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In publication since 1904, Missouri Medicine, a peer-reviewed, award-winning medical journal printed on acid-free paper, is indexed by MEDLINE, the National Library of Medicine, and is linked to PubMed Central, which is the U.S. National Institutes of Health digital archive of biomedical and life sciences journal literature. Missouri Medicine can be found on EBSCOhost databases, which provides researchers with the ability to search full-text articles, and are the most-used, premium online information resources for tens of thousands of institutions worldwide, representing millions of end-users. Missouri Medicine also provides featured content for www.medhelp.org,world's largest online health community that reaches more than 140 million users worldwide each year.

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Obama Evaluates Obama Care Positively

Some Analysts Disagree With His Conclusions

by Author H. Gale, MD



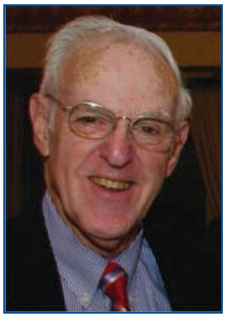
In the August 2, 2016, issue of the *Journal of The American Medical Association* (*JAMA*) President Barack Obama evaluates the Affordable Care Act (ACA) commonly known as Obama Care. Obama rightly declares that under the ACA more Americans have received health insurance coverage. He claims that the quality of health care has improved and that newer forms of health care delivery such as Accountable Care Organizations (ACOs) and bundled payments will improve health care and lower costs. He proposes a public option in certain areas of the country where competition is limited.[1]

Obama's article, written in academic style, contains multiple graphs and tables and has 44 references. It is unlikely that Obama actually wrote the article himself but merely approved it. [See Editor's Note.] Surely the leader of the free world has many more pressing problems than to spend many hours researching and writing a scholarly treatise about the Affordable Care Act. In my view it would have been more honest and more effective if he wrote an article in plain English that everyone could understand.

In the same issue are three editorials by analysts one of whom agrees with Obama's assessment of the ACA and two who do not.

Peter Orszag, PhD, an economist and self-anointed expert on health care, was the main architect of Obama Care. As expected he agrees with Obama, and writes in strong support of the ACA.[2] But Orszag has serious conflicts of interest that undermine his credibility.

Orszag is a poster child for the Washington elite. Unelected to any office he and other so called "experts" move seamlessly from academia to government and to Wall Street.



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In autocratic top down fashion these Washington elites determine the organization and goals of health care for the country. As the head of the Congressional Budget Office (CBO) and later the Office of Management and Budget Orszag persuaded Obama and other members of the team that designed Obama Care that fee-for-service was the main cause of high health care costs.[3] Orszag predicted that capitation by means of Accountable Care Organizations and bundled payments would lower health care costs.

After his stint of working for the government, Orszag moved to Citicorp, a Wall Street investment firm, where he made close to $4 million per year (presumably paid on a fee-for-service basis.) More recently Orszag went to work for another Wall Street firm, Lazard, where he is advising Aetna Insurance Company on its controversial acquisition of Humana.

The American Medical Association (AMA) has strongly opposed this merger. The AMA wrote a 17-page letter to the Department of Justice that the proposed mergers of Aetna and Humana and Anthem and Cigna would lead to price increases, a reduction in health care quality, and less consumer choice of doctors in already too narrow networks.[4]

All medical journals require conflict of interest statements from authors. The *JAMA* article mentions that Orszag works for Lazard but there is no mention of Orszag's work on insurance company mergers that are directly opposed to AMA policy. In the interest of full disclosure the article by Orszag should have stated this fact. Or the editor of *JAMA* Howard Bauchner, MD, should have rejected the article. In my opinion Orszag's declaration of support for Obama Care for which he was the main architect is a self-serving screed on behalf of the insurance industry, Wall Street interests that he represents, and Qrszag's own pocketbook.

The second critique of Obama's article is by Stuart Butler, PhD, of the Brookings institution.[5] Butler challenges Obama's assertion the ACA has moderated health care cost increases. He points out that he and most analysts agree that the decrease in the rise of health care costs was not due to the ACA because the decrease preceded the enactment of Obama Care.

Butler states that the ACA should more appropriately be called the "Medicaid Expansion Act." He asserts that under the ACA there has been "a large reduction in the number of uninsured individuals but that the sources of this coverage have been mainly due to Medicaid and the Children's Health Insurance Program (CHIP)." Butler goes on to say that "Medicaid and CHIP will cover an estimated 17 million more people in 2016 than the Congressional Budget Office's earlier assessment." Furthermore, the ACA's exchanges - the highly touted backbone of competition that was supposed to lower costs in the ACA - have enrolled 10 million fewer persons than expected. These surprising facts are almost never mentioned in the news media nor are they mentioned in the Obama and Orszag articles.

The reason for the lower enrollment in exchanges according to Butler is cost. He states that the premiums and out of pocket costs of the ACA exchanges are too high and beyond the reach of most Americans. Butler pulls no punches in his criticism of Obama Care: "For many households the president's promise of affordable coverage rings hollow and has not been realized…Those choosing Bronze plans… have coverage in name only." A recent report in the *Wall Street Journal* states that insurance premiums are going to rise even higher by 18% to 23% in 2017.[6]

The high cost of Obama Care was brought home to me recently by a patient with type 1 diabetes on both long-acting and short-acting insulin who said he could not afford health insurance for himself and his wife. He had avoided seeing me or any other doctor for over a year. He was a self-employed small business owner. He added that he could barely afford his medication which had almost doubled in the past few years.

The third editorial is written by Jonathan Skinner, PhD, of the economics department of Dartmouth College, and Amitabh Chandra, PhD, of the Kennedy School of Government at Harvard University.[8] The first thing these authors note is the difference in Congressional support Medicare had in 1965 compared to the Congressional support of the Affordable Care Act. In 1965 Medicare was passed by a 313 to 115 margin in the House and 68 to 12 the Senate. By contrast the ACA barely reached the filibuster proof of 60 votes necessary in the Senate and passed by a 219 to 212 vote in the House.

Like Stuart Butler the authors state that the ACA cannot take credit for slowing the rise of health care costs because health care costs began to moderate before the ACA was enacted. Furthermore, they ominously note a recent study showed that health care costs as a percentage of the gross domestic product rose significantly between 2014 and 2016. They also say that it is far too early to draw any conclusions on whether quality has improved under the ACA.

In his book America's *Bitter Pill, Money, Politics, Backroom Deals*, and the *Fight to Fix Our Broken Health Care System* (reviewed in *Missouri Medicine* November/December

2015) author Steven Brill describes how the Obama administration, in order to get the ACA passed, bowed to the demands of the medical industrial complex comprised of hospitals, insurance companies, and drug companies. Obama's brain trust stated that it was not politically feasible get the bill passed any other way. The bill was primarily intended to insure millions of Americans who would not otherwise have health insurance. Cost concerns would be addressed later. Obama and his brain trust believed competition would lower costs. Electronic health records through programs such as pay for performance and meaningful use would improve quality.

None of this has come about. There is virtually no competition under Obama Care. Instead monopolies have emerged from hospital consolidations and insurance company mergers. Drug company pricing is completely out of control. And just ask internists – actual doctors who treat patients, not MBAs - if the overall quality of care has improved with electronic health records. Perhaps EHRs will improve quality in the future, but they certainly do not improve quality in their current stage of development.

Obama's strategy of getting people insured first and then figuring out how to pay for the insurance coverage later has not worked out. Basically, most of the new enrollees in the ACA are in Medicaid not in the exchanges. And the exchanges aren't working. They're not affordable for many Americans. And even at their currently unaffordable rates insurance companies have lost hundreds of millions of dollars. They are now asking for another bailout from the government.

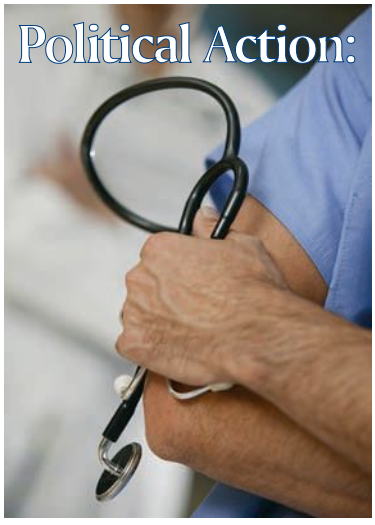
Since Obama Care is unsustainable, what is the next step? Can the American people through the democratic process determine the kind of health care system that benefits them instead of self-serving Washington elites and their special interest clients? This election, more than any election in recent memory, shows that the public is opposed to maintaining the status quo in Washington. We'll have to wait and see.

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Editor's Note

JAMA has published in the past the importance of eliminating or identifying ghost authors and giving authorship to those that have made significant contributions to an article. See http://jamanetwork.com/journals/jamainternalmedicine/fullarticle/1675881. It is my opinion that *JAMA* has likely violated their own guidelines. As Dr. Gale suggests, Barack Obama undoubtedly had the assistance of several experts that should legitimately have been identified as co-authors or the article was mostly or wholly ghostwritten, and Obama signed off and claimed authorship. **MM**



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As leaders in the health care community, it is important to inject your voices into the debate over health care reform. Who knows the practice of medicine and the needs of your patients better than you? Your voices - along with your votes - are vital tools that can have a profound impact on the practice of medicine in Missouri.

As the November elections heat up, you need to get to know the candidates who are friendly to medicine. Support those who support you. And support your physician colleagues who want to represent your profession and your patients in the Missouri General Assembly.



November 2016 Missouri General Election Physician Candidates

[MSMA member names in bold]

- State Senate District 1 (St. Louis County): **Randy Jotte, MD** (R) will face incumbent Scott Sifton (D).
- House District 64 (St. Peters): Mark Routberg, MD (D) will face incumbent Robert Cornejo (R).
- House District 8 (Cameron): Representative **Jim Neely, DO** (R) is unopposed.
- House District 121 (Rolla): Representative **Keith Frederick, DO** (R) is unopposed.



MSMA's Top Legislative Priorities for 2017

Prescription Drug Monitoring Program

MSMA will continue to push for a Prescription Drug Monitoring Program that will require dispensers to submit required information within 24 hours. It will also allow providers to access the system in accordance with a patient's treatment.

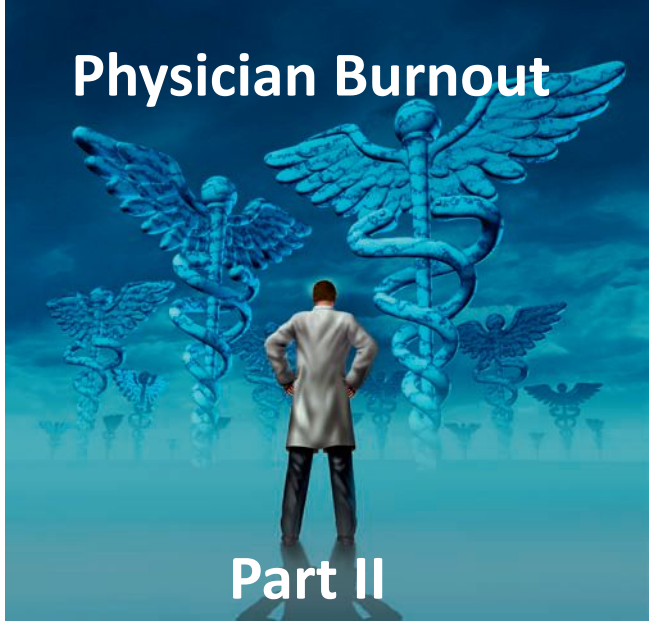
Collaborative Practice

MSMA will continue to oppose efforts that seek to weaken the collaborative practice act in varying degrees.

Predetermination of Benefits

MSMA is pushing legislation that would give patients the ability to know their cost-sharing requirements before receiving a health care service. Providers would receive this information from insurers on behalf of the patient using the same HIPAA-mandated codes that are required for the reimbursement of claims.

Contact Jeff Howell at jhowell@msma.org or Kenny Jackson at kjackson@msma.org or visit www.msma.org/advocacy.



by Dike Drummond, MD

Prevent Physician Burnout:
8 Ways to Lower Practice Stress and Get Home Sooner

In article one of this three-part series we discussed the causes, effects, and pathophysiology of burnout, published in the July/August 2016 Missouri Medicine. If you have not read that article it is important you do so soon. The tools that follow are not nearly as effective if you don't understand the fundamental blind spots and conditioning of our medical education.

In this article we will concentrate on methods to lower stress in your practice. Article three will focus on tools to build and maintain your energy and life balance.

Before we begin you must understand that burnout is not actually a problem. Let me explain.

Problems have solutions. When you apply a solution to a problem, what happens to the problem? It goes away … yes? So often physicians come to me asking, "What is the one thing I can do to lower my stress levels and make burnout go away?" Notice how this request presumes burnout is a problem that has a solution. When you can't find that "one thing," many doctors simply slide back into their old work habits and give up on the possibility that things could be different.

In reality, burnout is a dilemma. It does not have a solution, because it is not a problem in the first place.

Dilemmas are perpetual balancing acts. You are "between the horns of a dilemma" taking specific actions every day, week and month to maintain the balance you seek. You address a dilemma with a strategy, not a solution. By its nature a strategy has multiple parts and in order to maintain balance you have to be measuring how you are doing in some fashion.

The fundamental question at the heart of preventing burnout is this: "What is your burnout prevention strategy and how are you measuring your effectiveness?" The horns of the burnout dilemma are the amount of time and energy you put into your practice on one side and your ability to maintain a positive energy balance and your desired quality of life on the other.

Dilemmas are very common in health care. Here are just a few examples: burnout, your compensation formula, the best care at the lowest cost, your call schedule, your accounts receivable, work-life balance, and EMR.

From this point forward, we will be discussing tools to lower stress by increasing your efficiency at work and decreasing the time it takes to complete the tasks of your practice. One way to measure your effectiveness in this effort is to track the amount of time between your last patient leaving the office and you getting home – with your charts done.

Each tool is a potential component of your personal burnout prevention strategy. You may be utilizing some of these already. If so, make sure you read the Power Tips for that technique. As you read, take note of the tools that seem simplest to implement or feel most attractive to you. I will be giving you implementation pointers at the end of the article.

Remember nothing changes unless you change our actions. This is an active learning process. If you read this article and do not change your actions, you remain trapped in Einstein's insanity definition. I encourage you comb through this article and part three actively looking for one tool in each article you can begin to practice ASAP. Ready? Let's begin.

A Five-Part EMR Strategy

Here are five EMR strategy components we have tested and found effective in the real world.

1) From Hater to Power User

Notice your attitude. Do you feel your EMR program was written by the Devil himself in the fires of hell and his fingernails are digging into the backs of your hands every time you touch the keyboard? That is the definition of a hater. This attitude creates amazing avoidance behavior. You probably avoid your documentation until the end of the day and self-sabotage any attempts to improve your charting skills.

I have a simple question. Do you think EMR is ever going to go away? Then this behavior is insanity. It destroys your ability to get home on time. Take a big breath and let it go.

Devote yourself to becoming a Power User instead. The first step is to find and study the Power Users around you. Typically they are hidden, since to stand up and announce you like the EMR is not a popular thing to do in most groups. Notice that these people are using the same software, seeing basically the same patients and getting home on time. They know things you don't.

Ask the nurses who the Power Users are. If you are solo, ask your EMR vendor to connect you to one. Ask if you can watch them chart – they always say yes. Then sit right behind them while they are at the computer and get ready to yell "STOP" when they do some keystroke combination that magically completes a chart note. Take notes. Ask how they did that. Pick up two to three tools you can use. Before you leave ask if you can have their templates. They always say yes.

Two or three sessions later you are well on your way to becoming a Power User too. When the little hater voice comes up in your head, just say "Thank you for sharing" and let it go.

2) Always and Only Document a Minimal Data Set

There are three reasons to write a chart note. Billing, medicolegal, and what I will call "continuity" – providing the next person who sees this patient with enough information that they can take over where you left off. If what you are writing in the chart is not supporting your billing code, covering your "legal part" or helping the next provider in the chain, don't put it in your note.

Do not write the great American novel. You do not need complete sentences, or perfect spelling, you never need to touch the semicolon key, and remember that longer is not better.

3) Use the Software

The use of EMR software is meant to semi-automate your chart notes through the use of templates. Here is a test. If you piled up all your documentation from a week into a heap on your desktop … how much of it was produced by you free typing into the chart? If your answer is more than 30%, you are not as automated as you could be. The secret is to look for "Broken Record Moments" (BRMs).

This is when you notice, "OMG! This is the fourteenth time I have written the same note this week." The typical reaction to a BRM is to become frustrated. Don't stop there. Realize a BRM is a golden leverage point to get home sooner. It marks an opportunity to automate. Use this process:

- As you notice BRM, just write them down. Make a list.
- Once a week, take one off the list and template it. Ask I.T. or your Power User friend to help if you need to.

The templating process will only take 30 minutes or so. Here is the power.

- How many times do you need to make a template?
- For how long can you use that template?

In a month you will have transformed four BRM into simple keystroke combinations and be getting home sooner.

4) Team Documentation

You are programmed to be a Lone Ranger superhero perfectionist. You are almost certainly doing too many of the charting chores yourself. Realize that all documentation is team documentation. You don't have to do it all. However, if you want your team to help you will have to ask them. Because of your position at the apex of the care team and the one who gives the orders, your staff will not usually butt in and tell you to delegate a charting task to them.

Ask for help in an open ended way and see how they respond. It could sound like this. "Hey everyone, I am working on ways for us to become more efficient at charting. We are a team and all of us are in the chart at some point. What are your ideas about how we can share the work more effectively so I can get from patient to patient more quickly?" Then be quiet and see what they say. This is way more effective than trying to figure it out yourself and giving them orders.

5) Hire a Scribe in a Risk-Free Pilot Project

Across the nation physicians are pounding their administrator's desks demanding a scribe. They always say, "If I had a scribe, I could see more patients." I assure you the administrator is thinking, "Prove it." You see, administrators have two concerns you don't have: money and manpower. For you to have a scribe, they have to come up with the money and the scribe. That is a risk for them.

Here is how you can get a scribe with a process I have never seen fail. Take all the risk yourself.

There are several national scribe companies. They will find, hire and train a scribe for you. All you pay is about $25/hour for their services. Try this.

- Get your administration to OK a risk-free scribe pilot in your practice.
- Run a detailed production and billing report for your last three months.
- Hire and implement a scribe in your practice. You pay all the costs. The scribe provides the manpower.
- Dial them in as well as you can over a three to six months period, until you feel you are working at maximum efficiency.
- Run another three-month production and billing report, now with your scribe.
- Prove you are now seeing more than enough patients to pay for the cost of the scribe.
- Ask your group to take over those payments. This is known as a "claw back."

Broken Record Automation - Part II

You will find another category of BRMs in the patient education side of your practice. Your little voice will point out, "This is the thirteenth time I have said the same thing to a patient this week."

Once again, step one is to make the list of all of these moments. Write them down. Then decide how you will address this teaching going forward. There are four main methods.

1) Written

Make patient handouts to cover the BRMs in your practice. Keep them stocked in an accordion file folder. Put them on pastel colored paper. Put your nurse/MA in charge of keeping them stocked.

2) Video

Record a video of you doing your best teaching on your BRM subjects. Load it onto a set of cheap tablet computers your nurse/MA gives to the patient to review at the conclusion of the visit. Or put them up on YouTube.com and give the patient the URL or mount them in your patient portal for the patient to watch in the office or at home.

3) Delegation

Train your people to take over the broken record from you.

4) Combination

A combination of the above, like a handout with a video link, etc.

Eliminating BRMs, in both documentation and patient education is one of the quickest ways to get home sooner.

The BID Huddle

The BID team huddle is a time honored method of preventing fires from breaking out in your day. If you are not routinely holding a BID huddle in your practice, you are getting home later than you need to.

Huddle Basics

- Six minutes twice a day before each of the two halves of your day.
- Include all members of your patient flow team. Receptionist, whoever rooms your patients, the float nurse.
- Stand-up meeting. You go to them. Do not make them come to your office.
- Make sure one of you has the schedule for the coming half day in hand. Review the schedule together and do two things.
- Trouble shoot the patients on the schedule already. Know who is sick or upset, who has special needs, who needs specific equipment or a special room.
- Let your team know what to do with any open appointment slots. Know when your next available appointment is.
- Address any other issues the team is facing in the next four hours - such as the printer is down or we just ran out of flu vaccine, etc.

Huddle Power Tips

Check in with your team: Ask everyone how they are doing today? Get to know if there is anything going on here at work or in their personal lives that you need to know about, both good and bad. Know who's child is sick and who's child just got a college scholarship.

Say thank you: acknowledge and thank the members of your team for anything they have done in the last several days that help you or the team do a better job. Praise early and often and be specific. "Thanks for your hard work, we really appreciate it."

Delegate: ask your team to be on the lookout for things you are doing as the doctor that they could take off your plate and complete instead. "We are a team. Caring for patients and completing the documentation are team activities. We share the load. Any time you see something you could do instead of me, something that would help the team be more effective, please bring that idea to the next Huddle."

Clear and center the whole team: invite your team to take a deep cleansing breath to become clear and centered before you start seeing patients ... you all take this breath together and invite any stress or worry or tension out with your out breath.

Batch Processing

Doctors are a lot like dogs in some ways. If a dog is sitting on the porch and I get their attention by throwing a tennis ball … they can't NOT chase it. They can't resist. With doctors … the tennis ball is a refill request that pops up on your EMR screen. It is not urgent or important and yet how often do you drop what you are doing to address it?

We mistake every action as a urgent one and chase them just like the dog and the tennis ball. Add in test results, phone messages, referral paperwork, and your day is fractured into a hundred pieces for one simple reason. You are taking care of these items one at a time and allowing them to interrupt your patient flow.

The solution is batch processing. Take all the tasks that are non-urgent, put them into piles – batches – and run the batch twice a day at a time when you and our team can address them all at once. In the days of paper charts we used to put out a basket for each task type. Refills go in this basket, test results go in that one when they return.

In a standard office day where you have an AM and PM schedule, some good times to do batch processing are 11:30 a.m. and 4:30 p.m. That way the morning's work is done before lunch and the afternoon's work before you go home.

EMRs make this a little different because often these non-urgent tasks pop up as alerts on your tablet, laptop or desktop screen. These prompts are equally enticing to our dog-like "fetch" mechanism and even more powerful time wasters.

Batch these, too, by NOT addressing them when they come in. Make a "virtual basket" that you run in a batch twice a day.

What can you batch in your practice? Make a list of all the little things that interrupt your day repeatedly. As with your BRMs above, your first task is simply to make the list. Then bring in your team with a good question. "What tasks happen every day – things that are not urgent, yet have to be done before the day is over – that can we put in batches and do all at once, in batches twice a day?" Add their suggestions to the list as well. Now pick one item on the list and design a batch process.

- Where will you collect the items to be batched? Is it a physical basket where you will put physical forms or a virtual basket that will hold emails or test results?
- Who is doing the batch processing, you or one of your team members?
- What are the screening criteria that mean the physician must get involved?

Example: Your nurse screens all lab results as they come in alerting you to any abnormal values between patients. All labs are batched in a lab folder in your EMR which you run and process at 11:30 a.m. and 4:30 p.m.

Power Tip

Many EMR systems have a real time alert system on their face page telling you how many lab reports or emails or instant messages you have waiting. It is a nearly irresistible distraction and often a complete waste of time since the notice does not tell you about the urgency or importance of the alert. Work with IT to get these off your EMR face page. Have someone else screen these messages and alert you to the ones that actually demand your urgent attention. Sometimes you will find the alert box cannot be taken off the EMR face page. In that case you can still go old school.

Take a sticky note and trim it to the size that will cover the alert box. Stick it over that portion of your EMR screen and discipline yourself to peel it off and run the batch just twice a day.

Time to Pick a Tool and Take Action

It is easy to see an article like this one, with multiple suggestions for practice changes, and get completely overwhelmed. Your brain naturally focuses on how you can implement them all at once. The key here is to pick just one and take just the first step. That is all. Once you take the first step, the second one will become clear as crystal.

Go ahead and pick one tool that feels like a good place to start. What is the smallest step you can take to implement it? I suggest you tell your team what you are up to and ask for their help right up front. They always have fresh ideas you can't see when you are in the room with the patients. DO NOT read this article and fail to take action or you will have missed a chance to step out of Einstein's insanity trap. It is time to build your burnout prevention strategy.

In article three we will focus on life balance tools that allow you to recharge your energy accounts and build more balance into your week. **MM**



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War and Trauma: A History of Military Medicine - Part II

by Charles Van Way, III, MD

War is inhumane, and terrible. Yet, war has always been with us.

While military medicine by the beginning of the 19th century looked much better than at any time in the previous millennia and a half, both trauma care and military public health were primitive by today's standards. The development of what we now know as modern military medicine occurred over the course of the late 19th century, and into the 20th. While this evolution took place across Europe as well as in North America, we will concentrate upon the American experience. The European experience was essentially similar. Medical and trauma care made slow progress during the limited wars of the 19th century, but was greatly challenged by smaller wars in adverse environments. In the case of Europe, those would be the Crimean War and then the Boer War in South Africa. In our experience, this would be in the Caribbean and the Far East.

After the Napoleonic wars, which included our War of 1812, the United States had few major conflicts for 50 years. But then, we found ourselves in the bloodiest conflict of our history. The American Civil War was fought with mass armies, modern industrial technology, railroad transportation, and telegraphic communications.

Unfortunately, its health care was barely up to the 18th century. Both armies had physicians, but there was only a rudimentary hospital and evacuation system. Both armies depended heavily upon civilian physicians and makeshift facilities to care for their injured soldiers. Even "army doctors" were contracted civilians. Public health was terrible. Many soldiers died of disease, often even before reaching the battlefield. Sanitation was abysmal. Epidemics of dysentery, pneumonia ("camp lung"), and typhus swept the camps. And yet, nothing was done after the war to change things.

The next war, the brief Spanish-American War (1898), was fought in the tropics, notably Cuba and the Philippines. Typhoid, yellow fever, and malaria were new to American troops, and killed far more than enemy action. There was little organization, few supplies, and poor use of resources. But the war was highly publicized in the newspapers of the day. After the war, there was a great public outcry about disease. The so-called "typhoid board," often called the Reed commission, was set up during the war, and made a number of recommendations about sanitation, malaria control, and mosquito control. The Reed commission paved the way for the construction of the Panama Canal, overcoming the high rate of yellow fever among the workers in previous attempts to dig an Atlantic to Pacific canal. Walter Reed was an outstanding Army physician, one of the true heroes of the Army medical corps. (See Figure 1.)



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He had immense influence during and after the war. He died in 1902, of appendicitis, but his work was carried on. The subsequent Dodge commission conducted a much more comprehensive review of the shortcomings of the Army medical services. These included poor preparation, poor sanitation in the camps, and failure to organize nursing services. As a result, there was a major re-organization of the Army's medical support. So finally, during the first decade of the 20th century, the Army recognized the need for doctors, nurses, hospitals, corpsmen, and, in short, today's medical services. Immediately prior to World War I, the Army was headed by a chief of staff who was a physician, Leonard Wood, MD. (See Figure 2.) He oversaw much of the transition of the Army medical service into a modern military medical system.



Figure 1
Walter Reed, MD



Figure 2
Leonard Wood, MD

Why did it take so long, both here and in Europe? In all "civilized" countries, military medicine remained much worse than it should have been during the entire 19th century. There were three reasons. First, until the 20th century, most countries were run by aristocrats. Even in such ostensible democracies as England, they were the politicians, the generals, the senior military bureaucrats. Doctors were middle class, below the aristocracy. Simply put, nobody wanted to listen to them. This had been going on for centuries. Once, in the middle ages, physicians had a certain status as churchmen, but even that was incomplete. Barber-surgeons like Ambrose Paré were not only below the aristocracy, they were definitely lower class. Jean Larrey, a plebian, could succeed in only Revolutionary France. But such a man was looked down upon even in France, and would have been a second class citizen anywhere else in Europe. Second, public health itself was poorly understood. Cities down through the 19th century were, to put it bluntly, cesspools. Someone in the early 20th century commented that were it not for the automobile, city streets would have been three feet deep in horse manure. The countryside wasn't much better, just less densely populated. Epidemics swept through Europe at regular intervals. Similar epidemics swept through military camps on a regular basis. Third, senior military officers were taught strategy and tactics. Logistics was a poor third. And the sort of logistics which concerns caring for and evacuating the wounded is not a pleasant topic, nor one which will win prestige for an ambitious officer. Much less public health. A famous comment made by a Civil War era general to a physician who wanted to clean up the camp was, "Don't worry. All Army camps smell that way." There was a sort of pessimistic complacency. Senior officers knew that if they could keep down losses from disease, they would have more men to fight. But they didn't think anything could be done. Even if it could, they didn't want to do it themselves.

The First World War was fought largely in the trenches of the Western Front. That's not the full story, but it was and remains the public image. Trench conditions were miserable from a military standpoint. They were a disaster for public health. Sanitation was so bad that after a week or two in the trenches, troops had to be rotated back of the lines to be deloused, thoroughly cleaned, and provided with fresh clothing and equipment. Even so, disease was common, and wound contamination universal. Facilities were largely improvised, and soldiers were collected in the open to await care. All of this made wound care much more difficult. (See Figures 3 and 4.)

Even acknowledging all of the difficulties imposed by trench conditions, the casualty care system was still much better than in any previous war. Special military units, called ambulances were charged with picking soldiers from the battlefield and transporting them to aid stations, and then to field hospitals. So-called casualty clearing stations were used to collect the wounded, and load them onto hospital trains. These were staffed with nurses and orderlies, and equipped to care for even difficult wounds. There were base hospitals and



Figure 3
Aid Station and Ambulance in World War I.

convalescent facilities both on the French coast and in England. As the American Army deployed to Europe in 1917-18, hospitals, doctors, nurses, and ambulances went with them.

Wounds were usually contaminated with the mud of the trenches. For this reason, wounded soldiers were routinely given tetanus toxoid. Wound care emphasized debridement of devitalized tissue and thorough cleaning with antiseptic solution (Dakin's solution, to be precise). Aseptic technique was (usually) used in operating rooms, better anesthesia was available. Bowel injuries could be routinely repaired. Intravenous fluids were available, as were blood transfusions (sometimes). Radiography had only been invented some 16 years before, but was deployed on the battlefields by 1914. As an index of how much things had changed, mortality following amputation had been 25% in the American Civil War, and was 5% in World War I. Deaths from wounds dropped, but deaths from disease dropped even further. Far fewer soldiers died of disease as a percentage of total deaths than ever before. And this was despite the influenza epidemic of 1918-19, which claimed many victims at the end of the war.

An example of the greatly improved casualty care was the experience of Robert Graves, a young British officer who would later become one of the premier writers of the century. His open chest injury was so severe that he was triaged to "expectant," and his death reported in the London papers. Yet he survived the injury itself, empyema, and the resulting broncho-pleural fistula. After he was evacuated to England, he placed a notice in the papers to the effect that reports of his death had been much exaggerated.

The First World War claimed nine million soldiers, and at least seven million civilian lives. Civilian estimates vary widely, and the true figure is probably unknowable. In 1918-20, over the course of the influenza epidemic (misnamed the Spanish flu), some 20 to 40 million people died. Half of all American soldier deaths from disease were due to influenza, many in the training camps in the United States itself. The extent to which the war caused the flu epidemic has been debated ever since. But the epidemic probably killed more people than the war.



Figure 4
Aid Station in World Ward I.

Over the interwar years, and by World War II, many medical advances had been incorporated into military medicine. Blood and plasma transfusions, widespread use of intravenous fluids, antibiotics (but limited to penicillin and sulfonamides), endotracheal intubation, thoracic and vascular surgery, and the care of burn wounds. Plastic surgery had received a huge impetus from the World War I treatment of disfiguring wounds, and continued to advance before and during World War II.



This war's casualty lists were huge. There were some 20-25 million combatants killed, and 40-50 million civilians.

Both casualty care systems and public health continued to advance, but these were more a matter of degree than the much more dramatic improvements seen during World War I. (See Figure 5.) However, environments were equally challenging. Tropical environments were particularly difficult. It was a definitely mixed benefit that improved public health and sanitary measures enabled armies to operate in areas that were difficult even to live in. Tropical medicine began to assume a greater role in military medicine. And as always, at the point of the spear, casualties were high, resources limited, and medical support difficult. The many amphibious operations during the war were extremely challenging. Even when the operation was supported with hospital ships, initial care and evacuation offshore was difficult.

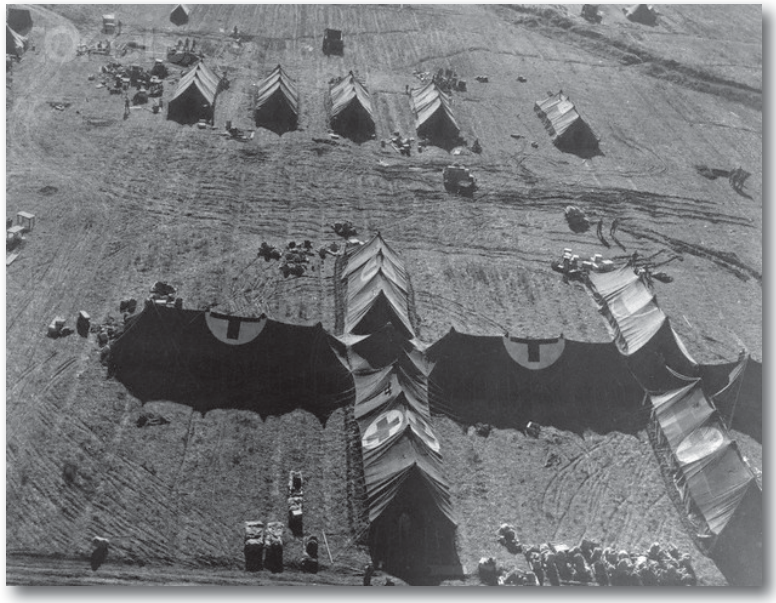


Figure 5
Field Hospital, Italy, World War II.

A major contribution of the 20th century was the widespread recognition and treatment of what we now call post-traumatic stress disorder, or PTSD. It has probably existed back into history. There are case reports from the Civil War, for example. During World War I, it was sometimes called "shell shock," which probably included cases of actual brain damage. More often soldiers suffering from PTSD were diagnosed as "cowardice." Soldiers were shot for it in the British, French, German, Austrian, and Russian armies. As the war dragged on, it became better recognized, but its treatment varied widely. The Russians tried to treat near the front lines, sending the soldiers back to their units as early as feasible. We adopted that practice, and in fact, armies today still treat psychiatric casualties this way. What may seem heartless, actually proved to be the most effective way to treat PTSD and to prevent long term sequelae. The recognition of PTSD as a psychiatric disease of war was not firmly established until World War II. They called it "combat fatigue." But whatever they called it, they recognized it and treated it.

Both the Korean and Vietnam wars proved to be severe challenges to the medical system, the former for cold weather operations, and the latter for tropical and jungle warfare. The medical services gradually adapted to these challenges. By the time of the Vietnam war, for example, operations could be done in contained, air-conditioned operating theaters that were containerized so as to be moved close to the battlefield. (See Figure 6.) Helicopter evacuation supplemented ground ambulances, and air transport replaced hospital trains. The system of progressive levels of casualty care has turned into doctrine, and remains the guiding principle for casualty care.

Operation during the 40 years since Vietnam have produced far fewer casualties, yet have challenged the military medical services in different ways. Small unit operations at greater and greater distances have increased reliance on medical corpsmen, who are now trained to at least the level of civilian Emergency Medical Technicians, and often higher. Casualty care and evacuation in a hostile civilian environment, always a problem in warfare, has been made more complex by opponents who refuse to respect the non-combatant status of medical facilities and personnel.

What can we say about military medicine today? Most of us focus on combat casualty care, as has been discussed over the past few paragraphs. And indeed, this is the primary focus of the system. We put huge resources into this, as well we should. The death rate for soldiers who survive long enough to reach medical care today is only a few percent. Overall casualty rates have decreased steadily since the middle ages, even though today's weapons are far more powerful than those our ancestors fired off at one another.



