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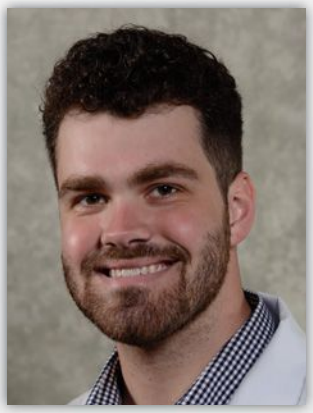
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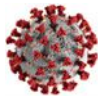


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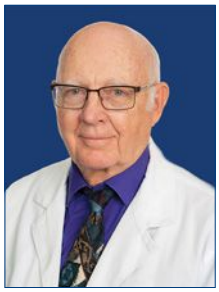
A Medical & Social Catastrophe in the Making: Missouri May Legalize Addicting High THC Marijuana in 2022



In the November 2022 state elections, the heinous marijuana industry may get legal recreational cannabis. This will eventually destroy Missouri's health and social fabric as it has in other states. This may be prevented, but only with immediate, widespread, effective opposition.

by John C. Hagan, III, MD

I'm not one to believe in miracles. Unless one fortuitously comes our way by November 2022, it is possible addicting high (80-90%) tetrahydrocannabinol (THC) recreational marijuana will be legal in Missouri. The hideous marijuana industry, hereafter referred to as "Big Weed," paid out over $8,000,000 to a Washington D.C. firm to collect enough signatures to put recreational marijuana on the ballot in November 2022. The firm has submitted close to 400,000 signatures to get the referendum on legal recreational marijuana on the November ballot. At the time of this writing, while the number of signatures is huge, certain of the eight congressional districts lack the required 8% of registered voters. If our miracle occurs Big Weed will not have enough signatures this year; if not, they will be back again, and again. Merit aside, odds are if recreational marijuana gets on the 2022 ballot it will pass unless responsible individuals and organizations take immediate action. That did not happen in 2018 when Missouri passed a sham medical marijuana amendment.



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.

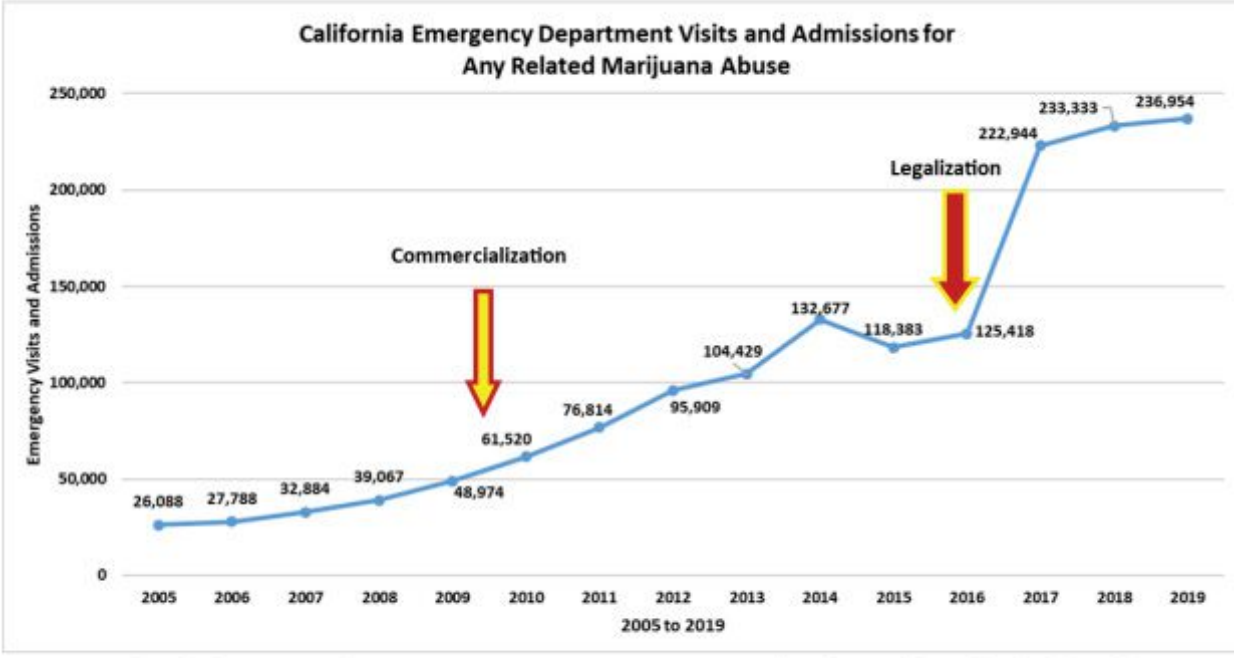
How Did This Happen?

In a March/April 2012 *Missouri Medicine* editorial: "Is Missouri Going to Pot? Reefer Madness: Legal or Medical Marijuana" I stated that marijuana was not a valid medicine, and had many harmful side effects. I expressed a belief that the sensible people of Missouri would keep cannabis' social and medical blight out of our state. A soaring number of studies published world wide confirm the deleterious medical and mental effects of marijuana. *Missouri Medicine* has published more than 20 such studies. Adverse effects are more common in states with sham medical marijuana laws; even higher in legal recreational use states. In the 22 years I have been editor of *Missouri Medicine*, not a single scientific study has been submitted to our journal showing any useful medical application for street level marijuana.

Why Would Missouri Want to Replicate the Disasters Pot Has Caused?

In states passing sham medical marijuana and legal recreational marijuana enormous problems have been created: dramatic increases in emergency department visits for cannabis complications, increases in cannabis-related hospitalizations (Figure 1), marijuana-related domestic violence, industrial and automobile accidents and deaths (Figure 2), educational problems like use at school with marijuana-related suspensions and expulsions. Marijuana use has been associated with rising rates of suicides, homicides and mass shootings (Figure 3). Some of these problems are already occurring in Missouri which regrettably passed sham medical marijuana in 2018.

Figure 1.



Source: Patient Discharge Data and Emergency Department Data, 2017-2019, Office of Statewide Health Planning and Development

Up to 50% of patients with cannabis-related psychotic symptoms presenting to the ED requiring hospitalization will go on to develop schizophrenia.

Source: https://doi.org/10.1016/j.psychres.2022.114387

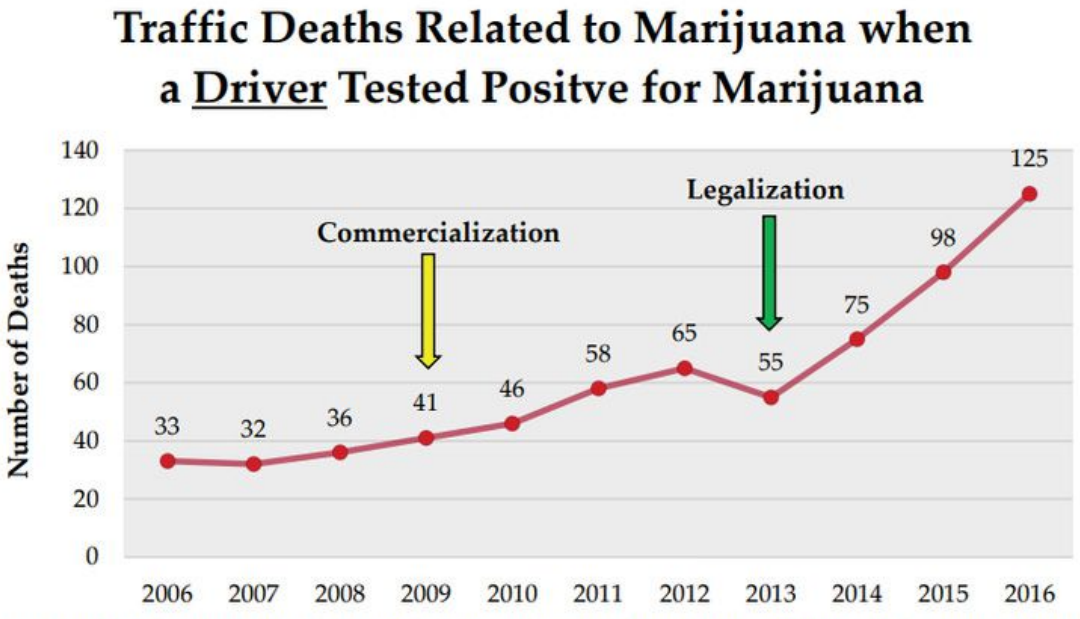
Revenue from taxes on cannabis sales have generally failed to achieve projections. When social, educational, and law enforcement costs are factored in, sham medical and recreational marijuana are net monetary deficits to most states. Because the taxes on legal sales of cannabis are so high, illegal sales and illegal marijuana 'grows,' some located in suburban homes or on public land, have flourished. These often are run by Mexican drug cartels. In my opinion, no state enacting easier access to marijuana is better off financially or healthier. Big Weed has successfully sold The Big Lie. Of course it helps to have a product that is habituating-addicting and creates its own demand and generates big money for the dross marijuana industry.

Lessons From the Unsuccessful Effort to Defeat Sham Medical Marijuana in the Missouri 2018 Elections

In the 2018 election, almost by default, I was the coordinator of a small number of organizations against legalizing sham medical marijuana. Big Weed had millions to spend, and spend they did on ads and commercials. Truth-challenged individuals including some physicians, remunerated by Big Weed, were brought to Missouri to tell their glowing, often contrived, stories. Big Weed flooded social media. Big Weed has been active in states, including Missouri, for over a decade preparing the way for legalization. They only need to win once.

While sham medical marijuana was opposed by all major medical organizations in the Show-Me State, none of these organizations developed or donated sufficient money for an effective publicity campaign against Big Weed.

Figure 2.



National Highway Traffic Safety Administration, Fatality Analysis Reporting System (FARS), 2006-2011 and Colorado Department of Transportation 2012-2016



Figure 3.

Credit: Jordan Vonderhaar/Getty Images

Marijuana use has been associated with psychosis, domestic violence, suicide, and mass shootings. Source: United States Secret Service, National Threat Assessment Center,
'Mass Attacks in Public Places-2019" US Department of Homeland Security, page 14

Above, law enforcement officers work the scene at Robb Elementary School in Uvalde, Texas, on May 24, after an 18-year-old gunman killed 19 students and two teachers. It is reported the shooter was a marijuana user, angry because his grandmother had tried to prevent him from smoking it.

Many other organizations refused to take a public stand against sham medical marijuana: Parent-Teacher Associations, school administrations, Mothers Against Drunk Drivers (shame on MADD), service organizations, teachers' unions, the Missouri Hospital Association, and organized religions excepting the Baptists. The major newspapers in St. Louis and Kansas City supported sham medical marijuana. Our tiny anti-weed consortium had about $10,000 to spend while Big Weed had tens of millions.

Legal High THC Recreational Marijuana Will Increase Our Drug Culture and Drug-Caused Violence and Deaths Like Opioids

The opioid industry, peddling claims of non-addiction, shilled by its highly paid 'pain' physicians and organizations, were directly responsible for addicting hundreds of thousands of people by enticing gullible physicians to use opioids for almost any amount of pain. As the legal and medical systems belatedly moved against easy opioids from physicians, addictives, mostly in the form of fentanyl, are pouring across our porous southern border. The chemicals come from India and China, the illegal drugs are manufactured in Mexico, and distributed by powerful, ruthless cartels across the United States. In 2021, there were over 107,000 over-dose/drug-poisoning deaths. High THC marijuana carries with it a unique set of risks and dangers and is a gateway drug to higher risk, illegal, often fentanyl-laced fake pills.

How did we as a profession, as parents, as a responsible society, let this happen? Do you believe in miracles? Then pray for one in the November vote on addicting-habituating-gateway legal recreational marijuana. Either that the number of signatures is not enough to put on the ballot or if it is on the ballot that responsible individuals and organizations will work together to defeat it.

Freely available, high THC marijuana is going to be a catastrophic problem for our country. **MM**



Cannabis and the Violent Crime Surge

by Allysia Finley

Heavy marijuana use among youths is leading to more addiction and antisocial behavior.

The stigma once attached to marijuana has vanished. Nineteen states have legalized cannabis for recreational use, and politicians of both parties increasingly treat it as harmless. Asked during the 2020 presidential campaign about her pot use in college, Kamala Harris giggled and said marijuana "gives a lot of people joy" and "we need more joy in the world." But the public needs an honest discussion of its social and public-health risks, which include violence and mental illness.

Alex Berenson, author of *Tell Your Children: The Truth About Marijuana, Mental Illness, and Violence*, pointed out that the *New York Times* had curiously removed from an article about the Uvalde school shooter a former co-worker's recollection that he complained about his grandmother not letting him smoke weed. The *Times* didn't append a correction to the story as it might be expected to do when fixing a factual inaccuracy.

Assuming the elided detail was accurate, it would fit a pattern. Mass shooters at Rep. Gabby Giffords's constituent meeting in Tucson, Ariz. (2011), a movie theater in Aurora, Colo. (2012), the Pulse nightclub in Orlando, Fla. (2016), the First Baptist church in Sutherland Springs, Texas (2017), and Marjory Stoneman Douglas High School in Parkland, Fla. (2018), were reported to be marijuana users. It could be a coincidence, but increasing evidence suggests a connection.

Isn't pot supposed to make you mellow? Maybe if you smoke only a joint on occasion. But youth nowadays are consuming marijuana more frequently and in higher doses than their elders did when they were young.



Allysia Finley is a member of the *Wall Street Journal* editorial board.

This article first appeared in the Wall Street Journal and is reprinted with permission.

This is leading to increased addiction and antisocial behavior. THC, the chemical that causes a euphoric high, interacts with the brain's neuron receptors involved with pleasure. Marijuana nowadays on average is about four times as potent as in 1995. But dabs—portions of concentrated cannabis—can include 20 times as much THC as joints did in the 1960s. It's much easier for young people to get hooked. One in six people who start using pot while under 18 will develop an addiction, which doctors call "cannabis use disorder." As they use the drug more frequently to satisfy cravings, they develop psychological and social problems.

That's what happened to Colorado teenager Johnny Stack. His mother, Laura, wrote a harrowing book chronicling his descent into cannabis addiction. He started smoking weed at 14, after Colorado legalized it, and progressed to using more-potent products such as dabs. He gradually withdrew from social activities and developed psychosis. Substance-abuse treatment and a stay at a mental hospital failed to cure him because chronic marijuana use permanently rewired his brain. Delusional, he jumped off a six-story building and killed himself. Alas, he's not an anomaly. "People who have taken large doses of the drug may experience an acute psychosis, which includes hallucinations, delusions, and a loss of the sense of personal identity," the National Institutes of Health notes.

Roneet Lev, an addiction specialist who previously led the Emergency Department at Scripps Mercy Hospital in San Diego, said in a recent interview with the American Council on Science and Health that California cannabis emergency-room visits climbed 53% in the three years after the state legalized recreational marijuana in 2016. Daily marijuana emergency-room visits in San Diego nearly quadrupled between 2014 and 2019. Cannabis-induced psychosis, she said, is fairly common. Some patients she treated experienced cannabinoid hyperemesis syndrome from long-term use, which causes "scromiting"—screaming and vomiting. There's no antidote. Some patients spend weeks in the emergency room waiting for placement in mental-health clinics.

Countless studies have also linked chronic cannabis use to schizophrenia. A meta-analysis in January examining 591 studies concluded that early marijuana use among adolescents was associated with a significant increase in the risk of developing schizophrenia. Researchers have yet to prove a causal relationship, but the weight of evidence is hard to dismiss. Some legalization proponents claim that other countries where marijuana is widely available have fewer mental-health problems than the U.S. But a study from Denmark last summer found that schizophrenia cases associated with pot addiction have increased three- to fourfold over the past 20 years as marijuana potency rose 200%. Young people are especially vulnerable to cannabis's effects because their brains are still developing. Scientists in a recent study reviewed scans of teenagers' brains before and after they started using pot. They found that parts of the brain involved in decision making and morality judgments were altered in pot users compared to nonusers.

But can pot make people violent? A study last year found that young people with such mood disorders as depression who were also addicted to pot were 3.2 times more likely to commit self-harm and die of homicide—often after initiating violence—than those who weren't. A meta-analysis found the risk of perpetrating violence was more than twice as high for young adults who used marijuana. It's possible that pot can trigger dangerous behavior in youths who may be predisposed to it for other reasons such as prenatal exposure to drugs. Also worrisome, legalization seems to be leading to more pregnant women using pot. About 20% of pregnant young women in California tested positive for marijuana in 2016. THC crosses the placenta and can impair neurological development. Prenatal exposure to marijuana has been linked to behavioral problems, mental illness and lower academic achievement in children and adolescents.

Maybe it's time that lawmakers and voters rethink their pot-legalization experiment before more young lives are damaged.

MM

Scan code to read more on Cannabinoid Hyperemesis Syndrome in the May/June 2022 issue of *Missouri Medicine*.



Nurses With a Doctorate in Nursing Practice (DNP) Should Not Call Themselves "Doctor" in a Clinical Setting

by Gary Gaddis, MD, PhD

A nurse calling themselves "Doctor" in a clinical setting may mislead patients, and it should probably result in discipline of their nursing license.

Introduction

Advanced Nurse Practitioners (ANPs) provide at least a portion of the clinical care received by some Missouri residents. A subset of these ANPs have earned a Doctorate of Nursing Practice (DNP) degree.

Patients generally value the care they receive from their ANP clinicians, be they a DNP, or not. ANPs are generally perceived to be likeable and competent. Of course, by law, ANPs' clinical competence is enhanced by the requirement that all Missouri ANPs must practice in conjunction with a "collaborating physician."[1] Fully independent practice in Missouri is reserved exclusively for physicians, the only clinicians who have the training that makes them actual medical doctors.



Gary Gaddis, MD, PhD, FFIFEM, MAAEM, FAAEM, FACEP, is a Clinical Professor of Emergency Medicine at Washington University School of Medicine in St. Louis.

Unfortunately, some ANPs who have achieved a DNP degree refer to themselves as "doctor" in clinical settings. This is problematic. Although it is true that DNPs have earned a doctoral degree from an accredited institution, they are not physicians. In an academic setting, they could appropriately ask to be called "Doctor." But, to call themselves "Doctor" in a clinical setting misleads the patient and perpetrates a fraud which defies their patient's trust.

The fraud exists because in claiming the title "Doctor" in a clinical setting, the DNP who is in essence impersonating a physician ignores the substantial knowledge and training gaps that exist between a physician and a non-physician. They also overlook the inherent and substantial limitations that these gaps convey. Ignoring those limitations can cost the trusting patient greatly.

Two recent cases of which I have become aware are illustrative:

Case #1

While working in the emergency department of a rural critical access hospital in April, I cared for a young diabetic patient who did not know if he was a Type I or Type II diabetic. He had an obvious cutaneous yeast infection in his groin fold. His Body Mass Index exceeded 40, and he reported his typical daily awakening

blood glucose level was typically 200-250 mg/dL. He was unaware of his hemoglobin A1-C level and indicated he had never heard of that test. His only medication for diabetes was once-daily long-acting insulin, and he identified a DNP as his "Doctor."

Within the Epic Electronic Health Record, this DNP did clearly designate that they had DNP degree, and made no written claim to be a physician. However, the patient said the DNP called herself his "Doctor" during his office visits. The patient told me he did not understand the difference between a physician and a DNP, so I explained that difference to him.

He reported that his DNP had never suggested referring him to an endocrinologist or adding any other medications to his once-daily insulin blood sugar control regimen. Further, she had never suggested that weight loss would benefit him.

I am neither an internist nor an endocrinologist. However, this patient clearly needed more than once-daily long-acting insulin to ameliorate his chronic hyperglycemia. He needed to be encouraged and enabled to lose weight. If he was truly a Type I diabetic, he needed a more effective insulin regimen. If he was actually a Type II diabetic, an addition of a Sodium Glucose co-Transporter 2 (SGLT-2) such as Jardiance™ (empagliflozin) and/or a Glucagon-Like Peptide-1 agonist such as Ozempic™ (semaglutide) could be useful not only toward better glucose control, but also toward facilitating weight loss.

I must wonder how many ANPs are aware of these recent additions to the diabetes armamentarium, their effects, indications, and contraindications. In Missouri, to function as an ANP, one must be licensed as an Registered Nurse (RN) and then obtain a Document of Recognition (DOR) from the state.[2] RNs in Missouri are not required to obtain continuing education credits to renew their nursing license.[3] However, to maintain a DOR, ANPs must provide documentation of completion of at least 60 hours of continuing education every two years.[4]

Case #2

Substandard care is not limited to nurse practitioners who may not be holders of a DNP degree. An ophthalmologist with whom I was discussing substandard, non physician-led care noted a case of a patient referred to his clinic. The patient was a young female with Type II diabetes, who identified her "Doctor" as a "CNP." It is not known what the patient was trying to communicate via this nomenclature, but she clearly had been managed only by a nurse practitioner for a prolonged period of time, during which numerous opportunities for better care were missed.

The patient reported that she had not undergone a thorough eye exam in at least 10 years, and the one that she had undergone was performed at a commercial optical office. By the time an ophthalmologist saw her earlier this year, she had developed proliferative diabetic retinopathy in both eyes, along with bilateral vitreous hemorrhages of varying ages.

The patient reported her NP had never suggested an annual exam by an eye specialist such as an ophthalmologist. She reported that her last Hemoglobin A1C was about 11 or 12%, and that her nurse practitioner had not cited this to the patient as problematic or done anything to improve it.

This is a patient at high risk of premature and avoidable blindness due to the retinopathy, and renal insufficiency due to diabetes-associated renal microvascular changes. Her quality of life and life expectancy will surely both be negatively impacted due to the poor quality of care she has received

The patient was unable to identify the physician supervising her nurse practitioner, and reported that she had never seen that physician. Of course, under Missouri statutes, an ANP's collaborating physician is not obligated to ever see the patient, whose care can be supervised from afar.[1] The required degree of physician collaboration can be provided by review of a subset of the ANP's clinic notes. One must wonder how much collaborating was going on between the doctor and the ANP in this case, and whether the fault for this was mostly due the ANP, the physician, or both. This case also clearly illustrates that a better definition of "collaborating physician" may be indicated.

Quality of Care is Important

Kianmehr et al. have recently demonstrated that diabetic patients with poor control of their Hemoglobin A1C, hypertension, low density lipoprotein levels, and body mass index suffer demonstrable harm via a shorter life expectancy.[5] The poor control of these patients' medical problems is likely to cost them years from their lives.

Physicians versus ANPs: A Huge Contrast in Outcomes

Many nurse practitioners can give good care, if they stay within their appropriate scope of practice.

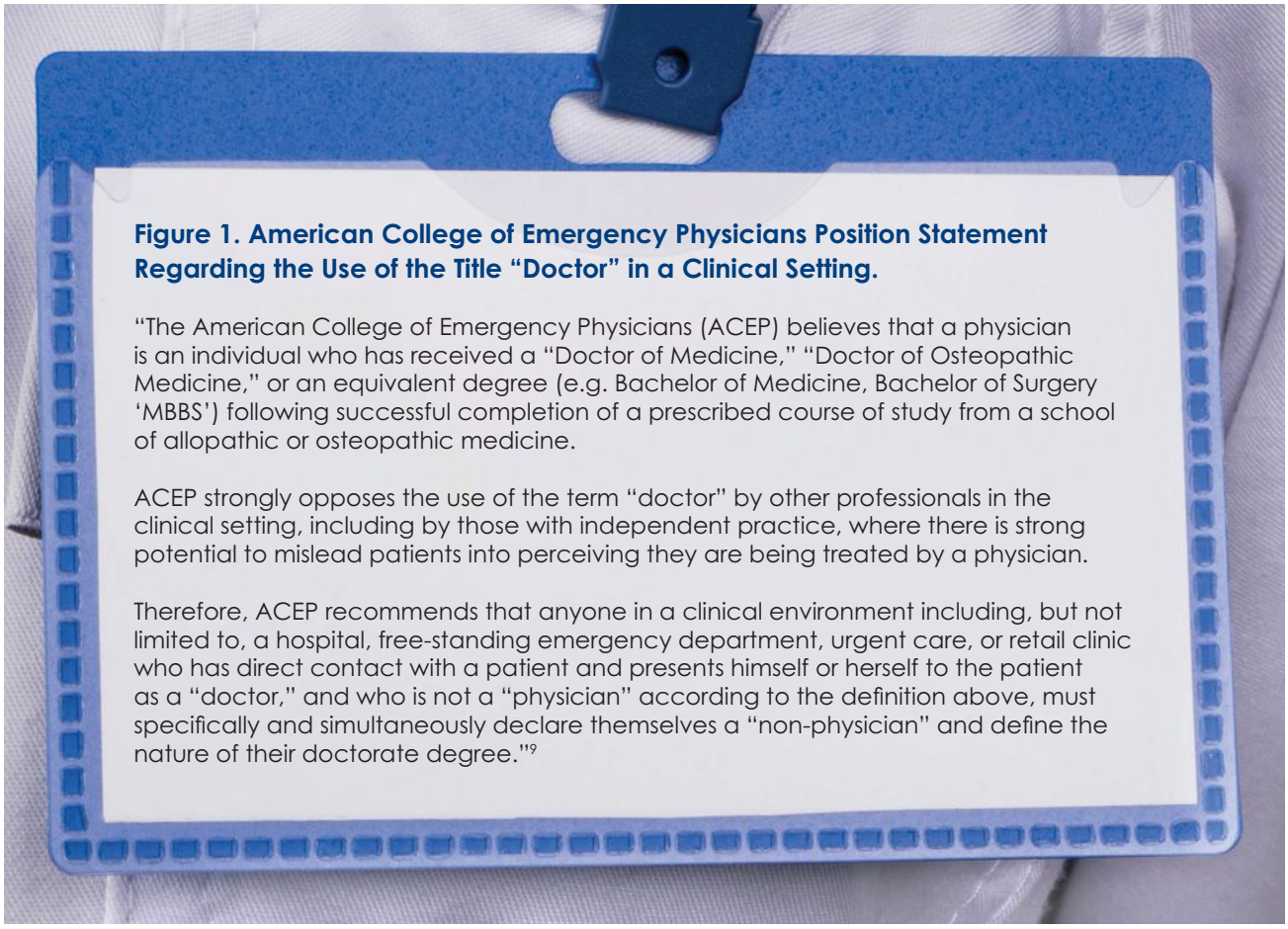


Figure 1. American College of Emergency Physicians Position Statement Regarding the Use of the Title "Doctor" in a Clinical Setting.

"The American College of Emergency Physicians (ACEP) believes that a physician is an individual who has received a "Doctor of Medicine," "Doctor of Osteopathic Medicine," or an equivalent degree (e.g. Bachelor of Medicine, Bachelor of Surgery 'MBBS') following successful completion of a prescribed course of study from a school of allopathic or osteopathic medicine.

ACEP strongly opposes the use of the term "doctor" by other professionals in the clinical setting, including by those with independent practice, where there is strong potential to mislead patients into perceiving they are being treated by a physician.

Therefore, ACEP recommends that anyone in a clinical environment including, but not limited to, a hospital, free-standing emergency department, urgent care, or retail clinic who has direct contact with a patient and presents himself or herself to the patient as a "doctor," and who is not a "physician" according to the definition above, must specifically and simultaneously declare themselves a "non-physician" and define the nature of their doctorate degree."[9]

And, that scope should include the careful and regular oversight of a collaborating physician, as provided by Missouri law.[1]

In my experience, ANPs can be willfully blind to the inevitable shortcomings arising from their truncated clinical training, when compared to that obtained by a physician. These deficits can easily perpetrate outcomes such as those illustrated above.

Unfortunately, clinically unsupportable statements demonstrating willful blindness exist from nurse practitioner organizations, regarding their alleged high quality of their care. Here is an example: "… it is well established that patient outcomes for NPs are comparable or better than that of physicians. NPs provide high-quality and cost-effective care."[6]

This statement is demonstrably false. Consider the recent data from a clinic in Hattiesburg, Miss., published earlier this year in the *Journal of the Mississippi Medical Association*[7] and publicized by the Physicians for Patient Protection[8] (PPP). This study documented that care provided by Advanced Nurse Practitioners (ANP) was markedly more costly than the care provided by physicians.

To quote a PPP news release: "The Hattiesburg Clinic in Mississippi—a large, multi-specialty facility with over 300 physicians—spent 15 years hiring more physician assistants, nurse practitioners, and other advanced practice providers (APPs). The clinic's goal was to provide the best care to patients at the best value. After analyzing years' worth of data, they reached an important conclusion: Replacing physicians with PAs and NPs resulted in higher costs, not lower."[8]

The cost difference was enormous, estimated at more than $28 million annually.[7] The bulk of the higher cost came from increased test ordering, increased specialist referrals, and more patients being sent to emergency medicine departments. Nurse practitioners, in particular, stood out as high-cost outliers.[7,8]

The authors "…disclosed that, based on "a wealth of internal data, the results are consistent and clear: by allowing APPs to function with independent panels under physician supervision, we failed to meet our goals in the primary care setting of providing patients

with an equivalent value-based experience."[7] Stated more simply, the PPP bulletin noted that replacing physicians with PAs, and especially with NPs, ends up costing patients more, while also degrading the quality of care.[8]

Physicians Alone Have the Expertise and Training to Lead Clinical Care Teams and Lead They Must

Physician organizations have long justifiably advocated for physician-led care. For instance, the American College of Emergency Physicians adopted a policy on the matter in 2014 and updated it in 2020 (Figure 1).[9] That policy clearly asserts that physicians should lead clinical care teams.

Some nurses' organizations opine differently. An author of an item published by "registerednursing.org" has stated: "Those who support using the title of "doctor" for DNP or PhD nurses have a few reasons why it should be allowed. First, it's a recognition of the level of expertise and clinical skills of a nurse. It represents that the nurse has achieved the highest degrees possible in nursing and should be considered an expert in his or her field. Second, it also can help build trust between the nurse and patient as the patient can be reassured of the nurse's competency. This is especially true for nurse practitioners who practice similarly to physicians. Additionally, if other professionals can refer to themselves as "doctor," why shouldn't someone who earned a Doctor of Nursing Practice?"[10]

There can be no way that just saying something is so makes it true. Use of the term "doctor" by a DNP in a clinical setting does not help the patient be "… reassured of the nurse's competency." Such a statement is misleading and conveys an illusion that overlooks several important facts:

- Master's level ANP programs exist which have admitted 100% of their applicants in 2019.[11] This group of admitted students has included substantial numbers of nurses with scant previous clinical experience. No medical or osteopathic school has ever admitted 100% of those who apply. This contrast speaks for itself.
- ANP programs provide their students with much less in-depth instruction in both the pre-clinical medical sciences such as anatomy and physiology, and the clinical medical sciences such as pharmacology or clinical pathology, than do schools of medicine or osteopathy. It is easy to discern the superficial levels of basic and clinical science understanding by many nurses, who are strong as regards caring and "pattern recognition," but woefully weak in their understanding of the underlying science that explains the patterns they observe. All physicians, myself included, have gained highly valued lessons from the nurses with whom we have worked. Those lessons generally don't involve deep dives into the sciences that underpin the medical decisions we make as physicians. Rather, they are vignettes passed from a teacher to a learner in the manner by which a master instructs an apprentice, passing along valued lessons learned via experience.
- Many ANP programs require their students to arrange their own site for their supervised clinical experience. This would be unthinkable for physician training in the United States, both for undergraduate and graduate medical education.
- ANP programs do not require those providing the evaluation of the ANP's supervised clinical training (which need exceed only 500 hours) to be faculty members of the degree-granting institution. This strikes me as a form of academic fraud.
- ANPs do not begin or complete any residency program to sharpen their clinical skills after they obtain their advanced nursing degree. Therefore, no organization equivalent to each medical specialty's Residency Review Committee (RRC) exists to provide third-party oversight of ANPs' postgraduate clinical training processes, because no such post-graduate training processes exist!
- Upon completion of their clinical experience while enrolled in an ANP program, the sum of the ANP's clinical training is markedly less extensive and less well-supervised than medical school clerkships. When totaled, an ANP's supervised clinical formation can include as few as 500 hours of such training. No state allows medical students to perform unsupervised medical practice after 500 hours of well-organized medical clerkships. No states allow residents who have logged at least 500 hours of well-organized, clinically-supervised care to become fully licensed physicians, either.

The education of physicians is a much more extensive and carefully regulated process, on a number of levels. The Liaison Committee for Medical Education (LCME) accredits medical schools and the various specialties' RRCs provide exacting accreditation and third-party oversight of residency training.

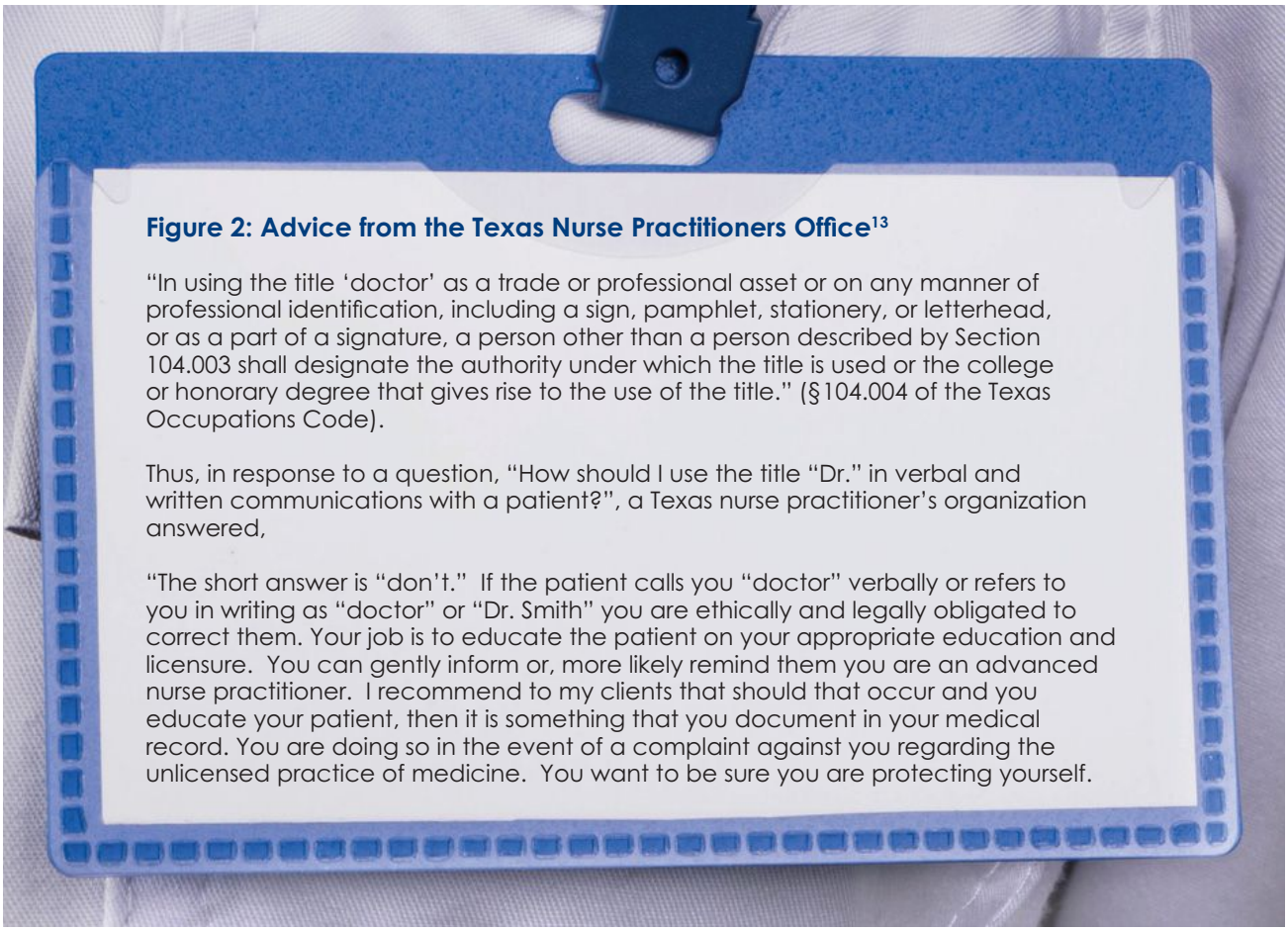


Figure 2: Advice from the Texas Nurse Practitioners Office[13]

"In using the title 'doctor' as a trade or professional asset or on any manner of professional identification, including a sign, pamphlet, stationery, or letterhead, or as a part of a signature, a person other than a person described by Section 104.003 shall designate the authority under which the title is used or the college or honorary degree that gives rise to the use of the title." (§104.004 of the Texas Occupations Code).

