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CONTENTS

EDITOR'S MESSAGE

Our Commitment to Serve

Paula Gregory, DO, MBA, FACOFP

At my workplace, we talk a lot about our hometown heroes—the physicians, nurses, and other medical professionals who go above and beyond every day. How do we find joy in the ever-changing medical environment as we see new diseases, illnesses, environmental health concerns, and issues that affect our communities? The chance of danger on all fronts seems ever increasing. I recently attended a medical humanities lecture that included a powerful discussion on the issues we confront beyond our day-to-day challenges. Called "Diastole Hour," the lecture was presented by Dr. Barry Meisenberg, chair of medicine and chief academic officer at Luminis Health.[1]

The new diseases and mounting pressures from disasters have fundamentally changed how we have come to practice medicine over the past few years. There is no safety from catching an illness, yet we continue to open our offices and hearts to our patients, risking illness ourselves. We are still examining our patients closely, bending forward to listen to their breathing. We do so to make sure we are not missing a diagnosis and because we want to connect with our patients. We are in this world together, and our commitment to serve is strong.

To all the family physicians of the world: your efforts are appreciated. You are the backbone of health care for your patients. You are the primary communicator, translating health goals, updates on illnesses, and instructions. You know and understand your patients, that they are there to see you, often taking time away from *the work that must be done for America*—the farming tasks or the businesses that absolutely would not run without them—because you also show up every day.

These issues are not taken lightly. The chances of that patient taking more time off—or even being able to take time off—to visit a specialist is less likely these days. Superimposed on these issues are the overwhelming needs of patients who are underserved. This is your day, and you are up for the challenge.

Every single day, you leave your problems at the door and come ready to help those who need you most. You have weathered diseases like COVID-19, hepatitis C, and HIV by learning all you could in a short amount of time. You have seen how fires and floods have affected your patients, or others, and are ready to assist in needed areas.

It is great to see the new osteopathic medical school expansions and the support our communities give to the progress. Our profession holds so much promise to improve health. Many of you have become involved in teaching clinically and days are filled with hope. The future student physicians are strong.

As we look at the need to graduate more physicians and as institutions open in areas that most need them, we applaud that growth. Osteopathic colleges teach beyond the basics of our profession; they teach the students what it's like to manage expectations in this ever-changing environment. The new colleges are adding much-needed information on connecting with patients and supporting them in environments that may or may not have other specialist support. As family physicians, we not only need to know how to communicate and diagnose, but we also must be able to advise our patients on diet, nutrition, and wellness as we seek to create a better picture of overall health.

Each one of our physicians is important every single day. You are heroes. I trust that the articles in this issue will speak to your busy schedule and needs.

1. "Diastole Hour" is a program for students, trainees, medical staff, and patients who use literary and visual arts to explore experiences unique to the practice of medicine. Physicians, patients, and others share their voices in a format that encourages group discussion. The goal of the program is to reflect on those experiences that are most meaningful to the practice of medicine. – Dr. Barry Meisenberg (bmeisenber@luminishealth.org).

FROM THE PRESIDENT'S DESK

Fellowship and Family: Engendering Lifelong Connections

Bruce R. Williams, DO, FACOFP

Being a member means being part of something. It means belonging. It means identifying with people who have similar ideas, concerns, passions, and desires, and even though you may use a different approach to achieve the same result, you are willing to work collaboratively with others who see the issue differently.

So is this politics? Well, politics suggests governance and power. While governance is inherent in membership to achieve organization (as opposed to power), membership is an identity—a statement—of what and who you are. I bring this up because membership organizations are experiencing a decline, and there has been significant speculation and investigation as to why. Many reasons are cited: cost, value, time commitment, recognition, association, and just plain apathy. All are valid, but I would like to explain some reasons why membership should be sought after—especially within ACOFP.

In our Osteopathic Oath, there are several statements. "I do hereby affirm my loyalty to the profession I am about to enter." "I will be mindful always of my great responsibility to preserve the health and life of my patients." "I will be ever vigilant in aiding in the general welfare of the community, sustaining its laws and institutions, not engaging in those practices which will in any way bring shame or discredit upon myself or my profession."

For me, this means I will be an advocate for my patients and my colleagues. Organized medicine is how we do this. We give our voice volume through membership organizations. When we can go to a legislator, a corporation, or a public forum and say we represent 20,000 osteopathic family physicians, residents, and students, that is meaningful and impactful. As issues are brought to ACOFP, they are studied, discussed, and debated, and a position is arrived at. We speak with one voice on behalf of our physicians and especially our patients. I have always believed that membership in my local, state, national, and specialty organizations is not only an option but also an obligation to honor and be true to the oath I took when I became an osteopathic physician.

My belonging to osteopathic membership organizations like ACOFP has helped me to grow and develop as a physician and as a person. Organized medicine has been the primary route through which I receive my continuing medical education—the path by which I renew, refresh, and update my osteopathic medical knowledge and skills. We have experts in the medical field across our profession who are committed to helping us achieve lifelong learning so that we can maintain and improve the levels of care we give our patients.

Furthermore, not everyone pursues a leadership path, but when I did, I was blessed to be mentored by the finest leaders in the profession—and I have grown in my ability to listen, consider differing points of view, be humble, and open the door for others to grow, develop, and succeed. Perhaps the most significant attribute of membership is fellowship. When I reached out to William Betz, DO, in 1988 for an application to join the Jackson County Osteopathic Association, I never dreamed it would lead me to where I am today. I was welcomed and embraced, and I was continually introduced to colleagues who had a genuine interest in me and what I had to say. Over nearly 35 years, this network has grown across the country, and my colleagues are also some of my closest friends.

Our medical conferences are reunions. It is more about seeing and catching up with friends and—yes—family, than it is about the CME. Sure, there are the lectures, the meetings, the discussions, and the occasional debate. But it is mostly about the fellowship. I am sure this is the case outside the osteopathic profession, but it is so much more present and potent within our profession. The bond we have with each other is obvious, and that carries over to our relationships with our staff and especially our patients. We are a family.

> When you are supported and held up by so many people who you truly love and appreciate, it is nearly impossible to live within yourself. Yes, I have grown over the years—and I thank my osteopathic family for that. Yes, my education prepared me to be an osteopathic physician, but the membership organizations—especially ACOFP—have been the glue, the bond, that has strengthened me.

I have been given incredible opportunities as a result of my involvement in organized medicine, and every day—owing to this involvement—new opportunities crop up to help, grow, and lead. I have met and become friends with special and influential people. I have been able to travel to extraordinary places. I have been challenged in ways I never could have predicted. And I have grown in insight, wisdom, and humility.

When you are supported and held up by so many people who you truly love and appreciate, it is nearly impossible to live within yourself. Yes, I have grown over the years—and I thank my osteopathic family for that. Yes, my education prepared me to be an osteopathic physician, but the membership organizations—especially ACOFP—have been the glue, the bond, that has strengthened me.

Cost? Value? I would say membership is priceless. Recognition? I have been given much more than I have sought. Association? My daily interaction is with some of the most respected individuals in not only the osteopathic profession but also the greater medical profession. Apathy? Not in my experience.

If you are an ACOFP member, you know what I am saying. If you are not, I invite you to join. As a member, you will be welcomed. We want to reach out to you to get to know you, discover your passions, and help you pursue them.

Are you looking to start a new practice, move to a different practice, expand your scope, or pursue administrative, academic, or research opportunities? Maybe you want to become more involved in the community—either locally, nationally, or globally. Are you looking for an opportunity to develop as a leader? Or simply to become more involved? Whatever it is you might be looking for, ACOFP can help you—and you will meet some amazing people who will become lifelong friends and family. If you haven't done so already, I invite you to join us this year and for years to come.

Osteopathically yours,

Bruce R. Williams, DO, FACOFP
2022–23 ACOFP President

CALENDAR OF EVENTS

DECEMBER 2–4, 2022
IOA 41st Annual Winter Update
Indiana Osteopathic Association
Indianapolis, IN
Inosteo.org

DECEMBER 5, 2022
Illinois ACOFP Membership Reception
Illinois Society of the ACOFP
Chicago, IL
acofp.org/Illinois

JANUARY 20–21, 2023
IACOFP Midwinter Osteopathic Family Practice Conference
ACOFP Iowa Chapter
Des Moines, IA
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JANUARY 26–29, 2023
Winter Family Medicine Update
Missouri Society of the ACOFP
Columbia, MO
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JANUARY 27–29, 2023
2023 Faculty Development and Program Directors' Workshop
American College of Osteopathic Family Physicians
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MARCH 29–APRIL 2, 2023
ACOFP 60th Annual Convention & Scientific Seminars
American College of Osteopathic Family Physicians
Orlando, FL & Virtual
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APRIL 20–23, 2023
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REVIEW ARTICLE

HOME BLOOD GLUCOSE MONITORING

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KEYWORDS

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Diabetes affects more than 37 million Americans. More than one-third of American adults (96 million) have prediabetes, so it is anticipated that the prevalence of diabetes will continue to climb in the generation to come. There have been major advances in the options for home glucose monitoring. Home glucose monitoring provides critical information and feedback for patients with diabetes to help them understand how daily activities affect their glucose levels and timely data to assist in behavior reinforcement and modification. Self-monitoring of blood glucose (SMBG) is of great value to those with type 1 diabetes and those with type 2 diabetes on insulin as it reduces HbA1c and rates of hypoglycemia. Currently, there is less support for long-term benefit of SMBG in those with type 2 diabetes not on insulin or insulin secretagogues. Continuous glucose monitoring (CGM) is becoming increasingly available to help manage diabetes. This form of monitoring provides benefits in terms of HbA1c, reduced time and rates of hypoglycemia, and increased time in range for those on insulin. CGM reports now include standardized reporting and target goals that will make widespread use easier to implement. This article will review the current data on home glucose monitoring for those with diabetes.

HOME SELF-MONITORING OF BLOOD GLUCOSE

Diabetes affects more than 37 million Americans.[1] More than one-third of American adults (96 million) have prediabetes, so it is anticipated that the prevalence of diabetes will continue to climb in the generation to come and will eventually affect more than one-third of the US population.[2] Blood glucose monitoring can offer important information when tailoring a diabetes treatment plan. Recommendations on when to test, how often to test, and how to interpret the results are variable and need to be individualized to the patient and the treatment regimen. When used as a tool to gather information for both the physician and patient, blood glucose monitoring can make a significant impact on achieving glycemic goals and patient engagement and satisfaction.

