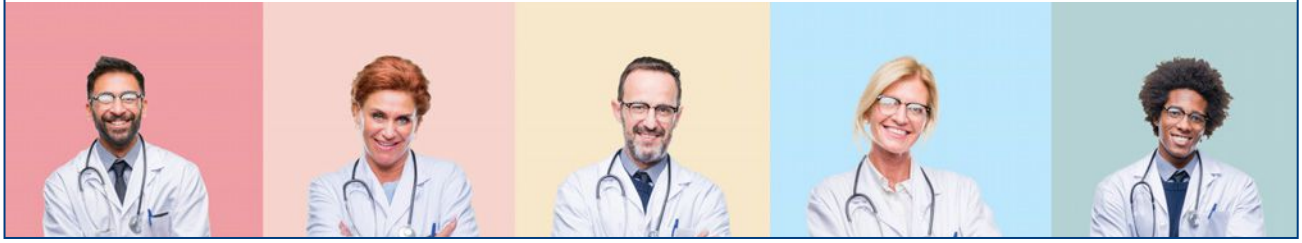
MPHP continues to provide advocacy, consultation, screening, referral, intervention and monitoring for physicians in need as well as creating awareness through education and outreach efforts. Services are available to all Missouri physicians, physicians in training and medical students. Looking ahead, one of our primary short- and long-term goals is to increase participation with physicians in need by eliminating client fees. Additionally, we are working to expand our operations to better serve the entire state of Missouri. **MM**

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Washington University in St. Louis
SCHOOL OF MEDICINE

Washington University's Ophthalmic Department: National Leader in Research, Education, and Eye Care

by Todd P. Margolis, MD, PhD

The Department of Ophthalmology and Visual Sciences at Washington University School of Medicine has a long history as a national leader in research, education, and eye care.

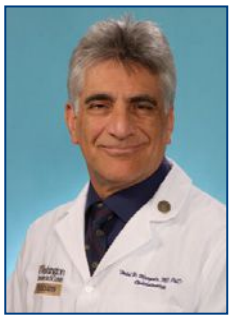
Several years ago, through a very generous gift of Jane Hardesty Poole, the Department was renamed the John F. Hardesty MD Department of Ophthalmology and Visual Sciences. With 55 full time faculty members, 15 staff optometrists, five interns, 15 residents, 10 clinical fellows, postdoctoral research fellows, and graduate students the department is a busy enterprise. Our outstanding clinicians cover all ophthalmic sub-specialties, at least three to every one, and provide over 130,000 eye care visits and 15,000 clinical procedures per year in 10 locations in the St. Louis area.

Our scientists and clinician-scientists make up an elite team of researchers that regularly rank in the top 10 in NIH funding, and cover cutting edge basic and translational science as well as clinical trials. More than 90% of our residents go on to complete fellowship training and 30% go on to full-time academic jobs. In addition, about 35% of our clinical fellows take full-time positions in academic medical centers.

The department has changed a lot in the past eight years since I joined Washington University as chair. We have hired five basic scientists, two clinician scientists, 12 clinician educators, and 16 staff optometrists. We have completely remodeled or replaced every one of our outpatient facilities, purchased two community practices in patient-centric locations, and are in the process of building out a large ambulatory care facility on North Ballas Road complete with 24 examination lanes, diagnostic testing suite, state-of-the-art refractive surgery center, and adjacent ambulatory surgery center.

In the course of our clinical expansion we have made sure that our practice is providing care for the community. We have tripled the number of patients cared for annually in University Eye Service, our practice that focuses on continuity clinics for our residents and fellows. We have also placed providers in CARE STL in North St. Louis, provide care at local free clinics and help fund and staff mobile eye clinics for children in underserved school districts.

Next year we will be building out clinical space in Florissant to ensure local care for the underserved community in North St. Louis. To quote the late Professor Daniel Koshland: "There is no clear line



Todd P. Margolis, MD, PhD, is the Alan A. and Edith L. Wolff Distinguished Professor and Chairman of the John F. Hardesty MD Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, St. Louis, Missouri.

between research and teaching, education and public service. As in every good symbiotic relationship, everyone benefits."

Research endeavors in our department cover the areas of glaucoma, lens, retinal degeneration, microbiology, immunology, developmental biology, biomedical engineering, and clinical trials. Nineteen departmental faculty members have laboratory-based research programs, eight have dedicated resources for clinical trials, and many of our clinicians are engaged in various forms of clinical and translational research. At the moment our faculty are involved in examining patients for 62 clinical trials. Historically, Washington University has been the center of excellence for clinician scientists, and this is reflected by the tremendous innovation and research in our department today.

Historically, Washington University has been the center of excellence for clinician scientists, and this is reflected by the tremendous innovation and research in our department today.

In this issue of *Missouri Medicine* six of our clinical faculty members, all with active translational and/or clinical research programs, have taken on cutting edge topics related to their interests and research. Steven Couch, MD, who has a long-standing interest in thyroid eye disease, discuses the data supporting the use of teprotumumab, the first and only FDA approved therapy for the treatment of this condition.As one of the investigators in the clinical trials of this drug, Dr. Couch has first-hand experience with the patients enrolled in these studies as well with how the data for these studies was analyzed.

Rithwick Rajagopal, MD, a retinal specialist with years of funded translational studies on the pathogenesis of diabetic retinopathy, discusses the role of weight reduction in the management of diabetic retinopathy, bringing to together his clinical expertise with a basic science understanding of the metabolism of the retina in patients with diabetes.

Carla Siegfried, MD, is a scientist, clinical expert in glaucoma and president elect of the American Glaucoma Society. Writing with her research collaborator Ying-Bo Shui, PhD, these two experts discuss racial disparities amongst African Americans with glaucoma. Amongst ophthalmologists the relatively high prevalence of open angle glaucoma in African Americans is well known. Less well known is the pathogenesis of this problem. Very careful research by Dr. Siegfried and Shui has revealed that greater oxidative stress at the level of the trabecular meshwork may be responsible for higher rates of blinding glaucoma in African Americans.

Augustine Hong, MD, is one of our cornea specialists who has been working on treatments for river blindness in west Africa funded by the Gates Foundation. In Dr. Hong's contribution to this issue he describes the research protocols that he and his collaborators are carrying out, as well as the challenges they are faced with, in trying to eradicate river blindness in Ghana.

Larry Tychsen, MD, the chief of our Division of Pediatric Ophthalmology, is a global expert and innovator in the field of refractive surgery for children, and has, perhaps, the greatest experience in the world in treating special needs patients for high myopia. He reviews his clinical outcomes, to date, of performing refractive surgery in this patient population.

Both patients and providers are excited about the potential of stem cell therapies, but there currently are no approved stem cell therapies for ocular disease. Furthermore, a number of patients with eye disease have been seriously and permanently injured by unapproved stem cell therapies. In the current issue, P. Kumar Rao, MD, a well-respected retinal specialist and ocular oncologist in our department, reviews the current state of the art in stem cell therapies for retinal disease.

I am certain that you will find this collection of manuscripts interesting, educational and stimulating. Thank you very much for the opportunity.

Disclosure

TM receives grant support from Research to Prevent Blindness and the National Institutes of Health. He serves on the Scientific advisory board of Rational Vaccines and SGN Nanopharma. **MM**

Teprotumumab (Tepezza) for Thyroid Eye Disease

by Steven M. Couch, MD

Washington University in St. Louis
School of Medicine

Significant improvement in proptosis, disease activity, diplopia, and QOL suggests a major role for the use of Teprotumumab in the treatment of many of our TED patients.



Steven M. Couch, MD, FACS, is in the John F. Hardesty MD Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, St. Louis, Missouri.

Abstract

Thyroid eye disease (TED) is an immune mediated infiltration and inflammation of the orbital and periorbital soft tissues leading to facial disfigurement. Classically broken into two "phases," active inflammatory and quiescent, disease modifying therapy and surgical intervention are used to improve a number of clinical aspects of TED. Many medical modalities have been utilized to halt the inflammatory phase of the disease including steroids, orbital radiation, and targeted steroid-sparing chemotherapy. Teprotumumab is currently the only Federal Drug Administration approved therapy for the treatment of TED. Significant improvements in proptosis, diplopia and quality of life are noted following its 24-week course of therapy.

Introduction

Thyroid eye disease (TED) is the most common orbital disorder in adults, predominately occurring during mid-adulthood.[1] This female-predominate disease occurs in up to 50% of patients with autoimmune thyroid disease, especially Graves' Disease, with a prevalence of up to 1/10,000.[2-6] Known to be more common and profoundly worse in smokers, this autoimmune mediated disease is propagated by autoantibodies targeting the thyrotropin receptor.[6,7] TED is characterized by an orbital inflammatory cascade leading to muscle and fat expansion, ultimately ending, in some cases, with progressive fibrosis. Infiltration of inflammatory cells and activated fibroblasts within the bony orbit can lead to proptosis, strabismus, eyelid swelling and eyelid retraction. Clinical findings include periorbital edema, conjunctival redness and swelling, eyelid retraction, strabismus, exophthalmos, and in rare cases, compressive optic neuropathy. Debilitating diplopia and facial disfigurement have profound psychosocial and functional effects on afflicted patients.[8,9]

Classically, the disease course is described by Rundle's curve (Figure 1), which illustrates an active inflammatory phase that reaches a peak of disease severity and plateaus into a static or quiescent phase. This biphasic, self-limited course is seen in most patients, with active phases lasting 6-18 months and with rare patients suffering from chronic inflammation for years.[9-12] Recurrences of disease can be seen in 15% of patients.[9,13] Most research in medical therapy for disease modification has been focused in the active phase of the disease with the goal of reducing inflammation, fibrosis and overall

disease burden. Surgical rehabilitation involving orbital decompression, strabismus surgery, and eyelid surgery is typically offered in the quiescent phase of the disease, unless required for significant corneal disease (usually due to exposure) or in active disease-inducing optic neuropathy.

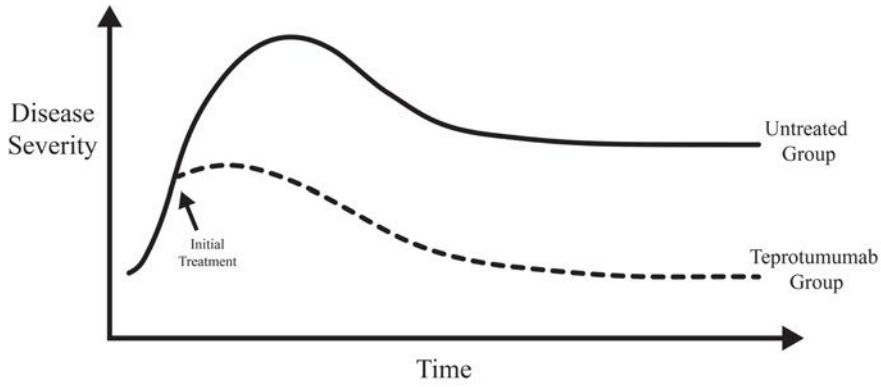


Figure 1.
Rundle's Curve illustrating a progressive active disease early in the course followed by a peak in severity and plateau to stability. With intervention, such as Teprotumumab, during the active phase, overall disease burden may be reduced.

In early studies, long-term oral steroids were utilized to reduce active inflammation; however multiple studies have shown a high rate of recurrence and significant adverse effects from this approach to therapy.[14,15] Orbital radiation is thought to induce terminal differentiation in inflamed orbital fibroblasts and is still commonly utilized by some TED specialists. Studies on radiotherapies role in the treatment of TED is conflicting.[16-18] Intravenous (IV) pulse dose steroids are another commonly utilized therapy, especially utilized in by European TED specialists.[19-22] In fact, in 2016 a consensus statement from the European Group on Graves' Orbitopathy suggests high dose IV pulse dose steroids as the first-line treatment for active TED.[23] Studies comparing pulse dose IV and chronic oral steroid favored IV steroids with lower adverse effects and improved efficacy.[15] Other off-label immunomodulatory medications including methotrexate, rituximab and infliximab have been utilized for active TED with variable success.[24-31]

Research involving the molecular process of inflammation in the orbit with TED has highlighted an interaction between the insulin-like growth factor receptor (IGF-R) and the thyroid stimulating hormone receptor (TSH-R).[32,33] The IGF-R is a toll-like receptor that is intimately associated with the TSH-R and acts as a "gate keeper" in activating orbital fibroblasts. During the disease, an upregulation of IGF-R and TSH-R is noted, and initial in vitro studies showed an inhibition of TSH-R stimulation with blockade of IGF-R.[34] In vitro studies also showed blockade of the IGF-R led to decreased production of extracellular matrix and cytokines in activated fibroblasts.[35-37] Progressive research in the understanding of the synergistic roles that TSH-R and IGF-R play in the development of TED[38-42] led to the development of Teprotumumab, a fully humanized monoclonal antibody targeted against IGF-R1. Originally, studied and found to be unsuccessful in the treatment of patients with metastatic solid organ tumors,[43,44] Teprotumumab was shown to decrease inflammatory factors in TSH-dependent fibrocytes.[45,46] Following randomized, placebo-controlled clinical trials, Teprotumumab (Tepezza™) became the first Food and Drug Administration (FDA)-approved therapy for TED.

Studies on Efficacy

In 2017, results of the Phase 2, multicentered, double-masked, randomized, placebo-controlled clinical trial were published in the *New England Journal of Medicine*.[46] Washington University was one of the study sites and the author was one of the investigators. Eighty-seven patients (42 Teprotumumab and 45 placebo) were randomly assigned to Teprotumumab infusion once every three weeks for eight doses or placebo. Teprotumumab infusions are weight-based dosing with first dose being 10mg/kg and all other infusions being 20mg/kg. Inclusion criteria included patients with active, moderate TED, clinical activity score (CAS) of four or more, diagnosed within nine months of the trial's initiation.[47] The primary outcome measurement was a decrease in clinical activity score (CAS) of two or more points and proptosis reduction of 2mm or more. At 24 weeks, 29 patients (69%) in the treatment arm of the study and nine patients (20%) in the placebo arm achieved the primary outcome response. Furthermore, onset of improvement in the primary outcome was achieved much earlier in the treatment group. In the



Figure 2a. Patient with active moderate thyroid eye disease causing orbital inflammation with proptosis and eyelid retraction. 2b. Same patient following 8 treatments using Teprotumumab.

treatment group, an average reduction in CAS by nearly 3.5 points was achieved as well as an average reduction in proptosis by nearly 2.5mm, with 17 patients (40%) achieving greater than a 4mm reduction in proptosis. Additionally, secondary outcomes of validated subjective diplopia scores and validated Graves' quality of life (QOL) analysis improved significantly more in the treatment group.[46]

A Phase 3 multicenter clinical trial for Treatment of Graves' Orbitopathy to Reduce Proptosis with Teprotumumab Infusions (OPTIC) was conducted with an emphasis on the treatment of proptosis.[48] Washington University was one of the study sites and the author was one of the investigators. Identical inclusion criteria and treatment protocol to the Phase 2 clinical trial were utilized and patients were randomized to treatment with teprotumumab or placebo. A total of 83 patients (41 Teprotumumab and 42 placebo) were enrolled. The primary outcome of proptosis reduction (2mm of reduction or more) and secondary outcomes, including "overall response" (reduction of CAS by two or more plus reduction in proptosis of 2mm or more), subjective diplopia scores, and Graves' QOL scores were evaluated at 24 weeks. Some patients underwent follow-up at 48 weeks. At 24 weeks, the reduction of proptosis was statistically significant with 34 patients (83%) in the treatment group and four patients (10%) in the placebo group achieving a reduction in proptosis of 2 mm or more. The average reduction in proptosis was 3.32mm, and all patients treated with Teprotumumab exhibited improvement regardless of baseline severity. Again, early response was noted in the treatment group with all secondary end points statistically significantly favoring the Teprotumumab group over placebo. Six patients in this study had pre- and post-treatment imaging which demonstrated reduction in proptosis with radiographically confirmed reduction in extraocular muscle volume, orbital fat volume or both. The average reduction in extraocular muscle volume was 35%.[48]

Combined data from Phase 2 and Phase 3 trials was evaluated by Kahaly et al.[49] to analyze treatment efficacy, subgroup analysis, adverse effects and long-term off-treatment durability. This pooled dataset included 171 patients, 84 received teprotumumab and 87 received placebo. In this study 65 (77%) patients in the Teprotumumab group as compared to 13 (15%) in the placebo group achieved a reduction in proptosis of 2mm or more. The mean reduction in proptosis was 3.14mm in the treatment group as compared to 0.37mm in the placebo group. Reduction of both proptosis and diplopia was further evaluated in a sub-group analysis that took into account gender, age, tobacco use, time of diagnosis of TED, time of diagnosis of Graves' disease, baseline CAS and baseline levels of anti-thyrotropin antibodies. In the analysis, patients exhibiting a reduction in proptosis had statistically significant similar effects amongst all sub-groups. Similarly, for those patients with a reduction in diplopia, all sub-groups achieved statistically significant improvement except active tobacco users.[49]

An open label extension study (OPTIC-X, NCT03298867) was created following the Phase 3 trial. Patients from the trial were offered entrance into the study if they did not have a therapeutic response in proptosis or had recurrence of proptosis during the follow-up period. The purpose of this extension trial was

to examine the efficacy and safety of a second course (24 week, eight infusions) of Teprotumumab (Figure 2). Results of this study were intended to indicate the efficacy of treatment regardless of disease duration, along with the effect of additional treatment in "non-responders" and patients with a relapse. These results have not been published in peer-reviewed literature to date, but Horizon Pharmaceuticals released data on July 31, 2020, and in a press release on November 13, 2020.[50,51] Fifty-one of 83 original OPTIC trial participants were included, 37 from the placebo group and 14 from the treatment group. Of the 14 from the treatment group in the original OPTIC trial, five had no initial response Teprotumumab and nine experienced a relapse of proptosis. At 24 weeks, 33 of 37 patients (89%) who had previously received placebo experienced improvement in proptosis of 2mm or more. Fourteen of 23 (61%) patients who started with diplopia experienced improvement at 24 weeks. Two of five patients who did not have a clinical response during OPTIC, experienced a significant response following a second course of therapy with Teprotumumab. Sixty percent of patients who experienced relapse after OPTIC achieved a response at 24 weeks after a second round of Teprotumumab.

Durability of Treatment

While the Phase 2 trial described above had some patients followed out to 48 weeks, this information was not presented in the representative manuscript. Full follow-up data was presented to the FDA in a briefing document used to encourage approval of the drug.[52] When followed out to 72 weeks, 18 of 29 (62%) patients treated with Teprotumumab had a long lasting therapeutic effect with 11 of 29 (38%) having relapse of TED defined by an increase in proptosis (2mm or more) or increase in CAS. Phase 3 trial durability data was released at a presentation at the American Academy of Ophthalmology and with public release of the 48 week off-treatment follow-up in the OPTIC-X data.[50,51,53] At 72 weeks following start of treatment, 19/34 (56%) of the proptosis responding group maintained a reduction in proptosis, and of the 15 that qualified as non-maintained response, 8/15 (53%) still had 2mm or more reduction in proptosis as compared to the amount of proptosis prior to treatment. Eleven of 19 patients (58%) who demonstrated a reduction in diplopia at 24 weeks continued to have reduction at 72 weeks. Composite data from patients treated in Phase 2 and Phase 3 data showed durability of proptosis treatment in 67% of patients and diplopia in 69% of patients.[49]

Safety

Teprotumumab therapy is generally well tolerated with most adverse effects resolving after completion or cessation of infusions. Rates for completion of infusion were similar for Teprotumumab and placebo in both Phase 2 and Phase 3 trials and similar adverse event profiles were seen.[46,47,49] Muscle spasms, typically of the lower extremities, occurred in 25% of patients treated with Teprotumumab. Hyperglycemia occurred in 10% of patients, of which nearly two-thirds had previous impaired glucose tolerance or diabetes mellitus. Hearing impairment is of concern because of IGF receptors located in the inner ear.[54-56] Hearing issues, including tinnitus and or hypoacusis, were noted in up to 10% of patients. Diarrhea occurred in 12% (8% in the placebo group) but generally was mild and reversible. Inflammatory bowel disease (IBD) is a relative contraindication to treatment with Teprotumumab after one patient in the Phase 2 trial experienced exacerbation of IBD and another patient developed new-onset colitis requiring surgical intervention.[46,57-59] Additional notable adverse effects of Teprotumumab treatment included nausea (14%), alopecia (11%), dysgeusia (8%), headache (8%), and dry skin (8%).