Thus, in response to a question, "How should I use the title "Dr." in verbal and written communications with a patient?", a Texas nurse practitioner's organization answered,

"The short answer is "don't." If the patient calls you "doctor" verbally or refers to you in writing as "doctor" or "Dr. Smith" you are ethically and legally obligated to correct them. Your job is to educate the patient on your appropriate education and licensure. You can gently inform or, more likely remind them you are an advanced nurse practitioner. I recommend to my clients that should that occur and you educate your patient, then it is something that you document in your medical record. You are doing so in the event of a complaint against you regarding the unlicensed practice of medicine. You want to be sure you are protecting yourself.

Clinical formation supervision by medical school and residency faculty is a task that requires 5,000 to 15,000 hours of preparation on the part of the learner, depending on the specialty. This supervision is provided by educators who are members of the degree-granting institution's faculty.

In contrast, the model that best describes ANP training is an apprenticeship, because the student finds the site and preceptor under which they are exposed to the clinical realm. Schools of medicine abandoned such an apprenticeship-type approach to education at the time of the Flexner report in 1910.[12]

ANPs Who Assert Being a "Doctor" in Clinical Spaces

Approaches in Selected Other States

Several states have statutes that consider the facts about the shortcomings of ANP training, and specifically limit ANPs from using the term "doctor" or "physician" to describe themselves in a clinical setting.

Texas

Texas nurse practitioners have recently been cautioned by the Texas Nurse Practitioners' Office not to mislead their patients (Figure 2). The cautions included, "The Texas Medical Board very-well may and often does open investigations into the practice of medicine without a license on nurse practitioners. To date, as long as the advanced nurse practitioner with a doctorate abides by the above law and it is extremely clear that one is not a physician but rather an advanced nurse practitioner with a doctorate, such cases eventually have been dismissed, but after the expense of a defense.[13]

Minnesota

Minnesota law also specifies that an ANP should clearly identify themselves as a non-physician. Advanced practice registered nurses (APRN) who have doctoral education often contact the Board regarding the appropriate and permitted use of the title "Doctor."

Information offered to Minnesota ANPs by the nursing board is contained in Figure 3.[14]

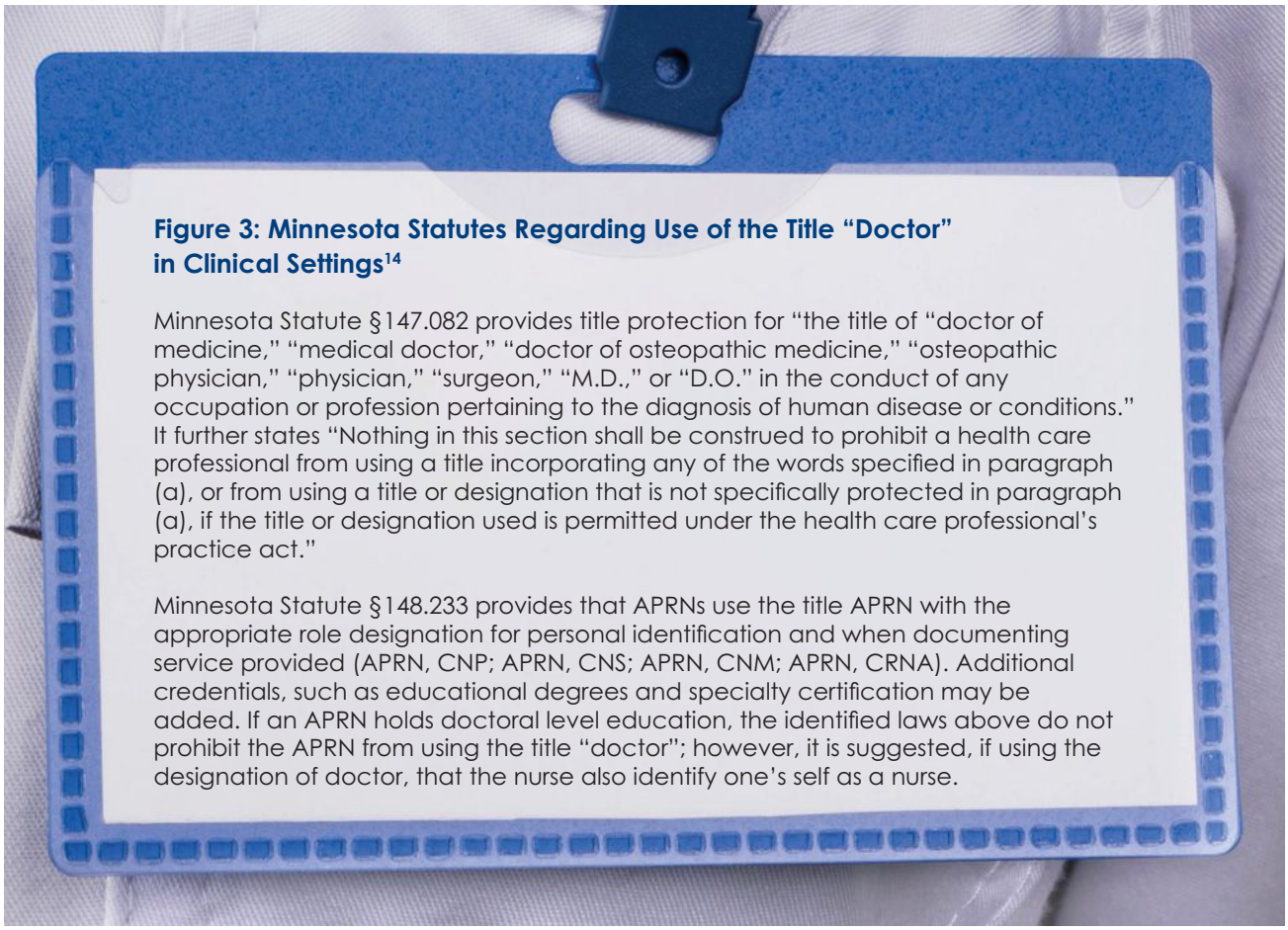


Figure 3: Minnesota Statutes Regarding Use of the Title "Doctor" in Clinical Settings[14]

Minnesota Statute §147.082 provides title protection for "the title of "doctor of medicine," "medical doctor," "doctor of osteopathic medicine," "osteopathic physician," "physician," "surgeon," "M.D.," or "D.O." in the conduct of any occupation or profession pertaining to the diagnosis of human disease or conditions." It further states "Nothing in this section shall be construed to prohibit a health care professional from using a title incorporating any of the words specified in paragraph (a), or from using a title or designation that is not specifically protected in paragraph (a), if the title or designation used is permitted under the health care professional's practice act."

Minnesota Statute §148.233 provides that APRNs use the title APRN with the appropriate role designation for personal identification and when documenting service provided (APRN, CNP; APRN, CNS; APRN, CNM; APRN, CRNA). Additional credentials, such as educational degrees and specialty certification may be added. If an APRN holds doctoral level education, the identified laws above do not prohibit the APRN from using the title "doctor"; however, it is suggested, if using the designation of doctor, that the nurse also identify one's self as a nurse.

Summary

Medical education is more selective than ANP education. Some ANP programs exist which admit 100% of their applicants, whether or not they have previous and extensive nursing experience. Data comparing ANPs against physicians, when considering their pre-clinical exposure to the medical sciences and their depth and length of supervised clinical formation, show that ANPs fall far short not only in the hours of preparation for their clinical roles, but also in the depth of instruction provided by the degree-granting institution, compared to allopathic and osteopathic physicians.

No school of medicine or osteopathy confers clinical degrees with the substantial lack of institutional oversight that characterizes many nurse practitioner programs, which typically allow their students to secure their own clinical formation training site, with supervision and evaluation by a non-faculty member of the degree-granting institution, at a clinical site that may not have been visited by a member of that institution's faculty. ANPs obtain clinical training in a model best described as an apprenticeship, an approach abandoned by medical schools since the Flexner Report of 1910.[12]

A physician's scientific and clinical training far exceeds that of any ANPs both in length and depth, whether the ANP is a holder of a DNP degree or not.

Data from the Hattiesburg Clinic clearly show that although ANPs earn a lower wage than physicians, they provide much more expensive care because they order more tests, they refer more patients to the emergency department, and they obtain more consults. This belies their general difficulty at efficiently reaching a clinical decision, a handicap that may derive from their being less extensively educated regarding scientific and other crucial clinical matters than are physicians.

Despite their more extensive training, physicians nonetheless commit clinical errors. By extension, it defies logic to suggest that any level of ANP, be they a holder of a DNP degree or not, could deliver clinical care with equivalent safety and cost-effectiveness to that provided by physicians.

ANPs are important and highly valued members of clinical care teams when they function with an appropriate scope of practice and supervision. However, it is a lie to assert that ANPs, with or without DNP training, can independently provide high quality care to complex patients with anything approaching that which can be expected from physician-led care teams. Further, for an ANP to refer to themselves as a "doctor" in a clinical setting compounds the degree of misrepresentation that begins with a misrepresentation of an ANPs educational processes and culminates when an ANP with a doctoral degree refers to themselves as "doctor" to their patients.

Future Directions

The American Medical Association adopted Council on Medical Education (CME) Report Number 4, that spoke to this matter during its 2022 Annual meeting.[15] That report stated, in part:

"Our AMA: (1) will advocate that all health professionals in a clinical health care setting clearly and accurately identify communicate to patients and relevant others their qualifications, and degree(s) attained, and current training status within their training program; (2) and develop model state legislation for implementation to this effect; and (3) supports state legislation that would make it a felony to misrepresent oneself as a physician (MD/DO); and (4) will expand efforts in educational campaigns that: a) address the differential education, training and licensure/certification requirements for non-physician health professionals versus physicians (MD/DO) and b) provide clarity regarding the role that physicians (MD/DO) play in providing patient care relative to other health professionals…"[15]

Given the information provided above, our Missouri State Medical Association would be wise to identify state senators and representatives sympathetic to our beliefs, and work to facilitate enactment of statutes patterned after those of Texas and Minnesota, and concordant with the American Medical Association's CME Committee Report #4, so that confusion in clinical settings regarding just what "doctor" means can be avoided in the future.

Conclusion

Only physicians should call themselves "doctor" in a clinical setting where clinical care is being provided to trusting patients.

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Reversing the Decreasing Life Expectancy: A National Health Priority



by Kate Lichtenberg, DO

The Center for Disease Control and Prevention (CDC)'s National Center for Health Statistics (NCHS) published a startling report in July 2021 documenting a decrease in the life expectancy of Americans to the lowest level since 2003.[1,2] This was the largest one-year drop since World War II. Not only did life expectancy fall, but the disparity between men and women continued to widen as it has since 2010.



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Changes in the U.S. Life Expectancy Rates

The decrease in life expectancy across the entire U.S. population was 1.5 years. Men had a decline of 1.8 years from 76.3 years to 74.5 years. Women experienced a decline of 1.2 years from 81.4 years to 80.2 years.[2] The gap between men (shorter life) and women (longer life) increased from 4.8 years in 2010 to 5.7 years in 2020.

The leading causes of death for 2020 were heart disease, cancer, and COVID.[3] Seventy-four percent of the decline in life expectancy was attributed to COVID while accidental and unintentional injuries contributed to 11% of the decline, homicide contributed 3.1%, diabetes contributed 2.5%, and chronic liver disease and cirrhosis contributed 2.3%.[1,2] The overall decline of 1.5 years would have been greater if there had not been offsetting effects of declining mortality due to cancer, chronic lower respiratory diseases, heart disease, suicide, and certain perinatal conditions.[2]

Across racial groups, there were differences in the decline as well as the reasons for lower life expectancy. The Hispanic population suffered the largest decline in life expectancy of 3 years with 90% of the decline due to COVID mortality. Unintentional injuries, diabetes, homicide, and chronic liver disease and cirrhosis accounted for the remaining reduction.[2]

The non-Hispanic Black population had the second largest drop of 2.9 years. COVID accounted for 59.3% of the decrease followed by unintentional injuries, homicide, heart disease, and diabetes.[2]

The non-Hispanic White population experienced the smallest decline in life expectancy of 1.2 years. Excess mortality due to COVID contributed to 67.9% of the decrease followed by unintentional injuries, chronic liver disease and cirrhosis, diabetes, and homicide.[2]

Changes in the Missouri Life Expectancy Rates

The Missouri Department of Health and Senior Services published a report in August 2021 providing details on the decrease in life expectancy for Missourians.[4] The overall decline was 2.1 years with male life expectancy dropping 2.3 years to 72.3 and females dropping 1.9 years to 78.4 years. The male to female gap is now 6.1 years, the largest since 1997. The report did not include information on differences in racial groups.

Deaths in Missouri outnumbered births for the first time since officials began tracking this statistic in 1911. Deaths increased by 18.9% and broke the record of an increase in deaths in a single year. The previous record was a 13.3% increase that occurred during the 1918 Influenza Pandemic. Approximately 66% of the increase in deaths in Missouri was due to COVID. Unintentional injuries, diabetes, nephritis, pneumonia and influenza, stroke and heart disease contributed to the remaining increase in deaths.

Drug overdose deaths (accidental poisonings) were the primary contributor to the increase in unintentional injuries. Deaths related to opioid use along with suicides and homicides increased by more than 25%. Deaths in this category have more than doubled since 2010. The report speculated that COVID may have contributed to the increase in these deaths since many people were more isolated and may have had problems accessing services.

The report also highlighted the record 28% increase in homicides since 2019. The 802 residents who died by homicide in 2020 is also nearly double the number in 2010. The number of suicides remained relatively stable, but is up 30% since 2010. Firearms continue to be a factor in both homicides and suicides and firearm-related deaths were up 14% between 2019 and 2020.

Working-Age Mortality

The National Academies of Sciences, Engineering, and Medicine released a report in 2021 detailing a decline in U.S. life expectancy from 2015 to 2017. This decline was primarily due to an increase in mortality among working age adults 25- to 64-years old.[5] Drug poisoning and alcohol induced deaths, suicide, and cardiometabolic diseases were identified as the causes of death most responsible for this increase.

Life expectancy disparities are widening based on race/ethnicity, socioeconomic status, gender, and geography (rural versus urban). The years of progress in closing these gaps are in danger of being wiped out completely and even moving backward due to excess COVID mortality.

Addressing Causes of Excess Mortality

There will always be a need for individuals to reduce unhealthy behaviors. However, implementing new public policies are likely the best opportunity to increase life expectancy. These public policies must address the immediate causes of morbidity and mortality, but also look at the upstream contributors including living conditions, access to nutritious food, and access to medical care.[5]

Improvements in life expectancy and decline of infectious disease throughout the 20th century were aided by medical advances. Jeff Levin, PhD, MPH believes, "a general improvement in the quality of life," was chiefly responsible.[6] He also states: "The political will to address social-structural and environmental causes of health disparities in vulnerable populations is not easily manifested."[6] Until society finds that will, it will be difficult to overcome further life expectancy decreases.

COVID

The emergence of the COVID virus has tested Public Health in the U.S. in a way not seen in

decades. Short-term studies, the changing and, sometimes conflicting recommendations, have generated significant confusion and mistrust in the general public. The unprecedented speed of research led to several effective and FDA approved vaccines but mistrust and misunderstanding have resulted in poor vaccination rates in many populations.

It is of paramount importance to learn from the mistakes of this pandemic in order to better manage endemic COVID and to prepare for future pandemics.

Accidental and Unintentional Injuries

The Substance Abuse and Mental Health Services Administration (SAMHSA) defines harm reduction as a "proactive and evidence-based approach to reduce the negative personal and public health impacts of behavior associated with alcohol and other substance use at both the individual and community levels."[7]

Connecting individuals with a substance use disorder to services that offer health care, social services, and treatment have been shown to decrease the spread of infectious disease, improve physical health, and reduce overdose deaths. Examples of harm reduction programs include distribution of naloxone to those who use opioids and needle exchange programs. Under consideration in the 2022 session, Missouri Senate Bill 690 would make needle exchange programs legal in the state.

Gun violence has been called a public health emergency by many organizations and individuals. Gun safety becomes even more urgent after the CDC reported in April 2022 that in 2020, firearm-related injuries became the leading cause of death in the 1- to 19-year-old age group.[8] Finding the balance between the rights of gun owners and protecting those at risk of harm will not be easy. In the last 30 years, policy changes have been mostly at the state rather than the federal level. Three interventions in particular have been supported across the political continuum.[9]

Safe storage sites for firearms decreases the number of firearm suicides and unintentional shooting by 8-19%. Twenty-nine states and the District of Columbia have implemented laws supporting this. The current evidence only supports this measure for children and adolescents. Continued research is needed to see if this extends to adults.

Virginia and Washington have laws that permit individuals to confidentially and voluntarily restrict their ability to purchase firearms from dealers. Those individuals may remove their names if they change their minds. A delay period is in place so the removal is not immediate.

Extreme risk protection orders, known also as red flag laws, have been implemented in multiple states. This entails a judicial process whereby individuals are restricted in their ability to purchase or possess a firearm if they are deemed at extreme risk to harm themselves, others, or both. There is considerable research ongoing on extreme risk protection orders and preliminary data suggests decreases in suicide risk of 5-10%.

Diseases Related to Obesity

Type II diabetes, cardiovascular diseases, and some cancers are related to obesity. Over the past 30 years, obesity rates have continued to climb at an alarming rate. Personal responsibility is only one part of the solution to this. There are many societal factors that need to be addressed at the community, state, and national levels in order to decrease the rates of obesity and the associated morbidity and mortality.

Food insecurity is defined as "the state of being without reliable access to a sufficient quantity of affordable, nutritious food."[10] During 2020, 13.8 million U.S. households experienced food insecurity.[11] Calorie insufficiency initially prompted programs like food stamps and the Special Supplementation Nutrition Program for Women, Infants, and Children (WIC). The paradigm has now shifted to nutrition security rather than calorie security. Nutrition security is "having consistent access, availability, and affordability of foods and beverages that promote well-being and prevent…disease."[10] Food deserts also need to be addressed and eliminated. If a gas station or a dollar store are the only options for grocery shopping, calories may be obtained but at the cost of nutrition.

Having a safe place to exercise is also key to decreasing obesity rates. The ability to safely walk in your neighborhood is associated with an increase in physical activity and a decrease in chronic conditions.[12] Socioeconomic factors also impact walkability. Low-income Black and Latinx neighborhoods have lower Walk Scores than most low-income White neighborhoods.[12] Investment in the built environment is critical to impacting this.

Guidelines recommend 150 minutes of exercise

A Second Missouri Compromise

by George P. Hubbell, MD

Abortion has always been a complex, and obstetric medical, ethical, religious, and philosophical evaluation.

In late June, the federal Supreme Court issued a judgement in *Dobbs v. Jackson Women's Health* and by a 6-3 decision voted to uphold a Mississippi district court's decision to proscribe performing or inducing an abortion after 15 weeks. This decision, in effect, eliminated the constitutional right to obtain an abortion, rescinding the 49-year-old *Roe v. Wade* decision, as well as *Planned Parenthood v. Casey*; decisions that were precedent in all 50 states. By declaring these decisions wrongfully decided, the judicial branch further removed the Supreme Court from future decisions by stating the constitution is neutral on the issue. The power for those decisions immediately shifted to individual state legislatures.

Polling conducted by the Associated Press showed that a majority of Americans preferred to see the court leave *Roe v. Wade* alone, and a majority of Americans support abortion access with certain restrictions. About a third thought abortion should be legal in all cases, roughly another third believed it should be legal in most cases. About one-fourth of respondents thought abortion should be illegal in most cases, and about one in ten think it should be illegal in all cases.[1]

In Missouri, the attorney general recognized the court decision by signing an opinion almost immediately after the Court issued its decision. The opinion activated a "trigger law," making Missouri the first state to do so. Soon after, the governor issued a proclamation to that effect. The trigger law, HB 126, was passed by the 2019 state legislature and holds that an abortion may only be performed based on "reasonable medical judgment," a condition that "so complicates the medical condition of a pregnant woman as to necessitate the immediate abortion of her pregnancy to avert the death of the pregnant woman or for which a delay will create a serious risk of substantial and irreversible physical impairment of a major bodily function of the pregnant woman."[2]

The current statute offers no exceptions for rape, incest, lethal anomalies, psychological, or emotional conditions. Further, physicians in Missouri performing abortions now face a Class B felony, defined as a conviction requiring at least five but not more than 15 years of prison, which is the same criminal classification as manslaughter. Additionally, loss of license with applicable discipline by the state board is permitted. The pregnant woman is not assessed any criminal penalty under the new statute.

Abortion has always been a complex, and obstetric medical, ethical, religious, and philosophical evaluation. Before specific statutes in states were adopted, it was legal under common law extending back to the colonies. Common law held if the mother died during the procedure, the person performing it was guilty of murder. In some areas, it was not illegal up through the 20th century until quickening—when the mother sensed the baby moving. Legislatures initially established statutes in individual states beginning with Connecticut in 1821. The issue now returns to the states once more, where legislators will individually decide abortion policy.

Worldwide abortion to protect a woman's life is allowed and legal in 98% of countries. Three countries including the U.S. have curtailed abortion rights in the past 20 years, while 31 have expanded abortion rights in the past two decades. Access to abortion is protected in 16 states and the District of Columbia, while 17 states have trigger laws banning the procedure, creating a country further divided on this single issue.[3] Since 2018, one licensed clinic existed in the state, in St. Louis, MO, and is now closed.



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Missouri State Medical Association

Press Release

FOR IMMEDIATE RELEASE/July 19, 2022

Missouri's Largest Physician Organization Issues Statement Regarding the Overruling *Roe v. Wade*

JEFFERSON CITY - On June 24, 2022, the Supreme Court of the United States voted to eliminate the constitutional right to an abortion, overruling the *Roe v. Wade* decision of 1973. This decision left the issue of abortion's legality to each state to decide. In Missouri, the opinion means that a trigger law passed in 2019 by the state legislature is now in effect. The law bans abortion in Missouri, with the exception of abortions that are performed "in cases of medical emergency" (188.026, RSMo).

The MSMA Council created the following statement:

"As physicians, our utmost responsibility is to the health and well-being of our patients. MSMA supports legislation that protects physician-patient autonomy, and opposes the criminalization of medically-necessary healthcare, and policies that restrict Missourians' ability to access healthcare in Missouri and other states."

The health and safety of patients is paramount to Missouri's physicians. Patients are put at risk when they feel they cannot speak openly with their physician about medical decisions. Physicians and patients should be free to discuss and pursue medical procedures based on each patient's individual set of circumstances and their physician's best medical judgment without fear of intrusion from outside entities.

MSMA will continue to engage with legislators at the Missouri State Capitol as we advocate for physicians, patients, and the sacred and confidential physician-patient relationship.

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Abortion is a complicated, non-binary issue. It is not simply defined by pro-life or pro-choice groups, but it will be defined on a continuum by each state. Out of all the current chaos, hopefully we can move beyond moral judgments and have meaningful discussions about what kind of medical care best serves our patients. The fear and uncertainty created by the criminalization of the procedure will likely be addressed by the state legislature next session. The MSMA lobbyists will continue to be our ears in Jefferson City. When discussing such an emotional topic, it can seem like there is no middle ground, but compromise must be found. The single issue of abortion shouldn't have us all forget the collective good our profession brings to us and our patients. To know how we will practice women's health after *Dobbs* will take all of us. Hopefully, we'll reach common ground with a second "Missouri compromise."

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Report of the American Medical Association Annual Meeting

by Charles W. Van Way, III, MD & the Missouri AMA Delegation

In person at last! The 2022 Annual Meeting of the AMA House of Delegates (HOD), was held in Chicago, in person, with all of the excitement and drama, June 10-15. It's been three years since an in-person meeting has been held, and all of the delegates were very happy to put the pandemic behind them. Well, mostly. Drs. Van Way and Barbe were unable to attend, because of COVID. The pandemic is still very much with us

The Annual Meeting considered many issues, setting policy for the AMA. It also included inauguration of the President, elections for President-Elect, Board of Trustees (BOT) and several Councils, and re-election of the Speaker and Vice-Speaker.

Outgoing President, Gerald "Gerry" Harmon, MD, spoke of the AMA Recovery Plan for America's Physicians. Physicians have been taking care of everyone else, and now it's time to take care of physicians. It's time to rebuild. The Recovery Plan has five elements: fixing prior authorization, reforming the Medicare payment system, fighting "scope creep" of non-physician practitioners, supporting telehealth, and reducing physician burnout. Worthy goals, indeed. Will they come to pass? We shall see.

James Madara, MD, AMA Executive Director, highlighted the 175-year history of the AMA. He emphasized that we need to address three areas: reshaping medical education to meet the demands of coming generations, removing obstacles from patient care, and fighting the surge in chronic disease. As well, he emphasized the Recovery Plan.

Jack Resnick, Jr, MD, was inaugurated as the 177th president of the AMA. A dermatologist from California, Dr. Resnick spoke of the challenges of the COVID years which have made them an uphill battle for physicians. These include political partisanship, vaccine misinformation, overwhelmed ICUs, and fear of personal and family illnesses. He talked about the need for the AMA to help physicians recover and move forward. Specifically, he advocated changes to the Medicaid payment system, doing away with prior authorization, combating physician burnout, and correcting inequities in our health system. He opposed criminalizing aspects of health care, including contraception, abortion, and gender affirmation.

Jesse Ehrenfeld, MD, MPH, was elected as President-Elect. An anesthesiologist and clinical informaticist, he is a Senior Associate Dean at the Medical College of Wisconsin. He will be the first openly gay President of the AMA. Elections for members of the BOT and the various Councils were also held.

The HOD conducts the real business of the AMA, setting policy and recommending action to be taken. This is done in one of two ways. First, resolutions may be directly submitted to the HOD proposing policy or action. The HOD considers each of these, and may accept, reject, or modify them. Second, the BOT or one of the Councils may submit a report with recommendations for policy changes or actions. These recommendations are then discussed by the HOD, Often, these reports are the result of resolutions from a previous meeting.

There were many reports and resolutions affecting medical education. Council on Medical Education (CME) Report #3 advocated expanded and subsidized childcare for medical students, residents, and fellows.



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As most of us are well aware from our own past experience, child care is a serious issue for trainees at all levels. Other concerns about medical education included the use of "residency" and "fellowship" to describe non-physician training (CME Report #4, Resolution #329), the effect of non-physician training upon physician training (CME Report #5), and the continued problem of medical education debt (Resolution #301). Physician wellness during training was addressed in resolutions calling for standardized reporting of wellness initiatives and of suicides among medical students and residents (Resolutions #326, #327). Resolution #309 called for decreasing bias in medical student performance evaluation. Resolution #301 called for a study on cancellation of medical education debt. A Missouri resolution (#241) addressed the problem of MD graduates who fail to match. It called for other states to provide ways for MD graduates to work as "assistant physicians," as is done in Missouri. There was strong opposition to this, and it failed to pass.

The unsupervised practice of medicine by non-physicians such as APRNs is an ongoing concern. Sometimes called "scope creep," non-physicians are steadily encroaching on medical practice. Where supervised properly, non-physicians are a vital part of the health team. But independent practice is a step too far. Resolution #222 called for the AMA to support studies of the impact of such practices on patients, and proposed drafting model state legislation. On a similar issue, Resolution #201 called for a report on the impact of mid-level providers on medical education. Dealing with a different concern, Resolutions #250 and #252 opposed any attempt by legislatures to criminalize any aspect of medical practice.

A number of resolutions addressed issues of health care coverage. Council on Medical Services (CMS) Report #3 addressed how to prevent health care insurance losses after the COVID emergency ends. It made a number of technical recommendations to facilitate transition to more stable coverage, and prevent loss of coverage. CMS Report #4 addressed Medicare drug price negotiation, recommending changes in the AMA position towards this issue. This is a highly complex issue, involving both drug pricing to patients and physician reimbursement for physician-administered drugs. The AMA is active in working with Congress. In general, the AMA will favor drug price negotiation as opposed to the use of international price indices.

CMS Report #2 discussed prospective payment models. Existing models are not well-suited for independent private practice. A resolution from a previous meeting called for this report. The report called for consideration of additional prospective payment models, and established several principles. Whether this will resolve the issue remains to be seen; prospective payment remains a continuing concern.

Similarly, prior authorization requirements are a perennial concern. Resolution #731 called for restrictions in order to preserve patient autonomy. As adopted, it called for both patients and physicians be given access to an electronic prior authorization system in order to monitor the process. Resolutions #701 and #710 called for the AMA to continue existing efforts, and in addition to establish CPT codes for administrative burdens relating to the prior authorization process.

Public health is a continuing concern of the AMA. Council on Science and Public Health (CSPH) Report #2 advocated transformation of rural community public health through a number of initiatives, encouraging local physician involvement in such systems, and encouraging research to better define the needs of the rural community. This represents an update and renewal of much existing policy concerning rural public health.

An important BOT Report #15 addressed public health disinformation and misinformation put out by health care professionals, especially on social media. The report encouraged professional societies and licensing boards to take action against such disinformation, and local medical societies to act to dispel disinformation. There was concern that this might well lead to censorship of physician-patient communications, but the focus of the report was on dissemination through social media, and not individual patient contact. The AMA in the past has been fiercely protective of the rights of physicians to free communications with their patients. However, with physicians running for public office from both parties, this policy could be challenged as a restriction on free public speech.

BOT Report #17 and Resolution #217 advocated expunging criminal records of marijuana convictions, in states where marijuana is now legal. This might seem to conflict with AMA policy, which opposes legalization. But the justification is that individuals should not suffer consequences for past illegal acts when two-thirds of states have made such acts legal today. In line with existing policy was Resolution #501, which called for marketing "guardrails" for cannabis marketing. The AMA Cannabis Task Force is active in this area. There was particular concern about cannabis marketing to children, pregnant women, and other vulnerable populations. Finally, Resolution #505 called for restrictions on marketing of cannabidiol (CBD) oil.



The MSMA Delegation to the American Medical Association hard at work representing Missouri at the 2022 AMA Annual Meeting in Chicago in June.

There continues to be concern about access to birth control and contraceptives. Resolutions #511 and #518 both advocated over-the-counter access to oral contraceptives, without restriction by age. This would allow the AMA to urge the Food and Drug Administration (FDA) to change the status of all or some of these pharmaceuticals.

Resolution #208 calls for treating homemade firearms (often known as "ghost guns") as traditional manufactured firearms. This reflects a recent policy change by the Bureau of Alcohol, Tobacco, and Firearms, and aligns the AMA with current administration policy on such weapons. AMA policy is already quite robust in favoring firearms regulation, and has been active in promoting tighter regulation. Resolution #625 called for candidates for public office to refuse contributions from organizations who do not support "evidence-based measures to prevent gun violence." AMPAC has long had a "no litmus test" rule, feeling that no single test should allow or prevent it from supporting candidates. Just how this resolution will affect AMPAC will remain uncertain.

There were efforts to address climate change. Resolution #607 called for the AMA to declare climate change to be a public health emergency. It also directed the AMA to urge health and life insurers to divest investments in fossil fuels, much as has already been done for tobacco companies. Resolutions #420 and #430 were similar, advocating for a strategic plan for the AMA to combat global warming.

Several physicians from Missouri serve in leadership roles. David Barbe, MD, represents the AMA on the world stage as Immediate Past President of the World Medical Association. Edmond Cabbabe, MD, serves as Vice Chair of the Council for Long Range Planning and Development. Elie Azrak, MD, serves on the Board of AMPAC, the AMA Political Action Committee. Jerry Kennett, MD, serves on the AMA Foundation Board. Marc Mendelsohn, MD, is on the Council of the Young Physicians Section. Sue Ann Greco is the AMA Alliance Past President. Charles Van Way, III, MD, serves on the Steering Committee of OSMAP, the Organization of State Medical Association Presidents.

All of the business of the meeting, as well as summaries of the addresses by Drs. Harmon and Reznick, are available on the AMA website. Highlights from the meeting can be found at https://www.ama-assn.org/house-delegates/annual-meeting/highlights-2022-ama-annual-meeting. More complete proceedings as they become available, will be at https://www.ama-assn.org/house-delegates/annual-meeting/proceedings-2022-annual-meeting-house-delegates. The Interim Meeting of the HOD will be in Honolulu, Hawaii, November 12-15, 2022. **MM**

Genetic Testing: Disclosure to Patients and Payors and the Risks In Between

by Elicia Grilley Green, JD & Tracey Toll, JD

Physicians should strive to accurately communicate all results of genetic or genomic testing that could affect the patient's ability to make informed decisions regarding present or future medical treatment.

Genetic Testing

Upon publication of the full human genome sequence in April of 2022, those in the field of genome research emphatically recognized the immense influence this would have on the study of human disease.[1] In line with this prediction, ever-increasing technological advances have allowed health care to "transition[] from genetics to genomics, in which single-gene testing for diagnosis is being replaced by multi-gene panels, genome-wide sequencing, and other multi-genetic tests for disease diagnosis, prediction, prognosis, and treatment."[2] Due to the breadth of information revealed, genomic testing ordered with the goal of identifying risk for a specific disease or condition, may inevitably show a more complex picture, placing the physician in a position to determine what specific findings to disclose to the patient.



Elicia Grilley Green, JD, (left), Associate, and Tracey Toll, JD, (right), Senior Associate, both from the Dallas office of Husch Blackwell, wrote this article. Husch Blackwell represents a full spectrum of healthcare providers and other businesses in developing compliance strategies, filing copyright registrations, preliminary enforcement measures, and litigation matters. The information contained in this article should not be construed as legal advice or a legal opinion on any specific facts or circumstances. The contents are intended for general information purposes only, and readers are encouraged to consult their attorney concerning specific situations and specific legal questions.