Home blood glucose monitoring, also called self-monitoring of blood glucose (SMBG) utilizes a lancet to obtain capillary blood from a fingerstick that is then measured in a glucometer. Glucometers are available over the counter and by prescription and vary in insurance coverage. The US Food and Drug Administration (FDA) and the International Organization for Standardization have guided regulatory standards for glucometers. In 2020, the criteria became more strict, stating that for over-the-counter glucometers, 95% of all blood glucose readings should be ±15% of comparator results across the entire measuring range of the device.[3] Additionally, glucometers that require a prescription should show 95% of all readings, including those ≤75 mg/dL, and should be within ±12% of comparators.[4] These standards ensure both accuracy and precision when urgent treatment depends on a blood glucose reading. A full range of glucometers, as well as continuous glucose monitors are available for review in an annual issue of *Diabetes Forecast*, a journal published by the American Diabetes Association (ADA).[5]

Clinical case:

Sixty-two-year-old male with a 12-year history of type 2 diabetes. He used to check every morning, but says he can "feel" what his glucose is, so he stopped checking. He is taking metformin 1000 mg bid, glipizide 5 mg bid, and insulin glargine 48 units per day. He is surprised as his HbA1c is consistently between 8.5%–8.9% but when he occasionally checks his glucose in the morning, it typically runs between 58 mg/dL–162 mg/dL.

For many patients with diabetes, multiple daily SMBG was the standard of care. But as treatment options evolve, so has the need for monitoring. Several groups of individuals may benefit from continuing multiple daily SMBG checks. Those with type 1 and type 2 diabetes on insulin need SMBG to direct insulin therapy. Many of those patients choose to use continuous glucose monitors, but some prefer to continue SMBG by fingerstick. Even those with continuous glucose monitors should have a fingerstick glucometer as a backup means of checking blood glucose in the event the monitor malfunctions.

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However, many patients with type 2 diabetes may not require multiple fingerstick glucose checks. Treatment algorithms now rely less on insulin and other medications that have a high risk of hypoglycemia. For example, the ADA now recommends considering glucagon-like peptide-1 receptor agonists (GLP-1 RA) as first-line agents when initiating an injectable medication instead of insulin.[6] The therapeutic effect of GLP-1 RAs involves glucose-dependent insulin secretion, so the risk of hypoglycemia is very low.[6] Other medications for the treatment of type 2 diabetes that have a low incidence of hypoglycemia include metformin, pioglitazone, dipeptidyl-peptidase IV (DPP-4) inhibitors, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors. In patients with type 2 diabetes on treatments with low risk of hypoglycemia, routine SMBG may not be necessary. The drawbacks of home SMBG include cost, time, and inconvenience. Although glucometers are usually inexpensive ($9–$60), glucose testing strips can sometimes be expensive ($15–$100 per month) depending on insurance coverage and availability.[5] Another study looked at the cost-effectiveness of SMBG in those without insulin. In this modeling study, costs were estimated in patients completing SMBG >7 times a week. This testing was associated with a 0.25% reduction in HbA1c at the incremental cost per quality-adjusted life year of $113,643 (based on current commercial pricing).[7]

Carrying the glucometer everywhere and the time needed to test can be inconvenient and there is some pain associated with multiple daily fingerstick glucose readings. That is why it is important to use shared decision-making to identify when SMBG will benefit the patient.

Self-monitoring of blood glucose does not improve outcomes in patients with type 2 diabetes who are not at risk for hypoglycemia. A large study found that in patients with an HbA1c of 6.5%–9.5% who are not on insulin, there was no significant change in HbA1c, hypoglycemia frequency, healthcare utilization, or insulin initiation between groups with or without SMBG.[8] A meta-analysis showed those using SMBG had improvements in HbA1c at 12 and 24 weeks but no difference at one year of follow-up.[9,10] Another study explored patient perspectives on the role of SMBG in diabetes management. Patients reported that when there was no actionable plan for their glucose readings and when doctors focused on HbA1c and showed a lack of interest in the SMBG readings, the practice was not worth continuing and readings became associated with "good and bad" behavior and a reminder of not achieving success.[11]

A Cochrane review was completed on the benefit of SMBG in patients with type 2 diabetes who are not on insulin. The findings revealed that when diabetes duration is more than 1 year, the overall effect of self-monitoring of blood glucose on glycemic control in patients with type 2 diabetes is small up to 6 months after initiation and subsides after 12 months.[12] However, the authors recommended that further study be completed "to explore the psychological impact of SMBG and its impact on diabetes-specific quality of life and well-being, as well as the impact of SMBG on hypoglycemia and diabetic complications."[12]

The International Diabetes Federation states, "SMBG should be used only when individuals with diabetes and/or their healthcare providers have the knowledge, skills, and willingness to incorporate SMBG monitoring and therapy adjustment into their diabetes care plan in order to attain agreed treatment goals."[13] When structured SMBG has been utilized and treatment changes have been made based on the results, studies have shown improvement in glycemic control in noninsulin-using type 2 diabetes, improvements in postprandial glucose management, reduced cardiovascular risk, and improvements in other health parameters, such as body weight, quality of diet, level of physical activity, and mental health.[10] The goal of SMBG is to provide data for both the patient and physician. This data can then be utilized to change health behaviors and pharmacologic therapies only if the patient and the physician know how to interpret the data (table 1).[14]

When glycemic goals are not being met, evaluating glucose patterns is essential and can facilitate treatment changes and improve HbA1c.[15,16] Patients can gain insight into the effect food choices, physical activity, stress, and medications have on their blood glucose. This empowers the patient to take an active role in decision-making. Physicians can recognize the need for increased treatment of fasting glucose or postprandial glucose and employ targeted medication changes. Utilizing tools such as glucose logbooks or tracking apps can make it easier to identify patterns. Data can be collected at the same time for as little as 3–4 days, then analyzed.[17]

Another important time to utilize structured SMBG is at the onset of type 2 diabetes. One study looked at newly diagnosed patients with type 2 diabetes and divided them into two groups: SMBG intervention or monitored by HbA1c alone. Higher rates of regression (HbA1c<6% on metformin alone) or remission (HbA1c 6%–6.4%) were achieved in the group with SMBG, as well as greater reductions in HbA1c and decreased body mass index (BMI).[18] It is also important to teach the skill of checking SMBG to those newly diagnosed before they need the skill, such as if they develop symptomatic hypoglycemia or develop an acute illness and have hyperglycemia. The American Diabetes Association suggests that SMBG should be prescribed as part of a diabetes self-management education and support program for all patients receiving insulin and may be helpful for patients on noninsulin therapies when altering diet, physical activity, or medications.[19]

TABLE 1:

ADA recommendations for self-monitoring blood glucose[17]

Type 1 diabetes	4–10 times daily or CGM
Gestational diabetes mellitus	4 times daily until controlled; then 1–2 times daily
Type 2 diabetes on insulin	Before every insulin injection
Type 2 diabetes on insulin secretagogues	As needed to identify and prevent hypoglycemia or as part of an acute illness
Type 2 diabetes: no insulin, no insulin secretagogues	FSG monitoring may not be needed. Best used when treatment is being adjusted, acute illness is present, or symptoms of hyperglycemia are present

The role of HbA1c alone in glycemic assessment:

HbA1c has become a powerful measure of glucose control. It is a validated reference marker for assessing glycemic control and predicting the risk of developing long-term complications in both type 1 and type 2 diabetes.[16,17] The assay has been rigorously standardized, can be drawn in the fasting or nonfasting state, and is widely available in labs and as a point-of-care test in the office. The HbA1c provides an estimate of mean glucose over the last 2–3 months, but it is more heavily weighted to more recent control.[18]

However, the weaknesses of HbA1c are many, including measurements that are affected and become less accurate in patients who have anemia, a hemoglobinopathy, iron deficiency, recent blood loss or transfusion, or pregnancy.[19,20] HbA1c also does not shed light on the lived experience of glucose control over time. This includes daily glucose excursions, glucose variability, or time in range. It also is weighed toward more recent events, and it does not predict rates of hypoglycemia.[19]

Hypoglycemia is a particular concern not well addressed by HbA1c. In type 1 diabetes, HbA1c was a poor predictor of rates of severe hypoglycemia, whereas 13.2% of the patients with an HbA1c <7.0% had severe hypoglycemia. Those with an A1c of 8%–9% had a 13.7% incidence, and even those with an HbA1c >10.0% had a 12.1% incidence.[21] In type 2 diabetes, rates were high across all HbA1c levels (14.4%–29.8%) but lowest in the 8%–8.9% group (14.4%) and highest in those who take insulin (39.4%), insulin secretagogues (48.3%), those who had diabetes lasting more than 10 years (57.4%), and those on 4 or more medications (71%).[22] In another outpatient study of 108 patients with type 2 diabetes treated at a specialty center (64 of whom were on insulin), a blinded CGM was placed for 5 days. Surprisingly 53 participants (49%) had at least one episode of hypoglycemia with a mean of 1.74 episodes over the 5-day period and equal rates of hypoglycemia in the daytime and at night. The great majority of the participants were asymptomatic and not aware of these episodes (75%). Twenty-one percent reported hypoglycemic symptoms when there was no SMBG or CGM evidence of hypoglycemia.[23] These results underscore the need for data tosupport glycemic excursions as patient symptoms are unreliable in identifying hypoglycemia and hyperglycemia.

Recent attention has focused on glucose variability caused by both hyperglycemia and hypoglycemia as a contributor to increased complications. Glucose variability and hypoglycemia have been linked to microvascular and macrovascular complications.[24,25] It is important to not only achieve an HbA1c, which is linked to complications, but also to look at how a person gets to that HbA1c based on glucose variability along the way. This is often hard to capture with SMBG and is now best captured with CGM.

CONTINUOUS BLOOD GLUCOSE MONITORING IN 2022

Continuous glucose monitoring systems use measurement of subcutaneous interstitial fluid to provide glucose measurements at 1- to 5-minute intervals. These correlate well with blood glucose measurements but provide a more comprehensive view of glucose excursions, including glucose trends and rate of change of glucose. When taken in summary, a more complete picture of glycemic patterns is seen, including variations during the day and overnight. Variability of glucose levels also provides important information about the timing, frequency, and duration of hypoglycemia, which can be central to prevention. The first 10 years has seen a dramatic expansion and improvement in the precision and ease of use of CGM systems. Originally CGMs were not more precise than blood glucose monitors and they required multiple daily calibration (table 2). Currently, two CGM systems require no blood glucose monitoring calibrations and can be used independently to guide medication, including insulin dosing.