Future Studies

While Teprotumumab has been evaluated for the treatment of moderate to severe active TED, we do not know is efficacy in the treatment of patients with longer active phase disease courses, chronic TED, patients in the quiescent phase of TED, or those with dysthyroid optic neuropathy (DON).

Chronic TED

While the data that was released from the OPTIC-X trial is suggestive of efficacy in patients with TED disease with a duration of over one year, data on the effectiveness in patients with chronic TED is lacking. Case reports have suggested a role for Teprotumumab in the treatment of chronic TED,[60,61] however, the results of randomized controlled trials for this patient group are not yet available. A clinical trial of Teprotumumab for chronic TED in patients with stable measurements for three or more years is planned.

Optic Neuropathy

It is known that DON primarily occurs because of compression of the optic nerve in the orbital apex from enlarged muscles and less commonly from stretch of the optic nerve secondary to proptosis.[6,13] Because some studies have shown a reduction in the volume of EOMs,[48,62] it is conceivable that patients with mild compressive optic neuropathy will experience a benefit of treatment with Teprotumumab. Several case reports have suggested improvement in patients with DON with rapid resolution of compression following initiation of treatment.[63-65] Due to the limited data, this may be an option for poor surgical candidates experiencing DON, but trials are needed to compare Teprotumumab efficacy with the current gold standard of treatment, orbital decompression surgery.

Conclusion

Never before has a targeted treatment been available in our armamentarium for the management of TED. The use of Teprotumumab for the effective and safe management of TED through inhibition of the IGF-R is now supported by both laboratory and clinical studies. Significant improvement in proptosis, disease activity, diplopia, and QOL suggests a major role for the use of Teprotumumab in the treatment of many of our TED patients. Adverse effects of the drug including muscle cramping, hyperglycemia and hypoacusis need to be monitored and managed, and in some cases, therapy may need to be halted. However, this cost-prohibitive drug must be evaluated in the entire spectrum of TED including chronic disease, recurrent disease, and DON. Furthermore, its use should be directly compared with other available treatments including medical and surgical therapy. Teprotumumab is currently the only FDA-approved medical therapy for TED and is an effective and relatively safe treatment for active moderate-severe TED.

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Weight Reduction as an Adjunctive Management Strategy for Diabetic Retinopathy

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Control of the underlying diabetes can be far more effective for DR than aggressive ophthalmic therapy.



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Abstract

As rates of global obesity and diabetes increase, diabetic retinopathy continues to grow as a frequent cause of visual impairment. Despite tremendous recent strides in therapy, a significant fraction of patients remain poorly responsive to modern interventions. Adjunctive therapy in such settings could be widely beneficial. A growing body of evidence suggests that weight reduction strategies for obesity-related diabetes have the potential to serve as important supplements to modern ophthalmic care for preservation of vision.

Introduction

Diabetic retinopathy (DR), among the most frequent causes of vision loss in working-age adults, affects about one-third of all patients with diabetes mellitus (DM). Incidence rates of DR and type 2 DM are rising, likely stemming from rising global rates of over-nutrition and obesity.[1]

Although DR was historically associated with relatively poor visual prognosis, a major development in therapy came about with retinal photocoagulation for diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR).[2,3] An even greater transformation in DR therapy came with the advent of ophthalmic pharmaceuticals that antagonize vascular endothelial growth factor (VEGF), the primary molecular culprit in clinically-manifested DR. Many such agents, including bevacizumab, ranibizumab and aflibercept, not only prevent vision loss among patients with DR, but often provide visual improvement. Despite such efficacy, these therapies – and other contemporary treatments such as ophthalmic corticosteroid therapy – are ineffective in about a third of patients, highlighting remaining needs for improvement of DR care.[4]

In this regard, management of DR requires management of the underlying systemic illness. The benefits of glucose, lipid, and blood pressure control are well-established.[5] In our practice, we also advocate the use of fenofibrate given its efficacy in preventing DME and PDR.[6,7] In type 2 DM, strategies for weight loss can also be powerful, as even modest reductions in obesity can have tremendous beneficial metabolic effects.[8] The effects of these approaches on DR are incompletely studied, falling far short of the evidence needed to make broad recommendations

for patient care – but they deserve attention and further study. Here, I review a case study from my practice along with selected preclinical studies and small clinical trials that offer some insight into the effects of weight reduction strategies on DR. Moreover, I also briefly review the evidence for the effects of glucagon-like peptide 1 receptor agonists (GLP1-RAs) on DR, since these drugs have received wide acclaim for their beneficial effects on type 2 DM control and obesity reduction while gaining notoriety for risk of promoting vision loss.

Case Example

A 56-year-old Caucasian man with a 15-year history of type 2 DM was referred to me for severe vision loss in both eyes. He was taking metformin and glyburide, achieving moderate glycemic control on that regimen with a glycated hemoglobin index (HbA1c) of 7.8%. Like many patients with type 2 DM, he had elevated blood pressure and dyslipidemia, and was being treated for both conditions.

His initial eyesight was 20/100 in the right eye and 20/150 in the left eye. Retinal examination, including the use of optical coherence tomography (OCT), indicated thick, center-involving DME in the setting of severe non-proliferative DR in both eyes. A notable and worrisome finding was the presence of thick subfoveal hard exudates especially in the left eye, as shown on his photos and initial OCT scan (Figures 1A, B, G, H). This finding is typically associated with poor visual outcomes, as shown in the Early Treatment for Diabetic Retinopathy Study (ETDRS).[9]

After considering several options, we agreed to start with intravitreous injections of 0.3 mg ranibizumab to both eyes. Despite injections spaced four weeks apart, his DME was not reduced and his hard exudates worsened. More importantly, his vision remained unimproved. We added fenofibrate 160 mg daily, as the ACCORD and FIELD trials showed an approximately 30% risk reduction in need for DME therapy using this drug.[6,7] We also switched his treatment to 2 mg aflibercept monthly, since this drug has good visual outcomes in patients with poor baseline vision.[10] Yet, his vision and retinal exam only nominally improved (Figures 1 I, J). We then switched to corticosteroid injections – in the form of bolus triamcinolone (4 mg) and fluocinolone implant – but these therapies also were not successful, and his vision deficits remained (Figure 1 K, L). He preferred not to undergo vitrectomy, though this could have been helpful, and instead opted to defer all further treatment.

This gentleman returned several months later, at which point I expected to see fully blossomed bouquets of macular edema involving both eyes. Instead, he had – for the first time in years of therapy – a significant reduction in macular thickness (Figure 1 M, N). Noticing that he appeared a lot thinner, I inquired about his general health. He had begun an intermittent fasting regimen on his own accord, resulting in a ~30% loss of body weight and lowering of body mass index (BMI) from 32 to 27 over a span of only several weeks. More importantly, he found the regimen much easier to adhere to compared to other dietary modifications he attempted in the past. His HbA1c improved to 6.5%, and he managed to come off of the sulfonylurea. Furthermore, he noticed improvement in vision. Indeed, on exam he improved to 20/50 in the right eye and 20/100 in the left eye. Remarkably, his hard exudates were also reduced in size (Figures 1 C, D). Given his recovery without ophthalmic treatment, we deferred further therapy, and monitored his progress every three months. From the moment he began intermittent fasting – a regimen that he continued to maintain – his macular thicknesses continued to decline and his vision gradually kept improving. A year later, he was seeing 20/25 in the right eye and 20/40 in the left eye. He has a residual hard exudate in the left eye, much smaller than on the initial examination, and minimal residual exudate in the right eye (Figures 1 E, F, Q, R). He had received no ophthalmic intervention since beginning intermittent fasting, is no longer receiving any pharmacologic therapy for type 2 DM, and has a HbA1c of 5.7%.

Of note, the initial gain in eyesight that he achieved with anti-VEGF therapy (20/70, improved from 20/100 in the right eye) would likely have been considered a treatment success (i.e., 15-letter improvement or more) in trials

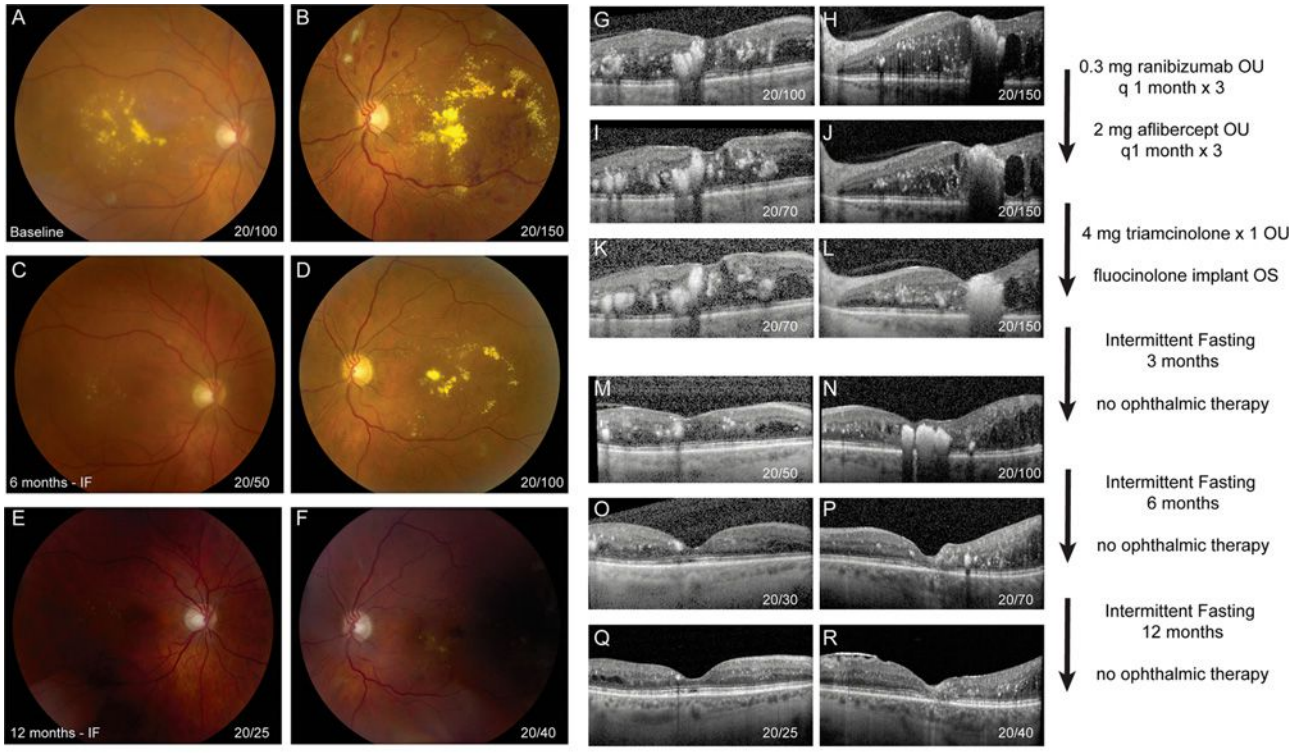


Figure 1. Impact of an intermittent fasting (IF) diet on treatment-resistant diabetic macular edema. Retinal photographs from the right (A, C, E) and left (B, D, F) eyes of a 56-year-man with type 2 DM and vision loss. Baseline images (A, B) show center-involving macular edema, delineated by the presence of yellow, hard exudates and scattered intraretinal hemorrhages. After beginning IF, his disease severity lessened progressively with reduced hemorrhages and exudates at six months-post diet (C, D) and nearly resolved lesions by one year-post diet (E, F). His central macular thickness, shown by optical coherence tomography (G – right eye, H – left eye), was poorly responsive to ocular pharmacotherapy (I, J, K, L), but gradually improved three months (M, N) and six months after IF (O, P). By one year after IF, he had near-normal retinal thicknesses in both eyes and vastly improved visual acuity (Q, R).

such as RISE/RIDE, VISTA/VIVID and DRCR Protocol I.[11] Yet, visual acuity of 20/70 in the better eye is far less than ideal for many individuals, including this particular patient who was actively employed as a salesperson and hoped to resume independent driving. Moreover, diabetes-induced deficits of many other aspects of vision that may not be routinely measured in clinical setting or in studies – such as contrast sensitivity, color discrimination, and dark adaptation – often have even poorer responses to anti-VEGF treatment. This gentleman's case illustrates the remaining limitations of currently-available ophthalmic pharmaceuticals for the treatment of DME and highlights the need for adjunctive interventions. While his experience is an isolated example, I have cared for several other patients with similar success stories using intermittent fasting, restrictive caloric intake, bariatric surgery, or rigorous exercise regimens in the management of type 2 DM who improved their eyesight without ophthalmic intervention. Combined, these anecdotes offer a glimpse into the potential for nutritional and lifestyle-associated adjustments in treating diabetes, including those that ophthalmologists could endorse. Time and again, surveys among patients with diabetes show that the fear of losing vision provides a powerful motive to improve their metabolic control, putting the ophthalmologist in a key position to participate in the holistic care of people suffering from diabetes while simultaneously helping them preserve a cherished form of sensation.

Body Mass and Diabetic Retinopathy

The strongest predictors of DR risk include metrics of plasma glucose concentration and duration of exposure to diabetes.[12] Less consistent

are associations between obesity indicators and risk of DR, with some studies showing positive relationships, others showing inverse relationships, and several failing to find any association at all.

One confounding factor accounting for these inconsistencies are varying definitions of obesity. The most common definition of obesity relies on the BMI. According to the World Health Association, a BMI of >30 kg/m^2 is considered obese, but this cutoff value may not be appropriate for persons from different parts of the world.[13] In certain individuals, for example those from India, China, and Japan, metabolic disease manifests at lower BMI levels. In such groups, better assessments of obesity could include waist circumference (WC) and the waist-to-hip ratio (WHR), since these measurements better reflect abdominal or visceral obesity – a form of excess body weight that is linked to disease. High WC, for example, is one of the five diagnostic criteria for the metabolic syndrome, and is a good predictor of cardiovascular risk among South Asians.[14] Few studies have carefully studied the association of WHR or WC as independent risk factors for DM, but those that have suggest a positive risk relationship.

Second, obesity may have different effects on different types of DM. At least one study suggests that type 2 DM could be classified into three subdivisions.[15] Two of these subdivisions are associated with high BMI, but only one has elevated insulin resistance. A third type involves normal BMI and mild progressive insulin resistance with advancing age. The relative risk of DR between these various subtypes remains incompletely described and inclusion of all such patients into obesity-DR risk studies could mask important effects of obesity in a particular subtype.

Third, few studies have systemically assessed the effects of weight reduction as an intervention on DR risk. Nonetheless, the benefits of weight reduction for cardiovascular health in DM are high and therefore should be advocated for general health. Effects may vary depending on the form of weight reduction used, but here we will review some of the available evidence for these various methods.

Caloric Restriction

Intermittent Fasting

Weight reduction by intermittent fasting has becoming an increasingly popular eating program but was originally described as early as the 1930s.[16] Multiple regimens exist, although a commonly-used one involves time-restricted feeding intervals in which the majority of daily calories are consumed within a several hour period each day (e.g., 16-hour fast, 8-hour feed; or 20-hour fast, 4-hour feed patterns).[17] No cap is placed on the amount of calories consumed during feeding periods, nor are there restrictions on the types of allowable foods in the diet – features that many people find appealing compared to other diets.

Intermittent fasting schemes have demonstrated benefits on cardiometabolic health in clinic settings and on longevity in animal studies.[18] However, the evidence for a specific beneficial effect on DR is limited. Lifestyle changes in general are very likely to prevent the incidence of DR in at-risk groups. In one study that randomized patients with pre-diabetes to a multi-pronged four-year lifestyle intervention regime consisting of 5% weight reduction, caloric restriction, and exercise, the five-year incidence of retinal microaneurysms was approximately 40% lower than in a control group that was not subjected to such intervention.[19] However, no clinical trial to date has specifically tested effects of intermittent fasting regimens on DR incidence or severity.

Preclinical evidence shows that intermittent fasting robustly preserves vision in experimental diabetes and this protective effect may occur through both retina-intrinsic and non-intrinsic mechanisms. In a common mouse model of type 2 DM associated with hyperphagia and obesity, forced intermittent fasting prolonged overall lifespan, reduced retinal capillary damage and lessened leukocytic infiltration into the retina compared to control animals on a standard feeding regimen.[20] An independent study using the same mouse model, showed that intermittent fasting increased the local neuroretinal activity of a protective molecule known as Sirtuin1 – belonging

to a class of molecules that have long been implicated in mediating the protective effects of caloric restriction on mortality.[21]

Carbohydrate Reduction

Other popular modern dietary regimens include the Paleolithic diet and ketogenic diets. The Paleolithic diet is based on the premise that feeding patterns among human ancestors prior to modern agricultural practices are more concordant with our inherited metabolic programs. It stresses the avoidance of grains, dairy, legumes, refined sugars and starches, as well as highly-processed foods. Ketogenic diets (similar to the Atkins diet that gained popularity in the 1980s) emphasize reduction in daily carbohydrate intake, with many plans aiming for 7% or less daily caloric intake from carbohydrate. Essentially, Paleolithic and ketogenic diets are carbohydrate-restrictive and both promote metabolic switching of fuel from liver-derived glucose to adipose-derived ketone bodies, thereby fostering reduction of adiposity. Although sparse, some compelling data exist to support the use of these regimens for metabolic control in DM, with effects on weight loss, improvement in insulin resistance, lowering of blood pressure, and improved serum lipid profiles. There are no available data on their efficacy in DR, although in a case report, a switch to ketogenic diet was associated with spontaneous regression of proliferative DR with traction retinal detachment – a finding that may have some merit since this stage of disease is rarely reversible without intensive ophthalmic intervention.[22]

Bariatric Surgery

Surgery for weight loss, encompassing many procedures such as gastric bypass and gastric band placement, have immense beneficial effects on glycemic control in patients with type 2 DM. Their reported effects on DR are highly mixed, with some studies reporting worsening of DR after surgery.[23] One reason for this observation is the early-worsening phenotype due to rapid correction of glucose following surgery, similar to the phenotype seen in the Diabetes Control and Complications Trial (DCCT) where rapid diabetes control using intensive insulin therapy was associated with transient increases in DR severity. In studies with one year or less follow-up, significant proportions of patients had worsening DR severity.[24,25] Considering studies with >5 years follow up only, far fewer instances of DR worsening are seen.[26,27] Therefore, early worsening of DR severity after sudden correction of glycemia with bariatric surgery could eventually normalize without loss of vision, as was observed in DCCT. A major caveat is that all available studies on bariatric surgery and DR risk are vastly underpowered to make any definitive conclusions.