Fiduciary Relationship

A unique relationship exists between physicians and their patients. This relationship is predicated on a knowledge imbalance, with the more vulnerable patient being in a position of reliance on the physician to convey information and direction. Fiduciary relationships have long been legally recognized for the purpose of protecting a more vulnerable party who must rely on the honesty and care of another.[3] It is fitting then, that courts have established that a fiduciary relationship exists between physician and patient.[4] "A physician occupies a position of trust and confidence as regards his patient—a fiduciary position. It is his duty to act with the utmost good faith. This duty of the physician flows from the relationship with his patient and is fixed by law[.]"[5] The medical profession has similarly acknowledged that fiduciary duties exist in the physician-patient relationship: "The relationship between a patient and a physician is based on trust, which gives rise to physicians' ethical responsibility to place patients' welfare above the physician's own self-interest or obligations to others, to use sound medical judgment on patients' behalf, and to advocate for their patients' welfare."[6]

Informed Consent

Trust is an essential element of the fiduciary relationship between physician and patient. The practice of shared decision making is crucial in establishing and maintaining trust between these two parties. Further, competent individuals have a legal right to decide what will be done to their bodies by making their own health care decisions.[7] By its very definition, shared decision making requires physicians to provide patients with the information necessary to make informed choices regarding their care and treatment.

Hence, the legal doctrine of informed consent was created with the aim of ensuring that these principles can be met. "The root premise is the concept, fundamental in American jurisprudence, that '[e]very human being of adult years and sound mind has a right to determine what shall be done with his own body. . . .' [W]e ourselves have found . . . 'the physician's duty to reveal to the patient that which in his best interests it is important that he should know.'"[8] Other cases have analogized informed consent to include a materiality standard in the duty to disclose: "If a reasonable person in the position of the plaintiff would consider the information important in choosing a course of treatment[,] then the information is material and disclosure required."[9]

Malpractice

Generally speaking, breach of a fiduciary duty, often expressed as breach of the duty of care or the duty to inform, is a primary element in establishing negligence, which serves as the foundational analysis for malpractice.[10] The existence of a physician-patient relationship, which, as discussed above, establishes fiduciary duties, is often used by courts to implicate a physician for breaching a duty.[11]

The few cases that have explicitly discussed the duty to inform or disclose in the context of genetic or genomic testing have, at times, considered a breach of this duty to constitute malpractice. In *Houser v. Kaufman*, a physician failed to disclose genetic test results to a young female patient. When the woman later gave birth to a disabled child, the court "held that the physician had no duty to the son, as too much time had gone by, but the mother was permitted to recover in medical malpractice for her injuries as a result of the missed diagnosis[.]"[12] Here the court explicitly recognized, that if "the original patient him- or herself is directly harmed and sustains injury if a positive . . . test result is not conveyed[,] . . . the patient may state a claim for malpractice against the doctor."[13]

Further, in *Walker v. Sonora Regional Medical Center*, the court considered a case involving claims against a physician who failed to disclose that the patient "tested positive as a carrier of cystic fibrosis."[14] Here, in essence, the court recognized that "when a laboratory test is ordered by a patient's physician, there is an existing patient-physician relationship with respect to the subject matter of the laboratory test[,]" which obligates the physician to disclose the results directly to the patient.[15] Moreover, in some cases, the duty to disclose has been found to include a patient's relatives, with the court emphasizing that "in any circumstances in which the physician has a duty to warn of a genetically transferable disease, that duty will be satisfied by warning the patient."[16]

There have also been analogous cases involving other forms of testing. In *Downing v. Grossmann*, malpractice claims were brought against a physician who "failed to disclose to patient that a kidney mass had been detected on computerized tomography (CT) scans taken while treating patient for other conditions."[17] In *Buck v. Charletta*, the "[h]usband of patient who died from lung cancer filed wrongful-death medical malpractice action against radiologist" for not reporting a finding that the radiologist thought might show a malignant tumor on an MRI that was ordered to assess an unrelated orthopedic condition.[18]

Disclosure of Genetic Information to Insurers

With access to genetic information more widely available, there is also an issue of whether the law provides any protection for individuals not to disclose if they have a high risk of diseases to insurance carriers to avoid higher premiums or denial of insurance. In some instances, the law protects individuals from such disclosures. For example, health plans are prohibited from asking for genetic information when individuals apply for health insurance or change policies. Additionally, individuals can restrict providers from disclosing protected health information ("PHI") to health plans where the disclosure is for payment or health care operations purposes, and the restriction pertains solely to the item or service for which the health care providers involved have been paid out-of-pocket in full. That said, the law does not prohibit other insurers such as disability, life, or long-term care insurers from asking questions related to genetic information and genetic testing. In those instances, the information can be used to determine coverage or premiums. The applicable law is discussed in more detail below.

The Genetic Information Nondiscrimination Act ("GINA"), the Patient Protection and Affordable Care Act ("ACA"), and the Health Information Technology for Economic and Clinical Health Act ("HITECH Act") and subsequent modifications have helped to strengthen an individual's privacy protections and reform how health information such as genetic information, may be used by health insurers. Federal

regulations define "genetic information" to include information about genetic tests of an individual or family member; the manifestation of a disease or disorder in family members of such individual; or any request for, or receipt of, genetic services, or participation in clinical research which includes genetic services, by the individual or any family member of the individual.[19] A "genetic test" means analysis of DNA, RNA, proteins, or metabolites, if the analysis detects genotypes, mutations, or chromosomal changes; however, it does not include an analysis of proteins or metabolites that is directly related to a manifested disease, disorder or pathological condition.[20]

Title I of GINA prohibits discrimination based on an individual's genetic information in health coverage.[21] Specifically, GINA prohibits group health plans, health insurance issuers, and issuers of Medicare supplemental policies from increasing premiums, requesting or requiring an individual or family member to undergo genetic testing, or requesting genetic information prior to enrollment.[22] Section 105 of Title I required revisions to the Health Insurance Portability and Accountability Act ("HIPAA") Privacy Rule to provide new privacy protections for genetic information such as clarifying that genetic information is health information, and to prohibit group health plans, health insurance issuers (including HMOs), and issuers of Medicare supplemental policies from using or disclosing genetic information for underwriting purposes.[23] "Underwriting purposes" include (1) the determination of benefits, premium computations, and the application of any pre-existing condition under the plan, coverage, or policy; and (2) other activities related to the creation, renewal, or replacement of a contract of health insurance or health benefits.[24] Accordingly, when individuals apply for health insurance, renew, or change policies, their genetic information cannot be used for eligibility determinations, to increase premium rates, or to apply pre-existing condition exclusions.

However, although GINA protects against initial discrimination based on knowledge of genetic information, it does not prohibit a health plan from adjusting premium or contribution amounts after an individual enrolled in a plan later manifests a disease or disorder.[25] Additionally, once an individual is enrolled, a plan is not prohibited from obtaining genetic information incidental to the requesting, requiring, or purchasing of other information concerning any individual.[26]

The ACA implemented protections that prohibit insurance companies in the individual and small group markets to deny or limit coverage based on pre-existing conditions or to charge higher premiums for pre-existing conditions.[27] Group health plans and health insurance issuer offering group or individual health insurance similarly cannot impose a pre-existing condition exclusion or use genetic information to determine eligibility.[28] That said, there are exceptions such as "grandfathered plans" that do not have to cover pre-existing conditions or can charge higher premiums for pre-existing conditions.[29]

The HITECH Act enables an individual to request a covered entity to not disclose the individual's PHI to a health plan (1) where the disclosure is for payment or health care operations purposes (and not for the purpose of treatment), and (2) the PHI pertains solely to the item or service for which the health care provider involved has been paid out of pocket in full.[30] A covered entity must comply with such a request if the aforementioned requirements are met unless the disclosure is "otherwise required by law."[31] Section 1848(g)(4) of the Social Security Act, known as the Medicare Mandatory Claims Submission Act, requires physicians, suppliers, and other persons to submit claims for covered services.[32] As such, covered entities are required by law to submit claims to Medicare for covered services and they do not have to honor all Medicare patients' requests to restrict disclosures of PHI.

Lastly, there are no federal laws explicitly protecting an individual from having to disclose genetic information or genetic testing results to insurers that are not health plans. For example, disability, life, and long-term care insurers can ask questions and request information related to genetic testing and use genetic information when making coverage determinations and setting premium rates. Due to this, although there are some legal protections for individuals to prevent disclosure or to not experience health insurance discrimination, individuals may be discouraged from performing genetic testing which otherwise may be helpful to determine an individual's propensity for certain diseases and conditions and if there are any preventative measures to reduce the risk of such diseases and conditions manifesting.

Conclusion

Disclosure of genetic or genomic information and protecting such information are sensitive and

important issues that greatly affect individuals.

It is a fundamental ethical requirement that a physician should at all times deal honestly and openly with patients. Patients have a right to know their past and present medical status and to be free of any mistaken beliefs concerning their conditions. . . . Ethical responsibility includes informing patients of changes in their diagnoses resulting from retrospective review of test results or any other information.[33]

Therefore, and in line with the duties encompassed in the physician-patient relationship, and furthered by the doctrine of informed consent, physicians should strive to accurately communicate all results of genetic or genomic testing that could affect the patient's ability to make informed decisions regarding present or future medical treatment. In order to fully meet this obligation, physicians may need to educate themselves so that they possess the level of knowledge of genetics and genomics necessary to understand and relay all test results and are encouraged to seek assistance from genetic counselors and medical geneticists in situations in which a highly-specialized explanation is necessary to facilitate full disclosure to the patient.[34]

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per week. That number can be discouraging for many individuals. Emerging evidence has shown that light-intensity physical activity may offer health benefits especially to groups that are inactive.[13] Delivering the message that some activity is better than no activity may result in more at-risk individuals starting an exercise program.

Conclusion

The U.S. currently ranks #46 in the world for life expectancy.[14] There is a long road ahead to reverse the recent declines in life expectancy. Engaging individuals to start exercising, lose weight, eat better, and stop smoking and using drugs are all needed. Proven social and public health policies at the community, state, and national levels are necessary and may be equally or more effective than individual efforts.

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- Urology
- Vascular Surgery

MSMA Members in the News

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



The Liberty Hospital Board of Trustees has appointed **Raghu Adiga, MD**, to serve as interim president and chief executive officer, following the retirement of the current president and CEO, David Feess. Dr. Adiga, an Infectious Disease specialist, has served as Liberty Hospital's chief medical officer since 2018. He will take on the role effective July 11 while the search for a new CEO moves forward.







Liberty Hospital has achieved national accreditation by the American College of Surgeons' Commission on Cancer Care for delivering high-quality, patient-centered care to cancer patients. Serving on the Cancer Committee are MSMA members **Justin Albani, MD**, **Chakshu Gupta, MD**, and **Amy Patel, MD**. This accomplishment came via a partnership between Liberty Hospital and Saint Luke's Cancer Institute.

Dr. Patel, Breast Radiologist and medical director of the Breast Care Center at Liberty Hospital, has also been named among the "Innovators and Influencers" by IN Kansas City magazine. The recognition is offered to Kansas Citians from a wide variety of professions, whose goal is to make the city more inclusive, vibrant and welcoming.





MSMA members **Brian Biggers, MD**, General Surgery, and **Melissa Gaines, MD**, Geriatric Medicine, have been honored with Preceptor of the Year awards in their respective specialties. Both practice at CoxHealth in Springfield.

MSMA member physicians have swept the top three spots in the Best of the Northland - Orthopedic







Physician category. Above, OSI Orthopedic & Sports Medicine physicians **Alan Cornett, DO**, and **Angela Walker, DO**, practice at Cameron Regional Medical Center, while **David Paul, DO**, practices at OSI's North Kansas City location.



Kelsey Davis-Humes, DO, has been appointed medical director of Scotland County Hospital's Memphis Medical Services. Dr. Davis-Humes shares her time between the Memphis and Wyaconda locations, where she also serves as medical director.



Christine Livek, MD, has been voted the best Family Medicine doctor in Lake Lifestyles Best of the Lake Community Choice Awards. Dr. Livek practices at Lake Regional Clinic in Lake Ozark.



Tim Long, MD, a retired Family Practice physician and long-time MSMA member, has been honored with the Lifetime Achievement award by Mercy Clinic Four Rivers. Along with running Mercy's Marthasville clinic for 36 years, Dr. Long is a co-founder of Washington Overseas Mission which has served thousands of people in Ghana, Honduras and Haiti over the past several decades.



The medical staff of Perry County Health System has recognized **Sandeep Rao, MD**, as Physician of the Year. Dr. Rao is the sole Hospitalist serving Perry County Memorial Hospital and is the first to receive this honor.



NEW MSMA MEMBERS!

John Abraham, MD – Family Practice – Springfield
Steven Ballard, DO – Family Practice – Kansas City
Harathi Bandaru, MD – Neurology - Jefferson City
Molly Black, MD – Orthopedic Trauma – Kansas City
Nancy Buchser, MD – Ophthalmology – St. Louis
Meredith Byers, MD – Diagnostic Radiology – St. Louis
Salim Chahin, MD – Neurology – St. Louis
Joan Chandra, MD – Gastroenterology – Lenexa
Oge Chukwu, MD – Family Practice – Brookfield
Alexander Croft, MD – Emergency Medicine – St. Louis
Hetvi Desai, DO – Psychiatry – Joplin
James Dinkel, MD – Family Pratice – Kansas City
Benjamin Farnia, MD – Radiation Oncology – Jefferson City
Shaun Hanson, MD – Hematology/Oncology – St. Louis
Brittany Herrin, DO – Family Practice – Cedar Hill
Michael Hesseler, MD – Dermatology – Bridgeton
Rose Hiner, MD – Internal Medicine – St. Louis
Christine Jacobs, MD – Family Practice – Saint Louis
Arihant Jain, MD – Family Practice – Cameron
Matthew Jones, MD – Orthopedic Surgery – Columbia
Richard Jones, MD – Ophthalmology – West Plains
James Kelly, MD – Urology – Saint Louis
Christopher Kling, MD – Dermatology – Grover
Daisuke Kobayashi, MD – Pediatrics/Cardiology – St. Louis
Bryant Loosle, DO – Anesthesiology – Springfield
Nathan Mall, MD – Sports Medicine/Ortho Surg – Chesterfield
Charles Moon, MD – Dermatology – Cape Girardeau
Kyle Mueller, MD – Family Practice – Excelsior Springs
Todd Naismith, MD – Neurology – St. Louis
David Nasrazadani, MD – Ophthalmology – Springfield
Nuzhat Nisar, MD – Pediatrics – O'Fallon
A Rashed Nizam, MD – Ophthalmology – Moberly
Matthew Rohers, DO – Family Practice – Lincoln
Rosemarie Romain-Tyson, MD – Psychiatry – Kansas City
Gregory Sainnoval, MD – General Surgery – Clinton
Jignesh Shah, MD – Nephrology – Overland Park
Stephen Sides, DO – Radiology – Jefferson City
Kristen Soehngen, MD – Pediatrics – Mexico
Amanda Sommerville, MD – Internal Med/Peds – Kansas City
James Steffen, MD – Pediatrics – Kansas City
David Wilson, MD – Cardiovascular Disease – Liberty
James Wright, MD – Anesthesiology – St. Louis
Gregory Wu, MD – Neurology – St. Louis

1 PICTURE = 1,000 WORDS

Dementia Incidence Based on Physical Activity Level

Physical Activity Level	Dementia Incidence per 1,000 Persons-Years
Inactive	27.0
Insufficiently Active	22.2
Active	18.0
Highly Active	14.1

Source: MDedge News

Based on data for 62,286 individuals aged 65 years or older from the Korean National Health Insurance Service database. Source: JAMA Nework Open. 2021 Dec 16;4(12):e2138526

COVID and the Tenth Amendment

The article by McKinsey et al., "COVID-19 in Missouri 2020-2021" in *Missouri Medicine* May/June 2022 claims that "For more than 200 years health officials have been granted the authority under the Tenth Amendment to the U.S. Constitution to 'control the spread of dangerous disease.' "

Actually, the Tenth Amendment reads as follows, in its entirety: "The powers not delegated to the United States by the Constitution, nor prohibited by it to the States, are reserved to the States respectively, or to the people."

In no way does the Tenth Amendment give "health officials" the authority to "control the spread of dangerous disease." Perhaps the authors meant to say that the Tenth Amendment does not prohibit States from giving "health officials" some authority with regard to "dangerous disease." Exaggerated claims about the powers of "health officials" undermine the public's trust in the government's health departments.

Bruce Schlafly, MD
St. Louis, Missouri

COVID and the Tenth Amendment Response

Dr. Schlafly correctly notes that the succinct 10th Amendment to the U.S. Constitution does not address the authority of states to implement public health measures.

In the 1819 U. S. Supreme Court ruling on *McCulloch v. Maryland,* Chief Justice John Marshall wrote that a constitution that spelled out every detail of its intended application "would partake of the prolixity of a legal code, and could scarcely be embraced by the human mind."

The Court then unanimously ruled in 1824 that states possess police powers within their borders including the ability to impose quarantine and isolation (*Gibbons v Ogden*).

This decision was upheld in 1902.[1] Thus our statement that health authorities have the constitutional authority to control the spread of dangerous disease is supported by federal legal precedent over a period of two centuries.

We wholeheartedly agree with the importance of strengthening the public's trust in our health agencies, especially given that some in positions of authority now seek to reduce their long-held, effective powers.

David S. McKinsey, MD & Joel P. McKinsey, MD
Neil B. Hampson, MD & Maithe Enriquez, APRN, PhD
Kansas City, Missouri

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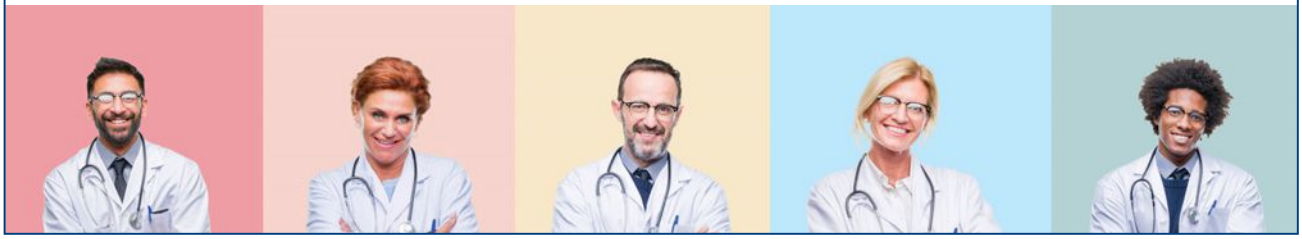
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KANSAS CITY
MEDICAL SOCIETY

KCMS Provides Leadership, Adapts to COVID-19 Challenges

by Scott W. Kujath, MD, KCMS President & Annette Small, MBA, KCMS Interim Executive Director

The COVID-19 pandemic has called on physicians and the entire health care field to rise to meet extraordinary challenges and demands that at times have seemed overwhelming. Throughout these past two years, the Kansas City Medical Society has supported physicians in their efforts and provided leadership and advocacy to the community in promoting the prevention of this deadly disease.

Issues Leadership

KCMS has been outspoken in favor of policies—including mask-wearing and vaccination—that help protect our citizens.

- In August 2021, facing the rapid spread of the delta variant and rising case counts, we sent a letter to 17 area school districts in Missouri and Kansas asking that masking of students and faculty be made policy for the 2021-22 school year. Our letter was cited directly as encouraging four districts to adopt mask-wearing policies. It also generated media coverage including television interviews with our KCMS president.
- In August 2020—before vaccines were available—member physicians joined to create a two-minute video pleading the importance of mask-wearing. Nine physicians appear in the video. It gained a reach of more than 20,000 on Facebook.
- Throughout 2020 and 2021, KCMS has adopted and disseminated statements in support of mask-wearing and vaccination.
- We have joined in active support with the Kansas City community's pro-vaccine coalition, Comeback KC, which brings together stakeholders from across many segments of business, health care, government and more.

Besides COVID awareness, we have been working with the Johnson County, Kan., Department of Health and Environment on general health education. We are presenting a series of "Doc Talk" webinars featuring discussing heart-healthy behaviors including blood pressure control, diet, exercise, stress reduction and more. Four webinars were presented in 2021; six are scheduled for 2022. Speakers at the webinars are members of our Retired Physicians Organization. A series of "Your Health Minute" videos on blood pressure and diabetes also was produced.

Medicaid Expansion Advocacy

In conjunction with our charitable arm, the Kansas City Medical Society Foundation, we have been ardent supporters of Medicaid expansion in Missouri and Kansas. This realizes the critical role of Medicaid in ensuring access to care for our most vulnerable citizens. To help promote the passage of the August 2020 Missouri voter referendum on Medicaid expansion, we placed full-page ads in the *Kansas City Star* and *Kansas City Business Journal* containing the names of 400 local physicians endorsing the constitutional amendment. In response to the Missouri legislature's 2021 move to block funding for Medicaid expansion, we published a letter to the editor in the *Kansas City Star* calling for expansion to move forward.

Also in 2021, the Foundation launched a series of webinars for physicians and community partners advocating for Medicaid expansion in Kansas and updating Missouri's implementation. Speakers have included leading legislators, physicians, and policy experts in both states; these webinars have grown so they now are attracting over 100 participants each.

Our advocacy in support of Medicaid expansion has been made possible by major grants to the Foundation from the Health Forward Foundation.

Supporting Physicians

Throughout the pandemic, KCMS has been a source of information and support for physicians.



At the October 2021 KCMS annual meeting, President Scott Kujath, MD, left, is pictured with honorees John Hagan III, MD; Ruth Ramsey; Maninder Pabla, MD; Amy Patel, MD; Michael Weaver, MD; Andrew Schlachter, MD; Todd Beardman, MD; and Denny Fugate, PharmD.

We adapted and found ways to reach our members virtually when in-person was not possible.

Insightful webinars on COVID-19 leadership and the introduction of vaccines helped physicians understand and forecast what was on the horizon for the fast-evolving pandemic.

Through the KCMS website and member emails, we have provided a host of information including vaccine resources, links to current COVID data, and details on pandemic-related financial assistance available to physician practices.

We developed a series of "Get Care" graphics for practices to use to encourage patients to continue to seek medical care instead of delaying it out of COVID fears.

In fall 2021, we held a highly successful Leadership Book Study group where participants read and discussed the book "Harvard Business Review's 10 Must Reads on Leadership." The group was expertly facilitated by two of our leading members, Sarah Hon, DO, FAAN, who is part of the American Academy of Neurology (AAN) Women Leading in Neurology Program, and Betty Drees, MD, FACP, FACE, dean emerita of the University of Missouri-Kansas City School of Medicine.

Our 40-member Leadership Council, which meets quarterly, has been an invaluable source of input and guidance. Composed of physicians representing hospitals, medical schools, and private practices throughout Kansas City, the Leadership Council is the forum that takes the pulse of area physicians and identifies issues for KCMS to pursue. Each meeting offers a vigorous discussion of physician concerns and often leads to action steps. The Leadership Council develops and recommends the KCMS advocacy priorities for the year.

The pandemic has led to internal changes at KCMS as we have needed to refocus our budget and staffing on our core priorities. Annette Small, RN, BSN, MBA, was appointed KCMS interim executive director in May 2021. She also is the chief executive officer of Midwest Aortic & Vascular Institute and is the former chief executive officer of St. Mary's Medical Center in Blue Springs, Mo.

On the Foundation side, we have continued to serve hundreds of uninsured patients each year through the Metro Care and Wy Jo Care programs, overcoming pandemic-related challenges. The Foundation is leading a Wyandotte County, Kan., coalition of agencies working to increase minority employment in health care occupations.

The 2021 year culminated with our first in-person event since the pandemic, our October 26 annual meeting. Themed "A Nite for U – Unplug, Unwind, Unite," the event was designed to thank and celebrate the work of physicians during the pandemic. The setting for the informal reception was J. Rieger & Co., a popular distillery near downtown Kansas City. J. Rieger generously donated their facilities and beverages as their way of thanking physicians during this extraordinary time. **MM**

On the Cutting Edge of Medical Education

UMKC's conceptual approach to medical education, which was well ahead of its time, remains on the cutting edge of training future leaders in our profession, guiding students into both our BA/MD and the traditional MD track programs.

by Mary Anne Jackson, MD

It has been my honor to serve as a faculty member for over three decades and as the dean of University of Missouri - Kansas City School of Medicine since 2018. On June 4, 2022, we celebrated our 50th Anniversary at a Gala event with more than 800 attendees.

As a class of '78 graduate, I have always had a deep admiration for E. Grey Dimond, MD, our first provost, and Richardson K. Noback, MD, our first dean. It was their bold and transformative vision that launched our accelerated BA/MD program over five decades ago. They championed the docent system, which provides small group community learning teams for our students, promoted peer to peer student mentorship, and supported a team-based approach to optimize clinical care. This conceptual approach to medical education, which was well ahead of its time, remains on the cutting edge of training future leaders in our profession, guiding students into both our BA/MD and the traditional MD track programs. From the beginning, our community-based medical school has relied on our strong clinical partnerships to allow our students to train with a unique and diverse patient base within University Health, Children's Mercy, St. Luke's Health system, Research Medical Center, the Center for Behavioral Medicine, the Kansas City VA, Advent Health, and Liberty Hospital. And, in 2021 we launched our additional campus and welcomed our newest affiliate, Mosaic Life Care, to recruit, prepare, and encourage the students training in the St. Joseph community to become part of the primary health workforce in rural Missouri counties.

Our recent efforts have been to focus on initiatives to build diversity, enhance our learning environment, expand student centric curriculum, and value-added advanced degree and research opportunities. Our experiences in navigating the unprecedented pandemic challenges which disrupted the traditional structure of medical education, did reveal a silver lining. Integrating new curriculum, developing faculty, fine tuning plans to address wellness, and advancing research took center stage as we urgently had to adapt on the fly.

UMKC's faculty perfected digital learning, and our students became part of the COVID diagnosis, treatment, and vaccine teams, and actively engaged in behavioral intervention-based health studies research to identify and eliminate healthcare disparities for those living in our community. Our faculty has continued to advance scientific discovery and we've seen an eight-fold increase in our external awards since 2016 as our talented researchers unraveled the science to improve outcomes for the most difficult to treat diagnoses. We are pleased to announce two new Endowed Chairs, Jannette Berkely Patton, PhD, the Merl and Muriel Hicklin Chair in Medicine and Cuthbert Simpkins, MD, the Sosland Chair in Trauma Research.

Our award-winning students and faculty continue to garner national recognition. Sophie Bernstein, class of 2024, was selected for the 2022 Excellence in Public Health Award from the U.S. Public Health Service Physician Professional Advisory Committee, on the basis of her national efforts to address food insecurity.



Mary Anne Jackson, MD, FAAP, FPIDS, FIDSA, a Pediatrician in Infectious Disease, is Dean and Professor at the University of Missouri - Kansas City School of Medicine and Children's Mercy Hospital, Kansas City, Missouri.



A new UMKC School of Medicine campus in St. Joseph in partnership with Mosaic Life Care will increase rural health care by addressing physician shortages in Missouri.

Three of our senior students, Yen Luu, Christy Nwankwo, and Madhavi Murali just completed the yearlong NIH Medical Scholars Research Program (MRSP), which, over the last seven years, has advanced the research careers of approximately 50 students per year from medical schools across the country. Between 2014-2021, 12 UMKC SOM students were selected through competitive application, and completed this program, advancing their research expertise ahead of their entering the national academic medical community. Ms. Nwankwo was just elected to serve as Vice President of the National Medical Student Organization.

On the faculty level, Amy Patel, MD, '11, is President Elect of the American Association for Women in Radiology, and the first female recipient of the American College of Radiology Howard Fleishon MD Advocate of the Year Award recognized for her efforts to promote breast cancer imaging. Betty Drees, MD, was recognized by the American College of Physicians in April, with the prestigious Elizabeth and Emily Blackwell Award for Outstanding Contributions to Advancing the Careers of Women in Medicine. Mamta Reddy, MD, '98, the Vijay Babu Rayudu Endowed Chair for Patient Safety, launched our one-year Faculty and Student Scholars Programs in Quality Improvement and Patient Safety.

Our rural healthcare program at our Mosaic campus has been recognized with a $13 million dollar senate appropriations to further build out our space, and an additional $1.5 million has been added as part of ARPA funds for Higher Education. And we look forward to work needed for building a new combined medical and dental school building at the Health Science District campus in Kansas City.

Through our innovative medical education program, we continue to graduate some of the best and brightest, most caring and well-rounded physicians and recruit talented and accomplished faculty who are passionate about serving the underserved. This current issue of *Missouri Medicine* dedicated to the description of thyroid disease is edited by Professor of Medicine and Dean Emerita, Dr. Drees, an accomplished endocrinology researcher and includes review and updates from faculty from our Departments of Obstetrics and Gynecology, Geriatrics, Radiology, Ophthalmology, and Section of Endocrine, on topics ranging from thyroid disease in pregnancy, to thyroid eye disease, risk stratification of thyroid disease based on ultrasound features and management of thyroid storm.

A lot has changed over the first 50 years of our School of Medicine, but the purpose and excellence of it have remained the constant. We are excited as we launch our next 50 years! **MM**

UMKC School of Medicine

Thyroid Disease: Perspectives and Health Impacts

by Betty M. Drees, MD, Brandon Barthel, MD & Rajib K. Bhattacharya, MD

It is clear that the care of patients with thyroid disorders crosses many clinical and basic science disciplines and continues to evolve.



Betty M. Drees, MD, FACP, FACE, (above), is Professor of Medicine, Department of Internal Medicine and Department of Biomedical and Health Informatics, University of Missouri-Kansas City School of Medicine, and President, Graduate School of the Stowers Institute for Medical Research. Brandon Barthel, MD, is Assistant Professor of Internal Medicine and Program Director Section of Endocrinology and Metabolism, University of Missouri-Kansas City School of Medicine. Rajib K. Bhattacharya, MD, FACE, is Professor of Internal Medicine and Chief of Endocrinology and Metabolism, University of Missouri-Kansas City School of Medicine. All are in Kansas City, Missouri.

The presence of the thyroid gland in the neck has been known for hundreds of years, with descriptions of goiters dating back to ancient Chinese, Indian, and Egyptian writings.[1,2,3] Goiters were depicted in sculpture from the Gandhara civilization in what is now northern Pakistan from as early as the second century AD[4] and in religious Byzantine paintings as early as the ninth century AD.[5] Goiters are also depicted in religious and secular art after the Middle Ages, including in paintings by Leonardo da Vinci and Edouard Manet.[6] As dissection became more available, the anatomy of the thyroid could be described, with Leonardo da Vinci making the first detailed illustrations.[2,3]

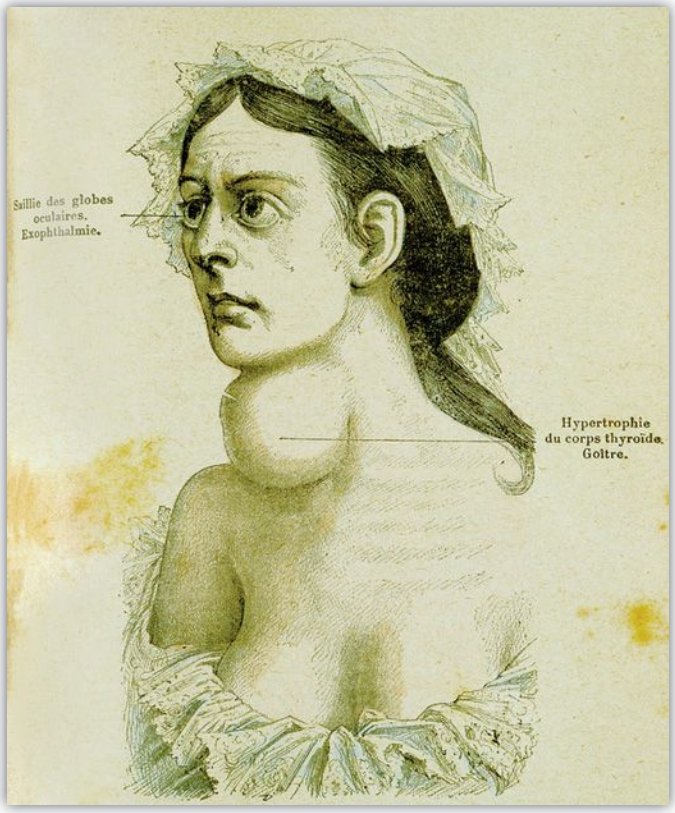
In 1656, Thomas Wharton is credited with naming the thyroid after *thyreos*, an ancient Greek shield, due to its shield-like appearance over the larynx.[7] The location of the thyroid contributed to the belief that the function was either as a protector of the larynx or an esthetic filler to make the neck more beautiful.[3,7] (Goiter was common in some societies and considered a sign of beauty in women.) Although the pathophysiology of clinical hypothyroidism, hyperthyroidism, and thyroid ophthalmopathy and their association with the thyroid gland was not known until the late 19th and early 20th centuries, these conditions were being treated empirically well before.[7,8] Thyroid surgery for a goiter was described in detail by Albucasi in the 10th century, but it did not become common until modern surgical antisepsis, anesthesia, and techniques were developed to make the surgery safer.[2,7] Dr. Theodor Kocher (1841-1917) was a pioneer in these techniques, for which he was the first surgeon to receive the Nobel Prize in 1909.

The late 19th century and early 20th century saw an explosion in the discovery of the pathophysiology of thyroid disease that led to the understanding of the physiology of thyroid hormones in metabolism, the description of the role of iodine, the implementation of public health programs for iodine supplementation to prevent goiter, and the use of thyroid

hormone replacement — initially with animal extracts and then with synthetic levothyroxine developed in 1927. These were followed by the development of non-surgical treatment of hyperthyroidism with radioactive iodine and thiouracils.[7,8]

Two developments in improved diagnostic technology deserve special mention. First, the development of radioimmunoassay to precisely measure the small quantities of circulating thyroid hormones and pituitary hormones in the 1960s-1970s allowed accurate diagnosis of primary and secondary hyper- and hypothyroidism.[9] For this work, Rosalyn Yalow (1921-2011) received the Nobel Prize in 1977. (Her co-investigator Solomon Berson died five years earlier and was not eligible to receive the prize with her.) With sensitive and accurate measures of hormones available, this work revolutionized all of endocrinology, not just thyroid work. Second, the development of ultrasound technology in the 1960s allowed accurate, non-invasive evaluation of thyroid anatomy, specifically thyroid nodules.[10] This technology is the basis of evaluating malignant risk of thyroid nodules and developing guidelines for fine needle aspiration cytology, molecular evaluation, and surgery (Haugen).[11]

From the ancient recognition of the structural location of the thyroid and goiter to the modern setting where we understand the widespread impact of thyroid hormones on metabolism and have the availability of advanced diagnostic tools and therapeutics, it is clear that the care of patients with thyroid disorders crosses many clinical and basic science disciplines and continues to evolve. In this *Missouri Medicine* issue on thyroid disease, there are articles and updates from the perspectives of University of Missouri-Kansas City School of Medicine faculty in endocrinology, radiology, obstetrics, ophthalmology, and geriatrics that cover treatment of hyperthyroidism and thyroid eye disease, the diagnostic evaluation of thyroid nodules, and the presentation of thyroid disease in the special populations of pregnant women and older adults.