TABLE 2:

ADA recommendations for continuous glucose monitoring (CGM)

1. When prescribing CGM, robust diabetes education, training, and support are required for optimal device implementation and ongoing use. (Expert opinion)
2. When used properly, CGM, in conjunction with insulin therapy, is a useful tool to lower HbA1c levels and reduce hypoglycemia in adults with type 1 diabetes. (A-level evidence)
3. When used properly, CGM, in conjunction with insulin therapy, is a useful tool to lower HbA1c levels and reduce hypoglycemia in adults with type 2 diabetes. (B-level evidence)
4. Real-time CGM devices should be used as close to daily as possible for maximal benefit. (A-level evidence)
5. Blinded CGM data, when coupled with diabetes self-management education and support, can be helpful in identifying and correcting patterns of hyper- and hypoglycemia in patients with type 1 and type 2 diabetes. (Expert opinion)

Outcomes indicate that CGM can provide benefits, including increased time in range, reduced hypoglycemia, and improved HbA1c levels. This has been shown both in type 1 diabetes[20,21] and type 2 diabetes.[22,23] A recent study looked at the real-world impact of universal coverage for intermittently scanned CGM for type 1 diabetes and found that unrestricted reimbursement of CGM in patients with type 1 diabetes resulted in less severe hypoglycemia and less work absenteeism while maintaining quality of life and HbA1c.[24] Recently, a 3-year follow-up to this study found HbA1c reductions of −0.96% in multiple daily insulin dosing individuals and an HbA1c reduction of −0.71% in those on insulin pump therapy. Further, those on CGM had a 68% reduction in hypoglycemia and 100% reduction in diabetic ketoacidosis rates over the 3-year observational period. These changes resulted in per-person savings of $3,555–$6,747 over the course of 3 years.[25]

Another study in adults with poorly controlled type 2 diabetes utilized CGM as a motivational tool for behavior change. Over a 3-month period, the CGM group saw an HbA1c reduction from 9.1% to 8.0%, versus SMBG 8.7% to 8.3%, $P = 0.004$. Further, the CGM group saw an improvement in self-care behaviors, including a significant reduction in total daily calorie intake, weight, and BMI and a significant increase in total exercise time per week.[26]

While CGM systems are widely available, healthcare professionals will need to learn how to access and interpret the data to provide the biggest impact. In 2019, an international committee met to develop standards and targets for CGM data (table 3). These were developed to maximize the benefit of CGM use in patients with diabetes and provide a structure for interpretation of the data.[27] Key metrics to consider from a CGM report (ambulatory glucose profile) include target range, below target, above target, glucose variability and time range, and glucose management indicator—an HbA1c estimate based on readings obtained from CGM.[27] This will require substantial physician education about how to incorporate systems into the practice and how to share results with patients.

TABLE 3:

Goals for time in range on an ambulatory glucose profile from a continuous glucose monitor

DIABETES TYPE	GLUCOSE GOAL RANGE	GOAL TIME IN THIS RANGE
T1 and T2	Overall target range 70 mg/dL–180 mg/dL	>70%
	Hypoglycemia: below target <70 mg/dL (low) <54 mg/dL (very low)	 <4% <1%
	Hyperglycemia: above target >180 mg/dL (high) <54 mg/dL (very low)	 <25% <5%
Older high-risk adults T1/T2	Hypoglycemia: target range <70 mg/dL Hyperglycemia: >250 mg/dL	>50% <1% <30%

For glucose monitoring to have the greatest effect, there must be goals to help address specific issues. More recently, continuous glucose sensors have become available. These sensors provide ongoing feedback that provides even more information about glucose responses to eating, exercise, and other activities. This has served as the ultimate feedback tool for some. However, when these technologies are applied to the 34 million Americans with diabetes, this can prove costly to the healthcare system and may not provide equal benefit to all users.

Self-monitoring of blood glucose is of greatest value in patients with type 1 and type 2 diabetes who are taking insulin or medications that can cause hypoglycemia. There is little evidence of long-term benefits of SMBG in patients not using insulin who are on secretagogues to manage their diabetes. Optimal use of SMBG relies on "targeted testing" that identifies specific glycemic challenges to address with the patient. Continuous glucose monitoring use has become much more widespread since the last review on this topic. These systems benefit patients on insulin the most but can be used as a powerful educational tool when part of a comprehensive diabetes self-management education plan. Physicians can have an impact on the utility of SMBG. A well-informed physician able to download and interpret the data can provide more meaningful feedback to the patient completing SMBG. Useful reviews are available for a physician hoping to utilize CGM in their practice.[17,28,29]

Clinical case follow-up:

As a reminder, our patient was on metformin, glipizide, and insulin. He was frustrated that his glucose monitoring did not match his HbA1c levels and he stopped checking regularly. The patient was placed on a 14-day glucose monitoring system and asked to return to review his results. To his surprise, his glucose dropped low pretty regularly, followed by long periods of time when he became hyperglycemic afterward. He was not feeling these hypoglycemic events (known as hypoglycemic unawareness). The treatment team first stopped his glipizide and his hypoglycemic episodes went away. He initially focused on his fasting glucose. With minor changes in his basal insulin, his morning glucose was at the target range of 100 mg/dL–150 mg/dL set for him. The treatment team then asked him to stop the morning SMBG and move to checking 90 minutes after one meal per day. He found that these readings were higher at 150 mg/dL–250 mg/dL. The team discussed that he would need some treatment to help better cover his meals. He agreed to reduce carbohydrates at meals and to start an SGLT-2 inhibitor. He continued on metformin and insulin glargine 54 units daily. He was happy to report that his glucose readings improved and his next HbA1c was 7.2%. He was looking forward to checking his glucose as the results now made sense and he could respond to them.

CONCLUSION

Glucose monitoring without patient education or advisement may have limited value. However, recent research has supported the value of targeted glucose monitoring and even continuing glucose monitoring in patients with diabetes—even those who are not taking insulin.

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REVIEW ARTICLE

COVID-19 IN PATIENTS WITH ASTHMA: REVIEW AND IMPLICATIONS FOR CARE OF ADULT PATIENTS WITH AN OSTEOPATHIC COMPONENT

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KEYWORDS

Asthma

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Management

Inhaled corticosteroids

Severity

ABSTRACT

Patients with asthma who have COVID-19 typically present with rhinitis, rhinosinusitis, cough, and shortness of breath and rarely with wheezing. Family physicians should consider a patient's asthma subtype, pertinent medical history, and medications. Maintenance medications, including inhaled corticosteroids (ICS), should be continued for most patients. Whether to start ICS in patients with asthma who have COVID-19 should be considered, as the risks and benefits are unclear, and systemic corticosteroids should be avoided in patients with asthma who have COVID-19 if alternatives exist. Pregnant patients with both asthma and COVID-19 should be comanaged by an obstetrician, with consideration for early induction of labor. Behavioral health topics and osteopathic principles and manipulative techniques should be considered in patients with COVID-19 and asthma. Generalities are challenging to make, but patients with asthma do not seem to have worse outcomes with COVID-19 than patients without asthma.

INTRODUCTION

Discovered in 2019, the SARS-CoV-2 virus is an enveloped positive-sense, single-stranded RNA virus. Within the virus family *Coronaviridae*, it is the seventh subtype of the human coronavirus (CoV), similar in structure to past SARS-CoV and MERS-CoV viruses. COVID-19, the syndrome that the SARS-CoV-2 virus causes, may include such mild symptoms as cough, rhinitis, rhinosinusitis, anosmia, dysgeusia, myalgia, fatigue, and fever. Severe illness may be characterized by atypical pneumonia, pulmonary edema, acute respiratory distress syndrome, multisystem organ failure, and septic shock.[1]

Patients with asthma with heterogeneous origins of varied symptoms and treatment challenges are a unique cohort of patients. The objective of this article is to review the pathophysiology of the SARS-CoV-2 virus, the sequelae of COVID-19 syndrome, the basics of asthma physiology, and the implications of care for patients with both asthma and COVID-19 in an effort to educate and empower readers toward evidence-based management recommendations.

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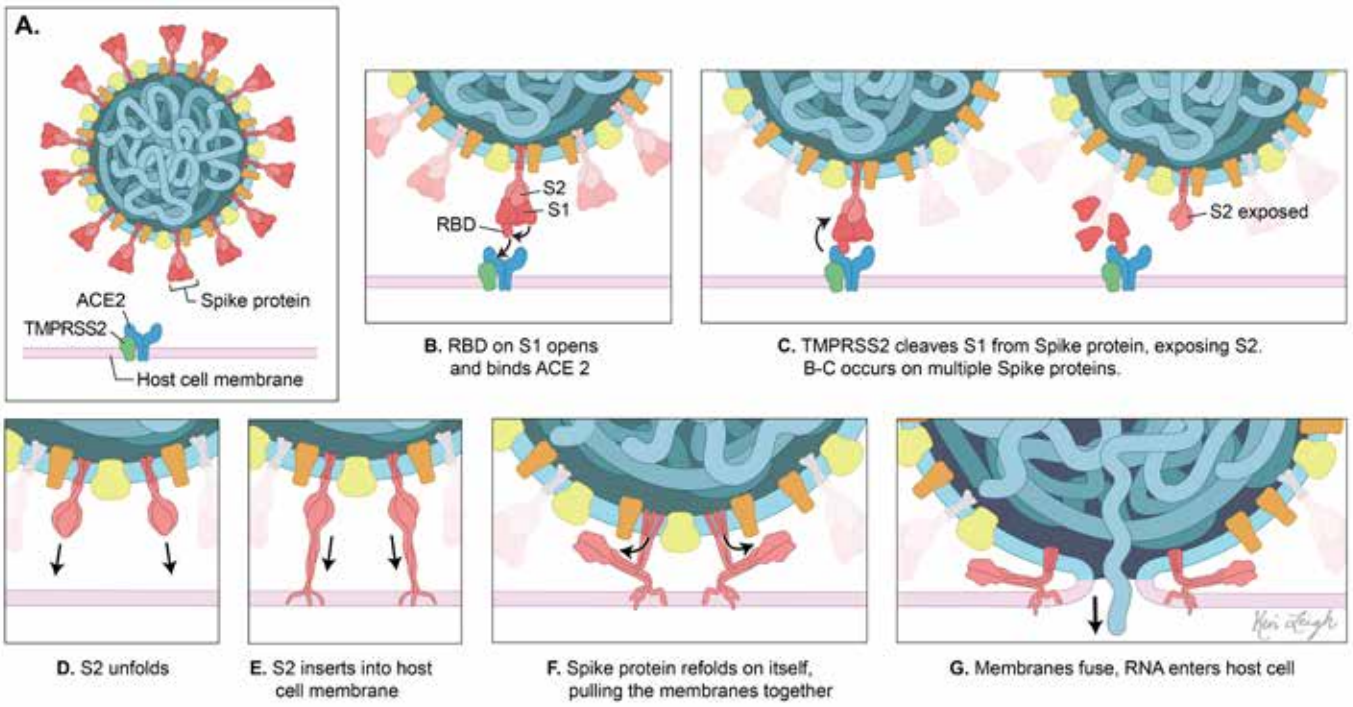
SARS-COV-2 VIRUS PATHOPHYSIOLOGY