Exercise

Our bodies evolved to accommodate high levels of physical activity to provide for many basic needs of life, including finding food, procreating, and fleeing from or fighting against threats. As the conveniences of modern society have reduced the need for us to move in order to achieve these goals, our resulting sedentary lifestyles are poorly matched to suit our inherited metabolic programs. Indeed, these lifestyles are a major contributor to common modern diseases, including DM. Exercise – perhaps by restoring the balance between our fuel availability and expenditure – has numerous benefits across multiple axes of health, in patients with or without DM. Potential mechanisms include improved insulin sensitivity, reduced inflammation, and weight loss itself.[28]

Clinical studies examining the relationship of exercise on DR have produced inconsistent results. In WESDR, DR risk was lower in physically-active women with early-onset DM (<30 years old at diagnosis) compared to those who were sedentary.[29] In several cross-sectional and smaller trials, a protective relationship between exercise and DR severity was recapitulated in people with type 2 DM.[30-32] However, both the Pittsburgh study of Physical Activity and Diabetes Complications and the whole-cohort analysis of the WESDR (including those with older onset DM) failed to show any association between exercise and DR risk.[33,34] Finally, although some authors historically advocated for avoidance of exercise in patients with advanced stage DR, such as proliferative disease, due to potential

risks of vitreous or retinal hemorrhage with vigorous activity, the real risks of these events are negligible.[35,36]

At least one potential confounder with many of these studies is that change in body weight was not taken into consideration, either because of the nature of the study design (cross-sectional) or because it was not chosen as an outcome measure. Therefore, it remains unclear whether weight loss from exercise itself has an independent impact on DR risk.

Glucagon-Like Peptide-1 Receptor Agonists

Glucagon-Like Peptide-1 receptor agonists (GLP1-RAs) are a novel class of antihyperglycemic agents used in the management of type 2 DM. Given their impressive effects on glycemic control, they have emerged as a valuable second-line tool in the care of patients with refractory DM. An added benefit to these drugs is their tendency to promote weight loss. The effect was confirmed in a highly-touted clinical trial, with recent approval of one agent for obesity management.[37]

Despite such enthusiasm, fears remain concerning the safety of these agents – specifically in regard to vision. On such GLP1-RA – semaglutide – was associated with worsening DR, with a 76% increase in severe DR complications compared to placebo.[38] These results led to black box warnings, causing worry among patients with DR and their non-ophthalmologist care providers. However, in a subsequent study, escalating doses were not associated with increased DR adverse events.[39] An important limitation is that many GLP1-RA studies recorded DR outcomes based on adverse event reporting rather than dedicated retinal imaging. Reassuringly, a randomized trial that primarily aimed to examine the safety of liraglutide on retinal health failed to reproduce any significant adverse effects in terms of DR.[40]

Based on the combined data, the evidence supports the use of GLP1-RAs for the treatment of type 2 DM with low concerns for detrimental effects on vision. On the contrary, it remains possible that the dual effects of these drugs on glycemic control and weight reduction could impact long-term retinal health positively. Preclinical evidence shows that GLP1 receptors are located within the neural retina and engage neuroprotective programs when activated. Although clinical evidence for an independent and bona fide protective effect on the retina is lacking, I have been an ardent supporter of the use of GLP1-RAs among my own type 2 DM patients with manifest DR who have poor control with metformin alone.

Conclusions

Modern therapy for DR has evolved greatly over the past 20 years but remains inadequately effective for a significant proportion of patients. As outlined in the case above, control of the underlying diabetes can be far more effective for DR than aggressive ophthalmic therapy. While glycemic control can be difficult to achieve in many patients, weight loss strategies could offer powerful tools for metabolic control in a subset of them. Although it is likely that these strategies – including intermittent fasting, carbohydrate reduction, bariatric surgery, exercise, or GLP1-RA treatment – have benefits on ocular health due to improvement in glycemic control, they may have independent effects on the retina – a concept that deserves further attention and investigation.

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Racial Disparities in Glaucoma: From Epidemiology to Pathophysiology

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It is crucial that, as health care professionals and scientists, we thoroughly study and increase our understanding of the underlying epidemiologic factors of socio-economic status, health literacy, cultural sensitivity, and community care influences on disease disparities.



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Abstract

Among individuals of African and Latinx descent compared to those of European background, there is a higher prevalence, earlier onset, more rapid progression of primary open angle glaucoma and greater incidence of blindness. Although some suggest that outreach, education and screening programs may expand earlier diagnosis, and attention to access, cost of treatment, and adherence will improve outcomes, there is increasing evidence of genetic and physiologic differences which may be associated with these disease disparities.

Introduction

Disparities in health care have been repeatedly documented over the last few decades across a broad range of medical conditions. Members of minority groups are more likely to receive lower-quality care than their White counterparts, even following adjustment for income levels, insurance status, and education, as noted in a report from the National Institute of Medicine.[1] An important example of the impact of racial and ethnic disparities on chronic disease includes glaucoma, a leading cause of irreversible blindness worldwide (Figure 1). Glaucoma is a progressive optic neuropathy with a common endpoint of retinal ganglion cell death. Lowering of intraocular pressure (IOP), the only known modifiable risk factor, has been shown to reduce risk of developing glaucoma and progression to vision loss and blindness at all levels of disease severity. Thus, adherence to provider appointments and therapies, both medical and surgical, leads to improved outcomes. However, Latinx and Black patient status represents an independent risk factor for inconsistent follow-up in a glaucoma clinic[2] and lower rates of ancillary glaucoma testing relative to risk, although these rates did improve somewhat from the 1990s compared to a decade later.[3,4] Cost, access, and health literacy issues also contribute to racial disparities of glaucoma. Unfortunately, these were likely magnified by the COVID-19 pandemic. Not only may Black patients be surgically undertreated, but they are also at increased risk for surgical failure. Additionally, the markedly low numbers of Latinx and Black ophthalmologists in the United States (<2%) may negatively impact physician-patient communication and potentially lower patient trust and satisfaction.

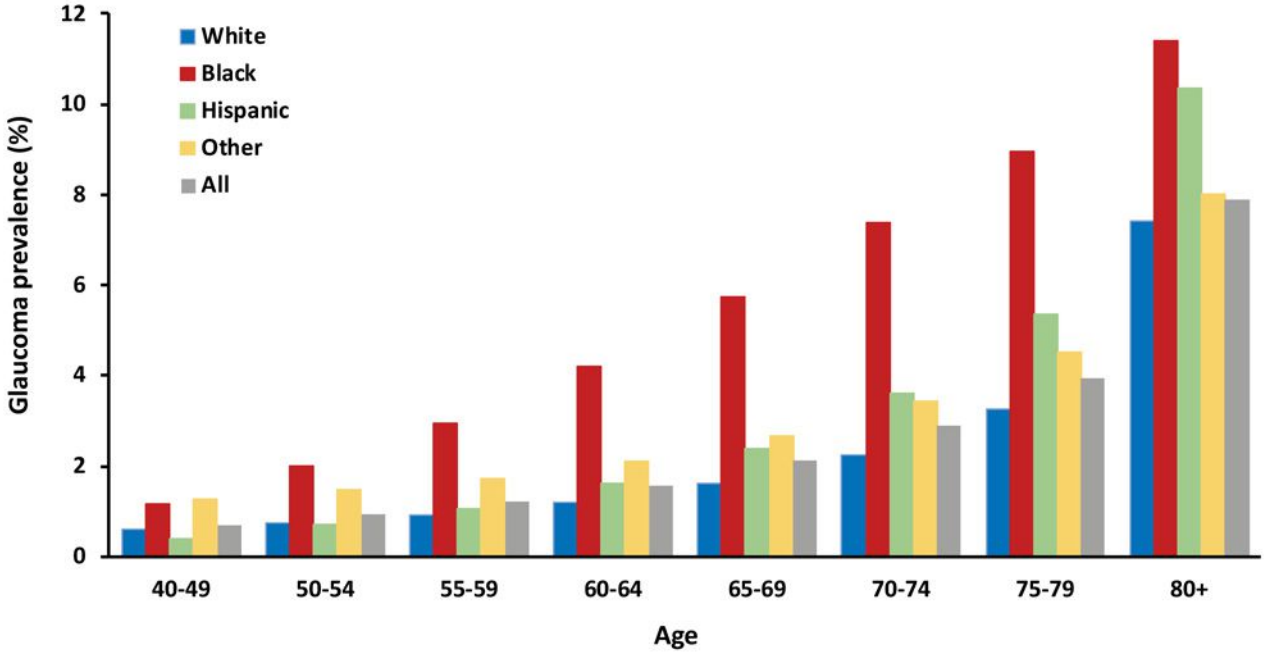


Figure 1. US prevalence rates of glaucoma by age and race in 2010

Source: https://www.nei.nih.gov/learn-about-eye-health/resources-for-health-educators/eye-health-data-and-statistics/glaucoma-data-and-statistics/glaucoma-tables

However, there is more to the story of identification of glaucoma disparities in populations of both Latinx and African descent than solely such socio-demographic factors.

What is Race?

There is no simple definition of race. According to Merriam Webster's dictionary, race is defined as "any one of the groups that humans are often divided into based on physical traits regarded as common among people of shared ancestry." In contrast, ethnicity refers to shared culture, such as language, ancestry, practices, and beliefs. Many individuals in the United States and worldwide have a heterogeneous genetic background of "mixed" ancestry representing a great challenge for binary classification. Race classification by self-report on a patient questionnaire is often used in epidemiological studies.[5,6] Discrepancies in the evaluation of large population studies highlight questions of proper racial stratification. Self-reports are often unreliable and correlate poorly with true racial origins, affecting the genomic assessment of individuals in identifying disease loci and predicting disease outcomes.[7] Accurate identification of ancestral background is critical to truly stratify individuals but is rarely performed in scientific studies. High quality donor DNA may now be utilized to perform genomic ancestral composition detection by microarray analysis. For example, in Missouri, mean African ancestry of self-reported African American (AA) subjects is 75-80%.[8]

Epidemiology

Large, population-based studies have revealed that glaucoma is more prevalent in Black and Latinx populations.[9] In the United States, the Baltimore Eye Survey found that the prevalence of glaucoma in individuals of African descent was six times the levels of the European American (EA) population in some age groups.[10] Primary open angle glaucoma (POAG) is the leading cause of blindness in the AA population, where it is six times more likely to result in blindness than in EA.[11,12] Glaucoma is diagnosed 10 years earlier and shows more rapid progression in the AA population.[13] Ocular hypertension, defined as elevated IOP, is the most important and only modifiable risk factor for the development of POAG. This finding occurs 12 years earlier in the AA population,

with a higher percentage of Blacks progressing to the development of glaucoma.[13] Population-based studies outside of the United States in Barbados, the West Indies and East Africa have also confirmed the high prevalence of glaucoma in those of African descent.[14-16] The precise pathogenesis of POAG has not been fully elucidated as it represents a variety of different pathologies, genetic predispositions and contributing environmental factors.

Vascular Disease Considerations

Patients of European descent have lower risk of systemic vascular complications compared to those of African background. Arterial hypertension and arterosclerotic vascular disease may contribute to ocular vascular compromise, and the higher rates of arterial hypertension and diabetes mellitus in both Latinx and AA patients likely explains an increased risk of stroke and cardiovascular disease. In contrast, the Barbados Eye Study, predominately consisting of patients of African descent, determined that lower systolic blood pressure and systolic ocular perfusion pressure were predictors of POAG progression.[17] Correlations between systolic and diastolic blood pressure with ocular hypertension and glaucoma prevalence are complex and not currently clearly delineated. Associations between diabetes and POAG are also not definitive as studies have shown both increased risk and enhanced protection against the development of glaucoma.[18,19]

Genetic Studies

Despite abundant data indicating increased prevalence and severity of glaucoma in Black subjects, no definitive physiologic differences have been identified to explain these disparities. Genome-wide association studies (GWAS) have identified several genetic mutations linked to glaucoma, yet these currently represent a small percentage of glaucoma cases.[20] Several studies indicate genetic contributions to the risk of developing glaucoma by mapping chromosomal regions associated with dominantly inherited risk of open angle glaucoma, including subjects of African descent in Barbados. However, it is not surprising that glaucoma genetic susceptibility alleles in White subjects may not be integral to risk in those of African ancestry.[21] GWAS studies of AA individuals included in the ongoing Primary Open-Angle African-American Glaucoma Genetics (POAAGG) study[22] are now providing valuable information about family history, gender, and genomic variants in this population.[23]

Similar GWAS studies in the Latinx population have identified multiple genetic variants associated with glaucoma risk factors of vertical cup-disc ratio and central corneal thickness leading to development of genetic risk scores.[24] Causative genetic modifications at these loci have yet to be identified and functions of many genes lying within the mapped intervals are yet unknown. By identifying the physiologic basis of the increased glaucoma risk in individuals of African and Latinx descent, this information could have significant global impact on therapies for this blinding disease. GWAS represent a major advance in genetic research, enabling the assessment of genetic risk factors associated with complex diseases via large-scale, population-based studies. However, GWAS results have limited translational qualities,[25] and functional genomics must be coordinated with this data to fill this knowledge gap to enhance understanding of physiology.[26] Tissue-specific gene expression and protein transcriptional differences may provide additional insights into the pathophysiology of glaucoma. Differential endothelial cell gene expression by AA vs. EA has identified significantly different stress responses between racial groups.[27] This represents an example of how genetic differences may have implications for the role of endothelial cells in addressing racial disparities of vascular disease, diabetes mellitus, cancer, and potentially glaucoma burden in the AA population.

Racial Disparities in Other Diseases May Yield Clues of Biological Differences

Racial disparities exist in several other important diseases, including diabetes mellitus, atherosclerosis, and prostate, colon and breast cancer, with higher incidence and worse prognosis in AA compared to EA individuals. Studies of the molecular basis for disparities in AA men with prostate cancer have revealed differences in androgen receptors, growth factors, and variants of genes of enzymes involved in androgen biosynthesis and metabolism.[28] A recent review identified that ethnic differences of

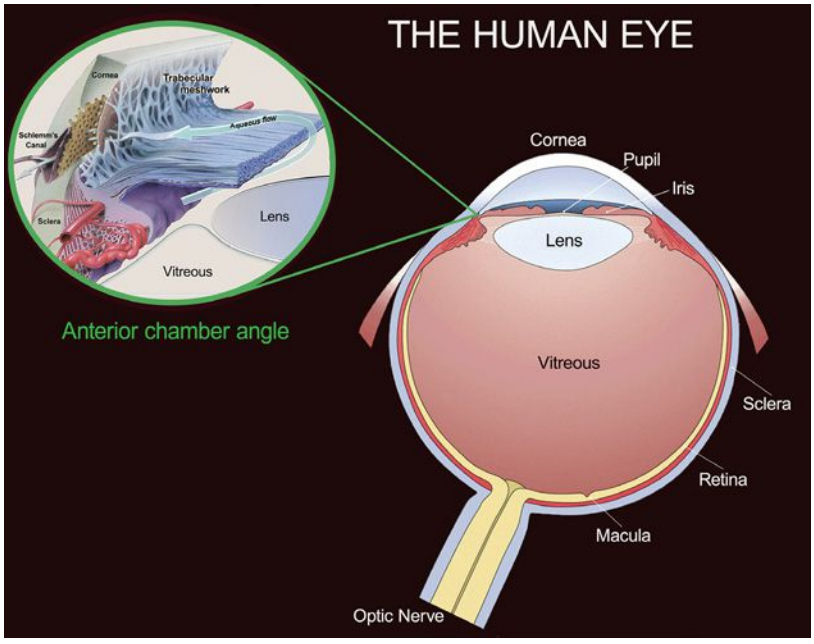


Figure 2. Anatomical image of the eye with focus on anterior chamber angle structures and the aqueous humor outflow pathway.

genetic variations of nuclear DNA encoding mitochondrial proteins may contribute to cancer disparities.[29] Important breakthroughs in genomics, metabolomics and other molecular biotechnologies will facilitate translational research advances to improve our understanding of racial disparities and identification of novel disease mechanisms.

Trabecular Meshwork and IOP Control

The trabecular meshwork (TM) and its specialized cytoskeleton architecture in the anterior chamber (AC) angle are responsible for the drainage of aqueous humor through the conventional outflow system into Schlemm's canal, ultimately flowing into the episcleral venous system (Figure 2). The physiology and regulation of aqueous humor outflow by the TM cells is not fully understood. Neural control, both muscarinic and adrenergic, actomyosin contractile changes, nitric oxide signaling, and mechanosensitive reflexes play a role in IOP regulation and have been or are currently being studied to expand the pharmacologic treatment of glaucoma. Ultrastructural changes in both the TM and the extracellular matrix, important for the maintainance and integrity of these specialized cells, contribute to IOP dysregulation and subsequent glaucoma development.

Oxidative Stress and Glaucoma

Oxidative stress contributes to several systemic and ocular diseases including macular degeneration, uveitis, age-related cataract and glaucoma. As a candidate for its contribution to the pathology of glaucoma, Alvarado et al. suggested that aging and oxidative stress underlie the degeneration of TM cells in glaucoma patients.[30] Subsequent studies provide evidence for oxidative damage and reduced resistance to oxidative stress in the outflow pathway and retinal ganglion cell degeneration.[31] "Oxidative stress" is defined as an increase over physiologic values in the intracellular concentrations of reactive oxygen species (ROS). The unknown source(s) of oxidative stress may be linked to higher molecular oxygen (pO_2) in the anterior chamber (AC) angle that we found in AA eyes compared with EA eyes undergoing cataract and/or glaucoma surgery.[32]

Briefly, an optical oxygen sensor (Oxylab pO_2 optode; Oxford Optronix, Oxford, England) was introduced throught a 30-gauge needle entry track. The tip of the flexible fiberoptic probe was positioned for three measurements in all patients (1) near the central corneal endothelium, (2) in the mid-AC, and (3) in the AC angle (Figure 3). We also discovered a correlation of pO_2 in the AC angle with thinner central corneas, an established independent risk factor for development and progression of POAG.[33] Notably, AA individuals have thinner corneas as compared to EA.[34] The greater oxygen concentration in the aqueous humor outflow pathway may be a source or byproduct of ROS, depleting antioxidant defenses. Its contribution to the risk of developing glaucoma requires further study.[35] Additionally, oxidative damage to DNA is greater in TM cells in glaucoma

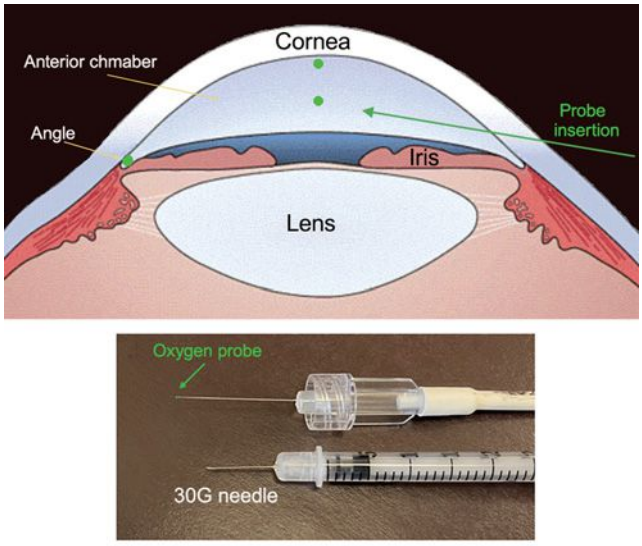


Figure 3. Locations of pO_2 measurements in the human eye in vivo during ophthalmic surgery (upper image) Oxygen probe used for measurements shown with 30G needle for entry through peripheral cornea (lower image)

patients compared to controls and correlates with both IOP level and visual field loss.[36] AA patients have increased levels of systemic oxidative stress compared to EA, following adjustment for differences in cardiovascular disease risk factors and inflammation.[37] However, many studies of oxidative stress do not include or consider effects of diverse racial background as they recruit from EA populations, nor consistently include consideration of sex differences, metabolic disease or smoking history.