Figure 5
Field Hospital, Oregon, ca 2004.

Yet it is just as important to look at military medicine as a system of disease treatment and prevention. Deaths from disease have dropped far more than deaths from battle. In the Civil War twice as many soldiers died of disease as from battle. In World War I, for the U.S. Army, the numbers were about equal. In World War II, only half as many, and in Vietnam, only one-fifth. These great improvements have come from the disciplines of what we now term "deployment medicine." We have learned, often painfully, that these are as important to the overall health of the military forces as the system of casualty care. Perhaps, from a purely military standpoint, even more so. A soldier ill from disease is removed from the combat strength as surely as one who is wounded. Yet, the illness is usually preventable. Deployment medicine is, in the Army's unique jargon, a "force multiplier."

As we watch combat operations on the nightly news, most of us look at these environments with horror and disgust. Everything looks destroyed, broken down. That's true. In the first place, wars are not usually fought in vacation spots. Even when fighting occurs in pleasant places, they quickly become unpleasant places. Differences in climate aside, one war zone looks much like another. To maintain the health of armed forces, deployment medicine must address many issues. Adverse environments, with heat, dust, sand, wind, and/or cold. Insect-borne diseases such as malaria, yellow fever, and typhus. Food and waterborne diseases, such as cholera and dysentery. Epidemics, such as meningitis and hepatitis. Skin diseases. Parasitic diseases. And above all, the inevitable social breakdown, with civilian suffering, refugees, and the inevitable victimization of the weak by the strong.

There are five basic constraints which deployment medicine must overcome. Resources are always scarce. The environment is always adverse. Populations are usually hostile, if not deadly. Disease is always present, lurking in the corner. And finally, change itself is constant.

War is inhumane, and terrible. Yet, war has always been with us. The 20th century has been a century of war. Future generations will no doubt call it, "The Awful Twentieth Century." But one of our greatest medical accomplishments of the last 100 years, among a host of other accomplishments, is the system of military medicine. Today's military medicine combines combat casualty care with public health. As William Tecumseh Sherman put it, "War is all hell." But we can take pride that we have done and are doing as much as humanly possible to reduce the horrors, and to save those who have been broken on the modern battlefield.

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E-Cigarettes: Safer Than Tobacco?

by Ravi S. Johar, MD



Studies have led the U.S. Preventative Services Task Force to not recommend e-cigs as a smoking-cessation device.

While the President's Forum is often used to discuss large global topics affecting all the physicians in Missouri, it is also used to address a single topic that has wide ranging ramifications. One topic that addresses both these issues is tobacco use either with combustible cigarettes or electronic cigarettes.

This issue has recently come back into the public discussion as St. Louis County has proposed an ordinance restricting purchase of tobacco products to those 21 years of age or older. St. Louis City has indicated that if this is enacted in the county, they will pass the same restrictions in the city. In this respect, St. Louis is fashionably late to the party. It will actually be the seventh city in Missouri to pass this law. Columbia was the first on December 15, 2014. This was followed by Kansas City, Independence, Gladstone, Grandview, and Lee's Summit.

Proponents of similar laws nationally show statistics that teen smoking rates have dropped by up to 50% in cities where this has been enacted. The intent of the law is not just to discourage smoking among 18-20-year-olds, but even more importantly to prevent smoking in the younger teenagers, the 13-, 14-, 15-year-olds that have older teenagers as friends. This young group often does not have 21-year-olds as friends that would be willing to buy cigarettes for them, but does have 18-year-olds that might.

I have listened to the public debate on this issue, and am encouraged by the excellent information and facts being discussed about the risk of combustible cigarettes. I am, however, dismayed by the rhetoric and misrepresentation of the risks of e-cigarettes and "vaping."

Voices have been raised claiming that vaping is safe and should be exempted from the Tobacco 21 (T-21) bill. Claims are also made that vaping is non-addictive and that it is not being marketed to children and adolescents. In addition, it



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has been argued that e-cigarettes are "safer" than tobacco and do not contain "harmful" ingredients, and finally that e-cigs help people to stop smoking conventional cigarettes.

As the President of the MSMA, I have the privilege of talking to physicians throughout the state that take care of patients who are suffering the effects of tobacco as well as e-cigarettes. I have had the opportunity to hear from these physicians as well as organizations they are members of.

As physicians, we are trained to evaluate facts and tune out the rhetoric. When one reads the available medical studies, it becomes very obvious that the arguments of the proponents of those wanting to exclude e-cigarettes from this bill are simply not true.

A study from the University of North Carolina at Chapel Hill linked e-cigarettes to a host of medical risks. One arm of that study showed that 53 genes that are associated with immune response (the body's ability to fight infection) were significantly diminished.

One ingredient that was incredibly suppressive of immune gene was Cinnamaldehyde (a form of formaldehyde) which is the by-product of the cinnamon flavoring in e-cigs. These innocuous flavorings actually produce toxic substances which could, in large enough quantities, be fatal.

The e-cig proponents report that their cigarettes do not have nicotine which makes them "safer." However, a study by New York University's Langone Medical Center showed that while nicotine-laced vapors affected over 148 genes in the brain that led to significant behavioral changes, the non-nicotine vapors actually affect a whopping 830 genes in the same area. Almost seven times worse. In fact, some of the behavioral changes were similar to those seen with mental illness.

Yet another study at the University of Louisville in Kentucky showed that cigarette smoking showed evidence of atherosclerosis or heart disease, but that e-cigarettes were even more prone to cause cardiovascular plaque leading to heart attacks and severe cardiovascular problems.

These are only a few of the increasing number of studies showing very serious concerns with e-cigarettes. In fact, it is these concerns that have led the FDA to begin regulating the nicotine and contents in e-cigarettes.

A survey by the Center for Environmental Health of 97 different e-cig products showed the chemical acetaldehyde to be present. Acetaldehyde is associated with asthma and cancer. In addition, they found lead, cadmium, nickel, tin, and other heavy metals that are associated with nervous-system and respiratory problems.

A final argument of the pro e-cigarette lobby is that e-cigarettes help people to stop smoking; unfortunately, again, the studies do not back this argument.

A study showed no difference between e-cigs and nicotine patches in helping people to stop smoking. Another study actually found that teenagers who smoke and vape tend to actually smoke more conventional cigarettes than those who smoke and don't use e-cigs.

In fact, these studies have led the U.S. Preventative Services Task Force to not recommend e-cigs as a smoking-cessation device.

To sum it up, as a physician there is simply no reason to exempt e-cigarettes and vaping from a very well thought out and comprehensive bill.

I am proud that the Missouri State Medical Association, after a spirited but cordial debate, voted to support T-21 on a statewide basis and that we are on record supporting tobacco control efforts wherever we can be helpful. **MM**

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MSMA Members in the News

Read more about what our members are doing at www.facebook.com/momedical

Missouri Medicine announces a new member of its Editorial Board. Board members are selected on the basis of exceptional professional accomplishment and expertise in their specialty.



Gary G. Singer, MD, MSMA member since 2005, is the new Nephrology board member. Dr. Singer is Assistant Professor of Clinical Medicine, Washington University School of Medicine, St. Louis, Mo., and founding partner of Midwest Nephrology Associates in St. Peters, Mo.



The Adrian Community Library has been hosting Story Time and Crafts, with John Bustle, MD, talking to children about doctor visits, vaccines, and articles used when a child is sick. Dr. Bustle has been an MSMA member since 2010. (Photo courtesy of The Adrian Messenger)



Danielle Carron, MD, joined MSMA as a young physician in 2015. We wish her all the best in her recent practice move to Saint Francis Healthcare System in Farmington.



An MSMA member since 2004, Marsha Fisher, MD, of St. Louis has been named medical director for Anthem Blue Cross and Blue Shield in Missouri.



Wesley Frevert, MD, has joined Rockhill Orthopaedics in Kansas City. His father practices there, too, and they have been members of MSMA for a combined total of 25 years.



A new MSMA member this year, Daut Gjoni, MD, has expanded his services from Cameron into Lathrop.



MSMA member since 1988, Stephen Halpin, MD, has been honored by Beth Haven Nursing Home in Hannibal for his commitment to healing, touching lives, and providing quality health care.



Brett Hosley, DO, recently joined Hannibal Regional Medical Group as medical director for inpatient rehabilitation, and has been an MSMA member for 25 years.



MSMA wishes to congratulate James B. Kelly, Jr., MD, of Kansas City, for his appointment to the State Board of Registration for the Healing Arts by Governor Jay Nixon. Dr. Kelly has been an MSMA member since 1993.



Christopher Montgomery, MD, was chosen to speak before the ribbon cutting ceremony of Saint Francis Health Center in Dexter on July 22, and he's been an MSMA member since 2006.



Mohammad Mozayen, MD, is a new MSMA member this year, and also the first physician to treat chemotherapy patients at Carroll County Memorial Hospital.



Cory Offutt, MD, has been an innovative force in MSMA since 2009 as an officer in the medical student section and a continued member through his residency. He set up practice this summer in Mountain Grove with Texas County Memorial Hospital.



An MSMA for the past 35 years, Randy Tobler, MD, has been recognized as a 2016 Outstanding Advisor by Indian Hills Community College. His work with Midwest Ambassadors for the Culinary Arts is sure to be a huge success as well.



Luke Weaver, MD, has been an MSMA member since he was a medical student at KCU in 2012. He is an inspiration to many, as a cancer survivor, and for recently joining the staff of the very same team of physicians in St. Louis who once treated him, to complete his medical residency.



One of the first people to walk a lap on the new cardiac rehabilitation track at Golden Valley Memorial Hospital in Clinton is an MSMA member since 1977, Gus Wetzel, MD.

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

Someday I'll Complete My Bucket List

Enjoyed your essay on your "Bucket List" in the January/February 2016 issue. Yes, we should all "Do it now." It reminded me of Denis Waitley's poem about happiness. It's called "Someday Isle," but refers to "Someday I'll…"

There's an Island fantasy
A "Someday I'll" we'll never see
When recession stops, inflation ceases
Our mortgage is paid, our pay increases
That Someday I'll where problems end
Where every piece of mail is from a friend
Where all the nations can go it alone
Where we all retire at forty-one
Playing backgammon in the island sun
Most unhappy people look to tomorrow
To erase this day's hardship and sorrow
They put happiness on lay-away
And struggle through a blue today
But happiness cannot be sought
It can't be earned, it can't be bought
Life's most important revelation
Is that the journey means more than the destination
Happiness is where you are right now
Pushing a pencil or pushing a plow
Going to school or standing in line
Watching and waiting, or tasting the win
If you live in the past you become senile
If you live in the future you're on Someday I'll
The fear of results is procrastination
The joy of today is a celebration
You can save, you can slave, trudging mile after mile
But you'll never set foot on your Someday I'll
When you've paid all your dues and put in your time
Out of nowhere comes another Mt. Everest to climb
From this day forward make it your vow
Take Someday I'll and make it your now!

George Bohigian
MSMA member since 1977
Ophthalmology / St. Louis, Mo.

Distinguished Editorial Service Recognition

Thanks to the MSMA and *Missouri Medicine* for the recently implemented Editorial Board recognition program and service awards. You have done a fantastic job with the Journal and you also deserve the recognition.

Edmond B. Cabbabe, MD
MSMA member since 1979
Plastic Surgery Editorial Board Member, St. Louis

I was pleased to receive correspondence regarding service on *Missouri Medicine.* I was very proud to have the privilege and honor of being the Editor of that fine publication, and again appreciate being recognized in that fashion.

J. Regan Thomas, MD
Head and Neck Surgery, University of Illinois at Chicago, College of Medicine

Correction: Dr. Thomas' term as Editor was incorrectly stated in the May/June 2016 issue. He served as Editor from 1993-2000.

Thank you for the recent letter and certificate recognizing me with the distinguished editorial service for *Missouri Medicine*. It is our privilege to contribute to this fine publication, and the Association's recognition of our effort makes that even more satisfying.

Harvey M. Tettlebaum, JD
Husch Blackwell

Missouri State

TAYLOR HEALTH AND WELLNESS CENTER

Missouri State University is accepting applications for PHYSICIAN, MEDICAL STAFF in the Taylor Health and Wellness Center.

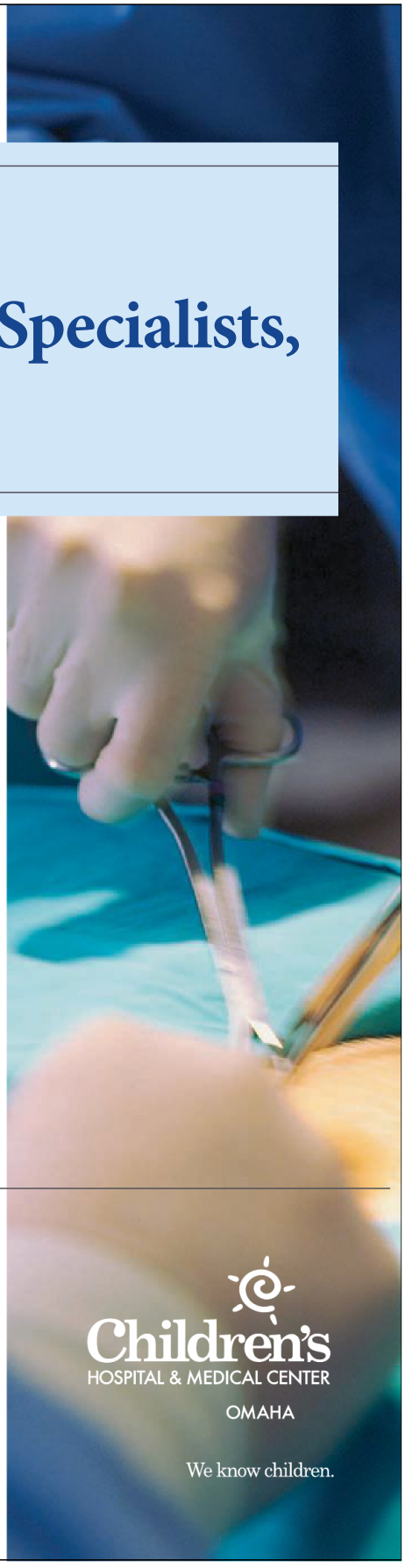
Responsibilities include providing quality health care for the University community in an out-patient, clinic type setting located in the Taylor Health and Wellness Center; functional responsibilities include the diagnosis and treatment of patients using the most current medical knowledge and techniques.

For req. qualifications and app. procedures: https://jobs.missouristate.edu or call (417) 836-4683. Pay Grade: Unclassified. Salary: $135,000\ann.

Successful candidates must be committed to working with diverse student and community populations. Employment will require a criminal background check at University expense.

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The Burden and Benefits of Teenage Life with Type 1 Diabetes

by Amelia G. Cooper & Blake A. Cooper, MD

Being able to manage the trifecta of medicine, exercise, and food is vitally important for teens.

Amelia Cooper: Living With Type 1 Diabetes

Thank you to the editors of *Missouri Medicine* for inviting me to write this article and share my experience as a teenager with type 1 diabetes. By writing about diabetes from a young patient's perspective, I hope I can bring insight based on my experience with what works, what does not, and how to keep motivated.

Diabetes management is a daily burden. By using the most up-to-date medical devices as well as being proactive with diet and exercise, the disease is manageable. Burnout from this rigorous regimen is common and keeping engaged and upbeat is a big issue — especially for teenagers.

On July 13, 2012, at age 12, I was diagnosed with type 1 diabetes (T1D). That summer was very hot in Missouri, but I was drinking even more water than my friends - several large glasses an hour. Without any family history of this chronic disease, the diagnosis was a complete shock to my family and me. While my friends worry about homework, social events, and the latest fashions, I have the added stress of blood-sugar control. Diabetes is unrelenting, yet manageable, and it has altered the shape and trajectory of my adolescence. With tremendous support of friends and family, and by utilizing state-of-the-art technology, I have been able to successfully navigate this stage of my diabetic management. I have also journeyed into scientific research and advocacy with a goal of the betterment of T1D care.

My diagnosis came out of the blue. I was scared and overwhelmed in the hospital during my inpatient stay. While I would not have believed it at the time, I was actually much luckier than most kids in my situation. Kansas City has the nationally famous Children's Mercy Hospital with superb pediatric endocrinologists. My dad is an ophthalmologist, so the new medical jargon of diabetes was easy for him to understand. Perhaps most significantly, my mom fought for me to get an insulin pump and a continuous glucose monitor (CGM) as soon as possible. Most insurance companies make a patient wait six months to get an insulin pump and a CGM, but I received mine within six weeks.

The insulin pump and CGM allowed me to quickly establish a new, relatively manageable routine, and to continue doing well at school. Still, school started only four weeks after my diagnosis, and this was all new, so I had a couple weeks of finger pricks and insulin shots during the school day. (See Figure 1.) While I waited for my CGM and insulin pump, my mom had to check my blood sugar a few times each night and wake me up for correction shots or to drink juice. With an insulin pump and CGM, most of those nightly disturbances are avoided. (See Figure 2.) Having diabetes is exhausting enough without waking up three or four times per night to test and correct a high- or low blood sugar. Also, with the insulin pump, I did not have to endure a shot just to eat a snack with my class. More importantly, the CGM alerted me when my blood sugar started trending up or down, allowing me to adjust my basal rate (hourly dosage of insulin), give myself a correction bolus or eat a piece of candy. The CGM is also vital for my sport, cross-country running. (See Figure 3.) With it, I could plan how much I needed to eat before practice each day and feel confident that I would be alerted to a dangerous low while running. Luckily, my two cross-country coaches were very supportive and interested in helping me do well. They even carried Skittles with them at all times in case I needed a sugar boost.





Amelia Grace Cooper, 16, is a junior at The Pembroke Hill School in Kansas City. Blake A. Cooper, MD, MSMA member since 2004 and vitreoretinal surgeon in private practice in Kansas City.
Contact: blakecooper@kcretina.com



Figure 1
Before Amelia got her insulin pump and CGM, she and her mom had to get up several times during the night to measure her glucose, make medication adjustments and treat lows.



Figure 2
Amelia shows off her CGM which has made her much healthier and happier and able to participate in exercise and athletics.



Figure 3
With a GCM and an insulin pump, Amelia is able to run competitively and recreationally. Her father Blake Cooper, MD, can barely keep pace.

The new technology was not without problems, as it caused me anxiety and distractions at school. The CGM buzzed and beeped throughout the day, in the middle of class and even during tests. I hated drawing that kind of attention to myself and interrupting the teacher. Both the OmniPod and Dexcom sensors sometimes fail. When these mishaps occur, their receivers make a high-pitched alert that frightened me at first. Since my school does not have a nurse, I must go home to change my insulin pump or sensor. We live nearby, so I can dash home from school, change out devices, test my blood sugar, and get back within an hour. With a much better understanding of the disease, the medical devices and the timing of insulin, diabetes management takes about twenty minutes out of my day unless I have a random pump or sensor failure.

Particularly in middle school, my teachers and principal were very involved in my diabetes management. Without a school nurse, their willingness to learn about diabetes and the treatment of low and high blood sugar as well as the use of a glucagon pen were particularly important. My dad met with the middle-school administrators and all six of my teachers and gave them a half-hour lesson on T1D and its management. All of my teachers keep glucose tablets in their desks and my friends and sister carry glucose tab keychains on their backpacks. There are now five kids in my high school (of 400 students) with T1D so I can always ask one of them for help as well. We definitely keep an eye out for each other.

Eighth grade students at my school engage in a one-day "internship." My dad had met people from the blog Diatribe (www.diatribe.org) at an endocrinology conference and was very impressed with their work. Since their offices are in San Francisco, where my grandma lives, my dad and I decided to spend a day with Diatribe. This intelligent group of young professionals is working hard to improve health and education and how it affects diabetics (both type 1 and type 2). Many Diatribe staffers are type 1 diabetics. They are proactive. Only if you have ever experienced a high blood sugar reading followed by the excruciatingly long wait for insulin to take effect, would you understand the "light bulb" moment when I saw someone in the Diatribe office treat his high blood sugar with a quick jog. Diatribe asked me to write for their online publication. I chose "Top Ten Things I Wished My Parents Knew When I Was Diagnosed." It was so exciting to see my name attached to an article in a professional journal. I began to recognize some upside of



Figure 4
Amelia was selected to testify before the Senate Special Committee on Aging about the challenges and rewards of living with T1D.

View testimony here: https://www.c-span.org/video/?c4544517/amelia-coopers-testimony

living with type 1 diabetes and finding my voice.

By this time, I was realizing that I was better off than some of my peers with diabetes. My mom and the moms of my closest friends have learned to cook low-carb meals. My dad runs with me on the weekends and my mom manages my insulin pump and CGM at night. My sister, Lilly, never complains about the absence of bread in our house. Being able to manage the trifecta of medicine, exercise, and food is vitally important for teens. I decided to volunteer as a junior ski instructor for a T1D camp to teach kids how to juggle these things while skiing. Two of my non-diabetic friends came along for the three-day camp. Together, we checked blood sugars in the cold Wisconsin weather. This experience inspired me to investigate how altitude and the cold weather affect glucose management. That same year, during an independent-study week at our school, two of my closest friends and I conducted an experiment that tested the effects of altitude on blood sugar. Our results showed that higher altitudes did affect my blood sugar levels, while those of my non-diabetic peers were not affected at all. I was surprised to find that at sea level, my blood sugar average was extremely close to that of my friends.

These results gave me hope that with proper management, I can be just as healthy as a non-diabetic person. Our experiment and findings were presented as an abstract at the American Diabetes Association (ADA) annual meeting in June 2015. The success of our first experiment prompted my friends and me to conduct another experiment. This time we examined the relationship between stress (cortisol levels) and blood sugar levels. We each wore a CGM during the day of a mid-term exam and again during a relaxed day during winter break. Our results showed that while stress did not affect blood sugars of non-diabetics, stress did elevate my blood sugar considerably. Our stress-cortisol levels were similar during our ski week. This emphasizes the importance of diabetics proactively lowering and managing stress. This second project was selected for a poster presentation at the August 2016 American Academy of Diabetes Educators meeting. (See Sidebar.)

I have become active with the Kansas City Juvenile Diabetes Research Foundation (JDRF). When they opened up applications to attend the Biennial JDRF Children's Congress, I jumped at the chance to apply. When I was selected, I was thrilled for the opportunity to be an advocate for the JDRF in Washington D.C. I was able to experience the intricacies (and frustrations) of government firsthand. To prepare for our congressional meetings, the delegates went through a "Hill Blitz" training session. We learned how to thank members of Congress for renewing the Special Diabetes Program; how to encourage co-sponsorship of certain diabetes bills. On the Hill, I spoke with U.S. Senators Roy Blunt and Claire McCaskill and U.S. Representative Emanuel Cleaver II. I was selected to testify before the Senate Special Committee on Aging to tell my story about the challenges and rewards of young people living with T1D. (See Figure 4.) See my testimony at http://www.c-span.org/video/?c4544517/amelia-coopers-testimony. This experience invigorated me to stay healthy and advocate for medical-research funding.

Unfortunately CGM technology is still not available to Medicare patients. While 95% of private medical insurers cover the costs of CGMs, Medicare lags behind. This is a huge problem for older type 1 diabetics who are at a greater risk of severely low blood sugars. As diabetics age, these low blood-sugar levels are difficult

to sense with the normal physical cues (sweating, shaking, disorientation, etc.). I strongly support the necessity of CGMs for short-term and long-term health in diabetic patients. With continued work, I hope the Medicare CGM Act becomes law.

The T1D Exchange Clinic Registry's mission is to "improve the lives of all people touched by T1D by facilitating better care and accelerating new therapies through a collaborative data collection and sharing network." In May 2015, the Exchange published in Diabetes Care Hemoglobin A1c data from more than 16,000 patients ages 2 to 95. Sadly, my peer group in the Registry did the worst. Adolescents averaged a 9.0% A1c compared with the 9.5% registered by the same age group two decades ago. The American Diabetes Association recommends that adolescents should have an A1c that is lower than 7.5. Even with all that is available, many teenagers still struggle with managing their diabetes.

I am positive and a hard-working optimist. I believe that not only universally available better treatment is in store but eventually a cure is on the horizon for all forms of diabetes.

Blake Cooper, MD: Comments From Amelia's Father

As a vitreoretinal surgeon, I spent my first decade of practice helping patients with advanced complications from diabetic eye disease. I understood the pathophysiology of how and why patients lost their vision. I was even was able to halt the progression or at times reverse to damage of diabetic eye disease. I have been fortunate to practice during a time when anti-VEGF agents and small gauge vitrectomy surgery were developed. This has dramatically improved the outcomes for my diabetic patients.

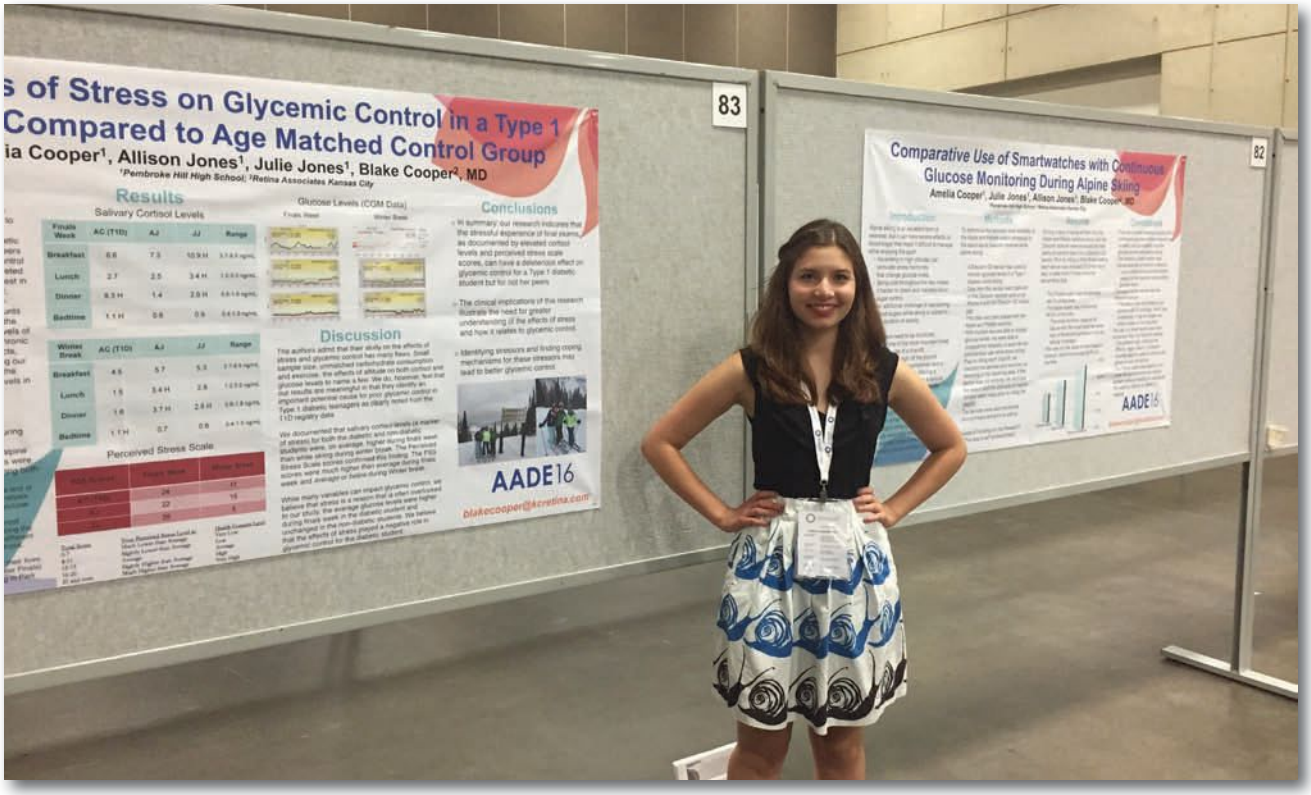
What I did not understand was what it was like for my patients to live with diabetes and how they got to the point of developing visual loss. I will never fully know this but over the last few years caring for my child with T1D, I am beginning to have a better understanding. I truly believe that this has made me a better physician. As such, I want to be able to "fix" my patients. As a parent I want to protect and "fix" the problems my child faces. With this in mind over the last four years, I have realized that "fixing" diabetes means trying to figure out a way to reduce the treatment burden and minimize the complications of hyperglycemia.

To this end I attend several endocrine meetings each year trying to learn as much as possible. I am searching for a cure for my diabetic daughter but also a better understanding of how to help all patients with diabetes. It is truly amazing the progress and change that has occurred since I finished my training. During pharmacology in medical school, I only had three classes of antihyperglycmic agents to learn. Now there are a least 12 different classes of medications with an ever-expanding number of combination drugs. This means better options and outcomes for our patients. I would love nothing more than to never have to treat another patient with diabetic eye disease. Sadly, that day is not in the near future. I do believe that in the future preventing diabetic eye disease will be possible. The future is promising for patients that are able to access the best care we have to offer. However, only about half of the patients that need care are receiving it. Also many diabetics are not invested with adhering to optimal self-care (e.g. weight management, nicotine avoidance, exercise, diet, etc.) We can and must do better. The hardest part is getting state-of-the-art devices and treatments to those that need them. Whether it is our patients or loved ones, it is important to remember that everyone deserves the best possible care, support, and understanding.

Editor's Note

Amelia Cooper, age 16, is the youngest person to author a featured article in *Missouri Medicine*'s 112 year history. Kudos to her for her intelligence, tenacity, optimism, clinical research, and her abiding commitment to make life better and longer for all diabetics.

Amelia is one year younger than Chelsea Grigery, MD, who, in September/October 2005, at age 17 was the youngest published author in the Journal's history with an article on Bacteriocidal Activity of Lizard and Mouse Serum for Borrelia Ionestari, Putative Agent of a Lyme-Like Illness in Missouri, based on a science project in her junior year of high school in Sikeston, Missouri. Miss Grigery went on to graduate from UMKC School of Medicine and a residency in Pediatrics from St. Louis Children's Hospital-Washington University School of Medicine. Dr. Grigery practices in Cape Girardeau, Mo. **MM**



Sixteen-Year-Old Diabetic High School Student Conducts & Presents National Research

Amelia Cooper (see above) age 16, a type 1 diabetic and a student at Pembroke School in Kansas City, is shown with educational posters at the annual meeting of the American Association of Diabetic Educators. She presented three posters highlighting original research done by her, other non-diabetic student collaborators, and her father Blake Cooper, MD, a retina specialist.

One poster was entitled, "The Effects of Stress on Glycemic Control in a Type 1 Diabetic Compared to Age-Matched Control Group." In this study, Amelia and non-diabetic friends measured blood sugars by continuous glucose monitors (CGM). They measured their salivary cortisol levels and completed a Perceived Stress Scale survey to determine their stress levels. Measurements were taken during the week of midterm exams and later during winter break when they went skiing. They concluded that diabetic blood sugars were negativity affected by the stress of finals while non-diabetic blood sugars were not.

"Comparative Use of Smart Watches with Continuous Glucose Monitoring During Alpine Skiing" was the second reported study. Skiing is an excellent form of exercise. It comes with challenges especially for a person with diabetes. The ability to check blood sugar when cold, vasoconstricted, and fatigued is difficult. A CGM makes this task easier. Coupling a GCM and smart watch makes blood sugar available at a glance. The high school students compared the usefulness and reliability of the Pebble and Apple Watch to the Dexcom receiver. They found both smart watches gave accurate results. This was their most popular poster.

The last poster featured research done with her ophthalmologist father. It was titled, "Knowledge Base of a Typical Diabetic Patient Seeking Care in a Vitreoretinal Surgeons Office." They surveyed 100 consecutive type 1 diabetic patients evaluating their level of diabetic knowledge, then compared their results to their levels of diabetic retinopathy. The results identified the highest level of diabetic knowledge among type 1 diabetics who had the disease for less than five years, showed no active signs of diabetic retinopathy, and exercised daily. Higher scores were found in patients with a recent HgA1c between 7-9 than in those who had an HgA1c below 7 or above 9. The survey was also used to direct educational efforts and correct incorrect knowledge in the diabetic survey takers. **MM**

Reducing the Burden of Diabetes Mellitus in the State of Missouri: A Call to Action

by Betty M. Drees, MD & Shumei Yun, MD

Diabetes mellitus places a staggering health and economic burden on communities across the United States, including Missouri. There is much that has been done in the past two decades to understand treatment and prevention of diabetes mellitus.

Background

Diabetes mellitus is a major national health concern due to the burden of disease in terms of prevalence, complications, increased mortality, and cost. The state of Missouri is no exception, with diabetes mellitus being identified as a high priority for prevention and treatment by Missouri legislature and the Missouri Department of Health and Senior Services (DHSS).[1] In the 2014 legislative session, a "Diabetes Care and Control" amendment to the public health bill (SB 716) introduced by Representative Diane Franklin requires MO HealthNet and the DHSS to "collaborate to coordinate goals and benchmarks associated with diabetes."

Furthermore, the bill mandates a report on the status of diabetes care in Missouri every two years. The first of these biannual reports was published in January 2015 and provides a comprehensive review of diabetes care and strategic goals from the DHSS. Prevalence of diabetes varies across individual communities and counties, but Missouri has an overall prevalence of diagnosed diabetes mellitus in adults of 11.1% in 2014.[2]

Over 25% of people with diabetes are not diagnosed[3], and thus the actual prevalence of diabetes in adults in Missouri is about 15%. Furthermore, over a third of adults have prediabetes (blood glucose higher than normal, but not high enough to diagnose diabetes). For the state's six million residents[4], that equates to about 700,000 individuals with diabetes (of whom 170,000 are undiagnosed) and another 1.4 million with prediabetes (of whom 90% or more are unaware of their condition).

This burden of diabetes mellitus and prediabetes in our state is staggering in terms of impact on health and health care costs. This burden is even heavier in some racial and ethnic groups and older age groups. Both diabetes mellitus and prediabetes increase with age, such that a quarter of the population over age 65 has diabetes mellitus, and half have prediabetes. Geographically, the largest relative burden of diabetes and prediabetes is in the southeast area of the state. (See Figure 1.) Prevalence of diagnosed diabetes is over 18% in three counties in this region (Carter, Pemiscot, and Washington), based on the 2011 County-level Study funded by the Missouri Foundation for Health.[5]

Although progression of prediabetes to diabetes mellitus rates varies by age, race/ethnicity, and degree of impaired glucose metabolism, it is estimated that between 15% and 30% will develop diabetes within five years if left untreated. Using a more conservative estimate of 20% progression of prediabetes to diabetes mellitus over 10 years[6], approximately 280,000 adults in Missouri are at high risk for this progression to diabetes mellitus.

Economic Costs

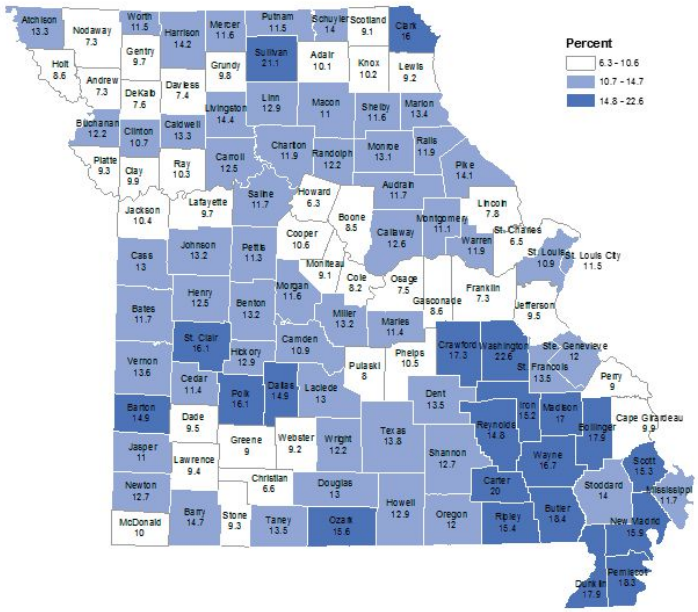
Nationally, the economic burden of diagnosed diabetes mellitus[7] is $245 billion, with $176 billion in direct costs, and an additional $69 billion in indirect costs due to reduced productivity (missed days of work, lower productivity while at work, inability to work, etc.). Health care spending on people with diagnosed diabetes accounts for over one in five of health care dollars. Most of the health care expenditures are on inpatient hospital stays and diabetes medications and supplies. Spending on physician office visits accounts for less than 10% of health care spending on diabetics. The average cost of care





Betty M. Drees, MD, FACP, FACE, (left), MSMA member since 2000 and *Missouri Medicine* Contributing Editor, is Professor of Medicine and Dean Emerita at the University of Missouri-Kansas City School of Medicine in Kansas City, Missouri. Shumei Yun, MD, PhD, (right), is a State Chronic Disease Epidemiologist, Office of Epidemiology, Missouri Department of Health and Senior Services Jefferson City, Missouri.
Contact: DreesB@umkc.edu

Figure 1
Prevalence of Diabetes in Missouri Counties, 2011 (5)
County-Level Study funded by the Missouri Foundation for Health
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for an individual with diabetes is over twice that of one without diabetes.