Exposure to SARS-CoV-2 typically comes from aerosolized droplets (commonly 1–5 µm in diameter) several meters from an infected person[1] or by long-range transmission from environmental pollen bioaerosol complexes linked with the virus.[2] After a person is exposed, the spike glycoprotein (S protein) of the virus binds to the angiotensin-converting enzyme 2 (ACE2) receptors of both type I and type II pneumocytes of the host (Figure 1). Following attachment, the transmembrane serum protease 2 present on the extracellular membrane of the epithelial cells will cleave the S protein into subunits, which facilitate the transmission of the uncoated RNA genome of the virus across the membrane and into the cell.[3]

Each RNA genome creates replicase transcriptase polypeptides, which create more viral RNA. This, in conjunction with the upregulation of the expression of the ACE2 receptors in the presence of the S protein, causes an exponential increase in viral load. This S protein of the SARS-CoV-2 virus has a 10–20-fold increase in binding capacity compared with its distant relatives, the SARS-CoV and MERS-CoV viruses, suggesting a key point in the virulence of this virus.[4]

FIGURE 1:

SARS-CoV2 entering a host cell



ASTHMA PATHOPHYSIOLOGY

Asthma encompasses obstructive lung disease with airway inflammation, bronchial smooth muscle contraction, increased mucus production, and bronchial hyperresponsiveness. Common symptoms include cough, shortness of breath, chest tightness, and wheezing.[5] The two most common asthma subtypes reported are "atopic" and "nonatopic." Atopic asthma is more common, associated with baseline increased histamine, total IgE, attenuated interferon (IFN) response, a Th2-skewed immunity, and increased eosinophils.[2,3] Nonatopic asthma is typically associated with obesity, metabolic syndrome, and smoking, though without a clear origin or etiology. It often includes a Th1- or Th17-mediated immune response and may be associated with an increased IFN response, including interleukin 6 (IL-6), which is common and difficult to control.[4,6]

EXACERBATIONS REVIEW

Asthma exacerbations describe worsening of baseline symptoms, with respiratory infections as common triggers secondary to increased, attenuated IFN response.[7] The CoV viral subclass is a common trigger.[1,8] Estimates of 80% of respiratory triggers secondary to CoV are documented, although one study countered with no strong link between CoV and asthma exacerbations.[9]

ISOLATION CONSIDERATIONS

A Dutch study showed that patients with asthma exhibited higher rates of fear of becoming infected with SARS-CoV-2 compared with controls.[10] Patients with asthma seem more motivated to reduce the risk of respiratory viral infections by using behavioral interventions such as social distancing and mask-wearing, compared with patients who do not have asthma.[11,12] Furthermore, patients with asthma were more likely to avoid clinics and hospitals for non-COVID issues secondary to concerns about COVID-19 and hospital-acquired infections.[10,13] A Greek retrospective cohort study theorized that primary care effectively managed patients with asthma and that such patients had decreased environmental exposures with limited aggravating factors, were avoiding health care secondary to fear of COVID-19, and showed a 68% reduction in admissions since the onset of the pandemic.[14]

COVID-19 AND ASTHMA PREVALENCE

An accurate prevalence of asymptomatic and mild COVID-19 patients with asthma remains unclear secondary to lack of testing in asymptomatic patients and those with mild symptoms, varying diagnostic criteria, and decreased hospital presentations of patients with asthma.[14] Patients with both asthma and COVID-19 were most likely to present with rhinitis and rhinosinusitis

symptoms. Diagnosing asthma remains challenging secondary to the closure of pulmonary function testing laboratories, secondary to the aerosolization of the procedure.[13,15] Hospitalized patients often demonstrate cough and shortness of breath, with wheezing as a rare feature.[1] Patients with asthma who have COVID-19 generally have other comorbidities such as obesity, sleep apnea, and GERD.[16]

A review of the literature postulates that early studies from China and Italy significantly underrepresented asthma in COVID-19 patients.[7] A retrospective cohort study from Illinois showed that the prevalence of COVID-19 patients with asthma was 14.4%,[16] though a Spanish study showed a prevalence of 4.45%.[9] An Israeli retrospective cohort study conducted a chart review of all patients with documented asthma, showing 10.2% were positive for COVID-19 by PCR testing, not statistically significant compared with patients who did not have asthma. Further analysis showed that the use of systemic corticosteroids (SCS) or biologic therapy did not increase the risk of COVID-19 in patients with asthma.[17,18] Data reported here can be compared with the national asthma prevalence in the United States of 8.0% based on the US Centers for Disease Control and Prevention's (CDC) National Reported Prevalence of 2019.[19] The heterogeneity of the studies and varied data mean that generalities about association or correlation with COVID-19 and asthma are difficult to make.

COVID-19 SEVERITY AND COMPLICATIONS

The CDC reports that asthma is a risk factor for severe COVID-19.[4,19] The severity of COVID-19 correlates directly with the magnitude of innate immune response and cytokine storm within the lower respiratory tract.[4] The nonatopic subtype of asthma tends to be proinflammatory with increased baseline levels of IL-6, showing a significant association with severe infection.[4,20] Alternatively, atopic asthma shows a Th2-skewed immunity with a decreased cytokine and overall antiviral response to SARS-CoV-2.[2-4,11,12] The decreased IFN response of many patients with asthma decreases expression of ACE2 on the cell membrane, decreasing available binding sites for the S protein and decreasing viral replication within the pneumocytes.[3,21] In conclusion, severity, need for ICU-level care, and mortality are not significantly different for patients with asthma compared to those with no underlying chronic respiratory disease.[9]

A retrospective cohort study showed that hospitalization rates were not different between COVID-19 patients with or without asthma.[16] Compared to patients with chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA), and other chronic respiratory diseases, asthma patients have been found to have a lower risk of mortality with COVID-19.[1] Hosoki et al. proposes the varying presentations and pathophysiology between atopic and nonatopic asthma, and the inability to separate them upon review helps explain the diversity of data in the literature.[1] Palmon et al. postulated that a portion of patients with asthma may have had unresolved postviral hyperreactivity of the airway from prior non–SARS-Co-2 infections, leading to increased risk of complications.[21] Strauss et al, a review of the Cleveland Clinic COVID-19 Research Registry, demonstrated patients using intranasal steroids for rhinitis had a lower risk of hospitalization, ICU admission, and in-hospital mortality.[22]

Inflammatory markers, including C-reactive protein (CRP), lactated dehydrogenase (LDH), and ferritin were lower in patients with asthma compared with patients without asthma.[16] Eosinophilia is common in patients with atopic asthma, a feature of the innate immune response implicated in increased disease severity, frequent exacerbations, and tissue remodeling.[9] Conversely, eosinopenia, which is common with severe COVID-19, has been demonstrated to have a dose-dependent relationship to risk of ICU-level admission. Thus, the eosinophilia of patients with asthma is theorized to be protective.[9,17]

Low-quality evidence shows that ICS use blocks RNA replication and minimizes the cytokine response.[8,23] ICS use in patients with asthma did not increase the risk of COVID-19-related hospitalizations in the United States, and a Japanese case series suggests that ICS may assist with COVID-19 recovery.[24] Systemic corticosteroid use was a notable risk factor for moderate-to-severe COVID-19 with increased mortality compared to nonuse, with outcomes showing a statistically significant dose-responsive increase in severity. Biologic therapy use showed no increased risk of COVID-19 severity or mortality compared to nonuse.[17]

PREGNANCY CONSIDERATIONS

A Washington state study following 46 pregnant patients with asthma and COVID-19 showed that pregnant patients with asthma have a higher risk of contracting severe COVID-19 and experiencing delivery complications. This suggests comanagement with obstetrics and consideration of preterm induction and delivery may decrease risks of complications, including improved neonatal lung function.[25]

BEHAVIORAL HEALTH CONSIDERATIONS

Patients with asthma often have an association with depression or anxiety secondary to physical limitations, fear of respiratory distress, and increased cholinergic activity.[7,26] A Dutch study showed patients with asthma had a higher rate of fear of becoming infected with SARS-CoV-2 compared with controls, with many people with asthma avoiding clinics and hospitals in an effort to reduce the risk of COVID-19 exposure and hospital-acquired infections.[7]

OSTEOPATHIC CONSIDERATIONS

Osteopathic examination should focus on breathing mechanics; lymph circulation and mobilization of immune cells by targeting somatic dysfunctions of the thoracic spine, ribs, and diaphragm; and viscerosomatic reflexes.[27-29] Haney et al. (2021) succinctly describes various osteopathic manipulation treatment options to consider based on patient presentation.[30] A 1999 randomized controlled trial showed a statistically significant improvement in peak expiratory flow in pediatric patients compared to those receiving sham therapy.[28]

CONCLUSION

Family physicians should consider a patient's asthma subtype, pertinent medical history, medications, and symptoms at onset as part of an effort to individualize treatment. Most patients who have both asthma and COVID-19 will complain of rhinitis, rhinosinusitis, cough, shortness of breath, and, rarely, wheezing. Maintenance medications such as ICS should be continued for most patients. Starting an ICS should be considered individually, and SCS should be avoided if alternatives exist. Pregnant patients are at high risk for complications and should be comanaged with obstetrics, with consideration for preterm induction of labor. Behavioral health and osteopathic considerations should be made individually. The CDC states that asthma is a risk factor for severe COVID-19, but varied studies reviewed do not demonstrate this correlation. However, generalities are difficult, and family physicians should be empowered to make individualized recommendations.

LITERATURE SEARCH

The authors searched PubMed, Google Scholar, the Elsevier COVID-19 collection, and DeGruyter.com resources, beginning April 10, 2021, after invitation to write the review, through the submission date of August 24, 2021. A repeat literature search was conducted on April 6, 2022, to find up-to-date articles for the second revision. Key words are COVID-19, SARS-CoV-2, asthma, inhaled glucocorticoids, atopic, osteopathic, anxiety, and depression. Each article was reviewed, summarized by the authors independently, and included if the article added value to the objective of describing the relationship between asthma and COVID-19.