Woman With Goitre
Source: Universal History Archive

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MM

Thyroid Eye Disease

by Jason Szelog, MD, Hollister Swanson, MD, Matthew C. Sniegowski, MD & David B. Lyon, MD

Thyroid eye disease is the most common inflammatory orbital disorder, is associated with autoimmune thyroid dysfunction and may have protean manifestations.



Jason Szelog, MD, PGY-4 Resident, Hollister Swanson, MD, PGY-3 Resident, **Matthew C. Sniegowski, MD**, Assistant Professor and **David B. Lyon, MD, FACS**, Professor, (above), are all in the Department of Ophthalmology University of Missouri- Kansas City School of Medicine, Kansas City, Missouri.

Abstract

Thyroid eye disease, although rare, is the most common inflammatory orbital disorder and is associated with autoimmune thyroid dysfunction. It is a progressive disorder with symptoms and signs that may cause significant facial disfigurement, visual disability, but rarely blindness. We will review the diagnostic criteria, immunologic basis, clinical course, and medical and surgical treatments for thyroid eye disease. Recent developments in the use of biologic agents to treat this disorder appear to be changing its progression curve and offer the first specific and preventative therapeutic options.

Definition and Diagnostic Criteria

Thyroid eye disease (TED) is an autoimmune inflammatory disorder of the orbit that may cause considerable ocular morbidity. A diagnosis of TED is made by either of the following two criteria outlined by Bartley.[1] When eyelid retraction is evident, the additional presence of abnormal thyroid function or regulation, exophthalmos, optic nerve dysfunction, or extraocular muscle (EOM) involvement provides the diagnosis, after excluding confounding causes. If eyelid retraction is absent, then diagnosis is made via exophthalmos, optic nerve dysfunction, or EOM involvement in the setting of abnormal thyroid function or regulation. In about 90% of cases, TED is associated with Graves' disease, requiring multispecialty collaboration between ophthalmology, endocrinology, and otolaryngology.

Pathophysiology and Epidemiology

TED is characterized by orbital inflammation due to fibroblast activation.[2] Historically, numerous pathogenic models have been proposed, but more recent study has demonstrated the importance of orbital CD34+ fibroblasts.[3] In response to molecular signaling, these fibroblasts differentiate into adipocytes and myofibroblasts. The CD34+ fibroblasts express thyroglobulin, thyroid-stimulating hormone (TSH), and other thyroid-related peptides. These signal molecules stimulate the TSH receptor and insulin-like growth factor I (IGF-1) complex, cascading to adipogenesis and fibroblast hyaluronic acid synthesis within the orbit.[3] Increased orbital adipose tissue and glycosaminoglycan sequestration within EOMs leads to soft tissue volume expansion, resulting in increased intraorbital congestion and pressure causing the pathogenic findings in TED.

The incidence of TED favors a female preponderance, with 16 cases per 100,000 females,

compared to 2.9 cases per 100,000 males.[4] Interestingly, severe TED is more common in males, 4:1[5] Additionally, males tend to have presentations later in life.[6] In the pediatric population, the incidence is 1.7–3.5 cases per 100,000 population per year, and 0.79–6.5 cases per 100,000 children.[7] There have been several different genetic polymorphisms associated with TED, however, sample sizes have been small and results variable.[8] In one large study, it was concluded that TED patients do not have specific genetic predisposition and the disease is more by environmental influences and epigenetic changes.[9] TED has numerous risk factors, with the most common being female sex, middle age, and most importantly smoking, as this is a modifiable risk factor.[9] Smoking plays a critical role as it not only increases the development in TED by seven-eight fold, but it also reduces the effectiveness of treatment.[8] Of note, the risk of TED is more closely associated with smoking after thyroid disease develops, which provides a critical opportunity for intervention in patients with newly diagnosed thyroid disease. Another known risk factor for TED development and progression is treatment with radioactive iodine, as it can result in difficulty maintaining euthymia.[10] Finally, statin use has demonstrated a reduced risk for TED development. However, it is uncertain whether there is a direct effect or it is secondary to cholesterol reduction.[10,11]

Clinical Findings and Grading Systems

Signs and Symptoms

The most common sign of TED is upper eyelid retraction, unilateral or bilateral, that occurs in over 90% of patients[12,13] (Figure 1). The resultant wide-eyed appearance allows for chronic eye exposure, especially during sleep. Foreign body sensation, dryness, and tearing occur initially. Over time, severe keratopathy may develop which increases risk of corneal scarring, ulceration, perforation, and endophthalmitis.[14]

Exophthalmos, or proptosis, is the second most common sign with 60% affected, due to EOM and/or fat expansion, and may also increase the risk of exposure.[12,13] Lagophthalmos, or incomplete eye closure, is seen in half of TED patients.[13] Elevation of the temporal portion of the upper eyelid contour, known as a temporal flare, is often noted.



Figures 1A and B. A 45-year-old male with active TED demonstrating severe proptosis, upper and lower eyelid retraction and conjunctival injection and edema.

EOM dysfunction is seen in 40% of patients, and often results in diplopia if ocular misalignment ensues.[13] The inferior and medial rectus muscles are most commonly affected, inducing hypotropia (downward deviation) and esotropia (inward deviation) respectively and limiting eye movements if the muscles fibrose. Dull, pressure-like eye pain is experienced by 30% of patients.[12,13] Eyelid edema and erythema, conjunctival injection, and chemosis (conjunctival edema) are less common. Dyschromatopsia (color vision loss) or visual acuity loss secondary to compressive optic neuropathy is seen in about 6% of cases, and implies severe disease.[13]

Curiously, TED may be unilateral or highly asymmetric. It has a vast spectrum of findings and disease severity. Obviously, sight-threatening disease is the greatest concern, consisting of corneal scarring and optic neuropathy, and requires proper identification and urgent treatment.

Differential Diagnosis

Minor symptoms such as tearing and conjunctival injection may appear similar to allergic conjunctivitis, though itchiness and a papillary reaction of the palpebral conjunctiva would be expected in the latter.

Myasthenia gravis may cause variable diplopia and ptosis. Diplopia in TED is not usually variable, and ptosis is not typically associated with TED. Chronic progressive external ophthalmoplegia (CPEO) presents with severe ocular motility deficits and ptosis. It is generally symmetric, painless, and slowly progressive over several years which distinguishes it from TED. Orbital tumors may induce unilateral proptosis and EOM dysfunction, but are unlikely to cause eyelid retraction. Carotid-cavernous sinus fistulas may result in marked chemosis, exophthalmos, and conjunctival hyperemia, however, the dilated corkscrew-like vessels seen in the case of a fistula would not be noted in TED.

Other inflammatory disorders including orbital myositis, idiopathic orbital inflammation, IgG4 disease, and granulomatosis with polyangiitis may all present with orbital or eye pain similarly to TED, but they are not associated with eyelid retraction. Orbital myositis is the second most common cause of EOM disease after TED and presents with painful diplopia due to inflammation of one or more muscles, usually unilaterally, with the inferior rectus rarely involved. IgG4-related orbital disease most commonly causes dacryoadenitis, enlarged orbital nerves or thickening of the lateral rectus. Granulomatosis with polyangiitis presents with pulmonary and renal pathologies as well as episcleritis or scleritis, which are not generally seen in TED.

CAS Scoring and VISA Classification

The Clinical Activity Score (CAS) system assesses TED activity using history and external exam findings and is commonly used in research studies. Patients are scored at their initial visit, receiving one point for each of the following symptoms: spontaneous orbital pain, gaze-evoked orbital pain, eyelid swelling, eyelid erythema, conjunctival injection, chemosis, and caruncle or plica semilunaris inflammation.[15] A CAS of three of more at initial encounter is considered active disease. On follow-up, patients are given an additional point for each of the criteria: ≥2mm increase in proptosis, decrease in motility of either eye by ≥5°, or a decrease in visual acuity ≥1 Snellen line.[15] Scores of four or greater indicate active disease.

The more current VISA (vision, inflammation, strabismus, appearance/exposure) classification assesses severity and activity.[16] Response to therapy is also scored, using a "same, better, worse" categorization. The vision section rules out optic neuropathy by assessing visual acuity, color vision deficits, pupillary responses, and optic nerve appearance. The inflammation section modifies the initial CAS criteria by excluding caruncle/plica semilunaris inflammation (including it under chemosis), and grading chemosis and lid edema on a scale of 0-2. Retrobulbar pain is graded as 0 = no pain, 1 = pain with movement, and 2 = pain at rest. Conjunctival and lid injection are graded as present or absent, and the score of the worst scoring eyelid (range 0-8) is recorded. The strabismus section tracks progression of EOM dysfunction and diplopia. The appearance/exposure section assesses for symptomatic exophthalmos, eyelid retraction, and dryness.

Active vs. Inactive Disease

TED usually develops within 18 months of the development of thyroid disease, but may occur years later. The course of TED follows a predictable curve (Rundle's Curve) in which active disease lasts for 6-18 months. Disease severity then decreases before plateauing in the inactive or quiescent phase. Although TED is usually self-limiting, the severity at the height of the active phase can be extensive enough to cause bothersome or vision threatening symptoms necessitating surgical intervention. Early intervention in the active phase can limit peak severity, ensuring the inactive plateau phase results in fewer or milder symptoms.

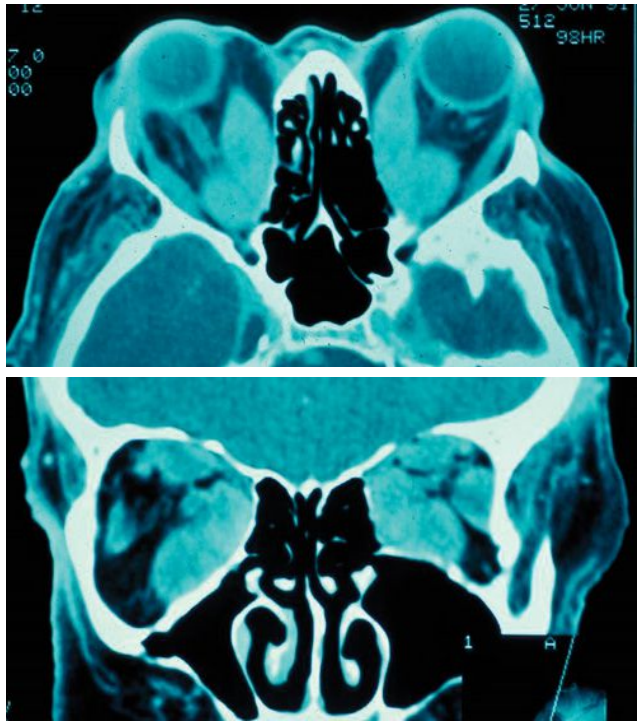
Thyroid Autoantibodies

Graves' disease results in hyperthyroidism induced by autoantibody stimulation of thyroid stimulating hormone receptor (TSHR). Thyroid-stimulating immunoglobulin (TSI) is the only known TSHR antibody that correlates directly with severity and activity of TED.[17] It may be used as a biomarker in children and adults, however, TED

may still occur without autoantibody formation. In a small number of TED patients, elevated TSI is the only initial serologic abnormality with thyroid dysfunction occurring later. Other thyroid autoantibodies that do not correlate with TED characteristics include anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg).

Imaging

TED is a clinical diagnosis and does not require imaging for confirmation. However, computed tomography (CT) may assist in the diagnosis of TED by identifying enlargement of EOM bellies with sparing of the tendons (Figure 2). The inferior rectus is most frequently affected, followed in decreasing frequency by the medial, superior, and lateral recti. Least commonly involved are the oblique muscles. CT is useful for orbital decompression surgical planning. MRI will also show EOM enlargement and additionally allows for assessment of orbital fat expansion and may reveal edema suggestive of inflammation.



Figures 2 A and B. Axial (A) and coronal (B) CT images of a 65-year-old female smoker with compressive optic neuropathy. Note severe enlargement of all rectus muscles impinging on the optic nerves in the retrobulbar orbit.

Treatment

Supportive

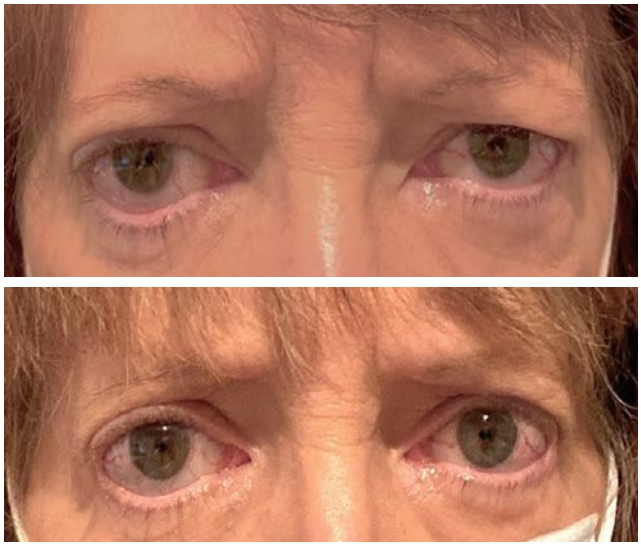
The treatment for TED is multifaceted and is based on the degree of clinical activity, progression and morbidity of the patient. Typically, treatment starts with normalization of thyroid function by the endocrinologist and modification of risk factors such as replenishment of vitamin D, if needed, and smoking cessation. Supplemental selenium, 200 micrograms per day for six months has also been shown to improve quality of life and slow the progression of disease in patients with mild TED.[18]

Hyperthyroidism is present in 90% of patients and has treatment options of anti-thyroid oral medications, radioactive iodine thyroid ablation and thyroidectomy. Most often in this country, thionamide suppression is the first line therapy to see if remission will occur. The other options are reserved for recurrent or persistent hyperthyroidism and there is evidence that patients with active TED are best treated with thyroidectomy.[19]

Ocular specific supportive treatment includes ocular lubricants (drops, gel drops, ointment) and protective eyewear when in the sun, wind and bright light. Sleep masks, eyelid taping and goggle-type devices at night benefit some patients. Head elevation during sleep may help reduce periorbital edema in the morning. The need for psychologic support for this potentially disfiguring disease should also be recognized and local support groups are often helpful.

Corticosteroids

The acute inflammatory phase of the disease is treated medically, if needed, with surgical intervention usually reserved for the post-inflammatory, or "burned out", chronic phase. Historically, corticosteroids have been the primary treatment for the acute phase. Oral corticosteroids, typically dosed 1 mg/kg of prednisone, can reduce the orbital congestion and soft tissue inflammation, but inadequate response, resurgent disease upon tapering and side effects limit usage today.[20] However, the ease and expedience of oral steroids in cases with compressive optic neuropathy and vision loss make it a useful first agent for many practitioners. The superiority of intravenous



Figures 3 A and B. Pre (A) and post (B) teprotumumab images for a 67-year-old female. Her CAS reduced from 4 to 0 and there was a 3 mm reduction in her axial proptosis of the right eye.

methylprednisolone over oral prednisone for moderate to severe TED has been shown by several European studies.[21,22]

Radiotherapy

Radiotherapy to the orbit is controversial even after many decades of use. The radiation is given in 10 fractions, total dose 2000 cGy, over two weeks, targeting the retrobulbar orbital soft tissues. Its effect is felt to be due to destruction or inhibition of inflammatory lymphocytes, macrophages and orbital fibroblasts and it continues to be used in many areas around the world. It may be used in the early active disease phase, usually in combination with corticosteroids, especially for patients with optic neuropathy, fulminant inflammatory changes or progressive motility restriction.[23] Radiotherapy is contraindicated in diabetics and pregnant women.

Steroid Sparing Agents and Biologics

Steroid sparing antimetabolites have long been used to treat autoimmune diseases. However, use of these drugs in TED has been limited and results have been variable. Several monoclonal antibodies, approved for other indications, have also been investigated for treatment of TED, usually for steroid refractory disease. Since they are off-label treatments, insurance approval and cost issues have limited use.

Rituximab is a monoclonal antibody to CD20 that is expressed on B-lymphocytes. A small case series found benefit for its use in moderate to severe TED, but larger randomized studies have found conflicting results.[24]

Tocilizumab is a monoclonal antibody directed to the interleukin-6 (IL-6) receptor and it has been effective in reducing inflammatory signs of TED in patients refractory to corticosteroids as measured by a reduction in CAS.[25] Like many cytokines, IL-6 is upregulated in TED. This agent has also been administered via a subcutaneous route with favorable clinical results in a case series of nine patients with moderate to severe disease despite a variety of prior treatments.[26]

Teprotumumab targets the IGF-1 receptor and is the only FDA approved (January 2020) biologic for treatment of TED. Basic research implicated this receptor on the CD-34+ orbital fibrocyte in the pathogenesis of TED. Randomized placebo-controlled studies, sponsored by industry, have shown statistically significant efficacy for proptosis (–3.0 mm vs. –0.3 mm, phase 2 study; –3.32 mm vs. –0.53 mm, phase 3 study), diplopia and CAS (–4.0 vs. –2.5, phase 2 study; –3.7 vs. –2.0, phase 3 study) reduction in steroid naïve patients compared to placebo.[27,28] Entry criteria required patients to be in the acute inflammatory disease stage (CAS greater or equal to four). This intravenous treatment, given in eight doses three weeks apart, is now in widespread use. Our early experience has been with 30 patients: 17 finished, eight in progress, four denied by insurance or deferred after approval, and one who stopped treatment after two infusions due to gastrointestinal symptoms and extreme fatigue. Those who have completed their treatment course, many with history of prior alternative therapies, had overall very favorable results for proptosis and CAS reduction mirroring the aforementioned studies (Figure 3). Its introduction has decreased our need for surgical intervention, especially orbital decompression.

This medication is expensive and the common adverse events reported with it include muscle spasms (25%), nausea (17%), alopecia (13%), diarrhea (13%), fatigue (10%), hearing impairment (10%), and hyperglycemia (8%). It is contraindicated for those with inflammatory

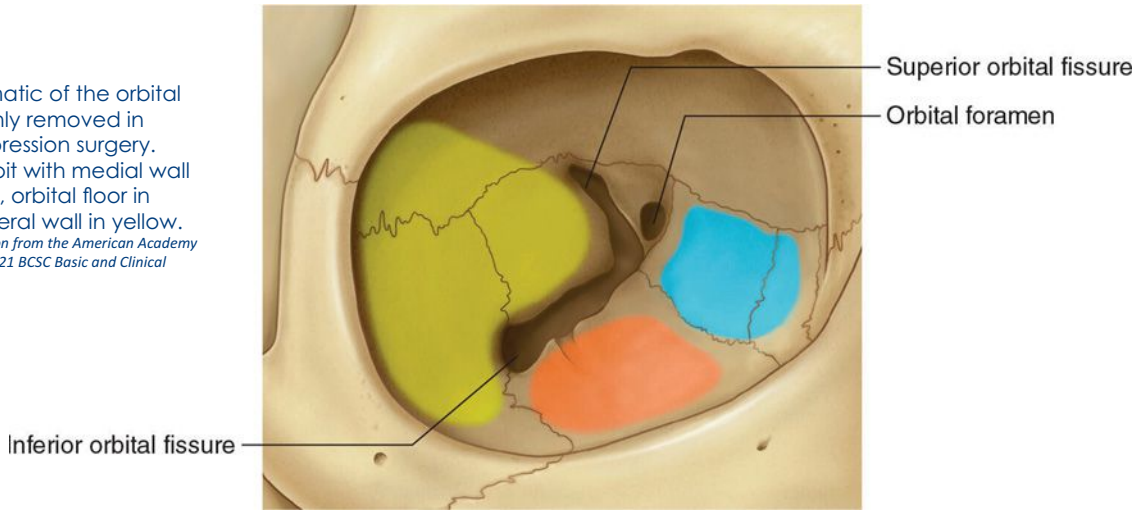


Figure 4. Schematic of the orbital bones commonly removed in orbital decompression surgery. This is a right orbit with medial wall outlined in blue, orbital floor in orange and lateral wall in yellow.
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bowel disease and who are pregnant. The long-term efficacy of this biologic remains to be seen and alternate dosing regimen studies have not been performed.[29] Its benefit for chronic TED (CAS 0-1), along with retreatment for non-responders and those with a subsequent disease flare-up has been recently reported.[30,31,32]

Surgical Management of TED

Surgical management of TED is typically reserved for quiescent disease, often termed the chronic fibrotic phase. The three main pathophysiologic changes requiring surgery in TED are: eyelid retraction, strabismus and proptosis. When proceeding to surgical repair, orbital decompression is traditionally performed first, if needed, followed by strabismus surgery and lastly eyelid surgery. The rationale for this staged approach is improved predictability in the final result.[33,34] The anatomical basis for this doctrine is that orbital decompression surgery can, in and of itself, induce or worsen strabismus, and strabismus surgery can change the position of the eyelids, especially with recession of the inferior rectus. More recent studies have suggested that orbital decompression can be successfully performed at the same time as lower eyelid retraction repair, reducing the number of operations required for rehabilitation, and there are no current studies that have demonstrated inferior results to combined approaches.[35] The ultimate decision for combined or staged surgery varies by institution as well as surgeon preferences and experience.

Eyelid Retraction Repair

Eyelid retraction is defined as an increase in the margin to reflex distance 1 or 2 (MRD1, MRD2). These measurements are obtained by shining a penlight at the eye and measuring the distance from the corneal light reflex to the upper and lower eyelid margins, respectively. Eyelid retraction can be addressed surgically in the upper eyelid via either a transcutaneous or a transconjunctival approach. In the transconjunctival approach, the eyelid is everted over a retractor and an incision is made at the superior aspect of the tarsal plate. A cautery device is then used to carefully incise and recess Müller's muscle, and when deemed necessary, a graded recession of the levator aponeurosis can be performed simultaneously. The transconjunctival recession of Müller's muscle is an effective procedure with less than 10% failure rate.[36]

Upper eyelid retraction repair can also be performed through a transcutaneous approach. The levator aponeurosis is accessed through an upper eyelid crease incision and dissection is performed to the tarsal plate. It is then carefully dissected off the tarsal plate and recessed. Spacer grafts, made of porcine dermis, cadaveric dermis, banked sclera, or harvested hard palate or cartilage, can be utilized. When a spacer graft is used, it is typically placed between the superior edge of the tarsal plate and the recessed edge of the levator aponeurosis.

Lower eyelid retraction can be addressed surgically through a transconjunctival approach with recession of the lower eyelid retractors; this can



Figures 5 A and B. (A) A 50-year-old female with inactive TED with proptosis and upper and lower eyelid retraction. (B) After bilateral orbital bony balanced decompression of the medial and lateral orbital walls.

be performed with or without placement of a spacer graft and techniques are largely surgeon dependent. In a large retrospective study of 400 patients, hard palate grafts, free tarsal grafts and scleral grafts were all found to be effective in reducing eyelid retraction, lagophthalmos and dryness.[37]

Strabismus Surgery

Inflammatory changes with subsequent fibrosis of EOMs will typically lead to the muscles staying in a restricted and inelastic state. This will lead to an eye(s) that is deviated downward (hypotropia), inward (esotropia) or both from involvement of the inferior and medial rectus respectively. The goal of strabismus surgery is to increase the field of binocular single vision, with particular attention paid to alignment in primary gaze. Recessions of the fibrotic muscles are typically the first-choice procedure. Cyclodeviations and combined vertical and horizontal deviations may require special surgical considerations.[38]

Orbital Decompression

Any of the four bony walls of the orbit can be decompressed, however, most commonly it is the medial wall, floor and lateral walls that are approached in orbital decompression surgery (Figure 4). The goal of this surgery is to increase the volume of the orbit, thus allowing the orbital tissues that have expanded due to ongoing inflammatory changes to fall back into the expanded orbit. Each wall of the orbit when decompressed will typically improve axial proptosis by about 2 mm. Many surgeons will also remove intraconal orbital fat as part of the procedure which can often result in up to 2 mm of reduction in proptosis. The decision to perform a fat-only, a single-wall, or a balanced two or three-wall decompression is typically based on the amount proptosis reduction needed. One of the more common approaches is a balanced medial and lateral wall surgery (Figure 5). The medial wall of the orbit can be accessed through a trans-caruncular approach or via an endoscopic approach either in conjunction with an otolaryngologist or by the oculoplastic surgeon. The lateral wall is typically decompressed through a small incision in the lateral canthal area. Patients with compressive optic neuropathy due to crowding in the orbital apex from enlarged EOMs and expanded orbital fat may also need decompression surgery. In these cases, particular attention is given to the posterior orbit, utilizing the same 1,2 or 3 wall approach, to achieve an improvement in visual acuity and field.

Orbital decompressions are not without potential risk, the most concerning are loss of vision from optic nerve injury, worsening or new onset diplopia, cerebrospinal fluid leak and infra-orbital hypesthesia. While orbital decompression surgery is a safe and reliable surgery in the hands of an experienced orbital surgeon, several new technologies are being implemented to improve safety such as the use of image-guided orbital navigation and piezoelectric devices that allow for emulsification of bone while minimizing soft tissue injury.[39,40]

Conclusion

Thyroid eye disease is the most common inflammatory orbital disorder, is associated with autoimmune thyroid dysfunction and may have protean manifestations. It is a progressive disorder with symptoms and signs that may cause significant facial disfigurement, visual disability and rarely blindness from optic neuropathy or corneal scarring. Although we have a better understanding of its immunologic basis, and now have a biologic medication specifically approved to treat it and alter progression, the clinical course and therapeutic options for each patient must

be individualized with input from the multidisciplinary team. The need for surgical treatment for TED is diminishing, especially orbital decompression. We no longer need to wait for "burned-out" fibrotic disease before considering rehabilitation.

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Disclosure

MCS is a Consultant/Advisor to Horizon Therapeutics. **MM**

Thyroid Disease in Aging

by Jon Dedon, MD

Thyroid disease often presents in older adults with nonspecific presentations such as falls, weakness, or cognitive impairment.



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Abstract

Thyroid disease is common in older adults. Increasing numbers of older persons will present to physicians for care in the United States as the U.S. and world populations age. It is expected that by the year 2030 that 19-20% of the U.S. population will be over 65-years old and by 2040 that 25% of the U.S. population will be over 65-years old. It is important for clinicians to be familiar with thyroid disease in this population because of its impact on the patient's functional and cognitive state. Thyroid disease often presents in older adults with nonspecific presentations such as falls, weakness, or cognitive impairment. Thyroid abnormalities may also be detected with routine testing.

Case Study

(Identifiers changed to preserve privacy)

An 85-year-old woman lived in her community for 50 years, continuing to live in her home after her husband passed away. Her family noticed that she was more forgetful, had an unsteady gait, and was falling. Her family took her to her physician who indicated she was just getting older, which was causing her weakness, falls, and confusion. Her family moved her out of her home into an assisted living facility as she continued to worsen cognitively and functionally. Finally she was so weak and confused she could not live in assisted living. Her family brought her to live with them, anticipating nursing home placement. They also brought her for a Geriatric Assessment Clinic evaluation. That afternoon in clinic she was weak, had an unsteady gait, and scored poorly on the Mini Mental State Examination, with a score in the dementia range. Evaluation included checking a thyroid stimulating hormone (TSH) level, which came back quite elevated at 92 uIU/ml, reference range 0.34-5.60. The patient's diagnosis was then hypothyroidism. Due to her advanced age with cardiac risk, her levothyroxine replacement was started low at 25 mcg orally daily, increasing the dose periodically until a daily dose of 100 mcg was reached. Her TSH was then in normal 0.34 – 5.60 range. The patient returned to Geriatric Assessment Clinic for follow up and her strength was improved, her gait stable, and her Mini Mental State Exam score was in the normal range. The patient had a remarkable improvement in gait and cognition. The patient and her family were very pleased. At that time she did not need nursing home placement.

The lesson: anytime an older person presents with confusion, falls, gait instability, weakness, weight change, or unexpected behavioral change, check thyroid function.

Hypothyroidism

Hypothyroidism can be present in up to 5% of older people, while subclinical hypothyroidism can be present in up to 15% of people 65-years old or older. TSH tends to increase a little with increasing age, with the 97.5th percentile of TSH distribution of 6.3-7.5 mIU/L in adults 80 and older.[1] With older age, thyroxine (T4) secretion decreases, but this is balanced by decrease in T4 clearance, so T4 levels are unchanged. Triiodothyronine (T3) levels also remain unchanged until a slight decrease can occur with extreme old age.

Hypothyroidism can present with slowly progressive weakness, falls, cognitive impairment, gait disturbance, dry skin. Hypothyroidism among the elderly is often due to Hashimoto's Disease/ autoimmune thyroiditis. Elevated TSH serum values are required to diagnose hypothyroidism in older people. For older adults abnormal laboratory values should be repeated to confirm accuracy of the result. Subclinical hypothyroidism may present with TSH > 4.5 mIU/L and normal free T4, and is defined by lab values despite absence of clinical symptoms. Often, treating the older adult with hypothyroidism with levothyroxine replacement is not started until TSH is 10 or greater. TSH may change during an acute illness, then increase during the recovery from illness. Nonthyroid illness syndrome may cause abnormal thyroid function test results. Thyroid function tests that are difficult to interpret may require endocrinology consultation. Diagnosis of hypothyroidism requires persistent increase of TSH and low T4. A low or normal TSH with low free T4 suggests secondary hypothyroidism associated with hypopituitarism.

Replacement with levothyroxine for older people should start low, 25 mcg/day or 50 mcg/day, especially for those with coronary artery disease. For those with severe cardiac disease one may wish to start replacement at 12.5 mcg/day.[1] More frequent smaller adjustments of levothyroxine may be required in older adults.[2] Doses may be increased every four to six weeks until TSH normalizes. Levothyroxine combined with triiodothyronine is not recommended for the elderly due to cardiovascular risk. Older adults are at higher risk of myxedema coma or severe hypothyroidism. Most cases of myxedema coma occur in elderly patients. This should be considered when accompanied by hypothermia and bradycardia. Thyroid hormone replacement requirements may be lower in older people due to decreased clearance.

Central hypothyroidism from pituitary or hypothalamic failure is rare.[3]

We should remember that poor compliance is the most common cause for persistent elevation of TSH despite the patient being prescribed adequate thyroid replacement.[4]

Hyperthyroidism

Hyperthyroidism occurs in up to 2.3% of older people, with 15.25% of cases of thyrotoxicosis being in people 60-years old or older. The majority of hyperthyroidism in the U.S. is due to Graves Disease. Toxic multinodular goiter and autonomously functioning adenomas also occur. Hyperthyroidism in older people can present atypically with weight loss, tachycardia, skin changes, tremor, goiter, ophthalmopathy, atrial fibrillation, heart failure, and weakness. Low TSH combined with elevated T4 or T3 helps make the diagnosis. T3 toxicosis with elevated T3 but normal T4 is seen in some hyperthyroid patients. T4 toxicosis with low TSH, high T4, and normal T3 is also seen.

Graves Disease ophthalmopathy may be present.[5] Graves Disease and Hashimoto's Thyroiditis are often associated with antithyroid autoantibodies. Thyrotropin receptor antibodies, usually activating TRAb, are associated with Graves Disease. These antibodies are both highly sensitive and highly specific. Anti thyroid peroxidase antibodies, (anti TPO antibodies), are associated with Hashimoto's Thyroiditis. TPO antibodies are present in the vast majority of patients with Hashimoto's and are highly sensitive.

Amiodarone, a cardiac antiarrhythmic medication, contains a significant amount of iodine, and is stored in the body in fat, liver, lung, and myocardium, with a half life of about 50 days. An estimated 2% of patients taking amiodarone develop amiodarone-associated thyrotoxicosis.[6]

Apathetic thyrotoxicosis is almost exclusively seen in older people, presenting with depression, lethargy, inactivity, anorexia, weight loss, constipation, and weakness.

Up to 30% of older people with atrial fibrillation may have hyperthyroidism. Subclinical hyperthyroidism presents with a low TSH with normal T4 and T3, with or without signs or symptoms of typical hyperthyroidism. Prevalence increases with increasing age, up to 10% in the very old. Subclinical hyperthyroidism is associated with atrial fibrillation

and accelerated bone mineral loss with increased fracture risk.

Treatment of hyperthyroidism in older people and endocrine consultation is recommended due to increased risk of atrial fibrillation, congestive heart failure, osteoporosis, and increased mortality risk. Radioactive iodine (RAI) supervised by an endocrinologist is the treatment for most older people with Graves Disease or toxic nodular thyroid disease. Medications methimazole or propylthiouracil (PTU) are also used. Beta blockers can help with tachycardia, tremor, and anxiety. Some older patient's disabilities preventing safe RAI hospital treatment may need methimazole or PTU long term. Most RAI treatment for hyperthyroidism is done as an outpatient. Surgery is another option if RAI or long-term anti-thyroid drugs are not feasible. After RAI, patients should be checked with TSH for development of hypothyroidism or persistent/recurrent hyperthyroidism.

Nodular Thyroid Disease

Thyroid nodules are common in older adults in that 90% of women 70-years old or older and 60% of men 80-years old and older have thyroid nodules. Most are detected on imaging ordered for other reasons. Nonpalpable nodules are as likely to be cancerous as palpable nodules. Thyroid cancer is found in 4-6.5% of nodules, more in people 60-years old and older, and more in men. In older adults papillary and follicular carcinomas are more aggressive. Thyroid lymphomas are more common, and anaplastic thyroid carcinomas are much more common among older people. Constant stimulation of the thyroid to release thyroid hormones may cause the gland to enlarge to become a goiter.[7] The presence of multinodular goiter increases with increasing age. Those with multinodular goiter can develop iodine induced thyrotoxicosis after radiocontrast or with amiodarone.

The 2017 USPSTF guidelines recommend against screening generally for thyroid cancer. Screening for thyroid cancer is indicated for history of head and neck irradiation, Multiple Endocrine Neoplasia Type 2, family history of thyroid cancer, or high risk characteristics on imaging.

Indications for diagnostic thyroid ultrasound include cervical lymphadenopathy, thyroid nodules or multinodular goiter, selection of thyroid nodule for biopsy, guidance for fine needle aspiration (FNA), evaluation of nodule characteristics, nodules discovered on other imaging. Ultrasound is the most sensitive test for thyroid nodules, often rated by Thyroid Imaging Reporting and Data System (TIRAD), a five-point scoring system for thyroid nodules on ultrasound, developed by the American College of Radiology.[8] For older adults with nodules or goiter, ultrasound and thyroid function testing should be done. Autonomously functioning thyroid nodules are rarely malignant; cancer workup generally does not need to be done for a thyroid nodule with RAI uptake on a radionuclide thyroid scan, with a normal TSH. Generally, FNA is required to exclude malignancy in a nodule. Usually only thyroid nodules greater than 1 cm need evaluation for malignancy. After RAI is administered for high-risk thyroid cancers, or surgery is performed, levothyroxine suppression may be done to reduce recurrence, but osteoporosis and cardiac effects are possible. Beta blockers and bone mineral strengthening agents may be helpful. Please review the American Thyroid Association clinical practice guidelines for management and monitoring of thyroid malignancies.[9]

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Disclosure

None reported. **MM**

A Case-Based Comparison of the American Thyroid Association and Thyroid Imaging Reporting & Data System Guidelines

by Leslie Shang, MD, Rob Downing, DO, Betty Drees, MD & Lamont Weide, MD, PhD

Thyroid nodule management should be focused on efficient and effective detection of thyroid cancer while preventing overdiagnosis and incorporating goals of patient care.