The cost of care for people with diagnosed diabetes is only part of the cost of elevated blood glucose.[8] Individuals with undiagnosed diabetes, prediabetes, and gestational diabetes also have increased direct and indirect costs. Nationally, in 2012, the annual burden of excess cost averaged $10,970 per person for those diagnosed with diabetes, $5,800 for those with gestational diabetes, $4,030 for those with undiagnosed diabetes, and $510 for those with prediabetes. This makes the total annual cost of care for elevated blood sugar $322 billion ($244 billion direct costs and $78 billion indirect costs), which is $77 billion over the excess cost of care for just those with diagnosed diabetes. Part of this additional cost is due to the fact that complications of elevated glucose, especially cardiovascular complications, start at glucose levels below the threshold for diagnosis of diabetes.[9] The estimated total excess costs of care for people with elevated glucose levels in Missouri is just over $5.9 billion. (See Table 1.)[8]

In regard to the health complications of diabetes mellitus, the microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (stroke and myocardial infarction) complications are well known. Lower extremity amputations result from a combination of microvascular and macrovascular processes. Diabetes mellitus is present in over half of the adults who have non-traumatic lower extremity amputations, and is the primary cause of nearly half of new cases of renal failure.[3] Rates of myocardial infarctions, strokes, and death from cardiovascular disease are one-and-a-half to two times more common in people with diabetes mellitus than those without. Diabetes mellitus is the seventh leading cause of death, both nationally and locally[10], but is likely underreported on death certificates as an underlying cause to mortality. Cause of death[11] is more likely to be hyperglycemia crisis (i.e. ketoacidosis) or hypoglycemia in type 1 diabetes (T1D), and more likely to be due to cardiovascular disease[12] in type 2 diabetes (T2D). Individuals with T2D have a high prevalence of co-morbidities that contribute to cardiovascular morbidity and mortality, specifically hypertension, hyperlipidemia, and tobacco use. Seventy-one percent of adult diabetics have elevated blood pressure and 65% have hyperlipidemia.[3] Hypertension management deserves special mention, since it is a contributing cause to both microvascular and macrovascular complications. Hypoglycemia also deserves special mention as it is increasingly recognized and tracked as a complication. Hypoglycemia accounted for over a quarter of a million emergency visits[3] in 2011 and is the major limitation to tight control of glucose levels, especially in individuals on insulin therapy, the very young, the very old, and those with a longer duration of diabetes.[13] Hypoglycemia is suspected in contributing to cardiovascular deaths in older individuals with more severe atherosclerosis.

In Missouri in 2013, diabetes accounted for 42% (857 out of 2,058) of individuals newly diagnosed with end stage renal disease (14), 73% (1,988 out of 4,135) of lower extremity amputations, and 4,135 emergency room visits with hypoglycemia as the principal diagnosis.[1]

Improving Outcomes

Despite the dramatic increase in obesity and T2D over the past 25-30 years[15], there is reason for hope that the burden of diabetes can be effectively addressed in our community. Based on research over the past two to three decades, we have good evidence-based approaches to both prevention of T2D, as well as treatment of T1D and T2D to reduce complications. Much of this research was publicly funded, especially by the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH). The evidence-based practice guidelines that have resulted provide an excellent example of how federally funded research can impact important health issues that affect a large segment of the population. Furthermore, this research spans both population health approaches as well as clinical care.

Table 1
Excess health care costs in Missouri in 2012 due to elevated glucose.

Condition	Direct Costs in Millions	Indirect Costs in Millions
Diagnosed Diabetes Mellitus	$3244	$1,243
Undiagnosed Diabetes Mellitus	$439	$164
Prediabetes	$817	
Gestational Diabetes Mellitus	$20	

Adapted from Dall et al., Diabetes Care, 20148

Medical Care Improvement

In regard to improving clinical care of diabetes, the Diabetes Control and Complications Research Group[16] and the UK Prospective Diabetes Study Group[17] provided definitive evidence that good glucose control reduces the rate of microvascular complications in both T1D and T2D. Despite the strong correlation between elevated glucose levels and cardiovascular disease[12] there is limited evidence that glucose control impacts cardiovascular outcomes, especially in relation to the impact of other risk factor interventions. Lifestyle modification, hypertension management, lipid-lowering therapy, and tobacco cessation are the most critical interventions in reducing cardiovascular morbidity and mortality, and there is good evidence of success in these approaches. Although certainly multifactorial causes are at work, diabetes complications dropped dramatically from 1990 to 2010, especially in acute myocardial infarction, which decreased about 68% among adults in the US.[18] The good news is that implementing standards of care[19] makes a difference in outcomes. Unfortunately, nearly half of adult diabetics[20] are not at treatment goals. Thus, there is significant opportunity to improve care and outcomes even more.

Prevention and Lifestyle Modification

There is also good news in regard to prevention of T2D. Adults at increased risk of T2D and prediabetes can be predicted based on good screening tools, including simple questionnaires from the CDC (http://www.cdc.gov/diabetes/prevention/pdf/prediabetestest.pdf) and the American Diabetes Association (http://www.diabetes.org/are-you-at-risk/diabetes-risk-test/?loc=atrisk-slabnav).

Prediabetes is defined as a glycated hemoglobin of 5.7%-6.4%, a fasting glucose of 100-125 mg/dl, or 2-hour oral glucose tolerance test of 140-199 mg/dl. The National Diabetes Prevention Program (DPP) demonstrated that lifestyle modification can reduce the risk of progression to T2D by 58% through 150 minutes of physical activity weekly and modest weight loss[21] The effect is even more pronounced in older adults, with a 71% reduction in risk in those over age 60. Recent reviews of combined physical activity and diet programs by the Community Preventive Services Task Force for individuals at risk for T2D provide evidence that these programs are both clinically effective[22] and cost effective.[23] The US Preventive Services Task Force (USPSTF)[24] now recommends (Grade B) behavioral counseling on diet and exercise to reduce cardiovascular disease in those at higher risk (including obesity, hypertension, and diabetes). In October 2015, the USPSTF finalized new screening guidelines for prediabetes and T2D; it supports screening for prediabetes and T2D for individuals at high risk[25] http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/screening-for-abnormal-blood-glucose-and-type-2-diabetes). The USPSTF recommendations are of great importance to the clinical practice community, payers, and the public, as they form the basis for the required full coverage of preventive services by private plans under the 2010 Patient Protection and Affordable Care Act.[26] The current list of required coverage for preventive services includes screening for T2D in individuals with hypertension and diet counseling for those at "higher risk for chronic disease." (The full list of required preventive services is available at https://www.healthcare.gov/preventive-care-benefits/.) The median costs of behavioral intervention programs are approximately $500 per person, and vary by location and setting.[23]

The CDC certifies DPP programs that are year-long, intensive behavior modification programs. In the Kansas City area, the YMCA is currently the only CDC-certified DPP provider, with programs available throughout the metropolitan region. The Social Welfare Board provides services at their free clinic in the St. Joseph area. In the St. Louis area, there are three CDC-certified DPP providers, including Community Health-In-Partnership Services, Gateway Region YMCA, and the Community Wellness Project. The contact information of these providers can be found at the CDC website: https://nccd.cdc.gov/DDT_DPRP/Registry.aspx?STATE=MO There are also online or combination in-person/online DPP programs, which can also be found at the CDC website: https://nccd.cdc.gov/DDT_DPRP/City.aspx?STATE=OTH&CITY=OTH

With the increasing evidence of effectiveness of behavioral interventions, an increasing number of payers are covering behavior modification programs for prevention (including the YMCA DPP and other programs), and employers are increasingly providing programs in the workplace and incentives for lifestyle modifications. In March 2016, Health and Human Services Secretary Sylvia M. Burwell announced that Medicare will cover the DPP based on the report of the

Office of the Actuary in the Centers for Medicare & Medicaid Services (CMS) that certified the cost effectiveness of the DPP (https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/ActuarialStudies/Downloads/Diabetes-Prevention-Certification-2016-03-14.pdf). Currently, the State of Montana Medicaid Program covers the National DPP, and many other states are in varying stages of work on getting their Medicaid participants covered.The Missouri Department of Health and Senior Services is working with MO HealthNet Division, Missouri Consolidated Health Care Plan and county and city governments to explore the possibilities to have Medicaid participants, and state, county and city government employees covered.

The CDC and the American Medical Association (AMA) are working together to encourage health care professionals to refer patients with prediabetes to CDC-recognized lifestyle change programs by creating a toolkit to make it easier for health practices to incorporate screening, testing, and referrals. The tool kits can be found at http://www.cdc.gov/diabetes/prevention/pdf/STAT_Toolkit.pdf. In January 2016, the CDC, the AMA, the American Diabetes Association, and the Ad Council jointly launched a national campaign with public service announcements to raise the awareness of prediabetes (http://www.cdc.gov/media/releases/2016/p0121-prediabetes.html). Missouri DHSS also launched a large media campaign to raise awareness of prediabetes and the national DPPs among healthcare providers, people at higher risk for diabetes, and the general public in 2016.

Public Health Impact

Public health departments are increasingly addressing chronic disease prevention and management, including diabetes mellitus. A recent survey of local health departments in Missouri[27] reveals that our local health departments are very engaged in diabetes prevention through implementation of evidence-based practices in nutrition education, access to healthy foods, promotion of physical activity, and workplace initiatives for their own employees. Nutrition counseling deserves special mention with the increasing evidence that drinking sugar-sweetened beverages over time increases risk of T2D independent of obesity.[28] Health departments are also engaged in addressing the up-stream social and environmental factors that influence development of prediabetes, diabetes mellitus, and the related obesity epidemic. There is increasing evidence that the surge in these conditions goes well beyond the individual and is driven by socioecological conditions in communities, workplaces, and schools.[27] Poverty is a predictor of lower health status, and there may be multiple factors in low-income neighborhoods that contribute to obesity and diabetes, but environments that support physical activity may be especially important[24], and simply moving from a neighborhood with a high level of poverty to a lower level of poverty may reduce obesity and diabetes.[29]

The Role of Physicians in a Combined Medical/Public Health Model

Reducing the burden of diabetes in our community will require continuing both public health and clinical approaches.[30] Physicians have a critical role in reducing this burden, both on the clinical side with the care of individual patients to screen, diagnosis and treat both prediabetes and diabetes, but to also engage with health departments, the public, and elected officials on health policy and promotion of neighborhoods and communities with socioecological environments that support health in general. Physicians do embrace their public roles, with one survey indicating that 90% of physicians regard public service as important; the majority participate in public activities; and that they consider their role in socioeconomic issues that affect health as very important.[31] The efforts to reduce tobacco use over the past 50 years are an example of a successful partnership between physicians and public health to address an important health issue.[32] These efforts are continuing, and are especially important in reducing cardiovascular complications, since tobacco use and abnormal glucose are additive in cardiovascular risk.

In Missouri, there are an estimated 2.1 million individuals with diabetes mellitus and prediabetes, combined, including both diagnosed and undiagnosed. Effective diabetes prevention and treatment programs could potentially reduce morbidity and mortality through decreasing risk of complications, as well as prevent progression to diabetes mellitus in the 1.4 million of Missouri adults with prediabetes. The health and economic impact of improving prevention and treatment is profound. The specific actions physicians can take are in screening, treatment, assessment of quality, public health, and policy:

Screening

Patients at high risk for diabetes and prediabetes should be screened. There are effective behavior intervention programs in the community for prevention of progression of prediabetes to diabetes, and there is a good toolkit (Prevent Diabetes STAT) for physicians for screening and referral developed by the CDC and AMA (preventdiabetesstat.org). The behavioral approaches are increasingly available in the community and in the workplace, and are increasingly covered by payers. It is especially important to screen patients with other cardiovascular risk factors, including hypertension, hyperlipidemia, and tobacco use.

Treatment

Each patient with diagnosed diabetes mellitus should have an individualized treatment plan to prevent risk of complications based on evidence-based guidelines. Use of these guidelines and implementation of chronic disease care

strategies to prevent complications have proven to be effective over the past two decades, but there is still ample room to improve quality of care.

Assessment

Quality of care for both individuals and populations of patients should be continually assessed, so that care can be continually improved. Electronic health records and clinical registries can be helpful in assessing quality of care outcomes. Physicians must participate in the development and implementation of appropriate quality measures, and we must evaluate approaches to quality in the context of pragmatic, scalable, and sustainable clinical care.

Public Health

Physicians, health departments, and other community agencies need to partner on access to community services for health, nutrition, and physical activity. The diabetes epidemic and related obesity epidemic cannot be resolved by clinical treatment of individuals alone, and must include meaningful, sustained partnerships with public health and utilization of community resources for broad community lifestyle changes around nutrition and physical activity. Physicians should support and advocate for health departments in their mission to address the socioecological environment for health at the local, state, and national levels.

Policy

Physician participation in policy development is essential and is a key responsibility of physician professionalism. This participation can occur through the legislative process, through work with associations, and through serving as experts. It includes not only direct health policy, but also policy related to economic development, education, transportation, housing, safety, etc. Hospitals, payers, health departments, and the public are our partners in advocating for policies that support healthy communities broadly defined.

Summary

Diabetes mellitus places a staggering health and economic burden on communities across the United States, including Missouri. Based on good evidence from publically and privately funded research, there is much that has been done in the past two decades to understand treatment and prevention of diabetes mellitus. There is also much left to be done to apply that understanding. Physicians are critical to devising and implementing solutions that will work in our own region, and public health departments, employers, hospitals, payers, and the public are eager to work with us toward those solutions.

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Diabetes Update 2016:
What Bartleby the Scrivener Can Teach Us About Diabetes Care

by Clay F. Semenkovich, MD

This series of perspectives is designed to help practitioners evaluate some of the latest glucose management strategies in hopes of easing the hard work of providing diabetes care.



Between 1980 and 2014, the worldwide prevalence of diabetes increased from 4.3% to 9.0% for men and from 5.0% to 7.0% for women.[1] No country had a statistically significant decrease in prevalence during this time frame. About 422 million people in the world now have diabetes, and its current direct annual cost is about $825 billion. Half of all adults with diabetes live in five countries: China, India, the United States, Brazil, and Indonesia. These statistics do not include the large percentage of the population with metabolic syndrome who do not meet the criteria for a diagnosis of diabetes, yet are at risk for diabetes complications. Most of the diabetes burden is due to type 2 diabetes associated with the obesity epidemic, but the prevalence of type 1 diabetes is also increasing for reasons that are unknown.[2]

Pharmaceutical and medical device companies have responded by developing oral agents and injectable peptides with novel mechanisms of action, modified insulin preparations, continuous glucose sensors, and a wide variety of insulin delivery technologies. New approaches have great potential, but keeping up with diabetes management options has become hard work for both patients and providers.

Hard work is perhaps not the best way to ensure compliance, a notion reinforced by a character in a famous short story by Herman Melville, *Bartleby the Scrivener*. Bartleby, a legal secretary, goes through a particularly labor intensive period, and then responds to subsequent requests with "I would prefer not to."

Clinicians hear this or its equivalent today from diabetic patients asked to take another medication, change their glucose-monitoring regimen, alter their diet,



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modify their exercise routine, and reprogram their new insulin delivery device. In this issue, physicians at Washington University present a series of perspectives designed to help practitioners evaluate some of the latest glucose management strategies in hopes of easing the hard work of providing diabetes care.

Diet, exercise, and the generic drug metformin are reasonable initial therapies for most people with type 2 diabetes. However, there is no consensus optimum diet or exercise regimen in diabetes. Metformin, an agent with a still uncertain mechanism of action that may have benefits beyond simple blood sugar control, is sometimes poorly tolerated and often insufficient for reaching treatment goals. SGLT2 (sodium-glucose co-transporter 2) inhibitors, GLP-1 (glucagon like peptide-1) agonists, DPP-4 (dipeptidyl peptidase 4) inhibitors, and new insulin preparations are available to help patients control their diabetes. These new medicines, some like empagliflozin that have unexpected benefits on mortality, are reviewed by Drs. Sarah Bou Malham and Cynthia Herrick.

Despite some limitations, continuous glucose monitoring devices use an implanted catheter to provide glucose information that can decrease hypoglycemia and improve blood sugar control. Insulin pumps employing delivery systems ranging from the simple to the sophisticated are available, and some interface with glucose monitoring devices. Clinical trials are evaluating closed loop systems capable of controlling insulin delivery in response to glucose levels. Drs. Brian Muegge and Garry Tobin present an overview of how these technologies can enhance patient care.

While the prevalence of diabetes continues to increase, visual impairment due to diabetic retinopathy is declining in part because of therapies directed at some of the mechanisms that contribute to microvascular dysfunction. Antagonism of abnormal blood vessel formation and suppression of inflammation act at fairly late stages of diabetic retinopathy but they preserve vision. Drs. Stanford Taylor and Rithwick Rajagopal summarize the underlying rationale and the options available to treat eye disease in diabetes.

Metabolic syndrome, a common disorder that is a strong risk factor for the development of type 2 diabetes, shares clinical features with Cushing's syndrome, an uncommon disorder characterized by central obesity, insulin resistance, and hyperlipidemia. Drs. Kevin Bauerle and Charles Harris address the possibility that metabolic syndrome may represent a form of subclinical glucocorticoid excess and how pharmacologic disruption of glucocorticoid signaling might provide benefits for people with diabetes.

Advances in mechanistic-based treatments for cystic fibrosis, a common genetic disease, have substantially improved survival. In addition to pulmonary complications, patients with cystic fibrosis have pancreatic abnormalities. Because patients with cystic fibrosis live longer, their pancreatic dysfunction now commonly leads to diabetes, which has different clinical manifestations than other forms of diabetes. Drs. Marina Litvin and Schola Nwachukwu review state-of-the-art management for cystic fibrosis related diabetes.

One of the most dreaded complications of diabetes is renal failure. Proteinuria is a marker for renal disease in people with diabetes, but also indicates risk for cardiovascular disease in this population. Optimal management includes appropriate glucose control, blood pressure control through interruption of the renin-angiotensin system, and statin therapy in early stages of kidney disease. Drs. Victoria Bouhairie and Janet McGill provide recommendations for managing diabetic kidney disease including the importance of measuring the urinary albumin-creatinine ratio and estimating the glomerular filtration rate early in the course of disease.

Bartleby the Scrivener, the character in Melville's story, gave up and perished. A major goal of chronic diabetes care should be to support patients through multidisciplinary team approaches so that disease management becomes easy. No one should feel the urge to respond to new diabetes treatment options with, "I would prefer not to."

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New Pharmacologic Agents for Diabetes Treatment

by Sarah Bou Malham, MD & Cynthia J. Herrick, MD

Given the properties of newly available medications for diabetes, there are a number of considerations when choosing an agent for those patients who require therapy in addition to metformin, diet, and lifestyle modification to achieve glycemic goals.




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Abstract

Therapeutic options for diabetes management have expanded dramatically in the last five years. While there continues to be consensus that lifestyle modification aimed at 5-7% weight loss and metformin are the appropriate first line therapies for type 2 diabetes, there are many options for intensification of diabetes management. The American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) have released recent guidelines that prioritize use of the newer classes of medications.[1,2] There are a number of considerations in selecting medications, including risk of hypoglycemia, effect on body weight, adverse event profile, renal function, and cost/insurance coverage. The objective of this article is to discuss mechanism, efficacy, and safety for each new class of medications. We conclude with a quick reference for the use of these medications in primary and specialty care, based on their various attributes and patient and provider preferences.

New Oral Medications and Non-Insulin Injectables

SGLT2 Inhibitors

Mechanism

The sodium-glucose co-transporter 2 (SGLT2) is expressed in the proximal tubule of the kidney and is responsible for 90% of renal glucose reabsorption. Inhibitors of SGLT2 promote urinary excretion of glucose and lower elevated blood glucose levels. SGLT2 inhibitors rarely cause hypoglycemia since their effect is not mediated through beta cell function or increased insulin sensitivity. In addition, SGLT2 inhibitors are reported to decrease blood pressure and weight. [3,4]

Efficacy

SGLT2 inhibitors were first approved by the U.S. Food and Drug Administration (FDA) in 2013 (canaglifozin followed by dapagliflozin and empagliflozin) for patients with type 2 diabetes.

SGLT2 inhibitors compared to placebo have a modest effect on HbA1c ranging from 0.5 to 0.7% reductions.[3, 4]

Empagliflozin recently demonstrated a significant 38% relative risk reduction (RRR) in death from cardiovascular causes (3.7% for treatment vs. 5.9% for placebo), and a 35% RRR in hospitalization for heart failure (2.7% and 4.1%, respectively) in addition to a 32% RRR of death from any cause (5.7% and 8.3%, respectively). No difference was seen in non-fatal MI and non-fatal stroke.[5] These benefits were significant despite a minimal difference in glycemic control between treatment groups. Ongoing outcome trials are underway to determine if these findings represent a class effect. The Canagliflozin cardiovascular assessment

study, CANVAS, completed recruitment in March 2011 and is expected to report in 2017.[6] This study is being reviewed due to a possible increase in amputations, mostly of the toe. DECLARE-TIMI58 is a multicenter randomized double blind, placebo controlled trial that will evaluate the effect of dapagliflozin on the incidence of cardiovascular death, myocardial infarction and ischemic strokes in patients with type 2 diabetes. It is also expected to address safety related questions and will report in 2019. [7]

In addition to the reported cardiovascular benefit, SGLT2 inhibitors decrease weight. Trials with dapagliflozin, canagliflozin and empagliflozin reported a sustained 2 to 3 kg weight loss over 24-52 weeks.[3,4]

Safety

In December 2015, the FDA issued a warning about SGLT2 inhibitors and ketoacidosis based on 73 cases of ketoacidosis and euglycemic ketoacidosis in patients with type 1 or type 2 diabetes treated with SGLT2 inhibitors between March 2013 to May 2015.[8] Serum ketones should be obtained in any patient with nausea, vomiting, or malaise while taking SGLT2 inhibitors, and SGLT2 inhibitors should be discontinued if acidosis is confirmed.[9] These agents have also been associated with genital mycotic infections and urinary tract infections. Vulvovaginal candidiasis was reported in 10 to 15 % of women taking SGLT2 inhibitors.[10] In addition, 19 cases of life-threatening urosepsis and pyelonephritis were reported from March 2013 through October 2014.[8]

Given that these drugs work by inducing an osmotic diuresis, there is concern for dehydration and acute kidney injury. A basic metabolic panel, lipid panel, and blood pressure should be checked at baseline and periodically thereafter. Dosing and adjustments with renal and hepatic impairment are presented in Table 1.

Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists

Mechanism

GLP-1 is an endogenous incretin peptide that is released from intestinal L cells in response to meals. GLP-1 is rapidly inactivated by the enzyme dipeptidyl-peptidase-4 (DPP-4) and cleared by the kidneys. GLP-1 stimulates post meal pancreatic insulin synthesis and insulin secretion in a glucose dependent manner. It also slows gastric emptying,[11] inhibits glucagon release and promotes satiety. GLP-1 receptor agonists are structurally similar to GLP-1 but resist DDP-4 degradation. There are three formulations of these agents that are available as once weekly preparations (exenatide extended release, dulaglutide, albiglutide) and two immediate release preparations (exenatide, liraglutide).

Efficacy

Exenatide was the first GLP-1 receptor agonist to be approved by the FDA and has been available since 2005. GLP-1 receptor agonists reduce HbA1c by around 1% [12] and usually do not cause hypoglycemia in the absence of other therapies that cause hypoglycemia. GLP-1 receptor agonists can also improve satiety and result in weight loss.[13] A systematic review of 17 randomized trials comparing GLP-1 receptor agonists with placebo or insulin glargine, DPP-4 inhibitors, thiazolidinedione or a sulfonylurea demonstrated a 1.5 to 2.5 kg weight loss over 30 weeks with the former. [12] Another systematic review and meta-analysis of 25 trials demonstrated a mean weight loss of 2.8 kg (95% CI -3.4 to -2.3 kg) in patients with diabetes.[13]

In diabetes trials, liraglutide (0.6-1.8 mg daily) was associated with a significant 1.8 to 2.8 kg weight reduction compared to placebo.[14] Conflicting results are reported for weight loss with immediate and extended release exenatide.[15,16,17] Other head-to-head trials with GLP-1 receptor agonists revealed significantly greater reductions in weight with liraglutide than the once-weekly exenatide (0.9 kg difference), albiglutide (1.6 kg difference) or dulaglutide (0.7 kg difference).[18,19,20] Liraglutide 3.0 mg per day was approved for weight management in December 2014.[21]

Safety

Side effects of GLP-1 receptor agonists include nausea, vomiting, and diarrhea.[12] Nausea improves with duration of therapy and dose titration. There is insufficient data to confirm an increased risk of pancreatitis with GLP-1 receptor agonists, but it is prudent not to initiate GLP-1 receptor agonists in patients with history of pancreatitis and to discontinue therapy in patients who develop acute pancreatitis.[22] This class of medications also includes a black box warning regarding C-cell tumors of the thyroid because this complication was seen in rodents, but has not been confirmed in human studies. However, these medications should not be used in those with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2 (MEN2).

Dose titration for these medications is described below and summarized in Table 1.

Short Acting Preparations

Short acting exenatide is packaged in prefilled syringes of either 5 or 10 mcg doses administered subcutaneously (SC) twice daily within one hour before meals. Liraglutide's initial dose is 0.6 mg once daily for one week then 1.2 mg once daily for one week. If blood glucoses remain above target, the dose can be increased to 1.8 mg once daily.

Table 1: Summary of new oral agents and non-insulin injectables

Drug Class	Drug Name	Recommended Dose	Renal/Hepatic Adjustment	Benefits	Adverse Effects
SGLT2 inhibitors	Canagliflozin	100 - 300 mg PO once daily	Do not exceed 100 mg in moderate renal impairment. Do not use with eGFR < 45 ml/min (100mg) or < 60 ml/min (300 mg) No adjustment for hepatic impairment	No hypoglycemia Weight loss ↓Blood pressure ↓CVD events (Empagliflozin)	Genitourinary infections Hypotension Euglycemic DKA
	Dapagliflozin	5-10 mg PO once daily	Do not use with eGFR < 60 ml/min No adjustment for hepatic impairment		
	Empagliflozin	10-25 mg PO once daily	Do not use with eGFR < 45 ml/min No adjustment for hepatic impairment		
GLP-1 agonists	Exenatide	5-10 mcg SC twice daily	Do not use with eGFR < 30 ml/min or end stage renal disease.	No hypoglycemia Weight loss	Acute pancreatitis? Caution with gastroparesis Nausea/vomiting, diarrhea Thyroid C-cell tumor risk in rodents (contraindicated in patients with medullary thyroid carcinoma or MEN2 for all except twice daily exenatide)
	Liraglutide	0.6–1.8 mg SC once daily	No renal or hepatic adjustment but use with caution		
	Exenatide ER	2 mg SC once weekly	Caution: eGFR 30-50 ml/min Avoid use: eGFR < 30ml/min		
	Albiglutide	30-50 mg SC once weekly	No renal or hepatic adjustment but use with caution		
	Dulaglutide	0.75-1.5 mg SC once weekly	No renal or hepatic adjustment but use with caution		
DPP-4 Inhibitors	Sitagliptin	25mg-100mg PO daily	Use 50 mg eGFR 30-49 ml/min Use 25 mg eGFR < 30 ml /min Dose not defined in Child-Pugh class C.	No hypoglycemia No weight gain	Possible increase in heart failure hospital-izations (saxagliptin, alogliptin) Slight increase in naso-pharyngitis Joint pain
	Saxagliptin	2.5-5 mg PO daily	Use 2.5 mg eGFR ≤50 ml/min Hemodialysis: give dose after HD. Not defined dose in peritoneal dialysis. No hepatic adjustment		
	Linagliptin	5 mg PO daily	No renal or hepatic adjustment		
	Alogliptin	6.25-25mg PO daily	12.5mg eGFR 30-59 ml/min 6.25mg eGFR < 30ml/min Child-Pugh Class C: not defined; post-marketing reports of hepatic failure		
Dopamine receptor Agonist	Bromocriptine quick release	0.8-4.8 mg PO daily	No renal or hepatic adjustment but use with caution	Oral administration Well tolerated	Nausea/vomiting, headache, syncope, hypotension

Once Weekly Preparations

Exenatide extended release is dosed at 2 mg SC once weekly, at any time of day and with or without meals. Albiglutide's initial dose is 30 mg once weekly, which can be increased to 50 mg once weekly after six to 8 weeks if glycemic control remains suboptimal. Dulaglutide's initial dose is 0.75 mg once weekly that can be increased to 1.5 mg after six to eight weeks if blood glucose remains above goal. Exenatide extended release and albiglutide require additional preparation before administration. There is no defined laboratory monitoring recommended.

DPP-4 Inhibitors

Mechanism

DPP-4 inhibitors block the DPP-4 enzyme that deactivates multiple incretin peptides including glucose-dependent insulinotropic polypeptide (GIP) and GLP-1. DPP-4 inhibitors thus increase GLP-1 and reduce blood glucose by inhibiting glucagon release and stimulating insulin secretion.

Efficacy

Sitagliptin was first approved in 2006 followed by linagliptin, saxagliptin and alogliptin.

DPP-4 inhibitors reduce HbA1c ~0.5-1%.[23,24] DPP-4 inhibitor monotherapy is well tolerated with no reported effects on body weight or hypoglycemia. These agents are useful in patients with reduced renal function and mild diabetes, a group particularly susceptible to hypoglycemia with other therapies. Dosing and monitoring is reviewed in Table 1.

Safety

These drugs should be avoided in patients with pancreatitis. [25,22] DPP-4 enzyme substrates are ubiquitous, and include mediators of immune function, but adverse effects on immunity were not apparent in short-term clinical trials.[24] A meta-analysis of 18 trials demonstrated no overall increase in infection risk compared with placebo (RR 0.98 95% CI 0.93, 1.05). [26]

A number of trials evaluated the cardiovascular effects of DPP-4 inhibitors, demonstrating no increased risk of adverse cardiovascular events.[27] In 2013, a saxaglitpin cardiovascular outcome randomized controlled trial with a median follow up of two years did not detect an increase or decrease in the rate of ischemic events. There was an increase in the rate of hospitalization for heart failure (3.5% versus 2.8%, hazard ratio 1.27, 95% CI, 1.07 to 1.51; P=0.007), and the FDA has issued a warning.[28] A more recent FDA warning issued April 2016 included saxagliptin and alogliptin with recommendation to discontinue these medications in patients who develop heart failure. Results from the multicenter, randomized, double-blind, placebo-controlled EXAMINE trial, cited by the FDA, found that more patients randomized to the alogliptin group (106/2701, 3.9%) experienced at least one hospitalization for heart failure compared to patients randomized to placebo (89/2679, 3.3%).[29] Another analysis of EXAMINE data in 2015 revealed no increase in hospitalization for heart failure as a first event in the alogliptin group compared with placebo (85/2701 or 3·1% v. 79/2679 or 2·9% taking placebo with a hazard ratio of 1.07, 95% CI 0·79–1·46).[30] The clinical significance of this finding and whether it extends to other DDP-4 inhibitors remains unclear.

Bromocriptine

Bromocriptine is a dopamine agonist used for hyperprolactinemia and treatment of Parkinson's disease. A quick release formulation of bromocriptine is approved for treatment of type 2 diabetes, but the mechanism of action is unclear. Bromocriptine is well tolerated in patients with type 2 diabetes. Common side effects include nausea, vomiting, dizziness and headaches.[31] Bromocriptine has a small effect on glycemic control with a 0.4 to 0.5 % point reduction in HbA1c.[32] Dosing is reviewed in Table 1.

New Insulin Preparations

A rapid acting inhaled insulin and a new ultra-long acting basal insulin are now available. Some insulins are now available in pens in concentrated formulations, allowing the injection of high doses of insulin in smaller volumes to improve absorption. Because of the risk of hypoglycemia, concentrated insulin should be used with extreme caution and preferably in consultation with a diabetes specialist.

Inhaled Technosphere Insulin

In 2014, the FDA approved an inhaled technosphere insulin preparation. Technosphere insulin (TI) is a rapid acting inhaled insulin that provides mealtime coverage, representing an alternative to bolus insulin injections. It is approved for use in both type 1 and type 2 diabetics and used with injected basal insulin.

The peak action is estimated to be 15 minutes, faster than currently available SC rapid acting insulin. For patients requiring mealtime insulin who are averse to injections, this provides a possible alternative; however, there is not a practical method for administering large doses because it comes in cartridges of 4 and 8 units, and is administered via a specialized inhaler.

Major adverse effects include cough and a small reversible decrease in the forced expiratory volume in 1s (FEV1). TI is contraindicated, and carries a black box warning, in patients with chronic lung disease. Treated patients must receive periodic pulmonary function tests. [33,34] There is little clinical experience converting from SC to inhaled insulin, and dosing is approximate (e.g. patients on 5-8 units of rapid acting SC insulin would receive 8 units inhaled insulin), so close monitoring for hypoglycemia is essential.

Insulin Degludec

Insulin degludec is an ultra-long acting insulin that forms a subcutaneous depot of soluble multihexamers from which insulin is slowly and continuously absorbed into the circulation allowing a stable steady state.[35] Insulin degludec has a terminal half-life of more than 25 hours and a duration of action of more than 40 hours.[36, 37]

This may be a good basal insulin choice for patients at higher risk of nocturnal hypoglycemia. In a treat to target non-inferiority trial, insulin degludec was found to be non-inferior to glargine in HbA1c reduction at one year (0.4%

point reduction versus 0.39% point reduction, respectively). Though overall rates of confirmed hypoglycemia were similar between groups, the rate of confirmed nocturnal hypoglycemia was 25% lower with degludec than with glargine (4.41 versus 5.86 episode per patient-year of exposure, p= 0.021).[38] In addition, because of its longer duration of action, insulin degludec can be administered daily at any time of the day with variable injection timing without compromising glycemic control or safety.[39, 40] This characteristic allows for a more flexible schedule that can accommodate individual patient needs. It comes in prefilled pens with two different concentrations: 100 units/mL and 200 units/mL, and the adverse events profile is similar to insulin glargine. The 200 unit/mL pen allows for administration of up to 160 units of insulin in a single injection.

Table 2: Quick Reference for choosing agents for glycemic control intensification

Priority	Drugs to Consider
Weight loss	GLP-1 receptor agonists (Liraglutide>others) SGLT-2 inhibitors
Avoiding weight gain	DPP-IV inhibitors
Avoiding injections	DPP-IV inhibitors SGLT-2 inhibitors Bromocriptine quick release Inhaled insulin
Avoiding hypoglycemia	GLP-1 analogues DPP-IV inhibitors SGLT-2 inhibitors
Avoiding renal adjustment	Linagliptin
CVD risk reduction	Empagliflozin
Maximizing insulin absorption in individuals with high total daily dose	Concentrated insulins (U200, U300, U500)
Minimize cost	This will depend upon insurer formulary Most (including MO Medicaid) cover at least one GLP-1 receptor agonist and DPP-IV inhibitor; SGLT-2 inhibitors covered with additional authorization on MO Medicaid

U300 Insulin Glargine

U300 insulin glargine is a basal insulin that is concentrated at 300 units/mL. The prefilled pen contains 450 units and allows for delivery of the same number of insulin units as U100 insulin glargine but in a smaller volume. However, U300 insulin glargine appears to have a smaller glucose-lowering effect per unit of insulin than U100 glargine.