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REVIEW ARTICLE

COVID-19 VACCINE-INDUCED CARDIAC CONCERNS

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Myocarditis has been increasingly recognized as a rare complication of COVID-19 mRNA vaccinations, especially in young adolescent males. According to the US Centers for Disease Control and Prevention, the incidence of myocarditis in males 16–29 years of age is approximately 10.7 cases per 100,000. Of those diagnosed with myocarditis, roughly 69% were diagnosed 3–5 days after their second vaccination. Most recent reports have shown clinical presentations consistent with chest pain, elevated cardiac enzymes, ST elevations on ECG, and further echocardiogram or cardiac MRI findings displaying mild to moderate left systolic dysfunction. Although mechanisms in the development of myocarditis are still not clear, a promising hypothesis is that myocarditis is exacerbated by a hyperimmune response to the second dose of the vaccine. Children have a robust immune response to COVID-19, which has been exemplified by increasing cases of multisystem inflammatory syndrome in children. This report will review trends seen in patients with vaccine-induced myocarditis and highlight the benefit to risk assessment of cardiovascular complications associated with COVID-19.

INTRODUCTION

Myocarditis is an inflammatory cardiomyopathy, most frequently caused by viral infections, affecting about 10–20 individuals per 100,000 each year in the general population.[1,2] Myocarditis following vaccine administration has been traditionally reported as a rare event, accounting for 0.1% of more than 620,000 reports recorded at the Vaccine Adverse Event Reporting System (VAERS) over a period of 18 years.[2,3] Most events occurred after administration of live-attenuated smallpox vaccine and less commonly after other vaccines such as diphtheria, tetanus, polio, and influenza. In late December of 2020, initiation of COVID-19 vaccination efforts began in the United States in hopes of flattening the epidemiology curve and reducing COVID-19 hospitalizations.[1]

In phase 3 studies on the COVID-19 mRNA vaccines, no safety issues concerning post-vaccine myocarditis were reported.[2] It was found that the incidence of serious adverse events with BNT162b2 vaccine (Pfizer-BioNTech) and mRNA-1273 vaccine (Moderna) was comparable in the vaccine and placebo groups by 0.6% and 0.5% respectively.[1,2] As of June 2021, a total of 1,226 reports of probable myocarditis or pericarditis were filed in the VAERS after the administration of approximately 300 million COVID-19 mRNA vaccine doses, resulting in a prevalence of 4.8 cases per 1 million doses administered.[2,4] This complication was most reported in young men between the ages of 15 and 30 years, 72–96 hours after receiving the second dose of Pfizer and Moderna vaccines. The Moderna, mRNA-1273, vaccine was associated with a higher incidence of cases of myocarditis. Clinical findings included chest pain (>85%), ST elevation or T-wave changes and elevated cardiac enzymes (>70% for both).[3] Most patients were admitted for hospitalization and fully recovered with no underlying cardiac damage by further follow-up studies.

Serious adverse events associated with receipt of vaccinations targeting COVID-19 are of great interest to the public, public health officials, and vaccine safety surveillance organizations. There is now increasing evidence of myocarditis as a rare complication of COVID-19 vaccination, especially in young adolescent males. Using the most up-to-date data, we will explore this complication to aid in the risk-benefit assessment of COVID-19 mRNA vaccines in regard to short- and long-term cardiovascular outcomes.

EPIDEMIOLOGY

Analysis of the US Centers for Disease Control and Prevention (CDC) Vaccine Safety Datalink revealed an increased risk of myocarditis or pericarditis among male individuals 12–39 years of age in a 7-day risk interval post-vaccination period with mRNA COVID-19 vaccines when compared with unvaccinated individuals [95% CI, 3.2–49.0].[2,5,6] Additionally, no patients were found to have a history of COVID-19 comorbidities, and all had good vaccine efficacy by protective spike protein antibody levels.[2] The Israeli Ministry of Health also reported a similar finding, reporting 148 cases of myocarditis among 10.4 million vaccinated individuals within 30 days of receipt of second BNT162b2 vaccine (Pfizer-BioNTech) mRNA vaccination.[7] The prevalence of myocarditis was

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1/20,000 for the 16–30-year-old group, compared with 1/100,000 in the general population receiving the Pfizer BioNTech mRNA vaccine.[6] Overall, individuals receiving Moderna vaccination were deemed to have a higher prevalence of myocarditis after the second dose.[8] Finally, of 2.8 million COVID-19 vaccinations administered by the Israeli Military Health System, 23 previously healthy male military members, with a median age of 25, were identified as having myocarditis approximately 4 days after administration of the second dose.[9]

CLINICAL PRESENTATION

Acute myocarditis was classified as probable or confirmed from the CDC working case definition. Probable acute myocarditis was based on presence of one or more symptoms of chest pain, discomfort, pressure, dyspnea, palpitations, syncope and one new finding of elevated troponins above the upper limit of normal, abnormal electrocardiogram (ECG), abnormal echocardiogram, or cardiac MRI.[10] Confirmed cases of acute myocarditis were classified as the probable criteria plus histopathologic confirmation of myocarditis or elevated troponin above upper limits of normal and cardiac MRI findings consistent with myocarditis.[10] A large study conducted in Israel, in which 54 vaccinated patients who met criteria for myocarditis, revealed chest pain to be the most common presenting symptom, found in 82% of cases.[1,2] Similarly, the CDC Advisory Committee on Immunization Practices found that in 484 probable cases of myocarditis, 86% reported chest pain on presentation.[11] ECG findings showed ST-segment or T-wave changes in greater than 57% of cases.[1,11] Vital signs associated with myocarditis/pericarditis were generally normal, with only a select few cases that reported hemodynamic instability as a result of cardiogenic shock. Vaccine-induced myocardial injury has been considered a prevalent finding in patients who met criteria for myocarditis. Out of 323 confirmed myocarditis or pericarditis cases, 64% displayed elevated troponins.[8,11] A study of 23 male military patients, with a median age of 25, revealed elevated troponin levels of 10-fold to 400-fold of their upper limits in all patients after the second dose of mRNA COVID-19 vaccination.[8] Patients who underwent further cardiac imaging, including an echocardiogram and cardiac MRI, displayed mostly normal systolic function and normal chamber size. These findings were further reinforced in a recent study published in *Pediatrics* in which 14% of patients had mildly decreased left ventricular function (ejection fraction 45%–54%) by echocardiography.[12] More concerning, however, were cardiac MRI findings of late gadolinium enhancement in the inferolateral and lateral walls of the left ventricle, a pattern consistent with nonischemic myocardial injury and necrosis.[7]

POTENTIAL MECHANISM OF COVID-19 VACCINE-INDUCED MYOCARDITIS

COVID-19 mRNA vaccines contain nucleoside-modified mRNA encoding the viral spike protein of the SARS-CoV-2, but not the live virus or DNA.[13,14] Once integrated within host cells, an adaptive immune response occurs to identify and destroy the virus expressing the spike protein. Although mRNA modifications have been shown to reduce innate immunogenicity, studies have suggested that some individuals may have a genetic predisposition in which the immune response to mRNA may not be turned down. Instead, aberrant persistent cytokine activation via toll-like receptors detect the mRNA in the vaccine as antigen, which results in a downstream cascade of pro-inflammatory modulator pathways in the heart that may play a role in the development of myocarditis as part of a systemic reaction.[13] Another proposed mechanism of vaccine-induced myocarditis includes cross-reactivity between mRNA vaccine spike protein antibodies and myocardial contractile proteins. Molecular mimicry can occur when a foreign antigen shares a sequence or structural similarity with a self-antigen. Antibodies directed to mRNA viral spike proteins may have a structural similarity to protein sequences of alpha-myosin heavy chain, an important myocardial contractile protein.[13,14] Essentially the autoantibodies generated will therefore target self-myocardial tissues, resulting in myocardial inflammation injury and myocyte cell death.[6] Finally, given that vaccine-induced myocarditis was vastly seen in male patients, this suggests a hormonal component hyperimmune response.[14] Testosterone is known to inhibit anti-inflammatory immune cells, which result in a potent T-cell-mediated response, whereas estrogen has pro-inflammatory signaling and properties which gives rise to a decreased cell-mediated immune response.[14]

RISK

A recent analysis has contrasted the risk of developing myocarditis following COVID-19 mRNA vaccines with the baseline. While myocarditis can be life-threatening, most vaccine-associated myocarditis events have been mild and self-limiting.[9,11] Most patients required minimal intervention and were discharged from the hospital within 2–3 days with full resolution of cardiac symptoms and normal echocardiogram findings. Given that the myocarditis risk in unvaccinated individuals with COVID-19 is 16–18 times higher than that of the general population, and the known complications with COVID-19 infections in younger adults have a known mortality rate of roughly 1%, the risk-benefit ratio remains significantly favorable for vaccination.[8,12] Vaccination not only prevents COVID-19-related hospitalizations, and deaths, but also decreases the risk of developing multisystem inflammatory syndrome in children (MIS-C), and post-COVID-19 infection sequelae.[8,10]

MANAGEMENT

Although vaccine-induced myocarditis is a rare phenomenon, clinicians should be aware of its presentation and clinical management. Initial evaluation with an ECG and troponin-T levels should be obtained upon admission. Further imaging, such as echocardiograms and cardiac MRIs based on clinical presentation, is generally warranted given abnormal cardiac markers or ECG findings. Treatment is primarily supportive. In published case reports, nonsteroidal anti-inflammatory drugs, steroids, and colchicine were used for management of selective patients with myocarditis after COVID-19 vaccination, in addition to supportive care.[15] Some patients were initiated on β-blocker and angiotensin-converting enzyme inhibitor therapy due to left ventricular systolic dysfunction.[8,10] Although most reported cases of vaccine-

induced myocarditis fully recover with minimal underlying cardiac damage, it is imperative to restrict strenuous physical activity and sports competition pending complete resolution of symptoms, further diagnostic imaging, normalization of cardiac biomarkers, and clearance from a cardiologist.[5,6]

CONCLUSION

Vaccines against COVID-19 have proved to be highly effective at preventing symptomatic disease. Vaccination flattens the case count per capita curve and significantly reduces the risk of COVID-19-related hospitalization, intensive care admission, and death in both young and elderly individuals.[16,17] COVID-19 vaccination also reduces the risk of COVID-19-associated acute kidney injury, arrhythmia, and thrombosis.[9,15] The prevalence of vaccine-induced myocarditis is approximately 1 out of every 100,000 individuals in the general population receiving the same mRNA vaccine.[6] In most cases of vaccine-induced myocarditis, individuals recovered without symptoms or long-term sequalae.[17] Therefore, COVID-19 vaccination retains a favorable benefit-risk ratio in spite of post–mRNA-vaccine-induced myocarditis and should be recommended in adolescent and adult populations. Strategies to reduce the risk of vaccine-associated myocarditis, in at-risk individuals, continue to be studied.