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Abstract

Thyroid nodules are a common clinical finding. Approximately 4-7% of the population have a palpable nodule on physical exam,[1] while up to 70% of the population have a nodule detected incidentally on ultrasound.[2] The vast majority of nodules are benign, however, approximately 5-13% of thyroid nodules detected on imaging are at risk of malignancy.[3] Some malignant nodules, especially those smaller than 1 cm, can exhibit indolent behavior and do not require aggressive treatment.[4] Therefore, thyroid nodules need to be accurately assessed to avoid overdiagnosis and overtreatment of nodules which would not otherwise affect patient morbidity. The American Thyroid Association (ATA) addressed this challenge by developing a set of ultrasound pattern-based guidelines for thyroid nodule management in 2009, which were updated in 2015.[5] Other societies have since published similar guidelines, such as the Thyroid Imaging Reporting & Data System (TI-RADS) by the American College of Radiology in 2017. TI-RADS was similarly intended to risk-stratify nodules based on ultrasound appearance, but uses a points-based approach. The purpose of this review is to provide an overview of thyroid nodule evaluation and management through a case-based comparison using the ATA and TI-RADS guidelines.

Overview of Thyroid Nodule Workup

Thyroid nodule assessment begins with a thorough patient history and physical exam. When taking the patient history, the physician should aim to identify risk factors for thyroid malignancy, such as age less than 20, age greater than 70, male sex, history of childhood head and neck radiation, family history of thyroid cancer, or family history of hereditary syndromes involving the

Table 1. Summary of the Sonographic Patterns and Their Ultrasound Features
Adapted from the 2015 ATA guidelines.

Sonographic Pattern	Ultrasound Features	FNA Threshold
High Suspicion	Solid hypoechoic nodule or solid hypoechoic component of a part cystic nodule **with any** of the following: – Irregular margins (infiltrative, microlobulated) – Microcalcifications – Taller-than-wide shape – Rim calcification – Small extrusive soft tissue component – Extra-thyroidal extension (ETE)	≥ 1 cm
Intermediate Suspicion	Hypoechoic solid nodule with smooth margins **without**: – Microcalcifications – Taller-than-wide shape – Extra-thyroidal extension (ETE)	≥ 1 cm
Low Suspicion	Isoechoic or hyperechoic solid nodule, or part cystic nodule with eccentric solid component **without**: – Microcalcifications – Irregular margins – Taller-than-wide shape – Extra-thyroidal extension (ETE)	≥ 1.5 cm
Very Low Suspicion	Spongiform or part cystic nodules **without** any sonographic features described in the low, intermediate, or high suspicion patterns.	Observation - vs - FNA ≥ 2 cm
Benign	Purely cystic nodules (no solid component).	No Biopsy

thyroid (MEN2, Cowden syndrome, FAP, etc.).[5] On physical exam, findings such as a firm and immobile nodule are suggestive of malignancy, while findings of hoarseness or dysphagia suggest mass effect or invasive disease.[1] A thyroid ultrasound should be performed on all patients with a suspected thyroid nodule or goiter. Nodule size, composition and other ultrasound findings then determine management as outlined by the ATA or TI-RADS guidelines.[4] Management can range from clinical observation to ultrasound surveillance or fine needle aspiration (FNA).

ATA Guidelines

The ATA guidelines are all-encompassing, from the initial evaluation of thyroid nodules to the treatment of thyroid cancers.[5] This review will focus on the ATA's recommendations for initial ultrasound evaluation and decision to perform fine needle aspiration. The ATA guidelines places nodules into risk "patterns" based on ultrasound features and recommends biopsy based on pattern and size. Nodules are assessed for their composition, echogenicity, margins, and the presence or absence of additional features such as microcalcifications. The combination of these ultrasound findings then determines placement into one of five patterns regarding risk of malignancy: High suspicion, intermediate suspicion, low suspicion, very low suspicion, or benign.[5] Features such as microcalcifications, irregular margins, and a shape that is taller-than-wide in the transverse plane are more associated with thyroid cancer, therefore, a nodule which exhibit these features will place it in a pattern which is at higher suspicion for

Table 2. A Summary of the American College of Radiology TI-RADS Point System.
Adapted from the ACR TI-RADS guidelines.

Composition (Choose 1)		Echogenicity (Choose 1)		Shape (Choose 1)		Margin (Choose 1)		Echogenic Foci (Choose all that apply)	
	Points		Points		Points		Points		Points
Cystic	0	Anechoic	0	Wider-than-tall	0	Smooth	0	None	0
Spongiform	0	Hyperechoic	1	Taller-than-wide	3	Ill-defined	0	Large Comet-tail Artifacts	0
Mixed Cystic & Solid	1	Isoechoic	1			Lobulated	2	Macrocalcifications	1
Solid	2	Hypoechoic	2			Extra-thyroidal extension (ETE)	3	Peripheral or Rim Calcifications	2
		Very Hypoechoic	3					Punctate Echogenic Foci	3

malignancy.[5] Conversely, a nodule which is hyperechoic, partially cystic, or spongiform, is often placed in a pattern which is less suspicions for malignancy.[5] FNA is recommended if any dimension of the nodule exceeds the size cutoff per pattern. A summary of the sonographic patterns and their ultrasound features are listed in Table 1.

Thyroid Imaging Reporting & Data System (TI-RADS)

TI-RADS was developed by the American College of Radiology with the intent to "identify most clinically significant malignancies while reducing the number of biopsies performed on benign nodules."[4] The system also includes a lexicon of standardized terminology for describing thyroid nodules and provides a structured method for nodule evaluation to improve reporting in clinical practice.

TI-RADS is a point-based system organized into five categories which are to be evaluated by ultrasound: Composition, echogenicity, shape, margin, and echogenic foci. A single best descriptor is chosen for the first four categories, and all applicable descriptors are chosen for the final category (echogenic foci). Each descriptor is associated with a specific number of points based on its risk of malignancy.

Table 3. American College of Radiology TI-RADS Management Recommendations from Point System.
Adapted from the ACR TI-RADS guidelines.

TI-RADS Level	Points	Suggested Management	
TR1	0	No FNA	
TR2	2	No FNA	
TR3	3	FNA if ≥ 2.5 cm	Follow if ≥ 1.5 cm (US at 1, 3, 5 yrs.)
TR4	4-6	FNA if ≥ 1.5 cm	Follow if ≥ 1 cm (US at 1, 2, 3, 5 yrs.)
TR5	≥ 7	FNA if ≥ 1 cm	Follow if ≥ 0.5 cm (yearly US for 5 yrs.)

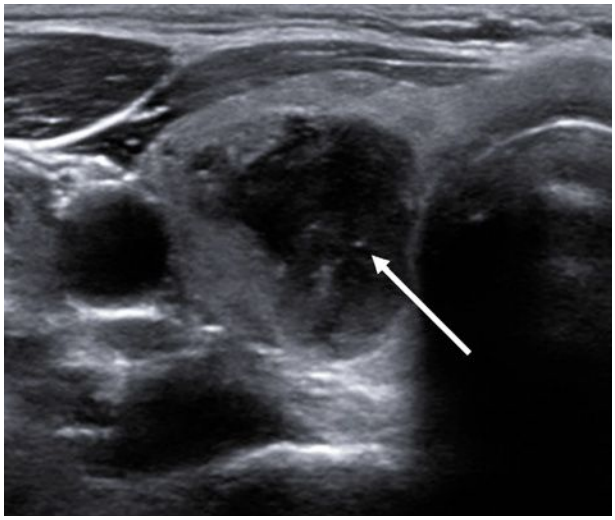
Points are then summed to classify nodules into one of five TI-RADS "levels." Zero points is TI-RADS level 1 or TR1 (benign), 2 points is TR2 (not suspicious), 3 points is TR3 (mildly suspicious), 4-6 points is TR4 (moderately suspicious), and ≥7 points is TR5 (highly suspicious).[4]

A summary of the point system is provided in Table 2. Suggestions for management, which include no further workup, serial ultrasound surveillance or FNA, are provided according to the TI-RADS level and nodule size.[4] A summary of these recommendations are provided in Table 3.

Applying ATA and TI-RADS Guidelines to Thyroid Nodule Management

The following cases will illustrate application of the ATA and TI-RADS guidelines to nodules with various levels of suspicion for malignancy.

Case 1: Nodule with high suspicion of malignancy on ultrasound. Cytology consistent with undifferentiated carcinoma



ATA Approach

This nodule is solid in composition, hypoechoic in echogenicity, taller-than-wide in shape, has lobulated margins and contains microcalcifications (white arrow). This combination of ultrasound features places the nodule within the "high suspicion" pattern. ATA recommends FNA for nodules in the high suspicion pattern beginning at 1.0 cm. This nodule measured 1.7 cm, so it qualifies for FNA.

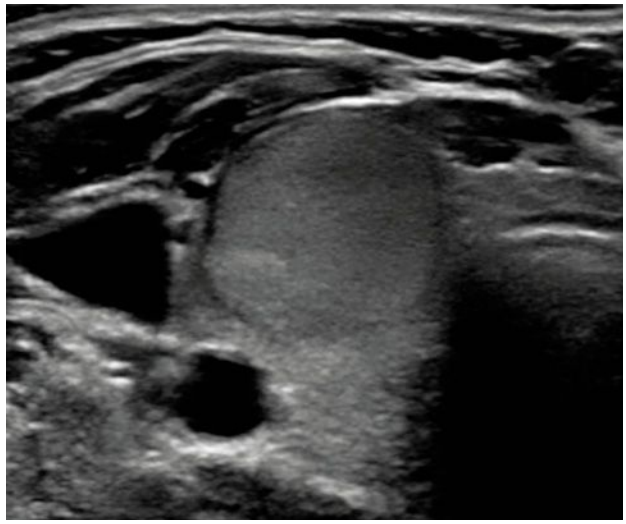
TI-RADS Approach

This nodule is solid in composition (+2 points), very hypoechoic in echogenicity as it is darker than the adjacent strap muscles (+3 points), is taller-than-wide in shape (+3 points), has lobulated margins (+2 points) and contains punctate echogenic foci (+3 points). This nodule receives a total of 13 points, placing it in TI-RADS level 5 (7+ points, highly suspicious). TI-RADS recommends FNA for TR5 nodules beginning at 1.0 cm. This nodule measured 1.7 cm, so it qualifies for FNA.

Comparison

Both ATA and TI-RADS recommend biopsy beginning at 1.0 cm for nodules at high suspicion of malignancy.

Case 2: Nodule with low suspicion of malignancy on ultrasound. Cytology consistent with follicular adenoma



ATA Approach

This nodule is solid in composition, isoechoic in echogenicity, and has smooth margins. It does not have additional suspicious sonographic features such as taller-than-wide shape or microcalcifications. This combination of ultrasound features places the nodule within the "low suspicion" pattern, for which FNA is recommended beginning at 1.5 cm. This nodule measured 2.0 cm, so it qualifies for FNA.

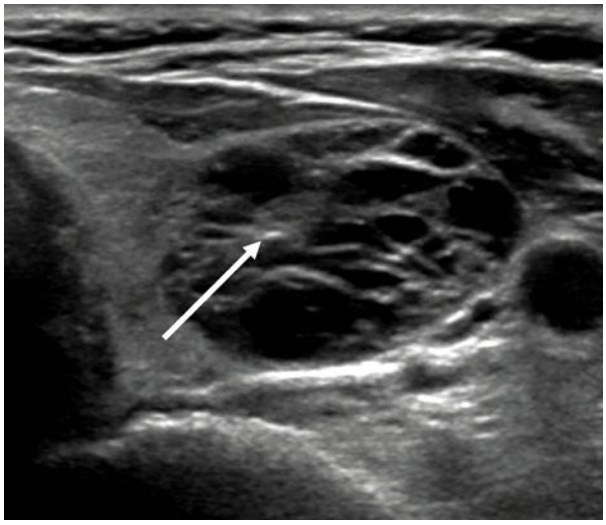
TI-RADS Approach

This nodule is solid in composition (+2 points), isoechoic in echogenicity (+1 point), has a wider-than-tall shape (+0 points), and has smooth margins (+0 points). There are no echogenic foci (+0 points). This nodule receives a total of 3 points, placing it in TI-RADS level 3 (3 points, mildly suspicious). TI-RADS recommends FNA for TR3 nodules beginning at 2.5 cm and ultrasound surveillance for nodules measuring 1.5 – 2.4 cm. This nodule measured 2.0 cm, so follow-up ultrasound would be performed at 1, 3 and 5 years.

Comparison

ATA and TI-RADS set different thresholds for biopsy of nodules at low and intermediate risk of malignancy (1.5 cm versus 2.5 cm and 1.0 cm versus 1.5 cm, respectively). This 2.0 cm nodule at low suspicion for malignancy would be biopsied under the ATA guidelines but would receive ultrasound surveillance under TI-RADS. Implications of this difference are discussed later.

Case 3: Nodule with very low suspicion of malignancy on ultrasound. FNA has not been performed



ATA Approach

This nodule has a classic spongiform appearance without any sonographic features seen in high, intermediate, or low suspicion patterns. This places the nodule in the "very low suspicion" pattern. ATA guidelines give the clinician the option of observation without FNA versus FNA beginning at 2.0 cm.

TI-RADS Approach

This nodule is spongiform in composition (+0 points) since at least 50% of the nodule volume is composed of small cystic spaces.[4] Spongiform nodules are presumed benign in TI-RADS and are not subject to further feature assignment. Small echogenic foci which represent the posterior wall of tiny cysts (white arrow) should not be misinterpreted as punctate echogenic foci, which would otherwise add 3 points. Nodules are not allowed be classified as spongiform if other features such as macrocalcification or rim calcification are present.[4] This nodule receives a total of 0 points, placing it in TI-RADS level 1 (benign). No FNA or ultrasound follow-up is recommended for this nodule.

Comparison

ATA classifies spongiform nodules as "very low suspicion" for malignancy while TI-RADS classifies them as "benign." Management under both systems is expectant, with ATA giving the clinician the option of biopsy beginning at 2.0 cm.

Results of Fine Needle Aspiration

FNA results are reported through the Bethesda system, a cytology classification system with six diagnostic categories: Nondiagnostic (Bethesda I), benign (Bethesda II), indeterminate (Bethesda III and IV), suspicious for malignancy (Bethesda V), and malignant (Bethesda VI).[6] This standardized system also provides recommendations for nodule management which include ultrasound surveillance, repeat aspiration or surgery.

Nodules with indeterminant cytology (Bethesda III or IV) usually prompt additional work-up such as a repeat FNA, repeat ultrasound risk stratification, or diagnostic lobectomy.[7] Molecular testing is used as an adjunct to reduce the number of unnecessary lobectomies as analysis of abnormal gene expression on FNA samples often reclassifies nodules as malignant or benign.[7]

Studies have shown that molecular testing was highly sensitive (94%) in differentiating benign from malignant nodules in samples originally classified as Bethesda III or IV.[7]

Conclusion

Evaluation of thyroid nodules requires a careful assessment of patient risk factors, physical exam findings, and visual inspection by ultrasound. Both ATA and TI-RADS guidelines drive nodule management though ultrasound findings, but do so with slight differences as highlighted in the cases above.

Studies comparing the diagnostic performance of these guidelines have found that both systems have a high sensitivity for detection of thyroid cancer and a negative predictive value ≥90%, a finding which reflects the overall parity of both systems and consensus in management of nodules at very low and high risk of malignancy.[8, 11]

Recommendations diverge, however, with nodules at low and intermediate risk of malignancy as reflected by the thresholds set for performing FNA. The lower size cutoff set by the ATA gives its system a higher sensitivity and negative predictive value, while the higher

size cutoff set by TI-RADS gives its system a higher specificity and positive predictive value.[8, 9] This trade-off has important clinical implications regarding detection of disease and overdiagnosis.

Studies have shown that a higher percentage of malignancies do not receive recommendation for FNA when TI-RADS is used compared to the ATA guidelines.[9, 12, 13] A recent paper has shown that most of these nodules: 1) undergo a five-year ultrasound surveillance period during which it is presumed that clinically-significant cancer will be detected; 2) are smaller than 1 cm and would not be routinely-biopsied under either guideline; or 3) are of low malignant potential and theoretical risk to the patient.[12]

Authors of this paper suggest the low rate of malignancy missed by TI-RADS to be acceptable and justifiable by the reduction in unnecessary biopsies and need to prevent overdiagnosis of thyroid cancer.[12] Conversely, ATA guidelines recommend FNA for a higher percentage of malignancies, but the simultaneous increased rate of biopsy on benign nodules sacrifices overall accuracy and cost effectiveness.[13, 14] Regardless of which set of guidelines are chosen, thyroid nodule management should ultimately be focused on efficient and effective detection of thyroid cancer while preventing overdiagnosis and incorporating goals of patient care.

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Disclosure

None reported. **MM**

Preexisting Thyroid Disease in Pregnancy: A Brief Overview

by Devika Maulik, MD, Valerie Chuy, MD & Shruti Kumar, MD

Increasing efforts to create community-based standards for management and a more personalized approach to thyroid disease during pregnancy may help optimize care in the future.



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Abstract

Maternal thyroid disease, with both an excess or deficiency of thyroid hormone, raises the risk profile of affected pregnancies with regards to preeclampsia, preterm birth, placental problems, thyroid derangement of the fetus and neonate, and neurodevelopment of exposed fetuses later in life. Fortunately, close and tight management of thyroid disease within the fluctuating physiologic milieu of pregnancy offers opportunities to significantly improve perinatal outcomes. However, despite guidelines offered by American College of Obstetrics and Gynecology (ACOG) and American Thyroid Association (ATA), controversy persists regarding interpretation of thyroid labs, screening for disease, surveillance, fetal and placental thyroid physiology, and optimal medication and management strategies. This is a brief overview of what is known and unknown regarding thyroid disease and its impact on maternal, fetal, and pregnancy health.

Introduction

Maternal baseline thyroid disease affects a significant portion of pregnancies annually. According to ACOG, hyperthyroidism affects 0.2-0.7% of all pregnancies, and hypothyroidism is seen in up to 10 of every 1,000 pregnancies.[1] Unfortunately, both hyper- and hypothyroidism increases the likelihood of perinatal complications such as preeclampsia, placental accidents, preterm birth, fetal thyroid, and neurodevelopment and metabolic growth of the fetus. Fortunately, proper surveillance and close management of preexisting thyroid disease can help mitigate this risk.

However, gestational thyroid surveillance is difficult due to normal physiologic alterations to thyroid synthesis with pregnancy. Even among the euthyroid, pregnancy elicits significant physiologic changes involving thyroid regulation to accommodate the needs of both the mother and the fetus; as a result, interpretation of thyroid labs and subsequent management can prove to be challenging. Generally, changes in maternal physiology lead to a compensatory increase in maternal thyroid hormone synthesis to guarantee appropriate maternal and fetal thyroid hormone availability.[2,3]

Pregnancy-Induced Alterations to Thyroid Function

Normal changes during the first trimester prompts a transient suppression of TSH and stimulation of thyroxine-binding

globulin (TBG) and total T3 and T4 levels. A rise in estrogen in early pregnancy stimulates a two-fold increase in sialyation and glycosylation of TBG in the liver, making it less susceptible to degradation, increasing its circulating concentration. As TBG binds the majority of circulating thyroid hormones, this rise in TBG stimulates a greater demand for total levels of T4 and T3 while free T3 and T4 levels remain unaffected.[3]

Concurrently, human chorionic gonadotropin (hCG) acts as a weak agonist of the TSH receptor, simultaneously stimulating the thyroid to secrete more T3 and T4 while inducing a partial TSH suppression. During the second trimester and third trimester, when hCG levels have decreased and its suppressive effect on TSH has diminished, there is normalization of TSH in the second trimester with a slight increase in the third. Free T3 and free T4 levels are slightly lower in later gestation due to an increase in thyroid hormone breakdown by placental type 3 deiodinase and urinary iodide clearance after the first trimester.[1] Total T4 and TBG values rise and plateau in the second trimester, thereafter, sustaining a high level for the duration of the third trimester.[2]

With these normal fluctuations in the thyroid metabolic pathway, target laboratory values that screen and assess thyroid function in pregnancy can be difficult to interpret. TSH and free T4 measurements during pregnancy are utilized in terms of both diagnosis and surveillance of thyroid disease during pregnancy. Previously, the recommended TSH upper-limit cut-offs were 2.5 -3.0 mU/l;[4] however more recently, the literature recognizes racial, ethnic, and population-level variation with both the upper and lower limits of a normal TSH range, which makes the previously recommended blanket cutoff appear arbitrary, more questionable and potentially less relevant.[5]

More than 90% of studies published since 2005 have shown population-based reference ranges for a TSH upper-limit well-above the previously established 3.0 mU/l;[4] though all studies demonstrated significant depression of the lower threshold for TSH ranges. Some of this population-specific variation is attributed to inconsistent rates of iodine deficiency, nutrition, other environmental exposures, and prevalence of genetic disposition and obesity.[5] In order to address these findings, the ATA revised recommendations in 2017, suggesting laboratory reference ranges for TSH and thyroid hormones should focus on values relevant to specific populations, prompting clinicians to seek local laboratory values.[4] If data regarding a specific practice location or similar patient population is not available, both ACOG and the ATA recommends the following adjustments: 1) subtracting 0.5 mU/I from the lower threshold for nonpregnant range for TSH; 2) subtracting 0.5mU/I from the upper threshold for nonpregnant TSH range; and 3) upper range of T3 and T4 increased by 50% after 16 weeks gestation. Regarding the upper range of TSH, the target range with the subtraction of 0.5 mU/l is equivalent to around 4 mU/l for most centers and above original recommendations of 2.5 mU/l or 3.0 mU/l.[1,4]

Fetal Thyroid

Monitoring maternal thyroid values in the setting of both hyper- and hypothyroidism is critical in ensuring proper fetal development and optimizing for overall pregnancy health. This is due to the reliance of the fetus on maternally-derived thyroid hormones and iodine to facilitate thyroid gland maturation and general physiologic development. The fetal thyroid is utilizing maternal iodine to secrete T4 as early as 10-12 weeks gestation.[2] By 18-20 weeks gestation, the fetal pituitary stimulates and modulates fetal thyroid hormone secretion. Even then, the fetus is still reliant on maternal thyroid hormone and iodine. Even at birth, 30% of the T4 found in cord blood is maternally derived.[1] For this reason, clinicians adjust medication to achieve a free T4 level that is high-normal to ensure adequate levels to maintain fetal health and development; however emerging data suggests that this cutoff may lead to overtreatment.[6] That said, why maternal thyroid is still so heavily concentrated even in late gestation, when the fetal thyroid is more mature, is incompletely understood.[7,8]

The placenta plays a role in modulating maternal contribution of thyroid support and promoting fetal thyroid function as well. Placenta and fetal pancreas are a significant source of thyroid releasing hormone (TRH).[9] TRH from these sources with relation to the maturing fetal hypothalamic pituitary axis is poorly understood, though some suspect it plays a role in prematurity and fetal lung maturation.[10]



Maternal thyroid disease, with both an excess or deficiency of thyroid hormone, raises the risk profile of affected pregnancies with regards to preeclampsia, preterm birth, placental problems, thyroid derangement of the fetus and neonate, and neurodevelopment of exposed fetuses later in life.

Hyperthyroidism

The vast majority of cases of hyperthyroidism is due to Grave's disease (90%) with immunoglobulins that stimulate thyroid hormone production, resulting in elevated thyroid hormone levels and severe depression of TSH levels. Though the placenta regulates and diminishes the amount of maternal thyroid hormone that can cross into the fetal circulation, excessive hormone levels are known to override this regulatory mechanism with a detrimental effect on the fetus, elevating the risk of miscarriage and stillbirth. For this reason, treatment with antithyroid medications/thioamides is critical in decreasing this risk. Also, close ultrasound surveillance of the fetus throughout the pregnancy, monitoring both fetal well-being, fetal heart and growth is critical. Symptoms seen with hyperthyroidism overlaps with common complaints seen with pregnancy or preeclampsia: nausea, vomiting, tachycardia, hypertension, heat intolerance, sweating. There is also concern about weight loss and appropriate maternal weight gain during the pregnancy.

Maternal hyperthyroidism is associated with an elevated risk of preeclampsia, preterm birth, fetal thyroid abnormalities (both hyper- and hypothyroidism), fetal growth restriction, and fetal goiter. As it is an autoimmune disease, there is an elevated risk of gestational diabetes as well. The US Preventative Taskforce recommends aspirin as an effective prophylaxis against preeclampsia for high-risk mothers at a nightly dose of 81-150mg. Additionally, aspirin has been shown to decrease the risk and diminish the severity of preeclampsia, reduce perinatal mortality and growth restriction, and lower the risk of preterm birth.[11]

Preterm birth and preeclampsia are a source of concern among affected pregnancies, but the direct effect of maternal antibodies on the fetal thyroid gland can pose a greater threat. The antibodies produced

with Grave's disease can cross the placenta and cause hyper- or hypothyroidism in the fetus, prompting fetal hyperthyroidism (1-5% of affected pregnancies) and fetal thyrotoxicosis in rare cases (1% of affected pregnancies).[7] Fetal thyrotoxicosis presents as elevated heart rate, growth restriction, hydrops from heart failure, and fetal goiter. Usually, a good indication of whether a fetus is at risk is the thyroid receptor antibody (TrAB) (this is used interchangeably with thyroid stimulating immunoglobulin or TSI) measurement early in gestation. If it is two to three times more than normal, a fetus is deemed high-risk, warranting close ultrasound surveillance for signs of thyroid disease.[4]

Fetal thyrotoxicosis is very rare because the normal immunologic changes of pregnancy suppress maternal antibody levels with increasing gestation. However, in the third trimester, there is greater permeability of the placenta to maternal antibodies in the fetal circulation; this is when the fetus is at the highest risk. Furthermore, formerly hyperthyroid mothers who have since been ablated still have antibodies that can affect the fetus; in such cases TrAB/TSI measurements are still useful in screening the risk for fetal thyroid disease. Treatment is maternal oral medication; in especially difficult cases, umbilical blood sampling may be necessary to test cord blood thyroid levels and administer IV medication.[7]

For treatment, either methimazole or propylthiouracil is typically used; however, both medications pose specific, potential risks to the pregnancy. Methimazole is infamously associated with certain congenital anomalies if used in the first trimester, specifically aplasia cutis as well as esophageal and choanal atresia; a study on 5,700 pregnancies found methimazole exposure in the first trimester increases the risk of congenital malformations twofold.[12] On the other hand, propylthiouracil (PTU) is associated with liver toxicity. Some guidelines recommend PTU in the first trimester with transition to methimazole in the second and third trimester to balance their risk-benefit profiles. Given the rarity of the risks described, many clinicians opt to maintain patients on their pre-pregnancy regimens, as consistent thyroid control is imperative in maintaining pregnancy health. In transitioning from one drug to another between the first and second trimester, there may be some difficulty in achieving immediate maternal thyroid control at a critical time of fetal thyroid development.

Regardless of the thioamide chosen, there is a risk of leukopenia which affects 10% of patients when starting the medication, which does not necessitate cessation; however, in the very rare chance (1%) that agranulocytosis develops, medication should be stopped.[1] Both medications do cross the placenta so the lowest dose to achieve control is recommended. That said after birth, the medication effect clears quickly. With fetal thyroid affected by maternal antibodies, the effect lasts significantly longer as maternal antibodies persist in the fetal circulation for some time after birth, necessitating surveillance and treatment.

If maternal tachycardia and palpitations are present, as is common with Grave's disease, beta blockers (usually propranolol) are utilized; that said, some level of tachycardia is normal with pregnancy, if it is below 120 bpm. Good control is also imperative to ward off the risk of thyroid storm, which presents in 1-2% of hyperthyroid pregnancies.[1]

Hypothyroidism

Hypothyroidism with pregnancy is typically seen with Hashimoto's thyroiditis. On laboratory assessment, the TSH is elevated while free T4 is decreased, but as mentioned before, given the dependence of fetal physiology on maternal thyroid support, current clinical guidelines recommend that free T4 levels should be maintained on the higher end of normal; according to the ATA, there is also consideration using total T4 in lieu of free T4 levels, with thresholds corrected for rises in thyroid-binding globulin.[4] Typically, affected mothers present with fatigue, cold intolerance, and weight gain. While the risk profile is similar to hyperthyroidism (increased likelihood of preterm birth, preeclampsia, placental accidents, stillbirth, and miscarriage), adequate control with medication greatly diminishes the risk. Fortunately, unlike Grave's disease, thyroid inhibitory antibodies do not cross the placenta in most cases at a level that can cause significant thyroid impairment in the fetus; as a result, the prevalence of fetal hypothyroidism in the offspring of women with Hashimoto thyroiditis is estimated to be only about 1 in 180,000 neonates.[12]

In certain areas of the world, maternal iodine deficiency, as opposed to autoimmune antibody

exposure, is more likely to result in insufficient maternal and fetal thyroid synthesis. The developing fetal thyroid is highly dependent on maternal iodine that crosses the placenta for adequate thyroid hormone synthesis and metabolic support; inadequate iodine stores can lead to overstimulated TSH levels, fetal hypothyroidism, and eventually fetal goiter. In the United States, maternal iodine deficiency is believed to be uncommon; that said, iodine supplementation is inconsistent within food sources (even fortified ones such salt and bread) and even prenatal vitamin formulations. A recent NHANES assessment of urinary iodide concentration (UIC) found that the mean value was less than the suggested values by the World Health Organization that are representative of adequate iodide stores.[13] Furthermore, maternal iodine stores are increasingly depleted over gestation and especially utilized in the postpartum period as iodine concentrates in breastmilk; adequate repletion is necessary especially during lactation. During pregnancy and lactation, respectively 220 μg and 290 μg of iodine are necessary to support the health of fetus and infant properly. Unfortunately, the prevalence of iodine deficiency among lactating mothers in the Unites States is not well characterized.[4]

Currently, with hypothyroidism, the risk of miscarriage is significant with poorly controlled hypothyroidism. Various studies estimate the risk of miscarriage is three- to four-fold higher with uncontrolled Hashimoto's thyroiditis.[14] For example, a study on 2,500 Dutch women found a linear correlation between TSH levels at initial obstetric visits and miscarriage.[15]

That said, proper management with medication appears to help. Levothyroxine remains the gold-standard in the treatment of pregnant patients with hypothyroidism worldwide. Adequate management with levothyroxine has been shown to decrease the risk of miscarriage and preterm births significantly among mothers with Hashimoto thyroiditis.[16] Finally, unlike thioamides, levothyroxine does not cross the placenta and only in small quantities, not unlike maternal thyroid hormones in general.

Children of hypothyroid mothers also have an elevated risk of developmental problems later in life and potentially certain types of cancer. In 2015, a National Finnish Birth Cohort evaluation of 9,362 women and 9,479 children found that maternal hypothyroidism correlates with impaired neuropsychological development and scholastic performance later in life.[17] In utero-exposure to autoimmune thyroid disease has also been reported to increase the risk of childhood acute lymphoblastic leukemia (ALL) in the offspring. A population-based case-control study in Finland of approximately 11,000 patients found the increased risk of lymphomas to be 3.66-fold when comparing mothers with hypothyroidism and those with normal thyroid function. It is unknown whether current goals for management affect outcomes regarding childhood ALL or neuropsychologic outcomes later in life.[18]

Areas of Controversy

In the management and screening of thyroid disease in pregnancy, there are few areas where the ATA recommendations differ from what ACOG suggests in clinical guidelines. For example, the ATA suggests mothers with thyroid disease have labs checked every four weeks, while ACOG recommends every four to six weeks.

There is even greater disagreement on euthyroid women who have laboratory evidence of thyroid autoimmunity with a positive thyroid peroxidase antibody or thyroglobulin antibody. Euthyroid women with thyroid autoimmunity can present with subclinical disease, but the clinical relevance of this finding is debatable, especially if a viable pregnancy is already achieved. Various studies have inconsistently demonstrated an elevated risk of miscarriage, stillbirth.[19,20] That said, the TABLET trial performed in the United Kingdom found treatment of euthyroid mothers with thyroid autoimmunity with levothyroxine did not alter the rate livebirths in this cohort.[21]

As seen in hypothyroidism, there is concern that subclinical hypothyroidism can affect later developmental progress of exposed children. A cohort study in the Chinese population published in 2010 studied pregnant women with isolated subclinical hypothyroidism, hypothyroxinemia, or euthyroid labs with elevated titers of anti-TPO antibodies and subsequent neuropsychological development in their offspring. Standardized intellectual and motor evaluation performed at 25-30 months of age confirmed that all three maternal thyroid abnormalities tested at 16-20 weeks' gestation were

separately associated with a statistically significant lower motor and intellectual development.[22] Given the potential impact of subclinical autoimmune thyroid disease on pregnancy and offspring, there continues to be debate about the utility of treatment in preventing these outcomes.

The ATA recommends checking TSH of euthyroid women with thyroid autoimmunity at the start of pregnancy and every four weeks. However, ACOG does not address this recommendation specifically but mentions that empiric treatment of this patient population does not affect pregnancy loss or neurocognitive outcomes of children later in life at ages three and five based on the Controlled Antenatal Thyroid Screening Trial in 2012 and the Maternal Fetal Medicine Units Network Trial in 2017.[23,24] Furthermore, the practice bulletin mentions that the likelihood of overt thyroid disease presenting during pregnancy among euthyroid women with thyroid autoimmunity and subclinical hypothyroidism is low. Checking for thyroid autoimmunity is not commonly done in our practice after pregnancy has been achieved but may be considered in the setting of recurrent early pregnancy loss and infertility.

Conclusion

Thyroid management in pregnancy has many well-established guidelines to improve perinatal outcomes, but clinical protocols are coming under scrutiny as certain set laboratory thresholds and subsequent interventions are of questionable relevance and long-term utility. In the coming years, increasing efforts to create community-based standards for management and a more personalized approach to thyroid disease during pregnancy may help optimize care in the future.

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Disclosure

None reported. **MM**

Clinical Review and Update on the Management of Thyroid Storm

by Reuben De Almeida, MD, Sean McCalmon, DO & Peminda K. Cabandugama, MD

Thyroid storm is a severe manifestation of thyrotoxicosis and can lead to multi organ failure with a high mortality rate.