Efficacy is similar in both glargine preparations. There is conflicting data regarding the incidence of hypoglycemia, with one trial reporting a significantly lower incidence in the U300 insulin glargine group.[41]

Conversion from once-daily U100 insulin glargine to once-daily U300 insulin glargine can be 1:1. However, a higher daily dosage of U300 insulin glargine will usually be required to achieve the same level of glycemic control as with U100 insulin glargine. When converting from U300 insulin glargine to U100 insulin glargine, a 20% reduction is advised.[42]

U500 Regular Insulin New Delivery Mechanism in Pens

The FDA recently approved a pre-filled device containing the highly concentrated formulation of U500 regular insulin (500 units/ml). This insulin is used to more conveniently treat patients requiring more than 200 units of insulin per day, by using smaller volumes to deliver more insulin. It is dosed with meals two to three times per day and covers mealtime and basal insulin needs. Prior to this approval, U500 regular insulin was only available in vials, administered with either a U100 insulin syringe or a tuberculin syringe. The pen formulation increases convenience and safety for the patient, eliminating the need for dose conversion. A pen contains 1500 units of insulin, allowing the delivery of up to 300 units in a single injection. Consultation with a specialist is recommended when prescribing concentrated insulin to avoid dosing errors because inadvertent overdose may result in a serious adverse reaction or life-threatening hypoglycemia. [43]

Conclusions

Given the properties of newly available medications for diabetes, there are a number of considerations when choosing an agent for those patients who require therapy in addition to metformin, diet and lifestyle modification to achieve glycemic goals. Table 2 highlights agents that may be considered for certain clinical priorities. For further detail, both ADA and AACE guidelines provide detailed algorithms for making these selections.

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Disclosure

None reported.

MM

Improving Diabetes Care with Technology and Information Management

by Brian D. Muegge, MD & Garry S. Tobin, MD

From low-tech structured self-monitoring of blood glucose to cutting edge closed loop insulin delivery systems, these approaches hold the potential for patients to achieve improved diabetes control with greater safety.





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Abstract

Patients and physicians in the 21st century require new tools to manage the growing burden of chronic illness. For providers responsible for the care of diabetic patients, developments in information management, real-time health education and feedback, and new approaches to self-monitoring and insulin delivery hold great promise to improve the quality and safety of diabetes care. This article will briefly highlight some of the major developments in the field, and the ways these technologies can be integrated into a typical practice.

A 52-year-old man with type 2 diabetes, hyperlipidemia, and hypertension returns to your office. A glucometer and a smart phone sit on the table at his side. Since his last visit, you've received a few messages from him through the patient portal about elevated fasting blood sugars, asking for your advice. His blood pressure is elevated today, and as you log into his chart the EMR reminds you that he is overdue for a foot exam and a colonoscopy referral. He needs refills on three medications and wants to ask you about a rash. Your next patient will be roomed in 12 minutes.

As clinicians are being asked to manage and prevent chronic illnesses, the scene described above is becoming all too common. For the care of diabetic patients, new approaches are needed that allow interaction and education outside of the traditional office visit. These tools will need to be easy to access and not overburden the provider or the patient. Ideally, these technologies should also improve patient safety and health outcomes. This article presents a number of tools, organized from low-tech solutions to higher tech solutions, which can improve care for diabetic patients in the primary care setting.

Collecting and Using Self-Monitored Blood Glucose Data

How can the health care provider make use of the self-monitored blood glucose (SMBG) data that the patient brings to clinic? How often should patients be asked to check their blood sugars, and how should the clinician access that data and modify treatment plans? Self-monitored blood glucose is clearly important to improve outcomes and decrease complications in patients with type 1 diabetes (T1D) and intensively treated type 2 diabetes (T2D). However, in adults with T2D who are not treated with intensive medication regimens, meta-analyses of trials using SMBG have not shown improvement in clinically meaningful endpoints, and the SMBG is associated with higher financial costs and patient dissatisfaction.[1,2] This is probably due to the somewhat random collection of SMBG data by patients, and the failure to develop a treatment plan that uses the collected information.

A

	Breakfast		Lunch		Dinner		
	Pre	Post	Pre	Post	Pre	Post	Night
Mon	X						
Tues		X					
Wed			X				
Thur				X			
Fri					X		
Sat						X	
Sun							X

B

	Breakfast		Lunch		Dinner		
	Pre	Post	Pre	Post	Pre	Post	Night
Mon	X	X					
Tues			X	X			
Wed					X	X	
Thur	X	X					
Fri			X	X			
Sat					X	X	
Sun							

C

	Breakfast		Lunch		Dinner		
	Pre	Post	Pre	Post	Pre	Post	Night
Mon							
Tues							
Wed	X	X	X	X	X	X	X
Thur	X	X	X	X	X	X	X
Fri	X	X	X	X	X	X	X
Sat							
Sun							

Figure 1
Examples of structured self-monitoring of blood glucose plans for patients not treated with multiple daily injections of insulin.

A) Staggered testing plan.

B) Testing in Pairs plan. Assesses the impact of prandial medications, dietary choices, and activity.

C) 7-point Self-Monitoring plan. Comprehensive monitoring for over short period of time, as used in the STeP trial.

Several studies have shown that the most effective use of SMBG is to link that data into a structured clinical action plan involving the patient and health care provider. The STeP trial was a cluster randomized control trial of 483 insulin naive adults with poorly controlled T2D. The intervention was collection of blood glucose monitoring in a standardized pattern for three days prior to clinic visits, and review of the data with the clinician. Over 12 months of follow-up, there was a small but significant improvement in HbA1c in the intervention arm compared to the control group, and a much higher likelihood of medication change (new diabetes medication or adjustment in dose of existing medication).[3] Patients also reported higher levels of self-confidence and autonomy in diabetes management in the structured self-monitoring arm of the trial.[4] This is just one of many examples of structured glucose collection plans that could be integrated into an office workflow to maximize the utility of information and utilize scarce resources including time and money for both patients and providers. (See Figure 1.)

In the simplest implementation, patients would be asked to bring paper diaries of glucose readings to the office visit. Alternatively, most glucometer manufacturers have readily available software that can be downloaded from the web or installed via CD on an office PC to enable providers to print summarized data from the patient's glucometer. The provider would also need an inexpensive transfer cable, obtained from glucometer manufacturers or an electronics store. This is an easy technological upgrade that can be provided at minimal cost and training, and should assist in improving the quality of the actionable data available at an office visit. Similarly, point of care HbA1c testing is an easy upgrade to provide immediate results during a clinic visit.

Provider and Patient Responses to Blood Glucose Monitoring

How can the patient and primary care provider use blood glucose monitoring to improve glycemic control? Linking the data to (i) real time decision support for the patient, and (ii) an aggregated summary of patient data for the clinician, are promising strategies. Several software approaches have been developed to achieve these goals. The ABACUS trial was a small, randomized controlled trial of adults with poorly controlled DM using multiple dose insulin therapy. The intervention was to provide a bolus dose calculator on the patient's glucometer that automatically recommends an insulin dose based on blood sugar reading and carbohydrate intake. The trial documented improved glycemic control and patient satisfaction.[5] Glucometers that provide this bolus calculation are commercially available (e.g. Accu-Chek Aviva Expert). Many patients are using one of numerous free or inexpensive apps for iPhone or Android that help to record medication administration, glucose logs and diets. Notably, while health behavior applications are popular with patients and frequently recommended by physicians, more than 80% of diabetes applications available for download have no privacy policies. Many actively transmit individual patient data to third parties without obtaining permission from the patient, suggesting against carte blanch recommendations of these tools.[6]

At the level of the health care delivery system, several companies are developing platforms for data collection and analysis. One such commercial platform (WellDoc) was tested in a cluster randomized trial that connected patient generated glucose monitoring with automated text message based responses to blood glucose values, telephonic and web based health coaching, and quarterly panel management reports for the provider. The study demonstrated significant improvement in glycemic control compared to usual standard of care without worsening distress or diabetes symptoms.[7] The technology is now an FDA licensed medical device,

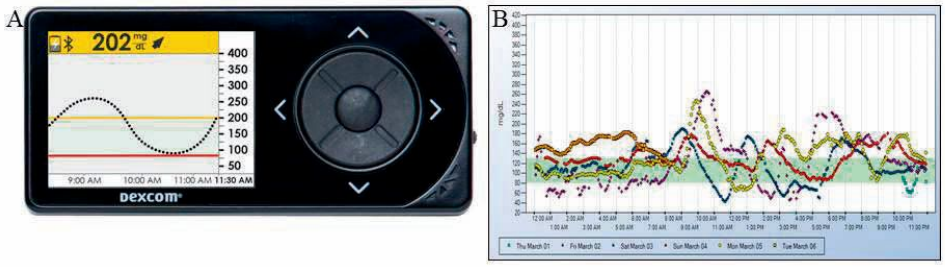


Figure 2
Continuous glucose monitoring.

A) Medtronic Dexcom G5 Receiver. Image used with permission of the company.

B) Sample data download from a CGM.

delivered to patients as a prescription mobile phone application. Another company, Glooko, markets a unified population management system to health plans and clinics. This includes hardware for downloading a wide range of glucometers, remote monitoring and telemedicine interventions for glycemic control, and a provider population management application.

Behavioral Modification and Real Time Feedback

The effective treatment of diabetes begins with patient education. In-person visits with certified diabetes educators have been documented to improve diabetes self-education and glycemic control, but not all patients have access to these sessions. Unfortunately, CDC analysis of insurance claims found that less than 10% of newly diagnosed diabetic patients participated in a diabetes self-management education class within the first year of diagnosis.[8] This unmet need has prompted study about the use of electronic delivery systems to deliver diabetes education. Most of these trials are small, and not surprisingly there is a great deal of heterogeneity in study design and patient population. A Cochran meta-analysis of 16 trials of 3,578 participants using computer-based interventions for diabetes education and self-care documented a small decrease in HgbA1c with computer only interventions, with larger effect in the group using text-messaging.[9] Text-based health coaching has also been studied in pediatric populations; the technology was well received by the participations and led to higher self-reported rates of medication adherence and self-efficacy, but no clear improvement in glycemic control.[10] Not surprisingly, dozens of trials are currently registered in the NIH Clinical trial database testing text message based strategies for behavioral intervention in general and selected populations of diabetics. As an example, the recently completed Mobile Insulin Titration Intervention (MITI) trial showed that patient reported fasting blood sugars with RN review and protocolled weekly adjustment of insulin glargine doses led to a significantly greater number of patients achieving optimal basal insulin doses during the trial with fewer clinic visits and increased patient satisfaction.[11] As discussed above, some of these services will be incorporated into health care systems with added fees covered by the patient and health plans.

Continuous Glucose Monitoring

The recent development of continuous glucose monitoring (CGM) devices has expanded the capacity for self-monitoring. CGM's measure interstitial glucose levels in the subcutaneous tissue via a small implanted catheter that is connected to an electrochemical recorder. The hardware can be discretely worn under clothing. Several challenges persist with the technology: 1) the CGM must be calibrated using a glucometer several times daily, 2) the glucose reading is not as accurate as capillary glucose measurements, and 3) the interstitial fluid lags behind the plasma compartment. Despite these limitations, the use of CGM has been shown to improve glycemic control and to avoid of hypoglycemia more effectively than SMBG alone in adults with T1D. Meta-analyses suggest that benefit from CGM is most pronounced in patients who wear the sensor for more days each week, and for patients who have higher HbA1c levels. (See Figure 2.)[12]

Insulin Pump Delivery and Closed Loop Delivery Systems

Technology also provides novel options to delivery of insulin to the patient. Syringes and pre-loaded pens work well for many patients using once daily or multiple daily injections (MDI), but some patients benefit from continuous subcutaneous insulin injection (CSII).[13] Figure 3 shows several commercially available insulin pumps. The most commonly used insulin pumps on the market use push button control panels to program and

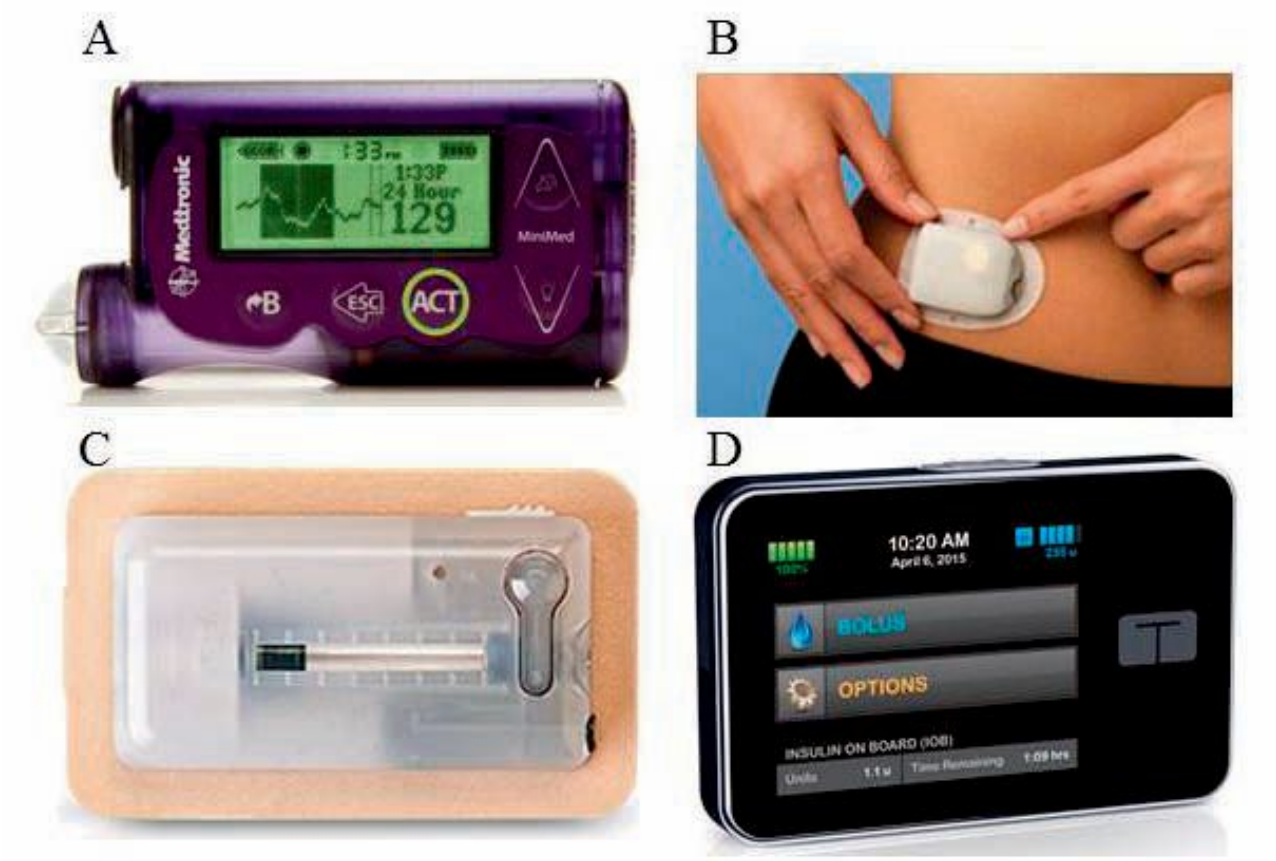


Figure 3
Examples of insulin pumps in clinical use. All images used with permission of manufacturer. A) Medtronic MiniMed 530G. B) Insulet Omnipod. C) Valeritas V-Go. D) Tandem t:slim.

direct basal and bolus delivery from an insulin reservoir (e.g. pumps from Medtronic, Animus). Increasingly, pumps are being designed with a touch screen control interface (e.g. Tandem t:slim), tubeless delivery systems (e.g. Insulet Omnipod), or wireless communication between the pump and the patient's glucometer as well as the CGM device. At the opposite end of the complexity spectrum, a simple pump is being marketed for patients with T2D that delivers basal insulin at one of three pre-set constant basal rates, and allows the user to provide boluses on demand in two unit increments (Valeritas V-Go). Patients receiving MDI insulin therapy who might be candidates for an insulin pump should be referred to an Endocrinologist for full discussion of treatment options.

What is the evidence that insulin pumps improve outcomes compared to MDI? In patients with T1D, meta-analyses have shown better glycemic control (as measured by HbA1c) and lower rates of hypoglycemia with CSII in adults[14] and children[15] when compared with MDI. Whether or not the use of a pump will lead to improvements in long term clinical outcomes compared to optimized MDI is still uncertain. One recent study from Sweden showed that among adults with T1D followed for 6.8 years, patients using insulin pump therapy had a 27% decreased risk of all-cause mortality, a 45% reduction in fatal coronary heart disease, and a 42% decrease in fatal cardiovascular disease.[16] The combination of a CGM device with CSII ("sensory augmented pump therapy") has been shown to have greater efficacy at reducing HbA1c than MDI with SMBG alone (7.5% vs 8.1%), and with greater likelihood of achieving a HbA1c $< 7\%$. These results were achieved without increasing the frequency or severity of hypoglycemic events.[17]

The most exciting technological development on the horizon is the development of closed loop insulin delivery devices. Known by a variety of names such as "artificial pancreas," "bionic pancreas," or "artificial beta cell," these systems use computer algorithms to automatically modulate drug delivery through an insulin pump based on real time data from a continuous glucose monitor.[18, 19] Some

manufacturers are also integrating glucagon delivery systems to treat hypoglycemia in "bihormonal" delivery systems.[20] No device has received FDA approval, but large national trials to establish safety of the devices and algorithms are ongoing. Washington University in St. Louis is one of nine centers expecting to begin enrollment of T1D patients in these trials.

Conclusion

The diabetic patient returns to your clinic for follow-up in six months. He has been collecting blood glucoses in a standardized pattern and uploading to your information management system through a secure website. The website analyzed his trends and suggested a dose increase in his basal insulin based on a pattern of fasting hyperglycemia. Today, his HbA1c today has fallen by 0.5%. Based on his answers to an intake survey, he's been receiving customized text messages every week with links to reduced carbohydrate recipes and reminders to log his pedometer count. His weight is down five pounds, and his blood pressure is now controlled.

Management of diabetes requires a multidisciplinary team approach, centered on the patient, to achieve ideal outcomes. The use of technology and effective information management should be an integral part of the approach, applied in a personalized way to each patient's particular needs. From low-tech structured self-monitoring of blood glucose to cutting edge closed loop insulin delivery systems, these approaches hold the potential for patients to achieve improved diabetes control with greater safety. These strategies may also help caregivers provide higher quality care more efficiently at relatively low cost.

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Disclosures

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Modern Strategies to Save Sight in Diabetes

by Stanford C. Taylor, MD & Rithwick Rajagopal, MD

Over the past three decades, improvements in treating diabetic retinopathy have occurred in parallel with advancements in understanding the pathophysiologic mechanisms responsible for disease onset and progression.





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Abstract

Owing to the global epidemic of obesity, the incidence of diabetes and its complications are rapidly increasing around the world. Yet, visual impairment caused by diabetic retinopathy is paradoxically on the decline. This improvement is due to better understanding of etiologic mechanisms, increased screening, and advent of newer therapies. Here, we discuss salient developments in the comprehension of the root causes of diabetic retinopathy and the molecular mechanisms underlying current treatment approaches.

Introduction

Diabetic retinopathy is a progressive visual disorder that complicates all forms of diabetes mellitus. The disease is staged based on ophthalmoscopic features, and is commonly divided into non-proliferative and proliferative forms. These features involve varying forms of microvascular pathology, ranging from disintegrity of the blood-retina-barrier, vascular proliferation, fibrosis, and generation of tractional force on the neural retina. Macular edema (See Figure 1), and macular ischemia, two major causes of vision loss in diabetes, can occur during any stage of retinopathy.

The incidence of diabetes-related eye disorders continues to grow at alarming rates, despite authentic advances in diabetes screening and care. Such increases are due, in large part, to the growing epidemic of obesity worldwide and the consequent explosion in rates of type 2 diabetes mellitus. Yet, despite these sobering facts, recent studies suggest the current incidence of diabetes-related visual impairment is smaller than that of 25 years ago.[1] A major reason for this improvement is the rapid evolution of diabetic retinopathy management that has occurred over the past ten years. In the following sections, we discuss current therapeutic techniques for diabetic retinopathy and how they curb vision loss in this devastating disease.

Systemic Therapy

Data from several clinical trials suggest a continuous relationship between glycemia and retinopathy progression. In the Diabetes Control and Complications Trial (DCCT), patients with relatively new-onset type 1 diabetes were randomized to intense blood glucose control (target glycated hemoglobin $< 7\%$) or standard control (target $< 8\%$). The relative risk of retinopathy progression was 54% and 76% lower in the intensely-controlled patients compared to controls, among those with or without preexisting disease, respectively.[2] Furthermore, long-term data from the continuation study, Epidemiology of Diabetes Interventions and Complications (EDIC), show that this initial period of intense glucose control had durable effects on retinopathy protection.[3] A linear relationship between average blood glucose levels and retinopathy progression was also seen in patients with type 2 diabetes, as shown in the United Kingdom Prospective Diabetes Study (UKPDS)[4]

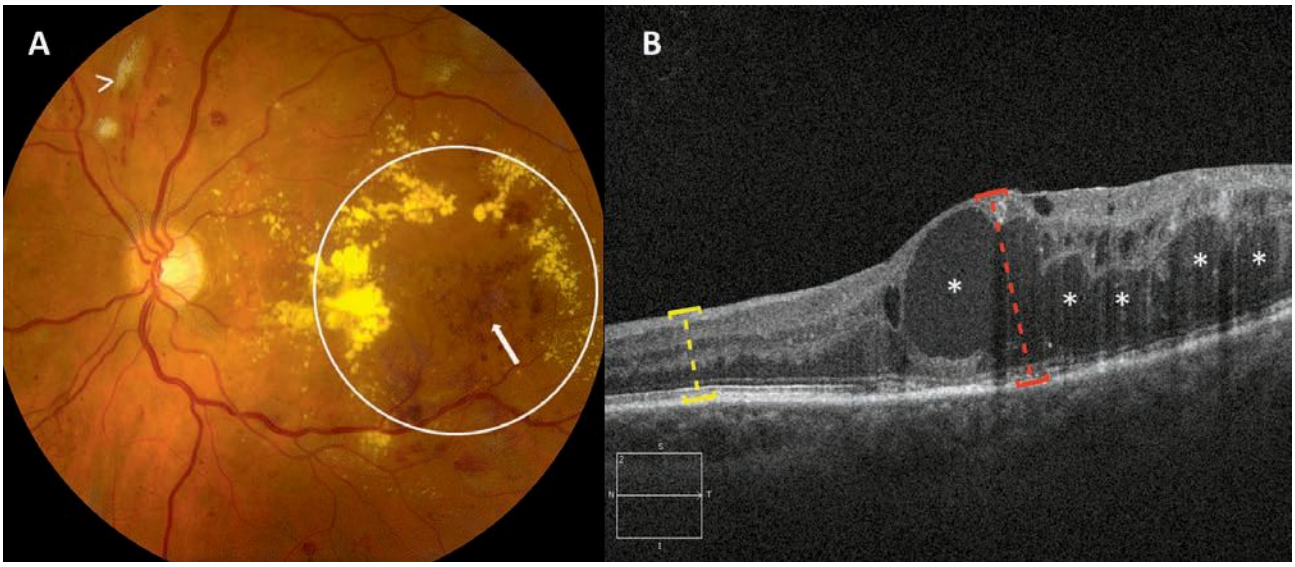


Figure 1
Macula edema from diabetic retinopathy. (A) Color fundus photograph centered on the optic nerve and macula demonstrating center-involving macular edema, demarcated by a ring of hard exudate (white circle). Also pictured are several features of severe non-proliferative diabetic retinopathy, including cotton wool spots (arrowhead) and intraretinal hemorrhage (arrow). (B) Optical coherence tomography (OCT) in a patient with macular edema, showing increased retinal thickness (red bracket) with fluid-filled 'cystoid' spaces (asterisks) compared to a relatively unaffected area (yellow bracket).

The robust effects of glycemic control on ocular health, in both type 1 and type 2 diabetes, have led to an increasingly glucose-centric view of pathogenesis in diabetic retinopathy. Preclinical investigation has linked hyperglycemia to multiple potential mechanisms of disease pathogenesis. For example, activation of protein kinase C (PKC) isoforms leads to increased vascular permeability and angiogenesis in animal models of diabetic retinopathy.[5] Moreover, inhibition of the beta isoform of PKC (PKCβ) with ruboxistaurin ameliorates retinal microvascular complications in animal models and in early phase clinical trials.[6] Hyperglycemia also leads to increased aldose reductase and polyol enzyme activity, resulting in sorbitol production and nicotinamide dinucleotide phosphate (NADPH) depletion. The deficit of NAPDH, a cofactor in the synthesis of nitric oxide, causes decreased nitric oxide production and, consequently, impaired retinal arteriolar vasodilation.[7] Hyperglycemia may increase oxidative stress by promoting formation of advanced glycation end products, which subsequently induce reactive oxygen species.[8] The final common pathway of these intracellular, hyperglycemia-mediated biochemical processes is often retinal capillary endothelium and pericyte apoptosis.

Although these animal and clinical studies strongly argue that glucose homeostasis plays a central role in the development of retinopathy, several lines of data suggest that multiple other causative pathways likely exist. For example, the aldose reductase inhibitor sorbinil failed to prevent visual loss due to diabetic retinopathy in a large clinical trial.[9] The clinical trials mentioned above establish a correlation between blood glucose levels and retinopathy, but do not provide any evidence that blood glucose itself is directly causing the microvascular disease. In fact, there is no clinical evidence allowing us to separate effects of glucose-lowering and direct effects of insulin supplementation or sensitization on retinopathy. Although the retinal endothelium primarily expresses GLUT1 and GLUT3 glucose transporters, which are insulin-independent, several retinal neurons and glia are responsive to insulin and express insulin receptors.[10] Such data raise the possibility that diabetic retinopathy may result from insufficient insulin-dependent signaling in the neural retina.

While intensive metabolic control using glycated hemoglobin levels as the primary index of therapy has clear microvascular benefits, this approach may also cause severe harm. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, patients in the intensive glucose control group (HbA1c $<6\%$) had a higher mortality rate compared to those in the standard control group, a finding that halted the trial prematurely.[11] Additional data from both inpatient and outpatient settings also suggested increased mortality and/or higher incidence of severe hypoglycemia with intensive glucose control.[12] Cumulatively, these studies raise a bona fide concern for increasing mortality with aggressive therapy aimed at lowering blood glucose, and introduce severe limitations to glucose-based therapy in high-risk patients with poor overall health.

Therefore, when brittle patients with progressive but sub-threshold retinopathy cannot tolerate aggressive glucose control, what other treatment choices are available for physicians to minimize or prevent the need for ophthalmic therapy?

A promising adjunct to glucose-based therapy to reduce microvascular disease in diabetes is lipid control. Two independent clinical trials have demonstrated the efficacy of fenofibrate in decreasing the progression of diabetic retinopathy. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, a multicenter, multinational trial based in Australia, fenofibrate treatment reduced the requirement for laser therapy for both macular edema and proliferative diabetic retinopathy.[13] Unexpectedly, this effect was independent of plasma triglyceride concentrations, raising questions about the mechanism by which fenofibrate protects microvessels. These results were corroborated by the ACCORD eye sub-study, which also assessed the role of fenofibrate in protection from diabetic microvascular complications. In ACCORD, fenofibrate reduced the progression of diabetic retinopathy to 6.5% from 10.2% in the placebo group, over a four years period. Surprisingly, fenofibrate therapy decreased the rate of retinopathy progression at a rate similar to intensive glycemic control, as shown in the ACCORD glycemia trial (7.3% and 10.4%, in the intense glycemic control and standard control groups, respectively). As in the FIELD study, the ACCORD eye trial did not show an association between the lipid effects of fenofibrate and the progression of diabetic retinopathy.[14] Despite these data, treatment of diabetic microvascular disease with fibrates has failed to gain widespread traction. Nevertheless, in 2013 Australia became the first nation in the world to approve fenofibrate therapy for the sole indication of preventing retinopathy progression.

There are several potential ways that fenofibrate may shelter the retina from diabetes-induced damage. The drug is a potent ligand for peroxisome proliferator-activated receptor alpha (PPARα). In mouse models, fenofibrate prevents development of diabetic retinopathy in a PPARα-dependent manner, and genetic deficiency of PPARα increases susceptibility for diabetic retinopathy.[3,15] PPARα is expressed in multiple retinal cell types, but its retinal targets remain unclear. Fenofibrate may also reconfigure the local lipid landscape of the retina in a manner that protects it from metabolic stress. For example, it alters lipid and triglyceride levels in a PPARα-dependent fashion to produce an environment inhibitory to angiogenesis and inflammation.[16] Fenofibrate may also upregulate ApoA-1, which acts as a reactive oxygen species scavenger and decreases local oxidative stress.[17] These findings are encouraging, but the precise mechanisms by which fenofibrate protects the retina in diabetes are still elusive. While current investigative efforts are focused on direct actions of the drug in the retina, acting through PPARα, an indirect action occurring via modification of circulating lipids may be responsible for its beneficial ophthalmic effect.

Retinal Laser Photocoagulation

For decades, laser photocoagulation was the mainstay of treatment for advanced diabetic retinopathy. Diffusely scattered peripheral retinal treatment (known as pan-retinal photocoagulation) reduces the risk of severe vision loss in eyes with severe non-proliferative diabetic retinopathy and proliferative diabetic retinopathy by 50% compared to untreated eyes.[18] More directed and limited treatment of the macula (known as focal or grid laser photocoagulation) reduces vision loss in patients with macular edema by nearly 50%.[19] Eyes with more advanced vision loss at baseline (poorer than 20/40 ETDRS), are also more likely to have a visual gain of six or more letters with photocoagulation compared to observation only.[19,20]

Although much older than most current therapies for diabetic retinopathy, laser photocoagulation remains the standard against which other therapies are measured. Laser photocoagulation induces a local thermal burn at the site of application, ablating cells in the deep layers of the retina and its supporting epithelium, eventually causing a scar at the treated site. Photocoagulation is thought to improve retinal edema through various actions. For example, it may upregulate the activities of support cells known as the retinal pigment epithelia (RPE), induce proliferation of RPE, or directly promote closure of leaking vascular abnormalities by direct thrombosis. However, evidence to support these proposed mechanisms is lacking. More likely, photocoagulation of all types is effective in diabetic retinopathy because ablation of retinal tissue leads to diminished metabolic demands.

While the efficacy of laser photocoagulation in diabetic retinopathy is well established, this treatment is employed at great expense. Retinal laser treatment is inherently associated with visual loss at the site of application – but the goal of therapy is to spare central vision at the cost of more eccentric vision (akin to amputation of ischemic limbs). Excessive energy used during laser photocoagulation may lead to progressive atrophy around the burn site, even years or decades after treatment. (See Figure 2.) Laser therapy

may also lead to premature presbyopia (farsightedness) and nyctalopia (inability to see in low light), since rod photoreceptors are much more numerous in the peripheral retina.

Anti-inflammatory Agents

Diabetes increases numerous cytokines in the retina, including interleukin-1β, tumor necrosis factor α (TNF-α), intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and angiotensin II.[21] In particular, TNF-α causes retinal injury by promoting angiogenesis, enhancing leukocyte adhesion to endothelial cells, increasing reactive oxygen species, and inducing endothelial cell dysfunction and apoptosis. Furthermore, leukocyte entrapment in retinal vasculature has been implicated as an early finding in the development of retinopathy in animal models.[22] Together, these aberrant inflammatory signals impair the integrity of the blood-retina barrier, thereby promoting diabetic macular edema. Corticosteroids block these signaling pathways by inhibiting arachidonic acid formation and downstream inflammatory cascades. Expression of vascular endothelial growth factor (VEGF), a potent effector of microvascular pathology, is also reduced by corticosteroid administration.[23]

Corticosteroids are effective in reducing macular edema when delivered into the vitreous in bolus doses.[24] Furthermore, periodic intravitreous monotherapy with triamcinolone (at either 1-mg or 4-mg doses) is superior to focal/grid photocoagulation for diabetic macular edema in terms of visual acuity gains among patients who have already had cataract surgery.[25] Intraocular corticosteroids are frequently associated with cataract formation and intraocular pressure rise. Consequently, they are most often used in cases of macular edema refractory to other therapeutic modalities or in patients without glaucoma who have previously undergone cataract extraction.

Extended-release steroid implants for vitreous injection or implantation (including dexamethasone 0.7 mg implant and fluocinolone 0.2 g/day insert) are now also approved for use in diabetic macular edema. The dexamethasone implant delivers a low dose of medication over a period of six months[26] and the fluocinolone insert is active for up to 36 months,[27] which provides an advantage over other therapies that require more frequent administration. At three years follow-up, 22.2% of individuals treated with the 0.7 mg dexamethasone implant experienced greater than 15-letter ETDRS visual acuity improvement compared to 12.0% of patients receiving sham therapy.[26] Similarly, at two years of follow up, 28.7% of patients given the 0.2 g/day fluocinolone insert gained 15 or more ETDRS letters of visual acuity compared to only 16.2% of patients receiving a sham injection.[27] While the use of these agents offers the potential of reducing treatment needs, their higher side effect profile compared to vasogenic antagonists usually relegates them to a second tier treatment modality, albeit one that is highly useful when designing individualized therapy based on specific patient features.

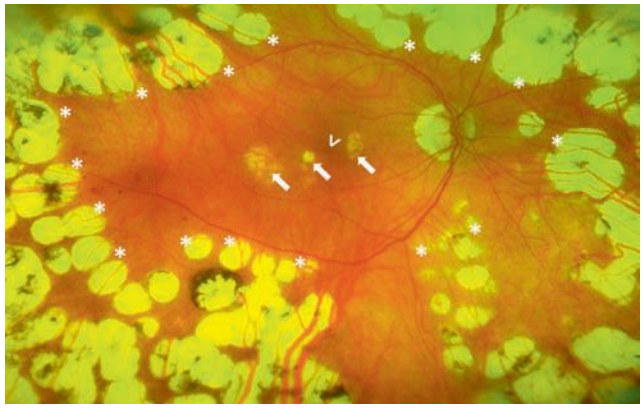


Figure 2
Extensive chorioretinal atrophy from prior laser photocoagulation. Image from a scanning laser ophthalmoscope showing retinal scarring from pan-retinal photocoagulation encroaching on the macula (asterisks) and focal macular laser scarring (arrows) immediately adjacent to the fovea (arrowhead).