COVID-19 VACCINE UPDATES

On June 18, 2022, the Advisory Committee on Immunization Practices (ACIP) and the US Food and Drug Administration updated the emergency use authorization for the Moderna COVID-19 vaccine mRNA-1273 for the prevention of symptomatic COVID-19 in children from ages 6 months old to 5 years old. Soon thereafter, the Pfizer-BioNTech COVID-19 vaccine was also authorized. Studies have shown that children who have received COVID-19 vaccines during testing developed high levels of antibodies to protect against COVID-19.[18] A great benefit of COVID-19 vaccinations in this population, is the potential to prevent multisystem inflammatory syndrome in children, and hospitalization. Side effect profiles of both the Pfizer BioNTech and Moderna vaccines in children 6 months to 5 years were relatively benign, with the most common symptoms being pain at injection site, swelling, fever, headache, chills, and irritability, which lasted roughly 2–4 days.[18] Vaccine-induced myocarditis in this population has not been well studied at this time. However, the benefit-risk ratio is favorable for the vaccine and its known efficacy to decrease severe illness and hospitalizations.

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REVIEW ARTICLE

POLYPHARMACY IN THE ELDERLY

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KEYWORDS

Polypharmacy

Family physician

Medications in the elderly

Polypharmacy in the elderly

ABSTRACT

Polypharmacy is the regular use of multiple medications and is often seen in older adults and individuals with multiple comorbidities. The commonly accepted definition of polypharmacy is the use of five or more medications by any individual. As patients become more multimorbid, the use of medication therapy increases and in turn raises the risk of polypharmacy. Polypharmacy is often associated with adverse outcomes, including increased mortality, falls, drug interactions, drug reactions, increased length of stay in the hospital, and increased readmission to the hospital after discharge. Patients over the age of 65 are often not included or well represented in drug trials, which can make medical decision-making challenging for evaluation of risk versus benefit in this patient population. There are several important factors to take note of when evaluating patients with polypharmacy.

INTRODUCTION

Polypharmacy is the regular use of multiple medications and is often seen in older adults and individuals with multiple comorbidities.[1] As patients become more multimorbid, the use of medication therapy increases to treat each condition. Multimorbidity is generally defined as having two or more disease states.[1,2] The commonly accepted definition of polypharmacy is the use of five or more medications in any individual.[3] While prescribing medications can satisfy specific quality metrics and mitigate disease-specific concerns, it also increases the risk of adverse consequences from polypharmacy. Patients over the age of 65 are often not included or not well represented in drug trials, which can make medical decision-making challenging for evaluation of risk versus benefit in this patient population. Polypharmacy is often associated with adverse outcomes, including mortality, falls, drug interactions, drug reactions, increased length of stay in hospital, and increased readmission to the hospital after discharge. There are several important factors to take note of when evaluating patients with polypharmacy.

While numeric classification of polypharmacy is convenient, it is not always efficient as it is often too simplistic.[3] The use of more than five medications is not always problematic in a well-optimized patient without medication side effects. Therefore, there are also qualitative definitions of polypharmacy, defined as the use of multiple unnecessary medications. This includes medications that are unnecessary, ineffective, harmful, or the product of side effect treatment. To do this, polypharmacy reduction strategies should encompass the reduction of the number of medications prescribed while addressing unnecessary or ineffective medications.

CONSEQUENCES OF POLYPHARMACY

Polypharmacy contributes to a significant number of negative outcomes for both patients and healthcare systems.[4] Specifically, there is an increased financial burden from taking multiple medications that can be associated with increased healthcare costs and the increased risk of drug-related adverse events and interactions. These consequences can be seen across the multiple settings of medical practice and can have significant detrimental effects on patient wellness. In part, this can be attributed to the disproportionate use of medications in the geriatric population in the United States. According to data published by Medicare,[5] approximately 15% of beneficiaries receive up to 35% of prescription medications in the United States. These data also report that older adults account for approximately 66% of the over-the-counter and supplement use in the United States.

Another consequence of polypharmacy is adverse drug events.[6] It has been estimated that up to 35% of outpatients and 40% of hospitalized elderly adults will experience an adverse drug event. Multiple studies have demonstrated that patients taking more than five medications can be up to four times more likely to be hospitalized from an adverse drug event. Common drug classes associated with these events include anticoagulants, antihypertensives, antibiotics, anticonvulsants, antiglycemic agents, nonsteroidal anti-inflammatory drugs, opiates, and benzodiazepines. Several of these medications can be prescribed

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in one individual, leading to a further increase in the risk of drug interactions and also to adverse drug events.

It has been demonstrated that polypharmacy is associated with an accelerated decline in functional status, worsening of geriatric syndromes, and increased medication nonadherence. The Women's Health Initiative Observational Study[7] found that the use of five or more medications was associated with a reduction in the ability to perform independent activities of daily living. This functional impairment can further contribute to lack of adherence to a medication regimen.

Nonadherence to medications is frequently complex and multifactorial. There are often multiple reasons why any one individual will have medication nonadherence, including side effects, cost of medications, and complicated medication regimens. While nonadherence may be mitigated through the use of a pill pack system, it may create difficulties with changing medications and deprescribing.[8] These complicated medication regimens and nonadherence issues are associated with increased hospitalization and disease progression.

SOURCES OF POLYPHARMACY

Multimorbidity and patient perception of health can both contribute to polypharmacy. With each new diagnosis, an alteration in medication regimen is often made. For example, on diagnosis of diabetes, patients often are started on antiglycemic medications, cholesterol regulation medications, and renal-protective antihypertensive medications. In just one diagnosis, the patient has already been started on at least three medications. This does not take into consideration any additional comorbidities or over-the-counter medications the patient may also be taking. Based on survey data,[5] 34% of the population between 60 and 79 years old takes five or more prescription medications.

It has been noted that patients over 65 are the largest consumers of over-the-counter vitamins and supplements in the United States.[6] The supplements are often advertised to increase overall well-being and treat a multitude of conditions. Common over-the-counter supplements that are known to interact with prescribed regimens include St John's wort, saw palmetto, ginseng, ginkgo biloba, garlic, and green tea extract. These medications are all well known to have interactions with prescription medications and liver enzymes. It is of growing importance to ask all patients about their use of nonprescription medications and supplements.

INDICATIONS FOR DEPRESCRIBING

Evaluation for deprescribing should not wait until there is a problem. Periodic evaluation of medications can easily occur multiple times throughout a calendar year.[9] During a patient's annual wellness exam, their medication list should be reviewed by a provider. With each transition of care, the medication list should be reevaluated for changes, drug interactions, over-the-counter vitamins or supplements, and medications used to treat side effects. The American Geriatric Society recommends not prescribing any new medications without conducting a review of the current drug regimen. This is also supported by the American Society of Health System Pharmacists, which also recommends evaluating for over-the-counter and dietary supplements concurrently.

CHALLENGES TO DEPRESCRIBING

In our training, providers are taught how to start medications and find new diagnoses, but we are not educated on how to evaluate and reduce medications. As osteopathic physicians, we have a unique capability to use a holistic approach to care for patients. In this approach, we can use our osteopathic tenets to decrease the need to start medications. Interventions such as osteopathic manipulation and motivational interviewing for lifestyle modifications can lead to decreased medication intervention. Once patients are already on medications, it is often challenging to discontinue therapy.

Unfortunately, there is no one validated tool to use for polypharmacy or deprescribing. Multiple tools are commonly discussed, such as the Beers list, Screening Tool of Older People's Prescriptions (STOPP), Screening Tool to Alert to Right Treatment (START), and the Medication Appropriateness Index. However, these tools can be time-consuming and may not always address patient concerns or complexity.

TOOLS FOR DEPRESCRIBING

Beers List

The Beers list provides a comprehensive list of medications that should be prioritized for deprescribing; however, it does not provide recommendations on how or when to stop medications. The *Journal of the American Geriatric Society* updates the AGS Beers criteria annually.[10,11] This was originally developed by Mark Beers, et al. in 1991[10,11] as a list of medications to avoid in older adults due to increased morbidity and mortality. In more recent years it has been transitioned to being governed by the American Geriatric Society. While this is an extensive list of medications, it is subdivided into different categories to help facilitate appropriate medication management: avoided by most older people, avoided by older people with specific[10,11] health conditions, avoided in combination with other treatments because of risk of harmful interactions, used with caution because of the potential for harmful side effects, and dosed differently or avoided among people with reduced kidney function. The Beers list content is incredibly detailed and can be intimidating to providers. Enlisting the help of a pharmacist can help mitigate the confusion with the Beers list.

STOPP/START

The next tool would be of best use for prescribers looking for recommendations on appropriate treatments versus potentially harmful medications for a variety of disease states in elderly patients. The Screening Tool of Older People's Prescriptions and the Screening Tool to Alert to Right Treatment were both created by a consensus panel of 18 experts.[12] The contents of each are unique and look at criteria by organ system. The intention of the STOPP/START criteria is to provide explicit

evidence-based guidelines to potentially prevent inappropriate prescribing and correct potential omissions. An additional aim is to prevent adverse drug events while reducing drug costs.

STOPP/START look at medications that should be removed or considered in adults over age 65 where there are no other contraindications. This tool evaluates the gastrointestinal, cardiovascular, respiratory, endocrine, urogenital, and musculoskeletal systems as well as the central nervous system. A unique facet to this tool is that it includes a scoring scale for anticholinergic burden based on medication and medication class. This allows an evidence-based approach to deprescribing in elderly populations who are often excluded from drug trials.

Medication Assessment Index (MAI)

To examine a single medication and assess the risk versus benefit, the Medication Assessment Index[13] can be used. The MAI is a 10-question tool used to evaluate the benefits and risks of medications. This tool helps the clinician look at the medication in relation to the patient and their other medications, focusing on indication, directions, drug-drug interactions, and drug-disease state interactions. This tool, like the Beers list, can be intimidating and may also be time-consuming. Recruiting the help of a pharmacist may decrease the time burden of this tool.

MedStopper

When attempting to discontinue multiple medications for patients with polypharmacy, it may be difficult to determine how to prioritize removing medications. MedStopper[14] is a tool designed to rank which medications might be the best to discontinue for a patient. The application analyzes the medication's potential to improve symptoms, reduce risk of future illness, and likelihood of causing harm based on its indication. In addition, it provides taper instructions and potential withdrawal symptoms to be aware of if the medication will be discontinued. Each medication will also display whether the medication is included on the Beers list/ STOPP criteria.