Gene Expression in Trabecular Meshwork

As noted above, exploring "deeper" into gene expression and protein composition of tissues may provide greater information of specific disease processes as compared to whole genome analyses. Looking further into this concept of oxidative stress, we evaluated specimens of TM from patients with glaucoma obtained during glaucoma surgery. Assessment by RNA-sequencing identified different levels of gene expression comparing AA and EA patients. Specifically, the most highly significant gene expression differences were identified in genes encoding for mitochondrial elements, with nearly all displaying upregulation in AA subjects compared to EA. Although the mechanism/physiologic consequence of these gene differences is unknown, this finding may help explain differences in oxygen metabolism in AA.[32,38] Upregulation of these key mitochondrial components of oxidative phosphorylation complexes may indicate compensatory mechanisms of mitochondrial dysfunction in AA patients. A complex I defect is associated with glaucomatous TM cell degeneration and complex I mitochondrial gene mutations have been verified in POAG as well as dysfunctional mitochondrial calcium regulation.[39,40] However, racial impact on these findings has not been studied. Our preliminary results suggest that racial differences in mitochondrial protein gene expression profiles may explain differences in oxygen consumption and intracellular ROS metabolism. We continue to explore these findings by studying ATP synthesis, ROS production and antioxidant defense mechanisms in TM cells from AA compared to EA. In this manner, we may verify the significance and therapeutic potential of mitochondrial-targeted antioxidants as novel therapies for glaucoma.

Conclusions

There is strong evidence that both race and social determinants of health and disease greatly impact the prevalence and outcomes for patients with many systemic conditions, including primary open angle glaucoma. It is crucial that, as health care professionals and scientists, we thoroughly study and increase our understanding of the underlying epidemiologic factors of socio-economic status, health literacy, cultural sensitivity, and community care influences on disease disparities. Importantly, we must also rigorously study the scientific aspects of these disease differences of prevalence, rates of progression, and blindness. Both genetic studies of disease risk factors and pathophysiologic mechanisms must include subjects of diverse backgrounds in order to better delineate individual risk and disease mechanisms as we look forward to the development of future precision therapies.

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Disclosure

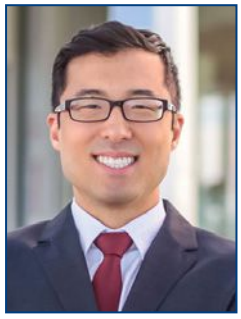
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New Research Aims to Optimize Therapy Against Onchocerciasis

by Augustine R. Hong, MD, Nicholas O. Opoku, Gary J. Weil, MD, Eric M. Kanza, MD & Michael E. Gyasi

Washington University in St. Louis School of Medicine

The quest to discover and test improved treatments for onchocerciasis has been a decades-long journey.



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Abstract

Onchocerciasis is a parasitic disease that is the second most common cause of infectious blindness in the world, affecting 25 million people, mostly in sub-saharan Africa. Mass drug administration (MDA) with ivermectin has been the mainstay of a successful international effort to reduce the burden of vision loss. Despite improvements in infection rates and blindness through MDA with ivermectin, adult worms are not killed or permanently sterilized by this drug and can live for greater than 10 years. Therefore, new treatments for onchocerciasis are critical to accelerating the rate of elimination of this blinding disease. Here we discuss an ongoing study of a new treatment for onchocerciasis.

Introduction

Onchocerciasis, commonly known as "river blindness," is an infectious disease caused by the nematode parasite *Onchocerca volvulus* that is transmitted by the bite of a Simulium black fly that lives and breeds in fast flowing rivers. Onchocerciasis is a common cause of blindness in sub-Saharan Africa. The World Health Organization (WHO) estimates that 25 million people are infected, and that onchocerciasis is the world's second leading cause of infectious blindness.[1] An estimated one million people are blind or have severe vision loss due to onchocerciasis.[2] Many programs have been launched over the last 50 years to decrease the burden of vision loss caused by onchocerciasis. The mainstay of these efforts has been periodic (usually annual) mass drug administration (MDA) of ivermectin (IVM) to affected communities. MDA with ivermectin has proven effective at reducing the global burden of onchocercal blindness.[1,3,4,5] However, infected individuals still require treatment with ivermectin once yearly for 10 to 15 years. Thus, onchocerciasis remains a difficult disease to eliminate. More rapid elimination of onchocerciasis in sub-Saharan Africa depends on development of new therapies that can better sterilize/kill adult worms in endemic areas.





Left: Study clinicians at the School of Public Health, University of Health and Allied Sciences, Hohoe, Ghana. Right: Clinical team members outside of School of Public Health, University of Health and Allied Sciences, Hohoe, Ghana.

Clinical Trial

Faculty members of the Washington University School of Medicine (WUSM) are collaborating with a clinical research team in Ghana on a clinical trial of a new treatment for onchocerciasis. This article focuses on the importance of ophthalmology monitoring for the study. In addition to testing the safety and efficacy of a new treatment, the trial provided us with an opportunity to improve our understanding of ocular disease caused by onchocerciasis through the use of modern imaging technology. Moreover, the trial provided new upgraded equipment, training and facilities to a regional health center in eastern Ghana in order to improve patient care and build capacity for future ocular research on onchocerciasis and other ophthalmic diseases.

The medical treatment for onchocerciasis has evolved in the last half century. Early efforts to control the disease focused on the control of Simulium black flies that carry *O. volvulu*s. Diethylcarbamazine (DEC) was the mainstay of medical treatment until the introduction of IVM in 1987. One downside of DEC was that its use was sometime accompanied with serious adverse immunopathology due to its rapid killing of larval parasites, microfilariae (Mf), in the skin and eyes.[6, 7] Ocular adverse effects included corneal scaring, ocular inflammation, and vision loss.[8] IVM has proven to have a better ocular safety profile and is more effective at clearing microfilariae from the skin and eyes.[6] Thus, mass drug administration of IVM has replaced DEC as the treatment of choice for onchocerciasis. Although IVM is very effective against Mf (which are necessary for disease transmission), adult worms, which can live up to 15 years in the host, are stunned, but not killed, by the drug.[9]

Our study was designed to evaluate the safety and efficacy of a triple drug cocktail comprised of IVM, DEC and albendazole (collectively known as IDA).[10] Although DEC fell out of favor as a treatment for onchocerciasis for many years, scientists became interested in DEC when it was found to contribute significantly to treatment of another related parasite, *Wuchereria bancrofti*, that causes lymphatic filariasis.[9] Several clinical trials demonstrated that the IDA drug cocktail was superior to other treatments for lymphatic filariasis and safe enough for mass use.[11, 12] Because lymphatic filariasis is often co-endemic with onchocerciasis in sub-Saharan Africa, our research team hypothesized that



Performance of slit lamp examination.



Color fundus photography (of left eye centered on the macula (m) of a participant with small yellowish drusen (d) and chorioretinal scars (crs) not affecting central vision. OCT scan shows normal retinal architecture and sparing of the fovea.

the administration of IDA in co-endemic areas might be a cost-effective solution to both diseases.[10] Our team also was interested in knowing whether IDA is more active against adult *O. volvulus* worms than ivermectin alone. Since ivermectin clears Mf from the skin and eyes of patients with onchocerciasis, we hypothesized that IDA might be safe to use in patients with onchocerciasis if parasite loads in their skin and eyes were greatly reduced by pretreatment with ivermectin.

Modern diagnostic imaging of the eye is revolutionizing evaluation of ocular disease and the changes that occur in the eye in response to new therapies. While many diseases of the anterior segment of the eye are readily identified by slit lamp examination, a technique that has been around for decades, multiple new techniques are now available for improved imaging of the posterior segment of the eye. Optical coherence tomography (OCT) is a newer imaging modality that is now the gold standard for evaluation of many retinal and optic nerve diseases. This accurate, quick, safe, and non-invasive imaging technology captures three-dimensional cross-sectional scans of both the anterior and posterior structures of the eye with high resolution.[13] The clinical trial that we carried out in Ghana that evaluated a new treatment strategy for river blindness (described in detail below), was the first to employ OCT technology to evaluate the optic nerve and retina in patients with onchocercal eye disease, including the use of this technology to monitor for ocular adverse events related to therapy.

Trial Method and Challenges

In Ghana, we performed an open label, randomized clinical trial for the treatment of onchocerciasis. Participants with onchocerciasis were randomized into three treatment arms: i) IVM with albendazole; ii) a single dose of IDA; or iii) three daily doses of IDA. Our primary safety objective was to compare rates and types of adverse events due to dying Mf as a result of treatment. Study participants in all three arms were pretreated with IVM to reduce Mf counts in their skin and eyes. Our primary efficacy objective was to compare the effect of the three treatment regimens for killing or sterilizing adult female *O. volvulus* worms that live in subcutaneous nodules.

The logistical challenges that we faced in executing this study were formidable. Participants were recruited from an endemic region in the Volta region of eastern Ghana. The clinical trial was performed in facilities on the campus of University of Health and

Allied Sciences (UHAS) School of Public Health in the small city of Hohoe (a four-hour drive south of the patient recruitment zone). Large vans shuttled study participants between these sites. Following administration of the IDA therapy or IVM with albendazole, study participants remained onsite at Hohoe in a comfortable housing facility for one week before being transported back to their homes. General physical exams as well as full ocular exams were performed both before therapy, and at three days, seven days, and three months after treatment, in order to carefully assess study patients for the onset of adverse events.

It was important to establish trust between researchers and study patients. Participants spoke Konkomba and/or Twi, and most needed to communicate with study staff through an interpreter. Although the UHAS team had worked in the study area before, local community leaders were critically important for establishing relationships with study participants.

The UHAS research center is well-recognized for its long history of clinical research on onchocerciasis. New equipment was flown in from the U.S. to Accra, Ghana, and installed in redesigned examination rooms in Hohoe. Internet connections were upgraded. A testing room was outfitted with a digital fundus camera, LED slit lamp with a smartphone camera adapter, indirect ophthalmoscope, portable slit lamp, and an OCT instrument. Equipment for visual field testing was already on site. In order to protect electromagnetically sensitive equipment, the examination room was renovated to provide a stable and safe source of electricity. On-site technical assistance from equipment manufacturers was unavailable; all troubleshooting was performed over the phone between local research team members and support staff in Germany and the U.S.

As an exploratory safety trial of a new treatment regimen, it was important to identify and exclude patients with severe baseline eye disease from the study. Because DEC can cause severe ocular adverse events in patients with onchocerciasis, we did not want to further compromise the ocular health of patients with pre-existing severe ocular disease. Rigorous review of imaging data and documentation was also used to monitor for adverse events following treatment. Two ophthalmologists, one at WUSM and one in Ghana, were assigned to review data files and ophthalmology exam documentation, including FDT visual fields, OCT scans, retinal fundus photos, and slit lamp photography. Assessments between reviewers were compared and any ocular adverse events or concerning findings by examiners or reviewers were promptly communicated to the study group. Researchers from Africa and the U.S. also worked together to troubleshoot problems related to equipment and data management. Large data files (encrypted and de-identified) were transferred between investigators via a secure cloud-based server.

Capacity building and collaboration with local ophthalmic providers and staff was critical to ensure a high quality of standardized ocular examinations for this study. Prior to any patient enrollment, didactic and hands-on training sessions were attended by all team members. This involved technical instruction and practical experience using the slit lamp and imaging equipment. During enrollment, quality and safety measures included regular site visits, training sessions, virtual meetings, regular electronic communication, and proofreading of images. The final result was an advanced clinical center carrying out a very rigorous schedule of screening and follow-up exams.

The emergence of COVID-19 during enrollment posed an unexpected challenge to this study. Although the incidence of COVID-19 in the Volta region of Ghana was low during our study, the project was suspended for two months. Ethical review committees in Ghana approved resumption of the study based on modified protocols that included social distancing measures, personal protective equipment, and enhanced sanitation procedures. The study adhered to World Health Organization and Ghanaian national public health directives. We are not aware of any study patient who acquired COVID-19 related to their participation in our study.

Successful completion of this clinical trial was challenging due to inclement weather, poor road conditions, travel restrictions, data transfer issues, and of course the COVID-19 pandemic. However, 154 participants were enrolled, and they completed three-month safety evaluations. No excess adverse events were observed in persons treated in either IDA arm compared to those treated with the reference treatment ivermectin plus albendazole. The study is now in the follow-up phase, and efficacy evaluations (based on examination of adult worms in nodules surgically excised from participants) will be completed in early 2022.

Conclusion

The quest to discover and test improved treatments for onchocerciasis has been a decades-long journey. Our data to date suggests that IDA can be safety administered to onchocerciasis patients in carefully controlled conditions after ivermectin pretreatment. If the triple drug regimen turns out to be more effective than ivermectin plus albendazole, it will provide a new tool in the fight to eliminate lymphatic filariasis and onchocerciasis in Africa.

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Disclosure

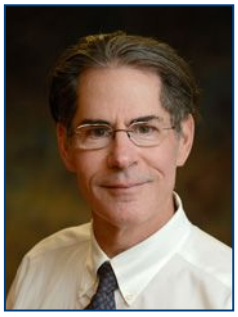
This work was supported by an unrestricted grant to the John F. Hardesty MD Department of Ophthalmology and Visual Sciences from Research to Prevent Blindness. This study was funded by a grant from the Bill and Melinda Gates Foundation (OPP1190749).

MM

Refractive Surgery for Special-Needs Children with High Myopia

by Lawrence Tychsen, MD

What we know to date is that select children in need can benefit substantially from refractive surgery.



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Abstract

Refractive surgery is useful in children with high isoametropic or anisometropic myopia who are aversive to spectacles or contact lenses. The majority have a neurodevelopmental disorder and the equivalent of legal blindness before surgery. Correction of myopia < 6 Diopters (D) is achieved by photorefractive keratectomy (PRK). Those with myopia > 6 D benefit from phakic IOL implantation, clear lens extraction (CLE), or refractive lens exchange (RLE). The rate of adverse events is low.

Introduction

Refractive surgery is an innovation useful for treating special-needs children.[1] For some it is the only cure for functional blindness, and for others it is an effective way to boost treatment of amblyopia. Summarized here is work from our group at Washington University Medical Center/St. Louis Children's Hospital and that of other investigators. A general strategy is outlined, with explanation of the benefits and risks in pediatric eyes.

Children with Anisometropic Myopia Who are Spectacle Aversive

These children are suitable for refractive surgery if compliance with spectacles is poor and the anisometropia is amblyopiogenic. Poor compliance can be defined as wearing glasses 25% or less of the time during waking hours. Amblyopiogenic magnitudes of myopia are in the range of ~ 3-4 D.[2,3] The prevalence of any amblyopia (defined as ≥ 2 optotype lines difference between the eyes) in preschool children who have > 1 D of anisometropia is 66%. The prevalence of moderately severe (≥ 4 lines difference) amblyopia is 38%. Children with higher magnitudes of anisometropia have higher prevalence and greater depth of amblyopia. The prevalence and depth of amblyopia also increases with duration (i.e. age). At each level of anisometropia, older preschoolers have more amblyopia than younger preschoolers. [2]

The majority of anisometropic children do well in glasses. A minority can be managed with a contact lens. But a substantial fraction will not wear glasses and are unsuitable for contact lens wear. These special-needs children include anisometropes with neurodevelopmental disorders, and neurologically-normal children who reject standard correction. Intolerance in some is attributable to spectacle-induced aniseikonia and aniso-vergence, with chronic asthenopia or diplopia. [4,5] For other special-needs children and

their parents the glasses may represent a social stigma subjecting the child to ridicule. Contact lenses may not be a practical option. Contacts can be difficult to insert and remove, frequently lost, irritating to the eye, or too costly. In these anisometropic amblyopic children, refractive surgery is indicated.

Children with Myopic Isoametropia Who are Spectacle Aversive

The typical child treated in this category has bilateral spherical-equivalent myopia exceeding ~ 4-5 D. The uncorrected myopia equates to a distant acuity of 20/200 or worse (legal blindness).

A number of neurodevelopmental disorders impede spectacle wear. The most common are: cerebral palsy (i.e. Gross Motor Function Classification Scale levels 3-5),[6] autism spectrum disorder (ASD), Angelman syndrome, Down syndrome, and seizure disorders and other encephalopathies.[1] The uncorrected ametropia tends to aggravate the neurobehavioral disorder. The child experiences a cocoon of blur, promoting fearfulness, reduced interest in their environment, and blunted social interactions (a constellation labeled "visual autism."[7,8] The extreme myopia may be one of several visual deficits. Co-morbidities include: strabismus, amblyopia, optic neuropathies, foveopathies, and nystagmus.[1] Co-morbidities do not mean that the refractive error is unimportant or that correcting the error would not improve visual function. Too many ophthalmologists—after examining a child with an intimidating array of neurobehavioral and visuomotor deficits—assume mistakenly that correcting the myopia is unimportant. The myopic blur is dismissed as "good enough for a child with multiple handicaps."

Why is prescribing glasses ineffective? Many of these children are aversive to wearing head or facial appliances. They dislodge glasses repeatedly, despite heroic efforts to enforce compliance on the part of parents, teachers, therapists, and care-givers. If the battle is won to keep the glasses in place, the benefit may be negated by poor motor control of the head, neck and trunk, or gaze palsies and apraxias. [6] The motor-control disorders cause chronic viewing over, around or at the edges of spectacle lenses. Contact lenses are seldom an effective option. Insertion and removal may require bodily restraint by multiple family members and vigorous eyelid manipulation to overcome intense blepharospasm. Repeated rounds of this exhaust – physically and emotionally – even the most committed parents.

Surgical Techniques

The surgical techniques, goals, pre- and post-operative care employed for refractive surgery in adults require adaptations for children. Obtaining the pre-operative quantitative information needed often requires multiple sets of measurements by examiners skilled in the examination of uncooperative children, supplemented by a confirmatory set obtained during a brief examination-under-anesthesia (EUA). The surgical techniques used, from least-to-most invasive, are: photorefractive keratectomy (PRK) using the excimer laser;[9-12] implantation of a phakic intraocular lens (IOL);[13-15] and clear lens extraction (CLE) with or without insertion of a posterior chamber IOL (RLE, refractive lens exchange).[7,16]

Following is the strategy we have found most effective. Children with refractive errors - 3 to 6 D are treated using PRK. Children with refractive errors beyond this range, who have corneal diameter > 10.8 mm and anterior chamber depths ≥ 3.2 mm, receive a phakic IOL. The remainder usually require CLE/RLE. All surgeries are performed under brief general anesthesia, with the average operating time 30 to 40 minutes. All of the procedures are outpatient (day) surgeries with children discharged home an average 90 min after surgery.

Photorefractive Keratectoy

After induction of general anesthesia and placement of a laryngeal mask airway, an EUA is carried out for tonometry, slit lamp bio-microscopy, pachymetry, anterior chamber depth and axial length measurement using immersion ultrasound, keratometry, corneal diameter and indirect ophthalmoscopy of the retinal periphery. The child's head is positioned with a pneumatic pillow so that the orbital rim is orthogonal to the axis of the laser beam. A mixture of lidocaine/20% alcohol is applied to the cornea and the epithelium is removed using an automated rotatory brush. Laser auto-tracking is employed (Alcon/WaveLight Allegretto EX500, Fort Worth TX) to negate minor respiratory-related oscillations of the head, with laser centration on the pupil. Following laser ablation, a plano bandage

contact lens is applied to the operated eye(s), and disposable goggles are fitted.

As in adults, the corneal epithelium heals in 3-6 days.[9,17] Topical drops are instilled beginning the first post-operative day. Children tend to tolerate the discomfort and photophobia better than adults, resuming normal play. About 10% will require per oral narcotic analgesia for the first 48 hours. For post-operative awake exams in the office, an adequate view of the healing cornea(s) often requires restraint and use of a portable slit lamp. Despite the best efforts of parents, ~20% of children can be expected to dislodge the goggles, rub and poke their eyes, and lose the contact lens in which case the surgeon's staff reinserts a new bandage lens.