Vasogenic Antagonism

A little over ten years ago, the treatment paradigm for diabetic retinopathy was radically altered when a novel class of targeted molecular therapy antagonizing the effects of VEGF was introduced into ophthalmic practice. Multiple retinal disorders are associated with increased VEGF levels, including diabetic retinopathy, suggesting that this molecule plays a central role in their pathogenesis.[28] VEGF disrupts the blood retina barrier in diabetic retinopathy by increasing vascular permeability via activation of PKCβ.[21] This results in phosphorylation of the tight junction protein occludin, which leads to disassembly of tight junctions and increased vascular permeability.[29] Macular edema then ensues. In the development of neovascular disease, VEGF acts as a potent mitogen for the retinal endothelium, upregulates expression of cell adhesion molecules, and orchestrates metalloproteinase-mediated basement membrane proteolysis.[30]

The canonical growth factor signaling network associated with VEGF therefore offers an attractive pathway that can be manipulated to ameliorate retinal disease. Multiple pathway antagonists, including humanized mouse monoclonal antibodies against VEGF (e.g. bevacizumab

and ranibizumab) or a chimeric VEGF receptor decoy (aflibercept), are highly effective in treating diabetic macular edema when injected into the vitreous cavity. While each of these three medications is molecularly distinct, utilization of aflibercept, bevacizumab, and ranibizumab result in similar visual acuity improvements in eyes with mild (visual acuity 20/32 – 20/40) center-involved diabetic macular edema. Such superior visual acuity outcomes are amplified among patients with severe macular fluid burdens at baseline.[31] Further, treatment with any of these agents is associated with better visual outcomes when compared to laser treatment alone.[32] It comes as no surprise then that injectable therapy with VEGF pathway blockers has largely supplanted laser monotherapy as the initial treatment choice for central diabetic macular edema among retina specialists. Injections of VEGF antagonists can be used to treat proliferative diabetic retinopathy and, in many patients, these medications are non-inferior to pan-retinal photocoagulation, which is currently the standard-of-care.[33]

But the enthusiasm for use of VEGF blockers must be bridled by an understanding of their potential adverse effects. A major limitation of all currently used ophthalmic VEGF antagonists is the need for frequent re-treatment, especially early in the course of therapy. Bevacizumab, a full length IgG molecule, has a half-life of approximately 5.6 days in the vitreous. The half-life of ranibizumab, an immunoglobulin fragment with 1/3 of the molecular mass of bevacizumab, is 3.2 days. Aflibercept, which is both larger and more broadly avid for VEGF isoforms compared to anti-VEGF antibodies, has an estimated half-life of 4.8 days.[34] Accordingly, the therapeutic effect of each of these medications lasts no more than six weeks, necessitating frequent re-injection to treat active disease. Multi-year follow-up data involving all three therapies suggest that treatment requirements do in fact decline following the initial year, when study protocols involving combination therapy are strictly followed.[33] Complications of intravitreous injections of anti-VEGF agents are rare. Endophthalmitis, the most visually devastating complication, occurs at a rate of 0.053%.[35] While initial clinical trials raised concerns over slightly increased risks of cardiovascular and hemorrhagic events using these agents, subsequent analyses have failed to substantiate them.[36] A seldom-discussed undesirable effect of chronic VEGF antagonism is the disruption of trophic homeostasis of the retina. VEGF is secreted by multiple retinal cell types, and receptors for VEGF are littered throughout the healthy neural and vascular retina.[37] In long-term studies of VEGF antagonism in age-related macular degeneration, a dose-dependent increase in neuroretinal atrophy is observed.[38]

Although VEGF levels are elevated in the ocular fluids of patients with diabetes and in animal models of diabetic retinopathy, the precise mechanisms of secretion (including which cell types are responsible) are still being delineated.[28] The oxygen-sensitive von Hippel Lindau (VHL) – hypoxia inducible factor alpha (HIF-1α) axis is a primary transcriptional regulator of VEGF.[39] However, several other retinal disorders, including retinal vascular occlusion and retinopathy of prematurity, are also dependent on HIF-1α stabilization with subsequent VEGF release, suggesting that this pathway represents a common final effector for a multitude of pathological insults. In diabetic retinopathy, the precise upstream initiators of this cascade have not yet been identified. Potential mechanisms include altered retinal fuel utilization due to deficient insulin action, neuroretinal inflammation from metabolic insults (as discussed above), direct neuroretinal glucotoxicity or lipotoxicity, endothelial dysfunction as a result of diminished insulin signaling or excess glucose, or miscommunication between the neural retina and the retinal microvasculature, which are normally joined in harmony by a sophisticated neurovascular unit – an entity that is still poorly understood.[40] The future of research into the underlying pathophysiology of diabetic retinopathy offers exciting prospects for discovery related to each of these potential causative pathways.

Conclusion

Over the past three decades, improvements in treating diabetic retinopathy have occurred in parallel with advancements in understanding the pathophysiologic mechanisms responsible for disease onset and progression. Pharmacotherapies, including VEGF pathway inhibitors and glucocorticoids, have provided useful adjuncts to laser treatment. This has resulted in a decreased incidence of diabetes-related vision loss, despite the expanding epidemic of diabetes. Yet, all current ophthalmic therapies are directed at late stages of diabetic retinopathy. Future treatment should be directed towards earlier pathophysiology and may include manipulation of metabolic pathways in the retina, particularly those affected by PPARα signaling.

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Disclosure

None reported.

MM

Glucocorticoids and Diabetes

by Kevin T. Bauerle, MD & Charles Harris, MD

Given the associated increase in mortality and morbidity in these patients, studies are actively underway to better understand the utility of small molecules capable of modulating glucocorticoid signaling.





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Abstract

Glucocorticoids (GCs), stress hormones produced by the adrenal gland, are involved in many pathways in physiology and metabolism including glucose homeostasis and inflammation. Excess GC signaling results in Cushing's syndrome and possibly metabolic syndrome. Diabetes, central adiposity, and hyperlipidemia are components of both syndromes. Here, we discuss the mechanisms of GC action, clinical syndromes of GC excess, modulation of glucose homeostasis by GCs, and future treatments for diabetes based on GC signaling.

Introduction

Type 2 diabetes mellitus (DM) affects nearly ten percent of the population of the United States and is associated with a host of microvascular and macrovascular complications. Healthcare expenditures aimed at the management of diabetes and its complications exceed $245 billion yearly[1-3]. As the incidence of diabetes continues to rise, there has been a major effort to identify novel molecular targets that may be of therapeutic benefit.

Obesity is a strong risk factor for the development of insulin resistance, a process that is central to the underlying pathophysiology of DM. As insulin resistance increases, the pancreatic β-cell is initially able to compensate and augment insulin secretion to maintain euglycemia. Eventually, pancreatic β-cell failure leads to a deficit of insulin and the onset of DM. The underlying mechanisms of insulin resistance continue to be an active area of research. Adipocyte dysfunction in response to chronic nutrient overload has been implicated. In lean individuals, free fatty acids (FFA) are sequestered in the form of triglyceride (TG) during periods of caloric excess and released to meet energy demands by the process of lipolysis. In contrast, the adipocyte of obese individuals is dysfunctional, in large part due to the inflammatory milieu that accumulates in adipose tissue in response to prolonged fuel-storage efforts. This was first observed in mouse models of diet-induced obesity[4] and soon after confirmed in the human condition[5]. The end-result is impaired FFA storage, accumulation of ectopic lipid, and rising serum levels of FFAs and inflammatory cytokines, resulting in systemic insulin resistance[6].

Glucocorticoids (GCs) are stress hormones involved in the regulation of glucose homeostasis, adipocyte development, and inflammation. Clinical syndromes of glucocorticoid excess are characterized by the development of diabetes and visceral adiposity in a majority of cases, and mouse models of localized adipocyte-specific GC excess develop visceral adiposity and insulin resistance[7,8]. In this review, we will further explore the mechanisms regulating glucocorticoid production and metabolism, the clinical and basic science literature supporting a role for glucocorticoids in the pathogenesis of DM, and their potential role as a therapeutic target in DM.

Glucocorticoid Regulation and Action

Glucocorticoids are steroid hormones produced by the adrenal cortex. Circulating levels of glucocorticoids are regulated by the hypothalamic-pituitary-adrenal (HPA) axis, a neuroendocrine feedback circuit, whereby production of corticotropin releasing hormone (CRH) by the hypothalamus drives production of adrenocorticotropic hormone (ACTH), which in turn stimulates the adrenal gland to synthesize cortisol, the primary active GC in humans. The HPA axis is activated in response to stress, circadian rhythms, and other acute stimuli. Circulating GCs feedback at the level of the hypothalamus and pituitary to suppress the production of CRH and ACTH and subsequent synthesis and release of GCs from the adrenals. Only about 5% of circulating cortisol is in the free, bioactive form. The remainder is bound to cortisol-binding globulin (CBG) and albumin[9].

The effects of glucocorticoids are mediated by the glucocorticoid and mineralocorticoid receptors (GR and MR). GCs and mineralocorticoids bind MR with equal affinity, but GCs circulate at much higher concentrations than mineralocorticoids (aldosterone). How then do mineralocorticoid responsive tissues retain sensitivity to the less abundant aldosterone? Tissue-specific regulation of GCs is achieved by 11β-hydroxysteroid dehydrogenases (11βHSD). 11βHSD2 is expressed primarily in mineralocorticoid responsive tissues such as the kidney and catalyzes the inactivation of cortisol to cortisone, preventing excessive activation of MR by GCs and facilitating activation of MR by the less abundant ligand, aldosterone. 11βHSD1, on the other hand, is expressed primarily in metabolically active tissues implicated in the pathophysiology of metabolic syndrome such as liver and adipose, and catalyzes the converse reaction. GCs exert the majority of their effects on glucose metabolism through activation of GR[9,10].

GR is a member of the nuclear hormone receptor family of transcription factors. Binding of GCs to GR results in dissociation of GR from its cytosolic HSP90 complex and promotes translocation to the nucleus where GR regulates the transcription of GR target genes. Activation of transcription is induced by GR binding to GR response elements (GREs) and interaction with transcriptional coactivators. Repression of transcription is induced by GR binding to GREs with subsequent interaction with transcriptional corepressors or by the DNA-independent direct interaction of GR with other transcription factors, a process known as tethering[11].

Clinical and Subclinical Glucocorticoid Excess

Chronic glucocorticoid excess is associated with the development of Cushing's Syndrome (CS). Clinically, this disease is characterized by central adiposity, muscle atrophy, loss of bone mass, hyperpigmented abdominal striae, skin thinning, neuropsychological disturbances, resistant hypertension, and insulin resistance/diabetes. The biochemical diagnosis of CS is often challenging and relies on the confirmed loss of the diurnal variation in cortisol levels (as assessed by midnight salivary cortisol measurements), impaired attenuation of cortisol production in response to exogenous glucocorticoids (as assessed by an overnight dexamethasone suppression test), and/or measurement of frankly elevated 24-hour urinary free cortisol levels[12,13]. Further discussion of the diagnosis of CS is beyond the scope of this review.

GCs have long been used for their anti-inflammatory properties in the treatment of a number of common autoimmune disorders, and long-term exogenous GC therapy continues to be the most common cause of Cushing's syndrome. Cushing's syndrome related to exposure to endogenous GCs may be either ACTH-dependent or -independent. In the vast majority of cases, ACTH-dependent CS is the result of an ACTH-secreting pituitary adenoma. Rarely, cases are the result of an ACTH-secreting neuroendocrine tumor, classically small cell lung cancer. ACTH-independent CS is less common and often secondary to direct production of cortisol by the adrenal gland (adenoma or hyperplasia)[12,13].

Diabetes is a common complication of CS. About 50% of individuals have altered glucose metabolism, classified as impaired fasting glucose, impaired glucose tolerance, or DM, at the time of CS diagnosis. Of these patients, two-thirds have DM[14]. Using fasting hyperglycemia to diagnose DM in patients with CS is limited. In one series, nearly two-thirds of all patients with CS had normal fasting blood glucoses. This finding highlights the effect of GCs in promoting post-prandial glucose excursions and suggests that hemoglobin A1C and oral glucose tolerance testing may be more useful in the diagnosis of GC-induced DM. However, there was a positive correlation between fasting plasma glucose and morning plasma cortisol levels, indicating that derangements in fasting glucose values are likely to be more common in individuals with more severe hypercortisolemia[15]. With exogenous GC therapy, the incidence of diabetes after initiation of GCs, as expected, is proportional to the dose and duration of GC administration. A case-control study demonstrated that patients were more than two times likely to develop new-onset DM after initiation of GC therapy compared to controls, as determined by the need for initiation of either insulin or other oral diabetic therapies. This effect is dose-dependent, as illustrated by odds ratios for the development of diabetes of 3.02, 5.82 and 10.35 for patients receiving the daily equivalent of 50,

Figure 1

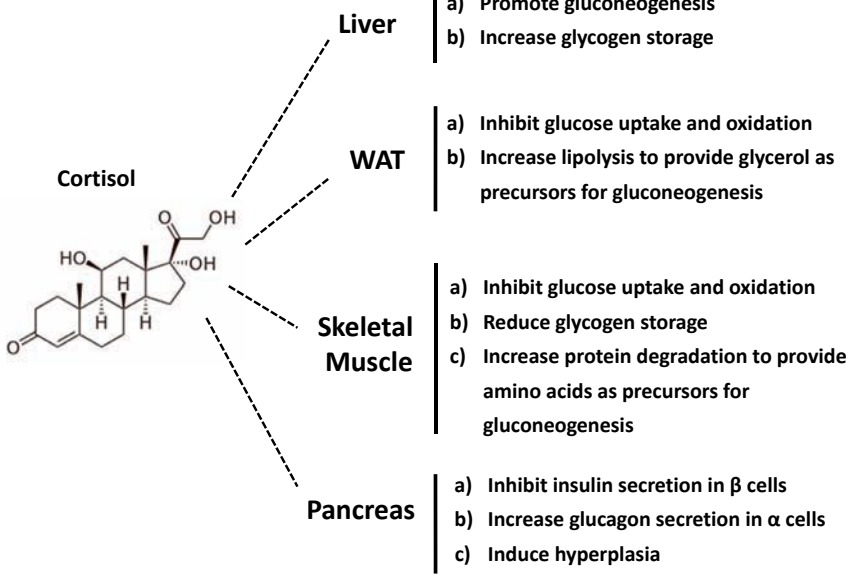


Figure 1
Functions of Glucocorticoids in Peripheral Tissues to Regulate Glucose Homeostasis.
Figure provided by Jen-Chywan Wang and adapted.

100 and greater than 120 mg of hydrocortisone, respectively (a healthy person synthesizes the equivalent of 15 mg hydrocortisone per day)[16,17]. The increased incidence of DM in CS undoubtedly contributes to the two-fold increase in mortality observed in affected patients[12].

As expected, in diabetic patients treated with exogenous glucocorticoids, insulin requirements increase significantly, and glycemic control often deteriorates. This observation holds true across the various etiologies of DM, including patients with type 1 DM, type 2 DM, and cystic fibrosis-related DM[18]. In hospitalized patients treated with at least 40 mg of prednisone, hyperglycemia, as defined by a blood glucose of greater than 200 mg/dl, occurred in 56% of patients, and nearly two-thirds of those patients experienced recurrent hyperglycemia[19]. In a study utilizing continuous glucose monitoring to assess circadian patterns of glycemic control, hyperglycemia occurred more frequently in the afternoon and early evening, providing some rational to the use of increased prandial insulin coverage or the addition of NPH insulin, which has a peak activity at 6-8 hours, to the patient's insulin regimen[18,20,21]. The degree of increase in insulin requirements is difficult to quantify and is dependent on steroid dose and potency. In one study of type 1 diabetic patients receiving 60 mg of prednisone (equivalent to ~240 mg hydrocortisone) daily for 3 days, insulin requirements increased by an average of 70%[22].

CS is a rare condition with an estimated incidence of approximately two individuals per million in the United States. However, the description of metabolic syndrome (MetS)[23], a condition that affects nearly one-quarter of adults and is characterized by obesity, hyperlipidemia, and insulin resistance[24], prompted the realization that MetS may represent a subset of patients with CS or subclinical CS (SCS). SCS is most commonly associated with cortisol-producing adrenal adenomas rather than pituitary Cushing's disease and is characterized by mild hypercortisolism and metabolic abnormalities, including obesity, hypertension, and insulin resistance, without the classical clinical signs of CS. Remarkably, the incidence of clinical hypercortisolism in individuals with diabetes or MetS has been reported to approach 3-10% of those screened[25].

Studies testing the hypothesis that MetS represents a milder form of overt Cushing's syndrome have failed to demonstrate strong associations between circulating cortisol levels and features of MetS. While some have observed subtle changes in HPA axis activity in metabolic syndrome patients, these do not fully explain the etiology of MetS[26]. However, the description of tissue-specific conversion of inactive GCs to active GCs by 11βHSD1 in tissues prone to GC-induced insulin resistance has rejuvenated interest in GCs as the underlying etiology of metabolic syndrome. Indeed, rodent models employing targeted overexpression of 11βHSD1 in the adipocyte demonstrated a phenotype similar to that of metabolic syndrome, characterized by insulin resistance, hyperlipidemia, and visceral adiposity[8]. Furthermore, human studies have shown a correlation between expression levels of adipocyte 11βHSD1 and intra-abdominal fat as well as impaired insulin sensitivity[27]. These findings have led to the development of the so called "dehydrogenase hypothesis" to explain the tissue-specific amplification of GC action as a mechanism behind the development of tissue-specific Cushing's syndrome and systemic metabolic syndrome[28,29].

Regulation of Glucose Metabolism by Glucocorticoids

Glucocorticoids impact all aspects of glucose metabolism by exerting their collective effects on the liver, endocrine pancreas, skeletal muscle, and adipose tissue to

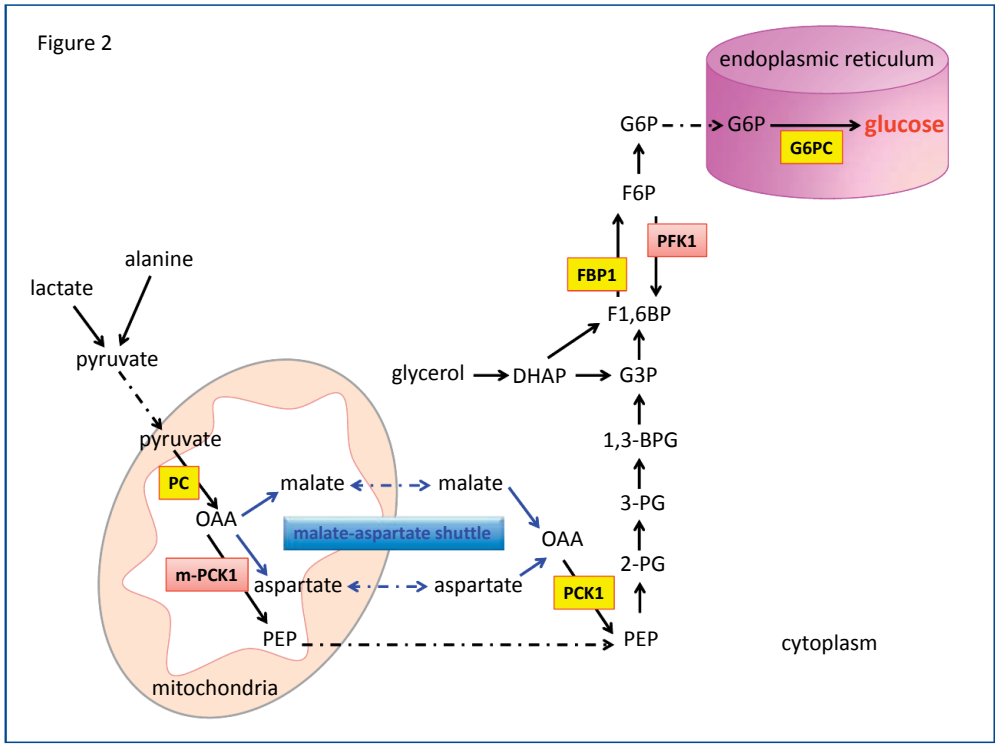
antagonize insulin action (See Figure 1). The consequences of GR activation highlight the catabolic effects of glucocorticoid excess favoring the liberation of energy stores. In the short-term, these effects are critical for adaption to acute stress and illness in an effort to preserve circulating glucose levels and facilitate continued brain function. However, as described above, the long-term consequences of GC excess include hyperglycemia and insulin resistance. The effects of GC excess in each target tissue will be discussed below as it pertains to glucose utilization, gluconeogenesis, glycogen metabolism, and pancreatic endocrine function[30].

Gluconeogenesis occurs primarily in the liver and is the process by which glucose is generated from the non-carbohydrate substrates lactate, glycerol, and amino acids. An in depth discussion of this pathway is beyond the scope of this review, but the key GC-regulated steps will be described (See Figure 2). GCs are critical for the generation of gluconeogenic precursors by promoting lipolysis of triglyceride stores in adipose tissue and protein degradation in muscle, resulting in the production of glycerol and gluconeogenic amino acids, respectively. GCs also positively regulate gluconeogenesis by inducing binding of GR to the glucocorticoid response elements in the promoter region of several genes encoding enzymes involved in gluconeogenesis, including glucose-6-phosphatase and phosphoenolpyruvate carboxykinase, the rate limiting step of gluconeogenesis[30,31].

Regulation of glycogen metabolism by GCs is distinct from gluconeogenesis in that it is tissue-specific. In the liver, GCs induce glycogen formation by increasing the activity of glycogen synthase[30,32]. In contrast, GCs primarily impair insulin-stimulated glycogen synthesis in skeletal muscle by attenuating the activity of glycogen synthase[30,33].

Glucose utilization and oxidation takes place in white adipose tissue and skeletal muscle in response to insulin signaling. The mechanism by which GCs antagonize insulin signaling in the skeletal muscle is, at least in part, dependent on attenuation of insulin-induced GLUT4 translocation to the cell membrane[30,34]. GCs also appear to promote insulin resistance in skeletal muscle by regulation of a number of GR target genes involved in the insulin-signaling cascade, resulting in an apparent post-receptor defect with reduced downstream phosphoninositide-3-kinase and AKT activities[35,36]. GC-induced generation of lipid mediators in the form of fatty acids from the adipocyte and ceramides from the liver may also play a role in the development of systemic insulin resistance as these products accumulate

Figure 2
Gluconeogenic Pathway in Hepatocytes. Gluconeogenic precursors (lactate and alanine) are converted to pyruvate, which enters the mitochondria and is converted to oxaloacetate (OAA) by pyruvate carboxylase. Through the malate-aspartate shuttle, OAA exits the mitochondria to form phosphoenolpyruvate (PEP). OAA may also be converted to PEP directly within the mitochondria. PEP then feeds into the gluconeogenic pathway. In addition, glycerol is metabolized to dihydroxyacetone phosphate (DHAP), which is then converted to fructose-1,6-bisphosphate (F1,6BP). The final product, glucose, is produced in the ER by the glucose-6-phosphatase catalytic subunit (G6PC). The key enzymes are boxed, with GR primary targets shown in yellow. Abbreviations: OAA oxaloacetate, PEP phosphoenolpyruvate, DHAP dihydroxyacetone phosphate, G3P glyceraldehyde-3-phosphate, F1,6BP fructose-1,6-bisphosphate, 2-PG 2-phosphoglycerate, 3-PG 3-phosphoglycerate, 1,3-BPG 1,3-bisphosphoglycerate, G3P glyceraldehyde-3-phosphate, F1,6BP fructose-1,6-bisphosphate, F6P fructose-6-phosphate, and G6P glucose-6-phosphate. Enzyme abbreviations: PC pyruvate carboxylase, m-PCK1 mitochondrial phosphoenolpyruvate carboxykinase, PCK1 cytosolic phosphoenolpyruvate carboxykinase, FBP1 fructose-1,6- bisphosphatase 1, PFK1 phosphofructokinase 1, G6PC glucose-6-phosphatase catalytic subunit.
Figure provided by Jen-Chywan Wang and adapted.



in the liver and skeletal muscle[6,30,37]. The mechanisms contributing to impaired glucose utilization by GCs in the adipocyte are less clear at this time but likely to involve modulation of GLUT4 function and the insulin signaling cascade[30]. GCs are also involved in the differentiation and expansion of adipocyte precursors, a process that may further exacerbate insulin resistance and adipocyte dysfunction[30,38].

In the endocrine pancreas *in vivo*, treatment with GCs results in secondary β cell hyperplasia in an effort to generate sufficient insulin to maintain normoglycemia in the setting of the peripheral insulin resistance in various target tissues[30]. However, studies with isolated islets in culture have demonstrated conflicting results. Direct treatment of isolated islets in culture with GCs induces β cell apoptosis[39]. Glucose-stimulated insulin secretion (GSIS) depends on the influx of plasma glucose via the GLUT2 transporter present on β cells as well as glucokinase activity to generate glucose-6-phosphate (G6P) for entry into the glycolytic cycle. This process results in an increase in the ATP/ADP ratio and drives membrane depolarization in response to closure of ATP-sensitive potassium channels, leading to calcium influx via voltage gated calcium channels and ultimately exocytosis of insulin-containing granules. Notably, GCs impair GSIS on multiple levels[30]. GCs promote the degradation of GLUT2 and reduce expression levels of glucokinase[40,41]. Additionally, the activity of glucose-6-phosphatase is increased, further impairing the entry of G6P into the glycolytic cycle[42]. GCs also enhance repolarization of the β cell by upregulation of the Kv1.5 voltage-gated potassium channel, thus attenuating calcium influx and exocytosis of insulin-containing granules[43]. Indeed, *in vivo* overexpression of GR in the β cell to address the discrepancy between these *in vivo* and *in vitro* findings has demonstrated glucose intolerance and impaired insulin secretion in these transgenic mice[30,44].

Summary and Future Directions

Glucocorticoids play an intricate role in all aspects of glucose metabolism. Our review has focused on mechanisms of GC regulation and signaling, clinical and subclinical syndromes of GC excess, and the physiology of GC-regulated glucose homeostasis. While the utility of GC upregulation during a short-term stressful event remains clear, long-term GC excess, whether endogenous or exogenous, is wrought with complications. Overt clinical GC excess is observed in the setting of CS, while subclinical GC excess may be present in those with metabolic syndrome.

Given the associated increase in mortality and morbidity in these patients, studies are actively underway to better understand the utility of small molecules capable of modulating GC signaling. These agents are of significant interest clinically in the treatment of Cushing's syndrome, insulin resistance/DM, and autoimmune/inflammatory conditions. The development of selective glucocorticoid receptor modulators (SEGRMs) capable of harnessing the anti-inflammatory properties of GCs while avoiding the long-term metabolic consequences remains an attractive concept but has proven difficult in practice because of the overlap that exists between GR transrepression and transactivation in the regulation of these two paradigms[45]. More recently, mifepristone, a GR antagonist, was approved for the treatment of Cushing's syndrome with glucose intolerance/DM in patients refractory to standard surgical management[46]. However, the systemic use of a glucocorticoid antagonist in patients without glucocorticoid excess for the treatment of diabetes is likely to be associated with symptoms of adrenal insufficiency. Consistent with the dehydrogenase hypothesis, liver-specific GR antagonists are in development for the treatment of diabetes. One such compound is a GR antagonist fused to a liver targeting bile acid. Such compounds should reduce hepatic gluconeogenesis without affecting the HPA axis[47]. Another promising approach is the generation of antisense oligonucleotides targeting GR mRNA specifically in the liver[48]. Lastly, the use of 11βHSD1 inhibitors as a means of attenuating GC action at the tissue level continues to hold promise as these agents demonstrate measurable improvements in insulin resistance and blood glucose measurements as well as other indices associated with metabolic syndrome. However, the consequences of the resulting long-term upregulation of the HPA axis and immunomodulatory effects remain unclear[49].

In summary, the mechanisms underlying the relationship between glucocorticoids and diabetes are not fully understood. What remains clear is that GCs are capable of regulating aspects of glucose homeostasis in each target organ by antagonizing the effects of insulin either directly or indirectly. The marked interest in the modulation of GC signaling as a therapeutic tool for diabetes and metabolic syndrome will undoubtedly lead to a better understanding of these complex mechanisms in the years to come as our ability to dissect the complex tissue-specific effects of GCs in the laboratory improve.

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Disclosures

None reported.

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Cystic Fibrosis Related Diabetes: a Unique Challenge in Diabetes Care

by Marina Litvin, MD & Schola Nwachukwu, MD

As patients with cystic fibrosis live longer, they may develop complications of cystic microvascular fibrosis-related diabetes.





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Abstract

Cystic Fibrosis (CF) is a common autosomal recessive disease that affects multiple organs due to a defect in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR). This transporter is present in various organs and tissues, including the airway epithelium, sinuses, pancreas, intestine, biliary tree, the vas deferens, and the sweat ducts, making CF a multi-system disease[1]. As CF patients are living longer, pancreatic function declines and diabetes emerges, further complicating the nutritional status and care of these patients.

Introduction

Cystic fibrosis is the most common autosomal recessive disease among Caucasians, affecting up to 1 person per every 2,000-3,000 live births[2]. Cystic fibrosis also affects Hispanic (1:9,200) and African American (1:10,900) patients, with the lowest prevalence in the Asian Population (1:30,000)[1,2]. CF is becoming more widely diagnosed, and is being diagnosed earlier, due to the advent of newborn screening in the U.S. and other developed countries[3,4]. Similarly, the number of newly recognized cases of CF continues to increase with the appreciation of its variable phenotype, which can be mild at presentation, or even limited to a single organ system[5].

The pathophysiology of CF rests with the CFTR, which functions to regulate pH and ionic balance of secretions. In the lungs, the CFTR is involved in bicarbonate secretion, leading to alkalization of fluid, producing a more bactericidal environment[6]; proper CFTR function also allows to prevent airway mucus from being to thick, to promote proper mucociliary clearance.[56] When the CFTR channel does not function properly, such as in the case of CF, the patient is predisposed to bronchiectasis and frequent infections, and may progress to respiratory failure. In addition, CFTR malfunction can lead to exocrine and endocrine pancreatic insufficiency, malabsorption, intestinal obstruction, sinus diseases, hearing loss, liver diseases and male infertility. Due to the effect on chloride secretion by the defective CFTR in sweat glands, chloride content of sweat is elevated, forming the basis for the diagnostic sweat test.[1]

As therapies for organ dysfunction in CF continue to evolve, patients with CF are living longer. The predicted age of median survival has increased from 32.2 years (95% CI 30.3-34.9) in 1998 to 40.7 years (CI 37.7-44.1) in 2013[7,2]. As patients with CF age, the prevalence of CF related diabetes (CFRD) increases. According to the annual report from the Cystic Fibrosis Foundation Patient Registry, the prevalence of CFRD in patients < 18 years of age is only about 6.5%, but increases to 34.3% in patients greater

than 18 years old, with some series reporting up to 50% prevalence of CFRD in adults[2,8,9]. As CFRD is encountered more frequently in the clinical care of the CF patient, understanding the pathophysiology of CFRD, and the effect of glycemic control on outcomes for patients with CF is paramount. Impaired glycemic tolerance and poor glycemic control in patients with CFRD have been associated with CF exacerbations, worse lung function, lower BMI, and higher mortality[10,11,12,13,14].

Cystic Fibrosis Related Diabetes

Cystic Fibrosis Related Diabetes (CRFD) is a unique disease process, which combines the pathophysiology of type 1 and type 2 diabetes, exhibiting both decreased insulin secretion and increased insulin resistance[15]. The challenges in the treatment of CFRD include dealing with increased caloric requirements for people with CF, resulting in high carbohydrate intake and frequent snacking, which exacerbates the hyperglycemia, as well as increased insulin resistance during times of illness, and the episodic need for glucocorticoid therapy[16,17]. Coexisting glucagon deficiency, increased energy expenditure, altered GI tact motility and absorption further complicate the management of CFRD[18]. Additionally, novel drug therapies correcting and/or potentiating the function of the affected CFTR channel, may influence weight, nutritional status, and insulin sensitivity and secretion[15,19]. Patients with cystic fibrosis may also not view CFRD as a priority, focusing more on other health-related effects of CF, which they may view as more life-limiting[20,21].

CFRD does not occur in all patients with CF. It is more prevalent among CF patients with more severe defects of the CFTR[22,23,24]channel, and is more likely to occur in patients with exocrine pancreatic insufficiency[25,26]. Specifically, patients with CFTR Class I and Class II mutations[24], which lead to defective CFTR synthesis at the endoplasmic reticulum, and defective CFTR trafficking, respectively,[15] are more likely to develop CFRD than patients with more mild genotypes. Additional risk factors for developing CFRD include: female sex, worse pulmonary function, liver dysfunction, glucocorticoid use, and family history of diabetes.[24] Supplemental nutrition/tube feeds and infection can further exacerbate glycemic control[27].

Pancreatic exocrine insufficiency, which is more likely to occur with severe CF genotypes, is a risk factor for development of CFRD and often predates the diagnosis of CFRD[28]. When pancreatic CFTR function is deficient, the altered, bicarbonate-poor, acidic secretions cause pro-enzyme precipitation, obstructing the pancreatic ducts, leading to inflammation, amyloid deposition, fatty infiltration, necrosis and eventual fibrosis and atrophy of the pancreas[15,18,29]. This process eventually leads to insulin deficiency due to decreased β-cell mass. In addition to fibrosis, increased ER stress from misfolding of the CFTR protein, and deficiency of anti-oxidants due to chronic malabsorption, may contribute to the development of CFRD[30].

Immune-mediated destruction of the endocrine pancreas may exacerbate β-cell dysfunction[15]. Clinically, weight loss and worsening lung function are seen before the development of overt CFRD. This process may reflect the imbalance of pro-inflammatory cytokines (IL-17 secreted by T-helper 17 lymphocytes) that leads to both β-cell dysfunction and decreased lung function[31]. Underlying vitamin D deficiency from chronic malabsorption may contribute to the immune dysfunction adversely affecting the pancreatic β-cell[32].

It is unlikely that fibrosis of the pancreas is the only pathogenic mechanism in CFRD. In a well-characterized ferret model of CFRD, the absence of functional CFTR channels causes abnormalities in glucose tolerance and first phase insulin secretion before these animals develop overt pathology (fibrosis) of the pancreas[33]. This suggests that intrinsic abnormalities in insulin secretion occur early in CF, likely due to altered insulin secretion caused by defective CFTR channel activity. The concept of an intrinsic defect in insulin secretion by the CF pancreas is further supported by Wooldridge et al. who examined insulin secretion in CF patients without CFRD during an OGTT, and found that the insulinogenic index (a measure of the capacity for insulin secretion) in pancreatic sufficient patients with CF was significantly lower than in control patients without CF[34].

Due to the underlying intrinsic defect in insulin secretion secondary to the aberrant CFTR channel, patients have delayed and blunted first-phase insulin response[18], as the glucose peak occurs early during the two-hour oral glucose tolerance test[13]. Initially, patients may develop hyperglycemia only at times of illness, or when treated with glucocorticoids. Upon screening of stable patients, post-prandial hyperglycemia is the earliest detectable abnormality in glucose homeostasis, and is a sensitive indicator of defective insulin secretion. As the disease progresses, fasting hyperglycemia occurs.

As β-cells are destroyed, the simultaneous destruction of glucagon producing β-cells may make treatment of CFRD especially challenging, rendering patients susceptible to severe and prolonged hypoglycemia if they are being treated with insulin. However, severe hypoglycemia appears to be more common in people with type 1 diabetes as compared to matched patients with CFRD[21].

Decreased incretin (GLP-1, GIP) production due

Table 1
Diagnostic criteria for Cystic Fibrosis Related Diabetes (CFRD) during stable health..

Time	Normal Glucose Tolerance (glucose in mg/dL)	Impaired Fasting Glucose (glucose in mg/dL)	Impaired Glucose Tolerance (glucose in mg/dL)	CFRD (glucose in mg/dL)
0 min (fasting)	< 100	≥ 100 AND <126	< 100	≥ 126
1 hour	-----	-----	-----	------
2 hour	< 140	< 140	≥ 140 AND ≤ 200	≥ 200
Confirmatory Testing		May predict increased risk of CFRD; repeat test in 6 weeks[55]. Monitor blood glucose during illness	May predict increased risk of CFRD; repeat test in 6 weeks[55]. Monitor blood glucose during illness	Confirm result by any modality recommended by ADA (HbA1c, repeat OGTT, fasting plasma glucose)

Table 2
Diagnostic criteria for CFRD during illness.