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Abstract

Thyroid storm is a severe manifestation of thyrotoxicosis. Thyroid storm is diagnosed as a combination of thyroid function studies showing low to undetectable thyroid stimulating hormone (TSH) (<0.01mU/L) with elevated free thyroxine (T4) and/or triiodothyronine (T3), positive thyroid receptor antibody (TRab) (if Graves' disease is the underlying etiology), and with clinical signs and symptoms of end organ damage. Treatment involves bridging to a euthyroid state prior to total thyroidectomy or radioactive iodine ablation to limit surgical complications such as excessive bleeding from highly vascular hyperthyroid tissue or exacerbation of thyrotoxicosis. The purpose of this article is a clinical review of the various treatments and methodologies to achieve a euthyroid state in patients with thyroid storm prior to definitive therapy.

Introduction

Thyroid storm is a severe manifestation of thyrotoxicosis. In the United States, up to one in six hospitalizations for thyrotoxicosis were related to thyroid storm, with a 12-fold higher mortality.[1] It is most commonly seen in Graves' disease but can also occur in toxic multinodular goiter and with solitary toxic adenomas, and can be precipitated by thyroid or non-thyroid surgery, trauma, infection, acute iodine load, parturition, amiodarone use, and non-compliance to anti-thyroid medications.

Thyroid storm is diagnosed as a combination of thyroid function studies showing low to undetectable thyroid stimulating hormone (TSH) (<0.01mU/L) with elevated free thyroxine (fT4) and/or free triiodothyronine (fT3), positive thyroid receptor antibody (TRab) (if the underlying etiology is Graves' disease), and with clinical signs and symptoms of end organ damage. The fT3 may be normal in severely ill patients due to reduced conversion of peripheral fT4 to fT3.[2] Symptoms that highly correlate with thyroid storm include fever ≥ 38°C, tachycardia ≥130 beats per minute, central nervous system manifestations, congestive heart failure, and gastrointestinal/hepatic manifestations.[2,3,4] Two validated severity rating scales for thyrotoxicosis are the Burch–Wartofsky Point Scale (BWPS) and the Japanese Thyroid Association (JTA) scale. A BWPS of ≥45 or JTA categories of thyroid storm 1 (TS1) or thyroid storm 2 (TS2) with evidence of systemic decompensation require aggressive therapy.[2,3,4] Once diagnosed, all patients with thyroid storm

should be admitted to the ICU for aggressive medical management. Management then includes both addressing end organ damage and attaining a euthyroid state.

Definitive treatment involves either total thyroidectomy or radioactive iodine ablation of the thyroid gland. Initial treatment involves bridging to a euthyroid state prior to definite treatment. In the case of considering total thyroidectomy, the goal is to limit surgical complications such as excessive bleeding from highly vascular hyperthyroid tissue or exacerbation of thyrotoxicosis.[5] Both the American Thyroid Association (ATA) and the JTA do not specify recommended definitive treatment, likely due to the clinical variability of severity and response to initial medical treatment.[2,3] In general, those with more severe thyroid storm may benefit from total thyroidectomy, whereas those with milder thyroid storm who respond well to initial treatment may benefit from radioactive iodine ablation for definitive treatment if no other contraindications are present. There are several safe and effective pharmacological options available to achieve a euthyroid state, including a combination of modalities that can be used. The purpose of this article is a clinical review of the various treatments and methodologies to achieve a euthyroid state in patients with thyroid storm prior to definitive therapy.

Treatment Options

Antithyroid Drugs

First-line treatments include propylthiouracil (PTU), carbimazole, and methimazole (MMI), which are antithyroid medications that inhibit thyroid hormone synthesis by acting on thyroid peroxidase.[6] Carbimazole is not widely used in the United States. PTU inhibits the peripheral conversion of T4 to T3 by inhibiting type-1 deiodinase.[6] PTU is preferred over MMI due to its effects on peripheral conversion and has been shown to have a more significant effect in lowering serum T4 and T3 within 24 hours compared to MMI.[3,7] The JTA prefers MMI over PTU due to findings that MMI corrected thyroid hormone levels more rapidly than PTU, and a more favorable safety profile of MMI.[2,8] Ultimately, choosing between PTU and MMI depends on patient characteristics and tolerability. In the first trimester of pregnancy, PTU is preferred over methimazole due to increased risk of birth defects.[6]

Dosing of PTU is a 500–1000 mg load, then 250 mg every four hours, which can be given orally or intravenously.[3] The recommended maximum dose of PTU is 1600 mg per day.[2] Dosing for MMI is 60-80 mg/day, with maximal dose of 100 mg/day.[2,3] MMI is not available as intravenous dosing in the United States. However it should be noted that there have been cases of both MMI and PTU being given per rectum.

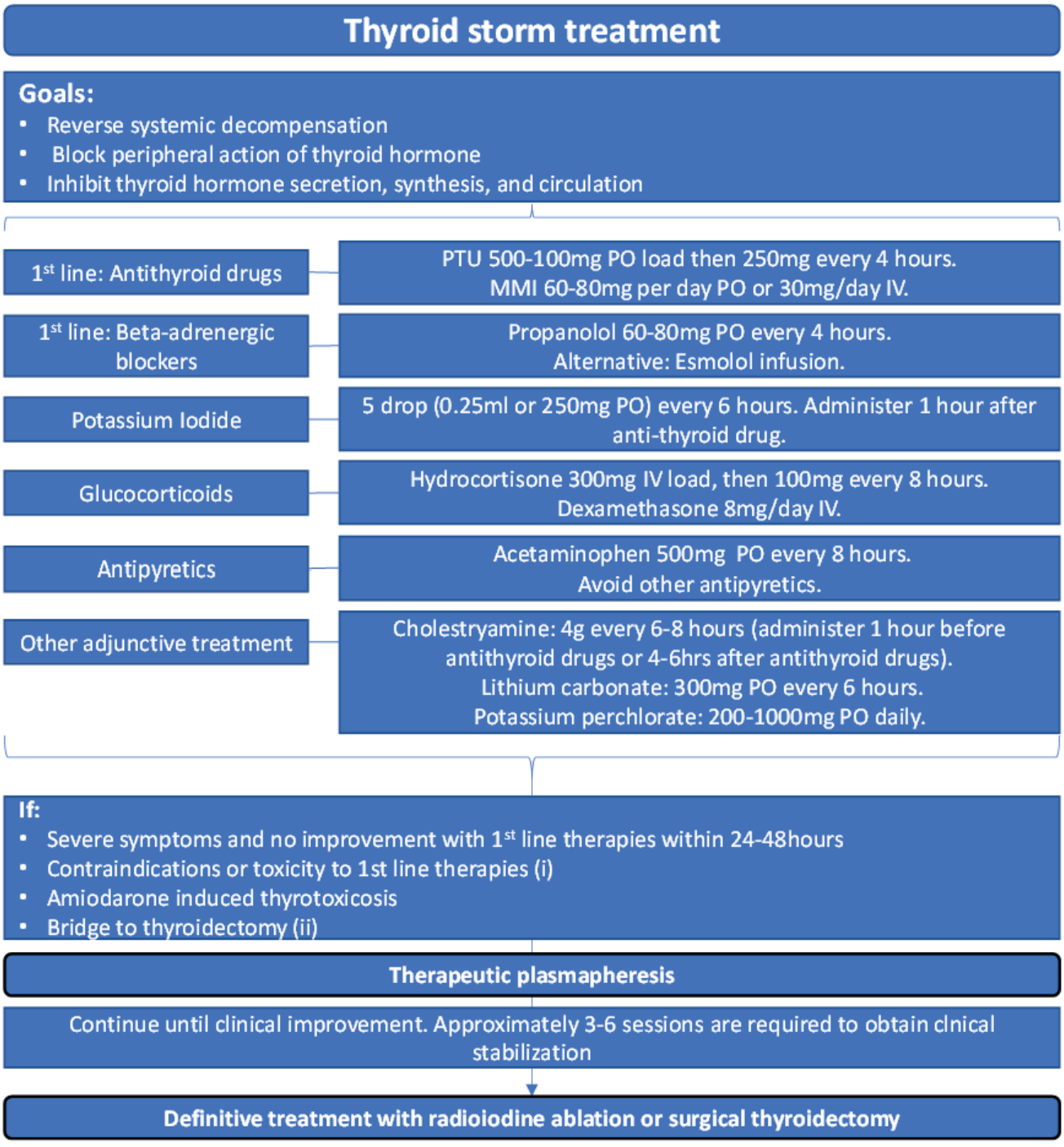
The major adverse effects of PTU and MMI are agranulocytosis, hepatotoxicity, and ANCA positive vasculitis.[6] In men of Asian descent, MMI is associated with hypoglycemia secondary to autoimmune insulin syndrome.[6] Minor adverse reactions include cutaneous reactions, arthralgias, gastrointestinal upset, abnormal taste sensation, sialadenitis, and lymphadenopathy.[6]

Iodine

Iodine acts to inhibit thyroid hormone via the "Wolff-Chaikoff effect" that reduces hormone biosynthesis by inhibition of iodine organification.[9] In preparation for total thyroidectomy, short-term iodine solutions are given as adjunctive therapy with either anti-thyroid thionamides or other non-thionamide medications. When administered preoperatively, iodine helps to decrease gland vascularity and blood loss.[10] Another advantage of iodine pretreatment is potentially lower doses of thionamides required to achieve the euthyroid state, reducing overall drug toxicity. Takata et al. (2010) and Sato et al. (2015) demonstrated that 15 mg/day of MMI combined with potassium iodide was significantly more effective at achieving a euthyroid state and had fewer adverse effects than 30 mg/day of MMI alone.[11,12] Note that in patients with iodine deficiency, toxic adenoma or toxic nodular goiter, treatment with iodine may actually increase thyroid hormone production due to increased availability of substrate. The ATA recommends iodine should either be avoided or only given an hour after thyroid synthesis inhibition with thionamide administration. However, the JTA recommends iodide supplementation at the same time as the thionamide due to no findings of increased thyrotoxicosis adverse effects.[2,12] In patients intolerant to thionamides, iodine is given as pretreatment pre-operatively.

Dosing of potassium iodide is either 5–7 drops (0.25–0.35 mL) of Lugol's solution (8 mg iodide/drop) or 1–2 drops (0.05–0.1 mL) of saturated solution potassium iodide (SSKI) (50 mg iodide/drop) three

Figure 1.Algorithm for the management of complicated thyrotoxicosis or thyroid storm. (i) Examples include acute liver failure and agranulocytosis associated with antithyroid drugs. (ii) Therapeutic plasma exchange allows a thyrotoxic patient to reach a euthyroid state prior to thyroidectomy or radioactive iodine ablation. IV, intravenous; MMI, methimazole; PO, oral; PTU, propylthiouracil. Figure adapted from Vinan-Vega et al., 2020.[31]



times daily mixed in water or juice for 10 days before surgery.[3] Up to 200mg/day of total iodine can be administered, with higher doses given to patients with suspected decreased gastrointestinal absorption.[2]

Adverse effects may include acne, loss of appetite, or upset stomach, fever, weakness, unusual tiredness, swelling of the neck or throat, mouth sores, skin rash, nausea, vomiting, stomach pains, irregular heartbeat, numbness or tingling of the hands or feet, a metallic taste in the mouth, anaphylaxis, sialadenitis, and esophageal ulcers.[13]

Lithium

Lithium has been shown to inhibit TSH stimulated thyroxine release via inhibition of the TSH-mediated cyclic adenosine monophosphate (cAMP) secondary signaling.[14] Due to its narrow therapeutic range and side effect profile, lithium is reserved for patients with contraindications to thionamides. In patients with thyrotoxicosis, lithium at therapeutic doses was shown to decrease serum thyroxine levels by ~25% within 4-10 days.[15,16] In amiodarone-induced thyrotoxicosis, lithium in combination with PTU was shown to achieve a euthyroid state within ~4 weeks, compared to ~11 weeks with PTU alone.[15] The dose of lithium is 300–450mg orally every 8hrs.[17] Ng et al. (2006) used a median dose of 750mg/day, with a range of 500-1500mg/day.[16] Adverse effects include tremor, nausea, vomiting, obtundation, cerebellar signs.[16]

Potassium Perchlorate

Perchlorate acts on the sodium iodide symporter and competes for iodine, and in addition, it discharges stored intrathyroidal iodide.[18] Amiodarone-induced thyrotoxicosis is partly mediated by high iodine load from the amiodarone molecule. Perchlorate administration helps to decrease the iodine burden.[19,20] It is often used in conjunction with thionamides, depending on patient tolerance.[20] The dose ranges from 200mg to 1000mg daily.[19] Common adverse effects include irritation, rashes, drug fever, lymphadenopathy, nephrotic syndrome, and agranulocytosis. Rarely, it can lead to aplastic anemia.[17]

Glucocorticoids

Glucocorticoids reduce the peripheral conversion of T4 to T3 and reduce thyroxine production in patients with Graves's disease.[17] Thyrotoxicosis is associated with adrenal insufficiency states [21,22] and steroid co-administration helps reduce the risk of exacerbation of adrenal insufficiency. The dose of hydrocortisone is a 300 mg intravenous load, followed by 100 mg every eight hours, or dexamethasone 8 mg/day.[3] Adverse effects are related to the short course of steroids, and include high blood pressure, hyperglycemia, and immune suppression.

Cholestyramine

T4 and T3 are concentrated in the liver and secreted in bile as either free form or conjugated to glucuronides or sulfates.[23] Cholestyramine is a bile resin, primarily used as a treatment for hypercholesterolemia. It has been shown to help reduce serum T4 and T3 in patients with hyperthyroidism refractory to thionamides by interfering with the enterohepatic circulation mediated reabsorption of thyroid hormone.[24,25,26] In a randomized control study, Tsai et al. (2005) demonstrated that in patients with Graves' hyperthyroidism, treatment with a combination of PTU, propranolol, and cholestyramine showed a significant decrease in serum T3/T4 at weeks two and four, compared to patients treated with PTU and propranolol alone.[25] Mercado et al. (1996) showed similar findings in a randomized study using methimazole and propranolol instead of PTU and propranolol in combination with cholestyramine.[24]

Dosing is 1-4 grams orally one to four times per day. It is administered one hour before other medications since it may reduce their absorption. The above noted studies indicated cholestyramine given for short four-week durations is well tolerated. However, known adverse effects are bloating, constipation, and flatulence.

Beta Adrenergic Blockers

Beta-adrenergic blockade (BB) is recommended in all patients with thyrotoxicosis for symptomatic control. The mechanism of action of BB is still unknown as they have no discernible effect on the thyroid gland itself, and studies have found conflicting effects on the reduction of peripheral T4 and T3.[27] Propranolol, at high doses of 120-160mg per day, is the only BB agent shown

to decrease peripheral T3, an effect not mediated by beta-adrenergic receptor blockade.[28] The main effects are related to controlling symptoms related to the sympathomimetic state of hyperthyroidism such as tachycardia, palpitations, tremor, and nervousness. In a randomized control study, Tagami et al. (2012) found that in patients with mild Graves' thyrotoxicosis, the combination of MMI and propranolol or atenolol significantly improved heart rate and subjective symptoms and quality of life compared to those treated with MMI alone after four weeks.[29] However, there was no significant effect on fT4 or fT3 between the groups.

Propranolol, the preferred agent, is administered at 10-40 mg three to four times per day. Atenolol dosing is 25-100 mg once to twice daily and is avoided in pregnancy. Metoprolol is dosed at 25-50 mg two to three times per day. Nadolol is dosed at 40-160 mg once daily. For severe thyroid storm requiring ICU management, esmolol at 50-100 ug/kg/minute can be administered.[3] Adverse effects include exacerbation of bronchospasm in patients with obstructive airway disease, and Raynaud's phenomenon.

Therapeutic Plasmapheresis

In cases of refractory severe thyrotoxicosis unresponsive to standard therapy, plasmapheresis is a useful modality for inducing a euthyroid state.[30,31] Plasmapheresis works through extracorporeal separation and removal of plasma from the body using centrifugation, including removal of plasma proteins with bound T3/T4 such as thyroid binding globulin and albumin, auto-antibodies, cytokines, and catecholamines.[30,31] Replacement plasma, albumin and crystalloid are returned to the circulation. This results in a rapid reduction of thyroid hormones that were bound to plasma proteins and anti-thyroid antibodies. In a retrospective study examining 46 patients who required plasmapheresis for severe thyroid storm, Simsir et al. (2018) found that after a median and interquartile range (IQR) of four sessions of plasmapheresis, there was a significant 45% reduction in fT4 and a 60% reduction in fT3, with no significant difference in number of sessions required between Graves' and non-Graves'-related thyrotoxicosis.[32] These findings were similar to other studies.[33,34,35,36,37] Plasmapheresis was also shown to be a safe option in pregnancy.[32,36]

The specific indications for plasmapheresis are: [30,31]

- Poor response to initial medical management with BB and PTU/MMI (agranulocytosis, leukopenia, hepatitis);
- Patients with severe symptoms and rapid deterioration;
- Contraindications to medical therapy - Liver disease or leukopenia precluding use of PTU/methimazole, hyperthyroidism caused by molar pregnancy, Graves' disease-related ophthalmopathy;
- Amiodarone induced thyrotoxicosis due to the long half-life of amiodarone; and
- Bridge to thyroidectomy or radioactive iodine ablation.

On review of prior case studies, it takes on average four to six rounds of plasmapheresis to achieve a euthyroid state, and should be continued until clinical improvement.[33,34,35,36,37] Serum free T3/T4 should be monitored daily. Once a euthyroid state is achieved, patients can either undergo radioactive iodine ablation or surgical thyroidectomy.

Plasmapheresis is generally well tolerated. Reported severe adverse effects of plasmapheresis include anaphylaxis and other allergic reactions, coagulopathy, hypocalcemia, hypotension, plasma-exchange related transfusion reactions, vascular injury, volume-electrolyte shifts, tetany and seizure, citrate-related nausea and vomiting, respiratory distress, and catheter related reactions.[2,34]

Conclusion

Thyroid storm is a severe manifestation of thyrotoxicosis and can lead to multi organ failure with a high mortality rate. There are various treatments and methodologies to achieve a euthyroid state in patients with thyroid storm prior to definitive therapy. Management and choice of therapy is based on clinical judgement and the patient's tolerance for the various treatment modalities. See Figure 1 for an algorithm for the management of thyroid storm.

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Disclosure

None reported.

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Food Addiction in Application to Obesity Management

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Food addiction is tied to complex underlying psychosocial factors and a preference for highly processed foods with addictive properties associated with lower success in weight loss strategies.



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Abstract

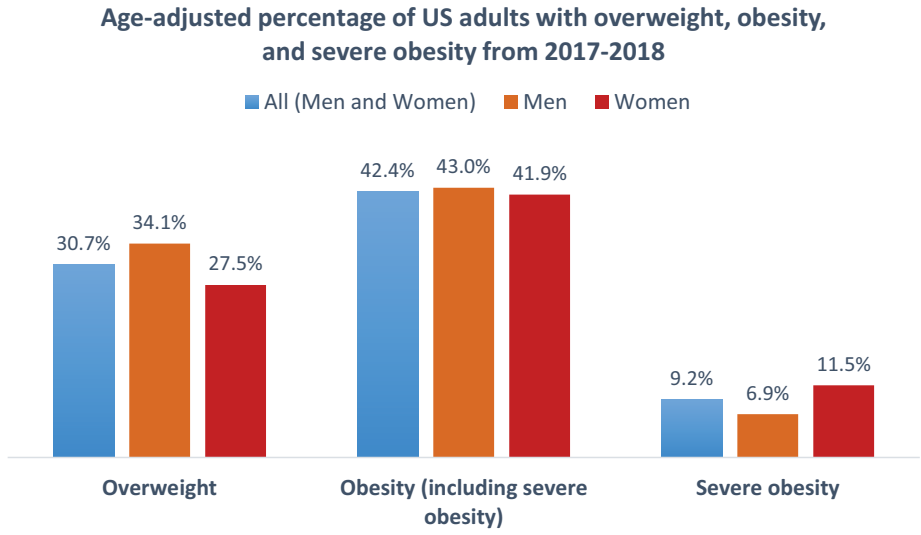
Nascent and rapidly growing research into defining the concept of "food addiction" (FA) in relation to obesity is currently underway. Food addiction is present in a subset of patients who are overweight or have obesity, and its presence is associated with other psychosocial disorders such as depression, anxiety, eating disorders, impulse control disorders, and lower quality of life. Food addiction is associated with higher intake of and preference for highly processed foods that have addictive-like properties such as cravings, reward sensitivity, and impaired control. Food addiction is associated with less weight loss in patients with obesity utilizing diet and lifestyle-related interventions. In clinical practice, identifying the subset of patients with obesity with FA-related psychosocial constraints and continued emphasis on avoiding highly processed foods may improve obesity and weight management outcomes.

- **Food addiction is thought to be an addictive-like phenotype.**
- **Food addiction is noted to have significant overlap with substance use disorder (SUD) and other eating disorders, but is currently not classified a diagnosis by DSM-IV and DSM-V criteria.**
- **Food addiction has similarities to SUD, such as cravings, reduced control over intake, increased impulsivity and altered reward-sensitivity.**
- **The Yale Food Addiction Scale, which is a clinical scale modeled by the DSM-IV and DSM-V criteria for SUD, has been used to quantify and study FA.**

Introduction

In the United States (U.S.), about 39% of the population is considered overweight or obese, and that number is expected to trend higher.[1] Obesity, now considered a chronic disease, is clinically challenging to manage as it involves lifelong lifestyle changes. Development of obesity is multifactorial and involves environmental influences, genetic influences, and complex brain and gastrointestinal signaling that mediate hunger, satiety, and reward pathways.[2-7] Nascent and rapidly-growing research into FA and its role in obesity is currently underway. The purpose of this clinical review is to focus on the clinically applicable outcomes of FA related research in respect to clinical obesity management.

Figure 1



Overweight is defined as BMI 25-29.9. Class I obesity is BMI 30-34.9. Class II obesity is BMI 35-39.9. Class III obesity (severe obesity) is BMI >40.

Data from: Fryar CD, Carroll MD, Afful J. Prevalence of overweight, obesity, and severe obesity among adults aged 20 and over: United States, 1960–1962 through 2017–2018. NCHS Health E-Stats, Centers for Disease Control and Prevention. 2020. Updated February 8, 2021. Accessed January 29, 2021. www.cdc.gov/nchs/data/hestat/obesity-adult-17-18/obesity-adult.htm

Defining Food Addiction

Food addiction has similarities to substance use disorder (SUD) that help us understand and research the concept, although it is not recognized as a SUD, eating disorder, or as a behavioral disorder in the DSM-IV and DSM-V.[2] Similarities between FA and SUD include cravings, reduced control over intake, increased impulsivity and altered reward-sensitivity.[6] To quantify and study FA, researchers developed the Yale Food Addiction Scale (YFAS), which is a clinical scale modeled by the DSM-IV and DSM-V criteria for SUD.[7,8] Similar to DSM-IV and DSM-V criteria for SUD and behavioral disorders, the "diagnosis" of FA is not retained if clinical impairment or distress is not present, even if other symptoms are present.[8]

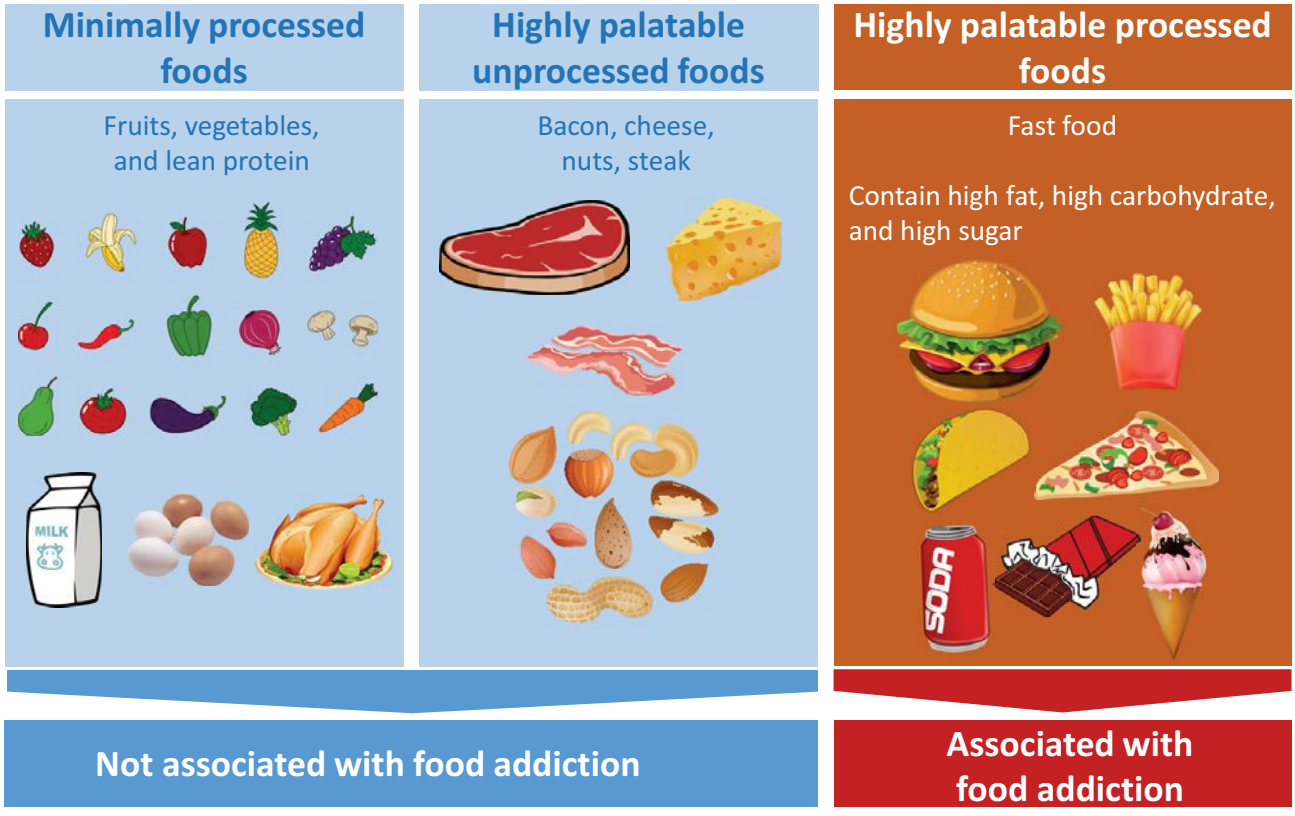
The prevalence of FA has been reported by Penzenstadler et al. and varies between 16.2% and 19.9%.[7] Food addiction was higher in overweight patients, patients seeking weight loss, and in patients with an eating disorder (ED) such as binge eating and bulimia nervosa, depression, and anxiety.[7] In patients seeking bariatric surgery, the prevalence of FA ranged from 14% to 57.8%, and was not to associated with pre-surgical weight or postsurgical weight outcomes.[7]

Metabolic and Psychosocial Characteristics of Patients with Obesity and Food Addiction

Food addiction itself may not lead to obesity or metabolic syndrome related risk factors. Kiyici et al. found that there was no statistically significant difference between patients with and without FA in terms of metabolic syndrome-related measures such as body mass index (BMI), fat percentage, waist circumference, serum insulin, insulin resistance, hemoglobin A1c, lipid parameters, and vascular adiposity index (n=224 patients).[5] Fasting plasma glucose was found to be lower in FA patients.[5] In contrast, in a larger cohort of older (age 55-75) patients with obesity undergoing a randomized six-year intensive lifestyle intervention study (n=448), FA was associated with higher BMI and waist circumference.[9] However, similar to Kiyici et al. FA was not associated with lipid profile, insulin resistance, and total energy expenditure.[5,9] Other studies have also found equivocal associations between FA, BMI, and metabolic syndrome-related measures (Figure 1).[2,4]

Although FA itself may not directly lead to obesity and metabolic syndrome-like risk factors, it may modulate factors that either contribute to obesity or poor outcomes in weight loss management such as depression, impaired impulse control, eating disorders, and preference for highly palatable foods (Figure 2). For example, patients with obesity and FA were more likely to have depression.[5,9,10] Depression was found to be higher in women who are obese, and depression itself was related to a significantly higher daily caloric intake and lower physical activity.[11] In a double blind study, women with obesity (n=61) with known emotional eating who were induced into a sad state had significantly greater preference for a sweeter carbohydrate rich beverage compared to a protein rich beverage.[12]

Figure 2

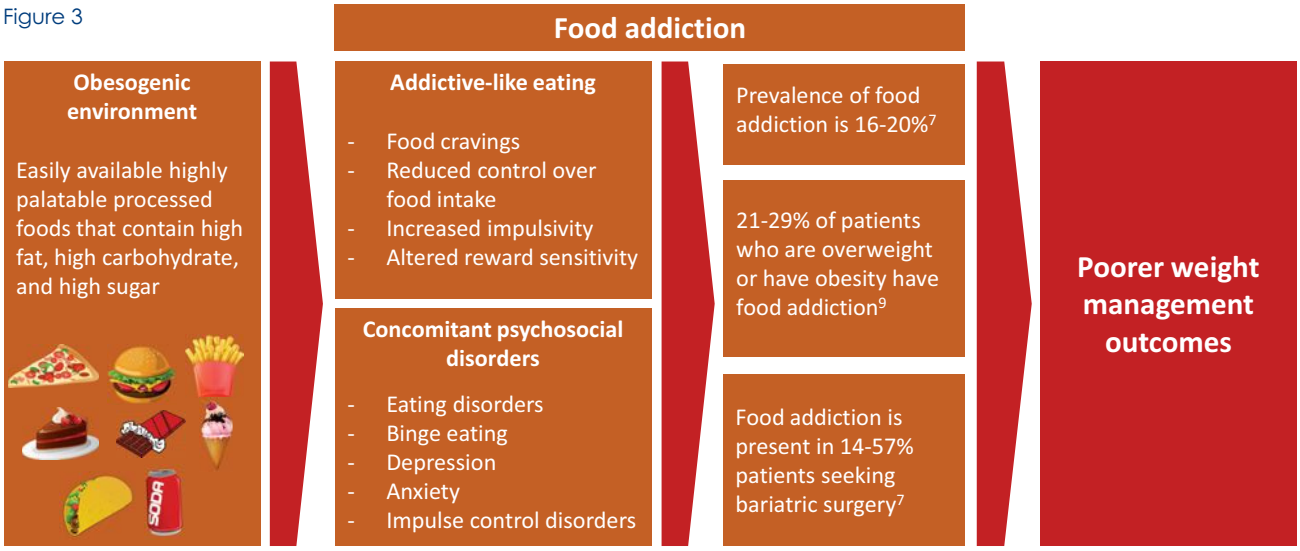


With the associations of FA and eating and impulse control disorders such as binge ED and bulimia nervosa, perhaps there is subset of patients with obesity and FA who may benefit from interventions that target such disorders. Munguia et al. studied outcomes of 16 weeks of cognitive behavioral therapy (CBT) in patients separated by subtypes and severity of EDs and food addiction.[13] Cognitive behavioral therapy included cognitive restructuring, problem-solving, emotion management techniques, and normalization of eating behavior.[13] Patients with EDs had higher FA than those with obesity alone or those with obesity and milder forms of EDs. [13] The patients with both an ED and FA had the poorest outcomes after 16 weeks of CBT compared to patients with obesity and FA.[13] In the subset of patients with obesity and FA, incorporating therapies that target addiction like behaviors may be warranted. The review by Adams et al., describes ongoing early phase studies of behavioral interventions that modulate addiction-like behaviors such as impulsivity, self-control, response inhibition, and attention bias towards highly palatable foods.[6] Perhaps in the subset of patients with obesity and psychosocial risk factors such as depression, emotional eating, and eating disorders, FA may hamper the ability to manage their weight with diet and lifestyle changes. The following section will explore this concept further by highlighting studies that found associations between FA and preference for highly palatable foods.

Highly Processed and Highly Palatable Foods Are Associated with Food Addiction

The association of FA to SUD-like addiction has been explored in animal and human studies, and includes addiction-like behaviors such as cravings, inability to cut down or stop eating, reward sensitivity, impaired impulse control, and reduced response inhibition.[6] These addictive-like behavioral changes are associated with preference for highly palatable foods with addictive properties. An animal study by Lenoir et al. demonstrated that rats preferred the non-nutritive sweetener saccharin (sweet taste without calories) and sucrose (sweet taste with calories) to cocaine, an effect also seen in rats who were already made to be addicted to cocaine.[14] Human studies,

Figure 3



on the other hand, have not shown that sweet taste and highly palatable foods produce tolerance and withdrawal effects that would define a DSM-V SUD.[3] The most common FA-associated symptom was the inability to cut down or stop eating.[7] Joyner et al. found that FA was significantly associated with higher ratings of food craving and higher BMI. Food craving itself was associated with higher BMI and binge episodes.[15] Craving for fats was significantly associated with addictive-like eating and higher BMI.[15] Cravings for sweets significantly mediated the relationship between addictive-like eating and binge eating episodes, but not BMI.[15] Cravings for foods high in non-sugar carbohydrates also significantly mediated the relationships between FA and binge eating episodes, but not BMI.[15]

Food addiction is associated with preference towards highly processed and highly palatable foods (Figure 3). Schulte et al. sought to examine whether highly processed foods were more closely associated with SUD, such as greater loss of control, liking, pleasure, and craving compared to highly palatable but unprocessed foods such as bacon, cheese, nuts, and steak, or minimally processed foods such as fruits, vegetables, and lean protein.[16] Highly processed foods were significantly associated with loss of control, liking, pleasure, and craving, indicating greater abuse liability when compared to unprocessed foods (n=501 participants).[16] In another study, women who were overweight or had obesity (n=44) were asked to rate subjective food craving during a taste test of *ad libitum* foods.[17] Highly processed, relative to minimally processed, foods were more associated with indicators of abuse liability in those with FA (38.6% of the study population). The question remains on whether FA is associated with an increase in intake of highly palatable foods.

Studies in humans have shown that FA is associated with higher intake of highly palatable and highly processed foods.[18] In a prospective cohort study comprising data collected from 127,000 female nurses, FA was positively associated with consumption of highly palatable foods and processed foods with a combination of carbohydrates and fats such as "fast foods" (hamburgers, fries, pizza), candy bars, and low fat or low-calorie snacks and beverages.[19] Interestingly, FA was inversely or not associated with consumption of more non-processed and non-artificial types of foods such as certain sweet foods (cakes), refined grains (pasta, potatoes, white rice), homemade cookies, dark chocolate, full-fat cheese, and sugar-sweetened beverage intake.[19] Similarly, university students with FA (n=120) significantly rated preference for highly processed foods with added amounts of fat and refined carbohydrates/sugar (for example: chocolate, pizza, cake), whereas unprocessed foods were least associated with YFAS scores.[20] Highly processed foods with higher fat and glycemic index had a stronger association towards problematic and addictive like behaviors compared to unprocessed foods.[20] Similarly, in a larger cohort of Turkish university students (n=851), highly palatable foods were significantly correlated with FA, however this study did not compare processed vs. unprocessed foods specifically.[21]

Food addiction is also associated with higher intake of highly processed foods in patients with obesity. In patients who were overweight or had obesity with FA, significant differences were found in patients without FA (n=29) to those with FA (n=29) with the FA group having significantly higher caloric intake per kg of body weight, higher carbohydrate intake, higher fat intake, and significantly higher amounts of dietary sugar, sodium, potassium, calcium, fat, saturated fat, trans fat, and monounsaturated fat.[22]

There are several limitations to the studies showing associations between FA and intake of highly palatable and processed foods. Recall bias is an evident limitation as patients were asked to provide subjective estimates of types and amounts of foods and micronutrients eaten over the past 12 months.[18,22] Self-report and subjective scoring of food preference may have a recruitment bias from participants who have an interest in answering questions about eating behavior. As noted by Schulte et al., it is difficult to conclude that the magnitude of the subjective experience towards highly palatable foods are as addictive as DSM-V SUD substances.[17] Future studies may benefit from examining patients with identified DSM-V SUD and their subjective propensities towards highly palatable foods.