Phakic Intraocular Lens

The implant we have preferred to use for the last five years is the foldable, sulcus-positioned intraocular collamer lens (Visian ICL, Staar Surgical, Monrovia CA).[14] In the 10 years preceding the introduction of the Visian ICL, we used the PMMA iris-enclaved myopic (Verisyse) lens supplied in the U.S. by Ophtec Inc. (Boca Raton FL).[13] Precise sizing of the ICL requires accurate white-to-white measurement of corneal diameter. In cooperative children this can be achieved using the Nidek IOL Biometer or IOL Master. Alternatively, the measurement is performed using digital calipers during a planning EUA. Proper vaulting of the ICL in the posterior chamber – between the anterior surface of the crystalline lens and posterior surface of the iris – and lower long-term risk for corneal endothelial cell loss, requires a corneal diameter 10.8 mm or more and an anterior chamber depth ≥ 3.2 mm. An iridotomy is created during the procedure to circumvent pupillary block ocular hypertension. In cases of high bilateral ametropia, the eyes are implanted sequentially, with several days to a week elapsing before operation on the second eye. Because children's eyes heal rapidly, a superior 3.2 mm clear cornea incision can be employed, which achieves the therapeutic effect of a relaxing limbal incision. Common with-the-rule, pre-operative astigmatism is reduced by ~50%. If pre-operative astigmatism exceeds 2.5 D, a myopic-toric ICL is implanted. Absorbable 9-0 polyglactin sutures are used to close the corneal incision, avoiding re-anesthetizing the child for suture removal. In some children, to prevent eye rubbing, arm restraints will need to be fitted for the first several post-operative weeks.

Clear Lens Exchange-Refractive Lens Exchange

For children with myopia exceeding 16 to 24 D (the upper limit for ICL or Ophtec phakic IOL power, respectively), corneal diameter less than 10.8 mm, or anterior chamber depth less than 3.2 mm, CLE/RLE is required.[7,16] Standard pediatric lensectomy, posterior capsulectomy and pars plana vitrectomy techniques are employed, using a high-speed 25 gauge vitrector and separate anterior chamber infusion. If needed to achieve emmetropia, a foldable, acrylic IOL (Alcon SA60AT or MA60) is injected into the capsular bag – depending on axial length and lens power calculations. A primary capsulectomy/anterior vitrectomy is advisable because of the high rate of formation of dense, posterior capsule fibrosis in pediatric eyes when the capsule is preserved. We perform an EUA a few weeks to a month before the planned lensectomy. The peripheral retina is examined in detail by depression. Accurate, immersion axial length measurements are obtained. If the axial length exceeds ~29 mm, barrier diode laser therapy may be applied to reduce the risk (estimated ~2 %) of future, aphakic/ pseudophakic retinal detachment.[18,19]

Visual Acuity and Quality of Life Improvements

The measure of effectiveness in children non-compliant with spectacles is uncorrected visual acuity (UCVA). Work from our group, and that of other investigators, show gains in UCVA using either PRK, phakic IOLs, or CLE/RLE. Impressive gains are achieved in bilateral ametropes.[7,8,13,14] Modest but consistent gains are achieved in the amblyopic eyes of anisometropes.[9-12,16]

In children with bilateral ametropia averaging 7.1 D (and visuomotor co-morbidities)—treated using PRK—the average UCVA gain was 13-fold. [8] From a mean visual acuity of 20/810 to a mean 20/60 after therapy. In the subset of these children who would wear glasses during testing, the gain in best-corrected visual acuity (BCVA) was an average of 2-fold. In children with ametropia averaging 15 D, treated by phakic IOL implantation, the average UCVA gain was 60-fold. [13] From a mean visual acuity of 20/3400 to a mean 20/57

after therapy. The average BCVA gain was 2-fold. Similar UCVA (100-fold) and BCVA gains have been reported in children with bilateral ametropia, averaging 19 D, treated by CLE/RLE.[7]

Most reports on pediatric refractive surgery have described using PRK to treat anisometropic amblyopia.[9,20,21] These case series show a reliable response, i.e. initial correction of large refractive error to ± 1.5 D of emmetropia in ~90 % of treated eyes. The gains in UCVA or BCVA range from mild to excellent (2 to 7 lines improvement), with no reported losses of acuity. One-half or more of the children treated have improved binocular fusion and stereopsis.

Beyond the gains measured in office testing of acuity or binocularity, refractive surgery has also been shown to have positive effects on children's day-to-day visual function.[13,14] Enhanced visual awareness, attentiveness, and social interactions have been reported in ~80% or more of children treated for high bilateral ametropia. When measured using Likert-scale visual function questionnaires[22] before and after refractive surgery, scores for eye contact, tracking, finding and avoiding, judging depth and distance, and reading improved by an average of 73% in bilateral ametropes and 58% in anisometropes.[13]

Adverse Events in Pediatric Refractive Surgery

Complications reported after pediatric refractive surgery have been low. This in noteworthy in that the majority of children treated are difficult to manage and examine due to neurodevelopmental disorders. The caveat is that follow-up in the majority of studies has not extended beyond several years.

Photorefractive Keratectomy

PRK is safe in children, if safety is gauged as a negligible rate of sight-threatening complications.[21] LASIK (laser-assisted in situ keratomilieusis) has been employed in older children,[23,24] but PRK is the preferred method—in children of any age—for important reasons. Trauma-induced displacement of a LASIK flap is a serious, potentially permanent, sight-threatening complication.[25] Children cannot be trusted to avoid eye rubbing, and children's behavior and activities entail a high probability of some eye trauma. By avoiding creation of a 160-200-micron thick flap, PRK permits treatment or re-treatment of higher levels of ametropia than LASIK. PRK leaves a thicker bed of untreated stroma for greater corneal integrity. Children also tend to be less bothered by the discomforts associated with healing after PRK, and they neither demand nor expect immediate restoration of clarity. For all of these reasons, in pediatric eyes, there is little to be gained and more to be lost by use of LASIK, when compared to PRK.

The biggest downside to PRK, or any photoablation technique in the pediatric eye, is the higher rate of refractive regression. [9,26,27] Seldom is this due to increasing axial length. After age 2-3 years, axial length changes tend to be minor in highly myopic phakic pediatric eyes. [7,8] The high rate of regression is attributable to the enhanced healing properties in young eyes, e.g. keratocyte-mediated regrowth and epithelial hyperplasia. Average regression is ~0.6 D/year. It is unclear when the regression stops or plateaus. From our own work we estimate five to eight years post treatment. For myopic children with treatment beyond 10 D, the regression may be 33% over a span of ~3 years.[26] Application of topical corticoseroid drops (e.g. fluorometholone 0.25%) and use of oral vitamin C for up to one year after surgery may reduce regression. Mitomycin 0.02% can also be applied during surgery to inhibit regression.[28,29] To help counteract regression, treatment nomograms for pediatric PRK may require deliberate over-correction. For myopic children age 10 years or younger, 1-2 D overcorrection may be useful.

Phakic Intraocular Lens

Phakic IOL implantation is not subject to significant regression and may be considered the preferred method currently for surgical correction of pediatric myopia beyond the range of PRK. The anterior chamber depth required for an iris-enclaved IOL precludes the use of this lens in many children under age three years. Children who have high lenticular myopia after retinopathy of prematurity may also be unsuitable because of their shallow chambers due to arrested anterior segment growth.[30] The major concern with use of any phakic IOL in a child is the long-term effect on the corneal endothelium. Experience to date indicates that endothelial cell loss is no greater than that reported in adult implantation.[13,14] However, accurate endothelial cell counts are difficult to obtain in the children who may benefit most

from implantation. It is important to note that any refractive surgery procedure, including PRK or CLE/RLE, can be expected to cause some reduction of endothelial cell density. What we do not know currently, and need to know is the comparative loss. Posterior-chamber phakic IOLs, notably the Visian ICL, have also been implanted in children. Our group at Washington University has reported the largest number of implanted Visian ICLs. The rate of adverse events has been remarkably low. [13,14,30]

CLE/RLE

This is the only option for highly myopic children with shallower anterior chambers who are beyond the range of effective PRK treatment, and who have corneal diameters and/or anterior chamber depths too low for phakic IOL implantation. Removing the lens abolishes the ability to accommodate. The major long-term risk is retinal detachment, with an estimated prevalence of ~3 %. [18,19]

Conclusion

The majority of children with high myopia – unilateral or bilateral – do well with glasses or contact lenses. But a minority do not. Pediatric refractive surgery fills an important need for this minority. The surgery deserves careful study of benefits and risks, and reporting of successes and failures. What we know to date is that select children in need can benefit substantially from refractive surgery.

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Stem Cell Therapies for Intraocular Disease

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In this era of exploding knowledge and new technologies, our role as advisors is even more critical. Physicians are entrusted with sifting through the onslaught of new information and distilling the information down to understandable advice.



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Abstract

Irreversible blindness resulting from retinal or optic nerve diseases continues to devastate patients. The use of stem cell technology to reverse blindness promises great individual and societal benefit. Stem cell therapies seek to replace or enhance the function of damaged tissues. Currently, there are no FDA approved and commercially available products in this arena. Numerous clinical trials are underway, but as of today, we are still awaiting rigorous study data. Meanwhile, physicians and patients are desperate to restore vision and are lured to clinics claiming success. It remains our duty to vet these claims and guide our patients with their best interests in mind.

Introduction

In the future, stem cell therapies may become a mainstay for degenerative diseases of the eye. These therapies are currently being designed, developed, and evaluated in animal models and in some cases, early clinical trials. The promise of such interventions has encouraged the development of "ocular regenerative medicine", a field which takes advantage of both the relative accessibility and immune privilege of the eye.

As any developing field grows, often there are advances and setbacks. This is certainly true in the area of ocular regenerative therapies. As we learn more about the benefits and risks of stem cell-based treatments for ocular disease, regulatory institutions will need to ensure both efficacy and safety of the proposed therapies while still encouraging innovation. This article reviews the current status of intraocular stem cell interventions, as well as some critical precautionary advice. Why? Because we need to be very critical of the state of the field as we attempt to help our patients understand the landscape and prospects for the use of stem cell therapy in the management of ocular disease. As most of the public is aware there already have been instances of misguided physicians who have attempted to side step FDA guidelines on stem cell therapies and put patient safety at risk.

The promise of ocular regenerative medicine derives from the ability of stem cells to differentiate into function-specific cells. In the eye, this means using stem cells to replace tissues damaged by degeneration, trauma or ischemia. In the posterior pole of the eye this means replacing damaged cells in the retina, retinal



Figure 1. Normal Retinal Appearance

pigment epithelium, and optic nerve. Less obvious, but of possible great value, is the regenerative potential for stem cells to replace supportive tissues, such as glial cells, which are critical for the normal structure and function of the retina and optic nerve (Figure 1.)

Types of Stem Cells

One type of stem cell, the pluripotent stem cell, has possibly the greatest potential for the field of ocular regenerative medicine. Pluripotent stem cells are dividing and differentiating most actively during embryonic development, but also in tissues that continually replenish, such as the corneal epithelium. Leveraging the ability of embryonic pluripotent stem cells to develop into numerous tissues would be a natural start when considering tissue replacement therapy. One can think of the use of pluripotent stem cells as using a forward-moving development process to induce cell proliferation into the tissue of interest. Another method for ocular regenerative medicine is to coax partially differentiated cells backward in their developmental lineages and then redirect them onto a different pathway to the desired end tissue. De-differentiation is frequently accomplished through the use of Yamanaka factors, the transcription factors Oct-3/4, Sox2, KLF4 and cMyc. In contrast to embryonic stem cells (ESC), induced pluripotent stem cells (IPS) are derived from mature tissues such as skin or bone marrow that have been treated with the Yamanaka factors. If IPS are harvested from a patient, manipulated for transplant, and re-injected into the donor in an autologous manner, the donor is unlikely to need immunosuppression. However, there is the theoretical risk that these manipulated cells may demonstrate unchecked growth or tumor formation.[1, 2]

Trials, Methods and Targets

Researchers are testing multiple methods of stem cell delivery for patients with sight threatening diseases. A search of clinicaltrials.gov revealed 150 clinical trials of stem cell-based therapies for eye diseases ranging from dry eye to immune-related retinopathy. Twenty-eight of these trials are currently recruiting patients, 18 in the United States. The remainder of the trials are in various states such as completed, paused, terminated, withdrawn, or suspended. Trials for stem cell treatment of posterior eye disease include approaches to treatment of Age-Related Macular Degeneration, Ischemic Optic Neuropathy, Glaucoma, and Diabetic Retinopathy.[3] (Figure 2 and 3) Stem cells have been delivered to study eyes by multiple routes, including intravenous and intraocular injections.

Most clinical trials for the treatment of ocular disease with stem cell therapies have been small, designed to demonstrate feasibility and safety. Some have used patient derived bone marrow CD34+ and mononuclear cells, extracted and then re-injected in an autologous manner. In trials using autologous cells conducted by Park and Siqueira to treat retinal vascular occlusion, nonexudative age related macular degeneration, retinitis pigmentosa, or rod-cone dystrophy, 11/11 patients did not develop serious complications. However, the patients also failed to have any functional recovery of vision, perhaps due to the advanced course of the disease.[4, 5]

Intra-ocular therapies in development have been primarily directed at restoring retinal ganglion cells (RGC), retinal pigment epithelial cells (RPE), and photoreceptors. RGCs, the innermost cells of the retina that project to the thalamus through the optic nerve, do not naturally replicate or regenerate. One approach to regenerate these cells has been to induce retinal Mueller cells, a type of glia, to differentiate into RGCs when driven by the proper cytokine stimulus. However, harvesting, differentiating and properly integrating these cells back into the retina has proven to be challenging.

In contrast, work has moved more rapidly on the therapeutic use of mesenchymal stem cells. When injected into the eye these stem cells appear to play a neuroprotective role for existing RGCs, a different approach than trying to replace diseased RGCs. These fibroblast-like stem cells found in blood, adipose, and

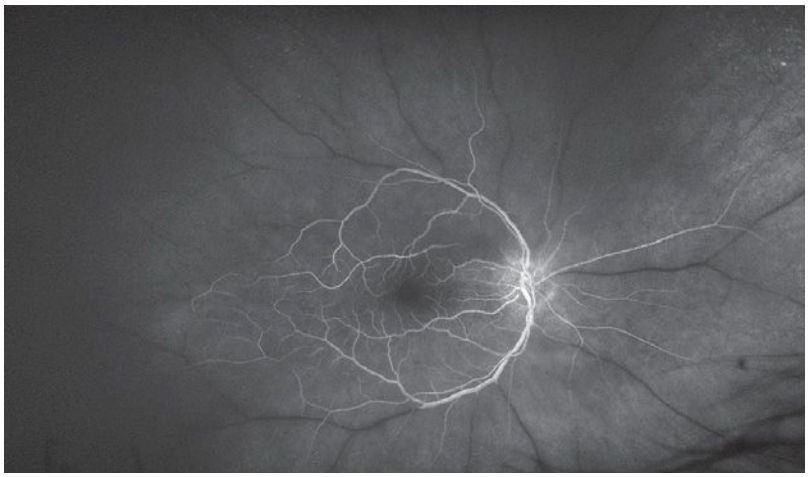


Figure 3.
Fluorescein angiography demonstrating massive non-perfusion of retinal vessels due to central retinal artery occlusion. White dye is seen only in patent, perfused area of the retina.

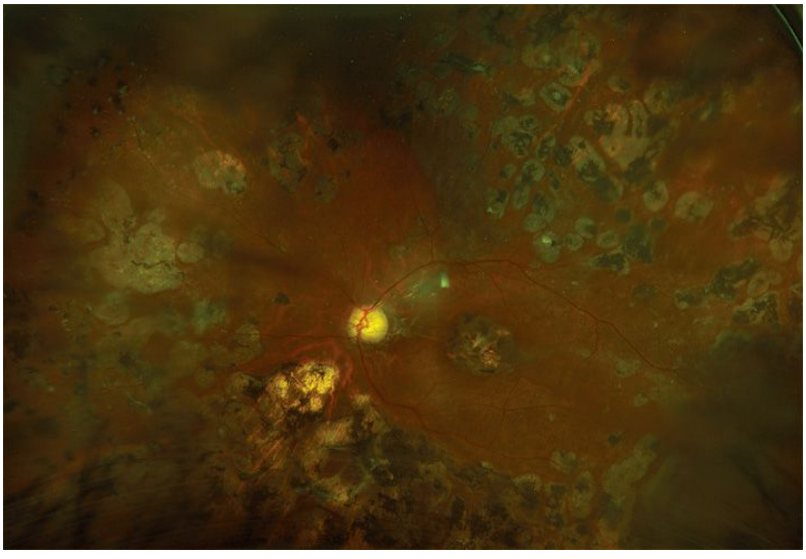


Figure 2. Massive retinal destruction from laser therapy for proliferative diabetic retinopathy.

bone marrow appear to produce factors that protect existing RGCs from immune-mediated inflammation as well as possibly inducing proliferation of retinal stem cells.[6-8]

The interaction between RPE and photoreceptors is essential for visual function. Damaged RPE occurs in Age-Related Macular Degeneration and RPE dystrophies, such as Stargardt disease. Subretinal transplantation of pluripotent stem cells to treat these diseases may be possible, and several small phase 1 trials have been performed demonstrating safety of this approach.[9-11] Most of these studies have looked at delivery of cell suspensions, however, placement of sheets of cells into the sub-retinal space may prove to be more effective in preserving tissue architecture and perhaps allow better integration of the stem cell derived tissue into the retina-RPE complex. [12, 13]

Damaged photoreceptors do not regenerate and are affected in Age-Related Macular Degeneration, diabetic retinopathy and degenerative conditions such as Retinitis Pigmentosa. Photoreceptors may be easier to restore than other retinal cells in that the regenerated cells probably need to make fewer functional connections. Several studies demonstrate the feasibility of total thickness pluripotent stem cell retinal sheets or subretinal photoreceptor progenitor cells.[14, 15]

FDA and Innovation

While a number of small, controlled studies of stem cell therapies for retinal disease have been carried out demonstrating some degree of safety under very tightly regulated conditions, the concept of stem cell therapy has become part of the popularized regenerative medicine industry, with internet communication enabling an explosion of online marketing of unproven treatments.[16] As we await more evidence-based therapies, we rely on advice and oversight of the FDA. The FDA states that it is "responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices…FDA is responsible for advancing the public health by helping to speed innovations that make medical products more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health."[17]

A Cautious Approach Is Needed

There is enthusiasm for the therapeutic potential of stem cell technology, especially for degenerative diseases. While the FDA will regulate the use of stem cell therapy

to ensure both safety and efficacy, the use of autologous stem cells to regenerate damaged tissue may not fall under the regulation of this agency.[18] For example, the FDA may not have jurisdiction over treatment of autologous materials that are harvested and re-implanted as part of the same procedure. The desire to improve a patient's vision is understandable, but when approved therapies are not readily available for a given condition, desire may turn to desperation. Several high-profile cases of stem cell therapies for ocular disease have left patients with serious complications. In these cases, stem cells were injected intravitreally, resulting in scar formation, tractional retinal detachments, and vision loss.[19] In 2017 The FDA clarified its rules in an effort to help companies comply with Federal regulations. Enforcement of these rules was delayed to allow companies the opportunity to comply. In July of 2020, the FDA extended this enforcement deadline to May of 2021 due to the COVID-19 public health emergency.[20] According to this notice, the intention was never to "provide cover to bad actors," and the FDA continues "to take action against manufacturers and health care providers who are offering unapproved regenerative medicine products that have the potential to put patients at significant risk".

Conclusion

The promise of restored eye function based on these new technologies is alluring. To attain this goal, we need to evaluate new therapies in well-run and regulated clinical trials with appropriate ethical and safety reviews. These tenets of modern clinical trials may seem obvious; however, they cannot be stressed enough, especially when caring for people with debilitating diseases for which cures are not readily available. The desperation and fear that these patients experience is a set-up for the unethical profiteer. In this era of exploding knowledge and new technologies, our role as advisors is even more critical. Physicians are entrusted with sifting through the onslaught of new information and distilling the information down to understandable advice. To this end, the doctor must keep the source of information sacred, question all methods and the conclusions derived from published information, and vet any clinical trial open for enrollment before endorsing participation by the patient. Our role in this has not changed, whether it is FDA approved therapies or alluring but as of yet unproven, stem cell therapeutics.