CFRD Diagnosis Symptomatic Hyperglycemia	CFRD Diagnosis During acute illness	CFRD Diagnosis On Tube Feeds
Classic symptoms of DM (polyuria, polydipsia) AND	Fasting glucose ≥ 126 OR Random glucose ≥ 200	Random blood glucose ≥ 200
Random blood glucose ≥ 200 mg/dL	Hyperglycemia must persist beyond the first 48 hours of treatment (IV antibiotics, etc)	Document two occasions within 48 hours

to changes in the entero-pancreatic axis and increased insulin clearance may also contribute to the development of CFRD[15,35]. Additionally, insulin resistance associated with inflammation, as well as increased growth hormone, cortisol, and catecholamines, induced by acute pulmonary exacerbations, can further contribute to hyperglycemia. Poorly controlled CFRD is associated with reduced BMI and worsening pulmonary function (as measured by FEV1). Both of these findings can be present before the diagnosis of CFRD is made[36,37]. CFRD is associated with higher mortality, with up to six fold greater mortality reported in female patients with CFRD as compared to those without CFRD[38, 39]. This discrepancy in mortality may disappear with improved glycemic control[8]. CFRD can also increase the risk of graft failure and mortality in patients with CF undergoing lung transplant[40].

In addition to the adverse effects of CFRD on the clinical outcomes described above, patients with CFRD are also at risk for microvascular complications. The risk parallels that seen in patients with type 1 diabetes (T1D), as assessed by HbA1c[41]. Van den Berg et al. compared microvascular complications in patients with CFRD versus patients with T1D[41]. They found that overall, patients with CFRD and T1D had the same number of microvascular complications. However, retinopathy was more common in T1D (24% vs 10%, p=0.044), while prevalence of peripheral neuropathy was comparable between the two groups. Patients with CFRD had significantly lower BMI, and significantly lower cholesterol. Nonetheless, patients with CFRD had significantly more microalbuminuria (21% vs. 4.1%, p=0.003) than patients with T1D. The authors speculate that the higher rate of microalbuminuria in patients with CFRD is likely multifactorial, and may be related to factors unique to CFRD, such as chronic inflammation, insulin resistance, exposure to nephrotoxic drugs such as aminoglycoside antibiotics, and deficiency of renal cystic fibrosis transmembrane regulator protein function[41].

Macrovascular complications are rare in patients with CFRD and have not been reported to date. Unlike patients with type 1 and type 2 Diabetes, who are more likely to die from cardiovascular disease, patients with CFRD, despite their increasing survival into adulthood, most frequently succumb to their pulmonary disease, and are more likely to die from cardiorespiratory failure[42,2].

Screening and Diagnosis of Cystic Fibrosis Related Diabetes (CFRD)

Given the adverse effects of CFRD on nutritional status, pulmonary function, and mortality, annual screening for CFRD starting at 10 years of age is recommended[42].

Screening also applies to specific subpopulations of patients with cystic fibrosis, such as pregnant women, post-partum women with a history of gestational diabetes, and patients being evaluated for lung transplantation. Screening for CFRD using hemoglobin HbA1c is not recommended, since a normal HbA1c result lacks the sensitivity to diagnose CFRD. Although data have been conflicting, the majority of the studies did not find a reliable correlation between hemoglobin HbA1c and glucose tolerance in the CF population[42]. Similarly, fructosamine, urine glucose, and random glucose levels have a low sensitivity for detecting CFRD in patients with cystic fibrosis[42].

Patients can be screened using current American Diabetes Association (ADA) guidelines for oral glucose tolerance testing while their health is stable. As noted above, hemoglobin HbA1c should not be used for diagnosis. The 75-gram oral glucose tolerance test (OGTT) should be used to screen for CFRD. The test should be performed when a patient is in stable health, at least six weeks after a CF exacerbation. Patients not meeting criteria for CFRD may exhibit isolated impaired fasting glucose (IFG), or impaired glucose intolerance (IGT), and may potentially benefit from treatment. Abnormal OGTT results should be confirmed with another testing modality, or the OGTT should be repeated on another day. Table 1 lists the diagnostic criteria based on OGTT results. Patients who develop hyperglycemia with classic symptoms, during illness or while on tube feeds, may be diagnosed with CFRD without screening, as summarized in Table 2. Since CFRD rarely occurs before the age of 10, a diagnosis of type 1 diabetes must be considered in patients younger than 10 years of age who develop diabetes.

Treatment of CFRD

The prevalence of microvascular complications in patients with CFRD is low, and macrovascular complications are uncommon. Thus, the goals of treatment of CFRD are to prevent the catabolic effects of hyperglycemia, improve nutritional status and BMI, and reduce the frequency of pulmonary exacerbations while minimizing hypoglycemia. According to ADA guidelines, the hemoglobin HbA1c goal in CFRD is $< 7\%$[42].

Oral Agents

Given the complexities of CF therapies and the multi-organ involvement of most patients, many oral medications cannot be used safely and effectively in the treatment of CFRD. Metformin, for instance, is contraindicated in patients with cystic fibrosis. Treatment with metformin may be unsafe due to the increased risk of lactic acidosis in patients with frequent hypoxia and underlying liver and chronic kidney disease[43].

Thiazolidinediones are not recommended due to concern for hepatic toxicity in CF patients. Drugs limiting carbohydrate absorption are not recommended since CF patients exhibit significant malabsorption[43].

The use of sulfonylureas is not recommended due to concern for hypoglycemia. By affecting intracellular chloride transport, these medications may interact with new therapeutic agents that potentiate or correct the CFTR channel activity directly[43]. Unlike insulin, which has been shown to preserve beta cell mass, sulfonylureas may decrease beta cell mass[44].

Repaglinide is an oral anti-diabetic medication that lowers blood glucose by binding to the sulfonylurea receptor, stimulating insulin release. It is less likely to cause hypoglycemia than a sulfonylurea, since its action on insulin release occurs in a glucose-dependent fashion, and tends to be of shorter duration[45]. Moran et al have shown that repaglinide may have some limited benefit in patients with CFRD with regard to post-prandial hyperglycemia and improvement in BMI and chronic weight loss, although the beneficial effect on weight was not sustained beyond 6 months of therapy, and the effect on post-prandial glucose was less than that of insulin. [43,50]

No studies are available addressing the use of GLP-1, DPP-IV or SGLT-2 therapies for CFRD. GLP-1 levels are reduced in patients with CFRD, and it is possible that therapy with this agent may be of benefit in patients with CFRD[35]. Currently, due to lack of proven efficacy, oral or non-insulin therapy is not recommended for treatment if CFRD outside of a clinical trial[42]. An open randomized prospective multi-center trial examining the effect of oral therapy vs. insulin therapy in patients with CDRD without fasting hyperglycemia is ongoing [46].

Insulin Therapy

Insulin is currently the only recommended medical therapy for CFRD. Patients with CFRD without fasting hyperglycemia can initially be started on prandial insulin, which can reverse chronic weight loss[47]. It is reasonable to start therapy with prandial insulin at 0.5-1 unit of insulin for 15 grams of carbohydrates in patients requiring meal coverage. For patients with fasting hyperglycemia, basal insulin at 0.25 u/kg daily can be used[48].

Recommendations regarding insulin use in patients with isolated fasting hyperglycemia remain unclear. Limited studies show that insulin therapy in these patients may

improve BMI and lung function[47]. This effect of insulin therapy may be due to the anabolic benefits of insulin, possibly increasing respiratory muscle strength, rather than a direct effect of glucose lowering therapy[49]. Insulin therapy carries with it the burden of multiple daily injections, risk of hypoglycemia, and titration needed during times of acute inflammatory states, such as CF exacerbation, when insulin requirements can increase up to four fold[48]. In addition to fluctuating insulin requirements during illness, other challenges of diabetic management include gestational diabetes, and deteriorating control of CFRD after lung transplant, although incidence of diabetes after lung transplant is not increased in CF patients[42,50]. Enzyme supplementation and fat content of meals can also affect gastric emptying, making glycemic excursions more variable[49].

Pancreatic transplantation

Although pancreatic transplantation can improve both endocrine and exocrine pancreatic deficiencies, it is not commonly performed. Usatin et al report under-utilization of pancreatic transplants in patients with CF, despite up to 100% survival two years after a combined pancreas-kidney transplant[51].

CFTR correctors and potentiators:

Current development of medications to specifically target CFTR dysfunction makes this an a hopeful time for the treatment of CF and CFRD. Lumacaftor (VC-809) is an oral agent used for CFTR correction. The molecule facilitates proper maturation and delivery of the CFTR protein to the plasma membrane by directly interacting with the protein to facilitate proper folding. This medication is used in patients who are delta 508 homozygotes, targeting a Class II mutation. CFTR potentiators, such as ivacaftor, increase the flow of ions through the activated CFTR channel, and can be used in people with class III mutations of the CFTR cannel (such as those with the G551D mutation), who have normal amounts of protein at the cell surface but exhibit defects in channel gating[52]. These medications have shown to improve lung function and BMI in patients with CF. Additionally, these agents may improve insulin secretion, since the CFTR channel is present in the pancreas. A small pilot study involving five patients with CF taking ivacaftor for the G551D mutation demonstrated an improved insulin response to an oral glucose load within 1 month after starting therapy, suggesting that these agents can favorably affect insulin secretion[53]. Hayes et al. reported that a 25-year-old man with the deltaF508 G551D mutation, previously taking 20 units of glargine daily for CFRD, was weaned off insulin therapy within one year of starting irvacaftor[54]. The combination of lumacaftor/ivacaftor provides greater benefit for many CF patients. More targeted therapies affecting the CFTR channel and gene therapy are potential future treatments for CF and its associated comorbidities, including CFRD.

Future Directions

The emergence of CFTR targeted therapies, improved nutrition, and advances in treatment of underlying organ dysfunctions in CF have increased survival of patients with cystic fibrosis, and thus, also increased the prevalence of CFRD. As patients with cystic fibrosis live longer, they may develop microvascular complications of CFRD. Patients with CFRD pose a unique challenge to the management of diabetes and should receive care by multidisciplinary teams that can address the complexity of CF and the related comorbidities, including CFRD, to help patients achieve desired targets and optimal outcomes in the control of their disease.

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MM

Diabetic Kidney Disease

by Victoria E. Bouhairie, MD & Janet B. McGill, MD

Additional interventions are under investigation, but thus far no specific strategies have been shown to improve outcomes in patients with diabetic kidney disease.





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Abstract

Diabetic kidney disease (DKD) continues to be a chronic and devastating complication of diabetes. Despite improvements in glycemic control and lower blood pressure targets, the incidence of DKD has not declined substantially. Standards of care for persons with diabetes include screening for kidney complications and close follow-up. Preventive measures continue to rely on glucose and blood pressure control. However, additional measures to slow the progression of kidney damage are under investigation.

Introduction

In the United States, DKD is the leading cause of kidney failure. In 2008, the Centers for Disease Control and Prevention reported that approximately 44 percent of all new cases of kidney failure requiring renal replacement therapy were caused by diabetes mellitus[1]. The overall prevalence of micro- and macroalbuminuria is nearly 35 percent of persons with both types of diabetes[1]. Among patients with type 2 diabetes (T2D), chronic kidney disease is the only complication for which the incidence has not decreased despite improvement in diabetes control over the past 20 years[2]. Native Americans, Hispanics (especially Mexican-Americans), and African Americans have a higher risk of developing end stage renal disease than non-Hispanic whites with T2D. In addition to kidney failure, DKD is a strong independent risk factor for cardiovascular disease. The combination of diabetes and nephropathy increases cardiovascular disease risk by 20–40-fold, greatly increasing morbidity and mortality in patients with diabetes[3]. Thus, the presence of microalbuminuria is an indication for surveillance and management of cardiovascular risk factors.

Screening

The 2007 Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Diabetes and chronic kidney disease (CKD) recommend that initial screening for DKD should start five years after the diagnosis of type 1 diabetes (T1D) and at diagnosis in persons with T2D. Follow-up testing should be done yearly thereafter. Screening should include measurement of urinary albumin-creatinine ratio (UACR) on a spot urine sample and a serum creatinine (sCr). Elevated UACR should be confirmed in the absence of infection with two additional first void specimens collected over the next three to six months[4]. Lack of retinopathy, lack of autonomic neuropathy, and presence of albuminuria at the time of the diagnosis of diabetes all suggest a non-diabetic etiology for persistent albuminuria[5]. Also, exercise, heart failure, fever, menstruation, marked hyperglycemia and hypertension may elevate UACR independent of kidney damage. Microalbuminuria is diagnosed when UACR is between

30 – 300mg/g, whereas higher levels are considered to be in the macroalbuminuric range. Some authors have recommended changing the nomenclature from microalbuminuria to moderately increased albuminuria and from macroalbuminuria to severely increased albuminuria, arguing that the term microalbuminuria could be interpreted as a finding of minimal clinical importance[6]. The American Diabetes Association (ADA) continues to use the traditional nomenclature, which is what we use for this article.

Measuring sCr is also essential in the diagnosis and follow-up of CKD in patients with diabetes. The sCr should be used to estimate the glomerular filtration rate (eGFR). Most laboratories report eGFR using the Modification of Diet in Renal Disease (MDRD) formula, which has excellent correlation with more invasive measures of GFR in patients with impaired kidney function manifesting as GFR <60 ml/min/1.73m^2[2,7]. Higher levels of eGFR are reported as >60 ml/min/1.73m2 without providing an actual eGFR value. The Chronic Kidney Disease Epidemiology Collaboration (CKD – EPI) formula, which was developed after the MDRD equation, provides greater accuracy for eGFR calculations >60 ml/min/1.73m^2, and is the preferred method for calculating eGFR in this range[8]. The National Kidney Foundation 2003 guidelines define CKD as either the presence of kidney damage or GFR less than 60 mL/min/1.73m^2 for three or more months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies[9]. The presence of albumin in the urine is a well-established marker of kidney damage.

Progression of DKD has historically been taught as a multi-stepwise process with the initial step being the appearance of urinary microalbuminuria, followed by progressive increase in proteinuria that is accompanied by declining kidney function. The result is end stage renal disease (ESRD) with or without antecedent CV disease. However, approximately 30% of patients with DKD do not have albuminuria[10]. Recent studies have shown that in T1D, reduced eGFR can be observed before albuminuria appears[7]. Women with T1D, reduced eGFR and normoalbuminuria who underwent kidney biopsies had more advanced glomerular lesions than normoalbuminuric women with normal eGFR[11]. Also, advanced glomerulosclerosis has been reported in kidney biopsies from patients with T2D without albuminuria or proteinuria[12]. This suggests eGFR, and in particular decline in eGFR, is an important component of both the diagnosis and follow-up of DKD with or without the presence of albuminuria (See Figure 1).[13]

There is clearly a need to identify biomarkers of DKD that would precede the appearance of albuminuria. Biomarkers currently under investigation include kidney injury molecule 1(KIM-1), serum cystatin C and neutrophil gelatinase-associated lipocalin (NGAL)[14,15]. Cystatin C has been investigated as a more sensitive marker of GFR, but it has not been adopted for widespread clinical use[15].

Pathogenesis of Diabetic Kidney Disease

The renin-angiotensin system (RAS) is the single most significant contributor to the pathogenesis of diabetic kidney disease[16,17]. This is due to upregulation of local intrarenal RAS[18] that ultimately results in increased sodium reabsorption[19], preferential efferent arteriolar vasoconstriction and increased glomerular capillary pressure and permeability[20].

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min per 1.73 m^2) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red, very high risk.

Figure 1. Categories of albuminuria and GFR in CKD, and their relationship to risk of progression to end-stage kidney disease. Reprinted with permission, Kidney International. [13]

Hyperglycemia also plays a key pathogenic role. The effects of hyperglycemia are mediated through multiple pathways that result in oxidative stress[21], as well as release of proinflammatory[22] and profibrotic mediators[23]. Elevated glucose and critical changes in intrarenal hemodynamics cause alterations in glomerular permeability, glomerular hyperfiltration, glomerular basement thickening, mesangial matrix synthesis and ultimately glomerulosclerosis and interstitial fibrosis[24]. In addition, excess glucose combines with free amino acids on circulating or tissue proteins to generate advanced glycation end products (AGEs). These products may cause renal and microvascular complications through accumulation in tissues and crosslinking with collagen[25].

Another factor contributing to the pathogenesis of DKD may be endothelin-1. In rats with diabetes, the gene expression of endothelin-1 is increased in the kidney[26], which results in renal cellular proliferation, podocyte damage, matrix accumulation and fibrosis[27].

The predominant structural changes associated with diabetic kidney disease include mesangial expansion, glomerular basement membrane thickening and glomerular sclerosis[28]. The progression of DKD depends on many factors, and histologic patterns may be important[29].

Management of DKD

The primary treatment goal is prevention of DKD, but once DKD is diagnosed, the goal is to slow or prevent progression to ESRD. The mainstays of treatment have traditionally included glycemic and blood pressure control, with dietary therapy as a less established intervention. Additional measures should include avoidance of renal toxins and management of CV risk factors. Without specific interventions, about 80% of T1D patients who develop sustained microalbuminuria will experience an increase in urinary albumin excretion at a rate of 10-20% per year to the stage of overt nephropathy or macroalbuminuria over a period of 10-15 years[30]. Studies have shown that early decline of eGFR that exceeds 3 ml/min/1.73m^2 is predictive of progression to ESRD[31]. Early declines in eGFR will be missed if providers delay tracking until the eGFR is $<$60 ml/min/1.73m^2, thus the need to utilize the CKD-EPI formula for patients with stage 2 CKD. Higher levels of albuminuria and lower eGFR are risk factors for progression to ESRD, as shown in Figure 1.

Intensive glycemic control was compared to standard control in three large randomized controlled trials. Each found a reduction in progression to macroalbuminuria with intensive control. However, intensive control was associated with increased hypoglycemia. The renal endpoints of doubling of creatinine and progression to ESRD were too few to reach significance in early intervention studies[32–34]. The KDOQI guidelines recommend a target hemoglobin A1c (HbA1c) of 7.0%, but with possible adjustment to higher A1c goals for patients with co-morbidities, limited life expectancy or risk of hypoglycemia[4].

Hypertension in DKD is defined as a systolic blood pressure $\geq$ 130 mmHg or a diastolic blood pressure $\geq$ 80 mmHg. Hypertension in both T1D and T2D is caused mainly by volume expansion due to increased sodium reabsorption in the kidneys, low renin activity and peripheral vasoconstriction from dysregulation of factors that control peripheral vascular resistance[35]. Observational studies have shown that eGFR declines at a rate $>$10 mL/min/1.73m^2/yr in patients with DKD, poorly controlled hypertension and macroalbuminuria, but only 1-4 mL/min/1.73m^2/yr in those with well controlled blood pressure[4]. Treatment with angiotension-converting enzyme inhibitors (ACEi) or angiotension receptor blockers (ARB) is more effective in reducing the progression of DKD than treatment with other antihypertensive medications[36]. In addition, ACEi have been shown to reduce major CVD events in patients with DKD. Mann et al reported that in a large randomized trial of patients with diabetes, end-organ damage and atherosclerosis, ACEi and ARBs were equally effective in preventing progression of DKD. If sufficient blood pressure reduction is not achieved after 4-6 weeks of ACEi/ARB therapy, additional drug therapy is indicated[30]. The combination of the ACEi and ARB however, did not provide additional benefit and led to higher sCr levels, more hyperkalemia and increased rates of dialysis[37]. Currently, the American Diabetes Association (ADA) does not recommend the combined use of ACEi and ARBs[38]. The KDOQI guidelines recommend against the use of ACEi or ARBs for the primary prevention of DKD in normotensive normoalbuminuria patients with diabetes. However, they should be used in patients with albuminuria $>$30mg/g even if they are normotensive[4]. ACEi should be discontinued if the creatinine level increases by 30 percent above baseline in the first two months of therapy or if hyperkalemia (greater than 5.6mEq/L) occurs. Combined treatment with a mineralocorticoid receptor blocker has also been shown to reduce albuminuria by 23 to 61% compared with standard treatment. However, an increase in hyperkalemia with combined treatment raised the dropout rate to 17%[39]. Non-dihydropyridine calcium channel blockers have been found to reduce the level of albuminuria but no studies have demonstrated a reduction in rate of fall of GFR with their use[40]. In patients unable to tolerate ACEi or ARBs or whose blood pressure is not at goal on maximum doses of ACEi or ARB, blood pressure goals can be pursued with diuretics, calcium channel blockers, beta blockers and mineralocorticoid receptor blockers.

A low protein diet is also commonly advised in patients with CKD. In the Modification of Diet in Renal Disease (MDRD) Study, the mean change in GFR over three years was not significantly affected with dietary protein restriction (0.58 g/kg/day, versus a usual-protein diet of 1.3 g/kg/day)[41] in patients with baseline GFR 25 to 55 mL/min per 1.73 m^2. However, in secondary analyses, patients with advanced renal disease (baseline GFR, 13 to 24 mL/min per 1.73 m^2) a low-protein diet (<0.6 g/kg/day) slowed the GFR decline and reduced proteinuria[41]. The ADA recommends that dietary protein intake should be limited to 0.8g/kg per day in patients with rapidly progressive DKD[38]. A very-low-protein diet (<0.3g/kg/day) has been associated with increased mortality over the long term[42]. Higher levels of protein intake have been associated with worsening albuminuria, more rapid decline in GFR and CVD mortality[43,44]. High protein foods and dark sodas contribute to excessive phosphate and organic acid intakes that may be reflected in higher phosphate and lower bicarbonate levels in patients with advanced CKD[45].

Due to a higher risk of CVD in patients with DKD, statin therapy should be initiated in those with hyperlipidemia including patients with a kidney transplant. In addition to lowering cardiovascular risk, atorvastatin has been found to significantly reduce serum levels of AGEs in type 2 diabetic patients in a cholesterol lowering independent manner[46]. KDOQI guidelines do not recommend a statin in patients with ESRD on dialysis[4].

Patients with T2D and eGFR <60 ml/min/1.73m^2 may require adjustment of their anti-diabetes therapy. Metformin use can be associated with lactic acidosis, but the FDA has recently modified its recommendations to indicate that metformin may be safely used in patients with mild to moderate renal impairment. However, metformin should not be used in patients with an eGFR $\leq$30 ml/min/1.73m^2, and should not be started in patients with an eGFR between 30-45 ml/min/1.73m^2. Exenatide-based GLP receptor agonists should be discontinued when the sCr is $\geq$2 mg/dL. The same approach should be followed for alpha-glucosidase inhibitors. All of the dipeptidyl peptidase inhibitors (DPP4i) require dose adjustments at various eGFR cut-offs with the exception of linagliptin, which can be used in patients with any level of kidney dysfunction without dose adjustment. The GLP receptor agonists liraglutide, dulaglutide and albiglutide are not renally excreted, and may be used in patients with impaired kidney function, but side effects of nausea and vomiting may be limiting. The sodium-glucose co-transport inhibitors require dose adjustments at eGFRs of either 60 ml/min/1.73m^2 or 45 ml/min/1.73m^2 due to reduced efficacy and increased side effects. Sulfonylureas should be used with caution, especially glyburide, due to renal excretion that may cause higher drug levels in patients with stage 3 and more advanced CKD. Shorter acting sulfonylureas are preferred in these patients to limit the risk of hypoglycemia. While insulin is absolutely required in patients with T1D regardless of kidney function, it is often necessary in patients with T2D. Renal disease in both forms of diabetes increases risk of hypoglycemia due to reduced gluconeogenesis and reduced breakdown of insulin. More intense glucose monitoring and insulin dose adjustments may be needed as kidney function declines.

When should referral to a nephrologist be considered? Patients with atypical features, such as macroproteinuria in the absence of retinopathy may have another etiology for their kidney disease. Other reasons to refer include very heavy proteinuria, an active urine sediment and a rapid decline in GFR. Patients with eGFR <60 ml/min/1.73m2 are at risk for complications of CKD such as renal osteodystrophy, anemia, hyperkalemia, hyperuricemia and rarely systemic acidosis. Nephrology referral may be needed to manage difficult to control hypertension, hyperkalemia or the secondary manifestations of CKD. Patients with DKD should also be referred once they are in stage 4 CKD to improve quality of care and perhaps delay dialysis[48].

Conclusions

DKD remains a common and devastating complication of both T1D and T2D. Albuminuria at any level is an independent predictor of cardiovascular[33,49] and renal risk[49] in patients with diabetes. Health care providers should both screen and follow patients with annual measurements of both UACR and sCr. Optimal glucose control and blood pressure management with ACEi or ARB are the mainstays of treatment. CV risk reduction with statins is appropriate in patients with stage 2 and 3 CKD. Treatment of complications of CKD may help to slow progression and improve quality of life. Additional interventions are under investigation, but thus far no specific strategies have been shown to improve outcomes in patients with DKD.

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Death by Carbs: Added Sugars and Refined Carbohydrates Cause Diabetes and Cardiovascular Disease in Asian Indians

by Bhaskar Bhardwaj, MD, Evan L. O'Keefe, MS & James H. O'Keefe, MD

Programs to encourage reduction in consumption of sugar and all refined carbohydrates are urgently needed for the primary and secondary prevention of diabetes, stroke, and cardiovascular disease in this high-risk population.



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Abstract

By the year 2030, India will supplant China as the world's most populous nation. Rapid urbanization and an increasingly Westernized diet and lifestyle, in a population with genetic predisposition to insulin resistance is fueling a rising epidemic of non-communicable diseases in India. A diet that is high in processed foods, added sugars and other refined carbohydrates is a principle factor driving the growing epidemics of type 2 diabetes (T2D), hypertension (HTN), and cardiovascular (CV) disease (CVD). Immediate postprandial spikes in the blood levels of glucose and triglycerides cause immediate parallel rises in oxidative stress, inflammation, and endothelial dysfunction; eventually leading to T2D, and CVD. Furthermore the Asian Indian population is particularly susceptible to exaggerated rises in postprandial glucose and triglycerides because they are genetically predisposed to metabolic syndrome (MetSyn), insulin resistance, and T2D. A diet restricting the consumption of refined carbohydrates and limiting added sugars to not more than 5 grams/day should be adopted by Asian Indians to reduce risk of T2D, HTN, coronary disease, and stroke.

Introduction

Over the span of a few decades the lifestyles of modern humans have changed drastically from physically demanding lives and agrarian diets to physically inactive routines and chronic over-consumption of calorie-dense beverages and processed foods. In particular, the high intake of refined carbohydrates and foods manufactured with added sugars has driven the growing epidemics of type 2 diabetes mellitus (T2D), hypertension (HTN), stroke, and coronary artery disease (CAD).[1]

India is projected to overtake China as the world's most populous nation by 2030[2, 3] and India's influence worldwide continues to grow, especially in the United States (U.S.). Over the past half-century, the number of immigrants to U.S. who were born in India has risen 150-fold.[3] Now, with about three million Asian Indian immigrants living in the U.S., India is tied with China as the second biggest immigrant group in America by country of origin; only Mexico sends more immigrants to the U.S..[3]

In the midst of rapid urbanization and modernization,[4, 5] India is in the throes of an escalating epidemic of non-communicable diseases (NCDs),

with the prevalence of CAD, T2D, and stroke rising by at least 100% over the past two decades.[6-8] Cardiovascular (CV) disease (CVD) now accounts for about one out of every four deaths on the South Asian subcontinent (defined as the peninsula south of the Himalaya Mountains, which currently includes the following countries: India, Pakistan, Bangladesh, Nepal and Bhutan). Today about half of the total Indian population is ≤ 24 years of age.[9] India is projected to account for more than 20% of the CAD deaths worldwide by 2025.[5, 7, 10] A 15-year-long study comparing various racial groups in Canada reported that Asian Indians had the highest age-adjusted death rate due to CAD compared to other ethnicities including Chinese and European.[11] Importantly, the recent atherosclerotic CV risk assessment guidelines acknowledge that the standard risk factors underestimate risk among the Asian Indian population, perhaps due to an inherent predisposition to T2D and CAD.[12-14]

South Asians appear to have a genetic susceptibility to metabolic syndrome (MetSyn) and T2D even with modest increases in intra-abdominal fat. Furthermore, their traditional diet, which is very high in sugar and other refined carbohydrates, may be fueling the burgeoning epidemics of diabetes and heart disease.

Adverse Economic Impact of Epidemic Non-Communicable Diseases

Non-Communicable Diseases (NCDs) adversely not just a person's health, but also their productivity and economic well-being.[8] Because CV disease tends to present at a younger age in Asian Indians compared to other ethnicities, a larger percentage of fatalities occur during working-age years.[7, 15] In Western nations mortality from CV disease occurs predominantly in older individuals, with only 23% of CV deaths occurring in people under age 70.[7, 8, 16] In contrast, in the Asian Indian populace, over half of all CV deaths occur in people younger than 70 years of age.[17] This high rate of early CV mortality causes massive losses in productivity.[16] Developing countries, as compared to the wealthier nations, already have seven times as many residents who have been disabled from stroke.[5] Unless effective preventive measures are deployed, disability and death related to CV diseases alone will cost India $2.2 trillion by the year 2030.[8]

Genetic Predisposition to Metabolic Syndrome and Diabetes

Today 67 million people in India have T2D; twice that number will have the disease the year 2030[8, 18]. In part this is due to the large-scale migration from the rural villages into the urban centers of India. Waist circumference, a fundamental risk factor for T2D and CAD, is rapidly enlarging among the urban South Asians. Consequently, the prevalence of T2D has risen ten-fold over the past four decades in urban India.[19] People who have T2D typically die about 10 years earlier than individuals who do not have diabetes; and about two-thirds of deaths among diabetics are due to CV causes.[5, 6, 8, 19, 20] Added sugars, usually in the forms of sucrose—also known as table sugar, along with high fructose corn syrup (HFCS), are integrally involved in the genesis of T2D, which is especially relevant for individuals genetically predisposed to MetSyn and diabetes.[21] In fact, recent studies show that high intake of added sugars and other refined carbohydrates can cause T2D even in the absence of other risk factors.[22] The emerging body of scientific evidence suggests that excessive intake of processed foods rich in added sugars and other refined carbohydrates is a chief dietary factor driving the rising epidemics of diabetes and CAD, as well as the NCD-related morbidity and premature mortality seen among Asian Indians.

Already today India leads the world in number of residents with pre-diabetic conditions including impaired glucose tolerance and impaired fasting glucose; furthermore about one out of every three adults in India has MetSyn.[15] The South Asian population is particularly vulnerable to the adverse metabolic effects of excess body fat, especially when it is inside the abdominal cavity, which may be increased from consumption of excess caloric loads including added fructose.[6, 23-25] Even so, obesity as defined as a body mass index (BMI) > 30 kg/m^2 is rare among Asian Indians; in contrast approximately one-third of adults in the U.S. is obese by this definition.[8] In fact, today among the major countries, India has the lowest rate of obesity in the world.[26] Despite their low rates of obesity, the prevalence of T2D and CAD are rising rapidly among Asian Indians.[22, 24] Compared to people with European ancestry, individuals with South Asian ethnicity commonly develop pre-diabetes or frank T2D with even modest increases in weight.[27] Healthy waist measurements for most adult populations are < 88 cm for women, and < 102 cm for men.[27] Conversely, recent guidelines for optimal health specify that for people of Asian Indian ethnicity the adult waist measurements should be < 85 cm for women and < 90 cm for men.[27]

Fatty Liver Disease among Asian Indians

Individuals with South Asian ethnicity appear to have a genetic predisposition to non-alcoholic fatty liver disease (NAFLD), also called hepatic steatosis,[15] which has been described as the hepatic manifestation of the MetSyn.[28] NAFLD is one of the most pernicious risk factors for CAD,[28, 29] and is caused by chronic overconsumption of sugar and other refined carbohydrates, abdominal adiposity, and sedentary lifestyle, all of which are increasingly common

among the population of India and people with Asian Indian ethnicity.[11, 25, 28, 30] The latest evidence indicates that although about one out of every three adults among the Asian Indian urban population is afflicted by fatty liver,[31-33] the vast majority of these people are asymptomatic and unaware of their NAFLD. This is similar to the prevalence of fatty liver disease among the U.S. population, where NAFLD is seen in about 30% of adults.[32-34] Individuals with NAFLD are not just predisposed to CAD and cirrhosis, but also to liver cancer and exogenous malignancies of other organs.[28]

A prospective study recently reported that individuals with NAFLD often also have CAD with high-risk features on coronary angiography.[29] Among the 440 patients studied, NAFLD was seen in 40%. These patients with NAFLD were about three times more likely than people without NAFLD to have high-risk coronary plaque (59% vs 19% respectively). Moreover, the presence of fatty liver predicted dangerous coronary anatomy independent of the traditional CAD risk factors. This pathophysiological link between NAFLD and high-risk coronary plaque is hypothesized to occur because of shared risk factors and also system-wide inflammation triggered by the excess fat deposition in the liver.

The most effective treatments for regressing NAFLD remain uncertain, but the ones showing most promise include: a diet low in sugar and other refined carbohydrates, weight loss (especially mobilizing excess intra-abdominal fat), omega-3 supplementation, coffee consumption, exercise, avoidance of alcohol, intermittent fasting, and L-carnitine.[35]

Excess Sugars and Refined Carbohydrates Toxic to Asian Indians

Asian Indians in 350 BC invented refined sugar by crystallizing sugar granules from sugarcane juice.[36] The enjoyment of sweets is an integral part of many important traditions in the Indian culture. Indeed, for centuries it has been customary to "sweeten the mouth" after each meal. Many traditional Indian festivals include exchanging the sweets amongst friends and family. Thus, sugar plays a central role not only as a dietary staple but also as a cherished pleasure in the traditional Indian way of life.

Today, India is the largest consumer of sugar in the world.[36] This over-consumption of foods and beverages containing added sugar is among the most serious threats to Asian Indian health and wellness—both for individuals and the society as a whole.[23, 37]

Recent large and comprehensive analyses of populations from 173 countries found that the per capita sugar consumption is highly correlated with the prevalence of T2D among the various nations.[22, 38] The correlation between sugar consumption and adjusted risk of T2D was especially robust among South Asian populations, where even a modest increase in sugar intake (for example, 150 extra calories of added sugar) correlates with a significantly heightened risk for T2D.[22, 38]



Figure 1
Dietary Suggestions for Asian Indians: Added Sugars

The customary diet of India was already high in sweets, but this was less problematic as the sugar came from whole-foods (such as fruit that contains fiber, water, antioxidants, and other substances that buffer the sugar load) and was generally consumed in the ancestral rural environments of South Asia where obesity and sedentary lifestyles were virtually nonexistent. In contrast, about 66-70% of total calorie intake in the modern Asian Indian diet comes from carbohydrates, and mostly in the form of refined sugar, white flour, and white rice.[39] The World Health Organization (WHO) has described added sugar as a silent killer that is as deadly as tobacco—these two vices kill two people around the world every six seconds—one from sugar and one from tobacco.[40, 41] The consumption of added sugar and other refined carbohydrates increases the risk of T2D in a dose-dependent fashion. The incidence

of T2D doubles when the consumption of refined carbohydrates/added sugar reaches 330 gm/day, which is the average daily intake for an adult Asian Indian.[38, 41, 42]

The average U.S. adult consumes about 15% of daily calories in the form of added sugar, compared to 14% for Asian Indian adults.[36, 37, 39] Other data suggests the average intake is even higher—i.e., 152 lbs. per person per year, with 13% of the U.S. population consuming 25% or more of their total calories from added sugars.[37, 43, 44] Increased consumption of added sugar worsens risk of CV death in a dose-dependent manner.[37] Consensus dietary guidelines for Asian Indians currently recommend restricting sugar intake to less than 10% of total calories consumed.[15] In an effort to curb the obesity epidemic that is blossoming worldwide, the WHO recently went even further and recommended reducing sugar intake to 5% of total calorie intake, or about 25 g of sugar per day for an average-sized person.[45] The average adult in India consumes 58 g of sugar daily.[46] (See Figure 1.)