Pharmacists

Pharmacists[15,16] are another tool for prescribers to use. Though there are several tools available to help deprescribe medications, they can be time-consuming and overwhelming for clinicians. Pharmacists have the ability, training, and knowledge to quickly and effectively use these tools to make recommendations for medication regimens. Several studies support the use of pharmacists in deprescribing, showing positive outcomes, including reduced drug-drug interactions, cost, and improved adherence.[15,16]

A Stepwise Approach for Deprescribing

If a patient is suspected of polypharmacy or considered as a candidate for deprescribing, the most logical first step would be to collect an accurate medication list for the patient. A "brown bag" appointment where the patient brings in all their medications and goes over them with a pharmacist or nurse can help to identify gaps or duplicates in care. Having the patient verbally confirm how they take each medication can help identify nonadherence as well.[17] Once an accurate list of the patient's medications has been obtained, and adherence is assessed if possible, using one of the tools described above to identify any unnecessary medications would be the next step. Finally, time will need to be spent with the patient to provide them with education on benefits or any withdrawal side effects from eliminating medications.

CONCLUSION

We want to bring attention to the problems associated with polypharmacy in older adults and provide tools to providers to help address this issue. Recommendations include reviewing medication lists and having patients bring bottles to visits. Ask about all over-the-counter medications and, when possible, stop vitamin supplementation. Consider deprescribing medications if the patient is asymptomatic and monitor for symptoms.

Using tools such the Beers list and the START/STOPP tool can improve a provider's ability to stop unnecessary medications. These tools can also help avoid medication cascade and therefore minimize further polypharmacy. The presence of a pharmacist can help by simplifying the medication regimen, improving compliance, and consistently providing medication review at the time of outpatient visits. The American Geriatric Society regularly updates online resources and allows utilization of polypharmacy tools available to all providers. Primary care providers can be instrumental in the implementation of the abovementioned tools and improving polypharmacy in older adults.

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CLINICAL IMAGE

PROGRESSIVE ABDOMINAL DISTENTION: A CASE OF PROGRESSIVE ABDOMINAL GROWTH IN A PREMENOPAUSAL WOMAN

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A 21-year-old G0P0 female with a past medical history of GERD and headaches presented to her primary care physician for abdominal distension and growth for the past 10 months. She developed an uncomfortable tightness in her abdomen, with evident suprapubic tenderness and progression of pain into the umbilical and epigastric regions. During the month before presentation, her symptoms worsened and she developed nausea, vomiting, fatigue, pelvic pain/tightness, abdominal distention, indigestion, and increasing abdominal girth (Figure 1). She noted early satiety, which she attributed to possible food intolerance, and tried multiple diets without improvement (gluten-free, keto, and lactose-free diets). She also noted left upper flank numbness when sitting up and driving.

In addition to the physical pain, she experienced emotional distress and embarrassment as people frequently asked whether she was pregnant. She no longer fit into her clothes and tried hiding the abdominal enlargement with oversized clothes. She did not note changes in bowel habits. She denied weight loss or gain according to her home scale; however, she did notice increasing abdominal girth.

Menarche started at age 12 and her cycles had been regular at 5 or 6 days long every 28 days with heavy cramping. She has a family history of heart failure, type 2 diabetes mellitus, and gastric carcinoma from her paternal grandmother. She took famotidine daily and ibuprofen as needed.

FIGURE 1:

Preop. Weight 216 lbs.

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QUESTIONS

1. What is the most likely cause of this patient's presentation?

a. Appendicitis

b. Celiac disease

c. Crohn's disease

d. Ectopic pregnancy

e. Ovarian mass

2. What is the most appropriate treatment for this patient?

a. Antibiotics, rest, and IV fluids

b. Corticosteroids and follow-up with rheumatologist

c. Dietary restrictions

d. Medication-induced abortion/surgery

e. Surgical intervention and removal of mass

ANSWERS

1. What is the diagnosis of this patient?

Correct answer:
E. Ovarian mass

The signs and symptoms exhibited by this patient are consistent with the development of a slow-growing mass—in this case, a mucinous cystadenoma. Ectopic pregnancy is unlikely due to continued regular menstrual cycle, extensive abdominal enlargement, lack of distinctly localized pain, and vaginal bleeding. Crohn's disease is a chronic, autoimmune inflammatory disease that occurs in genetically predisposed patients with symptoms including diarrhea, malabsorption, and abdominal distention.[1] This patient did not exhibit symptoms similar to these. Appendicitis presents as pain in the periumbilical and right lower abdominal areas, fever, and anorexia.[2] The symptoms of appendicitis typically start suddenly and progress over hours to days. Celiac disease is an inflammatory disease that affects the small intestine and demonstrates symptom regression on maintaining a gluten-free diet.[3] The patient thought she was experiencing food intolerance and thus experimented with multiple diets, including a gluten-free diet, but did not experience relief.

2. What is the appropriate treatment protocol for this patient?

Correct answer:
E. Surgical intervention and removal of mass

The appropriate treatment for ovarian mucinous cystadenoma is a unilateral salpingo-oophorectomy or ovarian cystectomy.[4-8] Clinical recurrence is uncommon after surgical intervention, but if it does occur, the tumor may not have been completely resected or there may be a new primary tumor.[7] Medication-induced abortion would be the appropriate choice for treating ectopic pregnancy.[9] Corticosteroids and follow-up with a rheumatologist is an appropriate treatment course for Crohn's disease. The main goal of treatment is to induce remission from the current symptom flare-up and prevent complications of the disease.[1] Antibiotics, rest, and IV fluids are the recommended treatment for uncomplicated appendicitis. Surgical intervention is recommended for more severe cases of appendicitis.[2] Celiac disease is treated by following a strict gluten-free diet for life. Patients must avoid foods that contain wheat, rye, barley, spelt, and more. Symptoms improve with adherence to the diet.[3]

DISCUSSION

Ovarian neoplasms are classified into three categories based on tumor cell origin: stromal, germ cell, and epithelial with further subtypes as discussed in Table 1.[4,10,11] Epithelial tumors comprise approximately 60% of all ovarian tumors, with 40% of these being benign.[7] The two most common types of epithelial tumors are serous and mucinous cystadenomas, with their malignant counterparts being cystadenocarcinomas.[7] Mucinous cystadenomas are benign ovarian neoplasms of epithelial origin that comprise approximately 10% to 15% of all benign ovarian neoplasms.[4,7,11,12]

Table 1:
Subtypes of ovarian neoplasms

OVARIAN NEOPLASMS	
Stromal/sex cord tumors	Fibroma, granulosa-theca cell tumor, Leydig cell tumor, and Sertoli cell tumor
Germ cell tumors	Teratoma, dysgerminoma, endodermal sinus tumor, and choriocarcinoma
Epithelial tumors	Serous cystadenoma/cystadenocarcinoma, mucinous cystadenoma/cystadenocarcinoma, endometrioid tumors, clear cell tumor, and Brenner tumor

Mucinous cystadenomas are smooth tumors lined by a single layer of epithelial cells that secrete mucin.[11,13] The tumor size can range from a few centimeters in diameter to more than 30 cm.[7,11,12] There have been reports of tumors weighing up to 135 kg if there has been a delay in diagnosis.[12,13] The tumors are most likely to develop during the third to sixth decades, but they can occur in younger women (rarely less than 21 years of age).[4,5,7] They are unilateral in 95% of cases.[4,7,10,11,12]

The etiology of mucinous cystadenomas is currently unknown. There are associated risk factors, including obesity and tobacco use.[14,15] *Kirsten rat sarcoma viral oncogene (KRAS)* mutations have been documented in up to 58% of the cases.[5,7,8,14] *KRAS* is a proto-oncogene involved in the RAS/MAPK pathway responsible for cell proliferation.[8] *KRAS* mutations lead to an unregulated proliferation of cells and cause neoplasm formation. There are no current therapies available as *KRAS* has proved difficult to target with drug therapy; however, active research is being conducted to target *KRAS* mutations.[8]

Ovarian mucinous cystadenomas are generally asymptomatic in the early stages and are associated with nonspecific symptoms during growth.[6,7,11] Signs and symptoms experienced by patients commonly include pelvic pain, progressive abdominal distention, early satiety, heartburn, nausea, increased urinary frequency, urinary retention, and generalized discomfort.[4,7] The average tumor size upon discovery is typically 10 cm in diameter.[11] If not diagnosed early, the tumors can grow quite large, causing compressive or mass-associated symptoms as mentioned previously.[4,12,13] Complications of ovarian neoplasms can include torsions, hemorrhage, or rupture.[4,6,16] Rupture of cysts can lead to peritonitis, sepsis, and death from septic shock.[4,16] A rare but life-threatening phenomenon that can occur from a cystic rupture is called pseudomyxoma peritonei.[10,16-18] This involves widespread seeding of mucin-producing cells throughout the peritoneal cavity and can lead to bowel obstruction and peritonitis.[10,18]

The diagnostic workup for a patient with progressive abdominal enlargement and associated compressive symptoms is comprehensive and requires abdominal imaging.[6,13] A CT scan may be ordered first based on presenting symptoms such as abdominal distention, acid reflux, and nausea; however, the best initial evaluation of an adnexal mass is via ultrasound.[4,6,13] The pelvic ultrasound is not definitive and necessitates follow-up with a histopathological exam of the surgical specimen.[4,7] The histological findings of a mucinous cystadenoma will exhibit multiple cysts due to its multilocular nature and glands lined by simple nonstratified mucinous epithelium.[6,7,10,16] There will be no cytologic atypia or any mitotic figures present in the specimen consistent with a benign condition.[7] If the cysts do not contain septa, papilla, or solid components based on ultrasound results, the tumor can be closely monitored.[13] Surgical exploration should be considered if the mass changes in size or character.[13]

Mucinous cystadenomas can present with elevated tumor markers such as β-hCG, AFP, LDH, inhibin, CAE, CA-125, CA19-9.[4,5,11] Elevated tumor marker CA-125 has been documented in 80% of epithelial ovarian cancers and can be used for surveillance of disease recurrence.[5,10,11] Some guidelines recommend using CA-125 tumor marker for initial evaluation and management in women who present with symptoms suggestive of ovarian cancer; however, the use of tumor markers is not common practice.[5,10,11] If ovarian cancer is high on the differential, then the next step in management is an abdominal and pelvic ultrasound.[11]