From these studies, it seems that highly palatable and processed foods that contain both carbohydrates and fats are associated with FA compared to unprocessed foods or to sugars alone or carbohydrates alone. Highly processed foods appear to be more reinforcing, have greater abuse liability, addictive properties, and may lead to a greater risk for obesity in those with concurrent FA. The following section will explore FA and outcomes in weight loss management.

Food Addiction and Weight Loss Outcomes

The frequency of FA is high in patients with obesity seeking weight loss through dietary intervention or bariatric surgery.[5,23] In patients seeking diet and lifestyle intervention, FA is associated with poorer weight loss management outcomes. Camacho-Barcia et al. examined the role of FA on patients with obesity (n=448) in a randomized parallel-group intervention study that included an intensive lifestyle intervention with an energy-reduced Mediterranean diet, physical activity promotion, and behavioral support on primary prevention of cardiovascular disease (CVD) events.[9] FA at baseline resulted in a significantly higher weight regain after three years.[9] Gordon et al. examined whether patients with obesity (n=182) enrolled in a 22-month behavioral weight loss program had changes to FA and subsequent weight loss.[24] Reductions in consumption of "problem foods" as identified in the YFAS were significantly associated with reductions in FA symptoms at four months and 10 months, however, were also associated with a sharper rebound of FA symptoms over the 22-month period.[24] The initial reduction in problem food consumption were not associated with long-term reductions in weight.[24] Month-to-month changes in FA were not associated with month-to-month changes in weight, however higher overall FA scores were associated with less weight loss over 22 months.[24] In patients who were overweight or who had obesity enrolled in a 12-month healthy low-fat or healthy low-carbohydrate diet intervention (n=609), FA was significantly associated with increased odds of gaining weight at 12 months and higher attrition rates.[25]

Similarly, in patients with obesity undergoing a pre-bariatric surgery dietary intervention (n=110), FA was associated with significantly less weight loss.[23] These studies support an association between FA and less weight loss in patients with obesity utilizing diet and lifestyle related interventions for weight management.

The current research on bariatric surgery-related weight loss outcomes lacks sufficient data and long term follow up studies to draw conclusions regarding associations with FAA systematic review by Ivezaj et al. found only two out of 19 studies that included FA scores and post-bariatric surgery outcomes.[26] Pre-bariatric FA was 32-57%, with significant reductions in FA to 7.2% at six months, 2% at nine months, and 13.7% at 12 months post-operatively.[26] FA was not associated with weight regain and post-surgical weight loss outcomes.[26] The caveat of these studies were a high attrition rate post-surgically, which may have skewed the results,

and no data of post-bariatric outcomes longer than 12 months.

Currently, there is only one pilot study examining post-bariatric surgery outcomes longer than 12 months, however it was limited by a low number of post-bariatric patients who also met criteria for FA. Cassin et al., examined the outcomes associated with FA within post-bariatric surgery patients (n=100) who received telephone cognitive behavioral therapy (Tele-CBT) sessions (total of six sessions of one hour each) at one-year post-surgery and were followed for an additional 1.25- and 1.5-years post-surgery.[27] At one-year post-bariatric surgery, 13% of patients had scored for FA.[27] Those with FA had significantly higher scores for binge eating disorder, depression, anxiety, however a statistically insignificant 8% less total weight loss.[27] Compared to the control group (no Tele-CBT), patients who completed the Tele-CBT had significantly lower FA symptoms scores at 1.25 years, but not at 1.5 years. Only one patient in the Tele-CBT group met full diagnostic criteria for FA at 1.25 years and 1.5 years, and only two patients in the control group met the full criteria for FA at 1.25 years but not at 1.5yrs.[27] Thus, although this pilot study showed Tele-CBT was associated with improved FA post-bariatric surgery outcomes, it was limited by a small sample size. Due to the limited size, length, and high drop-out rates in bariatric management studies, it is currently difficult to ascertain whether FA plays a role in modifying surgical weight management in patients with obesity.

The presence of food addiction may modify weight loss outcomes in patients with obesity in respect to consumption of problem foods, long-term weight goals, and existing psychosocial/behavioral conditions such as binge eating, depression, and anxiety. A multifaceted approach to improve weight loss outcomes in patients with obesity and FA may be beneficial. A recent systematic review by Leary et al. of nine studies (total of n=812 patients) examined the efficacy of weight loss interventions targeted specifically to FA.[28] Interventions included diet and lifestyle modification, behavioral modification, medications, and surgical modifications. Five out of eight studies that included both pre- and post-intervention FA scores reported a statistically significant reduction in FA post-intervention.[28] Two of the five studies were medication interventions that used either naltrexone and bupropion or pexacerfont and reported a significant reduction in FA symptoms post-intervention.[28] In three studies with lifestyle modification interventions and two surgical interventions, there was a significant reduction in FA symptom scores in the intervention group only.[28] These few initial studies are very encouraging, however remain limited by small sample sizes and lack of long-term follow-up.

Conclusion

Obesity management is a challenging lifelong process. Food addiction is present in a subset of patients who are overweight or have obesity, and its presence is associated with other psychosocial disorders such as binge eating, depression, anxiety, eating disorders associated with poor impulse control, and lower quality of life. Food addiction is not recognized as a DSM-V defined SUD, however, there are similarities between FA and SUD such as cravings, reduced control over intake, increased impulsivity and altered reward-sensitivity. Studies in humans have shown that FA is associated with higher intake of and preference for highly processed and highly palatable foods. Thus far, studies have found equivocal associations between FA, BMI and metabolic syndrome-related measures. FA is associated with less weight loss in patients with obesity utilizing diet and lifestyle related interventions for weight loss. In bariatric weight loss management, there is insufficient data linking FA to weight loss outcomes and further studies with long-term follow-up are required.

As further research into food addiction continues, how can physicians apply this knowledge to guide obesity management? Food addiction is tied to complex underlying psychosocial factors and a preference for highly processed foods with addictive properties associated with lower success in weight loss strategies. Furthermore, higher intake of highly processed foods increases mortality.[29] The increasingly "obesogenic environment" with easily available highly processed foods also contributes to the challenge of weight management.[30] However addressing the availability of highly processed foods and ingredients is a complex problem with no clear short-term solutions. Early identification

of the subset of patients with obesity who have FA in addition to psychosocial factors that modulate FA, such as depression, eating disorders, and impulse control disorders, may be an important step in the initial assessment of obesity management patients. This may allow for targeted or multifaceted therapies for improving weight loss outcomes. Incorporating behavioral interventions such as CBT that modulate addiction-like behaviors such as impulsivity, self-control, response inhibition, and attention bias towards highly palatable foods may help improve long term obesity and weight management outcomes.

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Disclosure

None reported.

MM

Working Out: The Molecular Biology of Exercise

by Joel C. Eissenberg, PhD

"[W]hile exercise is an effective prescription to promote health, there is no minimum dose, no optimal dose, and no dose without risks or negative consequences."
-Daniel E. Lieberman



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Abstract

The many health benefits of exercise are well-known. Conversely, the pathologies associated with a sedentary lifestyle are also well-documented. However, science and medicine have only recently begun to explain how exercise does what it does. Here, I discuss recent insight into the biochemical mechanisms underlying the benefits of exercise and the pathologies of inactivity.

Introduction

The benefits of exercise are many. Exercise expands peripheral blood circulation, increases cardiac output and improves vascular elasticity. Load-bearing exercise stimulates bone deposition and counteracts osteoporosis. Exercise helps prevent clinical depression and appears to slow some forms of dementia.

While the benefits of an active lifestyle have long been known, the mechanisms underlying these benefits have only recently been defined. These mechanisms not only drive healthy adaptations but also antagonize the inflammation and metabolic consequences of atrophy and aging. Exercise increases the expression of key adaptive genes and promotes the secretion of molecules that signal adaptive responses in various tissues and slows age-related decline.

In this essay, I summarize some of the key mechanisms by which exercise promotes health and the biochemical pathways that underlie and serve these mechanisms, both in health and in disease. By harnessing this understanding, we can maximize the benefits of exercise and develop therapies and medications that provide the same benefits.

Evolved to Exercise

Anthropological and archeological evidence points to the conclusion that humans evolved anatomically and metabolically to sustain long periods of endurance exercise.[1] Our nearest living relatives—chimps, bonobos, orangutans, and gorillas—spend very little time and effort obtaining food and most of their time resting.[2] Based on the fossil record, so did our last common ancestor. But as hominins (chimpanzees and humans) speciated, the branches leading to modern humans became increasingly adapted to living on the ground and to a hunter-gatherer lifestyle. As our species evolved from its last common ancestor with the other primates, we evolved longer hind limbs and a more efficient walking gait.[1] Indeed, it is believed that when the first hominins became hunters, before they developed projectile weapons they would run their quarry to exhaustion.[3]

Studies on modern hunter-gatherers in Africa like the Hadza hunter-gatherers of northern Tanzania show that this lifestyle, most like our ancestors, is extremely active.[4] Hadza men walk an average of 12-14 km/day and women 6-8 km/day, which is more than the average American does in an entire week! Even at age 65, men and women walk 11 km/day and 5 km/day, respectively. Curiously, the Hadza don't burn significantly more calories than sedentary Americans when adjusted for nonfat body mass.[5]

Skeletal Muscle and Exercise

There are many ways to exercise. The physiological response to exercise varies depending on the type and duration. At the extremes, we can distinguish two types of exercise:[6]

Low-Load Endurance Exercise

Mechanical stress is low, but depending on the duration, metabolic disturbances can be severe and protracted. The outcome is characterized by an increase in structures supporting oxygen delivery (capillaries) and consumption (mitochondria). Examples include running, cycling, rowing, swimming, and cross-country skiing.

High-Load Strength Exercise

Here, mechanical stress predominates, and growth of muscle fibers occurs primarily through an increase in the amount of contractile proteins. Weight lifting and other forms of resistance training are examples.

Either type of exercise (and exercises that blend both) entails major physiological stressors of skeletal muscle such as mechanical load, hormonal, and metabolic changes and neuronal activation. The response to these stressors provokes molecular changes that adapt the muscle to future stress.

Mitochondria, Mitohormesis, and the Yin/Yang of Exercise

Mitochondria are the cellular organelles that provide much of the energy in our cells. While they are present in most cells, they are particularly important in the energy-intensive tissues of the central nervous system and muscles. Skeletal muscle cells are rich in mitochondria. A ca. 30-fold increase in intramuscular oxygen consumption accompanies strenuous exercise. Aerobic exercise training increases the number and volume of mitochondria, with an increase in muscle mitochondrial density of ca. 50-100% after six weeks of exercise training. This is accompanied by reduced carbohydrate consumption and smaller declines in ATP, the energy currency of the cell, with the same absolute power output in muscle.[7] The net effect of training is to increase endurance by enhancing fatigue resistance owing to a reduction in muscle glycogen depletion, tighter regulation of ATP consumption, and reduction in metabolic by-products that interfere with performance.

The benefits of exercise stress come at a price, though. Increased mitochondrial metabolism results in increased intracellular levels of free radicals that, if unchecked, can damage proteins, DNA, and lipids. How can exercise be beneficial if a direct cellular byproduct is toxic? The answer lies in a phenomenon called "hormesis," the adaptive response of cells to intermittent stress. Specifically in the case of exercise, "mitohormesis" refers to the mitigating response to the oxidative stress resulting from increased muscle mitochondrial activity that may temporarily impair or damage mitochondria. It ultimately stimulates a robust cellular response that confers stress resistance and improves mitochondrial and cellular function.[8] Repeated cycles of acute stress occasioned by aerobic exercise is a clear example of mitohormesis.

What is the source of cellular stress caused by exercise? Aberrant by-products of the natural energy-generating chemistry of the mitochondria include reactive oxygen species—superoxide, hydrogen peroxide, and hydroxyl radicals—that damage DNA, proteins, and lipids. The mechanism of mitohormesis senses the accumulation of these damaging reactive oxygen species and reduces them to harmless water.

A central molecule in the mechanism of mitohormesis is Peroxisome proliferator-activated receptor Gamma Coactivator-1alpha (PGC-1α). PGC-1α regulates key genes in skeletal muscles. Endurance training induces elevated levels of PGC-1α. The significance of PGC-1α expression to muscle physiology is demonstrated by genetic manipulation in rodents: overexpression in skeletal muscle increases mitochondrial density, respiratory capacity, and

Table 1. Myokines and their metabolic effects (modified from ref. 9)

Myokine	Metabolic Effects on Muscle	Metabolic Effect on Other Tissues
IL-6	Induce muscle growth, glucose uptake, glycogen breakdown, lipolysis	Increase lipolysis and free fatty acid oxidation in adipocytes, induce adipocyte browning
IL-15	Stimulate muscle growth and glucose uptake, enhance mitochondrial activity, antioxidant effects	Inhibit lipid accumulation in adipose tissue through adiponectin stimulation
Irisin/ FNDC5	Stimulate glucose uptake and lipid metabolism, involved in muscle growth	Induce adipocyte browning and lipolysis, stimulate glycogenesis and reduce gluconeogenesis/lipogenesis in liver
myostatin	Inhibit muscle hypertrophy	Myostatin inhibition results in adipocyte lipolysis and mitochondrial lipid oxidation, accelerates osteoclast formation
BDNF	Enhance fatty acid oxidation and glucose utilization	Induce adipocyte browning indirectly through FNDC5
BAIBA	Increase mitochondrial free fatty acid oxidation, ameliorate insulin signaling, anti-inflammatory	Increase mitochondrial free fatty acid oxidation and browning in adipocytes, reduce hepatic de novo lipogenesis and hepatic endoplasmic reticulum stress
LIF	Induce muscle hypertrophy and glucose uptake	Stimulate osteoblast differentiation, inhibit adipocyte differentiation
SPARC	Regulate muscle tissue remodeling, enhance glucose metabolism	Inhibit adipogenesis

improved exercise performance, while inactivation causes impaired mitochondrial function, and reduced capacity for, and slower recovery from, exercise.[7]

Another key player in mitohormesis is Nuclear factor erythroid 2-related factor 2 (Nrf2). This protein activates various genes that encode antioxidant enzymes. The oxidative stress generated by increased mitochondrial activity during exercise liberates Nrf2 from an inactivating complex in the cell cytoplasm, allowing it to enter the nucleus where it can dial up levels of antioxidant enzymes such as superoxide dismutase, glutathione synthetase, and heme oxygenase. Thus, Nrf2 activation counterbalances the elevated reactive oxygen species, resulting in net improved overall cellular function during exercise.[8]

Exercise and Angiogenesis

Another concomitant of exercise is increased angiogenesis. Mitochondrial content and capillary content are highly correlated in skeletal muscle. Increased blood flow induces shear stress that elicits the angiogenic response. Key to the mechanism by which increased skeletal muscle use drives angiogenesis is Vascular Endothelial Growth Factor (VEGF). Muscle contraction triggers the release of VEGF stored in vesicles into the extracellular space, where it acts through specific cell surface receptors to trigger capillary growth. Exercise induces VEGF expression in skeletal muscle via PGC-1α.[6]

The partial pressure of inspired oxygen (PiO2) in resting skeletal muscle is ca. 1/5th of the oxygen pressure of inhaled air. Acute exercise reduces PiO2 in contracting muscle to ca. 1/40th of that of inhaled air, creating a situation of transient hypoxia. Hypoxia-inducible factor-1 (HIF-1) is the master transcriptional regulator of cellular oxygen balance. HIF-1 is a transcription factor composed of two subunits, HIF-1alpha and HIF-1beta. Under normoxic conditions, HIF-1 alpha subunit is targeted for degradation. During hypoxia or reduced O2 tension, HIF-1alpha is stabilized and translocates to the nucleus to form an active complex with HIF-1beta. HIF-1 activation induces transcription of target genes involved in erythropoiesis, angiogenesis, glycolysis and energy metabolism in a manner analogous to exercise.[6]

Myokines and Exercise

Skeletal muscle is an endocrine organ. It produces signaling molecules in response to contraction that influence its own metabolism and the metabolisms

of other tissues and organs. Acting through cell surface receptors, these signaling molecules, called "myokines," have anti-inflammatory effects (Table 1). The founding member of the myokine family is Interleukin-6 (IL-6). In addition to opposing inflammation by inhibiting Tumor Necrosis Factor α (TNF- α), IL-6 stimulates glucose uptake.[9] Muscle-derived IL-6 levels in circulation are elevated by up to 100-fold during exercise, and are correlated with exercise intensity and duration.[10,11]

IL-6 is induced by muscle contraction that stimulates both glucose and lipid metabolism. IL-6 levels are increased by both concentric (e.g. biking or leg-kicking) and eccentric (e.g. strength training or running) contractions. Induction of IL-6 in skeletal muscle occurs via a calcium-dependent pathway. IL-6 promotes hypertrophy by stimulating proliferation of muscle stem cells (satellite cells) and by augmenting the rate of protein synthesis in muscle sarcomeres.[12]

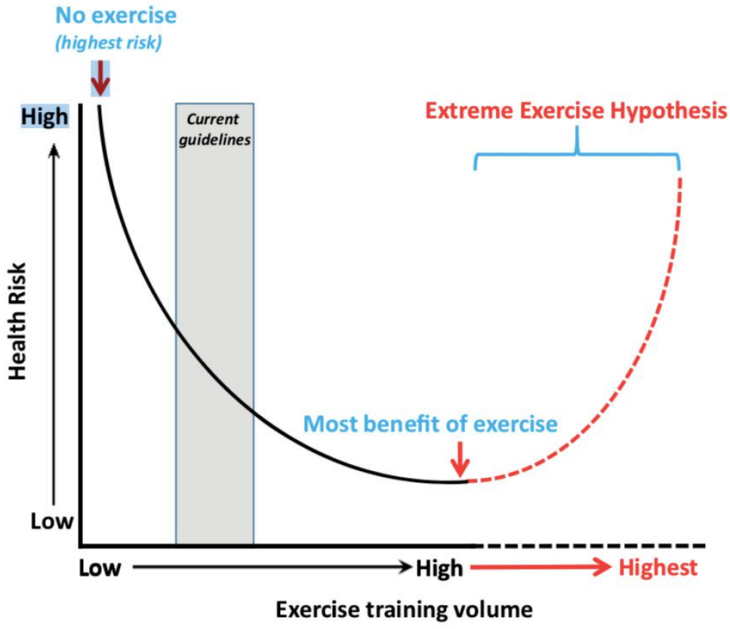


Figure 1. The Extreme Exercise Hypothesis posits that the benefits of exercise may be partially reversed when exercise training volume exceeds an optimal level.[14]

IL-6 has long been recognized as a cytokine secreted by immune cells and adipocytes to promote inflammation. Tociluzimab, a therapeutic antibody against the receptor for IL-6, is used clinically to treat cytokine release syndrome in, e.g., patients with severe COVID-19. The paradoxical benefits of IL-6 during exercise contrasts with the systemic pro-inflammatory effects of IL-6 during infections, and points to cell-specific roles for this cytokine.[13] More research is required to define the mechanisms underlying these antipodal effects.

An adaptive response to chronic exercise is an increase in muscle mass through the increase in muscle protein biosynthesis. Mammalian target of rapamycin complex 1 (mTORC1) is the key regulator of protein synthesis in skeletal muscle. mTORC1 can be activated or depressed depending on upstream signaling events whereby muscle mass is regulated mostly through modification of protein synthesis rather than through changes in protein degradation. mTORC1 is activated through membrane-bound receptors activated by insulin and growth factors.[6]

Muscle Satellite Cells and Exercise

Satellite cells are a heterogeneous population of cells. The majority of cells are committed myogenic cells, which, upon stimulation, undergo symmetric division, and differentiation. A smaller number of satellite cells (satellite stem cells) undergo asymmetric division, repopulate the satellite cell niche and maintain long-term muscle regenerative potential. Strength training increases skeletal muscle fiber cross-sectional area and satellite cell number. Androgens are steroids, and thus activate transcription of specific genes through an intracellular receptor that binds the enhancers of target genes. Androgens promote satellite cell activation and proliferation and further support skeletal muscle hypertrophy by elevating IGF- 1 levels. Myostatin is a myokine, a protein produced and released by myocytes that is a negative regulator of muscle cell growth and differentiation. It is a potent player in muscle mass homoeostasis,

Table 2. Benefits of Physical Activity and Exercise[23]

Improvements in Exercise Capacity
- Maximal Oxygen Consumption (Peak VO2)
- Estimated METs

Improvements in Lipids
- Total cholesterol
- HDL-C
- LDL-C
- Triglycerides
- Total cholesterol/HDL-C
- LDL-C/HDL-C

Reduction in Obesity Indices
- Weight
- Percentage Body fat
- Body Mass index

Improvements in Blood Rheology
- Reduction in Homocysteine Levels
- Improvement in Viscosity

Improvement in Psychosocial Factors
- Depression Score
- Anxiety Score
- Hostility Score

Major Morbidity and Mortality
- Reduction in Overall Mortality
- Reduction in Hospital Costs
- Reduction in Non-Fatal Myocardial Infarction

inhibiting protein synthesis, and activating catabolic pathways. It acts through a cell-surface receptor to turn on gene transcription. Androgens also suppress myostatin to promote muscle growth.[6]

The Price of Inactivity

Muscle tissue responds to demand by growing. Conversely, it responds to disuse—due to injury, sedentary lifestyle, and age—by atrophy. The absence of physical activity not only means foregoing the benefits of regular exercise, it has negative consequences. Within a couple of weeks, muscle wasting and increased plasma triglycerides and insulin insensitivity are observed. Muscle wasting is accompanied by degradation of myofibrils by the ubiquitin-proteosome pathway (reducing contractile force) and mitochondrial degradation (reducing endurance).[6] In the elderly, this exacerbates the natural progression of age-related sarcopenia.

Skeletal muscle wastage is an important consequence of continuously elevated glucocorticoid levels. Glucocorticoids suppress mTORC1, thereby inhibiting muscle protein synthesis. They also increase myostatin levels by increasing both myostatin expression and action, inhibiting muscle growth. Skeletal muscle wasting is also associated with elevated levels of pro-inflammatory cytokines such as Tumor Necrosis Factor α, IL-1, and IL-6.[6]

Extreme Sports: Too Much of a Good Thing?

If some exercise is good, more is better, right? When it comes to extreme endurance sports, the data suggest a shift in the risk-benefit ratio towards increased risk. The "extreme exercise hypothesis" holds that there is a U-shaped curve for the health risk of exercise training, where risks reach a low point at some intensity of training, but then increase when that optimum is exceeded (Figure. 1). Where, exactly, this exercise optimum occurs is unclear, although some data suggest that it may be at three to five times the current recommendations.[14] A study of 284 male amateur athletes found that the most active athletes had significantly higher levels of coronary artery calcification than the least active.[15] Importantly, the most active athletes had mostly calcified plaques, which show a high association with future cardiovascular events, while the least active athletes had a higher prevalence of mixed plaques.[16] Similar results were found in comparing 152 male veteran amateur athletes and 92 age- and risk factor-matched sedentary controls.[17] Other pathologies that have been associated with extreme sports include cardiac fibrosis and arrythmias.[18]

How does this translate into longevity? Does extreme exercise increase the chance of premature death compared to the general population? A meta-analysis of ten studies involving 42,807 elite athletes found 67% of the expected number of deaths based on the comparison population.[19] Importantly, deaths from cardiovascular disease alone were 73% of expected. A separate study looking at 57 studies including 465,575 elite athletes confirmed that the overwhelming majority of these athletes enjoyed superior life-span compared to their age- and sex-matched peers in the general population.[20] It must be acknowledged, however, that the elite athlete cohort likely consists of people who are already

among the healthiest and fittest in the population, so the quantitative contribution of extreme exercise specifically to superior longevity outcome is unclear.[20] It seems likely, then, that other factors benefit those who engage in intensive exercise that can offset the risks attached to arterial plaque formation alone.

Is Exercise Medicine?

The long and familiar list of benefits associated with regular moderate exercise, and the many pathologies associated with inactivity, testifies that exercise is potent medicine (Table 2). In aging adults, resistance exercise can increase healthspan by slowing age-associated sarcopenia, as well as improving balance to prevent falls. As with any medicine, the dose makes the poison, and evidence suggests that sustained extreme exercise may be toxic.

Unlike our hunter-gatherer ancestors, we are no longer obliged to walk and run long distances to obtain food. But there is a wide range of age- and lifestyle-appropriate exercise to be had in modern society that can trigger all the genes and signaling pathways to improve and sustain skeletal muscle, cardiovascular and CNS health. The challenge is to find rewarding and sustainable exercise matched to the abilities of each person, and to create work, school and home environments that encourage movement and physical activity.[21]

Conclusion

The benefits of regular moderate exercise are well-documented. Now, the molecular mechanisms underlying these benefits are being identified. With this new understanding comes the hope that these mechanisms can be harnessed to maximize benefits to healthy individuals and to develop pharmacological substitutes that provide similar benefits to those who, because of illness, disability or age, cannot engage in exercise.

Whether or not exercise is judged to be medicine, its benefits can be analogized to a drug. As Schwartz et al.[22] noted in these pages:

"Exercise might be best understood as a drug with powerful benefits, especially for cardiovascular health. As with any potent drug, establishing the safe and effective dose range is critically important—an inadequately low dose may not confer full benefits, whereas an excessive dose may produce adverse effects that outweigh its benefits."

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Disclosure

None reported. **MM**

COVID-19 Pandemic and Its Impact on Sleep Health: A Rapid Review

by Tracy L. Bezner, MD & Manjamalai Sivaraman, MD

Health Care

Based on the findings of our review the evidence already amassed for COVID producing negative impacts on sleep health due to the disease itself and its associated stressors brought on by the pandemic in general is significant.



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Abstract

This rapid review aims to elucidate the impact of coronavirus 2 (SARS-CoV-2) (COVID) disease—both in the acute phase and the "long-hauler" syndrome—on sleep health. Literature regarding the direct physiologic impact of COVID disease on sleep is sparse but has illuminated a toxic synergy between the immune response to COVID disease and the pro-inflammatory state brought on by obstructive sleep apnea (OSA). Primary care physicians and sleep medicine specialists should aggressively screen for OSA in COVID patients.

Introduction

COVID is the acute respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which emerged dramatically two years ago in Wuhan, China, sparking a worldwide pandemic and causing morbidity, death, and societal upheaval virtually unmatched by any other disease of the last 100 years. As of December 29, 2021, the WHO reported 281,808,270 confirmed global cases of COVID, including 5,411,759 deaths. The United States' share of this grisly toll was 52,543,602 confirmed cases and 812,577 deaths by the same date.[1] COVID was the third leading cause of death in the U.S. in 2020 behind only heart disease and cancer and the total number of deaths in the U.S. increased in 2019 by 17.7%— mainly attributable to the impact of COVID.[2] Those with pre-existing medical conditions, especially pulmonary, are most vulnerable to COVID, and strong links between mental and neurologic disorders and COVID morbidity have been established.[3] The societal response to the pandemic including lockdowns, remote work arrangements, school closures, and hospital overload—to name only a few—has caused widespread unrest, stress, and heated controversy. In this environment, sleep problems such as insomnia have risen in incidence and given rise to new terminology such as "coronasomnia."[4] The purpose of this rapid review is to explore the impact of the pandemic on sleep health with the aim of informing future sleep health strategies and minimizing negative impacts of the pandemic.

Methods

This rapid review is based on a literature search of articles published in English between December 2019 and October 2021. Pubmed and Google Scholar

were the primary engines used in the search. Keywords including "COVID," "SARS-CoV-2," "sleep," "sleep problem," and "insomnia," and their derivatives were used. The search included retrospective studies, cross-sectional studies, observational studies, letters to editors, editorials, and surveys. The articles were screened by two independent reviewers for relevance and eligibility for inclusion.

Results

A total of 78 articles were reviewed with 65 ultimately included. These can be roughly divided into three groups: those focused on the burden to the healthcare system and healthcare workers (HCWs) in general, those dealing with the stressors on the general population, and those dealing with the pathological effects of COVID disease itself.

Discussion

General Pathophysiology and Effects of COVID

It was clear early on that COVID is a cause of potentially fatal pulmonary disease due to the disturbingly high number of patients developing acute respiratory distress syndrome (ARDS) requiring mechanical ventilation and ultimately proceeding to multi-organ failure and death. It is now known that survivors continue to demonstrate impaired gas exchange for months after the infection.[5] It has also become clear that a more sinister phenotype of COVID associated with excessive systemic inflammation has emerged; in children it is now termed Multisystem Inflammatory Syndrome (MIS-C). In adults no name has been coined, but the clinical state is known to have features similar to hemophagocytic lymphohistiocytosis (HLH) and the antiphospholipid syndrome (APS), with virtually every organ system implicated in receiving some type of damage.[6,7] SARS-CoV-2 gains entry to the body via Angiotensin Converting Enzyme 2 (ACE2), an important counterregulatory enzyme which attenuates the volume-bolstering effects of the renin-angiotensin-aldosterone system (RAAS). Use of ACE2 effectively downregulates its attenuating effect on the RAAS, resulting in the hypertension and end-organ injury sometimes seen in COVID patients. Further, a long-term syndrome known as "long COVID," or the "post-acute COVID syndrome," or the "post-COVID condition" has increasingly gained attention in a subset of patients now termed "long-haulers." Studies conducted worldwide have revealed this entity can afflict those with a mild disease course as well as those who required hospitalization. "Long-haulers'" symptoms vary greatly with reports of atypical chest pain, neurocognitive difficulties, fatigue, anxiety, and depression leading the way. These appear to linger for months after infection.[8,9] It remains unclear if the SARS-CoV-2 infection causes these symptoms via primary organ involvement, aberrant immunological response, or exacerbation of already-known symptoms. What has become increasingly clear, however, is that "long-haulers" tend to be females of working age with lower serum IgG titers for SARS-CoV-2 and anosmia at disease onset. Initial reports suggest "long-haulers" suffer with substantial detrimental impacts on work and daily life, including sleep health.[9-11]

Psychologic Impact of COVID on HCWs and Society

Studies conducted across Asia, Europe, the Pacific rim, and the Americas through early and mid-2020 revealed high levels of psychological stress across all strata of society, but primarily concentrated in the health care community. This is understandable as HCWs are literally on the frontline of the pandemic, deeply involved in the diagnosis, treatment, and care of COVID patients. In COVID 'hotspots,' e.g. Wuhan, New York, and Italy, the huge workload, lack of personal protection equipment (PPE), and lack of ventilators and medicines were understandably contributory. Studies also showed that HCWs' fear of being infected and passing on the disease to family and friends gave rise to considerable reluctance to work, thoughts of resignation, and high levels of anxiety and depression. The long-term psychological consequences for health care workers are an open question at present and will require substantial study moving forward.[12] In the population at large, the effects of lockdown including unemployment, social distancing, and isolation have been noted to yield detrimental effects on physical activity, mental well-being, and sleep. The psychological impact of quarantine has been found to be wide-ranging, substantial, and long-lasting.[13]

"Coronasomnia" or "COVID-somnia" Resulting from COVID

Considerable research has already been conducted which shows that the COVID pandemic has resulted

in significant impact on sleep health, especially in terms of sleep deprivation. In the current pandemic, the phrase "coronasomnia" or "COVID-somnia" has been coined to describe this phenomenon.[4,14] It is well known that restorative sleep is essential for proper mental and physical health while lack of sleep is highly associated with impaired psychologic functioning and decision-making. Direct evidence for the spike in insomnia incidence has been gathered over the last year by researchers worldwide, mainly via surveys conducted at large and in smaller communities, e.g. college and university campuses. Unsurprisingly concurrent stress, depression, and uncertainty regarding the COVID—both the effects of the pandemic and fear of direct infection—were frequently cited by respondents as causes of their insomnia.[15]

Impact of "Coronasomnia" on Immunity

A lesser-appreciated but particularly salient point in the context of the current pandemic is the fact that sleep also plays a vital role in the maintenance of immunity, especially since disruptions in sleep quality are known to be associated with decreased immune response to vaccines and increased vulnerability to infectious disease.[20] Indeed, studies have revealed both higher rates of opportunistic and community-spread infection as well as increased carcinogenesis in those with disrupted circadian rhythm and sleep deprivation.[21] Mechanistically speaking, disruption of critical messaging by the suprachiasmatic nucleus is known to negatively impact circadian rhythms, thereby leading to worsened immune function. This is true of the population at large but is an especially sobering fact considering that HCWs and other essential workers may be at higher risk of disease because their sleep may be compromised.[22,23]

In the current environment, therefore, ensuring adequate sleep and proper treatment of sleep-limiting conditions such as obstructive sleep apnea (OSA), stress, and anxiety takes on additional significance. This is particularly challenging in the current environment since the uncertainties brought on by the COVID pandemic—particularly the fear of severe disease or death—have entered into toxic combination with the politicization of public health measures—heated and sometimes violent debate over mask use in public facilities and schools—school closures, and curtailment of sports and recreational activities. It is perhaps an understatement to say this has led to widespread and high levels of anxiety, stress, and anger. Poor sleep health in this environment seems an inevitability, yielding a greater responsibility for physicians- particularly primary care providers (PCPs) and sleep specialists—to emphasize the need for restorative sleep to their patients while ensuring their sleep-related issues are properly evaluated and treated.[24]

Direct Impact of COVID on Sleep Health and the Unfortunate Synergy with OSA

Evidence is very limited concerning the direct physical and psychosocial toll on sleep health imposed by contracting COVID. A small study in Australia reported actigraphy-assessed sleep parameters of four subacute COVID patients as they began the rehabilitative stage of recovery, finding impaired sleep quality in three patients (defined by Pittsburg Sleep Quality Index > 5).[25] Obstructive sleep apnea is thought to cause hypertension by RAAS dysregulation as well, an example of potentially destructive synergy we will touch on in more depth further in this article.[26] And finally, what about the impact of COVID on OSA, already well-known to disrupt restorative sleep? Recall that OSA is known to induce a pro-inflammatory state and is directly linked to higher rates of hypertension, diabetes mellitus, cardiovascular, and cerebrovascular diseases.[27] Since COVID infection is known to induce a highly inflammatory state it can be hypothesized that an infected patient with pre-existing OSA has a higher risk of worsening the inflammatory response.[28] Further, since COVID is now a known risk factor for pulmonary fibrosis—itself a risk factor for future development of OSA—the emerging relationship between these two entities is becoming known as both bi-directional and (unfortunately) synergistic.[29] PCPs evaluating and managing patients recovering from COVID should aggressively monitor and screen for subsequent OSA development with a low threshold for polysomnography and referral to sleep medicine specialists. PCPs and hospitalists can consider melatonin as a relatively benign but efficacious adjuvant treatment of COVID based on recent studies citing its anti-inflammatory and anti-oxidative properties as well as its anti-anxiety and mild sedative effects which can improving sleep quality in critical care patients.[30] Regarding outcomes in those with OSA who develop COVID, it is difficult to disentangle the two entities—risk factors for OSA

are known as predictors of poor COVID outcomes. It has not been possible (yet) to establish OSA as an independent risk factor for poor outcomes in COVID. A recent study of factors such as age, OSA under treatment, and microvascular or macrovascular complications concluded these are independently associated with risk of death at day seven of COVID disease, but more studies will be necessary to fully investigate the impact of OSA on COVID outcomes more thoroughly.[31,32] In the meantime the American Academy for Sleep Medicine (AASM) recommends OSA patients who develop COVID continue using Positive Airway Pressure (PAP) therapies at home with the caveat that individuals should isolate in a separate bedroom due to aerosolization concerns.[33] And finally, the aforementioned International COVID Sleep Study (ICOSS)—a multinational survey-based effort with the aim of gathering more systematic information on the effects of the COVID pandemic on sleep-wake rhythms—will hopefully provide more answers. Among its aims are to examine the relationship of sleep problems with demographic, environmental, and health-related factors, and further delineate how OSA, insomnia, nightmares, fatigue, exhaustion, and REM Sleep Behavior Disorder may be caused directly by COVID or to what degree it is associated with irksome confinement, anxiety, and other psychosocial factors brought on by the pandemic.[34,35]

Conclusion

Based on the findings of our review the evidence already amassed for COVID producing negative impacts on sleep health due to the disease itself and its associated stressors brought on by the pandemic in general is significant. At the time of this writing in December 2021, the pandemic is nearing its second birthday. Many specific COVID and sleep-related questions (e.g. impact of already-diagnosed OSA on COVID outcomes) remain only partially answered at present and will require more studies. Moving forward, it is incumbent upon clinicians to ensure patients with sleep health-related problems in the context of COVID receive up-to-date education, optimal treatment, and support. Since poor sleep is a stand-alone risk factor for suicidal ideation, suicide attempts, and suicide death, the health community must take steps to ensure patients are screened and treated for these problems appropriately.[36] Prioritizing good sleep and diet for patients, especially healthcare workers and children is more vital than ever in the current climate. Physicians should caution parents to limit screen time for themselves and their children during times of social distancing and work or school from home scenarios as this plays a crucial role in sleep hygiene and quality. Clinicians should be aggressive advocates for healthy sleep hygiene practices while providing high-quality education/information about various sleep-related resources (handouts, online platforms, etc.) as an avenue to promote physical, emotional, and mental health. Nonpharmacological approaches like Cognitive Behavioral Therapy for Insomnia (CBT-I) and progressive muscle relaxation (PMR) have been shown to improve sleep in the context of COVID disease/pandemic and should be considered in the appropriate clinical context.[37,38] Regarding governmental support, long COVID is now recognized as a physical and/or mental impairment by the US Department of Health and Human Services (HHS), enabling long COVID patients to qualify for disability under federal civil rights laws and receive accommodations and services.[39] Hospital administrators should prioritize the sleep health of their healthcare workers because it directly influences fatigue, burnout rates, and immune status. Ensuring adequate time off for sleep by promoting flexibility in work hours as well as promoting feelings of self-value and purpose have been shown to mitigate pandemic-related burnout.[12,40]

Our present understanding and knowledge about the acute and long-term effects of COVID will evolve as extensive ongoing research is currently underway, which is the primary limiting factor of this article. Further prospective studies will be essential to elucidate the long-term effects of COVID disease on sleep health. For example, tracing the effect of COVID disease on new incidence or worsening of OSA and progression to chronic insomnia by those experiencing the "coronasomnia" phenomenon. Other avenues of research include prospective studies to uncover the relationship of COVID with other sleep-related problems such as hypoventilation and parasomnias such as nightmare disorder or post-traumatic stress disorder (PTSD).