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Monounsaturated Fat vs Saturated Fat: Effects on Cardio-Metabolic Health and Obesity

by James J. DiNicolantonio, PhamD & James H. O'Keefe, MD

The intake of foods higher in monounsaturated fats compared to foods higher in saturated fat may reduce body weight, body fat and insulin resistance when consumed on top of a diet moderate to high in carbohydrates.





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Abstract

For over 40 years saturated fat, the fat found primarily in animal foods, was thought to be the main culprit for increasing cholesterol levels and causing heart disease. During this same time vegetable oils were promoted as being heart healthy because they could lower cholesterol. However, recently the evidence implicating saturated fat as being harmful to heart health has been challenged and more studies are beginning to show the harms from consuming industrially produced vegetable oils. Furthermore, monounsaturated fats, found in olives, olive oil, certain nuts and avocadoes have been promoted as being part of a healthy Mediterranean diet. This paper will provide a brief review comparing the effects of saturated fat to monounsaturated fat.

Introduction: Quick primer on fats

Dietary fats are generally categorized into three subsets, saturated, monounsaturated, and polyunsaturated. A saturated fat has zero double bonds in its carbon chain, whereas monounsaturated fat (such as oleic acid found in olive oil) has one double-bond, and polyunsaturated fats have more than one double-bond. There are numerous types of saturated fats such as small, medium, and long-chain saturated fats and different types of polyunsaturated fats. Below we will review the studies comparing saturated fat to monounsaturated fat.

Saturated Fat versus Monounsaturated Fat: Science Clear as Mud

There is a fairly large body of evidence in the scientific literature comparing saturated fat to monounsaturated fat (MUFA). The Kanwu study assigned 162 healthy people from five different countries to a diet high in either saturated fat or MUFA, but with both diets having the same total number of calories.[1] In the group eating more saturated fat, insulin sensitivity worsened a small amount, while no change occurred in the group eating more MUFA. A more interesting finding was that while individuals whose diet was 37% fat or higher (meaning, 37% or more of total calories coming from fat) there was no significant change in insulin sensitivity, individuals whose diets were lower

in fat did show a change: insulin sensitivity was 12.5% worse on the saturated fat diet and 8.8% better on the MUFA diet. On the lower fat diet, when more of the fat came from saturated fat, insulin sensitivity worsened, while it improved when more of the diet came from MUFA.

Different foods were consumed in each group in this study and thus a direct comparison between saturated fat and MUFA cannot be directly made in the study. Thus, the changes in insulin sensitivity could have been the result of differences in the food sources, themselves, rather than solely the type of fat they contain. Moreover, the diets in the Kanwu study were high in carbohydrates (around 45% of total calories coming from carbs). Thus, the Kanwu study showed that in people eating a relatively high-carbohydrate diet, when total fat intake is low, insulin sensitivity might worsen slightly when foods higher in MUFA are replaced by foods higher in saturated fat. To put this in context, the mean dietary intake of carbohydrates for American adults ≥ 20 years of age is 46% for males and 48% for females. The Dietary Guidelines for Americans recommends that carbohydrates comprise 45 to 65% of total daily calories consumed.

What might the effect of replacing saturated fats with monounsaturated fats be among people following low-carbohydrate diets? Would the effects be different if the saturated fats came from coconut oil and lamb tallow as compared to butter and cheese? How about if the monounsaturated fats came from macadamia nuts and avocado, as compared to olive oil? The effects might well be different, and the findings of such studies—if anyone ever decides to do them—shouldn't be extrapolated to diets where the fats come from other foods.

Food sources do matter. Palm oil, in particular, seems to induce hyperinsulinemia when added to a diet high in sugar.[2] In a study in healthy adults, a diet high in saturated palmitic acid (about 17% palmitic acid in a diet with 40% of total calories from fat) led to decreases in energy expenditure and the use of fat for energy. In the same study, people following a diet higher in monounsaturated oleic acid (31% oleic acid; 40% of total calories from fat) showed a slight increase in both the daily energy expenditure and the use of fat for fuel.[3] The high palmitic acid group also had a greater increase in body fat compared to the high oleic acid group. Thus, eating foods higher in monounsaturated fat compared to foods higher in saturated fat may have some benefits in the context of a moderately high carbohydrate intake—46% of total calories from carbohydrates, where replacing saturated fats with monounsaturated fats might lead to less body fat gain.

In another study comparing different proportions of fat in people's diets, a small group of obese but non-diabetic subjects followed one of three diets: 1) MUFA diet moderately high in fat (35-45% of total calories from fat, of which MUFA was > 20%); 2) Low-fat diet (20-30% of total calories from fat); or 3) Control diet (35% of total calories from fat, of which saturated fat was > 15%).[4] Compared to the MUFA diet, the control diet (high in saturated fat) significantly increased fasting glucose, fasting insulin and HOMA-IR (a measurement of insulin resistance), whereas only very small changes in these parameters were observed in the low-fat diet or the MUFA diet. However, the MUFA diet was a low-glycemic diet, whereas the low-fat diet was medium-glycemic and the control diet was high-glycemic. Thus, the diet that seemed to be the best for blood sugar control and healthy insulin levels had an overall low glycemic impact compared to the other diets. With these confounding factors, it's impossible to conclude that the beneficial effects of the MUFA diet were due solely to the presence of monounsaturated fats and not due to the absence of high-glycemic foods. Moreover, these results were, again, on top of a moderately high-carbohydrate intake. Many studies make the same mistake, comparing the effects on insulin in people consuming MUFAs versus saturated or trans fats in the context of a diet that is 50% carbohydrate.[5] It's impossible to say whether adverse effects on insulin are due to the change in the type of fat, or due to some way in which the different types of fat interact with a large amount of carbohydrate. Moreover, the MUFA diet was 45% carbohydrate, the control (high saturated fat) diet was 50% carbs, and the low-fat diet was 60% carbohydrate. Thus, the apparently beneficial MUFA diet was lowest not just in glycemic impact, but in total carbohydrate content as well. Whatever the results from a study like this—good, bad, or indifferent—where multiple factors regarding both fats and carbohydrates are altered (but all the diets tested are still high in carbohydrates), the findings cannot automatically be extrapolated to people following low-carb diets.

All this being said, monounsaturated fat may, in fact, have a slight edge over saturated fat in certain areas. In a study that followed overweight or obese men who ate a diet high in saturated fat and then switched to a diet where fat was predominately MUFA (or vice-



Sources of monounsaturated fats.

versa), and each diet was followed for four weeks, the men lost weight (and lost more body fat, as opposed to losing muscle) while on the MUFA diet than on the saturated fat diet, even though they ate the same number of calories.[6] Sources of fat in the saturated-rich diet were milk, butter, cheese and fatty meat, whereas the MUFA-rich diet contained olive oil, nuts, and avocados. All food was provided to the subjects by the researchers, and no other food was permitted. The study authors concluded, "Substituting dietary saturated with unsaturated fat, predominantly MUFA, can induce a small but significant loss of body weight and fat mass without a significant change in total energy or fat intake."[6]

These results occurred on top of a diet where carbohydrates supplied around 42% of total calories, and fat made up approximately 40% of calories. We can't say that these results would apply equally to people following a low-carb diet, but the evidence implies that for people eating a moderate amount of carbohydrate, replacing saturated fat with MUFA may help promote weight loss—specifically, fat loss, and will improve insulin sensitivity, even if one consumes same number of calories and the same amount of total fat as they were before.

There are other benefits to replacing saturated fat with monounsaturated fat. Subjects report feeling more physically energetic while following the MUFA-rich diet than while following the diet higher in saturated fat. Higher energy levels could potentially translate into becoming more physically active. Another noteworthy benefit of switching from saturated to monounsaturated fats was a significant decrease in mean arterial blood pressure. On the high saturated fat diet, mean arterial pressure increased by 1.5 mmHg, while it was decreased by 5.6 mmHg on the MUFA diet. These blood pressure changes might have been even more substantial if the subjects followed the diet for months, rather than weeks.

As for the loss in body fat, it wasn't just the amount of body fat that changed, but where it's stored in the body. While subjects on the MUFA-rich diet lost 3.75 pounds (1.7 kg) of fat (despite still eating a relatively high amount of carbs), subjects on the saturated fat diet gained 1 kg, and most of this fat was deposited in the abdomen (i.e., dangerous visceral fat).

The overall evidence suggests that, in the context of a diet moderately high in carbohydrate, consuming monounsaturated fats as compared to saturated fats leads to greater fat burning, increased satiety, reduced

Table 1. MCTs lead to a higher post-meal increase in thermogenesis.

Effects of Consuming Less Saturated Fat and More Monounsaturated Fat in the Context of a Diet Moderate-to-High in Carbohydrates [6, 10, 15, 16]	
Greater weight loss and greater fat loss	Less loss of muscle and lean tissue
Reduced blood pressure	Greater post-meal fat oxidation (burning fat, rather than burning carbohydrate)
Lower post-meal triglycerides	Higher post-meal HDL

body fat (particularly abdominal fat), and improved insulin sensitivity. This may be why many people living in the Mediterranean manage to stay slim and healthy while enjoying bread and pasta: first, while they do enjoy these foods, they don't gorge on them, and second, when they do eat them, they're often accompanied by a generous drizzle of olive oil. Nuts are also rich in MUFA and PUFA and are an essential feature of the traditional Mediterranean diet. In randomized controlled trials, a Mediterranean diet enriched with either nuts or extra-virgin olive oil produced cardiometabolic benefits including improvements in insulin sensitivity, cholesterol, inflammation, and vascular reactivity, and reductions in myocardial infarction, stroke and cardiovascular death.[7]

A large analysis of fifty epidemiological and randomized controlled studies encompassing over 500,000 people found that adherence to a Mediterranean diet can improve waist circumference, HDL, triglycerides, blood pressure, and blood glucose levels.[8] All of these factors are criteria for diagnosing insulin resistance and metabolic syndrome, so dietary changes that improve these are a good thing. The overall evidence in the scientific literature indicates that consuming more foods high in MUFA, and fewer foods high in saturated fat may be a beneficial change, especially if one is eating moderate to high amount of carbohydrates.

How does MUFA Beat Saturated Fat for Weight Loss?

Some of the studies we have discussed involved changes to the types of fat people ate, and the subjects lost body fat even though they were eating the same number of calories. How is this possible? If they were taking in the same amount of energy, and all that really changed was where that energy came from—for example, olive oil instead of butter—how did they lose weight?

One answer may be that oleic acid (the predominant fat in olive oil) has a greater oxidation rate than stearic acid (a saturated fat found in beef and chocolate).[9] A fat that has a higher oxidation rate liberates more energy and can thus reduce subsequent food intake due to increased satiety. In other words, if you get more energy from one type of fat than from another, eating that first fat is likely to leave you more satisfied and feeling less hungry later on. But there's more to it than that.

Fat loss doesn't just come from eating less. The change from saturated to monounsaturated fat in people's diets seems to actually increase fat burning at the cellular level. A study looking at the use of fat for energy (as opposed to carbohydrate) showed that, during the five hours after a meal whose main fat was olive oil, subjects burned more fat for energy than subjects whose meal fat source was cream.[10] In subjects with a large waist circumference (an indicator of insulin resistance), there was a significant increase in the thermic effect of food with the MUFA-rich meal versus the SFA-rich meal. The thermic effect of food is the amount of energy your body uses—that is, how many calories you burn—just to digest and metabolize that food, and it contributes to your overall metabolic rate.

The amount of energy required to process MUFA seems to be higher than that for saturated fat (again, in the presence of a moderate amount of carbohydrate), which may partially explain why studies have shown increased weight loss—and specifically, increased fat loss—with diets that are higher in MUFA compared to diets higher in saturated fat. For overall better health, it's fat loss that's important, and not necessarily weight

loss, as the goal is to lose body fat, rather than bone, connective tissue, or muscle.

These findings—that fat burning and the thermic effect of food are higher from monounsaturated fat than from saturated fat—have been replicated in multiple studies.[11] This even holds true for obese post-menopausal women, a group that has a notoriously difficult time losing weight. One study showed that, after consuming meals with equal calories, but one with fat coming from olive oil, and the other with fat coming from cream, women who ate the olive oil meal had higher rates of fat oxidation after the meal.[12] Meaning, in the hours after the meal, these women used more fat for cellular energy rather than carbohydrate—and if you want to lose fat, you've got to burn fat. In this study, among the obese women, the thermic effect of food (called "diet-induced thermogenesis") was significantly higher in the meal containing olive oil versus the meal containing cream—5.1% vs. 2.5%—approximately double.[12]

While many people lose body fat on low-carb diets, many do not like following these diets for prolonged periods of times. In individuals who consume moderate amounts of carbohydrates, getting more dietary fats from MUFA might help with fat loss and improved insulin sensitivity compared to getting more fat from saturated sources. Thus, strategic fats for a higher carbohydrate diet include more nuts, olive oil, and avocados, and less fatty meat, full-fat dairy (cheese, milk, butter) and chocolate.

One study found greater weight loss in people using MCTs compared to olive oil as part of a weight loss program.[13] Another study showed that, compared to a margarine enriched in long-chain saturated fats, consuming a margarine enriched with MCTs led to greater decreases in total body fat and visceral fat after 12 weeks.[14] The authors speculated that MCTs lead to a higher post-meal increase in thermogenesis. Table 1 summarizes the effects of consuming less saturated fat and more monounsaturated fat in the context of a diet moderate-to-high in carbohydrates.[6, 10, 15, 16]

Conclusion

The intake of foods higher in MUFA compared to foods higher in saturated fat may reduce body weight, body fat and insulin resistance when consumed on top of a diet moderate to high in carbohydrates. Further studies should be performed in individuals consuming low-carbohydrate diets to see if these effects would apply to these situations.

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Disclosure

JJD is Director of Scientific Affairs at Advanced Ingredients for Dietary Products. JOK is an owner of a nutraceutical company that sells omega-3 supplements. **MM**

Conversion of No-Show Patients to Telehealth in a Primary Medicine Clinic

by Lakshmi Priya, Patricia Carey & Fariha Shafi, MD

Telehealth allows patients to have a visit with their physician despite an ongoing global pandemic, forgetting appointments, and transportation issues.



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Abstract

No-shows in primary care clinics prevent patients from receiving essential care and decrease clinic productivity. The COVID-19 pandemic forced physicians to adjust to telemedicine as a necessary method to provide care. In this study no-show patients were converted to telehealth visits thereby allowing physicians to care for their patients and maintain hospital revenue. The most common reasons for "no-shows" were found to be forgetting appointments and transportation issues.

Introduction

Patients who do not show up to their scheduled appointment, known as "no-shows," cause a disruption in clinic productivity and patient care.[1] The reasons for no-shows are variable, but common issues are forgetting appointments and miscommunication.[2] Despite how widespread this issue is, finding a solution to decrease no-show rates has been a struggle for physicians and administrators.[3] The COVID-19 pandemic forced physicians to rapidly transition to telehealth to provide care.[4] This transition enabled physicians to continue to provide medical care and maintain hospital revenue at a time when many institutions were financially burdened. Despite the difficulty in the transition, telehealth has certain advantages for patients such as decreasing the stress of travel or missing wages.[4] It also enables patients to continue receiving regular preventative care. Patients who do not attend their appointments may have worse health outcomes. For example, patients with low attendance in diabetes clinics are associated with worse glycemic control.[5] The purposes of this study are to determine if no-shows can be converted to successful telehealth visits and to determine the most common reasons for patient no-shows, thereby potentially increasing productivity and lessening the gaps in patient care.

Methods

Overview of Design

This study occurred from December 2020 to March 2021 using information collected by medical students and clinic staff.

Study population

Patients aged 18 years or older who were scheduled for a follow-up visit to the Truman Medical Center Gold 7 Primary Care Clinic and were not checked in within twenty minutes of their appointment were included in the study. Patients scheduled for a new patient visit to establish care or a Well Women's visit were excluded from the study.

Methodology

Patients who were considered no-show, meaning they were not checked in within 20 minutes of their scheduled appointment time, were called using a secure hospital number by a medical student (Figure 1). If the patient did not answer, they were called again five minutes later. If the patient answered, they were asked the reasons for missing their appointment, and subsequently asked if they would like their missed appointment to be switched to a telemedicine visit. Patients who agreed to have their visit switched were immediately converted to a telemedicine appointment that was conducted by a medical student and the attending physician. Patients not interested in a telemedicine appointment were rescheduled for an in-person visit, as they normally would be by the clinic staff. For the purpose of this study, these patients were not followed up on as they were mostly scheduled for in-person visits. The patients' responses as to why they missed their appointment and if they were willing to have a telemedicine visit were documented in a de-identified manner on a spreadsheet.

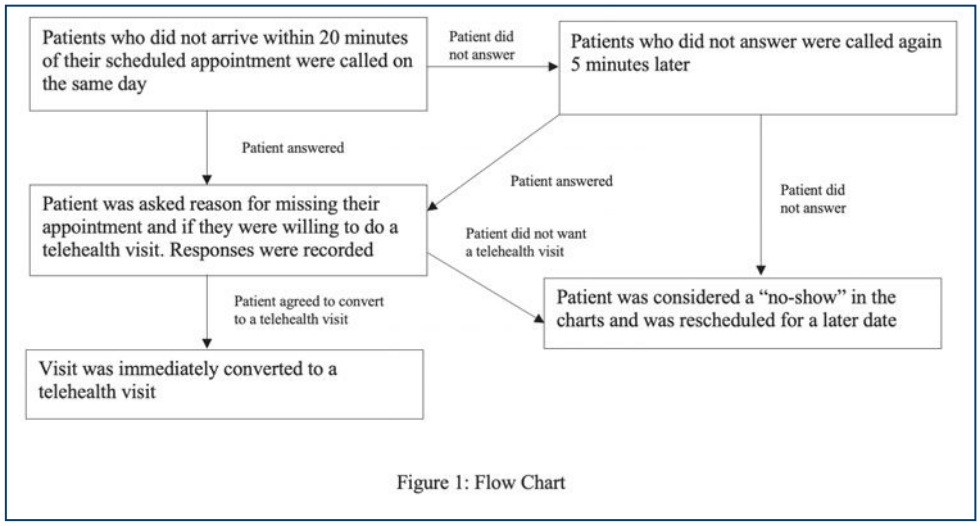


Figure 1: Flow Chart

Statistical Analyses

Only de-identified data was used in conducting the analyses. Patients scheduled for clinic on the days of the study were counted, and the rate of conversion to telehealth encounters was calculated. Patient responses as to why they did not attend their appointment were assigned to categorizes such as "forgetting" and "transportation" (Table 2). Statistical analyses were conducted on data derived from these clinical encounters (Tables 1, 2).

Results

Over the course of 20 clinic days and 215 total patients, 32% of the patients were no-shows and 79.41% of patients who answered the phone agreed to have their visit converted to telemedicine (Table 1). The most common reasons for no-shows were forgetting (50%), transportation difficulties (17.65%), timing (11.76%), and weather (8.82%) (Table 2).



Patients who were considered no-show, meaning they were not checked in within 20 minutes of their scheduled appointment time, were called using a secure hospital number by a medical student. If the patient did not answer, they were called again five minutes later. If the patient answered, they were asked the reasons for missing their appointment, and subsequently asked if they would like their missed appointment to be switched to a telemedicine visit.