Tumors of the ovary that present with diameters greater than 10 cm are referred to as giant ovarian masses.[6] The standard treatment is a unilateral salpingo-oophorectomy with intraoperative pathological evaluation.[4,6,7] Specific surgical techniques include drainage of

cystic fluid, cystectomy, oophorectomy, and/or hysterectomy.[4,12] Oophorectomy is the preferred and most common method because it has the lowest rate for local recurrence.[4-8,18] A minimally invasive laparoscopic approach is ideal, but open laparotomy procedures are more commonly practiced.[4,12] Laparoscopy has been shown to decrease recovery time and morbidity when compared with a laparotomy.[4,12] However, opting to perform a laparoscopy depends on several factors such as tumor size, susceptibility to rupture, and surgeon level of comfort.[4,12]

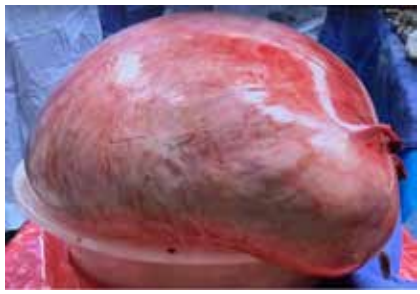
The prognosis of mucinous cystadenomas is excellent, with a five-year survival rate of 98% after surgical excision.[7,18] There are documented cases where patients prolong seeking health care for various reasons including access to health care, willingness to seek treatment, economic status, level of education, and emotional components like fear and anxiety.[4] If left untreated, the mass grows exponentially, affecting the patient's quality of life and increasing the risk of rupture.[4,6,16] Although there are no documented cases of intrabdominal rupture, continued growth without intervention can cause the cyst wall to thin.[12] Thinning of the cystic wall further complicates surgical removal and enhances the risk of rupture.[12] In these situations, the less common technique of intraoperative surgical aspiration before removal is the preferred method.[12] Surgical aspiration is not commonly done and is performed under special circumstances.[6] The preferred method is the removal of the tumor intact since aspiration of cysts before excision is associated with increased risks of recurrence, infections, bleeding, cystic rupture, peritoneal adhesions, or possible dissemination of malignant cells.[4,6,7,18]

The patient in this case sought care from her primary care physician after the development of abdominal distension and progressive compressive symptoms. She delayed seeking treatment for several reasons and thus presented with a large mass weighing 32.6 lbs. and measuring 42 cm in greatest diameter (Figure 2). She was immediately referred to an obstetrician-gynecologist for further evaluation and an abdominal and pelvic ultrasound was performed. The ultrasound revealed a large cystic mass with multiple septations measuring an estimated 20–30 cm. The mass was suspected to be a neoplasm originating from the left ovary. Four days after her initial presentation, she had an open left salpingo-oophorectomy via midline laparotomy incision from xiphoid to pubis (Figure 3). The final pathologic report revealed that the tumor was negative for atypia or malignancy and confirmed the diagnosis. The patient is recovering well from the procedure (Figure 4).

CONCLUSION

Ovarian mucinous cystadenomas are benign tumors originating from surface epithelium of the ovary and are diagnosed at an average age of 40–49.[4,7,11,18] They are large, multiloculated, cystic masses containing mucinous fluid that can grow unregulated until medical intervention is implemented.[7,10] These tumors typically require surgical excision.[4,5,12] The prognosis is exceptional, with a five-year survival rate of 98%.[7,18] Local recurrence is minimized with oophorectomy, and only rare cases of malignant transformation have been documented.[4,7,18] Early detection and treatment provide the best prognosis and improvement in quality of life.[4]

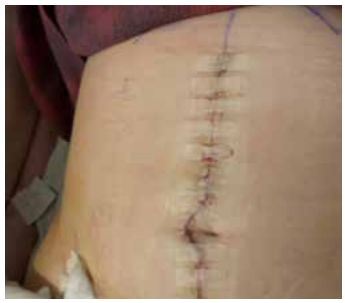
FIGURE 2:



Per pathology report: "Final pathologic diagnosis: mucinous cystadenoma, 42 cm in greatest dimension, negative for atypia or malignancy, histologically unremarkable fallopian tube."

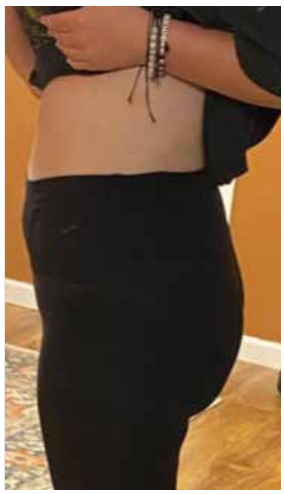
Gross description: "32.6 pounds, 42x30x29-cm fluctuant intact cystic ovary with an associated 30x.04-cm elongated fallopian surface. The largest cyst contains yellow-red watery fluid and additional smaller cysts contain translucent mucoid fluid. No significant solid or papillary are as identified."

FIGURE 3:



Postsurgical incision.

FIGURE 4:



Two weeks postop. Weight 178 lbs.

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PATIENT EDUCATION HANDOUT

acofp AMERICAN COLLEGE OF OSTEOPATHIC FAMILY PHYSICIANS

Cervical Cancer Screening

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WHAT IS CERVICAL CANCER?

Cancer can develop anywhere atypical cells divide without regulation (in an uncontrolled manner). In women, this can occur on the uterine cervix, which connects the vagina and uterus.

The cancer can lead to tumor formation on the cervix and, as it advances, the cancer can enter local organ structures or spread outside the reproductive system.[1] The American Cancer Society estimates that in 2022, there will be about 14,100 new cases and 4,280 women will die from cervical cancer.[1] Cervical cancer can occur in women at any age but is more common after age 40.

Risk factors for cervical cancer include the following[2]:

- Family history of cervical cancer
- Multiple sexual partners (or having sexual partners who have multiple sexual partners)
- Early age at which you first had sex (especially younger than 18 years old)
- Prior history of dysplasia (abnormal changes in the cells) on the cervix, vagina, or vulva
- Family history of cervical cancer
- Smoking
- Sexually transmitted infections
- Being immunocompromised
- Exposure to diethylstilbestrol (DES) before birth (having a mother who took a medication known as DES while pregnant)
- Infection with human papillomavirus (HPV)

Cervical cancer may cause no symptoms at all. However, here are some common symptoms of cervical cancer[2]:

- Abnormal bleeding, spotting, or watery discharge from the vagina
- Pelvic pain
- Problems with urination
- Swollen legs

WHAT IS HUMAN PAPILLOMAVIRUS?

Human papillomavirus is a virus that spreads through vaginal, anal, or oral sex and can lead to changes within the cells in your body. Many HPV infections are asymptomatic,[1] meaning, they don't cause symptoms, but over time they can result in abnormal changes to your cells. This can develop into cervical cancer as well as anal, vulvar, penile, or head and neck cancers.[2] Many sexually active people will have a genital HPV infection in their lifetime. In 2013–2014, high-risk genital HPV was found in about 45% of adults.[3] Some types of HPV are more likely to lead to cancer than others. Lower-risk HPV types can lead to genital warts.

You can protect yourself against HPV through vaccination. Vaccination works best if a person completes the series of vaccines before sexual activity begins. It is still helpful before a person is sexually active and potentially exposed to HPV and can also be given after a person has been sexually active. People can get vaccinated for HPV at any time, from ages 9–26 (it has been FDA approved for people up to 45 years old). The ideal age for HPV vaccination is around 11–12 years old. The vaccine requires 2 doses given 6–12 months apart.[4]

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HOW DO YOU SCREEN FOR CERVICAL CANCER?

Cervical cancer is a slow-growing cancer. Precancerous cell changes can be detected with regular screening. Deaths from cervical cancer have dropped significantly because of the increased use of the Pap test.[1] A Pap test looks for abnormal cells in the cervix. Pap tests can also be combined with an HPV test that detects high-risk HPV types, which are associated with an increased risk of cervical cancer. Regular screening can detect precancerous changes and lead to early intervention. Cervical cancer screening can be done by your family medicine or primary care doctor or by your obstetrician-gynecologist.

THE SCREENING GUIDELINES ARE BELOW[5]:

If you are less than 21 years old: no screening.
If you are 21–29 years old: Pap test every 3 years.
If you are 30–65 years old:

- Pap test and HPV test every 5 years.
- Pap test only every 3 years.
- HPV test only every 5 years.

If you are older than 65: *no screening.*

Exceptions to the screening guidelines are as follows:

- If you are immunocompromised, have HIV, have a history of cervical cancer, or were exposed to DES before birth, you may need more frequent screening.
- If you have had a hysterectomy with removal of the cervix (complete hysterectomy) and …
  - have a history of cervical cancer or moderate-to-severe cervical changes, you should continue screening for 20 years after your surgery; or
  - have no history of cervical cancer or cervical changes, you do not need screening.

WHAT CAN I EXPECT DURING A PAP TEST?

You will begin by lying down on your back on the exam table and placing your feet in the stirrups at the end of the table and relaxing your knees outward. Your doctor will insert a speculum with lubricant into your vagina to hold the vaginal walls open. This will allow the doctor to see your cervix and use a small brush to collect cells from your cervix.

If you have any questions before your Pap test, be sure to ask your doctor.

UNDERSTANDING YOUR CERVICAL CANCER SCREENING RESULTS

Normal is normal! Follow the screening guidelines above for the next time you should screen again.

There are many ways a Pap smear and HPV test could come back as abnormal. An HPV test may come back positive. With a Pap smear, if any abnormal cells are found, they may fall into the following categories[6]:

- Atypical squamous cells of undetermined significance (ASC-US)
- Low grade squamous intraepithelial lesion (LSIL)
- High grade squamous intraepithelial lesion (HSIL)
- Atypical squamous cells and cannot exclude HSIL (ASC-H)
- Atypical glandular cells (AGC)

Depending on your result, age, and other risk factors, your doctor may move on to more follow-up testing such as the following[6]:

- **Colposcopy**: using a microscope, the doctor can closely examine the atypical cells in your cervix.
- **Biopsy**: your doctor can remove a small sample of tissue and send it to the laboratory for further testing to find out the degree of changes to your cells as listed below:
  - **CIN 1**: mild changes that usually resolve on their own
  - **CIN 2**: moderate changes
  - **CIN 3**: severe changes
- **Endocervical sampling**: using a small brush, your doctor will take a tissue sample from the inside of the cervix, which can be sent to the laboratory for further testing to determine the degree of changes to your cells.

Follow-up testing will determine your risk of cervical cancer and next steps for possible removal (excision) or destruction (ablation) of abnormal cells. You may need more frequent screening after an abnormal Pap test.

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