Sweetened Beverages

Sugar-sweetened beverages, perhaps because they are widely available, heavily marketed, and usually contain HFCS have been shown to be very strongly associated with risk of T2D, even after statistical adjustment for total calorie consumption and abdominal obesity.[47-51] Each additional sugar-sweetened drink consumed on a daily basis raises the risk of developing diabetes by approximately 25%.[51-53] Sugar-sweetened beverages, along with other added sugars and refined carbohydrates also increase the risk of obesity, CAD, and CV death.[52-54]

In light of the heightened susceptibility of individuals with Asian Indian ethnicity to adverse metabolic effects from consumption of sugar and their propensity to develop T2D, fatty liver, and CAD with modest increases in abdominal fat, it may be particularly important for South Asians to restrict sugar intake to less than 5% of total calories. For the average adult (using 2,000 calories per day as a reference) this translates to not more than about six teaspoons per day, which is the amount of sugar in about six to eight ounces of a sweetened soft drink, for example.[55]

Post Prandial Glucose Spikes Cause Inflammation and CAD

Individuals with Asian Indian heritage are often genetically predisposed to insulin resistance, which makes them particularly susceptible to post prandial hyperglycemia. This issue is exacerbated by the fact that the typical Indian meal is rich in highly processed foods such as refined carbohydrate that trigger exaggerated post-prandial surges

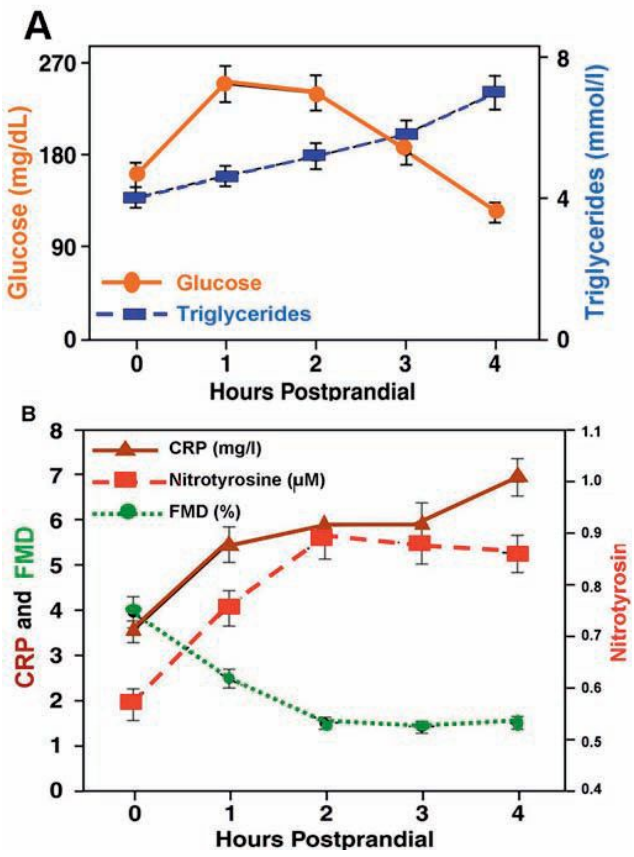


Figure 2
Post prandial stress: The immediate deleterious effects of a beverage containing 75 g glucose mixed with 700 kcal/m2 of whipping cream. Within 2 to 4 h glucose and triglyceride levels double, causing immediate oxidant stress (nitrotyrosine), inflammation (C-reactive protein [CRP]), resulting in deterioration in endothelial function.56
FMD % = Flow mediated dilation

in blood levels of glucose and triglycerides. These spikes in blood sugar and triglycerides cause parallel and almost instantaneous surges in systemic oxidant stress. The abrupt increase in free radicals in turn causes a cascade of atherogenic disturbances including inflammation, endothelial dysfunction, sympathetic hyperactivity and hypercoagulability. (See Figure 2.) This tendency to have post meal spikes in glucose is an independent predictor of adverse CV events even among individuals without diabetes.[56]

Direct correlations exist between post prandial glucose levels and future risks of both CV death and all-cause mortality.[57] The CV risk of post-prandial or post-glucose-challenge glycemia also shows a strong relationship with coronary atherosclerosis progression even in people without diabetes.[56, 58]

Fortunately, dietary modifications can exert dramatic and immediate improvements in post prandial glucose and triglyceride levels and will concomitantly lower

inflammation.[56] Effective dietary changes to blunt post meal spikes of glucose and triglycerides include: increase intake of minimally processed, high-fiber, plant-based foods such as vegetables and fruits, legumes, and nuts. In addition, lean protein, vinegar, tea, cinnamon, calorie restriction, weight loss, exercise, and fasting will each significantly improve post-prandial levels of glucose and triglycerides. This type of anti-inflammatory diet should be promoted to the Asian Indian population for prevention of CAD and T2D.[56]

Nuts and Yogurt—Healthy Options to Substitute for Refined Carbs

Nuts offer a unique and nutritious combination of protein, fiber, essential fats, phytosterols, antioxidants, vitamins, and minerals. A handful (about 1 ounce) of nuts provides a nourishing and satiating snack that is superior to processed food snacks, many of which are high in added sugar and other refined carbohydrates. More than 40 clinical trials have evaluated the effects of nut consumption on various biomarkers of overall and cardiac health, and have generally found improvements in blood glucose and lipid levels, as well as a reduction in markers of inflammation.[59] A recent trial reported that pistachio nuts when substituted for 20% of calories in a typical Asian Indian diet substantially improved not just glucose and total cholesterol levels, but also reduced abdominal obesity, lowered markers of inflammation and oxidative stress, and raised adiponectin levels.[36]

Nuts have a low glycemic index, are cholesterol-free, and have been strongly linked to superb health outcomes.[60] Studies show that eating one to two ounces of tree nuts per day may reduce risk of T2D, myocardial infarction (MI), stroke and CV death.[56-58] The benefit of tree nuts may be of special relevance to Asian Indians, considering the high rates of MetSyn, T2D, and CVD in this population.

A prospective epidemiological study reported that a higher intake of yogurt was associated with a reduced risk of T2D; however consumption of other dairy foods and beverages was not linked to lower rates of diabetes.[61] Unsweetened yogurt contains health-promoting nutrients such as probiotics along with calcium, vitamin D, protein and potassium, with lower levels of lactose due to the fermentation process, which metabolizes much of the sugar. These promising findings indicate that yogurt, which has traditionally played an important role the Asian Indian diet, should be encouraged as a healthy food option; though it is best to avoid yogurts with added sugars.

Focus on Prevention

Only one in ten residents of India has medical insurance, thus nine out of ten pay out of pocket for their medications and health care.[8] To make matters worse, have of the individuals living in India subsist on just $1 to $2 per day.[62] The most practical and affordable strategy for addressing these worsening pandemics of diabetes and heart disease is prevention, which will require focusing on dietary changes and increased exercise. Successfully deploying such a strategy in India will be difficult, as it has been in the U.S., and progress at a national level may require policy changes. These could ideally involve programs promoting healthy whole foods such as fruits, vegetables, nuts, and low-fat dairy, while at the same time discouraging intake of refined foods and beverages. Other measures might include government subsidies for healthy foods versus unhealthy foods,[63] employer-sponsored personal health incentives, and increased opportunities for urban exercise (bicycle paths, parks, etc.) along with other efforts to promote physical activity.[58, 63-67] Table 1 lists specific strategies for the prevention of diabetes and CVD among Asian Indians.

Conclusion

The excessive intake of sugar along with other refined carbohydrates is a major factor driving the epidemics of T2D and CVD among the Asian Indian population. Programs to encourage reduction in consumption of sugar and all refined carbohydrates are urgently needed for the primary and secondary prevention of diabetes, stroke, and CAD in this high-risk population.

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Disclosure

None reported.

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Calcific Aortic Stenosis: New Approaches to an Old Disease

by Jerry D. Kennett, MD & Benjamin Z. Galper, MD

It is important that we continue to move cautiously to ensure the lowest possible complication rate and the highest rate of success and long-term benefit for our patients.



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Abstract

Calcific aortic valve disease affects up to 25% of all adults over 65 years of age, with most only having focal valve thickening called aortic sclerosis. However, up to 5% of older adults have significant aortic stenosis (AS) with some degree of obstruction to left ventricular outflow. [1,3,4,5] Once even mild valve obstruction is present, hemodynamic progression is common, leading to severe symptomatic or asymptomatic AS that eventually requires aortic valve replacement in some fashion. [6,7] With our aging population, an increasing number of patients with AS will be presenting for evaluation and care.

Introduction

Aortic Stenosis is most commonly discovered on the basis of the finding of a systolic murmur on physical exam with echocardiography being the best diagnostic test to confirm aortic valve disease. The standard measures of AS severity are the maximum velocity (Vmax) across the stenotic valve, the mean transaortic pressure gradient (ΔP mean) calculated with the Bernoulli equation, and the functional aortic valve area (AVA) calculated with the continuity equation. Echocardiographic ΔP mean and AVA calculations have been well-validated against invasive measurements and are now the standard of care to diagnose the severity of AS. [1,8,9] Transaortic velocities and gradients vary with volume flow rate and may be misleading in high flow states such as concomitant aortic insufficiency, or low flow rates associated with left ventricular dysfunction, making the aortic valve area a critical measurement in determining the severity of stenosis.

Guidelines

The American College of Cardiology (ACC)/American Heart Association (AHA) have developed guidelines defining the four stages of aortic stenosis.[2,10] Stage A defines patients at risk of developing AS such as those with congenital bicuspid valves or those with aortic sclerosis. Stage B is a patient who, by echocardiography, has mild or moderate AS. Stage C refers to a patient who has hemodynamically severe AS without symptoms. Stage D refers to hemodynamically severe AS in a patient with symptoms. Hemodynamically severe AS is defined as a peak aortic jet velocity greater than 400 cm/s or a mean transvalvular pressure gradient greater than 40 mmHg or an aortic valve area (AVA) of less than 1 cm^2. The guidelines go on to say that aortic valve replacement for symptomatic, hemodynamically severe aortic stenosis is a Class I recommendation. Aortic valve replacement is a Class IIA recommendation for patients with moderate aortic stenosis (stage B) with an aortic velocity between 300 cm/s and 390 cm/s or a mean pressure gradient between 20 mmHg and

39 mmHg who are undergoing cardiac surgery for other indications.

Asymptomatic hemodynamically severe AS presents a more difficult decision-making process. The ACC/AHA guidelines divide this group into two subcategories. Patients who have asymptomatic severe AS and good left ventricular function with an ejection fraction of greater than 50% are categorized as Group C1 and patients with reduced left ventricular systolic function and hemodynamically severe AS are categorized as Group C2. Group C2 also have a Class I recommendation for aortic valve replacement. For patients with asymptomatic hemodynamically severe AS and normal left ventricular systolic function with an ejection fraction greater than 50%, the stage C1 group, aortic valve replacement should be considered with the Class I recommendation if the patient is scheduled to undergo other cardiac surgery or if symptoms are unmasked by additional testing, such as stress testing. For stage C1 patients who are, indeed, asymptomatic, even after stress testing, a plan of watchful waiting is reasonable with clinical followup every 6 to 12 months, including echocardiography at least yearly.[3,11,12]

The risk of hemodynamically severe AS is well-documented. Studies have demonstrated that up to 50% of patients will die within the three to five years from the date of diagnosis without intervention. Even in those who are asymptomatic, 70 to 80% of patients will develop symptoms requiring intervention within two years.[1, 6, 7,13,14] Several predictors of rapid hemodynamic progression of AS include smoking, dyslipidemia, male sex, diabetes mellitus, hypertension, chronic renal disease, and concomitant coronary artery disease.[2,15]

Evaluation

Patients with hemodynamically severe AS who, on initial questioning, appear to be asymptomatic should be evaluated further to determine if they are truly asymptomatic if, indeed, they are candidates for either a transcutaneous aortic valve replacement, (TAVR) (procedure or surgical aortic valve replacement (SAVR). The most common first symptom of hemodynamically severe AS is unexplained exertional dyspnea. Stress testing is valuable in these patients. An abnormal exercise stress test in these patients is defined as development of angina, severe dyspnea, presyncope, decreased exercise tolerance, or inadequate increase in systolic blood pressure of less than 20 mmHg. If any of these findings are present, it places these patients in a Class IIA category for proceeding with aortic valve intervention.1,16,17 In addition, measuring levels of brain natriuretic peptide (BNP) in asymptomatic patients may help predict symptom onset as well as postoperative survival, functional status, and LV function; although, exact levels are not currently defined.1

Unfortunately, there is no medical therapy that has been proven to be beneficial in hemodynamically severe AS. Multiple studies have been done to determine if statin therapy would slow the progression of aortic valve sclerosis or mild stenosis. To date, the vast majority of these studies do not show a benefit of statin therapy.[18,19]

Since the development of symptoms with hemodynamically severe AS predicts a poor prognosis with the associated high mortality rate over the next five years, aortic valve replacement or intervention definitely is indicated in this group of patients. Surgery in such patients improves symptoms and increases life expectancy.[14,20,21,22,23] Aortic valve replacement currently is the most common operation for valvular heart disease in North America. Bioprosthetic valves are most commonly recommended for patients over the age of 65, but may be used in some younger patients if they have an extremely active lifestyle or if the risk of chronic anticoagulation creates a problem[1,20]. The mortality associated with aortic valve replacement has decreased markedly over the past several decades. The STS database reveals a 30-day mortality of under 3% for isolated aortic valve replacement and under 5% for combined aortic valve replacement plus coronary artery bypass surgery.[25,26]

While SAVR is the mainstay of treatment of symptomatic severe AS, it also entails substantial risks for patients with severe comorbidities, and for patients considered at "extreme" risk, surgery may not be appropriate. In others, technical limitations, such as porcelain aorta, prior significant mediastinal radiation, or a patent left internal mammary graft lying beneath the sternum, SAVR may not be possible. Additionally, it is possible that less invasive approaches to aortic valve replacement (AVR) may be equivalent to SAVR for patients at high or even intermediate-risk of complications related to SAVR. As a result, TAVR has been developed for the treatment of patients with severe symptomatic AS who have an unacceptably high estimated surgical risk, or in whom TAVR is preferred due to technical issues with surgery.

TAVR is FDA approved for patients with either severe symptomatic native aortic valve stenosis, or for valve-in-valve treatment of failure of a bioprosthetic aortic valve,

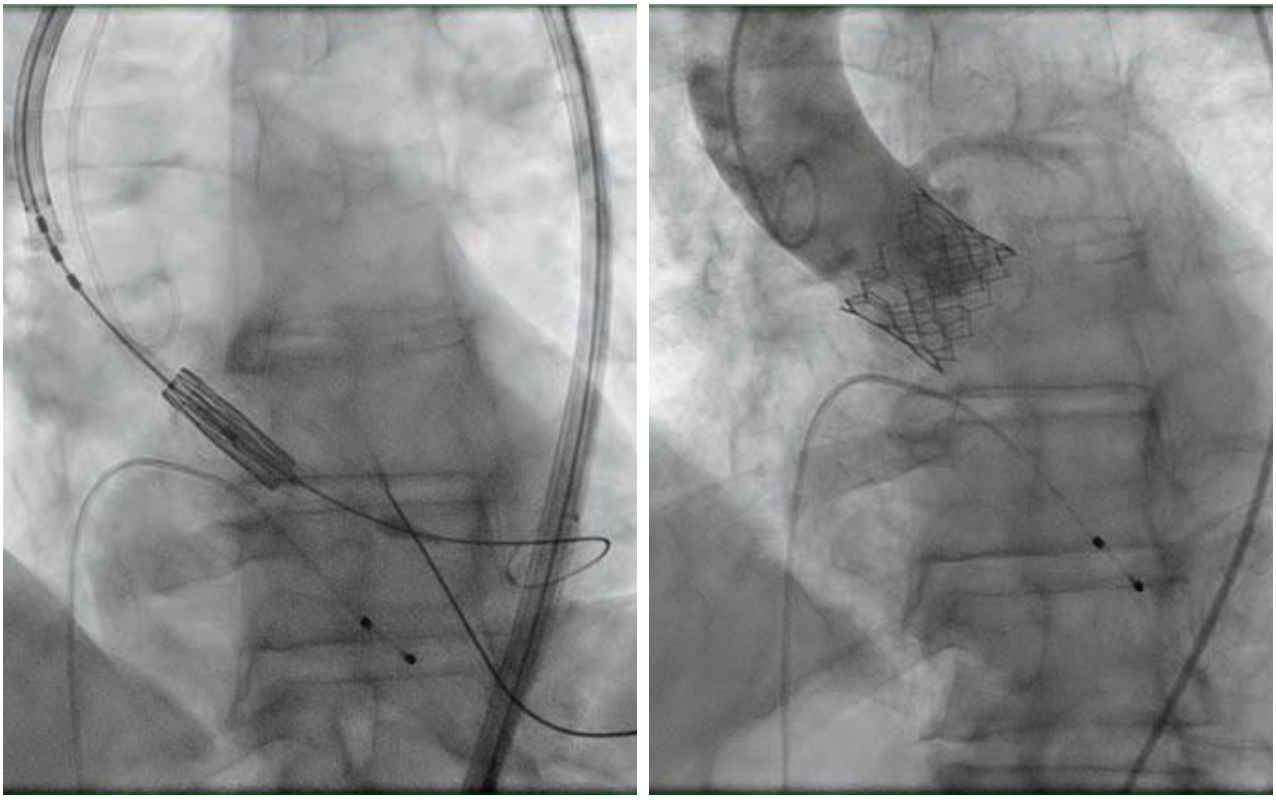


Figure 1
Placement of a Sapien S3 valve via the transfemoral route.

Panel A – Valve positioning, the valve is crimped on a valvuloplasty balloon and inserted to the aortic annulus over a stiff guide wire that is placed across the aortic valve into the left ventricle.

Panel B – Post-valve deployment. The valve is well deployed with no evidence of coronary obstruction or paravalvular leak.

who are either considered high risk or extreme risk for surgical AVR. Patients can be considered high-risk if either they have a STS calculated risk of 30-day mortality with SAVR of greater than 8% or if they have an STS risk of less than 8% but have been considered high-risk for SAVR by two cardiac surgeons. The preferred access site for TAVR is via a trans-femoral approach, but for patients with significant peripheral vascular disease that cannot accommodate the large size femoral sheaths alternative access approaches have been used. The two currently available TAVR devices in the United States are the balloon expandable Sapien valve (Edwards Lifesciences) which can be placed via a trans-femoral, trans-subclavian, trans-apical, or direct aortic approach, as well as the self-expanding CoreValve (Medtronic) which can be placed via a trans-femoral, trans-subclavian, or direct aortic approach. (See Figure 1).

Outcomes of TAVR to treat native aortic valve stenosis with either of these devices have been evaluated in randomized trials. The Sapien valve was first evaluated as part of the Placement of Aortic Transcatheter Valves (PARTNER) multicenter trial which had two arms, a comparison of TAVR to medical therapy including balloon aortic valvuloplasty for patients at prohibitive surgical risk, and a separate arm that randomized high risk patients to SAVR versus TAVR. For the inoperable arm, the investigators randomly assigned 358 patients with a mean age of 83 years. At one year, the mortality rate was reduced with TAVR compared to standard therapy with a 31% mortality with TAVR and a 51% mortality with SAVR. The benefit of TAVR persisted up to five-years of follow-up. Among survivors at one, two, three, and five years, functional class was better with TAVR versus standard therapy. However, the stroke rate was significantly higher in the TAVR group at 30 days and at three years, but by five-years of follow-up the stroke rates were equivalent.[27]

Among 699 high risk patients randomized to either SAVR or TAVR with the Edwards Sapien valve, the mean age was 84 years and the mean STS predicted risk

of mortality was 11.7%. Mortality rates in the TAVR and surgical group were similar at 30 days (3.4% and 6.5%), one year (24.3% and 26.8%), and five years (67.8% and 62.4%). Combined strokes and transient ischemic attacks were significantly more frequent after TAVR than after SAVR at 30 days (5.5% versus 2.4%) and at one year (8.7% versus 4.3%, $p = 0.04$) with no significant difference at five years (15.9% versus 14.7%). More patients undergoing TAVR reported symptom improvement at 30 days, but at one year, symptom improvement was similar in the two groups. TAVR was associated with more frequent major vascular complications while SAVR was associated with more frequent major bleeding and new-onset atrial fibrillation. Moderate or severe paravalvular aortic regurgitation was more frequent after TAVR than after surgery at two years (6.9% versus 0.9%) and the presence of significant paravalvular aortic regurgitation was associated with increased late mortality. The risk of permanent pacemaker placement was equal in the surgical and TAVR arms with a risk of 4.0% .[28]

In the CoreValve High Risk study 795 patients with severe AS and high surgical risk were randomized to either TAVR with the CoreValve self-expanding valve or SAVR. The mean age was 83.2 years and the mean STS predicted risk was 7.4%. Mortality at one year was significantly lower in the TAVR group than in the surgical group (14.2% versus 19.1%) and this mortality benefit persisted at two years of follow-up. Major vascular complications, cardiac perforation, and permanent pacemaker implantation were more frequent after TAVR. Life-threatening or disabling bleeding, acute kidney injury, and new-onset or worsening atrial fibrillation were more frequent after surgery. Compared to the Sapien valve, the risk of a patient needing a pacemaker post-TAVR was higher in patients treated with CoreValve (with rates greater than 20%)[29]. It is important to note that in both studies, patients treated with a trans-femoral approach had far better outcomes as compared to patients treated by alternative access routes. Additionally both studies demonstrated equivalent valve performance with similar valve areas and gradients across the valve at long-term follow-up for either TAVR or SAVR. Based on the results of these trials, TAVR was FDA approved for use in patients at either high or extreme risk for surgical aortic valve replacement.

While TAVR has been approved in high-risk patients there is growing evidence of patients at intermediate risk being treated with TAVR. The TVT database which tracks the use of TAVR in the United States demonstrated that the average STS score for patients undergoing TAVR is 5.0% which is far below the threshold for determining high risk which is 8.0%.[30] Additionally, recent randomized and observational data of TAVR using newer iterations of the original Sapien valve (Sapien XT and Sapien S3) have demonstrated at least equivalent outcomes of TAVR compared to SAVR in intermediate risk patients. The PARTNER 2A trial randomly assigned 2,032 intermediate-risk patients with severe aortic stenosis to undergo either TAVR or SAVR. The mean STS score was 5.8%. Prior to randomization, patients were separated into two cohorts on the basis of an evaluation of the peripheral arteries: 76% were included in the trans-femoral-access cohort and 24% percent were included in the transthoracic-access (trans-apical or trans-aortic) cohort. The rate of death from any cause or disabling stroke was similar in the TAVR and SAVR groups at two years, with rates of 19.3% in the TAVR group and 21.1% in the SAVR group. In the trans-femoral-access cohort, TAVR resulted in a significantly lower event rate than SAVR with a significantly lower risk of death or the combined outcomes of death and stroke. However, similar to prior studies SAVR resulted in less moderate or severe paravalvular aortic regurgitation (0.6%) as compared to TAVR (3.7%), and there continued to be a higher mortality during two-year follow-up for patients with moderate to severe paravalvular regurgitation.[31]

Lastly, an observational study suggested that TAVR with the balloon-expandable Sapien S3 valve may be superior to SAVR for intermediate-risk patients. The S3 valve is the newest iteration of the Edwards balloon expandable valve and was designed with a particular focus on reducing paravalvular regurgitation by affixing a skirt to the lower portion of the valve to seal the valve annulus and prevent leakage. Additionally it has a lower profile allowing for more patients to be treated via a trans-femoral approach. The study included 1077 patients with symptomatic severe AS with intermediate-risk who underwent TAVR with a SAPIEN 3 valve. TAVR was performed via the trans-femoral route in 88 percent of patients. Outcomes were compared with those for 944 patients in the SAVR arm of the PARTNER 2A randomized trial using a pre-specified propensity score analysis. At one-year follow-up, all-cause mortality for the TAVR group was 7.4%. Complications were incredibly low with a disabling stroke rate of only 2% and moderate or severe paravalvular regurgitation of only 1.5%. The

primary composite end point was death from any cause, all strokes, and incidence of moderate or severe aortic regurgitation. TAVR was superior to SAVR for the composite end point as well as for the individual outcomes of death and stroke.[32] The results of the Sapien S3 Intermediate Risk study are incredibly encouraging and likely mean that TAVR will soon be approved for the intermediate risk population. The SURTAVI trial of intermediate risk patients using the CoreValve device is almost complete and results should be announced soon. Like the Edwards device newer iterations of the CoreValve have been approved. The newest self-expanding valve the Evolut R valve also has a lower vascular profile and is repositionable and re-capturable which have led to a lower pacemaker rate and paravalvular leak rate than in the original CoreValve in provisional studies. Already it is clear that TAVR will move toward lower risk patients as both Edwards and Medtronic are beginning to enroll patients in studies of TAVR in low-risk patients.

While stroke rates in recent studies comparing TAVR to SAVR have been relatively equivalent, a recent study evaluating patients who underwent TAVR and were then evaluated by 4 D comuted tomography (CT) were found to have the presence of subclincial valve leaflet thrombosis. The presence of sub-clinical leaflet thrombosis was first noted in a randomized control trial of the Portico valve, which led to the study being briefly halted. Thereafter a number of registries were formed to evaluate the presence of sub-clinical leaflet thrombosis of other transcatheter and surgical bioprosthetic aortic valves. The combination of these registries included 132 patients, 105 of which had undergone TAVR and 27 who underwent SAVR. A total of 17 of these patients had reduced leaflet motion of the aortic valve, which represented 14% of the patients who underwent TAVR and 7% of the patients who underwent SAVR. While none of these patients demonstrated an increase in aortic valve gradients, they all had thrombus formation on the valve. Interestingly, patients who were placed on therapeutic anticoagulation with warfarin had resolution of the reduced leaflet motion.[33] While further investigation is required to determine the incidence, clinical significance, and appropriate management of subclinical bioprosthetic valve leaflet thrombosis, these findings raise the possibility that leaflet thrombosis could be a cause of an increased stroke risk with TAVR and may necessitate patients being placed on more aggressive anti-platelet or anti-thrombotic regimens post-TAVR in the future.

While outcomes with TAVR have significantly improved over the last few years, appropriate patient selection should be performed to ensure that the risks of complications with TAVR are mitigated. In order to determine candidacy for TAVR, patients should undergo CT angiography of the chest, abdomen, and pelvis with 3D reconstruction of the aortic annulus and peripheral vasculature. The CT study will determine if a patient has adequate ilio-femoral diameters for the preferred trans-femoral access route. Additionally by evaluating the CT the operator can determine the height of the coronary arteries from the aortic annulus as low coronaries place a patient at risk of coronary obstruction with TAVR. CT is useful to demonstrate the presence of significant annular and left-ventricular outflow tract calcium which place a patient at risk for annular rupture and paravalvular regurgitation as the calcium can prevent adequate sealing of the valve. Additionally, specific considerations should be given to patients with low ejection fraction as they may not tolerate the rapid ventricular pacing that is needed to place the Sapien valve or the balloon aortic valvuloplasty performed prior to the insertion of the valve in most TAVR procedures. Additionally, patients should undergo pre-TAVR coronary angiography to determine the need for percutaneous coronary revascularization prior to TAVR.

Summary

In summary, TAVR should be the treatment of choice for patients at extreme risk for SAVR with severe symptomatic AS and is considered equivalent if not superior to SAVR in patients who are at high risk for complications with SAVR and who can undergo trans-femoral TAVR. Data is emerging that TAVR may be a reasonable approach for intermediate risk patients and may provide equivalent results as compared to SAVR in this population. While newer iterations of currently available TAVR devices have been designed to reduce the incidence of vascular complications, permanent pacemaker placement, and paravalvular aortic regurgitation, considerations to further mitigate these complications should be taken as TAVR moves toward lower risk populations. The optimal medical management of patients post-TAVR is still being determined and may

be altered if the prevalence of sub-clinical valve leaflet thrombosis is more common than originally anticipated. Finally, pre-TAVR imaging and patient selection should be performed to ensure that the procedure can be performed with the lowest possible risk of complication. The dissemination of TAVR into the broader AS population has been rapid and will likely continue, it is important that we continue to move cautiously to ensure the lowest possible complication rate and the highest rate of success and long-term benefit for our patients.

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Disclosure

None reported.

MM

Warning: Medicare May Be Bad for Your Heart

by Scott Gottlieb, MD

Aortic valve replacements are superior to open-heart surgery and less risky. So why are they hard to get?

As people age, the main valve controlling the flow of blood out of the heart can narrow, causing heart failure, and sometimes death. In the past the only way to repair the damage was risky open-heart surgery. But an ingenious medical device now allows the heart to be repaired using a catheter that introduces a replacement valve through a main artery in the leg—another miracle of modern medicine.



A transcatheter aortic valve replacement, which can be used as a minimally invasive alternative to open heart surgery.

In 2011, more than four years after they hit the European market, the Food and Drug Administration finally approved aortic heart valves for use in the U.S. The total cost of the new procedure is about the same as open-heart surgery. But government bureaucrats feared that the new replacement valve's lower risks and easier administration would mean that many more elderly patients would seek to fix their failing heart valves, pushing up Medicare's total spending. To limit their use, regulators created coverage rules based on a set of strained medical criteria. It was a budget prerogative masquerading as clinical reasoning.

This episode is a vivid example of the government's increasing practice to regulate medicine and ration care. A series of landmark studies published earlier this month in the *Lancet* and the *New England Journal of Medicine*, and presented at the annual meeting of the American College of Cardiology in Chicago, makes clear how contrived the original Medicare guidelines were.

For a patient to be qualified for the aortic valve device, Medicare required two cardiac surgeons to certify first that a patient wasn't a candidate for the open-heart repair. Also mandated was the presence of a cardiothoracic surgeon and an interventional cardiologist in the operating room during the procedure.

While regulators argued that both doctors had to be on site to rescue the patient in case of a botched procedure (which is extremely rare), in reality this



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costly and redundant condition was a not-so-veiled way to squelch "competition" between the two different medical specialties that might stoke wider use of the valve device. Medicare also confined the procedure to primarily large academic medical centers.

The limits represented an unprecedented collaboration between Medicare and the FDA, which put labeling rules on the valves that enabled the restrictions. Such a clumsy and forceful intrusion into the practice of medicine would never let medical care evolve with the pace of scientific advance.

The studies unveiled in Chicago confirm that many more patients could benefit from noninvasive valve repairs, and with a lower risk of death and other complications associated with open-heart surgery.

Both the *Lancet* study and the even more rigorously designed *New England Journal* study showed that the replacement valves were superior to surgery in the patients examined. The Lancet study reported results from an evaluation of device maker Edwards' newest transcatheter heart valve—the Sapien 3—in patients who were at "intermediate risk" of death from open-heart surgery. This third-generation device proved superior after one year to open-heart surgery on every key measure, including all-cause mortality (7.4% versus 13.0%) and disabling strokes (2.3% versus 5.9%).

Yet most of the patients in each of these studies, having less severe risks of death, aren't eligible to receive the devices under current Medicare rules. As a result, many patients are opting for riskier open-heart procedures, or no fix at all. Similar benefits were seen in a third study that looked at outcomes in higher-risk patients three years after they received a comparable valve made by Medtronic.

The studies clearly show that more patients should get the devices. But it will take six months or longer for the FDA to update the product labels to reflect the new results, and another six months or more for a recalcitrant Medicare agency to conform its payment rules to the new medical standard.

Aortic valve devices have improved since Medicare first imposed its restrictive policies, as has the expertise in delivering these procedures. Proponents of Medicare's heavy hand will argue that without the agency's intervention the evidence unveiled in Chicago may never have been developed—a fair point.

But it isn't as if the federal regulators discovered the process for scientific inquiry that led to the Chicago results, or invented evidence-based medical practice. Progress would accelerate if doctors were able to practice medicine more freely, based on the latest science and not the restrictive coverage rules advanced by Medicare.

The alternative to this bureaucratic logjam is to leave the decisions to market participants like health systems and insurers who will compete to offer patients good prices and timelier access to the best services. This is much more akin to the private Medicare insurance model advocated by House Speaker Paul Ryan and others. Embracing the current approach, with its clinical standards crafted in Washington, means getting used to more regulation over what patients can choose, and care that evolves at a pace set by government. **MM**

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- Neurology
- Neurosurgery
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AA/EOE

Mercy

Building a Targeted Asthma Education and Management Program

by Helen Murphy, BHS, Jamie Wolverton, BHS & Chitra Dinakar, MD

Asthma self-management education is an empowering strategy that creates understanding and self confidence in home management.







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Abstract

For individuals with asthma, self-management at home can be complex and overwhelming. The National Asthma Guidelines recommend education, ongoing assessment of control, and identification of those at high risk, as integral elements of improving outcomes for these individuals. Children's Mercy implemented standardized, patient-centered asthma education interventions along with institution of asthma control assessment tools and targeted management of high risk asthmatics. Many of these tools are applicable for use in primary care ambulatory practices.

Introduction

Asthma is a chronic lung disease that impacts the lives of over 142,535 children in Missouri[1] and accounts for 13,148 emergency room visits state wide (2013 data)[2] including 5,883 visits at the Children's Mercy Emergency Department during the same time frame. In addition to triggering increased health care utilization, poorly controlled asthma also negatively affects the quality of life of these children. In Missouri 57% of children with asthma had an asthma attack in the past year and 58% had to limit their activities due to asthma.[2]

Managing asthma on a day to day basis can be a struggle for patients and families. First, patients need to identify triggers and learn how to reduce and/or eliminate exposure. Second, there is a wide array of complex medications that not only look similar, but have different directions for use, different dosages, and different timings of the day when they need to be administered. And finally, patients and families need to learn self-management skills.

Asthma education therefore needs to be an integral component of any comprehensive asthma management program. Such education is essential to improving a patient's comprehension and confidence in their home management, and has been shown to improve patient outcomes. According to the 2007 National Asthma Guidelines, "the benefits of educating people who have asthma in self-management skills of self assessment, use of medications and actions to control or prevent exacerbations, include reduction in urgent care visits and hospitalizations, reduction of asthma related health care costs, and improvement in health status."[3]

Inception of a Novel Asthma Education Program

Recognizing the importance of asthma education, Children's Mercy

created an evidence based, metro-wide comprehensive asthma management and education program, the Kansas City Childhood Asthma Management Program (KC CAMP)[4] in 1998. This program was based on a framework of evidence-based guidelines, use of written asthma action plans, and the availability of trained asthma educators at all points of care. A cardinal feature of KC CAMP was the focus on empowering the child and family to take control of their asthma, with the introduction of asthma action plans and self-management education conducted by an educator at each patient visit within the hospital system. KC CAMP was also involved in reaching out to community practices in the Kansas City area and tailoring asthma educational modules to the needs of their staff.

In 2005, KC CAMP signed a contract with a health plan to manage their asthma population. During the review of the educational program employed by the health plan, it became clear that their methodology was inconsistent, asthma educational content was variable, and insufficient time was allotted to meet the asthma needs of the patient/family. An Asthma Coordinator was therefore hired to bridge the gap in educational oversight. A Flip Chart method was developed to provide consistent content during every educational session with an asthma patient. The Flip Chart is a stand-up, 8.5" x 11", two-sided chart. During education, the patient/family views relevant pictures on one side of the flip chart, while the educator narrates the educational content on the other side. The asthma educational content is based on the 2007 National Asthma Guidelines and consists of patient/family goals, asthma control, basic asthma pathophysiology, roles of medications, triggers, asthma action plan instructions and device techniques. The Flip Chart also employs health literacy techniques such as the use of pictures, fifth through seventh grade reading level, non-medical terms, and teach-back technique to aid in learning and retention of the content. Booklets containing the same information are provided to patients/families during the educational session.

The Flip Chart method was implemented in an inpatient Asthma Class in 2011. Each caregiver and /or patient admitted to the hospital for asthma was invited to participate in the class. The class promoted open communication between patient/family and educator in a learning environment conducive to a variety of learning styles such as VARK (visual, auditory, reading and kinesthetic) or viewing, listening, reading, and hands-on interactive activities. In order to evaluate its effectiveness, structured surveys were given to all attendees before and after the class to assess the caregivers' knowledge and comfort in managing asthma. Caregivers attending the class reported statistically significant greater comfort in managing asthma at home ($p<0.0001$), belief that they had the right information to know what to do when their child had an asthma attack ($p<0.0001$), and belief that they learned something new about asthma home management ($p<0.0001$). Due to the encouraging results the class was expanded to five days a week and opened up to the community. The Flip Chart became the standardized method for asthma education throughout the hospital system.