Discussion

Ability to Convert to Telehealth

This study highlights the importance of telehealth in providing medical care, especially when patients face barriers to attending in-person appointments. During the COVID-19 pandemic many patients feared coming into the hospital, especially the elderly and immunocompromised.[4] Telehealth platforms enabled physicians to continue providing medical care

Table 1: Total No-Shows and Conversions to Immediate Telehealth Visits

Total Scheduled Patients	215
Total No-shows	69
No-shows who did not answer their phone or were establish care visits	35
No-shows who answered phone	34
Total conversions to telehealth	27
Percent of total no-shows	32.09%
Percent of no-shows who answered the phone	49.28%
Percent of no-shows who answered the phone and agreed to immediate conversion to telehealth	79.41%
Percent of total no-shows converted to telehealth	39.13%

Table 2: Major Reasons for No-Show (from patients who answered the phone)

Forgot about appointment	17	50.00%
Transportation	6	17.65%
Would not be able to make appointment at scheduled time	4	11.76%
Other*	4	11.76%
Weather	3	8.82%
Total	34	

*Reasons such as illness, lack of childcare, or scheduling error

in a safe and socially distanced manner.[6] While the COVID-19 pandemic forced the medical community to utilize telemedicine, it has shown to be useful in also reaching out to patients who no-show to their in-person visits.[7] Overall, no-show rates declined at the Primary Care Clinics during the COVID-19 pandemic with the widespread use of telehealth. In December 2019 through February 2020 the average no-show rate at the Truman Medical Center Primary Care Clinics averaged at 30.22%, and from December 2020 through February 2021 the rate was 26.79% (Table 3). Although this study was conducted during the winter months, the no-show rate during these months was similar to the rate during other seasons. For example, the average no-show rate at the Primary Care Clinics from June 2020 to August 2020 was 27.56% compared to the no show rate from December 2020 through February 2021 which was 26.79% (Table 3). In this study, the no-show rate was 32.09% in the Gold 7 Primary Care Clinic and almost 80% of no-show patients who answered the phone agreed to have their visit converted to a telemedicine encounter decreasing the no-show rate by 6%. The most common reason for patients who answered the phone and refused telehealth was that they preferred to have an in-person visit, which was scheduled at a later time. In the Gold 7 Primary Care Clinics, clinics are run with medical students who make the initial phone calls for conversion. Additionally, the clinic staff was utilized to help with phone calls and scheduling. Once a patient agreed to a telehealth visit, the front desk staff was notified who immediately converted the appointment to a telehealth visit in the electronic medical record or rescheduled the patient for a later date. This did not create any major disruption in clinic flow as the general clinic policy of a 20-minute grace period for no-shows was followed.

Exploring Reasons for No-Show

In previous studies, the most common reasons for patients not attending their appointment were forgetting, feeling better and no longer seeing a need to attend appointments and transportation issues.[8] In addition, extreme weather has been associated with failure to attend scheduled appointments.[9] In this study the main barriers affecting adherence to in-person visits include forgetting appointments and lack of dependable transportation, which is similar to previous studies on no-shows in clinical practice. In the primary care clinics used in this study, patients are given a text message reminder one day prior to their appointment and a phone call a few days prior. Patients are also sent mail-in reminders if phones are not listed as the preferred method of communication. However, there are many patients who do not have cell phones or other reliable contact methods, including consistent mailing addresses, therefore excluding them from receiving these reminders. The use of data collection tools could be useful in tackling the issue of no-shows. By gathering information on reasons for frequent no-shows, solutions specifically tailored to those patients can be found.[10] Various methods such as sending text messages, phone calls, mail-in reminders or messages through a patient portal could be implemented to see what works best in a particular clinic.[10] These barriers, especially forgetting appointments, will be further investigated in future projects to determine how the clinic's reminder system can be optimized.

Transportation was the second most common reason for patients in this study to not attend their scheduled appointment. Access and type of transportation has previously been considered a social determinant of health as patients cannot attend in-person appointments without proper transportation.[9] In addition, travel distance is usually higher for lower income populations than higher income populations.[9]

By switching to telehealth visits, patients can receive care in the comfort of their homes without the additional stresses of arranging transportation to clinic. It is also important to note that this study began in the winter months, and periods of extreme weather, such as temperatures below 0°F and snowstorms, occurred during the study. Because weather was reported as a common cause for no-shows in this study, the results may have been different if conducted during another time of the year.

Effects on Patient Health

Patients who do not attend their appointments ma have worse health outcomes.[11] For example, patients who frequently miss their appointments are less likely to be up to date on their health maintenance and more likely to have higher hemoglobin A1c values and poore blood pressure control.[11] As missing appointments can lead to long-term negative health effects and impede patients ability to receive preventative care, it is important to decrease the number of no-shows in primary care clinics.

During the COVID-19 pandemic, reaching out to patients through telehealth became even more imperative as some patients feared coming into the hospital. As a result, the rates of emergency departmen visits for stroke, STEMI, domestic violence, and psychiatric issues declined.[12] While a telehealth visit may not be able to completely help a patient during an urgent care visit, it can at least provide a mechanism for physicians to quickly direct patients towards seeking appropriate and sometimes lifesaving care. While the effectiveness of telehealth visits are still being studied, it can be assumed that patients who converted to telehealth visits were able to have better continuity of health care than if they were never called after they missed their appointment. In fact, a previous study found that out of 1,734 patients surveyed, 94-99% of patients were "very satisfied" with telehealth and one third preferred telehealth to an in-person visit.[13]

Telemedicine and Social Determinants of Health

The hospital at which this study was conducted, Truman Medical Center, is a safety-net hospital in urban Kansas City, and its continued use of telemedicine is greatly impacted by the population it serves. In other studies, the increase in telemedicine was shown to be higher in areas with low poverty levels and within metropolitan areas.[7] This may be due to the fact that patients from lower socioeconomic backgrounds or rural areas may have difficulty accessing the stable internet connection and sophisticated technology needed for telemedicine.[14] Interestingly, those without insurance are more likely to prefer telehealth to in-person visits.[13] In addition, telemedicine also requires a degree of digital literacy which certain populations, such as the elderly, may struggle with. Consequently, telehealth has been demonstrated to be used less among older adults.[15] In the patient population of this study, many patients did not have video visit capabilities or were elderly and did not have the digital literacy to operate a video visit. However, many of these patients were comfortable with simply speaking over the phone. While telemedicine has shown to be beneficial in improving patient outcomes, physicians should be aware that not every patient will have the capabilities for a telehealth visit.

Table 3: Comparison of No-Show Rates before and during the COVID-19 Pandemic

Pre-Pandemic			
Month	Year	All Clinics No Show %	Gold 7 Clinic No Show %
December	2019	31.45%	22.73%
January	2020	30.50%	30.05%
February	2020	28.70%	28.77%
Average		30.22%	27.18%
Pandemic			
March	2020	31.86%	18.03%
April	2020	22.78%	20.50%
May	2020	34.22%	33.61%
June	2020	31.71%	No patients seen
July	2020	26.79%	29.48%
August	2020	24.17%	32.56%
September	2020	27.59%	25.54%
October	2020	25.95%	25.97%
November	2020	26.87%	19.35%
December	2020	27.34%	11.81%
January	2021	25.16%	19.89%
February	2021	27.88%	27.63%
March	2021	26.34%	16.28%
Average		27.59%	23.39%

Telemedicine and Insurance

It is important to note that before January 1, 2020, the use and payment of telehealth was inconsistent by state and insurance; thus, greatly limiting the use of telemedicine formats.[4] In January of 2020, telehealth use was expanded as the 2018 Bipartisan Budget Act was enacted, which removed some requirements to help expand the use of telemedicine. One of the reasons for

this expansion was because telemedicine was forecasted to save $557 million over the next 10 years for Medicare Advantage enrollees.[4] Although there is an economic case to be made, the main reason for telemedicine expansion should be to close the gaps in healthcare delivery and improve public health. Gaps in healthcare delivery can be met by telehealth visits and decrease the burden on a suffering healthcare system. When the COVID-19 pandemic became apparent in the United States, the Centers for Medicare and Medicaid Services relaxed rules using a temporary waiver allowing Original Medicare enrollees the same telemedicine benefits that were given to Medicare Advantage enrollees and providing equivalent reimbursement for video telemedicine and traditional in-person visits.[4] As these changes, among other provisions for telehealth, are using temporary waivers, the future of telehealth and reimbursement are unknown.[4] While many studies have shown the benefit of telehealth,[6,13] it is unlikely that it will be used to the same capacity in the future if there is not equivalent reimbursement for physicians.[4]

Hospital Revenue

Additionally, the COVID-19 pandemic led many hospitals and practices to lose revenue. Many elective procedures that typically generate large amounts of hospital revenue were suspended in order to conserve personal protective equipment and reduce the spread of the virus.[12] By reaching out to patients via telehealth, physicians can continue to provide essential care without facing major financial losses.[16] With telehealth, primary care physicians also have the ability to make referrals to specialists and order labs which results in helping maintain hospital revenue and quality patient care. The large patient no-show rate (32%) and the percentage of those who were converted to a telemedicine appointment (79.41%) demonstrate that telemedicine can be utilized to provide patient care and maintain clinic productivity (Table 1).

Conclusion

Telehealth allows patients to have a visit with their physician despite an ongoing global pandemic, forgetting appointments, and transportation issues. Virtual visits benefit healthcare professionals by increasing clinic efficiency, preserving hospital revenue and most importantly maintaining continuity of care for the patient. Despite limitations to this study such as the length of the study and a smaller sample size, the results highlight the value of telehealth to patient care. Telehealth may not work for all patient populations, so further studies need to be done to improve access to care for these patients. With the goal of increasing healthcare accessibility and eliminating barriers to care, Gold 7 clinics will incorporate this methodology into their daily clinics with hopes to expand to other Truman Medical Center clinics. Future studies will also examine patient satisfaction with telehealth visits and analyze the best scheduling methods to decrease no-show rates.

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Disclosure

None reported. **MM**

Update on Axial Spondyloarthritis

by Anne E. Winkler, MD, PhD & Micah Miller, PA-C

The pathophysiology of axial spondyloarthritis is now better understood which has led to the development of agents effective in treating these patients although there are still patients with limited response to agents presently available.



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Abstract

Understanding of the spondyloarthritis diseases has changed significantly in the last 15 years. It is now clear that there are patients with and without radiographic changes and the terminology has changed to reflect that: radiographic axial spondyloarthritis and non-radiographic axial spondyloarthritis. In addition, the importance of the presence of inflammatory back pain with spondyloarthritis in making the diagnosis is now well established. It is also clear that women are much more likely to develop axial spondyloarthritis than previously thought. Finally, there are treatments now available to treat axial spondyloarthritis and more hopefully to be approved in the next year.

Introduction

Better and more thorough information about the incidence, prevalence and natural course of the disease ankylosing spondylitis (AS) is now known and has changed our understanding of this disease. We now know that women are much more likely to develop this disease compared to what was initially understood. The development of MRIs has also led to the recognition of earlier disease in patients showing normal plain x-rays but abnormal bone marrow edema in the sacroiliac joints. With this there is now interest in renaming ankylosing spondylitis to reflect these changes – to radiographic axial spondyloarthritis (rAxSpA) for patients with plain radiographic changes in the sacroiliac joints and with those patients with normal plain x-rays now being designated as non-radiographic axial spondyloarthritis (nrAxSpA). And, although not universally accepted it is generally thought that patients with non-radiographic axial spondyloarthritis are part of the spectrum of disease with AS (i.e., rAxSpA).

History

Ankylosing spondylitis was first described from skeletal remains back in the late 1600s by Dr. Connor, an Irish physician.[1] In the 1890s at about the same time, three physicians, Dr. Bechterew (Russian), Dr. Marie (French), and Dr. Strümpell (German), attributed the signs of what we call AS to inflammation and considered it to be a rheumatologic condition[2-4] and in some medical literature, one will see that AS has also been called Bechterew's disease or Marie-Strümpell disease. The term ankylosing spondylitis was not coined though until 1904 by Dr. Frankel.[5] In the last 10 to 15 years with the use of MRI showing bone marrow edema (BME) in

Table 1. Inflammatory Back Pain versus Mechanical Back Pain

Inflammatory Back Pain	Mechanical Back Pain
• Onset prior to age 40	• Onset at any age
• No history of trauma	• Often history of trauma
• Pain better with exercise	• Pain usually worse with exercise
• Pain worse with rest	• Pain usually not better with NSAIDs
• Pain better with NSAIDs	• Pain usually improved with rest
• Alternating buttock pain	

Table 2. AxSpA Features

- Family history of ankylosing spondylitis
- Heel pain
- Uveitis
- Psoriasis
- Inflammatory bowel disease
- Peripheral synovitis
- Response to NSAIDs
- Elevated CRP/ESR

SI joints and with other typical features of AS in patients who do not have plain x-ray evidence of AS, it has been thought that there is a spectrum of disease ranging from nrAxSpA to frank rAxSpA. The term AS has been thought to be not as descriptive with the understanding that there are patients with normal plain radiographs of the sacroiliac region, but similar clinical features and evidence of bone marrow edema on MRI in the SI region. These patients have been called non-radiographic AxSpA, and with this, there has been a trend toward renaming AS to rAxSpA.

Incidence and Prevalence

Newer population studies have found that the incidence prevalence is about 1.5 to 2 million patients.[6,7] To put that in perspective, rheumatoid arthritis is thought to occur in about 1.3 million[8] and systemic lupus erythematosus in about 0.3 million.[9] However, rheumatology offices are as yet not seeing these numbers of patients. This may be in part due to patients not recognizing their symptoms as well these patients not being referred to a rheumatologist or not being correctly diagnosed even after being seen in rheumatologic practices. There is good data to show that it is about 10 years from onset of symptoms to patients being diagnosed with AxSpA. Initially it was thought that AxSpA was really only seen in men with a ratio initially thought 10:1 male to female. It is now clear that the ratio is more likely 2:1 men to women for rAxSpA and 2:1 women to men with nrAxSpA.[10]

About 20% of U.S. adults have chronic low back pain, but only 5%[7] will have Inflammatory Back Pain (IBP). Of those with IBP, somewhere between 14% to 25% will develop rAxSpA.[11] A recent retrospective study of about 150 patients with IBP were followed over 15 years. In this real-world study, about 25% of these patients developed rAxSpA and 50% had resolution of their symptoms. The other 25% developed either nrAxSpA or other diseases. Of patients with either form of AxSpA, 60% are a little more likely to have nrAxSpA form while the other 40% will have rAxSpA. For those who are initially diagnosed with nrAxSpA, about 60% to 90% will not develop further radiographic changes but about 10-40% will develop frank SI changes and become rAxSpA. Those initially diagnosed with rAxSpA will more likely continue to progress radiographically (60% to 70%) with about 30% to 40% not showing any further progression.[6]

Clinical Characteristics

A classic and key symptom of AxSpA is inflammatory back pain (IBP). This differs from mechanical back pain[11] in the following ways: first the onset of back pain is before age of 40 and not associated with a history of trauma. In addition, pain at night or early morning is also common. Unlike mechanical back pain, IBP is worse with rest and improves with exercise. NSAIDs usually seem to help IBP pain. IBP patients often have complaints of alternating buttock pain (Table 1).

What are called spondylitis (SpA) features (Figure 2) help to identify patients with AxSpA.[12-14] These SpA features do occur at the same incidence in both rAxSpA and nrAxSpA.[14] One of the most common SpA features is enthesitis. This is inflammation in the tendon areas near the joint and often occur in the heel and Achilles' tendons but also can occur in the knees, shoulders, hips and chest wall. Enthesitis is very commonly seen in AxSpA and is seen in about 30% to

50% of patients. Dactylitis which refers to a swelling of the whole digit (either toe or finger) is less common in AxSpA. In AxSpA, it occurs at about 6% while in peripheral spondyloarthropathies, such as psoriatic arthritis, it is seen about 30% to 50%.[11] Other SpA features include uveitis, which occurs in about 10% of patients with AxSpA as well as peripheral arthritis which is often asymmetric and involves joints such as the knees and hands in about 30% of patients.[12] Family history of AxSpA or a history of early onset of arthritis in family member occurs about 50%. Inflammatory bowel disease is also a SpA feature and occurs in only 5% to 10%. However, there is evidence of microscopic colitis (noted by random colon biopsies) in about 30% to 60%. And finally, psoriasis may be present in as many as 10% of AxSpA patients.[12]

Pathophysiology

There appears to be both environmental as well as genetic factors involved in the development of AxSpA.[15,16] Environmental factors include smoking as well as infections (possibly mycoplasma) and the gut microbiome. There are clearly genetic factors involved, and although the most common gene is the HLA B27 gene, there are at least 50 other genes associated with AxSpA including ERAP1. It is important to stress that though having the HLA B27 gene does increase the risk of developing AxSpA, its presence is NOT diagnostic for AxSpA since it is seen in patients who never develop AxSpA and is sometimes absent in patients with AxSpA. Of those with the HLA B27 gene, only about 6% will develop IBP. However, if one identical twin has AxSpA with the HLA B27 gene, the other twin has about 65% chance of developing AxSpA. First-degree relatives of AxSpA patients with the HLA B27 gene have about 20% chance of also developing AxSpA. In addition, the incidence of B27 varies with ethnicity: about 6% to 7% in Whites, 4% in Mexican Americans and about 1% to 3% in Blacks. As for indigenous populations in the U.S., HLA B27 is more prevalent with an incidence of 9% in Hopi, 11% in Navajo, and about 35% in Haida.

Biomechanical trauma is likely one of the environmental factors involved in the initiation of AxSpA and seems to be due to release of the cytokine interleukin (IL) 23 in enthesial areas which appears to lead to the develop of chronic inflammation. However, IL23 does not appear to be as important in inhibiting disease compared to the cytokines IL17 and Tumor Necrosis Factor inhibitors (TNFi). Different than other autoimmune diseases, we now know that innate as well has adaptive immunity plays a role in the pathogenesis of AxSpA. The immune cells that seem especially important in ongoing chronic inflammation in AxSpA include the Th17, cd8 negative, and Natural Killer (NK) cells. What is still unclear in the pathology of AxSpA is the role HLA B27 plays. There are several hypotheses, including HLA B27 contributing to misfolding of proteins, HLA B27 acting as arthritogenic peptide itself, HLA B27 impacting the intestinal microbiome so there are more antigenic bacteria, and B2 microglobin which is part of the HLA B27 heterotrimer separating and depositing in synovial tissues causing destruction.[17-19]

Diagnosis

Patients with axial spondyloarthropathies often do not get appropriately diagnosed for average of 10 years in men and even longer in women.[20] There are likely several reasons for the delayed diagnosis. It may be in part due to the difficulty in recognizing the disease since no clear-cut diagnostic markers have been identified. Although 80% to 90% of patients with rAxSpA and 70% of nr AxSpA are positive for HLA B27, about 6% of the normal White population also have the HLA B 27 gene. As previously mentioned, of those who are HLA B 27 positive, only about 6% to 10% develop inflammatory back pain, and approximately 10% to 30% of AxSpA patients will be negative for the HLA B27 gene. Standard measures of inflammation (ESR and CRP) are only elevated in 50% to 60% of patients.

The key feature in recognizing AxSpA is inflammatory back pain. As already mentioned, the classic features of inflammatory back pain that differentiates from mechanical back pain are as follows: onset of back pain without trauma and prior to age 45; back pain improves with exercise and worsens with rest, alternating buttock pain and improvement with NSAIDs (Figure 1). It is important to ask about the features of IBP to separate those patients with IBP and thus possible AxSpA from those with mechanical back pain and therefore not likely candidates to have AxSpA.

Recognizing the typical AxSpA features can aid in recognizing patients with AxSpA. The typical SpA features include[12,13] peripheral synovitis often asymmetric, heel pain (or plantar fasciitis), uveitis, psoriasis, family history, and inflammatory bowel disease. Response to NSAIDs also is seen in patients with inflammatory back pain. An assessment of pre- and post-test probability in patients with IBP showed the presence of family history alone increases pre-test probability from 6% to 51%. The presence of heel pain and response to NSAIDs also increase probability of diagnosis.[21] The presence of positive MRI and positive HLA B27 increases post-test probability in patients with IBP to 91%. An algorithm for diagnosis has been published[16] which emphasizes the importance of the SpA features in helping to narrow the diagnosis to AxSpA versus not AxSpA. If four or more SpA Features are present, then there is a high likelihood of AxSpA. If 0 to 1 are present, then AxSpA is unlikely. When two or three SpA features are present, then it is reasonable to order MRI of the pelvis and HLA B27 gene test to help direct toward or away from the diagnosis of AxSpA.