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Disclosure

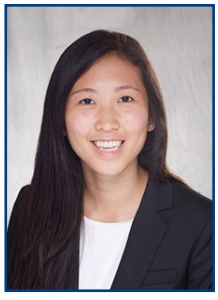
None reported. **MM**

Outpatient Primary Care Genetic Testing Primer: What to Order and Testing Considerations

by Angela Lee, MD, Julie Neidich, MD & Hoanh Nguyen, MD

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With advances in medicine, genetics has become a substantial part of patient care and PCP familiarity with genetic testing options and indications allow providers to deliver appropriate, up-to-date healthcare.



Angela Lee, MD, (above), Julie Neidich, MD, FACMG, FAAP,and Hoanh Nguyen, MD, are in the Department of Pediatrics, Division of Genetics and Genomic Medicine, and Dr. Neidich is also in the Department of Pathology and Immunology. All are at Washington University School of Medicine, St. Louis, Missouri.

Abstract

The field of genetics has evolved rapidly over the last few decades, from testing methods to genetic diagnoses, bringing new genetic testing guidelines and considerations for health care providers. Overall geneticists are limited in number and availability, particularly in non-academic settings, and many patients first present to a primary care provider. Here, we aim to review various modalities of genetic testing, their indications, limitations, and other pretest considerations for the primary care provider. In addition, we comment on the limitations of direct-to-consumer (DTC) genetic testing, which has seen a rise in popularity among the general population.

Introduction

Human DNA is packaged in 46 chromosomes, each with many bands and subregions. Within those areas are hundreds of genes that each have a specific nucleotide sequence. Available genetic testing targets various levels of genetic changes, from chromosome duplications or deletions to single nucleotide changes, with testing techniques and methods changing significantly over the last few decades. Concurrently, identified genetic conditions, now more than 5,000 rare disorders,[1] have expanded rapidly and identification of novel pathogenic changes continues at a fast pace. This has led to increased medical indications for genetic testing and further considerations towards the approach of broad genetic testing. This is true for both medical genetic testing and DTC genetic testing, including 23andMe, among others.

Types of Genetic Testing

Karyotype

Karyotyping was initially introduced in the 1950s, involving the pairing of the 22 autosomal chromosomes and the pair of sex chromosomes, allowing for diagnosis of chromosome number changes, such as monosomy X or trisomy 21.[2] In the decades that followed, various chromosome banding techniques were introduced, including the widely used Giemsa, or G-banding technique (Figure 1). This allowed for diagnosis of smaller chromosomal changes in the range of 5-10 million base pairs, or mega-bases, such as Cri-du-Chat Syndrome (5p- or a deletion of the

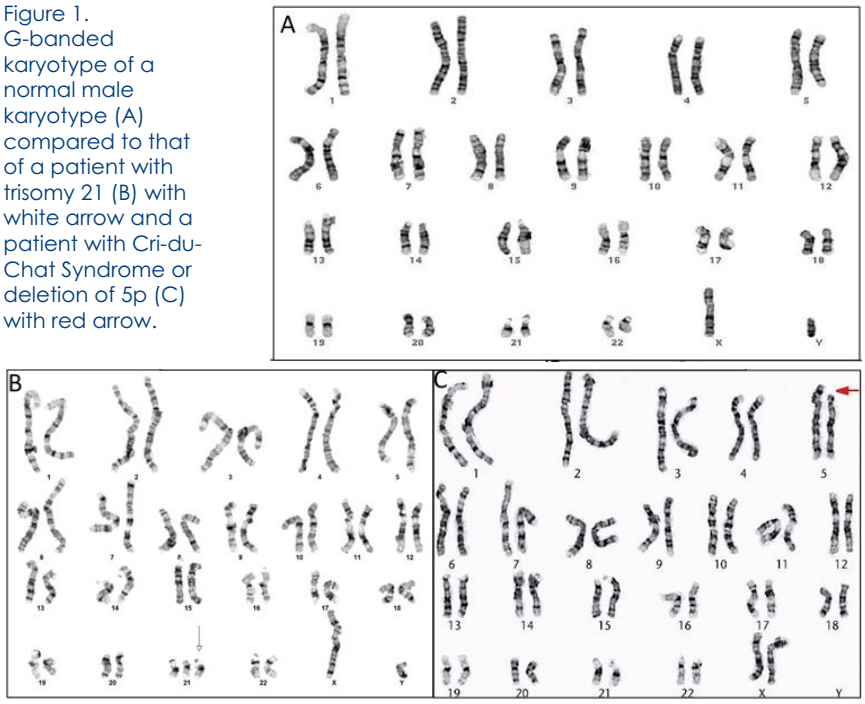


Figure 1. G-banded karyotype of a normal male karyotype (A) compared to that of a patient with trisomy 21 (B) with white arrow and a patient with Cri-du-Chat Syndrome or deletion of 5p (C) with red arrow.

short arm of the 5th chromosome), as well as other larger chromosomal rearrangements like translocations or inversions.

Fluorescence in situ Hybridization (FISH)

Developed in the 1980s, FISH used fluorescently labeled DNA probes to bind to specific nucleotide sequences of interest (Figure 2). This led to the ability to diagnose chromosome microdeletion and microduplication syndromes like 22q11.2 deletion syndrome (formerly known as DiGeorge syndrome). This technique is also utilized widely in cancer genetics, helping identify common chromosome changes in various cancer lines, often with prognostic or clinical management implications. Due to the fast turnaround time compared to other genetic studies, FISH testing remains useful for screening of common trisomies (trisomy 13, 18, 21), sex chromosome differences (XO Turner syndrome and XXY Klinefelter syndrome), and specific microdeletion or duplication syndromes. FISH testing is limited by the targeted nature of the test, as providers must select which probes or related condition the patient should be tested for.

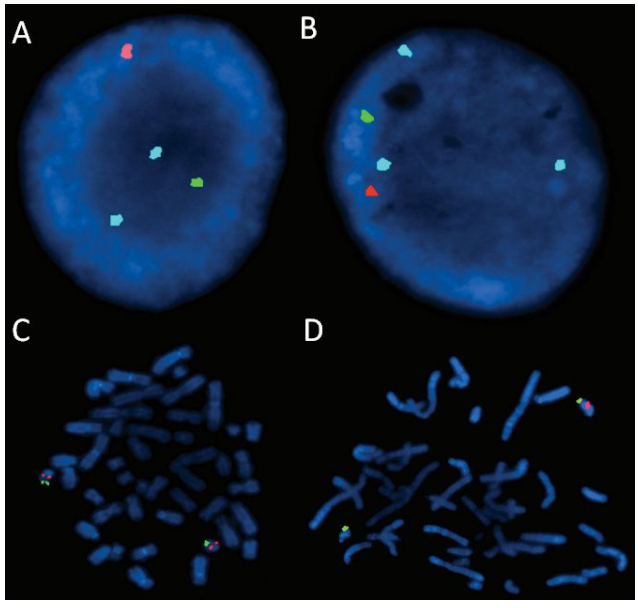


Figure 2. (A and B) FISH aneuscreen for X/Y/18. X chromosome in green, Y chromosome in red, chromosome 18 in aqua. A- Normal male individual with one X chromosome, one Y chromosome, and two copies of chromosome 18, notated as nuc ish(DXZ1x1,DYZ3x1,D18Z1x2). (B)Male with Trisomy 18 with one X chromosome, one Y chromosome, and three copies of chromosome 18, notated as nuc ish(DXZ1x1,DYZ3x1,D18Z1x3. (C and D) FISH for 22q11.2 microdeletion also known as DiGeorge syndrome. Red marker for the 22q11.2 area. Green marker for the 22q13.3 area that is used as a control. (C) Normal individual without a 22q11.2 deletion with 2 red and 2 green markers. (D) Individual with 22q11.2 deletion with 1 red marker and 2 green markers.

Chromosomal Microarray (CMA)

Later development in the 1990s and 2000s led to array- based comparative genomic hybridization and single nucleotide polymorphism (SNPs) arrays, involving thousands of probes on a slide that could be hybridized to patient DNA. The different ratios between patient DNA and each probe DNA could be visualized to detect copy number variants (CNVs) in the whole genome at a resolution of 25-250 thousand base pairs or kilo-bases.[1] This improved diagnostic yield of testing, with smaller detection resolution than banded karyotype and wider coverage than targeted FISH.[3] However, this type of testing is unable to identity balanced chromosomal rearrangements, for which karyotype is required. CMA is also known as molecular karyotyping or whole genome microarray.

DNA Sequencing

In 2003, the Human Genome Project completed the first rough DNA sequence of the human genome, identifying over 20,000 protein-coding genes and 2.1 million SNPs.[4] This then led to further development of sequencing technology, massively parallel sequencing, and improvement in efficiency and cost of DNA sequencing. Research on single gene disorders and identification of new disease genes grew exponentially. There are now many types of gene panels available, as well as whole exome and whole genome sequencing (WES/WGS).

Single and multigene panels are available through a variety of laboratories for targeted, disease-focused sequencing. Gene panels are often grouped by similar clinical phenotype. Broader testing includes WES, which analyzes all exons or known protein encoding regions. Comparatively, WGS analyzes total genetic material encompassing protein encoding and non-protein encoding regions. This broadens the diagnostic potential to include CNVs, upstream and downstream regulatory elements and other intronic regions, or non-protein encoding regions. However, many of these non-protein encoding regions are not well characterized and their pathogenicity remain unknown. WGS is starting to become more widely available, though was previously largely in the research realm. DNA sequencing is limited in identifying triplet repeat expansion disorders, disorders of methylation, or uniparental disomy, which includes conditions like Fragile X syndrome, Beckwith-Wiedemann syndrome, and Prader Willi syndrome, respectively. Separate molecular tests can identify these types of syndromes.

Table 1. Summary of genetic testing recommendations and indications. Metabolic screening is not universally recommended but is recommended by some. *WES/WGS is recommended as first line testing or second line testing after CMA.

WES-Whole Exome Sequencing. WGS-Whole Genome Sequencing. GDD-Global developmental delay. ID-Intellectual disability. ASD-Autism spectrum disorders. MCA-Multiple congenital anomalies. FISH-fluorescence in situ hybridization. CMA-Chromosome Microarray

Indications	**Recommended 1st line testing**
GDD/ID	WES/WGS* and fragile X if male
MCA	WES/WGS*
ASD	CMA and fragile X if male
Suspicion for particular underlying genetic disorder	Targeted testing
Noninvasive prenatal testing	FISH
Concern for balanced chromosomal translocations, inversions, etc.	Karyotype

Common Indications for Genetic Testing

Genetic testing is recommended for a wide range of indications, with the most common being global developmental delay (GDD), intellectual disability (ID), autism spectrum disorders (ASD), and multiple congenital anomalies (MCA). Global developmental delay is defined as significant developmental delay in 2+ developmental domains (e.g. speech and language, social, gross motor) that can be a predictor for future intellectual disability.[5] Intellectual disability is defined as significant limitations in intellectual functioning and adaptive behavior per the American Association on Intellectual and Developmental Disability. Autism spectrum disorders are defined by the DSM V criteria and require formal evaluation for diagnosis. Congenital anomalies have varying definitions, typically involving structural or functional anomalies present since birth that impact the patient and often require medical intervention.[6]

Current Recommendations for Genetic Testing

Genetic testing recommendations (Table 1) continue to evolve as evidence accumulates implicating genetic etiologies. Most recently in July 2021, the American College of Medical Genetics and Genomics

(ACMG) published guidelines recommending WES/WGS as first line or second line genetic testing for those with GDD, ID, and MCA, citing a diagnostic yield of 38%, compared to 21% for prior standard genetic testing,[6,7] as well as the potential for a more timely diagnosis. It is acknowledged that this may currently be cost limiting, but declines in test costs are anticipated with improved technology, health plan coverage, and cost savings compared to the step by step tiered genetic testing approach that would have been previously pursued. This recommendation did not include those with isolated ASD.

Prior to this, in 2010, the American Society of Human Genetics (ASHG) recommended CMA as the first line diagnostic genetic test for those with GDD, ID, ASD, and MCA, citing a diagnostic yield of 15-21%.[8-10] In 2013 the ACMG published guidelines endorsing the same.[11] Similar guidelines were released by the American Academy of Pediatrics (AAP) and the American Academy of Child and Adolescent Psychiatry, in the years following.[5,12,13] For those with GDD, ID, or ASD, fragile X screening is also indicated, particularly in males.[10,14] Other types of screening, including metabolic testing and MECP2 (for Rett phenotypes) are generally felt to be second line tests and are not routinely recommended unless there are suggestive physical exam findings or clinical symptoms.[10] There has been debate regarding targeted metabolic testing based on concerning signs or symptoms versus broad metabolic screening in this population.[5,10]

Prior to the above guidelines, G-banded karyotype was former first line genetic test. Yield of karyotype testing after normal CMA results is low, 0.78-1.3%, and is not routinely indicated as second line testing.[3] Uniparental disomy screening has been suggested in those with GDD or ID, however, did not have high clinical diagnostic utility.[15]

For those patients with clinical presentations that are highly suggestive of a particular genetic syndrome, targeted testing is the first line recommendation (e.g. particular syndromes, familial conditions).

Indications for Referral

Indications for geneticist involvement commonly include ID, GDD, ASD, and MCA, as well as high risk abnormal newborn screens, patients with dysmorphic features, and familial genetic conditions. The timing of referrals to genetics can be dependent on comfort of the primary care provider (PCP), specialist availability, and insurance testing coverage. Given the significant advances in genetics, many PCPs report not feeling comfortable with the current guidelines for indicated genetic testing, the ordering process, or the management of results.[16,17] Overall, ordering of genetic testing appears to be underutilized in the primary care setting.[18] Of patients with a diagnosis of ASD, ID, or GDD, only 32% of families reported a history of having undergone genetic testing.[19] It is also worthwhile to note that many health plans have requirements for genetic testing, which can include the specialty of the ordering provider or prior authorization and the genetics team may be most logistically able to navigate this. Unfortunately, many PCPs report not having access to genetic services, with over 53% of PCPs reporting limited access.[20] This may improve with the recent broader adaptation of virtual medical care.

Genetic Testing Considerations

Pre-Test Counseling

Prior to any genetic testing, genetic testing implications, and potential results should be discussed. This includes potential variants of uncertain significance (VUS), carrier status, secondary findings, paternity, consanguinity, and the Genetic Information Nondiscrimination Act (GINA). These considerations are reviewed below. Patients can proceed with, decline, or decline certain aspects of testing, once these issues are addressed. In addition, the diagnostic yield of genetic testing can be limited and expectations of diagnostic results should be reviewed with families prior to testing.

Variants of Uncertain Significance

Genetic variants are classified into 5 main categories: pathogenic, likely pathogenic, benign, likely benign, and VUS. Pathogenic and likely pathogenic variants are associated with disease and meet ACMG criteria for pathogenicity. Benign and likely benign are not associated with disease. Variants are classified as a VUS due to limited information and are often eventually found to be benign or likely benign as more evidence emerges with time. Over time VUS findings may be re-characterized based on the literature, animal models, or family cohorts. In

the meantime, these results are unsatisfactory and can be frustrating for patients and families.

Parentage

Genetic testing has become standard of care for a variety of indications and often testing is more useful if a patient sample is analyzed with parental samples. This can be done from the onset or later on to help classify the pathogenicity of variants identified in the patient. It can also shed light on recurrence risk and future family planning. However, it can also reveal non-paternity or consanguinity, and families should be counseled prior to testing regarding these potential results and implications. Patient-only testing can be performed medically to avoid non-paternity concerns, however DTC genetic testing typically contains an ancestry component that would potentially reveal parentage based on matched relatives within the ancestry platform. DTC testing that has inadvertently exposed unexpected parentage has been reported numerous times in mainstream media, including cases related to in vitro fertilization with embryo mix ups or alternate sperm use.

Pediatric Carrier Screening

Pediatric screening for carrier status or adult onset conditions without implications in childhood is not currently recommended per AAP, ACMG, and ASHG guidelines.[21,22] These conditions do not have implications during childhood and medical monitoring for these adult onset conditions begin in adulthood. The recommendation aims to support future decisional autonomy regarding testing for particular conditions or carrier status and avoid the harm of stigma, discrimination, or emotional burden of early testing. This recommendation extends to DTC services, particularly with concerns for validity of testing and the need for adequate, as well as developmentally appropriate, pre- and post- test counseling.

With increasing utilization of WES/WGS, carrier testing, and predisposition/risk screening, related ethical concerns are increasing. WES/WGS testing by definition is comprehensive and will sequence genes for adult onset disorders (e.g. high risk genes for Alzheimer's disease), cancer predisposition genes (e.g. BRCA1/2 associated with breast and ovarian cancers), carrier status for various conditions (e.g. Cystic Fibrosis) and other medically actionable findings that may not be related to the initial reason for obtaining testing. To address this, the ACMG publishes guidance for genes to be reported in secondary findings on WES/ WGS. The latest release from 2021 includes 73 genes. This list will be updated annually by the ACMG Secondary Findings Maintenance Working Group, who take into consideration the "actionability, severity, penetrance, impact and burden of available treatment modalities or screening recommendations."[23] During pre-test counseling for WES/WGS, secondary findings are explained and offered for families to opt in or out of.[24,25]

Genetic Information Nondiscrimination Act

Pre-test counseling also involves discussing the federal Genetic Information Nondiscrimination Act (GINA), which prevents employers and health insurance companies from discrimination based on genetic information.[26] This does not apply to disability insurance, life insurance, or long-term care insurance. These types of insurances can utilize medical information, including genetic information, for underwriting, pricing, and other aspects of insurance products. GINA does not extend to certain federal programs and groups, including the United States military and medical care through the Department of Veterans Affairs, or the Indian Health Service.

Direct-to-Consumer Genetic Testing

Direct-to-Consumer (DTC) genetic testing is marketed directly to customers, often via television, the internet, or telemarketing. Interested individuals can purchase these products online or in stores, send DNA samples to the company, and receive their genetic testing results directly. This process does not require the involvement of a health care provider or genetic counselor. The testing performed varies between companies, but can include medically pertinent testing like BRCA1/2, other cancer predisposition genes, carrier screening, and known risk genes for conditions like Alzheimer's disease. It can also include other genetic traits (e.g. eye color) and ancestry information. Common DTC genetic testing providers include 23andMe, EasyDNA, Helix, among others.

Direct-to-Consumer testing has increased in the last five years[27] and patients are presenting results

primarily to their PCPs for additional guidance and decision-making.[28] Because the majority of these DTC genetic testing companies do not require complete pre- and post-test genetic counseling, many individuals pursue testing without full understanding of potential implications,[7] leaving the bulk of this counseling to be done after receiving results, if at all.

Most DTC testing is based on SNP-chip genotyping, not DNA sequencing.[29] This process involves using thousands of probes on a slide that hybridized to patient DNA. The different ratios between patient DNA and each probe DNA can be visualized to detect genetic variants. This type of testing is well suited for common genetic variations, but can be very inaccurate for rare pathogenic variants. On analysis, there has been a 40%-96% false positive rate.[30,31] These companies often do not confirm these rare variants with Sanger sequencing or other internal methods of validation,[31] which is the standard for medical genetic testing. This is particularly relevant as some DTC companies have been granted FDA clearance to report BRCA1/2 variants, associated with increased breast cancer risk, and other medically actionable genes.[32] The rare variants identified may or may not appear in the direct report to the customer, but will be available in the raw genetic data. Many individuals request this raw genetic data, approximately 60-70%[28,33] by some reports, to have it analyzed through a third party. In addition to the high false positive rate associated with the raw data itself, third party analyses can vary widely in their classification of a particular variant as pathogenic, benign, uncertain, etc., based on their own definitions. The ACMG and the Association for Molecular Pathology have strict variant classification standards. The ACMG has defined criteria for variant classification and recommends result interpretation by a board-certified clinical molecular geneticist or molecular genetic pathologist.[34] There have been reports of raw data analyses that have characterized variants as pathogenic that would have been benign variants or VUS per ACMG criteria.[35]

When clinical decisions are made based on presumed pathogenic variants, whether from false positive data or inaccurate classification, unnecessary and at times harmful medical interventions are pursued. There are a number of case reports regarding patients who were thought to have a pathogenic variant by DTC testing and underwent multiple ED visits, subspecialty workup, extensive imaging, and even surgery. Subsequent confirmatory sequencing by a certified clinical laboratory of the "pathogenic variant" did not confirm DTC testing findings.[33] In addition to the unnecessary medical interventions, patients and their families undergo emotional, social, and potentially financial stressors related to the false test results from DTC testing.[33,36]

In general, reputable genetic testing laboratories have certification requirements, including certification through clinical laboratory improvement amendments (CLIA) and the College of American Pathologists (CAP), and must be in good standing of these rigorous requirements. They will confirm variants with internal validation or a secondary testing method and report the coverage of sequencing for particular genes. While DTC genetic testing can be informative and is directly accessible to the consumer, it has many limitations, and patients with medical concerns related to potential genetic causes should undergo genetic testing through appropriate channels.

Conclusion

Many patients initially present to their PCP with genetics related concerns and unfortunately genetic specialists can be limited in number or availability, making continued PCP education and familiarity with genetic testing modalities, indications for testing or referral, considerations for pre-test counseling, and limitations of DTC testing very important. Common referrals for genetic testing include DD/ID, MCA, ASD, patients with dysmorphic features, and familial genetic conditions. The first line testing recommendation for DD/ID and MCA is WES/WGS, providing a diagnostic rate of 38% in certain indications, in contrast to the prior diagnostic rates of 10-20%. Other modalities of genetic testing continue to be important in various contexts.

Due to implications of genetic testing outside of the patient's current medical concerns, pre-test counseling is essential for patients or the parents of patients who are minors. Unfortunately pre- and post- test counseling is often limited in DTC testing, which also has other limitations

including high false positive rates for rare genetic variants and genetic variant interpretation concerns. With advances in medicine, genetics has become a substantial part of patient care and PCP familiarity with genetic testing options and indications allow providers to deliver appropriate, up-to-date healthcare.

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Disclosure

None reported.

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Burnout Among Missouri Primary Care Clinicians in 2021: Roadmap for Recovery?

by Erin E. Sullivan, PhD, Danielle McKinstry, MHA, Joni Adamson, MBA, Lindsay Hunt, MEd, Russell S. Phillips, MD & Mark Linzer, MD

Data from Missouri shows challenging findings which may serve as a call to action in response to the crisis of burnout within medicine in general and primary care in particular.



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Abstract

Rates of burnout among clinicians have been exacerbated by the COVID-19 (COVID)pandemic. A survey of Missouri primary care professionals at federally qualified health centers was conducted during a COVID surge in August 2021 to assess burnout, stress, and job satisfaction as well as if respondents had sought assistance for burnout or attended resiliency training. Despite respondents reporting rates of burnout (56%) that exceed those reported nationally (48%), only 17% sought help for burnout. Most (81%) had not attended resiliency training; of those who did, 16% said sessions "make me feel less alone," while an equivalent number found sessions not useful, identifying an absence of resources within their organization. Comments focused on the need for dedicated time to receive support, including time to seek assistance during working hours, time to take breaks, and time for self-care. The data suggest one path forward to remediate burnout: provide the workforce with time to access support.

Introduction

Rates of burnout are at an all-time high among clinicians,[1] and especially concerning in primary care.[2] We recently wrote about one strategy to reduce burnout across numerous health systems in Minnesota.[3] In this article we share data from Missouri with challenging findings which may serve as a call to action in response to the crisis of burnout within medicine in general and primary care in particular.

Methods

Data were collected in partnership with the Missouri Primary Care Association (PCA) as a needs assessment for a grant application on improving burnout and mental health. We designed a brief survey, which included three Mini-Z items,[4] three open-ended questions related

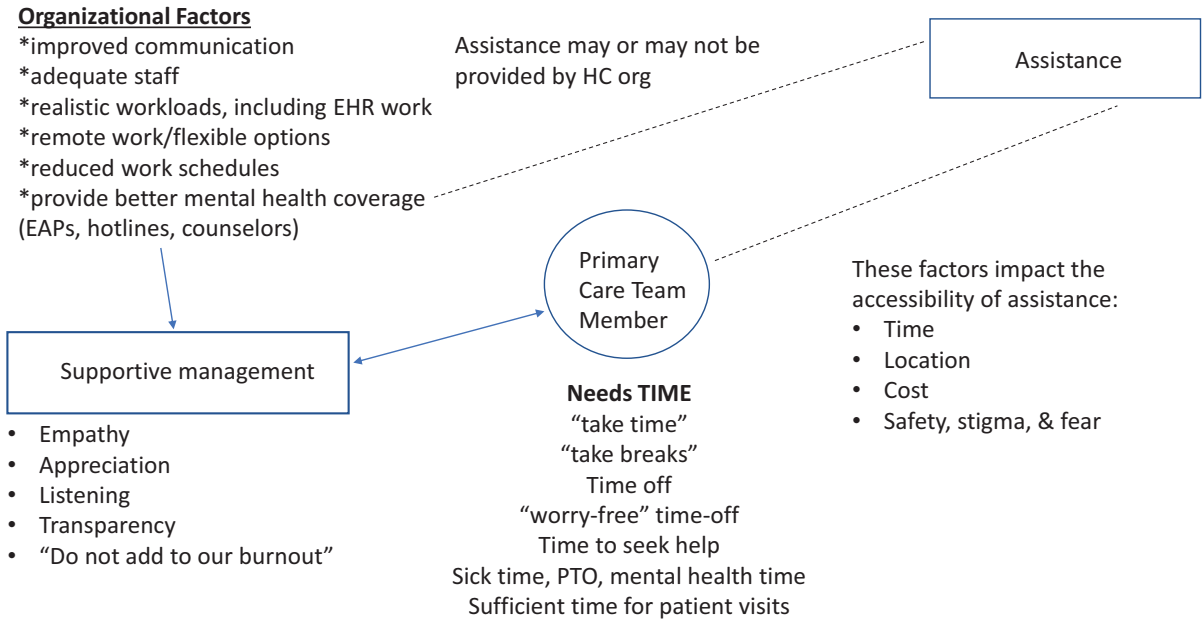


Figure 1. Variables that impact organizations, burnout, and healthcare workers' ability to seek assistance. Variables in the model come from the Missouri survey respondents and were adapted from other studies: the Physician Worklife Survey,[8,9] MEMO (Minimizing error maximizing outcomes) study,[10] and the Reducing Burnout Driver Diagram.[11]

to seeking assistance for burnout, and two questions on resiliency training.

A snowball sampling strategy was used: the survey was sent by the Missouri PCA to 56 federally qualified health center (FQHC) contacts in August 2021 during a COVID surge; contacts were asked to share the survey with primary care professionals within their FQHCs. Anonymous responses were received from 506 unique primary care professionals; the 2020 CMS Uniform Data System indicates approximately 5,200 FTEs in Missouri's FQHCs, thus we estimate at least a 10% response rate.

Burnout measurement used the Mini-Z single item, validated against the MBI emotional exhaustion subscale;[5] satisfaction and stress measurement used items from the Physician Worklife Survey.[6] Open-ended comments were assessed via inductive coding to allow themes to emerge from participants' responses about seeking help to address burnout; the emergent themes were then compared with existing literature to develop a conceptual model to guide remediation efforts. Statistics provided are mainly descriptive. The Harvard Institutional Review Board determined this was not human subjects research.

Results

Job satisfaction was present in 64% of respondents, low compared with national statistics of 72% in Internal Medicine[4] while 64% of respondents reported high job stress and 56% reported burnout (ranging from having one or more symptoms to feeling completely burned out and needing help). Despite burnout rates that were higher than national numbers during the pandemic (48%),[1] only 17% of survey respondents sought help for burnout, including counseling (44%), medication (23%), manager support (14%), and other strategies

Table 1. Time Categorizations by Respondents with Representative Quotes

Time Categorization	Representative Quote
Employer-paid time to seek assistance	"Being able to use sick time instead of vacation time when scheduling an appointment with mental health provider." "Available time off during work day/week to seek assistance." "Provide paid time off specific to stress management services or counseling."
Breaks during the work day	"It is often way too busy to step away to take a break or even a breath. Even regular breaks and lunch are often given up because of a busy schedule." "Breaks! Take breaks when needed. Walk away if you have to. We are human, and not super humans." "Provide frequent short mental breaks throughout the workday that allows the healthcare worker to actually walk away from the work and destress if needed. A designated stress-free room that is solely used to provide a relaxing environment even if for just 5-10 minutes."
Time for self-care or wellness activities	"Remain committed to the investment in self-care and wellness. It's easy to get busy and stay busy and think you don't have time for wellness, but we have to do it… Carve out time in schedules for wellness - even if it's 5, 15, 30, 45 minutes." "Take care of yourself by exercising, saying no to some social obligations, and getting enough sleep." "You cannot continuously pour from an empty cup. Find time for yourself and turn off all devices."
Worry-free time off	"It would be nice if we were fully staffed and could take a mental health day without feeling guilty for leaving everyone else drowning." "Time to get assistance with less worry about feeling guilty for taking the time to seek help." "Hire more help to allow vacations to be taken without getting further behind in work."

including exercise, meditation, and reducing work hours. In terms of resiliency training, a majority (81%) had not attended, and of those who did (n =86), 16% said sessions "make me feel less alone" and found solidarity with colleagues helpful. An equivalent number found sessions not useful, saying sessions were good, but there were no resources to implement in their organization. Open-ended comments regarding barriers to seeking assistance focused on needing dedicated time to receive support; comments highlighted other variables impacting organizations, burnout, and workers' ability to seek assistance (Figure 1). Time was categorized by respondents as employer-paid time to seek assistance beyond or during working hours, time to take breaks during the day, time for self-care, and "worry-free" time off (Table 1).

Discussion/Implications

Primary care burnout is at troubling levels in Missouri and in other states summarized in recent web posts[2]. Addressing burnout within each state is one strategy to consider to mobilize the nation's healthcare infrastructure to improve work conditions in primary care. These new

data show troubling but remediable findings within a large rural state where many patients depend upon primary care by local safety net providers. Thematic analysis highlighted time as a primary barrier to accessing support needed to reduce burnout. Survey respondents proposed interventions that could be facilitated by workflow redesign including dedicated time to seek assistance; robust mental health support, including available counseling during or after work hours; mental health days or flexible use of sick time; and manager support in modulating workload.

Conclusion

A statewide approach to reduce burnout, as taken by the Minnesota Hospital Association[3] in 93 heath systems throughout the state, may be an effective mechanism to address worklife and wellness in clinicians in Missouri. Given the emphasis on time pressure noted in this survey and in prior national studies,[7] a statewide approach to time (time for self-care, time for documentation, and time to listen to patients' concerns) is, we believe, a focus which could quickly build loyalty and trust among Missouri physicians. This approach has been supported by the American College of Physicians and the American Medical Association, among other large national organizations. Support by the federal government and insurance companies for sufficient time to carry out the important work of caring for patients will further support this effort.

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