To help embed the Flip Chart Method into the asthma educational culture of the hospital, each location was given its own Flip Charts and booklets. The asthma educators, consisting of nurses and respiratory therapists, were provided training on the effective use of the Flip Chart, while concomitantly enabling them to obtain continuing education credits for their discipline. The goal of the standardized Flip Chart Method was to ensure consistency in the education delivered at the first visit that patients/families made to the Children's Mercy system, regardless of the location (emergency department, urgent care, inpatient or clinic), along with repetition and reinforcement at each subsequent visit, thereby reducing patient/family confusion and improving retention. As per the 2007 National Asthma Guidelines, "Asthma self-management education should be integrated into all aspects of asthma care, and it requires repetition and reinforcement."[3]

Since asthma is managed and education completed in many different locations throughout the Children's Mercy system an internal asthma website was created to house, in one convenient location, patient and provider resources containing the standardized asthma educational content and quick access to evidence-based asthma management tools. An external asthma website was also built, specifically designed for patients/families/the community to have easy access to educational materials and links to reputable asthma information on the web. The website also contains asthma information for health care professionals including handouts, videos, and CME opportunities. (See Table 1.)

While websites are a great way for families to gather valuable asthma information, many of our families are increasingly involved in social media sites like Facebook and Twitter. According to Pew Research Center, "As of January 2014, 74% of online adults use social networking sites."[6] To reach the social media population we started an asthma twitter account, @breatheKC. Through this we are able to post helpful asthma tips and daily pollen and mold counts. Twitter chats are another way to have open discussions with the community and answer any questions about asthma. Twitter has been a helpful tool in connecting with the local asthma community, as well as to reach a regional and national audience.

Table 1

A table of different asthma resources being used at Children's Mercy Hospital. You can find most of these on the website: www.childrensmercy.org/asthma

Asthma Resource	Type	Description	Age	Language Available
Asthma Class Video 	Online Video	The video is a shortened, but interactive version of our in-person Asthma Class. Learn about asthma right at home	6-Adult	English
Pippy Learns about Asthma 	Activity booklet	A fun and educational activity and coloring book that teaches children about asthma	2-12 years old	English
Asthma Controller Calendar 	Paper Calendar with stickers	This calendar helps keep kids keep track of their daily medicine by using stickers to place on the calendar when they take their daily controller	4-16 years old	English
Asthma Booklet 	Paper Booklet	A comprehensive and health literate overview of asthma for the community	6-adult	English/Spanish
Asthma Diary 	Paper handout	The diary helps patients and families track daily asthma symptoms	6-adult	English/Spanish

The asthma website has valuable information for the community; however, it does not include what we consider to be one of our best resources - the "Asthma Class." While the Asthma Class is an effective tool for teaching asthma self-management, it requires attendance at a one hour class on a weekday, limiting its access to the family member who is with the hospitalized child. This leaves other family members and caregivers in the community without education on important asthma self-management tools. This observation prompted us to institute multiple interventions to enable asthma education to be more widely available in the community.

The first intervention we initiated was the "Asthma Class video." This video is an interactive condensed version of the actual Asthma Class, using the same evidence-based content and health literacy techniques. It was placed on the Children's Mercy's asthma website in November 2015 (www.childrensmercy.org/asthma). During the first three months the video received about 14 views per month. It was then introduced to community physicians in February 2016 through the Children's Mercy Progress notes e-mail and the views increased to 33 per month. To further broaden asthma education opportunities across the community we plan to introduce Saturday Asthma Classes. The first two classes will take place during the spring season with further classes offered during the busy fall asthma season. Enrollment in an Asthma Class can be completed on line or through a phone call. (See Table 1.)

The Asthma Class is geared towards adults and older children, but younger children can still learn about asthma in a fun and interactive manner. An asthma activity book was created to stimulate the minds of children. The activity book "Pippy the Puffin Learns about Asthma" follows the adorable Pippy and his RT teacher through the adventures of asthma. The book includes many educational activities including: coloring, word search, maze, seek and find and dot-to-dot for a fun asthma educational experience. (See Table 1.)

The Children's Mercy asthma program is continuously monitoring and updating the asthma educational materials to meet new evidence based guidelines and/or national

standards. It is currently working towards alignment with all nine standards recommended in the recently published National Standards for Asthma Self-management Education.[6] Although many of the standards are met, an Asthma Collaborative group is in place to provide the support needed for further implementation and monitoring of the standardized asthma educational program for the best possible outcomes for our asthma families as well as possible educational reimbursements by payors in the future.

Implementation of Guidelines-Recommended Asthma Control Assessment Tools

Asthma control is dependent upon a large number of variables including psychosocial and physiologic factors. The NHLBI Guidelines for the Diagnosis and Treatment of Asthma suggest that routine assessment of asthma control is an integral part of maintaining health and wellbeing[3]. These guidelines recommend use of a self-assessment questionnaire intended to capture the patient's and family's impression of asthma control, self-management skills, and overall satisfaction with care. One such tool is the Asthma Control Test™ (ACT)[7], and its pediatric version, the Childhood Asthma Control Test™ (C-ACT)[8]. Use of this self-assessment tool has been advocated for all patients presenting to an outpatient clinic at Children's Mercy.

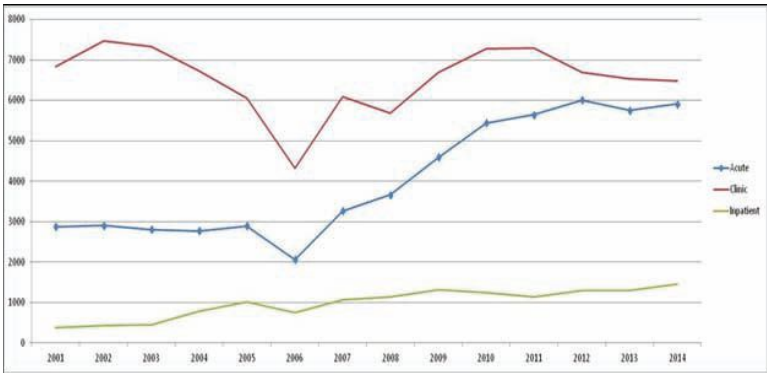
Following the advent of the NAEPP guidelines a quality improvement project was initiated at our institution aimed at improving adherence to guidelines including use of the ACT and C-ACT in routine clinic care. The project was initiated at the Allergy, Asthma and Immunology (A/A/I) clinics with gradual systematic involvement of Pediatric and Adolescent Clinics. Data collection began on March 13, 2007 and ended in July 13, 2008. Each asthma patient between the ages of 4-18 years (and caretaker as applicable) was given a paper copy of the ACT/C-ACT to complete at each clinic visit while in the waiting room. Following the clinic visit, each provider recorded ACT/C-ACT scores along with information on demographics, asthma self-management plans, spirometry, exhaled nitric oxide, current medication lists by class, self-reported medication adherence, provider assessment of asthma severity, and actions taken by the provider in response to assessments of asthma control on individual one-page 'visit planners'. Data from the 'visit planners' were extracted and stored in a web-based registry ("Asthma Control Tracker™") by designated and trained personnel[10]. Of the cohort of 1338 children (1787 visits) evaluated in primary and specialty asthma clinics 47% had ACT and c-ACT scores that suggested uncontrolled asthma, and changes in physician treatment plans were associated with changes in ACT/C-ACT scores, even when physicians were unaware of ACT/C-ACT results[11]. We determined that use of the web-based Asthma Control Tracker™ produced high levels of guideline adherence.

Bolstered by the results of the above project, process consisting of a paper ACT/C-ACT was initiated in 2011 to facilitate consistent completion at outpatient visits and subsequent documentation in the electronic medical record (EMR). A quality improvement project was implemented to improve the percent of ACT/C-ACT documented in the EMR from the baseline rate of 17%. This process involved a paper ACT/C-ACT given to the patient and the scores were manually entered into the EMR by the provider. In 2012, an iPad version of the ACT was implemented which allowed for patient to complete the assessment on the iPad and the results automatically integrated into the EMR. A year later, an ACT internet portal was placed on all exam room computers in the outpatient clinics for further ease of access. These improvements allow providers to track ACT scores over time and assess the impact of ongoing therapy on asthma control. Since July 2015 we have surpassed our institution-wide goal of 75%.

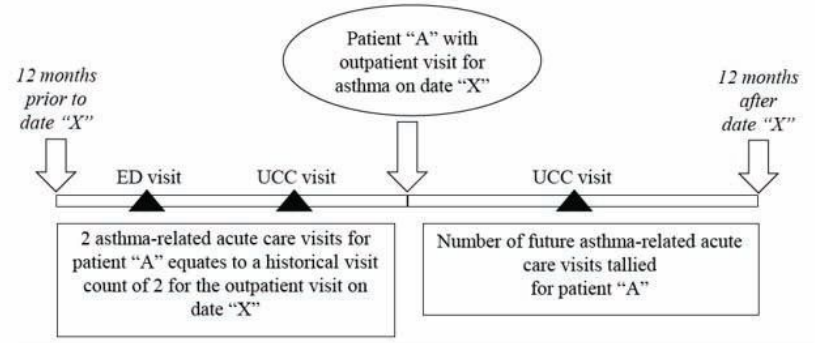
Implementation of a "High Risk" Asthma Management Protocol

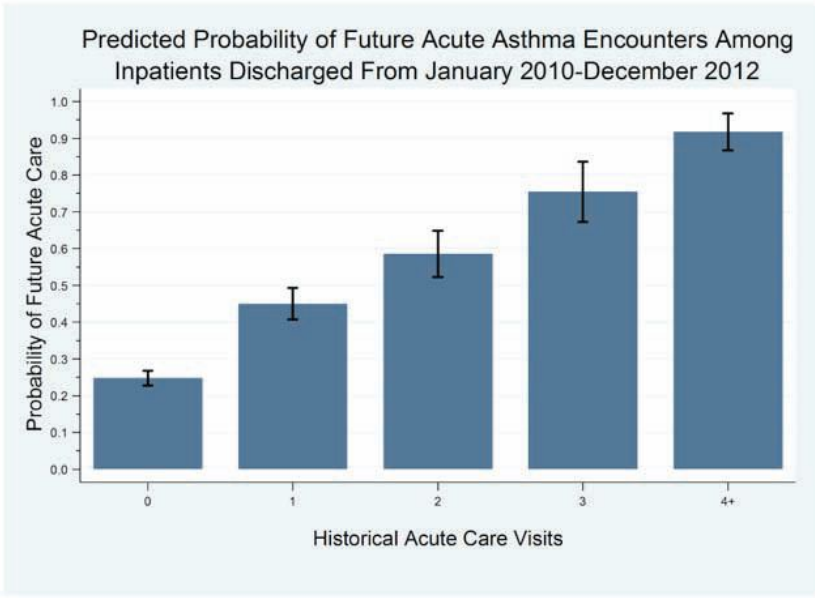
The Asthma Coordinator promotes evidence based asthma management and education while analyzing and reporting quality outcomes to providers and staff. While analyzing temporal data, we were able to identify a trend in rising acute emergency department visits between 2001 and 2014, and a slight upward trend in hospitalizations. (See Figure 1.) As per the 2007 National Asthma Guidelines, "Patients who are at high risk for asthma-related death require special attention— particularly intensive education, monitoring and care."[3] To meet this need, a risk stratification model was developed to determine the high utilizers of asthma care, i.e. those with repetitive visits to acute care settings such as with emergency department visits, urgent care visits and hospital admissions. The model[9] found that the historical count of acute care visits (ACVs) was predictive of future ACVs. (See Figures 2 and 3.) A significant increase in the probability of future ACVs was observed with each additional historical visit, effectively stratifying risk by the historical visit count. Notably, a small group of ambulatory patients accounted for a disproportionate number of future ACVs, namely, those with three or more historical ACVs were found to have a 60% chance of having a future acute care visit. This population was termed "high risk" meriting closer scrutiny and provision of enhanced asthma management services. Consequently, this is a simple model that can be used by

Figure 1
Identity of a trend in rising acute emergency department visits between 2001 and 2014, and a slight upward trend in hospitalizations.



Figures 2 and 3
The model below found that the historical count of acute care visits (ACVs) was predictive of future ACVs.





providers in all outpatient practices to identify asthma patients who may require focused attention.

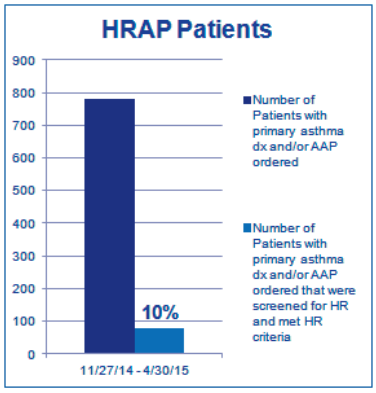
The same model was used with patients hospitalized for an asthma exacerbation. In 2014, a High Risk Asthma Protocol (HRAP) was launched in the inpatient setting using the parameters in the model as criteria for entry into the protocol:

- Greater than or equal to four ED/UCC/inpatient episodes in the past year (including the current visit)
- And/or current PICU admission or history of a cardiac arrest or intubation (admission resulting from ED/UCC visits counts as one episode).

The following ACV interventions were developed in order to decrease patient risk of future ACV: routine asthma inpatient care, provision of evidence based asthma action plans, asthma education through the Asthma Class, review of individual asthma action plans at the bedside and arrangement for follow up care. In addition, the high risk patient also receives a social work consult to assess for psychosocial barriers to ongoing follow-up care as an outpatient; an Environmental Health Referral for guidance regarding identification and avoidance of asthma triggers and, if indicated, a home evaluation; inpatient consultation with an asthma specialist as needed; ensuring that an outpatient follow up appointment is made to bridge the gap between emergency and primary care; and a summary of the inpatient visit and interventions sent to the primary care giver.

Based on our experience, we found that one of the most important aspects of the HRAP is the standardization of key outpatient interventions. The providers use the following interventions to assess asthma control to decrease risk of future ACVs: administration of the asthma control test to track asthma control, environmental health assessment, spirometry, exhaled nitric oxide testing, allergy testing, assessment for suitability of immune modulator therapy, influenza vaccine as needed, screening for the complications of systemic steroids, social work/case management and titration of asthma medications (step-up or step-down) as appropriate. Between November 2014 and April 2015, there were 78 high risk patients accounting for

Figure 4
HRAP Outcomes



Variable	n	Median Score (IQR)
HRAP Scores at Entry	78	5 (4,6)
HRAP Scores 1 year post Entry	78	0.5 (0,2)
There was a statistically significant (p<0.0001) decrease in HRAP scores from entry to 1 year post entry.		

Each patient scored at entry in to HRAP and one year post. Score: 1 point for every ED/UCC/hospitalization and 4 points for a PICU (admit resulting from ED/UCC visits counts as one episode)

10% of the hospitalized asthma population. Each patient was scored when enrolled into the HRAP and at one year post enrollment. The scoring consists of 1 point for every ED/UCC/hospitalization and 4 points for a PICU admission (admission resulting from ED/UCC visits counts as one point). There was a statistically significant ($p<0.0001$) decrease in HRAP scores from enrollment to one year post enrollment. (See Figure 4.) Our data suggests that use of a simple risk stratification model can help decrease acute care visits in the asthma population we serve.

Conclusions

For those living with asthma, home management of asthma can be complex and frustrating. Whether in a hospital setting, private practice, or in the community it can be challenging to dedicate the time patients and families need to address their asthma needs. Asthma self-management education is an empowering strategy that creates understanding and self confidence in home management. A consistent approach to education with reinforcement at every visit will help to improve retention, decrease confusion and increase confidence in self-management skills. Some of the lessons learned in creating a comprehensive asthma program at Children's Mercy may be able to be duplicated in primary care and specialists practices. Resources are available on our website www.childrensmecry.org/asthma. The Children's Mercy Asthma Coordinators are always available at 816-960-8907 to provide guidance and assistance.

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Acknowledgments

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Disclosure

None reported.

MM

Bridging the Radiology-Pediatrics Interaction Gap by Incorporating a PGY4 Radiology Resident into the General Pediatrics Team

by Munir Patel, MD, Randall Heller, MD, Danielle A. Cunningham, MSIV, Brett Donegan, MD & Lisa H. Hutchison, MD

Due to the ever increasing use of diagnostic imaging in medicine, knowledge of basic radiology concepts is necessary for today's practitioners.



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Abstract

To bridge the gap between clinicians and radiologists, radiology residents rounded with inpatient pediatric medicine teams to present and interpret daily imaging studies, as well as assist with decisions and indications for radiologic exams. Surveys were sent to team members who rotated with radiology residents, and the consensus strongly favored having radiology residents on future rotations. Team members responded that they benefitted from a better understanding of radiology exams, their indications and limitations.

Introduction

According to the Association of American Medical Colleges, only 21.4% of medical schools require radiology clerkships[1]. Also, a recent report assessing radiology education in medical school found that only 34.9% of 444 senior medical students from a variety of institutions had experienced dedicated radiology training with only 10.8% required to take a dedicated radiology rotation[2]. The same study found that the large majority of students underestimated risks of imaging procedures. Further, the majority of students (77%) had never heard of the American College of Radiology (ACR) appropriateness criteria, which have been established by multispecialty panels to determine which imaging study is most indicated in various clinical situations[2]. Similarly, authors of another study found that 96% (213 of 223) of third and fourth year medical students had never heard of the ACR appropriateness criteria[3].

A study of PGY1 interns found that 63.7% were expected to independently preview imaging exams, but only 60.2% claimed high confidence in recognizing common emergent pulmonary findings, such as pneumonia, pneumothorax, or position of lines/tubes, on chest radiographs[4]. The same study noted that 80.2% of PGY1s had never heard of the ACR appropriateness criteria[4]. The findings of these studies suggest a radiology education gap in the medical school curriculum and residency orientation programs that may lead to poorly prepared interns.

The Accreditation Council for Graduate Medical Education (ACGME) implemented the Next Accreditation System (NAS) in July 2013, and is based on residents achieving specialty specific milestones in each of the six core competencies, including communication skills, patient care, professionalism, medical knowledge, systems based practice, and practice based learning improvement[5]. In

the past, various clinical services, including pediatrics, rounded daily in radiology allowing trainees in both departments the opportunity to observe, learn and practice interdisciplinary core communication skills that can lead to improved patient care and a better understanding of systems based practice. However, this valuable core experience has gradually disappeared with the introduction of PACS (picture archiving and communication system).

Our institution sought to address this loss of educational interaction by developing an innovative pediatric rotation. We incorporated a PGY4 radiology resident (PGY4RR) into the pediatrics inpatient team to increase radiology exposure and education for pediatric residents and medical students rotating on pediatrics. During a 24-month period, 24 PGY4RRs spent one month each with the pediatrics team. On daily rounds, the PGY4RR provided educational value by previewing and presenting imaging studies, reviewing and discussing indications for future studies, and advising the team on the imaging approach best suited to answer patient specific clinical questions. The PGY4RR was also available to lead brief daily didactic sessions with members of the team as requested.

The purpose of this study is to survey pediatrics team members to determine if they supported the rotation and if it was of educational benefit to them.

Methods

Over two years, 24 PGY4RRs each spent four weeks on pediatrics. Resident responsibilities included:

1) presentation of imaging studies on daily rounds,

2) teaching medical students and residents imaging indications, limitations, appropriateness and basic interpretation concepts,

3) review of various other imaging (including outside studies) as needed, and

4) assistance with decisions regarding future exams.

If the PGY4RR encountered unfamiliar subject matter, then he/she consulted an attending pediatric radiologist and reported back to the team. The Institutional Review Board (IRB) granted approval, and primary care team members were surveyed (n=143), including pediatric attendings, residents, and medical students (Appendix A). Survey completion was not incentivized, but was incorporated into the routine, electronic end-of-rotation survey. Survey completion was an inclusion criteria; each question had to have a response to advance to the next screen. Participants were informed their responses would be confidential and anonymous. One hundred and four responses were received (72.7%). Repeated reminders were sent to nonresponders to increase response rate.

We designed a survey to assess the subjective impact on pediatric team members. A literature search revealed no similar validated pediatric surveys. After developing approximately 40 items that were relevant to the construct of interest, we reviewed and consolidated items into nine questions. Items were grouped into questions on resident knowledge and educational impact on the primary team, questions on future inclusion of a PGY4RR on rounds, and a question on likelihood of providing further clinical history when ordering radiologic exams. Prior to pilot survey distribution, we performed informal cognitive interviews with several trainees who were not part of the study cohort to verify that respondents interpreted questions as intended[6-8]. A pilot survey was performed and adjustments were made in data collection techniques to maximize the response rate, including incorporation into routine end-of-rotation survey. Previously published survey development principles were followed[8]. Specifically, survey items were written in the form of a question using construct specific responses with an odd number using a 5 point Likert scale or a 10 point rating[6]. Data were compiled electronically using Microsoft Excel. This rotation evaluation survey was deemed exempt by the ethics review board.

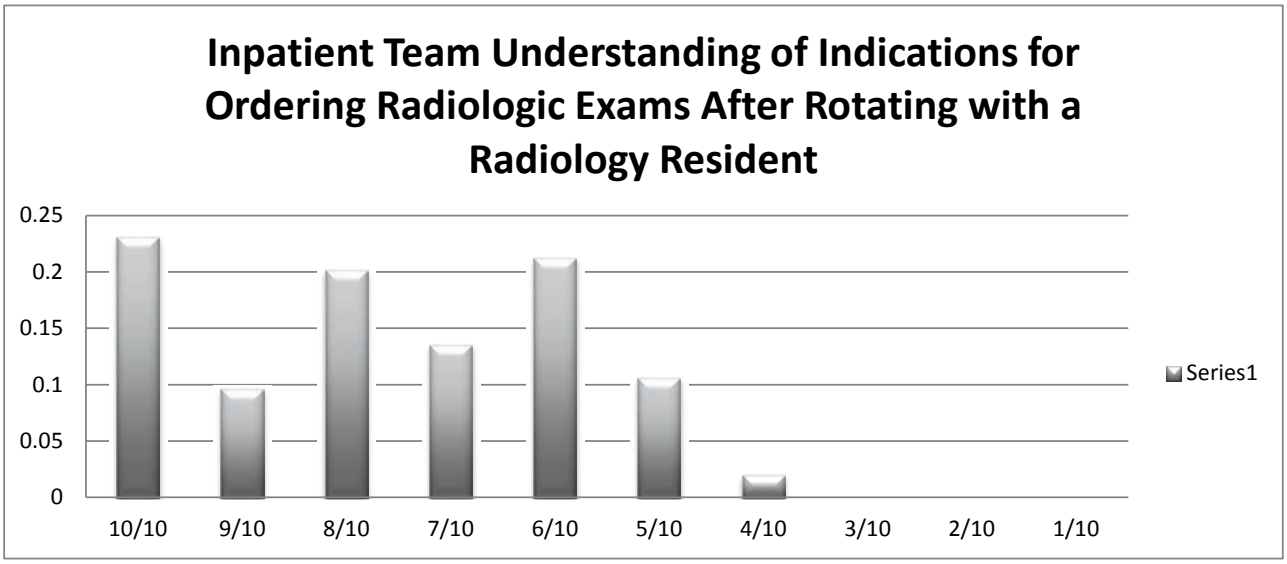
Results

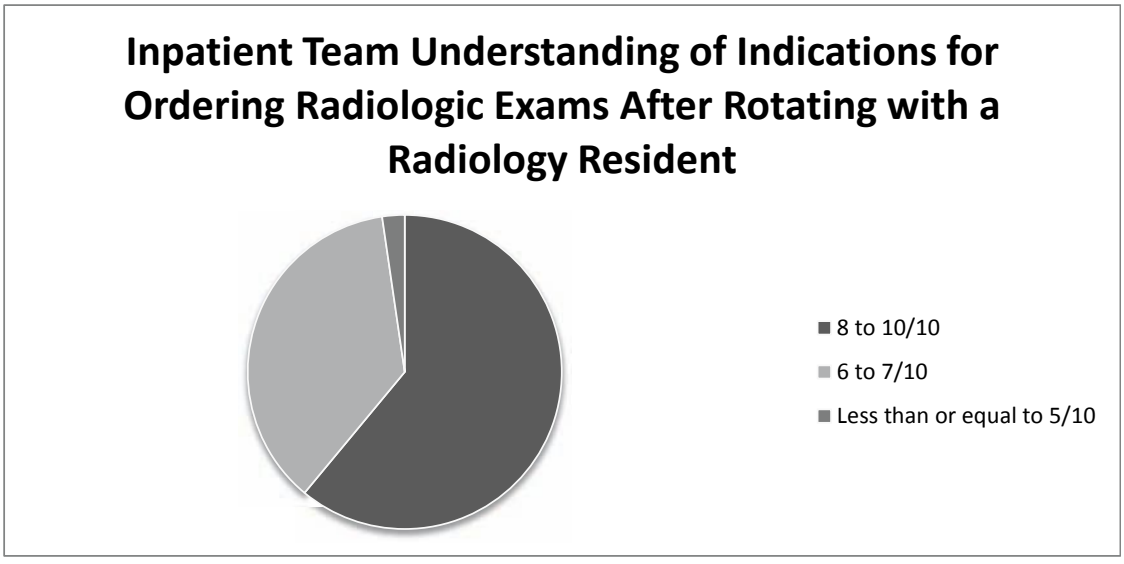
One hundred and four of 143 surveys (72.7%) were completed- all questions had a response selected- by pediatrics team members. Of the 104 respondents, 51 (49%) were medical students, 39 (37.5%) were residents, and 14 (13.5%) were attendings.

Questions on Resident Knowledge and Educational Impact on the Primary Team

Survey participants were asked how many weeks they rotated with the PGY4RR. Responses included 4 weeks (n=43 [41.3%]), 3 weeks (n=31 [29.8%]), 2 weeks (n=24 [23.1%]), and 1 week (n=6 [6%]).

Survey participants were asked to rate how knowledgeable the PGY4RR consultant was in his/her respective field. On a scale of 1-10, 1 was defined as not knowledgeable and 10 as very knowledgeable. The largest group (n=44 [42.3%]) rated the PGY4RR at 10, or very





knowledgeable. Ratings ranged from 9 (n=11 [10.6%]), to 8 (n=34 [32.7%]), to 7 (n=9 [8.6%]), and finally, 5 (n=6 [5.7%]). There were no ratings below 5.

Respondents were asked to rate their post-rotation understanding of indications for various radiology exams on a scale of 1-10 (1=no better understanding and 10=much better understanding). 88% of respondents gave a score of 6 or above, indicating improved understanding of exam indications. Ratings were 10 (n=24 [23.1%]), 9 (n=10 [9.6%]), 8 (n=21 [20.2%]), 7 (n=14 [13.5%]), 6 (n=22 [21.2%]), 5 (n=11 [10.6%]) and 4 (n=2 [2%]).

Next we asked team members to rate their understanding of limitations and appropriateness of various radiological exams on a scale of 1-10 after having the PGY4RR rotate with them (1=no better and 10=much better understanding). 80% of respondents gave a score of 6 or above, indicating improved understanding of limitations and appropriateness of radiologic exams. The responses were 10 (n=19 [18.3%]), 9 (n=10 [9.6%]), 8 (n=12 [11.5%]), 7 (n=23 [22.1%]), 6 (n=19 [18.3%]), 5 (n=17 (16.3%)], 4 (n=2 [2%]), and finally 1 (n=2 [2%]).

The next question asked team members whether the incorporation of a PGY4RR into pediatric rounds was beneficial to learning basic radiology concepts. 99% felt that having a PGY4RR was either very (n=67 [64.4%]) or somewhat (n=36 [34.6%]) beneficial. One responded

no harm or benefit (n=1 [1%]) and no one responded harmful.

Questions on Future Inclusion of a PGY4RR on Rounds

Respondents were asked if they would like to have a PGY4RR consultant on future pediatric rotations. 91% responded yes, definitely (n=80 [77%]), or probably yes (n=14 [13.5%]). 10% were neutral (n=10), and none responded probably or definitely not.

When respondents were asked whether they would like to have a PGY4RR round with them on other rotations, most 90.3% answered yes definitely (n=75 [72.1%]) or probably yes (n=19 [18.2%]), and a minority (n=10 [10%]) were neutral. None responded no. When asked "Which other rotation(s) would you like to have a PGY4RR (Select all that apply)?" Respondents selected: internal medicine (n=40), surgery (n=38), pediatrics (n=31), emergency medicine (n=29) and intensive care unit ICU (n=24).

Questions on Providing History

Finally, we asked, "Did having a PGY4RR on rounds change the likelihood that you will provide more history when ordering imaging exams?" The majority responded they were definitely (n=15 [30%]) or probably more likely (n=19 [38%]) to provide more history. The remaining responded no change (n=16 [32%]) and none responded less likely.

Discussion

Due to the ever increasing use of diagnostic imaging in medicine, knowledge of basic radiology concepts is necessary for today's practitioners[9]. Being able to diagnose basic, critical conditions (such as pneumothorax) is a necessary and expected skill for clinicians and interns to treat time sensitive, life threatening conditions effectively[10]. Although the addition of PACS in patient care has helped make imaging results rapidly available, the disadvantage is that the tradition of beginning rounds in radiology to view and discuss radiological studies has mostly been abandoned. To bridge this educational gap, we implemented an innovative rotation that allowed trainees to gain cross-specialty clinical exposure with case-specific discussions of imaging studies. Radiology residents were able to practice core communication consultation skills and members of the pediatrics team were able to gain knowledge of radiology procedures, including their indications and findings.

To our knowledge, no study of this size has evaluated the educational benefit or support for incorporating a radiology resident into rounds and none has specifically studied the impact on a core pediatrics rotation team members, including medical students and residents. One recent manuscript published under "The voice of experience" column in the *Journal of the American College of Radiology*, piloted a similar experience with a single senior radiology resident rounding daily for two weeks on internal medicine[11]. Although this pilot included only one resident for two weeks, the study showed positive feedback from the 20 clinicians surveyed after the rotation. Similar to our larger study, respondents agreed that the rotation improved radiology knowledge and strongly agreed that they would like to have a radiology resident on future rounds. However, much like our study, the authors did not specify if the responding clinicians were attendings, trainees or students, nor did they state if they continued the rotation[11]. Naeger et al's study, based on pre- and post-lecture surveys, showed that radiology residents gained a statically significant increase in perceived knowledge of what clinicians want in radiology reports pertaining to the topics discussed in a clinician driven multidisciplinary conference series[12]. They also reported a significant increase in resident desire to continue incorporation of clinicians into core radiology resident conferences[12]. Our study showed a similar positive response to interdisciplinary teamwork between pediatrics and PGY4RR: 99% and 98% felt it was beneficial to learning, and enhanced their understanding of radiology procedures. Further, our study demonstrates pediatrics team members understanding of radiology study limitations and appropriateness were rated as improved by 96% of respondents. This improved understanding of appropriateness is sorely needed if Saha et al.'s report showing that 80.2% of PGY1 residents were not aware of ACR appropriateness criteria is an indication[3,4]. Expanding clinician knowledge of limitations and appropriateness of radiologic exams may lead to more judicious use of imaging, thus potentially reduce radiation exposure and cost.

The importance of radiology involvement in morning report was demonstrated in a 1997 study by D'Alessandro et al.[13] Authors assessed the content of pediatrics morning report without a radiologist present and found that despite showing 559 imaging studies

during 338 case presentations, unanswered questions concerning radiological study indications, techniques and findings were common. Authors concluded that pediatricians must learn basic radiology interpretation methods, imaging indications and ways to use the radiologist as a consultant[13]. There is a known patient care benefit that comes from working in teams, and valuable opportunities for radiology trainees to hear clinicians explain their imaging needs and potentially improve their communication skills. Pediatric trainees have the opportunity to gain knowledge of radiology study indications, limitations, appropriateness and findings- each of which will be commonly utilized skills later as practitioners. After rotating with a PGY4RR, 68% of respondents said they were more likely to provide additional history when ordering radiology exams. Although we cannot say why the majority said they would provide more history, it is possible that pediatrics team members became more aware of the importance of history in image interpretation, as well as a better understanding of how to use the radiologist as a consultant[14, 15].

This study has several limitations. It was performed over two years at a single institution. The survey was completed by a larger number of medical students and residents (n=44) than attendings (n=6). This was likely due to the makeup of the team members, i.e. one attending with several residents and students. Because few attendings were surveyed, the results are unlikely to represent their opinions. While survey responses are rarely 100%, it is possible that our 72.7% response rate may have led to some degree of response bias due to a larger percentage of those who enjoyed the experience responding. To limit bias introduced in questions where one side of an issue was mentioned in the stem, responses were provided on both sides of the issue. Because the survey was educational and cross-sectional, it could not be randomized or controlled.

Future research could include validation of results and stratification of results into resident, medical student and attending categories. Although verbal feedback from residents indicates a very positive experience, a survey on the impact and opinions of the PGY4RR completing the rotation is planned after a sufficient number of residents have completed the experience. It may also be useful to study a similar rotation for radiology residents in a different specialty than pediatrics, especially since 90% of respondents stated they would like to have a radiology resident on other rotations.

This rotation was part of our radiology residency program and did not incur additional cost or manpower needs. The rotation is generalizable to other institutions with radiology residencies and the experience could be created on any core clinical rotations desired. Potential barriers starting such a rotation may include manpower needs and scheduling flexibility.

Conclusions

Incorporating a PGY4RR into the pediatrics team was strongly supported and beneficial to the learning environment. Pediatric team members responded that they increased their radiology knowledge, gained a better understanding of exam appropriateness, and indicated they would like to incorporate PGY4RRs into future pediatrics and non-pediatrics rotations.

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Disclosure

None reported. **MM**

When Did You Last Speak A Radiologist or Visit the Radiology Department?

by John H. Niemeyer, MD



Patient care suffers when clinicians and radiologists do not interact in direct face to face settings.

In the 20th century, before the pervasive presence of all things digital, an integral part of medical education and practice was daily radiology rounds. Each morning, medical students, interns, residents and attendings ventured into the imaging department, tracked down the film jackets of their patients imaged the previous day and brought them to the view box for review with a radiologist. Final reports often did not arrive on the chart for 24-48 hours and actionable information was needed sooner. What ensued was an incredible bidirectional knowledge flow. Medical students and house staff learned the rudiments of image interpretation, imparted by an expert radiologist. Decisions about appropriate follow up imaging were made cooperatively, in real time. Radiologists were provided more detailed information about each patient than available on the cryptic radiology requisition, allowing more nuanced and relevant interpretation of the imaging studies. The clinicians conveyed the most current concepts on complex diseases to the radiologists including how their findings impacted patient management. Comraderies developed. Life was good (except when the orthopedic surgeon had sequestered the needed film jacket in the trunk of his BMW).

All of that changed in the new millennium with the advent of Picture Archival and Communications Systems (PACS) and electronic medical records. Physicians can view imaging studies from any computer, smart phone or tablet in the hospital, office or from home along with a nearly instantaneously generated self-edited radiology report. Given the convenience of these PACS, it is the exceptional physician who now makes his/her way to radiology for image review and consultation The technology is so dazzling that the radiologist has become invisible to most physicians, like the man behind the curtain in the Wizard of Oz. This has created an interaction gap between clinicians and radiologists that is detrimental to all; most acutely to the trainees and young physicians who may never in their careers have participated in those old fashioned face to face rounds. Radiologists are often in the dark about what really is going on with their patients and what questions the physician wants answered. Clinicians make decisions about what imaging study is most appropriate in a relative vacuum. Patient care suffers.

In the nearby article, Drs. Patel et al. explore a novel approach to bridging the interaction gap between radiologists and pediatricians by incorporating a radiology resident into the patient care team. They demonstrate significant perceived benefit to having an embedded radiologist in daily rounds. This article should stimulate valuable dialog resulting in other creative solutions to the widening interaction gap between clinicians requesting imaging examinations on patients whom they know best and radiologists who are most expert on appropriate utilization and interpretation of those studies. For the sake our patients and quality of care the interaction between clinicians and radiologists must be improved. Patel and fellow articles are headed in the right direction. **MM**



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