Gender Differences

Women have long been thought not to have AxSpA, but it is now clear that the original estimate of 10:1 ratio was incorrect.[22] It is now recognized that females do get AxSpA—both rAxSpA and nrAxSpA, and the ratio men to women is about 2:1 in rAxSpA and 2:1 women to men in nrAxSpA. Diagnosis of AxSpA is generally delayed in both men and women, but usually there is a much longer delay in diagnosis of women with AxSpA. This is in part due to the failure of recognizing IBP in women (and men), but also the prevalence of misdiagnosis of women with other conditions—usually with fibromyalgia or depression. Women with AxSpA are more likely to have normal inflammatory markers and less likely to have response to TNF inhibitors. They are also more likely to have enthesitis and increased disease severity, peripheral joint involvement, and to present with neck and upper back pain.[23-25]

Differential Diagnosis

Diseases that may be confused with AxSpA include peripheral spondyloarthritic diseases such as psoriatic arthritis and diffuse idiopathic skeletal hyperosteosis. There are other health issues that can cause abnormal bone marrow edema (BME) in sacroiliac joints. Studies have shown BME in athletes, particularly runners and hockey players, and in women postpartum. And of course, there have been many patients, particularly women, who were diagnosed with fibromyalgia but actually had AxSpA. One famous example of misdiagnosis of AS were two Egyptian pharaohs—Ramses 11 and Amenhotep. For a number of years, archeologists thought that these pharaohs had AS based on thoracic spine x-rays of their mummies. However, further x-ray data showed no evidence of SI changes and now it is thought that these pharaohs have either DISH or psoriatic arthritis with axial involvement.

Comorbities

Like other inflammatory diseases, patients with AxSpA have increased risk of developing other conditions. AxSpA patients are four times more likely to have cardiovascular disease—including hypertension and coronary disease.[26] These patients are at very high risk of osteoporosis—about 25% will have osteoporosis and 40% with osteopenia within 10 years of disease. As a result, they are at high risk of vertebral fractures and approximately 10% will experience this type of fracture.[27] Fibromyalgia is seen in about 20% of patients (males and females) with AxSpA.[28] Depression is also not uncommon in both men and women with AxSpA.[29]

Treatment

Guidelines for treatment of AxSpA have been developed by organizations including ACR as well as SPARTAN.[30] NSAIDs are used first line and have been shown to be helpful for pain as well as possibly associated with slowing radiographic progression.[30] Conventional immunosuppressives such as sulfasalazine and methotrexate are NOT helpful with axial disease but might be useful with the peripheral arthritis.[30] Systemic steroids are also not indicated, but local injections may be beneficial as long as not done in areas where there is high risk for rupture of the tendon (such as the Achilles tendon). TNFi and IL17 inhibitors are now approved for both radiographic and non-radiographic AxSpA.[30] Results have shown that approximately 60% of patients on TNF inhibitors get at least 20% improvement in their

symptoms of AxSpA and 40% of these patients with AxSpA obtain 40% improvement. Cohort studies have shown less radiographic progression in patients on TNFi than those only on NSAIDs; however no formal study has been done to confirm this.

Studies with IL17 drugs have shown similar results. In terms of data, the trials have shown resolution or improvement of MRI bone marrow edema. Not yet approved but expected to be so in the next 12 months is the use of JAK inhibitors in radiographic AxSpA which in clinical trials have some similar response rates to IL17 drugs. The guidelines recommend that if a patient does not respond to one agent—primary failure—to switch to another agent with a different mechanism of action. If a patient is having a secondary failure—initially responding, then losing response over time—it is not unreasonable to stay with agents with the same mechanism of action. If there is no response, it may be reasonable to reassess by bone scan or MRI to see if there is still active inflammation present.

Conclusion

The understanding and approach to recognizing and diagnosis of the AxSpA diseases has dramatically changed in the last 15 years. Understanding the presence of BME in MRIs has helped to allow recognition of patients with AxSpA without plain x-ray findings. The pathophysiology of AxSpA is now better understood which has led to the development of agents effective in treating these patients although there are still patients with limited response to agents presently available. Unfortunately, we are missing or misdiagnosing patients, and finding better diagnostic tools is important. In closing, more and better agents are still needed for those AxSpA patients with limited or no response to the agents we presently have available.

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Disclosure

AW is a speaker for Lilly, Novartis, Pfizer, Sanofi, Astra Zeneca, Amgen, AbbVie, and Janssen. **MM**

A Review of Ketogenic Diet and Lifestyle

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Although ketogenic diets are popular and patients show great interest, their use must be approached with caution.



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Abstract

The ketogenic diet has become increasing popular in recent years. With 25.4 million unique searches, the keto diet was the most Googled diet in the United States in 2020.[1] With increased consumer interest, the "keto" food industry has grown rapidly, and as a result, the global ketogenic diet market was valued at $9.57 billion in 2019.[2] The ketogenic diet has been discussed in popular culture by celebrities, health magazines, and documentaries. The popularity of this diet, and diets in general may be explained by the obesity epidemic in the United States and Missouri.

Introduction

As of 2018, the prevalence of obesity in this country is 42%.[3] In Missouri, two-thirds of the adult population is overweight or obese.[4] Patients trying to lose weight often turn to popular diets, and in the past few years, the ketogenic diet has been a trendy option. With the increased interest in this diet, researchers are working to understand the impact of this pattern of eating on patients' health. There is evidence of benefit, especially regarding weight loss, but there are also risks and concerns. The goal of this review is to offer clarity to physicians counseling patients on the ketogenic diet with the latest literature about benefits and risks.

History of the Ketogenic Diet

In 1911, the first modern use of starvation for the treatment of epilepsy was noted. Two physicians in Paris reported that seizures were less severe in period of starvation.[5] While this was the origin for the ketogenic diet, it wasn't until 1921 that any physician tried to generate ketosis. Dr. Rollin Woodyatt noted that under conditions of starvation, acetone, and beta-hydroxybutyric acid appear.[5] Woodyatt also uncovered that acetone and beta-hydroxybutyric acid were observed if patients ate a low carbohydrate diet. Around the same time, Dr. Russell Wilder theorized that ketonemia could be produced for therapeutic benefit, but with a low carb diet rather than starvation.[5] He developed the term "ketogenic diet." The ketogenic diet become very popular in the treatment of childhood epilepsy.[5] As better epilepsy medications were developed throughout the twentieth century, the ketogenic diet lost prominence as an epilepsy treatment.

In the 1970s, nutritional ketosis was introduced as an idea for weight loss by Dr. Robert Atkins. In his book published in 1972, he describes how reducing carbohydrates "creates a unique chemical situation in the body…ketones are excreted, and hunger disappears."[6] Although the Atkins diet was one of the first, many other low carb diets have been popularized since

the 1970s, from the South Beach Diet to variations of the Paleo and Mediterranean diets. While the details of low-carbohydrate diets may have changed, they have remained a mainstream option for weight loss. Over the past few decades, many studies have sought to quantify the efficacy of low carb diets in terms of weight loss as well as evaluate the potential for amelioration of chronic disease. As research has investigated the mechanisms behind ketosis and weight loss, the ketogenic diet has become the de facto low carb diet of choice in the media and public dialogue.[1]

What is the Ketogenic Diet?

The mainstay of the ketogenic diet is that dietary carbohydrates are kept very low, with varying levels of protein and fat. The classic ketogenic diet is defined as a diet with one gram protein per kilogram of body weight, 10-15g carbohydrates per day, and the remaining calories from fat.[7] The goal of the diet is to induce ketosis. Ketosis is thought to alter metabolic pathways to induce weight loss and potentially improve other health outcomes, such as a reduction of hyperglycemia and improvement in lipid profiles.

What is Ketosis?

Under ordinary circumstances, the body primarily relies on carbohydrates for energy production. Insulin functions to extract and store energy derived from glucose. When the body has reduced carbohydrates available, insulin secretion is reduced. Initially, stored glucose in the form of glycogen is available for fuel, but after three to four days, this is depleted. Stored fat then becomes the most readily available fuel, and its breakdown into free fatty acids provides the raw materials for ketone production in the liver. Ketone production is primarily seen in times of starvation and prolonged exercise, but is also a function of adherence to a very-low carbohydrate diet. Importantly, in physiological ketosis, there is no change in blood pH versus pathological ketosis where there is a lowering of blood pH.

Ketogenic Diet Weight Loss Mechanisms

There is evidence that the ketogenic diet is an effective weight loss therapy. However, the exact mechanisms behind this weight loss remain unclear. For example, in a review of thermodynamic principles of weight loss, Feinman and Fine explain that low-carbohydrate diets have decreased insulin fluxes causing an increased rate of lipolysis.[8] In other words, insulin inhibits lipolysis, and decreased insulin in low-carb diets causes increased fat breakdown.[8] This theory is demonstrated in a study that follows 15 subjects for 12 weeks. The first six weeks they ate a low-carbohydrate diet and the next six weeks a low-fat diet. Blood results after the low-carbohydrate diet displayed decreased circulating triacylglycerol levels versus the low-fat diet.[9] This reiterates the idea that low-carb diets increase fat breakdown.[9]

Another proposed weight loss mechanism is with decreased carbohydrate intake, the body will have to undergo increased amounts of gluconeogenesis to provide glucose to the brain.[10] Gluconeogenesis is an expensive metabolic process.[10] Theoretically, restricting carbohydrates depletes glucose stores, and increases gluconeogenesis.[10] Another mechanism of weight loss is theorized to be direct appetite suppression. In a study with 17 men, subjects were given a high protein diet with two weeks of high-carb and two weeks of moderate-carb intake. During the low-carb, ketogenic diet phase, the participants reported significantly decreased hunger, leading the authors to hypothesize that ketosis itself may suppress hunger.[11] While these mechanisms provide insight into how the ketogenic diet promotes decreased appetite and fat loss, it is important to note that evidence shows weight loss from the ketogenic diet can be partially attributed to water loss. In another study, 20 obese subjects were followed for four months on a ketogenic diet. Utilizing body composition assessments, investigators noted a substantial reduction in weight due to free water loss early in the study.[12] It is important to look at length of duration in ketogenic diet studies as early, dramatic weight loss may be due to diuresis.

With these mechanisms in mind, numerous studies have evaluated the keto diet's weight loss efficacy. There are many examples of randomized controlled trials where significant weight loss is achieved. For example, a meta-analysis by Mansoor et al. looked at mean weight loss in 11 randomized controlled trials for six months with a total of 1,369 participants. In the trials analyzed, participants were randomized into low carbohydrate versus low-fat diet plans. This study found that compared to low-fat diets, low-carbohydrate diets participants lost 2.17 kg more than the low-fat diets (95% CI -3.36, -0.99).[13] However, the duration of some included studies was only six months. When looking at studies with a longer duration, the

weight loss is less superior. For example, in a meta-analysis by Bueno et al., they analyzed 13 randomized controlled trials with a total of 1,415 subjects that were followed for at least 12 months. Again, the very-low-carbohydrate ketogenic diet was compared to a low-fat diet. After twelve months, subjects adhering to the ketogenic diet had lost 0.91 kg compared to the low-fat diet arm (95% CI -1.65, -0.17).[14] While this was a significant result, the weight loss is less than what is seen in the shorter trials.

An interesting perspective is seen in a retrospective analysis of 89 subjects who were followed for 12 months. Subjects followed a diet plan which cycled between shorter periods of a ketogenic Mediterranean diet followed by longer periods of a traditional Mediterranean diet. For a majority (88.25%) of subjects there was substantial weight loss 100.7 ± 16.54 to 84.59 ± 9.71 kg.[15] This study gives a good example of a weight loss regimen that patients may find more feasible. It combines benefits of the ketogenic diet's short-term effects, with a maintenance diet that is less restrictive.

Ketogenic Diet and Diabetes Mellitus

Before the advent of insulin, diet was a mainstay in type 1 diabetes treatment. Famously Dr. Frederick Allen used a low-carbohydrate starvation diet to treat diabetes.[16] However, the use of such diets decreased with the discovery of insulin. More recently, there has been significant interest in the use of ketogenic diets to treat type 2 diabetes in conjunction with obesity. There are several proposed mechanisms that support the use of ketogenic diets to improve hyperglycemia. Most importantly, decreased circulating glucose and increased insulin sensitivity.[17]

Testing this hypothesis, investigators have looked to see if the ketogenic diet can help improve hyperglycemia. One small, shorter study recruited 28 participants to follow for 16 weeks. In this study all 28 subjects that were enrolled received ketogenic diet counseling with a goal of less than 20 grams of carbohydrates per day. At the end of the 16 weeks, 21 participants had completed the trial. The mean fasting glucose decreased by 16.6% from 9.08 ± 4.09 mmol/L at baseline to 7.57 ± 2.63 mmol/L at week 16 ($p = 0.04$).[18] The hemoglobin A1c decreased from 7.5 ± 1.4% at baseline to 6.3 ± 1.0% at week 16 ($p < 0.001$).[18] These results were encouraging, but with short duration and small sample size.

In a two-year, open label, non-randomized, controlled study, 349 participants received either standard care or were educated to follow a ketogenic diet.[19] At the end of two years, those who had followed diets to stimulate ketosis had a 0.9% decrease in HbA1c versus a 0.4% increase in the standard of care arm. In addition, those following the ketogenic diet decreased their use of diabetic medications by 81%, while medication use increased in standard of care patients.[19] Another similar trial looking at glycemic control outcomes after two years showed no significant difference in HbA1c levels between the low-fat and low-carbohydrate groups.[20] These studies show than in the shorter term, there seem to be clinically significant improvements in glycemia control outcomes. However, in the longer term, while there are examples of improved HbA1c and medication use, there is less extreme improvement.

A very recent meta-analysis by Goldenberg et al. evaluated the efficacy of low-carb and very-low-carb diets in type 2 diabetes that seemed to support the idea that while significant benefit in weight loss, glycemic control, and insulin sensitivity were seen in the short term, the benefits seemed to wane after 12 months.[21] Participants in some trials seemed to struggle with adherence to the very-low-carb diet, suggesting that loss of efficacy in longer studies may be related to difficulty in maintaining such a restrictive eating pattern over a long period of time.[21]

It is important to understand the impact of the ketogenic diet in patients with type 1 diabetes. Although it has not been studied extensively, there have been trials showing positive outcomes. One small trial with ten participants were randomized into a carbohydrate restricting arm versus a standard carbohydrate counting arm. They were followed for 12 weeks. At the end of 12 weeks, the carbohydrate restricted arm had significant reductions in HbA1c (8.9 to 8.2%, $p<0.05$) and a significant decrease in daily insulin use (64.4 to 44.2 units per day $p<0.05$).[22]

A critical point to mention is the hypoglycemic risk of the ketogenic diet in the type 1 diabetes population. In an observational study with 11 participants, subjects were followed on a ketogenic diet for three years. A main finding of this study was that participants had 6.3 episodes of hypoglycemia per week compared to on to two episodes a week, noted in previous literature.[23] Of similar concern, there are case studies indicating that the ketogenic diet in people with type 1 diabetes

can precipitate ketoacidosis.[24] Thus, significant caution would need to be observed in patients with type 1 diabetes who wish to follow a ketogenic diet.

Ketogenic Diet and Cardiovascular Disease

A common concern physicians have with the ketogenic diet is its effect on blood lipids and lipoproteins, and more broadly, its effect on cardiovascular disease risk factors. Despite the frequent concern that the ketogenic diet increases LDL-cholesterol, a recent comprehensive review of evidence by the National Lipid Association Task Force, showed variable responses of LDL-cholesterol.[25]

The meta-analysis by Mansoor et al. evaluated cardiovascular risk factors in addition to weight loss as noted above. They evaluated 11 randomized controlled trials with 1,369 participants placed into ketogenic versus low-fat diet arms. They found that the ketogenic diet participants, after six months, had decreased blood triglycerides (-0.26 mmol/l; 95% CI -0.37, -0.15), but an increase in both HDL-cholesterol (0.14 mmol/l; 95% CI 0.09, 0.19) and LDL-cholesterol (0.16 mmol/l; 95% CI 0.003, 0.33).[13]

In another meta-analysis, the authors reviewed eight randomized controlled trials lasting six months with 1,633 participants in a ketogenic versus low-fat randomization. In this analysis, they found no significant difference in LDL-cholesterol levels between groups (0.07 mmol/L; 95% confidence interval [CI], 0.02–0.13; P <0.009] [26]. HDL-cholesterol and plasma triglycerides at six and 12 months increased and decreased, respectively (0.08 mmol/L; 95% CI, 0.06–0.11; $P < 1 \times 10–5$ and –0.13 mmol/L; 95% CI, –0.19 to –0.08; $P < 1 \times 10–5$).[26]

Further analysis suggests that the variation in diet composition may have a significant effect on the lipid changes seen. The increase in LDL-cholesterol seen in some of the randomized controlled studies may be due to the increased intake of saturated fats when carbohydrates are lowered. One meta-analysis centered on randomized controlled trials analyzed long-term effects of low-fat versus high-fat diets. The meta-analysis included 32 studies with 8,862 participants that were followed for a minimum of 12 months. Results showed a decrease in total cholesterol (-4.55 mg/dL; 95% CI -8.03 to -1.07; p=.01) and LDL-cholesterol (-3.11 mg/dL; 95% CI -4.51 to -1.71; p<0.0001) were more prominent in the low-fat arm.[27] Further analysis showed that lower total and LDL-cholesterol were associated with lower saturated fat intake, and increased monounsaturated fat was related to high HDL-cholesterol and lower saturated fat intake.[27]

In summary, there are enough randomized controlled studies showing increased LDL-cholesterol in the ketogenic diet for it to be a consideration in certain patient populations. However, when looking at meta-analyses, the LDL-cholesterol response is variable. Diet composition likely plays an important role in the lipid changes seen in patients adhering to a ketogenic diet, so a high-quality diet with adequate intake of fruits and vegetables and low intake of saturated fats would be preferred. Ketogenic diets have been shown to repeatedly decrease triglycerides and increase HDL-cholesterol levels.

Ketogenic Diet in Pregnancy

There is evidence that women who become pregnant on low-carbohydrate diets have increased risk of birth defects. The National Birth Defects Prevention Study retrospectively looked at mothers with infants with stillbirths, anencephaly, or spina bifida (1,740) versus mothers with infants without defects (9,545). They found that women with restricted carbohydrate intake, defined as less than the fifth percentile among the control group were 30% more likely to have infants with neural tube defects (Odds ratio of 1.30, 95% (1.02, 1.67) p<.01) as well as decreased folic acid levels.[28] Women who plan to become pregnant should be advised to avoid restrictive low-carbohydrate diets. Adequate folate supplementation should be stressed if they choose to continue with a low-carb diet.

Conclusion

Although ketogenic diets are popular and patients show great interest, their use must be approached with caution. There is data showing impressive short-term weight loss, but most analyses suggest that long-term, their efficacy is comparable to other hypocaloric diets. At least part of this effect may be due to difficulty with long-term adherence to such a restrictive eating pattern. In addition, some of the weight lost during the acute period of following a ketogenic diet may be related to water loss, rather than true fat loss. Thus, the impressive short-term weight loss numbers may appear inflated. For patients with type 2 diabetes, it is likely that any weight loss achieved with the ketogenic diet could lower A1c and help reduce the

medication burden. Care must be taken to taper diabetes medications appropriately to reduce the risk of hypoglycemia.

Lastly, long-term safety and health have yet to be proven, especially with regard to lipid profile alterations and cardiovascular impact. Studies generally show improvement in HDL and triglycerides, but LDL response is variable. This may be due to significant variability in the content of the diet of each specific person. Those interested in the keto diet should be encouraged to limit saturated fat and ensure adequate consumption of fruits and vegetables in order to maintain micronutrient and fiber intake.

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Disclosure

None reported.

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